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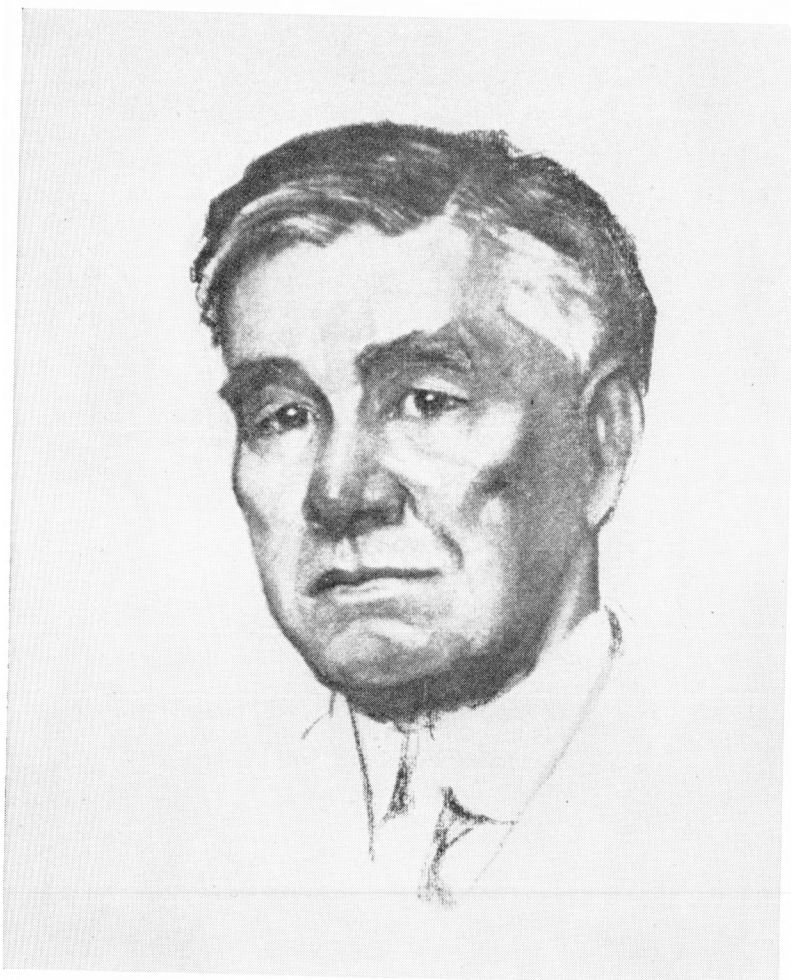
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EDWARD CURTIS FRANKLIN

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# Edward Curtis Franklin

## 1862–1937

Edward Curtis Franklin, President of the American Chemical Society in 1923, was born on March 1, 1862 in Geary City, Kansas, and died at Stanford University on February 13, 1937, after becoming in the intervening seventy-five years one of America's most honored and best loved scientists.

As a boy, Franklin was definitely not a scholar, though it is easily understandable why the primitive educational facilities of the schools in a frontier society should have had but little appeal when contrasted with the attractions to be found outdoors.

Kansas was in the hands of the Indians until 1854, and Franklin thus grew up in a country which had not yet been spoiled by the ruthless hands of civilization. The eagerness with which he availed himself of his surroundings has been recounted in a brief autobiographical sketch which describes his boyhood pleasures of hunting, of fishing, of swimming in the Missouri (even then it was noted as being muddy), and of collecting fossils from its limestone banks. Seemingly, there was an infinite variety of nuts, fruits and berries to be picked for use and of wild flowers to be admired. His delight in the beauties of the outdoor world, and particularly of the mountains, stayed with Franklin throughout his life.

As a youth, he roamed the hills along the Missouri; as a young man, he climbed the mountains of Colorado and crossed the Alps on foot during a year as a student in Germany. In his Stanford days, he was active in the Sierra Club until his fifties, having by then climbed five peaks over fourteen thousand feet high and many only slightly lower. At sixty-seven, as a guest to the South African meeting of the British Association for the Advancement of Science, his only regret was the inability to climb Kilimanjaro, seen on the return trip at a distance of thirty or forty miles, towering some nineteen thousand feet above the clouds. In later years, his mountain climbing was done with an automobile, and in 1933, he drove to the fourteen thousand foot summit of Mount Evans.

In the last few years of his life, he managed to see again most of the scenic wonders of our land as in 1936 when he drove to Kansas "by way of the Hoover Dam, Zion Canyon, Bryce Canyon, the North Rim of the Grand Canyon, Albuquerque, Santa Fe, and Boulder, Colorado," and thence on a "wild tour of thirteen thousand miles lecturing before groups of defenseless chemists through the Middle West to Philadelphia and Washington, and thence south to Florida and home by way of the southern route." To Franklin, the longest road was always the best if it offered the slightest promise of more interesting views, whether these be new or old.

In the period of 1914 to 1918 when I had the privilege of working with him, it was always Franklin who first succumbed to spring or fall fever and proposed that we play hookey on a Saturday afternoon and run away on our bicycles into the hills back of Stanford. The game which was sought might be dove, quail, or squirrels, or ducks that could be hunted from a "sneak-boat" on nearby San Francisco Bay. The return was

usually empty handed, but the treasured hours spent on these brief, back-to-nature jaunts were always followed by a vigorous and enthusiastic attack on the laboratory problem which had been so rudely abandoned.

At the age of fifteen, Franklin was sent away to a small sectarian college. There he found himself both physically and spiritually starved, and after two months, he ran away. Fifty years later, it still was possible to find schools in that region where the rations in the dining hall might keep a canary alive but certainly not happily singing. It is quite easy to understand that a man, who throughout his life was characterized by the blunt and honest frankness of his language, could hardly be content in a rigid, fundamentalist environment when, even as a youth, he was inclined to be a "free-thinker" and agnostic.

From 1880 to 1884, Franklin was a pharmacist's assistant in Severance, Kansas, where he also ran a small job-printing shop and played a cornet in the village band. It was with no thought of making a new start on an education that he visited his younger brother, then a student in the University of Kansas in the fall of 1884; but once on the campus, the congenial surroundings aroused his interest, and he decided to enroll as a special student in chemistry at the age of twenty-two. During the first three undergraduate years, he did odd jobs around the chemical laboratory and as a senior, acted as an assistant in qualitative and quantitative analysis.

Apparently, he showed promise as a teacher for he was retained on the faculty as an assistant in chemistry from 1888 to 1893, as an associate professor from 1893 to 1899, and became professor of physical chemistry in 1899 which position he held until 1903. However, he was still restless and footloose and felt uncertain about his future. Thus, we find him from 1890 to 1891 as a student in Germany and from 1893 to 1895 at Johns Hopkins where he gained his doctorate. These excursions might be regarded as part of an orderly preparation for a university career if one did not know that much of the year abroad was spent in sight-seeing rather than given over to serious study and had he not again taken leave in 1896 for a one year visit to Costa Rica as chemist and co-manager of a gold mine and mill. The fact is—and he has recorded his doubts—Franklin was still uncertain as to his fitness for the teaching profession. But, there was no such doubt in the minds of his students. As E. E. Slosson, a Kansas alumnus who was one of them, has so succinctly put it, "all of his former students are his friends, and that is more than can be said of most teachers."

Others have described him as relying but very little on books as a means of gaining knowledge but this conclusion is not warranted by the evidence. It is true that in the 1890's, the entire Kansas University chemical library was held in two small cases which were located in the department office and that the number of scientific journals received by the university as a whole was very small indeed. But each journal was impatiently watched for and eagerly read upon its arrival.

The story of the discovery of argon was hardly read when plans to check the separation were made. It is probable that the first samples of both argon and helium to be prepared in America were separated by Franklin. This was certainly true of Dewar vessels and one of the earliest, if not the first X-ray tube which was American made, was prepared for the use of Professor Blake of the Physics Department. He did rely on the written word for information, but the printed description of new and interesting discoveries was not sufficiently satisfying to him. He had to do them with his own hands and see them with his own eyes. (A considerable number of argon- and helium-containing Plücker tubes were prepared at this time and sent to friends and acquaintances in various universities. Franklin was proud of his glass blowing skill, as well he might be; one of his most satisfying experiences was to find on his arrival at Stanford that his gifts to that school had been stored in an exhibit case among other valued items.)

The diligence with which he trained himself in the laboratory arts, the eagerness with which he followed the chemical literature and the pleasure he enjoyed in repeating the more outstanding discoveries of the day offer additional evidence as to the diversity of Franklin's interest in the material world. The things which might be seen and experienced within the walls of a laboratory were now fully as appealing as the outdoor attractions had been to the youth. Like Kipling's Elephant Child of the "Just So Stories," Franklin was filled with the most insatiable curiosity about all things around him throughout his entire life.

However, while this repetition of the work of others was very interesting and satisfying, it did not reveal in him those characteristics which are the essentials of a creative worker. The spark which was to kindle the fire of Franklin's imagination came from one of his students, H. P. Cady. In the autumn of 1896 Cady, as an undergraduate, was working in the regulation course of quantitative analysis. "Observing after a time that the young man was becoming bored with his task, the writer (Franklin), at the time giving instruction in analytical chemistry, proposed to him that he prepare several of the cobalt-ammine salts and confirm the composition of one or two of them by analysis. Some days later with a beautifully crystallized specimen of one of these interesting salts in his hand Cady stated that the ammonia in these and other salts containing ammonia must function in a manner very similar to that of water in salts with water of crystallization. He suggested furthermore that liquid ammonia would probably be found to resemble water in its physical and chemical properties. As a direct conse-

quence of Cady's suggestion has followed all the work done in this country on liquid ammonia."

Franklin promptly ordered a cylinder of liquid ammonia and prepared the Dewar vessels and other apparatus needed in Cady's proposed study of ammonia as an electrolytic solvent. But the ammonia was slow in arriving and before the experiments were started, Franklin had left for Costa Rica. He returned to learn that Cady had found that many salts dissolve in ammonia to form conducting solutions, although the pure solvent still further resembles water in being practically a non-conductor.

These results, obtained with simple apparatus designed and built with his own hands, for the first time aroused Franklin's latent research instincts. No longer was the literature to be searched for interesting experiments worthy of repetition. The facts recorded therein were to be used as foundations for new information to be discovered by himself and his co-workers.

The years from 1897 to 1903 were richly fruitful for the new research team which was soon enlarged by the weaning of C. A. Kraus from the Physics Department. There seemed to be no limits to the work which Franklin's aroused imagination now saw immediately ahead. Typical titles of papers based in this productive period are "Liquid Ammonia as a Solvent"; "Determination of the Molecular Rise of the Boiling Point of Liquid Ammonia"; "Metathetic Reactions Between Certain Salts In Liquid Ammonia"; "Electrical Conductivity of Liquid Ammonia Solutions"; "Concentration Cells in Liquid Ammonia."

In the fall of 1903, this team of productive research men, each outstanding in his own way, was broken up. Kraus had left for M. I. T., Franklin was to go West to Stanford, and Cady was to remain at Kansas for his entire professional career.

Franklin's evaluation of the two junior partners is of interest. He said many times that Kraus was the most skillful glass blower and manipulator in all of the laboratory arts whom he had known. I dare to question the first part of this opinion; Kraus might equal but certainly could not excel Franklin as an artist and artisan in the designing and working of the old German soft glass. Chemists of today who are accustomed to placing a piece of cold Pyrex tubing directly into the flame of an oxygen-gas blast lamp can have no appreciation of the problem involved in the construction of one of the intricate cells used in some of the ammonia work. The patience of Job and the manipulative skill of a master were needed and these Franklin had.

The later research record of Kraus speaks for itself; an outstanding pupil graduated into an outstanding and productive research professor.

Cady was rated by Franklin as his most brilliant student and co-worker, and we believe that this was a fair evaluation. However, it is worthy of note that his most productive and active research years were spent under Franklin's stimulating guidance.

In 1903, Franklin left Kansas for Stanford University to fill the chair of organic chemistry left vacant by the death of Professor Richardson. Stanford was a rich school in those pre-earthquake days, and David Starr Jordan was adding outstanding research men to his faculty when he could find them. The change was a happy one. Franklin had been preceded in his western journey by several Kansas friends, and one of these, Vernon Kellogg, was instrumental in persuading him to accept the Stanford offer. The university lay in a beautiful setting. Rolling foothills which began at the edge of the campus soon merged into the coastal mountains and beyond these lay the Pacific Ocean only twenty miles from the university. While the Coast Ranges were comparatively low, the higher and much more rugged and scenic Sierras were only a hundred miles to the east. We can be sure that to Franklin, not the least of the attractions of this western wonderland were the mountains which he loved so well.

While Franklin's work at Kansas was more spectacularly interesting, because of the greater emphasis placed on physical-chemical measurements, the purely chemical work which was largely done at Stanford was much the more important. To quote Alexander Findlay, "From their earlier experiments . . . Franklin and his collaborators were led to an exhaustive examination of the parallelism between the chemical behavior of derivatives of ammonia dissolved in liquid ammonia and the behavior of derivatives of water, aquo-compounds as Franklin called them, in aqueous solution. The investigation of the behavior of the former class of compounds, the ammono compounds, to use Franklin's nomenclature, constitutes the chief and most characteristic contribution of Franklin to chemistry."

The record of this contribution is embodied in his monograph on the "Nitrogen System of Compounds." In this, his detailed classification, of the organic compounds of nitrogen as belonging to the ammonia system, has made the book a classic and a most stimulating guide to further investigations by others. Franklin wrote slowly and most painstakingly; hence this monograph was rewritten many times and was over ten years in preparation.

The step by step reports of progress in his forty years of research are contained in eighty-seven papers of which less than half bear his name due to his generosity toward the pupils who were his collaborators.

Franklin, as we have seen, was a great experimentalist, and the few who were fortunate enough to be accepted by him as a collaborator will insist that he was without a peer as a teacher of graduate students. Every one of these men acquired a

skill in laboratory technique which was far above the average, each learned to think independently and, in addition, learned to view his own experimental results with that critical skepticism which is the true measure of a scientist.

His lectures in organic chemistry were models of clear and orderly thinking though Franklin never acquired the smooth and polished delivery which was characteristic of Stieglitz. His own experimental interest and belief in teaching by example made his lectures unusually instructive because of the many elaborate and skillfully done demonstrations which illustrated them.

He had an infinite capacity for making lifelong friends, and these were of all ages from babes in arms to emeritus professors. The Christmas lectures which, like Faraday, he enjoyed giving to the children of his friends and colleagues were elaborately illustrated with demonstrations to fit the occasion and the audience. (I dare say that many a middle-aged matron of today has in her jewel box a glass ring, with a "red" stone, which was made by Dr. Franklin just for her during one of these lectures.)

To the end of his days, he was a welcome and honored guest in the home of every former student and associate in this and other lands. He delighted in talking of his own work and pleasures and equally enjoyed listening to the exploits of others.

From the beginning of his professional career until the year of his death, he was a regular attendant at meetings of the American Chemical Society, and of all the honors that he received, he valued his election to the presidency of this society the most highly.

His wife, Effie Scott Franklin, who was a student at Kansas at the time of her marriage in 1897, died in 1931 and the older of two sons, Charles Scott Franklin, was killed in an airplane accident in 1928. The two surviving children are also worthy of their parents. Dr. Anna Franklin Barnett is a happy wife and mother and a practicing physician as well. John Curtis Franklin, an electrical engineer, is now Manager of Oak Ridge Directed Operations for the Atomic Energy Commission.

HOWARD M. ELSEY

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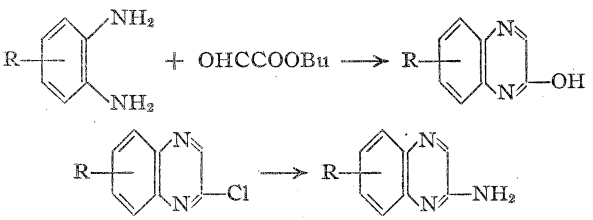
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# Substituted Sulfaquinoxalines. III. Extension of the Glyoxalate Synthesis of 2-Aminoquinoxaline[1]

BY F. J. WOLF, KARL PFISTER, 3RD, R. H. BEUTEL, R. M. WILSON, JR., C. A. ROBINSON[2a] AND J. R. STEVENS[2b]

The preparation of 2-aminoquinoxaline by the glyoxalate synthesis[3] offered a convenient method for procuring substituted 2-aminoquinoxalines and the corresponding sulfonamido derivatives, of which a series was desired for antimalarial testing.[4] In this paper sixteen 2-sulfanilamidoquinoxaline derivatives bearing substituents in the benzenoid ring are reported. As shown in the accompanying




equations, the requisite 2-aminoquinoxalines were prepared by condensing butyl glyoxalate with the corresponding *o*-phenylenediamine (R = alkyl, alkoxy, halogen, nitro, carboxy or sulfonic acid group) to give a 2-hydroxyquinoxaline, which was then chlorinated and aminated.

The necessary diamines were obtained by reduction of the corresponding nitroanilines or dinitro compounds. In some cases these diamines were converted without isolation into the hydroxyquinoxalines by addition of butyl glyoxalate to the reaction mixture resulting from the reduction. Generally, however, the diamines were isolated and purified as the neutral sulfates. The reaction with butyl glyoxalate performed in water or water–ethanol gave the 2-hydroxyquinoxalines in good yields. These compounds are high-melting solids, insoluble in most organic solvents, but soluble in dilute ammonium or sodium hydroxide.

Chlorination of the hydroxy compounds was achieved by treatment with phosphorus chlorides (usually phosphorus pentachloride in phosphorus oxychloride). The products were purified to white to yellow solids by recrystallization from ligroin or benzene. At this stage the isomers resulting from condensation of the unsymmetrical diamines with butyl glyoxalate in the two possible ways were separated by fractional crystallization. The pure chloroquinoxalines were aminated with liquid ammonia, usually in methanol solution, at temperatures and reaction times that varied widely for optimum yields with the differently substituted chloroquinoxalines. The amines are weakly basic, pale yellow compounds, soluble in warm dilute hydrochloric acid and conveniently crystallized from benzene or benzene–ethanol solutions.

The reactivity of the amino group in the differently substituted compounds (as indicated by the ease of reaction with *p*-acetylaminobenzenesulfonyl chloride) varied considerably, and in the cases of substitution of the benzene nucleus with strongly meta-directing groups (nitro, carboxy and sulfonic acid) the condensation failed under the usual conditions. Sulfonamides of the nitro compounds were obtained from the reaction of the chloro derivatives with *p*-acetylaminobenzenesulfonamide, while the carboxy derivatives were converted into the esters, and these reacted with *p*-acetylaminobenzenesulfonyl chloride. No sulfonamides were obtained from the sulfonic acid derivatives.

As noted above, the isomeric pairs that resulted when the diamines were unsymmetrically substituted were separated as the 2-chloroquinoxalines. Attempts to separate the isomeric 2-hydroxy or 2-amino compounds were unsuccessful. Furthermore, since the sulfonamides were used for pharmacological screening, no attempt was made to identify the isomers. Two isomers were observed in every case with the exception of the 6(or 7)-carboxylic acid. However, of three vicinally substituted diamines, two gave only one of the isomeric quinoxalines in appreciable quantity.

The compounds prepared are listed in the following tables. The higher melting isomeric chloro derivative has been arbitrarily labelled a, and the subsequent derivatives are related to the chloro isomers. A paper by Platt (*J. Chem. Soc.*, 1310 (1948)) which appeared after this contribution was in press describes the preparation by an ambiguous method of both 2-hydroxy-6-methylquinoxaline and 2-hydroxy-7-methylquinoxaline and their respective chloro and amino derivatives. A comparison of melting points indicates that our 2-chloro-6-(or 7)-methylquinoxaline a is in fact 2-chloro-6-methylquinoxaline.

## Experimental

### Substituted *o*-Nitroanilines

The compounds used were either purchased or obtained by standard preparation according to procedures in the literature. However, a new method of synthesis of 2-nitro-6-chloroaniline was developed using the method described in the literature for the preparation of 2-nitro-6-bromoaniline.[5]

(1) For the previous paper in this series see Wolf, Beutel and Stevens, THIS JOURNAL, **70**, 4264 (1948).

(2) (a) Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass.; (b) present address: J. T. Baker & Co., Phillipsburg, New Jersey.

(3) Gowenlock, Newbold and Spring, *J. Chem. Soc.*, 622 (1945).

(4) For the results of the testing, see F. Y. Wiselogle, Ed., "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, Mich., 1946.

(5) Holleman, *Rec. trav. chim.*, **27**, 153 (1908).

TABLE I

2-HYDROXYQUINOXALINES[a]

| Substituent | Yield, % | Analyses, %[6] Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|
| 6-$CH_3$[b,c] | 72 | 67.48 | 67.78 | 5.03 | 4.92 |
| 6-Cl[b] | 85 | 53.20 | 53.63 | 2.79 | 3.08 |
| 6-Br[b] | 81 | 42.69 | 41.91 | 2.24 | 2.53 |
| 6-$NO_2$[b] | 76 | 50.27 | 51.13 | 2.64 | 2.14 |
| 6-$OCH_3$[b,d] | 82 | 61.35 | 61.02 | 4.38 | 4.40 |
| 5-$CH_3$[e] | 65 | 67.48 | 67.64 | 5.03 | 5.34 |
| 5-Cl[e] | 79 | 53.20 | 52.96 | 2.79 | 2.94 |
| 5-$OCH_3$[b] | 93 | 61.35 | 61.64 | 4.58 | 4.63 |
| 5-$CH_3$-6-Cl-8-$CH(CH_3)_2$[b] | 68 | 60.88 | 61.05 | 5.54 | 5.72 |
| 5,7-$Cl_2$[b] | .. | 44.68 | 44.81 | 1.87 | 2.17 |
| 6-$SO_3H$[b,f] | 83 | | | | |
| 6-COOH[f,g] | 88 | | | | |
| 6-CN[f,g] | 85 | | | | |

[a] Mixtures of isomers were not separated, although purification may have resulted in enrichment of one isomer. [b] These products consist of a mixture of both possible substituted 2-hydroxyquinoxalines. [c] *Anal.* Calcd.: N, 17.50. Found: N, 17.45. [d] *Anal.* Calcd.: N, 15.99. Found: N, 15.63. [e] These products consist of 5- or 8-substituted 2-hydroxyquinoxalines. [f] These derivatives were not analyzed, but were converted directly into the corresponding chloro derivatives (Table II). [g] These products consist of 6- or 7-substituted 2-hydroxyquinoxalines.

**2-Nitro-6-chloroaniline.**—A solution of 100 g. of *o*-nitroaniline in 100 ml. of concentrated sulfuric acid and 275 ml. of 20% oleum was warmed at 160° for five minutes. The mixture was poured into 2 kg. of ice and water, and a solution of 50 g. of chlorine in 700 ml. of glacial acetic acid was added at 0–5° while the mixture was mechanically stirred. The mixture was allowed to stand twenty-four hours at room temperature and then filtered. The insoluble material (2–8 g.) was discarded and the filtrate transferred to 5-liter round-bottom flask equipped with a thermometer immersed in the liquid, a steam inlet, a condenser for downward distillation and an electric heating mantle. The mixture was gradually heated to 135°. At this temperature most of the acetic acid has distilled, and the product begins to steam distil. Dry steam was introduced and the product steam distilled. The temperature of the contents of the flask gradually rises to 150° during the distillation. Toward the end of the distillation the mixture foams badly, and the introduction of an anti-foam agent is helpful. The distillate (approximately 5 l.) was filtered and the product recrystallized from Skellysolve B. The product, 36.3 g. (29% yield), melts at 72–73°.

### Substituted *o*-Phenylenediamines

Most of the diamines used have been previously prepared by various methods. The two methods used in the experiments were reduction with iron and hydrochloric acid and catalytic reduction. The product was generally isolated as the neutral sulfate by adding sulfuric acid to the alcohol solutions obtained from the reduction until no more precipitate was obtained. The sulfate salts were found to be non-hygroscopic, stable derivatives and could be purified by recrystallization from water or ethanol–water. The preparation of 3-chloro-1,2-diaminobenzene has not been previously described.

**3-Chloro-1,2-diaminobenzene Sulfate.**—A mixture of 37 g. of crude 2,3-dinitrochlorobenzene, 840 ml. of ethanol, 56 ml. of water and 72 g. of iron powder was warmed to 50°, and 11.5 ml. of concentrated hydrochloric acid was added at a rate sufficient to maintain gentle refluxing.

(6) Microanalyses were kindly performed by R. N. Boos, W. H. Humphrey, E. Thornton, L. Rosalsky and E. Miess of these Laboratories.

TABLE II

2-CHLOROQUINOXALINES[a]

| Substituent | Yield, % | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|
| 6-$CH_3$, a | 98 | 102–104 | 60.51 | 61.15[b] | 3.95 | 3.95 |
| 6-$CH_3$, b | | 56–57 | 60.51 | 60.50[c] | 3.95 | 3.93 |
| 6-Cl, a | | 156–157 | 48.51 | 48.80 | 2.03 | 2.18 |
| 6-Cl, b | | 120–122 | 48.51 | 48.54 | 2.03 | 2.33 |
| 6-Br, a | 91 | 152–153.5 | 39.46 | 39.67 | 1.65 | 1.71 |
| 6-Br, b | | 118–120 | 39.46 | 39.65 | 1.65 | 1.64 |
| 6-$NO_2$, a | 96.5 | 184–186 | 45.84 | 45.85 | 1.92 | 1.81 |
| 6-$NO_2$, b | | 161–163 | 45.84 | 46.17 | 1.92 | 2.29 |
| 6-$SO_2Cl$, a | 74.5 | 127–128 | 36.52 | 36.63 | 1.53 | 1.71 |
| 6-$SO_2Cl$, b | | 98–98.5 | 36.52 | 36.74 | 1.53 | 1.56 |
| 6-$SO_2NH_2$, a | 81.5 | 251–253 | 39.44 | 39.63 | 2.48 | 2.45 |
| 6-$SO_2NH_2$, b | 41 | 238–240 | 39.44 | 39.82 | 2.48 | 2.43 |
| 6-$OCH_3$, a | | 102–104 | 55.55 | 55.42 | 3.62 | 3.78 |
| 6-$OCH_3$, b | | 70–71 | 55.55 | 55.73 | 3.62 | 3.82 |
| 6-COOH | 72 | 210–212 | 51.81 | 51.50[d] | 2.41 | 2.31 |
| 6-$COOC_2H_5$ | 75 | 93–95 | 55.82 | 55.86[e] | 3.83 | 3.98 |
| 6-CN | 90 | 178 | 57.01 | 57.23[f] | 2.13 | 2.08 |
| 6-$CONH_2$ | 94 | 229.5 | 52.07 | 52.07 | 2.91 | 3.03 |
| 5-$CH_3$ | 90 | 92–93 | 60.51 | 60.70 | 3.95 | 4.00 |
| 5-Cl | 70 | 138–139 | 48.51 | 48.23 | 2.03 | 2.07 |
| 5-$OCH_3$[g] | 87.5 | 85–87 | 55.55 | 55.84 | 3.62 | 3.71 |
| 5-$CH_3$-6-Cl-8-$CH(CH_3)_2$[h] | 92.5 | ..... | 56.50 | 56.63 | 4.74 | 4.86 |
| 5,7-$Cl_2$, a | | ..... | 41.15 | 41.39 | 1.30 | 1.35 |
| 5,7-$Cl_2$, b | | ..... | 41.15 | 41.08 | 1.30 | 1.47 |

[a] The isomers are designated a, for the higher melting and b, for the lower melting. Therefore, compounds labeled 6- are either 6- or 7- substituted 2-chloroquinoxalines, those labeled 5- are either 5- or 8- substituted 2-chloroquinoxalines, etc. The subsequent products are labeled a or b referring to the chloro compound from which they were derived. [b] *Anal.* Calcd.: N, 15.68. Found: N, 15.08. [c] *Anal.* Calcd.: N, 15.68. Found: N, 15.59. [d] *Anal.* Calcd.: N, 13.42. Found: N, 13.97. [e] *Anal.* Calcd.: N, 11.48. Found: N, 11.8. [f] *Anal.* Calcd.: N, 22.17. Found: N, 21.70. [g] The mixture which was obtained melted at 85–87° and was not analyzed. Separation of isomers was very difficult, but a small amount of material, m. p. 115–117°, was isolated and had the analysis listed. [h] This product is a mixture of both possible isomers.

After the addition was complete, the mixture was refluxed one hour, neutralized with sodium hydroxide and filtered through Supercel. The filtrate was treated dropwise with 50% sulfuric acid until a permanent pink tinge developed. The precipitated diamine sulfate was filtered, washed with alcohol and ether and dried. The product, shiny platelets which turn purplish on the edges on drying, weighed 33.0 g. (94% yield). The product was obtained in similar yield when the 2-nitro-6-chloroaniline was thus reduced.

### Substituted 2-Hydroxyquinoxalines

The general procedure is illustrated below.

**2-Hydroxy-5(or 8)-chloroquinoxaline.**—A suspension of 33.0 g. of 2,3-diaminochlorobenzene sulfate in 350 ml. of water and 140 ml. of 95% ethanol was neutralized by the cautious addition of sodium bicarbonate. Butyl glyoxalate, 18.3 g., was added and the mixture refluxed two hours. The solution was cooled and filtered, yielding crude product (29.3 g.). The crude product was purified by dissolving in 2.5 *N* sodium hydroxide, treating with decolorizing charcoal, and precipitating by acidification with acetic acid (24.4 g., 79% yield), m. p. 310°.

### Substituted 2-Chloroquinoxalines

The chloro compounds were prepared by chlorination of the hydroxy compounds with phosphorus chlorides. The isomers obtained were separated by fractional crystallization.

**2-Chloro-6(and 7)-bromoquinoxaline.**—A mixture of 89.5 g. of 2-hydroxy-6(and 7)-bromoquinoxaline, 63 g. of

TABLE III

SUBSTITUTED 2-AMINOQUINOXALINES

| Substituent | Yield, % | Reaction time, hr. | Reaction temp., °C. | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 6 (or 7)-methyl, a | | 8 | 175 | 178–180 | 67.89 | 67.97 | 5.70 | 5.40 | 26.39 | 26.23 |
| 6 (or 7)-methyl, b | | 8 | 175 | 171–173 | 67.89 | 67.87 | 5.70 | 5.82 | 26.39 | 26.21 |
| 6 (or 7)-chloro, a | | | 100 | 215–217 | 53.20 | 53.17 | 2.66 | 2.61 | 23.27 | 23.18 |
| 6 (or 7)-chloro, b | | | 100 | 194–195 | 53.20 | 53.50 | 2.66 | 2.86 | 23.27 | 23.35 |
| 6 (or 7)-bromo, a | 58 | 10 | 120 | 190–192 | 42.68 | 42.95 | 2.69 | 2.93 | 18.67 | 18.52 |
| 6 (or 7)-bromo, b | 74 | 10 | 120 | 187–189 | 42.68 | 43.03 | 2.69 | 2.78 | 18.67 | 18.60 |
| 6 (or 7)-nitro, a | 61 | 16 | 105 | 303–306 | 50.27 | 50.09 | 3.16 | 3.35 | 29.31 | 29.02 |
| 6 (or 7)-nitro, b | | 2.5 | 65 | 277–280 | 50.27 | | 3.16 | | 29.31 | 29.17 |
| 6 (or 7)-sulfonamide, a | 64 | 16 | 140 | 269–271 | 42.74 | 43.21 | 3.58 | 3.20 | 24.86 | 24.53 |
| 6 (or 7)-sulfonamide, b | | 16 | 140 | 266–268 | 42.74 | 43.50 | 3.58 | 3.78 | 24.86 | 24.64 |
| 6 (or 7)-sulfonic acid, a | 35 | 16 | 115 | Over 300 | 41.83 | 42.01 | 3.51 | 3.61 | 18.29 | 18.43 |
| 6 (or 7)-methoxy, a | 66 | 8 | 150 | 192–193[a] | 61.71 | 61.56 | 5.18 | 5.12 | 23.99 | |
| 6 (or 7)-methoxy, b | 54 | 8 | 175 | 193–195[a] | 61.71 | 61.93 | 5.18 | 5.30 | 23.99 | 24.02 |
| 6 (or 7)-carboxy | | 7 | 110 | 288 dec. | 57.17 | 56.87 | 3.73 | 3.73 | | |
| 6 (or 7)-carbomethoxy | 70[b] | | | 248.5 | 59.10 | 59.30 | 4.47 | 4.66 | 20.68 | 21.06 |
| 6 (or 7)-cyano | 64 | 15 | 120 | 265 | 63.51 | 63.70 | 3.53 | 3.67 | 31.93 | 32.52 |
| 5 (and 8)-methoxy | 37 | 5 | 105 | 233–235 | | | | | 23.99 | 23.78 |
| 5 (or 8)-methyl | 67 | 14 | 140 | 202–203 | 67.89 | 67.72 | 5.70 | 5.67 | 26.39 | 26.53 |
| 5 (or 8)-chloro | 68 | 3 | 120 | 219–220 | 53.20 | 53.74 | 2.66 | 3.67 | 23.27 | 23.58 |
| 5-Methyl-6-chloro-8-isopropyl (and isomer) | 72 | 18 | 100 | 250[c] | 52.91 | 53.11 | 5.55 | 5.53 | | |
| 5,7-dichloro (or isomer) | | | | | 45.72 | 45.01 | 2.34 | 2.50 | 19.55 | 19.32 |

[a] Mixed melting point 173–177°. [b] By esterification of acid. [c] Hydrochloride salt.

TABLE IV

SUBSTITUTED 2-N[4]-ACETYLSULFANILAMIDOQUINOXALINES

| Substituent | Yield, % | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|
| 6 (or 7)-methyl, a | 80 | 246–247 | 57.25 | 57.29 | 4.52 | 4.67 | 15.69 | 15.67 |
| 6 (or 7)-methyl, b | | 205–209 | 57.25 | 57.19 | 4.52 | 4.38 | 15.69 | 15.50 |
| 6 (or 7)-chloro, a | | 241–242 | 50.78 | 50.20 | 3.48 | 3.63 | 14.86 | 14.62 |
| 6 (or 7)-chloro, b | | 266–268 | 50.78 | 51.04 | 3.48 | 3.51 | | |
| 6 (or 7)-bromo, a | 73 | 266–267 | 45.35 | 45.64 | 3.12 | 3.29 | 13.32 | 13.04 |
| 6 (or 7)-bromo, b | 91 | 248–250 | 45.35 | 45.10 | 3.12 | 3.40 | 13.32 | 13.26 |
| 6 (or 7)-nitro, a | 56[a] | 272–273 | | | | | 18.26 | 18.40 |
| 6 (or 7)-nitro, b | 50[a] | 246–249 | 50.10 | 49.05 | 3.15 | 3.53 | 18.26 | 18.05 |
| 6 (or 7)-amino, b | 20[b] | 255–265 | | | | | 19.65 | 19.45 |
| 6 (or 7)-methoxy, a | 90 | 230–231 | 54.85 | 54.57 | 4.33 | 4.51 | 15.10 | 14.70 |
| 6 (or 7)-methoxy, b | 90 | 183 | 54.85 | 54.25 | 4.33 | 4.32 | 15.10 | 14.68 |
| 6 (or 7)-carbomethoxy | | 202 | 54.00 | 54.31 | 4.03 | 4.68 | 14.00 | 13.98 |
| 6 (or 7)-carbamido | | 277[a] | 52.98 | 52.96 | 3.92 | 4.40 | 18.18 | 17.51 |
| 5 (or 8)-methyl | 91 | 228–229 | 57.25 | 57.08 | 4.52 | 4.10 | 15.69 | 15.73 |
| 5 (or 8)-chloro | 62 | 252–255 | 50.78 | 51.15 | 4.48 | 3.80 | 14.86 | 15.14 |
| 5-Methyl-6-chloro-8-isopropyl (and isomer) | 88 | 215–235 | 55.64 | 55.72 | 4.67 | 4.92 | | |

[a] From the reaction of the corresponding chloro compound with acetylsulfanilamide in the presence of potassium carbonate and copper powder. [b] From the reduction of the corresponding nitro compound.

phosphorus pentachloride and 200 ml. of phosphorus oxychloride was heated on the steam-bath and stirred for one hour. The dark brown solution was slowly poured onto 1.5 kg. of ice and filtered. The wet precipitate was taken up in 2 l. of hot ethanol, treated with decolorizing charcoal, concentrated to 600 ml., cooled and filtered. The crude mixture of isomers, 80 g., was dissolved in 1.5 l. of hot Skellysolve B. On cooling, substantially pure isomer, a, m. p. 148–150 (26 g. 27% yield) was obtained. The mother liquor was concentrated to 1 l., cooled and filtered, yielding a mixture, m. p. 110–135° (12 g., 13.2% yield). The filtrate concentrated to 100 ml. yielded on cooling material melting at 117–119° (30 g. 31% yield, total yield 71%). Recrystallization of the first fraction yielded a product, m. p. 152–153.5°, and the last fraction yielded a product, m. p. 118–120°.

**2-Chloroquinoxaline-6(and 7)-Sulfonyl Chloride.**—A mixture of 2-hydroxyquinoxaline-6(and 7)-sulfonic acid (143.7 g.), phosphorus pentachloride (396 g.) and phosphorus oxychloride (443 ml.) was refluxed for one and one-half hours. The nearly clear solution was cooled and poured on ice while the mixture was stirred vigorously. When all the phosphorus halides were decomposed the crude product was filtered, washed with water and

TABLE V

SUBSTITUTED 2-SULFANILAMIDOQUINOXALINES

| Substituent | Yield, % | Method[a] | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| 6 (or 7)-methyl, a | 80 | II | 215–216 | 57.31 | 57.32 | 4.49 | 4.38 | 17.82 | 17.67 |
| 6 (or 7)-methyl, b | | II | 255–256 | 57.31 | 57.35 | 4.49 | 4.38 | 17.82 | 18.15 |
| 6 (or 7)-chloro, a | | I | 248–249 | 50.23 | 50.20 | 3.32 | 3.53 | 16.74 | 16.40 |
| 6 (or 7)-chloro, b | | I | 238–239 | 50.23 | 50.32 | 3.32 | 3.45 | 16.74 | 16.58 |
| 6 (or 7)-bromo, a | 91 | II | 244–246 | 44.35 | 44.34 | 2.92 | 2.92 | 14.78 | 14.62 |
| 6 (or 7)-bromo, b | 62 | II | 239–240 | 44.35 | 44.32 | 2.92 | 3.05 | 14.78 | 14.97 |
| 6 (or 7)-nitro, a | 80 | I | 220–221 | 48.71 | 48.75 | 3.21 | 3.56 | | |
| 6 (or 7)-nitro, b | | II | 224–226 | 48.71 | 49.02 | 3.21 | 3.81 | | |
| 6 (or 7)-amino, a | 67 | | 275–276 | 53.33 | 52.95 | 4.15 | 4.45 | | |
| 6 (or 7)-methoxy, a | 90 | II | 239–240 | 54.53 | 54.26 | 4.27 | 4.25 | 17.27 | 16.99 |
| 6 (or 7)-methoxy, b | 90 | II | 235–237 | 54.53 | 54.31 | 4.27 | 4.29 | 17.27 | 17.10 |
| 6 (or 7)-carboxy | 55 | II | 223 | 52.32 | 52.25 | 3.52 | 3.58 | 16.27 | 15.97 |
| 5 (or 8)-methyl | 97 | II | 205–206 | 57.31 | 57.68 | 4.49 | 4.72 | 17.80 | 17.60 |
| 5 (or 8)-methyl | 88 | I | 192–194 | 57.31 | 57.29 | 4.49 | 4.46 | 17.80 | 17.23 |
| 5 (and 8)-methoxy | | II | 105 | 54.53 | 54.12 | 4.27 | 4.09 | 17.27 | 17.30 |
| 5 (or 8)-chloro | 97 | II | 213–215 | 50.23 | 50.12 | 3.32 | 3.58 | 16.74 | 16.70 |
| 5-Methyl-6-chloro-8-isopropyl (and isomer) | 86 | II | 92–115 | 55.30 | 55.25 | 4.90 | 4.72 | 14.33 | 14.54 |

[a] I. Deacetylation carried out with ethanolic hydrogen chloride. II. Deacetylation carried out with aqueous sodium hydroxide.

dried, yielding crude product, m. p. 92–120° (124.3 g., 74.8%).

This mixture was separated with rather poor recovery by crystallization from benzene–ligroin mixtures to give equal amounts of the two isomers.

Isomer a crystallized as large colorless prisms from ligroin, m. p. 127–128°; isomer b was obtained as dendritic clusters of tiny colorless needles from ligroin, m. p. 98–98.5°.

**2-Chloroquinoxaline-6(or 7)-sulfonamide, b.**—Fifteen grams of 2-chloroquinoxaline-6(or 7) sulfonylchloride b was added to 250 ml. of concd. ammonia and the mixture heated on the steam-bath for five minutes. After standing overnight, the slurry was filtered and washed with water. The residue was purified by dissolving in 5% sodium hydroxide, treating with charcoal and precipitating with dilute acetic acid, yielding product, m. p. 225–235° (5.7 g., 41%). Crystallization of this material from glacial acetic acid gave prisms of m. p. 238–240° dec.

**2-Chloroquinoxaline-6(or 7)-sulfonamide, a.**—Fifteen grams of 2-chloroquinoxaline-6(or 7)-sulfonyl chloride, a, was converted into the sulfonamide as described above. After crystallization from glacial acetic acid, the product weighed 11.3 g. (81.5%), m. p. 251–253 with dec.

**2-Chloroquinoxaline-6(or 7)-carboxamide.**—A mixture of 30 g. of 2-chloroquinoxaline-6(or 7)-carboxylic acid, 66 g. of phosphorus pentachloride and 60 ml. of phosphorus oxychloride was heated two hours at 120°. The clear solution was concentrated to dryness *in vacuo* and the residue dissolved in 400 ml. of toluene. After treatment with decolorizing charcoal, the solution was concentrated *in vacuo* to about one-quarter of the initial volume. Five grams of the crude chloro acid chloride that separated was added in portions to 50 ml. of concentrated aqueous ammonia at room temperature. After allowing to stand one hour, the mixture was filtered yielding 2-chloro-6(or 7)-carbamidoquinoxaline (4.28 g.). Crystallization from methanol yielded material, m. p. 229.5°.

**2-Chloroquinoxaline-6(or 7)-carboxylic Acid.**—The mixture obtained by chlorinating 92 g. of 2-chloro-6(or 7)-carboxyquinoxaline, was poured into water and the resultant suspension stirred overnight. The crude product was dissolved in dilute sodium hydroxide and precipitated by acidification with dilute hydrochloric acid. Recrystallization of the crude, air-dried product from 500 ml. of isopropyl alcohol yielded material, m. p. 210–212° (75 g., 72% yield).

### Substituted 2-Aminoquinoxalines

In general, anhydrous ammonia was added to a solution or suspension of the chloro compound in methanol or ethanol and the mixture heated in a bomb under the conditions specified in Table III.

**2-Amino-5(or 8)-chloroquinoxaline.**—A mixture of 21 g. of 2, 5(or 8)-dichloroquinoxaline, 300 ml. of ethanol and 50 ml. of liquid ammonia was heated at 120° for three hours. The mixture was concentrated to dryness *in vacuo* and the residue dissolved in 250 ml. of hot 2.5 *N* hydrochloric acid and filtered from insoluble material, 0.3 g. The hot acid solution was treated with Darco G-60 (5 g.) and the product precipitated by adding a slight excess of 2.5 *N* sodium hydroxide. The flocculent precipitate was collected, air-dried and recrystallized from ethanol yielding light yellow granules, m. p. 218–220°, 10 g. Concentration of the mother liquor yielded a solid, (4.5 g., total yield 68%). A sample recrystallized from benzene was obtained as bright yellow platelets, m. p. 219–220°.

**2-Aminoquinoxaline-6(or 7)-sulfonic Acid, a.**—Hydrolysis of 2-chloroquinoxaline-6(or 7)-sulfonyl chloride a (19.5 g.) was accomplished by warming the compound on the steam-bath with a slight excess of 1 *N* sodium hydroxide. The nearly clear solution that resulted after fifteen minutes was filtered, made acid to litmus with hydrochloric acid and concentrated to dryness *in vacuo*.

The mixture of 2-chloroquinoxaline-6(or 7)-sulfonic acid a and salt thus obtained was suspended in 300 ml. of methanol and 60 cc. liquid ammonia and heated under pressure at 115° for fifteen hours. After the amination, the mixture was concentrated to dryness, and the residue was dissolved in the minimum quantity of water, treated with charcoal, filtered and made strongly acid with concd. hydrochloric acid. The white precipitate of 2-aminoquinoxaline-6(or 7)-sulfonic acid hydrochloride was collected, washed with 10% hydrochloric acid and dried, weight 6.0 g. (35.3% from the dichloro compound). Crystallization of this material from water yielded product with m. p. over 300°.

**2-Amino-6(or 7)-carbomethoxyquinoxaline.**—A solution of 10 g. of 2-amino-6(or 7)-carboxyquinoxaline (obtained by the usual aminating procedure) in 100 ml. of methanol containing 6 g. of anhydrous hydrogen chloride was heated at reflux two and one-half hours. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in warm water and the crude product precipitated by the addition of dilute ammonia water. The crude product, 8

g., m. p. 190–213°, was recrystallized three times from dioxane yielding a product that melts at 248.5°.

### Substituted 2-N⁴-Acetylsulfanilamidoquinoxalines

The amines were dissolved or suspended in pyridine and *p*-acetylaminobenzenesulfonyl chloride added while the mixture was stirred.

**2-N⁴-Acetylsulfanilamido-5(or 8)-chloroquinoxaline.**—To a mixture of 11.7 g. of the amine in 60 ml. of dry pyridine was added 16.7 g. of *p*-acetylaminobenzene sulfonyl chloride in four portions at ten-minute intervals, During the addition, the mixture warmed up to 35°. After being stirred for one hour, the resultant clear yellow solution was heated on a water-bath at 65° for one-half hour. The mixture was then poured into 800 ml. of hot water and the product, which crystallized when the mixture was stirred, was filtered and air dried. The crude product, 20.0 g., was dissolved in 250 ml. of 1.3 *N* sodium hydroxide and filtered; 4.45 g. of insoluble material, m. p. 208–210°, was obtained. The filtrate was acidified with glacial acetic acid yielding light yellow amorphous material, m. p. 245–252° (14.7 g., 62% yield). The analytical sample was crystallized from glacial acetic acid, m. p. 252–255°.

**2-N⁴-Acetylsulfanilamido-6(or 7)-carboxamidoquinoxaline.**—A mixture of 1.08 g. of 2-chloro-6(or 7)-carbamidoquinoxaline, 1.07 g. of acetylsulfanilamide, 0.65 g. of potassium carbonate and 50 mg. of copper powder in a Pyrex test-tube was stirred and heated at 180–190° in an oil-bath for fifteen minutes. The dark mixture was extracted with 10 cc. of 10% sodium hydroxide, filtered from the chloro compound that had not reacted and precipitated by acidification with dilute acetic acid. The oil that separated solidified on trituration with isopropyl alcohol. Recrystallization from glacial acetic acid yielded product, m. p. 277° about 500 mg.

### Sulfonamides

The acetyl derivatives were hydrolyzed by boiling with aqueous sodium hydroxide or ethanolic hydrogen chloride.

**2-Sulfanilamido-5(or 8)-chloroquinoxaline.**—A solution of 11.95 g. of the acetyl compound in 75 ml. of 2.5 *N* sodium hydroxide was heated for one-half hour on a steam-bath. The crude product, 10.25 g., 97% yield, was precipitated by neutralization with acetic acid. The crude product, m. p. 210–213°, was purified in 87% recovery by dissolving in hot 5 *N* ammonium hydroxide, treating with charcoal and precipitating with acetic acid, m. p. 213–215°.

**Acknowledgment.**—The authors are indebted to Dr. R. T. Major and Dr. Max Tishler for their kind encouragement and advice.

## Summary

The preparation of sixteen substituted derivatives of 2-sulfanilamidoquinoxaline is described, as well as the preparation of seventy-four other new quinoxaline compounds.

RAHWAY, NEW JERSEY RECEIVED MAY 28, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, AMERICAN HOME FOODS, INC.]

# 2-Acyloxyacetylthiophenes

BY FRANK KIPNIS,* HAROLD SOLOWAY AND JOHN ORNFELT

During synthetic work on substances containing the thiophene ring, it became desirable to prepare 2-hydroxyacetylthiophene (I) and a series of



I, R = OH III, R = Br
II, R = OCOR′

esters (II) derived therefrom. The intermediate which seemed to offer most promise was bromoacetylthiophene (III) which had been prepared by Brunswig[1] by the addition of bromine to a solution of 2-acetylthiophene in carbon disulfide stirred with a stream of carbon dioxide. In the present work, it was found more convenient to prepare this compound by treatment of the ketone in carbon tetrachloride with bromine in the presence of iron filings as catalyst.

By hydrolysis of the bromine compound with sodium formate in methanol,[2] 2-hydroxyacetylthiophene was prepared in fair yield. The esters, which are related to the phenacyl compounds, were prepared by several methods which gave acceptable yields. In view of the ready availability of 2-acetylthiophene[3] and 2-bromoacetylthiophene, it may be indicated that the esters would probably serve as suitable derivatives for carboxylic acids, supplementing those derived from the phenacyl halides.

* Present address: Oxford Products, Inc. Cleveland, Ohio.

(1) Brunswig, *Ber.*, **19**, 2891 (1886).

(2) Levene and Walti, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 5.

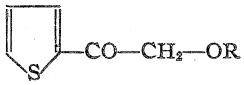
(3) Supplied by the Socony-Vacuum Oil Co., Paulsboro, N. J.

## Experimental

**2-Bromoacetylthiophene (III).**—To a 1000-ml. interjoint flask fitted with a sealed stirrer, reflux condenser with drying tube, dropping funnel and thermometer, was added 42 g. (0.33 mole) of 2-acetylthiophene, 300 ml. of dry carbon tetrachloride and a few iron filings. The mixture was stirred and heated on the water-bath to 60° (internal) and then the bath was removed. A solution of 53.5 g. (0.67 atom) of bromine in 100 ml. of carbon tetrachloride was then added at such a rate that gentle refluxing occurred (about twenty minutes). The solution was refluxed for an additional thirty minutes, at the end of which time evolution of hydrogen bromide had ceased and the bromine coloration was absent. The volatiles were removed by distillation under slightly reduced pressure, and the residue was fractionated through a 30-cm. Vigreux column at 95–98° (1.5 mm.) to give 55 g. (80% yield) of a slightly yellow, extremely lachrymatory oil ($n^{20}$D 1.6258) which solidified below room temperature. The product was rather unstable at room temperature, but could be stored without decomposition at −10°. In agreement with Brunswig,[1] bromoacetylthiophene on treatment with alcoholic ammonia gave a carmine coloration, followed by a deep red-blue color on standing.

**2-Hydroxyacetylthiophene (I).**—In a 500-ml. 3-neck flask fitted with a sealed stirrer, reflux condenser and drying tube was placed 20.5 g. (0.1 mole) of 2-bromoacetylthiophene, 13.6 g. (0.2 mole) of anhydrous sodium formate and 180 ml. of absolute methanol. The stirrer was started and the solution was refluxed for ten hours. The volatiles were distilled at slightly reduced pressure, acetone

TABLE I

2-ACYLOXYACETYLTHIOPHENES 

| R | Yield, % | M. p., °C. | Recrystallizing solvent | Formula | Analyses,[a] % C | H | S | Found C | H | S |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 38 | 73–74 | Hexane | $C_6H_6O_2S$ | 50.69 | 4.26 | 22.55 | 50.84 | 4.40 | 22.82 |
| $COCH_3$ | 58 | [b] | .... | $C_8H_8O_3S$ | 52.16 | 4.38 | 17.40 | 52.07 | 5.05 | 17.64 |
| $COC_6H_5$ | 80 | 95–96 | Carbon | $C_{13}H_{10}O_3S$ | 63.40 | 4.09 | 13.02 | 63.37 | 4.33 | 13.30 |
| $COCH{=}CHC_6H_5$ | 68 | 118–120 | tetrachloride | $C_{15}H_{12}O_3S$ | 66.16 | 4.44 | | 65.85 | 4.72 | |
| $COC_4H_3O$ (furoyl) | 43 | 93.5 | Hexane | $C_{11}H_8O_4S$ | 55.92 | 3.41 | 13.57 | 56.07 | 3.54 | 13.04 |

[a] Analyses by Oakwold Laboratories, Alexandria, Virginia. [b] B. p. 113–114° (3 mm.).

was added to the residue to complete the precipitation of inorganic salts, the mixture was filtered, the filtrate stripped and the residue fractionated at 93–95° (3 mm.) to give 5.4 g. (38% yield) of an oil which solidified on standing. The crystalline material was twice recrystallized from hexane to give colorless plates melting at 73–74°.[4]

**2-Acetoxyacetylthiophene** (II, R′ = $CH_3$).—A mixture of 16.4 g. (0.08 mole) of 2-bromoacetylthiophene, 13 g. (0.16 mole) of anhydrous sodium acetate and 200 ml. of glacial acetic acid was refluxed with stirring for ten hours. At the end of that time, the mixture was cooled, diluted to 1500 ml. with ice water and extracted three times with 150 ml. of ether. The solvent layer was washed with 10% sodium carbonate solution until neutral and then with 50 ml. of saturated sodium chloride solution, dried with calcium sulfate and filtered from the desiccant. The ether was stripped and the residue distilled at 113–114° (3 mm.) to give 8 g. (55% yield) of a light yellow oil.

**2-Benzoyloxyacetylthiophene** (II, R′ = $C_6H_5$).—Directions are given for the benzoyl compound, but the furoyl and the cinnamoyl derivatives have been prepared in the same way, and other esters could undoubtedly be synthesized in a similar manner. It may be noted that ethanol may replace ethylene glycol as a solvent, but consistently higher yields have been achieved with the latter.

(4) All melting points were taken with a Fisher–Johns apparatus.

A mixture of 16 g. (0.11 mole) of sodium benzoate in 40 ml. of water was made slightly acid to litmus with 10% hydrochloric acid and then 200 ml. of ethylene glycol was added, together with 20.5 g. (0.1 mole) of 2-bromoacetylthiophene. After refluxing for twelve hours, the cooled mixture was poured into an excess of 4% sodium bicarbonate solution with stirring, causing the separation of a solid which was removed by filtration. The precipitate was washed thoroughly with bicarbonate solution, air-dried and recrystallized, first from heptane and then from carbon tetrachloride (Norite) to give 19.7 g. (80% yield) of white crystals melting at 95–96°.

The properties and analyses of the compounds prepared are noted in Table I.

## Summary

2-Bromoacetylthiophene has been prepared in 80% yield by treatment of 2-acetylthiophene with bromine in the presence of catalytic quantities of iron filings.

From this bromoketone, it was possible to synthesize the α-ketol and a series of α-ketol esters.

MORRIS PLAINS, N. J. RECEIVED AUGUST 9, 1948

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[CONTRIBUTION NO. 54 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# 4-Hydroxybenzene-1,2,3-tricarboxylic Acid, 5-Hydroxybenzene-1,2,4-tricarboxylic Acid and their Derivatives

BY C. A. BUEHLER, R. BEECHER SPEES[1] AND PHILLIP A. SANGUINETTI[2]

In the identification of the degradation products of 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid lactone,[3] it was necessary to synthesize 4-hydroxybenzene-1,2,3-tricarboxylic acid, 5-hydroxybenzene-1,2,4-tricarboxylic acid, the two methoxy trimethyl esters and the two methoxy tricarboxylic acids as possible reference compounds. The syntheses of the 5-hydroxy acid and its derivatives were accomplished by the scheme

$$C_6H_3(CH_3)_3(1,2,4) \longrightarrow \underset{\text{I}}{} C_6H_2SO_2OH(CH_3)_3(1,2,4,5) \longrightarrow$$

$$C_6H_2(COOH)_3OH(1,2,4,5) \longrightarrow$$
III

$$C_6H_2(COOCH_3)_3OCH_3(1,2,4,5) \longrightarrow$$
IV

$$C_6H_2(COOH)_3OCH_3(1,2,4,5)$$
V

Pseudocumene, I, gave the 5-sulfonic acid, II, in good yield by treatment with concentrated sulfuric acid. This sulfonic acid on oxidation with potassium permanganate followed by alkaline fusion produced the hydroxytricarboxylic acid, III, in 55% yield. Treatment with diazomethane gave the methoxytrimethyl ester, IV, which on saponification yielded the methoxy acid, V.

The 4-hydroxy acid was synthesized in a similar manner from hemimellitene (1,2,3-trimethylbenzene). Sulfonation gave the 4-sulfonic acid

(1) Present address: Northern Illinois College of Optometry, Chicago, Illinois.

(2) Present address: Monsanto Chemical Company, Anniston, Alabama.

(3) Buehler, Harris, Shacklett and Block, THIS JOURNAL, 68, 574 (1946).

in good yield and oxidation followed by alkaline fusion produced the hydroxy acid in 33% yield. The 4-methoxy ester was obtained as above, but saponification with 15% aqueous sodium hydroxide for as long as twelve hours failed to yield the pure 4-methoxy tricarboxylic acid, perhaps because of steric hindrance. To obtain this acid it was necessary to convert the 4-sulfonic acid into the 4-phenol (yield 30%). The methyl ether of the latter gave what was probably 2-methyl-4-methoxybenzene-1,3-dicarboxylic acid by heating with aqueous potassium permanganate for five hours since the acid did not form an anhydride at 220°, but by heating for a longer period 4-methoxybenzene-1,2,3-tricarboxylic acid (crude form) was obtained in 30% yield.

An examination of the two series of derivatives indicates that the methoxy esters are to be preferred as reference compounds.

## Experimental

All melting points and boiling points are uncorrected.

**Pseudocumene (I).**—4-Amino-1,3-dimethylbenzene, 393.8 g., was converted by the method of Smith and Lund[4] into 70.2 g. of the hydrocarbon, b. p. 68.5–69° (22–22.5 mm.) and $n^{24}D$ 1.5031 (Smith and Lund give b. p. 68–68.5 (22 mm.) and $n^{24}D$ 1.5032).

**Pseudocumene-5-sulfonic Acid (II).**—Pseudocumene, 8 cc., was sulfonated by the method of Smith and Cass[5] to give 11.8 g. of purified acid, m. p. 111–112° after softening at 108° (Smith and Cass give 110–111°).

**5-Hydroxybenzene-1,2,4-tricarboxylic Acid (III).**—This acid was synthesized by a procedure essentially that of the French and German Patents.[6] Pseudocumene-5-sulfonic acid, 10 g., and 4 g. of sodium hydroxide were dissolved in 250 cc. of water and the solution was heated to 90–100°, after which 47.1 g. of pulverized potassium permanganate was added, with stirring, at such a rate as to prevent boiling. The oxidation was continued for twenty-four hours more at this temperature, after which the solution was decolorized by the cautious addition of alcohol. The precipitated manganese dioxide was filtered off by suction and extracted twice with 150-cc. portions of boiling water.

The combined filtrates were evaporated to dryness with occasional stirring to prevent caking and the pulverized residue, after being mixed with 40 g. of potassium hydroxide and about 5 cc. of water, was fused with occasional stirring at 200–220° for from four to five hours in a nickel crucible. The melt was then mixed with 60 cc. of water and the mixture in a beaker was acidified cautiously with concentrated hydrochloric acid. Water, 150 cc. more, was added and the solution was heated to boiling (if all the salts did not dissolve, sufficient concentrated hydrochloric acid was added to effect solution). To aid in the filtration for the removal of silica shredded filter paper was added. The filtrate was then evaporated to dryness to remove hydrochloric acid since 5-hydroxybenzene-1,2,4-tricarboxylic acid, in contrast to the inorganic salts, is more soluble in acid than in neutral solution. Treatment of the residue with 270 cc. of boiling water gave a mixture which, when cooled in the refrigerator, produced more solids. Purification by solution in 60 cc. of hot 5% hydrochloric acid solution followed by treatment with 1 g. of Norite and cooling yielded 7.2 g., m. p. 238° with effervescence. Two more crystallizations from 5% hydrochloric acid solution and drying *in vacuo* over calcium chloride gave the hydrated acid, m. p. 239.5–240° with effervescence (French and German patents[6] give 240° with effervescence), which gives a red color with ferric chloride.

*Anal.* Calcd. for $C_9H_6O_7 \cdot 2H_2O$: C, 41.23; H, 3.84; neut. equiv., 87.4; loss of weight on drying, 13.74. Found: C, 41.36, 41.28; H, 4.12, 4.05; neut. equiv., 87.1; loss of weight on drying, 13.79, 13.79.

Heating at around 102° for three hours gave the anhydrous acid, m. p. 240° with effervescence.

*Anal.* Calcd. for $C_9H_6O_7$: C, 47.80; H, 2.67; neut. equiv., 75.4. Found: C, 48.10, 48.03; H, 2.77, 2.86; neut. equiv., 75.2, 75.1.

**Trimethyl-5-methoxybenzene-1,2,4-tricarboxylate (IV).**—5-Hydroxytrimellitic acid in ethanol at 0° was methylated with diazomethane in ether in the usual manner. The product crystallized from ligroin melted at 62.5–63.0°.

*Anal.* Calcd. for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00. Found: C, 55.75, 56.03; H, 5.09, 5.08.

**5-Methoxybenzene-1,2,4-tricarboxylic Acid (V).**—The trimethyl ester was saponified with 5% aqueous sodium hydroxide solution to give a product, m. p. 224–225° with effervescence.

*Anal.* Calcd. for $C_{10}H_8O_7$: C, 50.01; H, 3.36; neut. equiv., 80.7. Found: C, 49.67, 49.75; H, 3.72, 3.54; neut. equiv., 79.8, 79.9.

**Hemimellitene.**—This hydrocarbon was prepared by two methods: (1) Benzyl chloride, b. p. 172–175°, 1416 g., was converted by the method of Smith and Spillane[7] into 77.4 g. of the hydrocarbon, b. p. 171.5–172.2° (741 mm.) and $n^{20}D$ 1.5130 (Smith and Spillane give b. p. 172.2–172.5° (741.4 mm.) and $n^{20}D$ 1.5130).

(2) *o*-Xylene was chloromethylated to give a mixture of 2,3-dimethylbenzyl chloride and 3,4-dimethylbenzyl chloride, which mixture was converted into pseudocumene and hemimellitene by forming the Grignard reagents and hydrolyzing. The hydrocarbons were separated by fractional distillation to give a product, b. p. 175–176° (740.5 mm.).[8]

**Hemimellitene-4-sulfonic Acid.**—Hemimellitene, 8 cc., was shaken with 16 cc. of concentrated sulfuric acid in a glass-stoppered flask until solution was complete (ten to fifteen minutes). This solution was added in 5-cc. portions, with stirring, to 32 cc. of cold concentrated hydrochloric acid, with cooling after each addition. Precipitation resulted, and after final cooling the solid was filtered dry by suction and crystallized twice from 100-cc. portions of cold 20% hydrochloric acid solution to give 11.5 g. of white plates, m. p. 115° (von Auwers and Wieners[9] give 111–114°).

**4-Hydroxybenzene-1,2,3-tricarboxylic Acid.**—This acid was prepared by a method similar to that used for 5-hydroxybenzene-1,2,4-tricarboxylic acid.[6] Hemimellitene-4-sulfonic acid, 10 g., was subjected to like treatment up to the point at which the filtrate was evaporated to dryness to remove hydrochloric acid. Then, upon the addition of 270 cc. of boiling water to the residue followed by heating for a short time, not all of the mono-potassium salt dissolved, but this amount of water was sufficient to dissolve the inorganic salts. Cooling in the refrigerator gave an additional amount of solid, the total of which, when crystallized five times from 40-cc. portions of 10% hydrochloric acid and dried in a vacuum desiccator, amounted to 4 g. and melted at 205–206° with effervescence.

*Anal.* Calcd. for $C_9H_6O_7 \cdot 1H_2O$: loss of weight on heating, 6.55. Found: 6.76, 6.89.

Heating at 102° for three hours gave the anhydrous acid.

*Anal.* Calcd. for $C_9H_6O_7$: C, 47.80; H, 2.67; neut. equiv., 76. Found: C, 48.28, 48.18; H, 2.89, 2.89; neut. equiv., 75.3, 75.0.

(4) Smith and Lund, THIS JOURNAL, **52**, 4144 (1930).

(5) Smith and Cass, *ibid.*, **54**, 1603 (1932).

(6) French Patent 816,718; German Patent 686,908.

(7) Smith and Spillane, THIS JOURNAL, **62**, 2639 (1940).

(8) We are indebted to Mr. Comer Shacklett of this Laboratory for the hemimellitene prepared by this preferred procedure. Details of the method will be published by him later. This product is the purer, the Bureau of Standards value, A.P.I. Res. Project 44 at NBS; "Selected Values of Properties of Hydrocarbons" Table 5a, dated June 30, 1945, for pure hemimellitene being176.15°(760 mm.).

(9) von Auwers and Wieners, *Ber.*, **58**, 2815 (1925).

**Trimethyl 4-Hydroxybenzene-1,2,3-tricarboxylate.**—The mother liquor from which the 4-hydroxy acid precipitated and the filtrates from the crystallization of the final product were combined and evaporated to dryness with occasional stirring. The pulverized residue in 500 cc. of dry methanol was saturated with hydrogen chloride and the mixture was refluxed for twenty-two hours while hydrogen chloride was introduced. Recovery in the usual manner and crystallization from 50% methanol gave 1.0 g. of white needles, m. p. 85.5–86°, which produce a red color with aqueous ferric chloride.

*Anal.* Calcd. for $C_{12}H_{12}O_7$: C, 53.73; H, 4.51. Found: C, 53.92, 53.99; H, 4.64, 4.84.

**Trimethyl 4-Methoxybenzene-1,2,3-tricarboxylate.**—The 4-hydroxy acid, 5 g., was methylated with diazomethane in the usual manner. The recovered product crystallized from methanol, 4.2 g., melted at 91.0–92.0°.

*Anal.* Calcd. for $C_{13}H_{14}O_7$: C, 55.32, H, 5.00. Found: C, 55.22, 55.45; H, 5.15, 5.21.

**4-Hydroxy-1,2,3-trimethylbenzene.**—This phenol was prepared by a modification of the method of von Auwers and Wieners[9] as follows: In a nickel crucible 120 g. of potassium hydroxide was heated to 250° at which time 65 g. of hemimellitene-4-sulfonic acid was added slowly with stirring while the temperature was allowed to rise to 325°. At this point a dark oil separated on top of the fused mixture. Upon cooling, the mixture was dissolved in 400 cc. of water and the solution was acidified with sulfuric acid, after which the phenol was removed by steam distillation. Extraction with ether and evaporation gave 13.5 g. of product. One crystallization from petroleum ether gave long white needles, m. p. 76–77° (von Auwers and Wieners obtained two crystalline forms: one on cooling the liquid, m. p. 69°; a second on crystallizing from solvents, m. p. 81°).

**4-Methoxyhemimellitene.**—4-Hydroxyhemimellitene, 14.7 g., was methylated with dimethyl sulfate and sodium hydroxide to give 13.1 g. of a colorless oil, b. p. 216–218° (728 mm.). Fractionation using an Anschütz thermometer produced a sample for analysis, b. p. 215.5–216.5° (740 mm.), $n^{20}D$ 1.5200.

*Anal.* Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.76, 79.72; H, 9.22, 9.39.

**2(?)-Methyl-4-methoxybenzene-1,3-dicarboxylic Acid.**—This procedure was a modification of that given by Grewe[10] as follows: In a 3-liter, three-necked flask, equipped with an agitator, a separatory funnel and a reflux condenser, 13.1 g. of 4-methoxyhemimellitene was suspended in 50 cc. of 10% aqueous sodium hydroxide solution. While the suspension was agitated vigorously on a steam-bath, a solution of 114 g. of potassium permanganate dissolved in 1760 cc. of water was added over a three-hour period and the mixture was allowed to react for two hours longer. Methanol was then added to reduce the excess of permanganate and after filtering the filtrate was concentrated to 300 cc. Acidification, evaporation to dryness and extraction with 350 cc. of acetone followed by evaporation gave 4.1 g. of a slightly yellow product. Several crystallizations from water produced small white crystals, m. p. 216.0–216.5°. No anhydride was formed when this acid was heated to 220° for fifteen minutes.

*Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80; neut. equiv., 105.1. Found: C, 57.05, 56.90; H, 4.60, 4.70; neut. equiv., 105.9.

**4-Methoxybenzene-1,2,3-tricarboxylic Acid.**—For a more strenuous oxidation procedure that given by Wilds and Djerassi[11] was modified as follows: In the apparatus described above, 4 g. of 4-methoxyhemimellitene was suspended in 324 cc. of 5% aqueous potassium hydroxide solution. While the suspension was heated on a steam-bath and agitated vigorously, 600 cc. of 0.35 *M* aqueous potassium permanganate solution was allowed to drop into the flask over a five-hour period. The mixture was allowed to react at this temperature until the purple color had disappeared, after which 25 cc. more of the permanganate solution was added over an hour period. When the color of permanganate had disappeared, another 25 cc. of the permanganate solution was added, and this process was repeated until a total of 725 cc. of the oxidizing solution had been added. At the end the excess permanganate was removed by the addition of sodium bisulfite and the mixture was filtered.

The most satisfactory method to remove the acid from the filtrate, concentrated to 500 cc., was that of Schultze.[12] After acidification with concentrated sulfuric acid, this concentrate was extracted twice with 200-cc. portions of ether (since the desired acid is insoluble in ether, only ether-soluble impurities are removed). The water layer was then saturated with sodium sulfate and extracted seven times with 250-cc. portions of ethyl acetate. Upon evaporating the combined portions of ethyl acetate to dryness, 2 g. of crude acid was obtained. Several crystallizations from small amounts of water gave 0.5 g. of white crystals, m. p. 215.0–216.0° with previous softening.

Crystallization from glacial acetic acid gave a product whose melting point was practically identical, but its analysis and neutral equivalent indicated that some anhydride formation had occurred.

*Anal.* Calcd. for $C_{10}H_8O_7$: C, 50.00; H, 3.36; neut. equiv., 80.0. Found: C, 49.96, 49.98; H, 3.27, 3.30; neut. equiv., 79.8.

## Summary

4-Hydroxybenzene-1,2-3-tricarboxylic acid and 5-hydroxybenzene-1,2,4-tricarboxylic acid have been synthesized from hemimellitene and pseudocumene, respectively. In addition, the methoxytrimethyl esters, the methoxytricarboxylic acids and several miscellaneous derivatives have been prepared. The methoxytrimethyl esters are to be preferred as reference compounds.

KNOXVILLE, TENNESSEE RECEIVED JUNE 30, 1948

(10) Grewe, *Ber.*, **71**, 910 (1938).

(11) Wilds and Djerassi, THIS JOURNAL, **68**, 1862 (1946).

(12) Schultze, *Ann.*, **359**, 141 (1908).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

# Reactions of Per Acids. I. The Reaction of Perbenzoic Acid with Some Simple Ketones

BY S. L. FRIESS[1]

It has been shown by previous investigators that per acids are capable of converting acetyl substituents on the steroid nucleus into acetate groups, in moderately good yields. For example, Marker[2a] and co-workers demonstrated that a mixture of acetic, sulfuric and persulfuric acids could convert allopregnanol-3($\beta$)-one-20 into a mixture of epimeric carbinols, presumably by way of the monoacetates. These carbinols were subsequently oxidized to androstanedione-3,17. Further work by Marker[2b] showed that allopregnanone-20 would be converted by persulfuric acid into a mixture of the compound possessing a 17-acetate grouping, and allopregnanol-21-one-20, corresponding to oxidation at carbon 21.

Subsequent work by Reichstein[3] using perbenzoic acid as the oxidizing agent indicated that the acetate of allopregnanol-3-one-20 could be converted into the corresponding diacetate, which in turn was characterized by saponification to the crystalline androstanediol-3($\beta$),17($\alpha$).

Most recently, Sarett[4] has shown that in certain instances relatively high yields may be obtained on oxidation of 17-acetyl steroids to the corresponding 17-acetates, using perbenzoic acid in chloroform solution. A specific example of the reactions cited in this work is the perbenzoic acid oxidation of pregnane-3($\alpha$)-ol-11,20-dione acetate in 85% yield, corrected for recovery of starting material, to the compound etiocholane-3($\alpha$),17($\alpha$)-diol-11-one diacetate.

In an effort to determine the general utility of this novel reaction, it was considered expedient to test it on somewhat less complicated systems than those found among the steroids. For this purpose, each member of the varied set of simple methyl ketones shown in formulas I-V was subjected to the action of perbenzoic acid in moist chloroform solution, at 23–26°, for a fixed reaction time of ten days.

| | R—$COCH_3$ | | R—O—$COCH_3$ |
|---|---|---|---|
| I. | R = cyclohexyl | VI. | R = cyclohexyl |
| II. | R = phenyl | VII. | R = phenyl |
| III. | R = cyclopropyl | VIII. | R = $\beta$-naphthyl |
| IV. | R = $\beta$-naphthyl | | |
| V. | R = mesityl | | |

It was found that the reaction of perbenzoic acid with a methyl ketone proceeds quite smoothly for the compounds cyclohexyl methyl ketone, acetophenone and $\beta$-acetonaphthone, resulting in the corresponding acetates VI, VII and VIII, respectively, in yields of 67, 63 and 67% based on ketone. This demonstrates quite clearly that the reaction is not confined to these alicyclic systems dealt with in the steroids, but is equally applicable to aromatic systems in the benzene and naphthalene series.

When cyclopropyl methyl ketone (III) was subjected to the action of perbenzoic acid in moist chloroform, however, the expected oxidation did not occur, and indeed only 10% of the theoretically required amount of perbenzoic acid was consumed during the standard reaction period. Furthermore, it would seem that the recovery of 36% of the starting material, unchanged, indicates that the lack of reaction is not to be attributed solely to the possible destruction of the ketone in solution before reaction with perbenzoic acid can occur, but rather to the non-reactivity of the ketone itself.

Having extended the reaction to aromatic systems, it was also considered desirable to ascertain whether the effective action of perbenzoic acid is restricted solely to methyl ketones. To investigate this point, propiophenone was subjected to the action of the per acid under the standard reaction conditions adopted in this work. It was found again that the reaction occurred easily, with the production of the single compound phenyl propionate in 73% yield as based on ketone.

Finally, to determine the possible effect of bulky ortho substituents on the course of the reaction, acetomesitylene (V) was sent through the customary oxidation procedure. It was found that 107% of the required amount of perbenzoic acid was consumed, but the complex reaction product has not been completely analyzed. Further work on this reaction is in progress.

Also in progress and contemplated are further studies on the generality of the reaction, and stereochemical and rate studies on the mechanism of the oxidation. Postulation of a reaction mechanism will await completion of this work.

## Experimental

**General Procedure.**—To 0.10 mole of the pure ketone was added about 315 ml. of a standardized, moist chloroform solution containing approximately 0.12 mole of perbenzoic acid. The resulting cloudy solution was swirled at intervals, and allowed to stand in the dark at 23–26° for ten days. An aliquot was then titrated for residual oxidizing agent in the customary way.[5] A titration was also made on a portion of the stock perbenzoic acid solution which had been subjected to these conditions, to

(1) Present address: Department of Chemistry, University of Rochester, Rochester, N. Y.

(2) (a) Marker, Rohrmann, Wittle, Crooks and Jones, THIS JOURNAL, **62**, 650 (1940); (b) R. E. Marker, *ibid.*, **62**, 2543 (1940).

(3) Burckhardt and Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

(4) L. H. Sarett, THIS JOURNAL, **69**, 2899 (1947).

(5) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 434.

TABLE I

REACTIONS WITH PERBENZOIC ACID

| Ketone RCOR' R | R' | Moles of per acid consumed[a] by 0.10 mole of ketone | Product ROCOR' B. p., °C. | Mm. | $n^{25}D$ | Yield,[b] % | M. p. α-naphthylurethan |
|---|---|---|---|---|---|---|---|
| Cyclohexyl | $CH_3$ | 0.100 | 74.5–76.5 | 23 | 1.4401 | 67 | 127–128 |
| Phenyl | $CH_3$ | .065 | 93–93.5 | 22 | 1.5200 | 63 | 133 |
| Cyclopropyl | $CH_3$ | .010 | | | | | |
| β-Naphthyl | $CH_3$ | .095 | M. p. 67–68 | | | 67 | 123[c] |
| Mesityl | $CH_3$ | .107 | 111–120 | 12[d] | | | |
| Phenyl | $C_2H_5$ | .073 | 98–99 | 18 | 1.5003 | 73 | 132–133 |

[a] Corrected for approximate degree of spontaneous decomposition of per acid. [b] Based on ketone and corrected for recovered ketone. [c] M. p. of the β-naphthol itself; not converted to urethan. [d] No mesitol could be detected upon attempted saponification with base.

determine the extent of spontaneous decomposition of the per acid during this time interval.

The chloroform solution was then shaken with dilute sodium carbonate solution to remove the benzoic and residual perbenzoic acids, and this treatment followed by a water wash. The chloroform was then distilled off, and the residual product separated into ketonic and non-ketonic fractions by the use, where possible, of Girard Reagent T. The ketonic fraction, when liquid, was converted to its semicarbazone for purification and identification, while the non-ketonic ester fraction was generally distilled directly under reduced pressure.

A portion of each ester fraction was saponified with base, and the resulting alcohol or phenol converted into its α-naphthylurethan for final identification purposes. In all cases, only a single α-naphthylurethan was obtained from each ester product.

The data obtained from the reactions studied are shown in Table I.

## Summary

The reaction of perbenzoic acid in moist chloroform solution with cyclohexyl methyl ketone, acetophenone and β-acetonaphthone for ten day periods at room temperature furnishes cyclohexyl acetate, phenyl acetate and β-naphthyl acetate, respectively, in yields approximating 65%.

The reaction of perbenzoic acid with cyclopropylmethyl ketone under these conditions does not occur.

Propiophenone reacts smoothly under these conditions to furnish the single product phenyl propionate in 73% yield.

LOS ANGELES, CALIFORNIA RECEIVED JULY 26, 1948

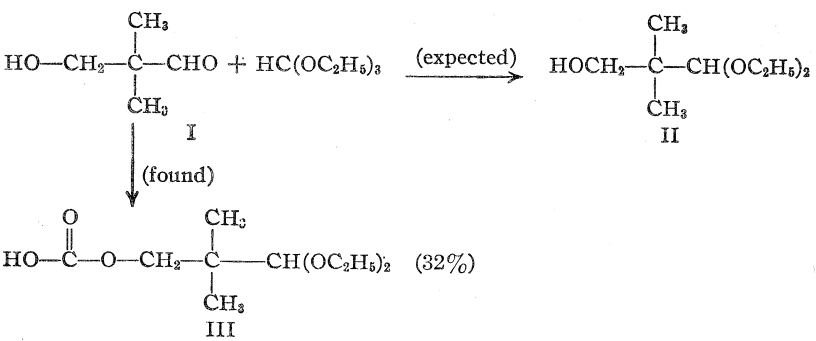
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Reaction of Hydroxyaldehydes with Ethyl Orthoformate. I. Hydroxypivaldehyde

BY ELLIOT R. ALEXANDER AND ELLIOT N. MARVELL[1]

During another investigation the preparation of hydroxypivaldehyde diethyl acetal (II) was attempted by allowing hydroxypivaldehyde (I) to react with ethyl orthoformate.[2] Instead of the expected hydroxy acetal (II), the only product




which could be isolated from the reaction mixture was 3,3-diethoxy-2,2-dimethylpropyl formate (III).

The structure of III was established by saponification of the ester with potassium hydroxide in dry ethanol. Potassium formate was isolated and a new compound was formed which had the correct molar refractivity and analysis for the hydroxy acetal (II). In addition, the structure for the formate ester (III) is supported by an infrared analysis (which showed the presence of an ester group but no hydroxyl group), by the correct molecular refractivity and by a molecular weight determination.

The formation of the ester (III) during the reaction was surprising. An examination of the literature has revealed that apparently the simultaneous formation of acetal and ester is novel in type. One explanation might be that an ester interchange occurred between the hydroxy acetal and ethyl formate or ethyl orthoformate. Experiment, however, has ruled out either of these possi-

(1) Present address: Oregon State College, Corvallis, Oregon.

(2) Claisen, *Ber.*, **29**, 1007 (1896).

bilities. When the hydroxy acetal (II) was treated with ethyl formate or ethyl orthoformate under conditions identical to those used for the preparation of 3,3-diethoxy-2,2-dimethylpropyl formate (III), a very complex mixture of products was formed but no ester could be isolated.

We, therefore, believe that the ester is formed not by a secondary process from the hydroxy acetal but as a result of the direct interaction of ethyl orthoformate with the hydroxy aldehyde. The scope and implications of the reaction are being investigated.

## Experimental[3]

**Reaction of Hydroxypivaldehyde with Ethyl Orthoformate.**—A mixture of 51.0 g. (0.5 mole) of hydroxypivaldehyde,[4] 75.0 g. (0.52 mole) of ethyl orthoformate, 75 ml. of dry ethanol and 1.0 g. of dry ammonium chloride was boiled under reflux for thirty minutes. The volatile products were removed by distilling the reaction mixture until the temperature of the vapors reached 80°. The residual material was washed with two 50-ml. portions of distilled water and the washings were extracted twice with 50-ml. portions of ether. The water washed product and the ether extracts were then combined and dried over anhydrous magnesium sulfate. After evaporation of the ether, the product was distilled through an eight-inch electrically-heated column packed with glass helices. Distillation yielded 31.0 g. (32%) of 3,3-diethoxy-2,2-dimethylpropyl formate, b. p. 93–94° (13 mm.), $n^{20}D$ 1.4200, $d^{20}_{20}$ 0.9633. An infrared absorption spectrum indicated the presence of a carbonyl group, ether linkages, and the absence of a hydroxyl group.[5]

*Anal.*[6] Calcd. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.94; MR 53.60; mol. wt., 204. Found: C, 58.90; H, 10.05; MR, 53.33; mol. wt., 203.

**Preparation of Hydroxypivaldehyde Diethyl Acetal.**—To a solution prepared from 7.0 g. (0.1 mole) of potassium hydroxide in 75 ml. of dry ethanol was added 20.0 g. (0.1 mole) of 3,3-diethoxy-2,2-dimethylpropyl formate. The mixture became warm, turned light yellow, and a flocculent white solid precipitated. Distilled water (1.5 ml.) was added and the mixture was boiled under reflux for three hours. After removing as much alcohol as possible on the steam-bath, the mixture was cooled, and 100 ml. of ether was added. Potassium formate precipitated and was removed by suction filtration. After drying on a clay plate the salt melted at 162–165°. A mixed melting point with an authentic sample melted at 164–165°.[7] After removing the ether from the filtrate, distillation yielded 14.5 g. (84%) of hydroxypivaldehyde diethylacetal, b. p. 55° (1.0 mm.), $n^{20}D$ 1.4259, $d^{20}_{20}$ 0.9335.

*Anal.* Calcd. for $C_9H_{22}O_3$: C, 61.33; H, 11.44; MR, 48.58. Found: C, 61.43; H, 11.48; MR, 48.36.

**Reaction of Hydroxypivaldehyde Diethyl Acetal with Ethyl Orthoformate.**—Hydroxypivaldehyde diethylacetal (10.0 g., 0.057 mole) was treated with ethyl orthoformate under conditions identical with those described for the reaction of hydroxypivaldehyde with ethyl orthoformate. After drying and removing the ether it was attempted to distill the reaction mixture as before. A small amount of ethyl orthoformate and some material boiling at 85–185° (1.0 mm.) was obtained but the major part of the reaction mixture remained in the distilling flask. No pure components could be separated from the volatile portion on redistillation. The high boiling point of this material showed that no hydroxypivaldehyde diethylacetal nor 3,3-diethoxy-2,2-dimethylpropyl formate could have been present.

**Reaction of Hydroxypivaldehyde Diethyl Acetal with Ethyl Formate.**—Freshly prepared hydroxypivaldehyde diethyl acetal (10.0 g., 0.057 mole) was treated with ethyl formate (4.2 g., 0.057 mole) under conditions identical with those described for the reaction of hydroxypivaldehyde with ethyl orthoformate. After removal of the ether, 4.4 g. of ethyl formate (b. p. 52–54°) was recovered which must have contained a small amount of alcohol. On attempted distillation only a clear tough resin was obtained.

## Summary

When ethyl orthoformate is allowed to react with hydroxypivaldehyde the only product which can be isolated is 3,3-diethoxy-2,2-dimethylpropyl formate. This product arises from the direct interaction of the hydroxyaldehyde with ethyl orthoformate and not as a secondary reaction product of hydroxypivaldehyde diethylacetal.

(3) All melting and boiling points are uncorrected.

(4) Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1787 (1942).

(5) We are indebted to Dr. Foil A. Miller and Mrs. J. L. Johnson for the determination and the interpretation of the spectrum of this sample.

(6) We are indebted to Miss Theta Spoor for the carbon–hydrogen microanalyses reported in this paper.

(7) The melting point of pure potassium formate is 165–167°.

URBANA, ILLINOIS RECEIVED AUGUST 26, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CORN PRODUCTS REFINING COMPANY]

# Osmotic Pressure Studies on Corn Amylose

BY F. C. CLEVELAND AND R. W. KERR

The average molecular magnitude of the two fractions of starch still is a matter of some uncertainty. Even for the amylose fraction of corn starch, which has probably received more attention than any other starch component, estimations of size have been made which vary by 100%, or more. On the basis of sedimentation and diffusion studies, Fox[1] set a minimum value of 540 glucose units by the use of the acetate of a subfraction of corn amylose in methyl acetate solutions. Dumbrow[2] used a similar product and obtained a value of 375 by similar methods. Foster and Hixon[3] calculated that the $DP_n$ for corn amylose was 260 from osmotic pressure measurements of the acetate in chloroform. Principally from viscosity measurements by Foster and Hixon,[4] Foster[5] has estimated that corn amylose, extracted

(1) T. J. Fox, Dissertation, Columbia University, New York, N. Y., 1943.

(2) B. A. Dumbrow, Dissertation, Columbia University, New York, N. Y., 1944.

(3) J. Foster and R. Hixon, THIS JOURNAL, **66**, 557 (1944).

(4) J. Foster and R. Hixon, *ibid.*, **65**, 618 (1943).

(5) J. E. Foster, Dissertation, Iowa State College, Ames, Iowa, 1943.

from the starch by water at 75°, has a chain length of 175 glucose units. Foster and Hixon used the starch fraction dissolved in ethylenediamine. Meyer, Bernfeld and Hohenemser[6] obtained a value of 270 by osmotic pressure measurements in tetrachloroethane of the acetate of amylose prepared by extensively extracting corn starch with hot water. Caesar, Gruenhut and Cushing[7] have recently reported a value of 220 for corn amylose, using the nitrate in ethyl acetate according to the isopiestic method of Barger.

Precise work in fundamental starch chemistry necessitates having a more accurate knowledge of the size of starch components than is currently available. Work based on improperly prepared fractions and their derivatives and on methods which lack a rigorous derivation may be eliminated from consideration. Even so, the remaining work leads to ambiguous conclusions. A series of osmotic pressure measurements made on the same sample of a carefully prepared corn amylose acetate in three solvents, chloroform, 2,4-pentanedione and pyridine, are reported below. These results are given to point out the magnitude of the problem and to establish perhaps a basis for the interpretation and correlation of available data on other physical measurements which have been reported.

## Experimental

**Preparation of Corn A-Fraction (Corn Amylose).**—Defatted corn starch was treated according to the method of Schoch[8] by using Pentasol to precipitate the amylose from an autoclaved sol. The product was recovered by means of a super-centrifuge, redissolved in hot water and recrystallized by the addition of butanol. The yield was 20.8% by weight. The amount of iodine absorbed by the product was measured potentiometrically by Schoch's[9] modification of the method originated by Bates, French and Rundle.[10] This value was found to be 19.2% and indicates exceptionally high purity.

**Preparation of the Acetyl Derivative.**—Acetylation was performed according to a modification of the method of Mullen and Pacsu.[11] The starch fraction was dispersed in hot aqueous pyridine, the water removed by distillation of the pyridine–water azeotrope and then acetic anhydride was added which accomplished the major part of the acetylation. The modification consisted of adding fused sodium acetate at this point and refluxing for two periods each of one hour on separate days. After recovery of the product by pouring the reaction solution into a large volume of water, the material was disintegrated by wet grinding for a few seconds in a Waring Blendor. The acetate was recovered by filtration and washed five times with 100 times its weight of water, each washing involving a forty-eight-hour soaking period in the wash water. The yield was 97% and the acetyl content, measured by the method of Murray, Staud and Gray,[12] was 44.8%.

(6) K. H. Meyer, P. Bernfeld and W. Hohenemser, *Helv. Chim. Acta*, **23**, 885 (1940).

(7) G. V. Caesar, N. S. Gruenhut and M. L. Cushing, THIS JOURNAL, **69**, 671 (1947).

(8) T. J. Schoch, THIS JOURNAL, **64**, 2957 (1942).

(9) T. J. Schoch, in Radley's "Starch and Its Derivatives," 3rd edition, in press.

(10) F. L. Bates, D. French and R. E. Rundle, THIS JOURNAL, **65**, 142 (1943).

(11) J. W. Mullen and E. Pacsu, *Ind. Eng. Chem.*, **34**, 1209 (1942).

(12) T. F. Murray, C. J. Staud and H. LeB. Gray, *Ind. Eng. Chem., Anal. Ed.*, **3**, 269 (1931).

**Osmotic Pressure Measurements.**—Osmotic pressure measurements were made in a cell substantially as described by Fuoss and Mead.[13] The cell was placed in a wooden box and completely surrounded by cotton waste except for the protruding capillary tubes, filling tubes and valves. A thermometer was fastened directly to the metal cell. The assembly was then placed within a glass windowed cabinet provided with heating and cooling coils, air circulation and a mercury thermoregulator. The temperature of the cell was maintained at 30.00 ± 0.05°. Liquid levels in the capillaries were measured by use of a Gaertner Model M-908 cathetometer with an accuracy of ±0.05 mm. The dynamic method for determining osmotic pressures described by Fuoss and Mead[13] was used. These results were in good agreement with frequent determinations by the static method when chloroform and pentanedione were used as solvents. In the case of pyridine, movement of solvent was so slow that measurements based on early dynamic readings created an appreciable error and static measurements were employed entirely. In several determinations with pyridine the results of the static tests at twenty-four hours were checked again at seventy-two hours. No further increase in pressure was observed after the first twenty-four hours.

Uncoated, du Pont No. 450 cellophane, pretreated as described below, was used for membranes. Treatment consisted of soaking the membrane for from six to twenty-four hours in a series of solvent mixtures

Water (50°)
50% water–50% ethyl alcohol
95% ethyl alcohol
50% ethyl alcohol–50% amyl alcohol
100% amyl alcohol
75% amyl alcohol–25% solvent
50% amyl alcohol–50% solvent
25% amyl alcohol–75% solvent
100% solvent

All solvents used were purified by usual procedures starting with reagent grade liquids. Chloroform was distilled over calcium chloride and gave a neutral reaction. 2,4-Pentanedione was purified according to the method of Denoon.[14] As prepared, its reaction was neutral, but the liquid gave a slight acid reaction when exposed to air. Pyridine was refluxed and distilled over barium oxide.

The treated membranes were tested for permeability to the amylose acetates by evaporation of the liquid in the solvent side of the osmometer. In no case was a non-volatile residue obtained.

In preparing solutions, a standard procedure was adopted unless otherwise noted. The acetate was wet with part of the solvent and allowed to stand in a flask overnight. The next morning the flask was heated for fifteen minutes at 55°. For pyridine a temperature of 95° was used. The flask was cooled to 30° and the solution made up to volume.

In setting up the cell, solutions of least concentration were used first with new membranes. After use, the cell was drained, rinsed with solvent and then washed three times with the next higher concentration. A new membrane was used at the beginning of each series. In no case was the membrane found to be permeable to the amylose acetate samples. Some adsorption of the amylose acetate on the cellophane membrane was noted. This was particularly true in very dilute solutions (of the order of 0.05 to 0.20 g. per 100 ml.) and very low osmotic pressures were obtained. Accordingly, measurements were made at concentrations of 0.35 g. per 100 ml. and higher and then only after several prolonged soakings and washings with solutions of the concentration under study.

The osmotic pressures observed were expressed as cm. head of water, divided by the concentration in grams per 100 ml. and these values were plotted against concentration. The curve was extrapolated to zero concentration

(13) R. M. Fuoss and D. J. Mead, *J. Phys. Chem.*, **47**, 59 (1943).

(14) C. E. Denoon, Jr., in Allen's "Organic Syntheses," Vol. 20, New York, N. Y., 1940, p. 6.

and the value $[\pi/C]_{c=0}$ determined. Molecular weights were calculated as $DP_n$ values from the equation

$$DP_n = \frac{RT}{[\pi/C]_{c=0} \times M} = \frac{2.57 \times 10^5}{[\pi/C]_{c=0} \times 288}$$

wherein

$R$ is the gas constant at 30°
$T$ is the absolute temperature
$M$ is the molar weight of an anhydro glucose triacetate group
$\pi$ is the osmotic pressure expressed as cm. head of water

## Discussion of Results

The results of osmotic pressure measurements on corn amylose acetate in solutions of chloroform, pentanedione and pyridine are shown in Fig. 1, and calculated; apparent $DP_n$ values are 455, 675 and 1370, respectively (Table I). All of the liquids employed are good solvents for the acetate, using "good" in the ordinary sense, when comparison is made with other solvents which have been used and reported for amylose and other carbohydrate esters, such solvents for example as methyl acetate, ethyl acetate, tetrachloroethane and benzene. The rate of solution was reasonably high, particularly in the case of chloroform and pentanedione. The solutions were sparkling clear and remained so after standing at room temperatures for several days. In the case of pyridine the observation was made, however, that on prolonged standing, *e.g.*, thirty days or more, solutions containing 1% of corn amylose acetate began to precipitate a gel-like material on the bottom of the flask.

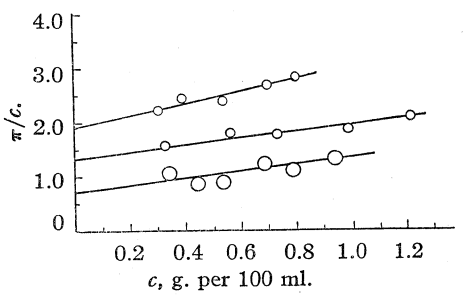



Fig. 1.—Osmotic pressure measurements of the acetate of corn amylose (no. 27) in: chloroform (top curve), 2,4-pentanedione (middle curve), pyridine (bottom curve).

It is well known that the amyloses are polydisperse.[15,16,17] Accordingly, one may expect some variation between samples when substantially the same procedure is used for isolation owing to minor variations in technique and the possibility of a subfractionating effect during repeated recrystallizations of the product. Another sample of corn amylose (no. 45), gave a value of 495 when the acetate was used in chloroform. Corn amylose prepared by butanol precipitation and recrystallization from aqueous butanol ($C$ 1/13), and previously used to prepare subfractions,[17] was converted into the acetate and from osmotic pressure measurements in chloroform a $DP_n$ of 435 was calculated in this solvent.

TABLE I

APPARENT $DP_n$ VALUES FOR CORN AMYLOSE ACETATE SAMPLES IN VARIOUS SOLVENTS AT 30°

| Sample | $DP_n$ in chloroform | $DP_n$ in pentanedione | $DP_n$ in pyridine |
|---|---|---|---|
| Corn amylose (no. 27)[a] | 455 | 675 | 1370 |
| Corn amylose (no. 45)[a] | 495 | ... | |
| Corn amylose (no. C 1/13)[b] | 435 | ... | |
| Corn amylose subfraction I | 250 | 370 | |
| Corn amylose subfraction II | 390 | 575 | |
| Corn amylose subfraction III | 525 | 795 | |
| Corn amylose subfraction IV | 675 | ... | |
| Corn crystalline amylose | 225 | 465 | |

[a] Pentasol precipitated. [b] Butanol precipitated.

Four subfractions of the amylose sample, $C$ 1/13, were prepared by ethylenediamine–ethyl ether phase separation technique.[17] These subfractions were acetylated and osmotic pressure measurements made in chloroform and in pentanedione solutions at 30°. The results for calculated $DP_n$ values are shown in Table I. Considerable variation, over 100%, was found in the chain lengths of the amylose subfractions. Again, higher values, about 50% higher, were found when pentanedione was used than when chloroform was employed as the solvent.

A corn amylose fraction, called corn crystalline amylose,[16] prepared by extracting corn starch with water at 75° and crystallizing the product from the extract by the addition of butanol, formed an acetate which had an apparent $DP_n$ of 225 in chloroform and 465 in pentanedione. This product is of the same type studied by Dumbrow[2] in methyl acetate solution. Foster[5] estimated a $DP$ of 175 for this fraction from viscosity measurements in ethylenediamine, as stated above.

The great variation in length of the amylose chains comprising any one sample no doubt explains in part the different values obtained when different systems are used for the measurement of average $DP$ values. It would be expected that osmotic pressure measurements from which number average molecular weights are calculated would give different results for corn amylose than viscosity or light-scattering data which are functions of weight-average molecular weight. Normally expected variations between samples would account for some discrepancy among the results of several investigators using the same system of measurement. However, these considerations do not account for the very large differences between the results, above reported, and presented in Table I when the same samples were used in the same apparatus and the solvent employed was the only variable. These data suggest that amylose derivatives are associated in organic solvents, to different extents, depending on the solvent.

(15) K. H. Meyer, P. Bernfeld and E. Wolff, *Helv. Chim. Acta*, **23**, 854 (1940).
(16) R. W. Kerr, *Arch. Biochem.*, **7**, 377 (1945).
(17) R. W. Kerr, THIS JOURNAL, **67**, 2268 (1945).

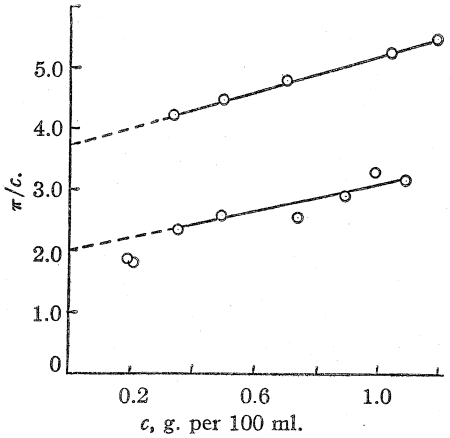



Fig. 2.—Osmotic pressure measurements, acetate of corn crystalline amylose in: chloroform (top curve), 2,4-pentanedione (bottom curve).

Doty, Wagner and Singer[18] have called attention to the fact that polymers may not be completely dissociated in solution and that the simple, difficultly refutable assumption that we are dealing with molecular dispersions in physical measurements on high polymer solutions is not always justified. This work deals principally with polyvinyl chloride polymers or co-polymers with the acetate, and the conclusions are limited by the consideration that linear organic halogen compounds might be expected to associate because of electronegative halogens. One would also expect the carbohydrates which have many hydroxyl groups along their chains to associate, for which reason they are usually derivatized for physical studies. However, carbohydrate esters, such as cellulose acetate, were shown by Doty and his coworkers also to give different osmotically determined molecular weights in acetone and in methyl "cellosolve." Cellulose acetate fraction 9 of Sookne and Harris[19] was found to have a molecular weight of 53,000 in acetone and 74,400 in methyl "cellosolve."

We had available a portion of this fraction 9 and found that its number average molecular weight in chloroform[20] at 30° was 47,600. This result invites drawing the general conclusion that linear carbohydrate acetates are associated to different degrees in various solvents and that association is least in chloroform.

Steurer[21] and others have proposed from the great difference in osmotic pressure of ethyl cellulose in the two solvents, chloroform and benzene, that the lower osmotic pressure curve for benzene solutions, relating $\pi/C$ to $C$, turns abruptly upward as infinite dilution is approached and at zero concentration $\pi/C$ equals the value for that of chloroform solutions. Possibly this is so. However, it should be noted that at concentrations of 0.1 g. per 100 ml. and less, the experimental error and inherent errors become very large and data taken in this concentration range are less reliable. Accordingly, we have made few observations at very low concentrations, but of those that were taken in pentanedione, the majority of values fell below rather than above the curve extrapolated from more reproducible values.[22] We have attributed these lower osmotic pressure values at low concentration to the effect of adsorption of solute by the new membrane. On the other hand, if one reuses cellophane membranes for very dilute solutions which have previously been employed at solute concentrations in the range of 0.3 to 1.2 g. per 100 ml., then one obtains, with amylose acetate at least, abnormally high osmotic pressures.

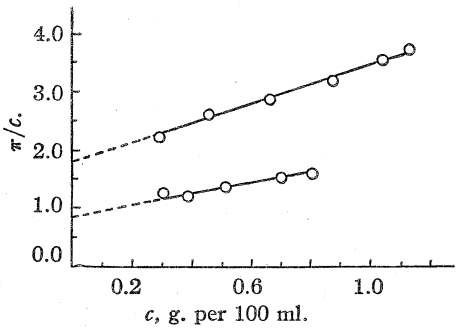



Fig. 3.—Osmotic pressure measurements in chloroform of the acetates of: corn amylose, no. 45 (top curve); tapioca amylose (bottom curve).

Even were curves obtained in some solvents which showed a radical change in slope from positive to negative within the concentration range below 0.1 gram per 100 ml., one could hardly expect to extrapolate these curves with any degree of certainty and the conclusion would still follow that the improper choice of solvent may lead to an inaccurate estimate of molecular weight. Furthermore, such data would not be inconsistent with the view that the solute associated more in these solvents than in those which gave a straight line relationship at some higher osmotic pressure level.

The association noted for corn amylose acetate in pentanedione and pyridine appears to be exaggerated for starch molecules, both linear and branched, which have a *DP* greater than that of the corn amylose samples. For example, Foster and Hixon[3] and F. Horan[23] observed that the amylose fraction from potato starch formed an acetate which swelled and only partially dissolved, even in chloroform. Tapioca amylose acetate (Pentasol precipitable fraction) appears to be very nearly the limit in respect to molecular size for visual solubility in chloroform, or rather lack of visual insolubility. The acetate swells at first and then appears finally to give a homogeneous dis-

(18) P. Doty, H. Wagner and S. Singer, *J. Phys. Colloid Chem.*, **51**, 32 (1947).

(19) A. Sookne and M. Harris, *Ind. Eng. Chem.*, **37**, 475 (1945).

(20) Contained by weight 2% added ethanol.

(21) E. Steurer, *Z. physik. Chem.*, **A190**, 1 (1941).

(22) Note, for example, lower curve, Fig. 2.

(23) F. Horan, Dissertation, Columbia University, New York, N. Y., 1944.

persion which is optically void on heating to 55°. The apparent $DP_n$ in chloroform was found to be 1050 at 30°. The effect was even more pronounced in the case of corn amylopectin acetate (fraction not precipitated by Pentasol). During acetylation of this fraction, the reaction mixture set to a gel when the ratio of carbohydrate to pyridine plus acetic anhydride was 2 to 100 and it was necessary to reduce this ratio to 1 to 100 in order to obtain a fluid medium and to complete the acetylation. The triacetate remained insoluble, for the most part, even with prolonged boiling in chloroform or mixtures of chloroform and alcohol. However, it was found that corn amylopectin subfraction III[16] forms a triacetate which dissolves in chloroform and for which a $DP_n$ value of 635 was found. The acetates of subfractions of higher molecular weight were only partially soluble. These experiments leave no doubt of the very great association which can exist between these carbohydrate molecules (or molecular entanglement), particularly in very high molecular weight ranges and which may operate to some extent even in the low molecular weight ranges.

The reluctance of carbohydrate derivatives to disperse molecularly in organic solvents leaves open to question the results of all physical measurements of molecular weight which involve a study of solutions whether the method consists of osmotic pressure, viscosity, light scattering or sedimentation measurements. It is believed that the extent of dissociation depends not only on the solvent which is employed but possibly also on the temperatures used and on the type of starch derivative, and that these considerations explain in part at least the wide spread in values reported in the past for the chain length of corn amylose.

For the present in fundamental studies it would seem wise to adopt the use of a readily prepared derivative, such as the acetate, and a solvent such as chloroform which gives a low order of molecular weight values by osmotic pressure measurements and a definite procedure in respect to temperature and time, until these values can be checked by a completely independent method. Boiling temperatures are suggested for preparing the solutions and 30° for measurement.

## Conclusions

The apparent $DP_n$ values for the acetates of corn amylose and its subfractions have been calculated from osmotic pressure determinations using selected solvents. Of those used, chloroform gave the lowest $DP_n$ values; the acetate of one corn amylose sample prepared by Pentasol precipitation was found to have a $DP_n$ of 455 and another 495. The acetate of a butanol precipitated corn amylose had a $DP_n$ of 435. Subfractions of the latter varied in $DP_n$ between 250 and 675.

Higher values for $DP_n$ were found in other solvents tried and this may be explained as being due to association of the acetates in these solvents. Starch acetate samples tend to become visibly insoluble, or partly insoluble in organic solvents as the $DP$ exceeds that of corn amylose. Tapioca amylose acetate appeared to be very nearly the limit in respect to molecular size for solubility in chloroform and showed a $DP_n$ of 1050 in this solvent.

ARGO, ILLINOIS RECEIVED JULY 16, 1948

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[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY]

# The Preparation of Boron Hydrides by the Reduction of Boron Halides

BY DALLAS T. HURD

It recently (1945) has been found that boron hydrides, specifically diborane and diborane monohalides, can be synthesized by the reduction of boron halide vapor with hydrogen in the presence of metals[1] at elevated temperatures.

In addition it has been discovered that the hydrides of the alkali and alkaline earth metals will reduce gaseous boron halides to diborane at temperatures above about 200°.[2]

## Experimental

**A. Reductions Involving Metals.—1.** Boron trichloride gas[3] and hydrogen in *ca.* 1:3 ratio were passed through a vertical bed of −20 mesh aluminum granules in a 1″ Pyrex tube heated to 350°. After a short induction period aluminum chloride was observed subliming out of the reaction zone and the gas issuing from the reactor became spontaneously inflammable, burning with a green flame.

Chemical tests on samples of the exit gas indicated the presence of boron hydrides. These included the standard tests such as the decolorization of hanging drops of permanganate solution, formation of chocolate brown precipitate on paper soaked in silver nitrate solution, formation of hydrogen bubbles in hanging water droplets, as well as other chemical reactions characteristic of the boranes. The exit gas gave negative results on all of these tests until the temperature necessary for reaction had been reached.

To study the reaction in more detail a larger apparatus was designed (Fig. 1) comprising a reactor tube $2^1/_2$ in. in diameter, heated in a cylindrical furnace, followed by a trap to collect the aluminum chloride formed during the reaction and by traps at −80 and −190° to collect the reaction products. The side arm leading from the reactor to the aluminum chloride trap was kept warm electrically to avoid deposition of the halide in the tube. The boron chloride and hydrogen were metered in through rotameters, the hydrogen being purified in a conventional set-up. The

(1) A general criterion for the metal is that it be more electropositive than boron.

(2) Mention should be made of the reactions in ether solution between boron halides and the hydrides of electropositive metals to yield boron hydrides discovered by H. I. Schlesinger and his coworkers at Chicago, Ill.

(3) Boron trichloride supplied by the Cooper Metallurgical Laboratories, Cleveland, Ohio; purity over 98%.

reaction temperature was followed by a thermocouple embedded in the charge of aluminum.

Upon distillation of the condensed products following a run it was observed that the material in the trap at −190° was mostly diborane together with some hydrogen chloride. The greater portion of the boron hydride was collected at −80° as diborane monochloride ($B_2H_5Cl$) along with excess boron trichloride. Hydrolytic analyses of the distillation fraction boiling at −92.5° established the identity of the principal reaction product as diborane.

A number of experiments were made in this and in similar but smaller apparatus with various ratios of gaseous reactants and at temperatures ranging from 300 to 500°. Representative data are tabulated in Fig. 2. The products initially were analyzed by slow distillation in a Podbielniak automatic still at atmospheric pressure.[4] (With this procedure the unstable diborane monochloride is decomposed into diborane and boron chloride during the distillation.) Later a method for determining the amount of diborane by direct hydrolysis of samples of the exit gas was employed.

In no case were the higher hydrides of boron found in the condensed products in amounts sufficient to be detected. There was evidence, however, that small quantities of solid boranes such as $B_{10}H_{14}$ were caught in the first trap along with the aluminum chloride.

The reaction apparently did not proceed at temperatures much below about 300°.

Upon removal of the tube from the furnace following a reaction, the granular aluminum charge frequently was found to be coated with a dark blue deposit. This blue deposit, readily soluble in dilute hydrochloric acid, conceivably may be connected with the mechanism of the reaction as an active intermediate since its character and amount did not seem to change with variation of the reaction time even in long runs where channeling of the charge due to removal of aluminum would occur. The rapidity with which the aluminum was dissolved by dilute hydrochloric acid indicated also that the usual oxide coating on the metal had been removed by the reaction.

Several analyses of used reactor charges were made by dissolving weighed samples in hydrochloric acid and weighing the insoluble residue as free boron. These indicated that only a very small percentage of the boron trichloride passing through the reactor was lost by reactions to form free boron. Except in the runs at very high temperatures where as much as 5% loss might be encountered, the amount of free boron generally was less than 1%.

Material balances on a number of the runs showed that in general the over-all loss of boron in the reactor was quite low. For example, 18 g. of boron trichloride together with hydrogen in 1–6 mole ratio was charged to the reactor at 360° during the extraction of a sample from the portion of the run measured. This amount of boron chloride is equivalent to 1.66 g. of boron. Collected in the sample trap was 13.5 g. of boron trichloride and 0.47 g. of diborane (after distillation) representing an amount of boron equal to about 1.60 g.

It was found advantageous to purify and dry the hydrogen used, not from any marked improvement in the reaction as a result, but because it avoided the plugging of lines and loss of material resulting from the hydrolysis of boron trichloride to boric oxide by traces of water.

Several types of aluminum were tried with no marked difference in performance except for a general increase in the conversion with the surface area of the metal. With very fine material, however, channeling and a resulting loss of contact area was encountered.

2. Magnesium, zinc and sodium (molten) behaved similarly toward mixtures of boron trichloride and hydrogen although the first two gave poorer yields than aluminum. There is reason to believe, however, that with a suitable method of providing contact between molten sodium and the gaseous reactants, good yields of diborane could be obtained.

3. Boron trifluoride and hydrogen in about 1:2 ratio were passed through heated magnesium powder. At about 375° a violent reaction ensued and the temperature of the charge rose rapidly. Small amounts of diborane were detected in the exit gas and some of this material was condensed and distilled. Upon completion of the experiment it was seen that the reaction must have been very exothermic since the charge was blackened and local overheating had warped the glass of the reactor tube. This very vigorous reaction and low yield also were encountered in trying to produce reaction of boron fluoride and hydrogen over aluminum.

(4) Distillation analyses were made by Dr. L. V. McCarty.

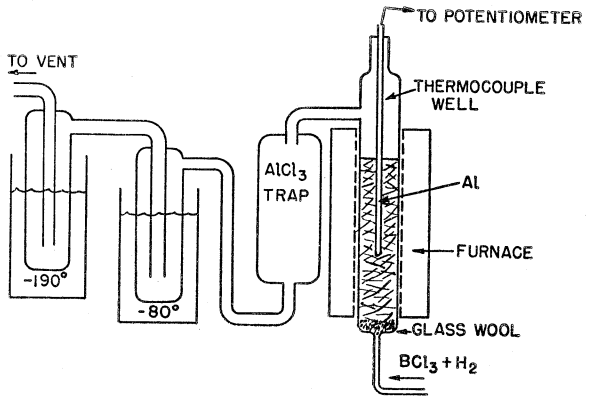



Fig. 1.—Diborane apparatus.

4. An experiment in which hydrogen was bubbled through boron tribromide at 25° and into a charge of granular aluminum at 250° produced aluminum bromide and small amounts of diborane. The yield was not high in the one reaction attempted.

**B. Reductions with Metal Hydrides.**—1. A charge of powdered sodium hydride[5] was placed in an inclined 1" Pyrex tube and a mixture of boron fluoride and hydrogen in *ca.* 1:2 ratio was passed through the charge while the temperature gradually was increased. At about 180° boron fluoride disappeared entirely from the exit gas and the presence of considerable quantities of diborane was confirmed. It later was shown that the presence of hydrogen was necessary to sweep the diborane product out of the hot zone to avoid pyrolysis. An experiment using nitrogen in place of hydrogen gave similar results so it is questionable whether either gas had any direct effect on the reaction.

The reaction was halted by the plugging of the reactor tube and it was found upon opening the furnace that much of the gray sodium hydride had been changed to a white salt, presumably either sodium fluoride or sodium borofluoride. No perceptible darkening of the charge which might indicate the deposition of free boron was observed.

Although no quantitative data as to the conversion of boron fluoride to diborane were obtained it seems quite likely, considering the total disappearance of boron fluoride from the exit gas, the amount of diborane produced, and the absence of pyrolysis products in the reactor, that the yield was high. With a suitable method of contacting gases with solids this method for the preparation of diborane may be of interest. There is the possibility, however, depending upon the reaction conditions, of losing boron fluoride by converting sodium fluoride to sodium borofluoride.

2. Boron trichloride and hydrogen passed through a charge of powdered sodium hydride at 200–220° reacted to produce diborane in the exit gas and sodium chloride in the charge. Both of these materials were identified by chemical tests. Boron trichloride alone passed rapidly over heated sodium hydride gave faint tests for diborane in the exit gas but the reaction was very exothermic and much darkening of the charge was noted. In all of these runs the tubes plugged quite rapidly due to build-up of sodium chloride in the charge.

(5) Sodium hydride generously supplied by the du Pont Electrochemicals Dept., Niagara Falls, N. Y.

Boron trichloride and hydrogen also reacted with crushed calcium hydride to produce spontaneously inflammable gaseous products which responded to the conventional tests for diborane. Calcium chloride was formed in the charge.

3. It is of interest to note in passing that some chemical evidence has been obtained for the formation of boron hydrides in the violent reaction that ensues upon heating mixtures of powdered anhydrous boric oxide and lithium hydride or sodium hydride. This hardly seems desirable as a preparative method, however.

## Discussion

It indeed appears surprising that a substance as thermally unstable as diborane can be synthesized under conditions that ordinarily would result in a rather rapid pyrolysis of this material. Several factors, however, may explain why so little pyrolysis actually does occur and why the losses of boron are small.

The actual contact time during which a unit of gas remained at elevated temperatures was in most cases rather short (Table I). This would tend to minimize pyrolysis losses. Also, there generally has been present in the reaction zone a large excess of hydrogen over the amount actually needed for the formation of boron–hydrogen compounds. Although the effect of hydrogen in inhibiting the decomposition of hydroborons at room temperature is well known, it well may be that this effect is not operative at elevated temperatures and the hydrogen may be effective largely by diluting the diborane product.

TABLE I

DIBORANE PREPARATIONS

| | T, °C. | $H_2$/$BCl_3$ | C. T.[a] | $Al_{size}$ | Condensed product, mole per cent. $B_2H_6$ | HCl | $BCl_3$ | Conversion, %[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 360 | 4–1 | 5″ | −12 | 2.9 | 4.1 | 93 | 6 |
| 2 | 320 | 3–1 | 12″ | −40 | 3.5 | 1.3 | 95.2 | 6.7 |
| 3 | 350 | 3–1 | 12″ | −40 | 5.8 | 0 | 94.2 | 11 |
| 4 | 350 | 6–1 | 15″ | −40 | 8.8 | 1.7 | 89.5 | 16.4 |
| 5 | 475 | 6–1 | 6″ | −30 | 12.4 | 1.7 | 85.9 | 20.4 |
| 6 | 500 | 6–1 | 4″ | −30 | 6.7 | 0.9 | 92.4 | 12.5 |
| 7 | 450 | 6–1 | 6″ | −30 | 17.2 | 3.9 | 78.9 | 30 |

[a] C.T. Calculated contact time in hot zone, 1″ dia. reactor. [b] Per cent. $BCl_3$ converted to $B_2H_6$, assuming no boron loss in the reactor.

In addition it may be possible that more stable monoboron compounds, *e. g.*, $BHCl_2$, $BH_2Cl$, may be the primary products of a stepwise reaction and that these transient compounds later undergo rearrangement into diborane and boron trichloride when out of the reactor hot zone.

In the runs where boron fluoride was used no inflammation was noticed even though large quantities of diborane were present at times in the exit gas. This may indicate either that diborane monofluoride ($B_2H_5F$) is not formed in the reaction or is not spontaneously inflammable if it is formed.

Reasoning from the experiments with metal hydrides, the reduction of boron halides with hydrogen over metals similarly may appear at first glance to involve the initial formation of reactive hydrides on the surface of the metal followed by replacement reactions. There is, however, little direct evidence to support this over other possible mechanisms, and at the present time the exact nature of the reaction is not known.

## Summary

Diborane and diborane monohalides have been produced by the reduction of boron halides with hydrogen over active metals at elevated temperatures.

The reaction of gaseous boron halides with active metal hydrides also has been found to produce diborane.

SCHENECTADY, NEW YORK RECEIVED JUNE 24, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

# Liquid–Liquid Solubility of Perfluoromethylcyclohexane with Benzene, Carbon Tetrachloride, Chlorobenzene, Chloroform and Toluene

BY J. H. HILDEBRAND AND D. R. F. COCHRAN

The extraordinary solvent properties of fluorocarbons which have come to light during the last few years have been considered in two recent papers from this Laboratory, one by R. L. Scott,[1] who gave "solubility parameters" for a number of fluorocarbons and showed their general harmony with available solubility data, and another by Benesi and Hildebrand[2] who reported a figure for the solubility of iodine in normal perfluoroheptane at 25° and showed that the remarkably small solubility, only 0.007 the solubility in an ideal solution, does not overstrain existing solubility theory for regular solutions.[3] This instance of the adequacy of theory to cope with an extreme departure from Raoult's law encouraged us to measure other fluorocarbon solubilities in the expectation that they would have much more than merely empirical value and could be used in connection with refinements in the general theory.

The large molal volumes of the fluorocarbons compared with the corresponding hydrocarbons leads to unusually low "internal pressures" or "cohesive energy densities," while their high

(1) R. L. Scott, THIS JOURNAL, **70**, 4090 (1948).

(2) H. A. Benesi and J. H. Hildebrand, *ibid.*, **70**, 3978 (1948).

(3) *Cf.* J. H. Hildebrand and R. L. Scott, "Solubility of Non-Electrolytes," 3rd edition, 1949, Reinhold Publ. Corp., New York, N. Y.

TABLE I

CONSOLUTE TEMPERATURES, °C., OF SOLUTIONS OF PERFLUOROMETHYLCYCLOHEXANE AT VARIOUS VOLUME FRACTIONS $\phi_2$, AND MOLE FRACTIONS, $x_2$, OF THE OTHER COMPONENT

| | $CCl_4$ | | $CHCl_3$ | | $C_6H_6$ | | $C_6H_5CH_3$ | | $C_6H_5Cl$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\phi_2$ | $x_2$ | $t$ | $x_2$ | $t$ | $x_2$ | $t$ | $x_2$ | $t$ | $x_2$ | $t$ |
| 0.909 | 0.953 | 3.0 | 0.960 | 26.3 | 0.956 | 61.1 | ... | .. | 0.950 | 86.9 |
| .900 | ... | ... | ... | .. | ... | .. | 0.943 | 63.7 | ... | ... |
| .833 | .910 | 17.5 | .916 | 41.0 | .916 | 76.1 | ... | .. | .905 | 110.4 |
| .800 | ... | ... | ... | .. | ... | .. | .880 | 83.1 | ... | ... |
| .769 | .870 | 23.4 | .890 | 46.6 | .876 | 81.6 | ... | .. | ... | ... |
| .714 | .834 | 25.5 | .858 | 48.9 | .845 | 83.9 | ... | .. | ... | ... |
| .700 | ... | ... | ... | .. | ... | .. | .810 | 87.7 | ... | ... |
| .667 | ... | ... | ... | .. | .814 | 84.7 | ... | .. | ... | ... |
| .625 | ... | ... | ... | .. | .785 | 85.1 | ... | .. | ... | ... |
| .600 | .752 | 26.8 | .784 | 50.2 | .767 | 85.3 | .733 | 88.9 | .742 | 126.8 |
| .500 | .669 | 26.7 | .708 | 50.1 | .687 | 84.9 | .647 | 88.6 | .657 | 126.7 |
| .400 | .574 | 25.2 | .618 | 49.0 | .593 | 82.7 | .550 | 87.2 | .561 | 123.5 |
| .333 | ... | ... | ... | .. | .523 | 79.2 | ... | .. | ... | ... |
| .300 | ... | ... | ... | .. | ... | .. | .440 | 82.0 | ... | ... |
| .286 | .447 | 19.9 | ... | .. | .467 | 75.7 | ... | .. | ... | ... |
| .231 | .377 | 14.4 | .422 | 38.6 | .397 | 69.3 | ... | .. | .365 | 108.1 |
| .200 | ... | ... | ... | .. | ... | .. | .314 | 68.7 | ... | ... |
| .167 | .288 | 4.0 | .327 | 28.9 | .305 | 58.9 | ... | .. | .277 | 92.9 |
| .100 | ... | ... | ... | .. | ... | .. | .169 | 42.8 | ... | ... |
| .091 | .168 | −8.0 | .195 | 7.2 | .190 | 35.0 | ... | .. | .161 | 65.7 |

molecular weights aid in maintaining them in the liquid state; the net result of which is to make many of their solutions with ordinary liquid hydrocarbons deviate from Raoult's law to such an extent as to form two liquid phases, a state of affairs comparatively rare among non-polar liquids. Since liquid–liquid solubilities are easily determined, we have used this means of further comparing theory with experiment.

**Materials.**—We are indebted to the Jackson Laboratory, du Pont de Nemours Co., for the supply of perfluoromethylcyclohexane. The benzene, "reagent grade, thiophene free," showed no color with concentrated sulfuric acid. It was dried with calcium chloride and distilled. The carbon tetrachloride, "reagent grade," was washed with concentrated sulfuric acid, then with water, and dried over calcium chloride. The chloroform, also "reagent grade," was washed successively with concentrated sulfuric acid, sodium carbonate aq., water, and dried over calcium chloride. The toluene was that used by Benesi and Hildebrand.[2] The chlorobenzene, "reagent grade," was dried over phosphorus pentoxide and distilled. All the above distilled within 0.1°.

**Procedure.**—The two liquids were measured by means of a carefully calibrated pipet made of 2-mm. capillary tubing into tubes 10 cm. long and 7 mm. diameter through capillary stems at right angles. The liquids were frozen in liquid nitrogen after introduction and sealed in. These tubes were heated above the consolute temperatures in a water-bath for 0 to 90° and in sulfuric acid for the range 90 to 130°. On slowly lowering the temperature while rocking a tube, the unmixing temperature of a solution could be accurately determined.

**Results.**—Table I gives the consolute temperatures of the different solutions together with the corresponding volume fractions of the fluorocarbon as measured at 25°, and the corresponding mole fractions. These temperatures are plotted against mole fraction in Fig. 1 and against volume fraction in Fig. 2. In Table II are given the critical mixing temperatures read from the maxima of these curves, also the critical compositions determined by aid of the assumption of rectilinear diameter, as in the analogous case of liquid–gas equilibrium.

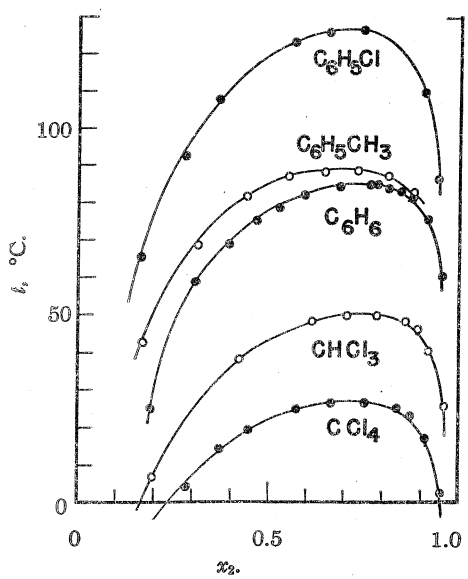



Fig. 1.—Consolute temperatures of perfluoromethylcyclohexane solutions *vs.* mole fraction of second component.

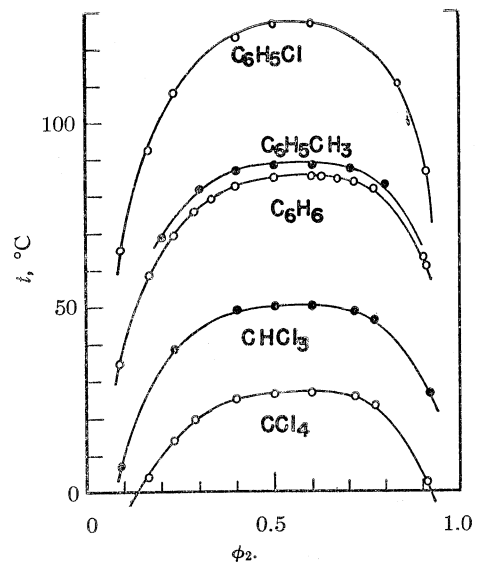



Fig. 2.—Consolute temperatures of perfluoromethylcyclohexane solutions *vs.* volume fraction of second component.

TABLE II

COMPARISON BETWEEN OBSERVED AND CALCULATED VALUES OF CRITICAL COMPOSITIONS AND TEMPERATURES FOR SOLUTIONS OF PERFLUOROMETHYLCYCLOHEXANE (COMPONENT 1)

| | v cc., 25° | Crit. $x_2$ obs. | Crit. $x_2$ calcd. | $T_c$ obs. | $T_c$ calcd. | $\delta_2$ | $\delta_1$ calcd. |
|---|---|---|---|---|---|---|---|
| $C_6F_{11}CF_3$ | 195 | | | | | | |
| $CCl_4$ | 97 | 0.70 | 0.74 | 300.0 | 269 | 8.6[1] | 5.8 |
| $CHCl_3$ | 81 | .74 | .78 | 323.5 | 325 | 9.0[a] | 6.0 |
| $C_6H_6$ | 89 | .73 | .76 | 358.5 | 360 | 9.15[1] | 6.0 |
| $C_6H_5CH_3$ | 102 | .69 | .71 | 362.0 | 324 | 8.9[1] | 5.8 |
| $C_6H_5Cl$ | 107 | .69 | .72 | 400.0 | 464 | 9.5[1] | 6.3 |

[a] This value is consistent with the solvent power of chloroform for other substances; the value of $(\Delta E^v/v)^{1/2}$ is 9.3. See J. H. Hildebrand, "A Critique of the Theory of Solubility of Non-electrolytes," *Chem. Revs.*, in press.

**Comparison with Theory.**—The regular solution equations[4] for liquid–liquid solubility are as follows, for the mole fraction at the critical point and the critical temperature, respectively

$$x_1 = \frac{(v_1^2 + v_2^2 - v_1v_2)^{1/2} - v_1}{v_2 - v_1} \qquad (1)$$

and

$$RT_c = \frac{2x_1x_2v_1^2v_2^2}{(x_1v_1 + x_2v_2)^3}(\delta_1 - \delta_2)^2 \qquad (2)$$

where the v's denote molal volumes, $x$'s mole fractions, and $\delta$'s are what we have been calling the "solubility parameters," which are ordinarily the square root of the energies of vaporization per cc., *i. e.*, $\delta = (\Delta E^v/v)^{1/2}$. In this paper we shall distinguish the fluorocarbon by the subscript 1.

It has been pointed out that eqn. 1 yields values of the critical composition not far from those obtained by the simpler assumption that the maximum occurs at equal volume fractions, *i. e.*, $\delta_1 = \delta_2 = 0.5$, as shown in Fig. 2. The curves are so flat at the top that this may suffice for ordinary purposes. It has been pointed out, further, that eqn. 2 yields values of $T_c$ not seriously different from a greatly simplified equation

$$4RT_c = (v_1 + v_2)(\delta_1 - \delta_2)^2 \qquad (3)$$

In Table II can be seen comparisons between observed and calculated values of the critical compositions and temperatures. The "observed" values of $x_2$ were taken from the solubility curves by aid of the assumption of rectilinear diameter, as in gas–liquid density curves. The curves are so flat around the maximum that these values are subject to an error of at least ±0.02. The "calculated" values were obtained from Equation 1 by substituting the molal volumes for 25°, given in the first column of figures. It would be preferable to use the molal volumes at the critical temperatures, but since we lack some of the necessary density data and in view of the uncertainty in fixing the "observed" values, a closer check is hardly to be desired.

We have found that values of $\delta_1 - \delta_2$ calculated from $T_c$ by eqn. 3 agree within a few per cent., *i. e.*, well within the limit of the unavoidable errors and uncertainties of the method, with those derived by aid of the more complicated eqns. 1 and 2, therefore eqn. 3 has been used in the following calculations. Substituting the observed values of $T_c$ and the v's for 25° gives $\delta_2 - \delta_1$, which, subtracted from the $\delta_2$-values in the next to the last column gives the calculated values of $\delta_1$ for perfluoromethylcyclohexane given in the last column. In so calculating we have neglected the effect of temperature upon both $\delta_1$ and $\delta_2$ and on this account alone we should not expect uniform values for $\delta_1$ "calculated." In addition, the dipole moments of chloroform and chlorobenzene might be expected to cause some disturbance. It is sufficient to find that these values of $\delta_1$ for the fluorocarbon derived from solubility data agree well with the value 6.0 at 25° set by Scott[1] long before this work was undertaken. Reversing the calculation, we have calculated $T_c$ for each solution using this value of $\delta_1$ in combination with the $\delta_2$-values given in the table. It will be seen that while the result is far from precise it has value, nevertheless, in giving the general region in which two liquid phases can coexist. The high critical temperature with toluene is not what its $\delta$-value, less than that of benzene, would lead us to expect. A similar reversal has been noted by Hildebrand and Jenks[5] in the solubilities of sulfur in these two liquids. An explanation of such facts must await refinements in the theory as well as additional data, such as partial molal volumes.

**Acknowledgments.**—We wish to express our appreciation to Dr. J. M. Tinker, Director of the Jackson Laboratory, E. I. du Pont de Nemours

(4) *Cf.* ref. 3, Chap. XVI.

(5) J. H. Hildebrand and C. A. Jenks, THIS JOURNAL, **43**, 2172 (1921).

Co., for the sample of perfluoromethylcyclohexane, and the Office of Naval Research for financial support of this research.

## Summary

Liquid–liquid solubility curves have been determined for binary mixtures of perfluoromethylcyclohexane with five other liquids, giving the following results for the critical solution temperatures in °C. and the mole fractions of the second components: carbon tetrachloride, 26.8°, 0.70; chloroform, 50.3°, 0.74; benzene, 85.3°, 0.73; toluene, 88.8°, 0.69; chlorobenzene, 126.8°, 0.69.

These values agree within the usual limits of error with those calculated by aid of the equations for regular solutions and the value 6.0, previously derived by Scott for the "solubility parameter" (the square root of the energy of vaporization per cc.) of the fluorocarbon.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

# The Kinetics of the Oxidation of 2-Deuteropropanol-2 by Chromic Acid

BY F. H. WESTHEIMER AND NICHOLAS NICOLAIDES

The rate of the chromic acid oxidation of isopropyl alcohol to acetone has been shown to be proportional to the concentrations of isopropyl alcohol and the acid chromate ion, and proportional to the square of the concentration of hydrogen ion.[1] Although these kinetics fix the composition of the activated complex in the oxidation, they leave unanswered many questions concerning the mechanism. Specifically, they do not show whether the oxidative attack upon the alcohol molecule is at the secondary hydrogen atom, at the hydroxyl hydrogen atom,[2] or elsewhere. This question can be answered by studying the rate of oxidation of 2-deuteropropanol-2.

Both experimental and theoretical considerations show that, if the deuterium atom of 2-deuteropropanol-2 is removed in the rate-controlling step of the oxidation, the 2-deuteroalcohol will be oxidized much less rapidly than the corresponding hydrogen compound. On the other hand, if the rate determining step does not involve the removal of this deuterium atom, the oxidation rates for the hydrogen and deuterium compounds should be almost if not exactly identical. This test for the direct removal of a hydrogen atom depends upon the fact that C–H and C–D bonds differ in their zero-point energies. The method is completely general[3]; it has been strikingly applied by Reitz[4] in a study of the rate of enolization of acetone and of the deuteroacetones. In the present work, it has been found that 2-deuteropropanol-2 is oxidized by chromic acid only about one-sixth as fast as is ordinary isopropyl alcohol; it follows unambiguously that the secondary hydrogen atom is removed during the rate controlling step of the reaction.

(1) Westheimer and Novick, *J. Chem. Phys.*, **11**, 506 (1943).

(2) Mosher, Abstracts, September, 1947, meeting of the American Chemical Society. Mosher and Whitmore, THIS JOURNAL **70**, 2544 (1948).

(3) Urey and Teal, *Rev. Mod. Phys.*, **7**, 34 (1935); *cf.* Taylor and Eyring, *Proc. Am. Phil. Soc.*, **72**, 255 (1933).

(4) Reitz, *Z. physik. Chem.*, **A179**, 119 (1937); *ibid.*, **A184**, 429 (1939); *cf.*, however, Wynne-Jones, *J. Chem. Phys.*, **2**, 381 (1934); Reitz, *Z. physik. Chem.*, **A176**, 363 (1936); and Maron and LaMer, THIS JOURNAL, **60**, 2588 (1938).

## Experimental

**Deuterium.**—The deuterium for these experiments was made by vaporizing 12.1 g. of Norwegian heavy water (Norsk Hydro Elektrish Kvaelstofaktieselskat 99.73% $D_2O$; $d^{20}_4$ 1.10516) over Grignard magnesium heated electrically to 490 ± 25° in a heavy-walled combustion tube.[5] The resulting deuterium gas was passed through alkaline permanganate and stored over a saturated solution of sodium sulfate.

**2-Deuteropropanol-2.**—2-Deuteropropanol-2 was made by the catalytic deuteration of acetone according to the directions of Anderson and MacNaughton.[6] Eighty-six grams of acetone (J. T. Baker reagent grade, previously dried with potassium carbonate and distilled) was deuterated with 10.8 liters of deuterium gas, by means of 1.62 g. of Adams catalyst promoted with a few crystals of ferrous chloride. The deuteration required five days, during which time the catalyst was reactivated several times by briefly stirring the reaction mixture in air.

The reaction mixture was then fractionated through a small Podbielniak column (about 25 theoretical plates) to remove the large excess of acetone. When all the acetone had been removed, 54 cc. of water was added in order to exchange the hydroxylic deuterium of the isopropyl alcohol with the hydrogen of the water. Then the distillation (through the same column) was resumed. The fraction collected was 15 g. of the azeotropic mixture of isopropyl alcohol and water. Some of this azeotrope was used directly for rate measurements; some was re-equilibrated with water. The latter portion was prepared by adding 8.5 g. of the azeotrope to 100 g. of water, and then redistilling the mixture through the same Podbielniak column. The composition of the azeotrope was calculated as 90.1% deuteroisopropyl alcohol and 9.9% water from the combustion analysis of the material. (Microanalysis by Wm. Saschek, C, 53.40; H, 12.82.) Both portions of the azeotrope (that equilibrated once and that equilibrated twice) had the same rate of oxidation.

The work of Anderson and MacNaughton[6] suggests that in the deuteration all the deuterium gas is taken up at the carbonyl group, and the resulting product should be pure $CH_3\underset{D}{C}(OD)-CH_3$. If this were the fact, the product after equilibration with water should have been pure $CH_3\underset{D}{C}(OH)-CH_3$. Regrettably, however, the isopropyl alcohol which we prepared was a mixture containing only about 55% of the desired 2-deuteroalcohol. Fortunately the qualitative

(5) Knowlton and Rossini, *Bur. Standards J. Research*, **19**, 605 (1937).

(6) Anderson and MacNaughton, THIS JOURNAL, **64**, 1456 (1942); see also Carothers and Adams, *ibid.*, **46**, 1675 (1924).

TABLE I

RATE OF OXIDATION OF 55% 2-DEUTEROPROPANOL-2

| Experiment[a] | Concn. $CrO_4$, mole/l. | Concn. alcohol, mole/l. | Concn. $H^+$, mole/l. | Ionic strength | $k$, min.$^{-1}$ (mole/l.)$^{-2}$ $k_H$ | $k_{DI}$[b] | $k_H/k_{DI}$ |
|---|---|---|---|---|---|---|---|
| I | 0.005480 | 0.2072 | 0.3143 | 0.40 | 2.04 | | 1.88 |
| D-I | .005520 | .2139 | .3140 | .40 | | 1.09 | |
| II | .001059 | .2061 | .3120 | .40 | 2.30 | | 1.90 |
| D-II | .001059 | .2139 | .3120 | .40 | | 1.21 | |
| III | .005480 | .02960 | .3143 | .40 | 1.73 | | 1.91 |
| D-III | .005520 | .03059 | .3140 | .40 | | .907 | |
| IV | .005591 | .2046 | .1083 | .40 | 2.77 | | 1.89 |
| D-IV | .005520 | .2138 | .1082 | .40 | | 1.47 | |

[a] In those experiments prefixed with the letter "D," the isopropyl alcohol used contained 55% deuterium on the central carbon atom. [b] The symbol $k_{DI}$ represents the rate constant for the isotopically impure 2-deuteropropanol-2.

conclusions here reached (see the discussion) do not depend upon the isotopic purity of the alcohol used. (The mixture of isopropyl alcohol and deuteroisopropyl alcohol used for the oxidations is hereafter called isotopically impure deuteroisopropyl alcohol, or, when the meaning is clear, simply "2-deuteropropanol-2"). The material was analyzed for deuterium by burning a sample in air on a sintered glass wick and determining by a float method the density of the water formed. The procedure of Brown and Eberly[7] was followed, and was found to be reliable to within 0.01 mole per cent. of the deuterium oxide in the water analyzed. In one experiment 0.4855 g. of the azeotrope was mixed with 1.3085 g. of pure, dry, ordinary isopropyl alcohol; before combustion the mixture was dried over lime and distilled. The water formed contained 2.01 mole per cent. deuterium oxide, corresponding to 0.65 gram atom of deuterium per mole of the (isotopically impure) 2-deuteropropanol-2.

Evidently the "2-deuteropropanol-2" contained a fairly large proportion of ordinary isopropyl alcohol, with hydrogen rather than deuterium on the center carbon atom. This hydrogen could not have come from the heavy water, which was of good quality (the residual heavy water left over from the investigation had a density, $d^{20}_4$, of 1.1040, corresponding[8] to 98.7 mole per cent. deuterium oxide); neither could the hydrogen have come from water vapor in the deuterium gas, since the latter was dried over calcium chloride before use. But hydrogen–deuterium exchange does occur between acetone or isopropyl alcohol and deuterium gas at room temperature in the presence of platinum black,[9] and therefore this exchange may have occurred here in the presence of Adams catalyst. A small amount (0.1 g. atom per mole) of deuterium was observed (see below) in the acetone obtained by oxidation of the deuterated isopropyl alcohol here prepared. If exchange occurred with all the acetone used in the hydrogenation to the extent of 0.1 g. atom per mole, this exchange would be sufficient to supply the hydrogen needed to form the isotopically impure isopropyl alcohol actually obtained. Extensive further research will be needed to decide whether the method of preparation of the catalyst and other experimental details control the extent of the exchange, or whether such exchange is inevitable in hydrogenations over Adams catalyst, although, because of the limited extent of exchange, it sometimes escapes notice. In any event, it was necessary to find how much of the deuterium was attached to the secondary carbon atom, and how much occurred in the methyl groups. The isotopically impure 2-deuteropropanol-2 was therefore oxidized to acetone. The oxidation method of Anderson[10] (where rather concentrated sulfuric acid is employed) was abandoned in favor of the gentler Oppenauer method.[11] Four and two-tenths cc. of the deuteroisopropyl alcohol and 16 g. of fluorenone (Eastman Kodak Co. m. p. 80.5–81.5°) were refluxed for six hours with 1.7 g. of aluminum tertiary butoxide[12] in 70 cc. of dry toluene. The reaction mixture was fractionated through a 50-theoretical plate Piros-Glover micro still. The resulting acetone was burned, and found to contain 0.105 gram atom of deuterium per mole. The deuteroisopropyl alcohol used therefore contained about 65.0 − 10.5 = 54.5% of the desired $CH_3\overset{OH}{\underset{D}{C}}—CH_3$.

The calculation just given is based on the assumption that little or no exchange occurs during Oppenauer oxidation. To test this assumption, ordinary acetone (6.9 g.) was put back into the reaction mixture from which the (deuterium-containing) acetone and isopropyl alcohol had been removed by fractionation. The mixture was refluxed and distilled under the conditions employed in the oxidation of the isopropyl alcohol. The recovered acetone contained only 0.01 gram atom of deuterium per mole. This finding indicates that the exchange with deuterium during the Oppenauer reaction is negligible.

**Rate Determinations.**—The oxidation rates for isopropyl alcohol and the (isotopically impure) 2-deuteropropanol-2 were determined at 40° by the methods and equations of Westheimer and Novick.[1] The analytical method, however, differed from theirs. Instead of titrating the unreacted chromic acid, the quantity remaining in solution was determined spectrophotometrically with a Beckman Quartz Spectrophotometer, model DU. It was found that all the chromic acid solutions used had an absorption maximum close to 3500 Å.; at this wave length, chromic ion absorbs hardly at all. Despite the equilibrium[1,13] between $HCrO_4^-$ and $Cr_2O_7^=$ ions, solutions of chromic acid within the range of acidity used very nearly obey Beer's law. Nevertheless, an empirical standardization curve was prepared. The samples withdrawn from the reaction mixture were pipetted into a standard solution of sodium acetate such that the resulting buffer had an acetic acid–acetate ion ratio of one to 0.18. Blank experiments showed that, in this buffer, the rate of oxidation of isopropyl alcohol was negligible. These buffered solutions were then examined spectrophotometrically.

**Results.**—The kinetic results obtained as described are shown in Table I. The figures for isopropyl alcohol agree well with those of Westheimer and Novick. The ratio of the oxidation rates for isopropyl alcohol and the isotopically impure 2-deuteropropanol-2 was uniformly about 1.9.

In all the experiments hitherto cited, the concentration of alcohol greatly exceeded that of the chromic acid, and the former was therefore essentially constant during any individual rate determination. For this reason, the rate constant during any one experiment did not "drift," despite the fact that isotopically impure material (55% 2-deuteropropanol-2 and 45% isopropyl alcohol) was used. A few experiments were made with equivalent concentrations of ordinary isopropyl alcohol (or isotopically impure 2-deuteropropanol-2) and chromic acid. Here the rate constant for the oxidation of ordinary isopropyl alcohol was

(7) Brown and Eberly, THIS JOURNAL, **62**, 113 (1940).

(8) Wirtz, *Physik. Z.*, **43**, 465 (1942).

(9) Farkas and Farkas, THIS JOURNAL, **61**, 1336 (1939); Friedman, Dissertation, Princeton University, 1947.

(10) Anderson, private communication.

(11) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

(12) Wayne and Adkins, "Organic Syntheses," **21**, 8 (1941).

(13) Neuss and Rieman, THIS JOURNAL, **56**, 2238 (1934).

essentially constant, whereas that for the oxidation of the isotopically impure deuteroisopropyl alcohol decreased during the course of the experiment. This drift was to be expected. Since isopropyl alcohol reacts faster than does the corresponding deutero compound, the latter forms the bulk of the residual material left toward the end of any oxidation.

It was possible to calculate for this latter type of experiment the chromic acid concentration anticipated at various reaction times (see Appendix and Table II). The first column of the table gives the times at which samples were withdrawn; the observed chromic acid concentrations of these samples are given in column three. The second column gives the fourth order rate constants, determined by the equation of Westheimer and Novick; the drift is obvious. Column four gives the chromic acid concentrations computed for various times on the basis of an assumed ratio (4.5) for the rate constants of the oxidations of ordinary and 2-deuteropropanol-2; column five gives the concentrations similarly computed on the basis of another assumed ratio (6). A few readings taken very early in the experiments and a few taken beyond the point of 90% reaction were erratic; these have been omitted from the table.

TABLE II

RATE OF OXIDATION OF ISOTOPICALLY IMPURE 2-DEUTEROPROPANOL-2

Initial concentration in moles/l: 2-deuteropropanol-2, 0.0537; chromic acid, 0.0693; isopropyl alcohol, 0.0433; $H^+$, 0.4944

| Time in minutes | "$k$," min.$^{-1}$ (m./l.)$^{-2}$ | Chromic acid reacted, m./l. Exp.[a] | Calculated with $k_H/k_D$ = 4.5 | = 6.0 |
|---|---|---|---|---|
| 11.4 | 0.88 | 0.00420 | 0.0042 | 0.0042 |
| 27.4 | .92 | .00952 | .0095 | .0093 |
| 56.5 | .92 | .01647 | .0163 | .0152 |
| 106.4 | .86 | .02371 | .0236 | .0221 |
| 204 | .79 | .0318 | .0314 | .0282 |
| 352 | .70 | .0379 | .0379 | .0358 |
| 661 | .60 | .0445 | .0445 | .0442 |
| 1146 | .52 | .0492 | .0500 | .0475 |
| 1851 | .45 | .0528 | .0535 | .0511 |
| 2785. | .41 | .0556 | .0561 | .0541 |
| 3645. | .40 | .0574 | .0579 | .0560 |

[a] Average values from two duplicate experiments.

## Discussion

The experiments here reported prove beyond doubt that 2-deuteropropanol-2 reacts with chromic acid much more slowly than does ordinary isopropyl alcohol. Since the deuterated material here used contained only 55% of 2-deuteropropanol-2, the exact ratio of the oxidation rates must be calculated on the (almost certain) assumptions (1) that the isopropyl alcohol and the 2-deuteropropanol-2 react independently, and (2) that deuterium in the methyl groups has little if any effect upon the oxidation rate. Calculations made on this basis indicate that pure isopropyl alcohol should be oxidized about 6.7 times as rapidly as pure 2-deuteropropanol-2; this value is roughly consistent with the rate ratio of about 5 obtained from the data (presented in Table II) for experiments in which the initial chromic acid and alcohol concentrations were equivalent. The rate ratio calculated from experiments with 55% 2-deuteropropanol-2 is likely to be somewhat in error. Although the probable error in the rate constants is small (of the order of 2%), the possible errors in the deuterium analysis and the questionable distribution of deuterium between the secondary carbon atom and the methyl groups make the computed oxidation rate for 2-deuteropropanol-2 somewhat uncertain. This uncertainty is such that the ratio of the rate of oxidation of the pure 2-deuteropropanol-2 to that of isopropyl alcohol should probably be written as $0.17 \pm 0.05$. Such uncertainty is, however, irrelevant for the conclusion here drawn. For if 2-deuteropropanol-2 is oxidized much more slowly than is ordinary isopropyl alcohol, it follows that the carbon to secondary hydrogen bond (or carbon to secondary deuterium bond) is broken in the rate determining step of the reaction.

## Appendix

The data in Table II were obtained by use of the equations derived below. In these equations, the symbols $b'$, $c'$, $K'$ have the meanings previously[1] assigned to them. The initial concentration of the ordinary isopropyl alcohol is represented by $a_H$, that which has reacted is represented by $x$; the initial concentration of the 2-deuteropropanol-2 is represented by $a_D$, that which has reacted is represented by $y$. The fourth order rate constant for the decrease in concentration of chromic acid during the oxidation of ordinary isopropyl alcohol is represented by $k_H$ rather than by $k$. The corresponding constant for decrease during the oxidation of the deuteroalcohol is $k_D$. Since the stoichiometry of the reaction demands that three molecules of alcohol react for every two of chromic acid, the rate constants for the decrease of the concentration of isopropyl alcohol and deuteropropanol-2 are respectively $3/2\ k_H$ and $3/2\ k_D$. It follows that

$$dx/dt = 3/8\ k_H\ (a_H - x)\ \{-K' + \sqrt{K'^2 + 8K'\ [b' - 2/3\ (x + y)]}\}\ [c - 8/3\ (x + y)]^2 \quad (1)$$

$$dy/dt = 3/8\ k_D\ (a_D - y)\ \{-K' + \sqrt{K'^2 + 8K'\ [b' - 2/3\ (x + y)]}\}\ [c - 8/3\ (x + y)]^2 \quad (2)$$

$$dy/dx = k_D\ (a_D - y)/k_H\ (a_H - x) \quad (3)$$

Equation (3) when integrated yields (4)

$$y = a_D - \frac{a_D}{\left(1 - \frac{x}{a_H}\right)^{k_H/k_D}} \quad (4)$$

From eqn. (4), the value of $y$ corresponding to any value of $x$ can be found for any assumed value of $k_H/k_D$. When the values of $y$ corresponding to various values of $x$ are inserted into eqn. (1), this equation can be graphically integrated. This graphical integration gives the theoretical relation between the amount of alcohol (or chromic acid) consumed and the reaction time for the particular value of $k_H/k_D$ used. The values thus computed are presented in Table II.

## Summary

1. When Adams catalyst, activated by ferrous chloride, is used, the deuteration of acetone is accompanied by some hydrogen–deuterium exchange. The product here obtained was a mixture containing 55% of 2-deuteropropanol-2.

2. The rate of chromic acid oxidation of this product was only 52% of that of ordinary isopropyl alcohol. On the basis of this result, it is calculated that the rate of chromic acid oxidation of pure 2-deuteropropanol-2 should be about one-sixth that of pure isopropyl alcohol.

3. The lower rate of oxidation of the 2-deutero compound (which arises from differences between the zero point energies of the C–H and C–D bonds) proves that the secondary hydrogen (or deuterium) in isopropyl alcohol is removed in the rate controlling step of the chromic acid oxidation.


CHICAGO, ILLINOIS RECEIVED MAY 13, 1948

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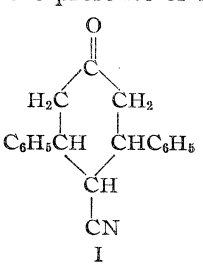
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane and Some Related Compounds[1]

BY C. S. MARVEL AND ALLEN C. MOORE[2]

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane (VI) was needed for another synthetic problem and it seemed probable that it could be produced readily by the addition of ethyl cyanoacetate to dibenzalacetone followed by hydrolysis, decarboxylation and reduction.

Kohler and Helmkamp[3] have prepared 1-cyano-2,6-diphenyl-4-cyclohexanone (I) by the addition of methyl cyanoacetate to dibenzalacetone followed by hydrolysis and decarboxylation of the addition product (II, R = $CH_3$). In our work the addition of ethyl cyanoacetate to dibenzalacetone ran smoothly in the presence of sodium ethoxide



I

to give an 88% yield of the cyclic cyanoester (II R = $C_2H_5$). Difficulty was experienced in hydrolysis of the ethyl ester although the methyl ester had not been difficult to hydrolyze.[3] It seemed probable that reduction of the carbonyl group would stabilize the cyclohexane ring so no reversal of the Michael reaction would occur under the conditions of alkaline hydrolysis. Accordingly, the keto ester (II, R = $C_2H_5$) was reduced by the Meerwein–Ponndorf–Verley method.[4] This reduction did not give the simple hydroxy compound but two other products. One was crystalline and proved to be a lactone (III). The other was a non-crystalline polyester (IV). The formation of lactones in this reaction is not unusual.[4] The lactone (III) was undoubtedly formed from the hydroxy ester intermediate with the *cis*-configuration for these groups and the polyester therefore was probably derived from the *trans*-isomer. Hydrolysis of this glassy material gave a 63% yield of the free acid (V) which did not readily form a lactone and this further confirms its *trans*-structure with respect to hydroxyl and carboxyl groups.

When the cyanolactone (III) was refluxed for three hours with 40% aqueous sodium hydroxide, the lactone ring was opened and decarboxylation occurred, giving an 80% yield of the hydroxy nitrile (VI). Decarboxylation of the free acid (V) also gave the hydroxynitrile (VI), in 50% yield. By continuing the alkaline hydrolysis of the cyanolactone for a total of thirty-one hours, there was obtained a 94% yield of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid (VII).

It became evident, from examination of the hydroxy acid (VII) derived from the hydroxynitrile (VI), that the acid had the *cis*-configuration. Thus, the hydroxy acid formed a second lactone (VIII) with ease, in 79% yield, when heated at its melting point. The action of such reagents as acetic anhydride, acetyl chloride and *p*-toluenesulfonyl chloride also brought about lactone formation. By contrast, the strictly analogous *trans*-4-hydroxycyclohexane-1-carboxylic acid prepared by Perkin[5] showed no tendency to yield a lactone when distilled, or when treated with hot 25% sulfuric acid.

When it is considered that the hydroxyl and carboxyl groups of the precursor of the cyanolactone (III) must have been *cis* with respect to one another, it follows that the nitrile and hydroxyl groups must have been in the *trans* configuration originally. It is clear then, that an inversion must have occurred to give a product (VII) of *cis* configuration. This inversion might have occurred during the opening of the lactone ring,[6,7] during

(1) This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(2) Present address: Research Laboratories, Parke, Davis and Co., Detroit 32, Michigan.

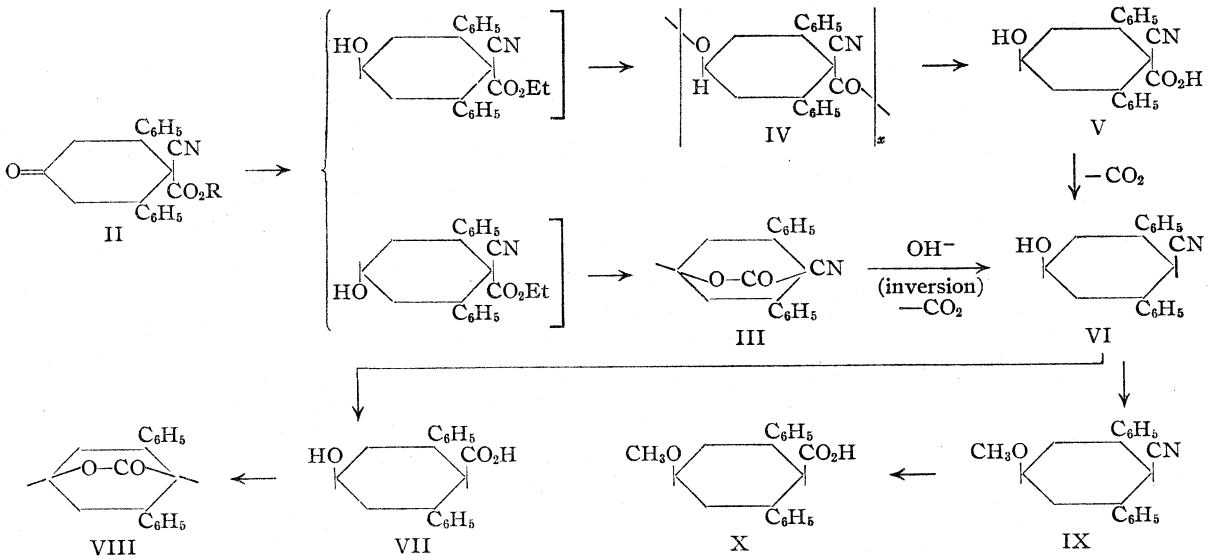
(3) Kohler and Helmkamp, THIS JOURNAL, **46**, 1018 (1924).

(4) Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 178 (1944).

(5) Perkin, *J. Chem. Soc.*, **85**, 416 (1904).

(6) Olson and Miller, THIS JOURNAL, **60**, 2687 (1938).

(7) Kohler and Jansen, *ibid.*, **60**, 2142 (1938).




decarboxylation, or during hydrolysis of the nitrile group. An exact interpretation of the site of inversion does not appear to be possible on the basis of the present facts since the configuration of the phenyl groups with respect to one another and with respect to the nitrile is not definitely known.

If one assumes, however, that the most plausible form of II is one in which the two phenyl groups and the nitrile are *cis* with respect to one another, then an inversion at carbon 4 during hydrolysis of the lactone (III) would serve to explain the foregoing data. This would, of course, necessitate the anomalous assumption that the alcohol C–O bond must have been broken, instead of the ester C–O bond.

If, on the other hand, one assumes that no inversion occurred at carbon 4, it becomes more difficult to explain why the same hydroxy nitrile (VI) was obtained by decarboxylation of the hydroxy acid (V) and the lactone (III).

Under the drastic alkaline conditions used to effect hydrolysis and decarboxylation of the lactone (III), racemization of the nitrile group of the hydroxy nitrile (VI) might be anticipated. That this clearly did not occur is probably best explained by the assumption that the two phenyl groups being in *cis* configuration hindered free approach to one side of the cyclohexane ring. Hence, in the event that an intermediate imino tautomer formed after the loss of carbon dioxide by the initial hydrolysis product of the lactone (III), the shift of the proton would probably be restricted so that retention or inversion rather than racemization would be favored.

Methylation of the hydroxynitrile (VI) was brought about by a modification of Purdie's technique for alkylating sugars,[8] in which benzene was substituted for the usual alcoholic solvent. A yield of 66% of 1-cyano-2,6-diphenyl-4-methoxycyclohexane (IX) was thus obtained. When this methoxynitrile was subjected to the same conditions used previously to hydrolyze the hydroxynitrile, no reaction occurred. Hot 50% sulfuric acid also failed to bring about a reaction, yet when the strength was increased to 75%, the hot acid appeared to cause extensive decomposition and nothing could be isolated from the mixture. Similar results were obtained with cold concentrated sulfuric acid. By refluxing the methoxynitrile (IX) for two days with saturated alcoholic potassium hydroxide, it was eventually possible to isolate a very small yield of 2,6-diphenyl-4-methoxycyclohexane-1-carboxylic acid (X). This greatly increased stability of the nitrile group following methylation of the hydroxyl is very difficult to explain since there appears to be no reason to assume that an increase in hindrance of the nitrile should occur.

The *p*-toluenesulfonic ester of the hydroxynitrile (VI) was prepared in 84% yield by modification of a procedure used previously for preparing cholesteryl *p*-toluenesulfonate.[9] This ester appeared to be completely inert in the presence of boiling methanol[10] which would have been expected to bring about ether formation. The *p*-toluenesulfonate ester did react when it was refluxed in alcoholic solution with sodium methoxide to produce a small yield of $\Delta^1$- and/or $\Delta^2$-1-cyano-2,6-diphenylcyclohexene.

Acetylation of the hydroxynitrile gave an 85% yield of 4-acetoxy-1-cyano-2,6-diphenylcyclohexane which, oddly enough, melted in the same range, 140–143°, as both the hydroxynitrile and its *p*-toluenesulfonate. Hydrolysis of the acetoxynitrile by hot 40% aqueous sodium hydroxide gave the lactone of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid (VIII).

The hydroxynitrile reacted with phosphorus

(8) Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

(9) Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

(10) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

pentachloride and thionyl chloride in the presence of pyridine to give small yields of a chloronitrile, m. p. 150°, of unknown configuration.

## Experimental

**Ethyl 1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate (II, R = $C_2H_5$).**—One hundred and three grams (0.44 mole) of recrystallized dibenzalacetone, m. p. 110–111°, and 58.6 g. (0.52 mole) of ethyl cyanoacetate were mixed with 1500 cc. of dry ethyl ether in a 2000-cc. Erlenmeyer flask and the mixture swirled until maximum solution had been effected.

A solution of sodium ethoxide was prepared by allowing 1.5 g. of clean, freshly-cut sodium to react with 50 cc. of absolute ethanol, then diluting with 50 cc. of dry ether.

While the ether mixture of the reactants was swirled, the sodium ethoxide solution was added dropwise intermittently until the tendency toward turbidity had ceased and a clear yellow solution resulted (10–20 cc. of catalyst solution was usually required). The reaction mixture became warm at this point, and small, feathery, white needles began to form. Additional catalyst solution was added dropwise with swirling, and the mixture transferred to a beaker. Under continued stirring, the mixture set up to a semi-solid mass. This was diluted with about 200 cc. of dry ether, stirred again, then set aside for thirty minutes in the ice-box. The solid was collected on a filter, pressed by a rubber dam, and finally washed twice with dry ether. The white material, after air-drying overnight, weighed 116 g., a yield of 76%, m. p. 132–134°. When the ethereal filtrate was concentrated, a second crop of solid weighing 18 g. was obtained, bringing the over-all yield to 134 g., or 88% of theoretical. Complete removal of solvent from the mother liquor left a thick brown oil weighing 17 g.

After two recrystallizations of a portion of the first crop from absolute ethanol, the melting point remained constant at 137–138°. The white compound failed to take up bromine, indicating that ring closure must have occurred.

*Anal.*[11] Calcd. for $C_{22}H_{21}O_3N$: C, 76.08; H, 6.06; N, 4.03. Found: C, 76.08; H, 5.94; N, 3.97.

The infrared absorption spectra[12] showed a very weak band at 2250 cm.$^{-1}$, the nitrile region, and strong bands at 1724 cm.$^{-1}$ and 1736 cm.$^{-1}$, the keto and ester group regions, respectively.

**1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic Acid (II, R = H).**—To a solution of 173 g. (0.5 mole) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate in 2 l. of hot ethanol, there was added 75 g. of potassium hydroxide in one liter of distilled water. The mixture was refluxed on the steam cone for nineteen hours, then the resulting wine-red reaction mixture was carefully neutralized while hot with dilute (1:2) hydrochloric acid. The clear, light yellow, neutral solution was concentrated to 2 l. and added dropwise, with stirring, to 2 l. of hot water. The mixture was warmed until most of the turbidity disappeared, then the dissolved portion was decanted from a brown, gummy insoluble residue. The gum solidified and, when dry, weighed 57 g.

The dissolved portion was treated with Darco, filtered, then added while hot to one liter of a stirred solution of dilute (1:2) hydrochloric acid. An off-white solid settled out readily and was removed on a filter, washed with water, and dried overnight at 80°. The product thus obtained melted with decomposition at 201° and weighed 66 g., a yield of 41% of theoretical.

A portion of this solid was recrystallized twice from benzene, then again from aqueous ethanol, giving a solid melting at 219–220° with rapid decomposition.

*Anal.* Calcd. for $C_{20}H_{17}O_3N$: C, 75.24; H, 5.33; N, 4.39. Found: C, 74.66; H, 5.48; N, 4.36.

1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic acid has been previously reported[3]; however, no melting point was recorded and the compound analyzed contained acetone of crystallization.

**Attempted Decarboxylation of 1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic Acid.**—Twenty-six grams (0.082 mole) of 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic acid, m. p. 208–209° dec., was heated under reduced pressure at 200–210° in an oil-bath until effervescence had ceased. The brown melt was cooled, then dissolved in ethanol and treated with Darco. A buff solid separated from the filtrate. After one recrystallization from ethanol, and two recrystallizations from benzene, this material melted with decomposition at 203–209°, indicating that it was most probably starting material. The filtrate could not be induced to yield any crystals.

**1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone (III).**—A solution of 260 g. (0.75 mole) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate in 1340 cc. of hot isopropyl alcohol was mixed while warm with 274 g. (1.34 moles) of freshly distilled aluminum isopropoxide. A gelatinous precipitate separated. The mixture, in a 3-l., round-bottomed flask, was refluxed under an 18-in. bead-packed column, mounted with a partial take-off type distillation head. Distillate was taken off slowly as reflux continued for approximately twenty-four hours, or until the distillate repeatedly failed to give a positive test for acetone with 2,4-dinitrophenylhydrazine.[4] The alcohol was then removed by distillation until the volume was reduced to about one-half that of the original. The mixture remaining was then transferred to a beaker surrounded by ice, and when cold, acidified with approximately one liter of dilute hydrochloric acid (220 cc. concentrated acid to 1100 cc. of water). The mixture was stirred and let stand until all gelatinous material had dissolved. If, at this point two layers resulted, additional isopropyl alcohol was added with stirring until only one liquid phase remained. After standing in the ice-box to allow for complete sedimentation, the liquid portion was carefully decanted, leaving a slurry of white granular crystals. This was diluted with 50% aqueous isopropyl alcohol containing some hydrochloric acid, and the solid removed on a filter. The crystals were washed on the filter, first with more acidified aqueous isopropyl, alcohol then with cold isopropyl alcohol and finally with water. The product, after drying at 80° for three hours, was a fine white crystalline powder, m. p. 226–227°, weighing 110 g. or 48.5%. Recrystallization from acetone gave a solid melting at 227–228°.

*Anal.* Calcd. for $C_{20}H_{17}O_2N$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.45; H, 5.63; N, 4.74.

The infrared absorption spectra showed a very weak band at 2265 cm.$^{-1}$, the nitrile region, and a strong band at 1766 cm.$^{-1}$, the lactone region.

In a run similar to the one above, the decanted solution was combined with washings and then concentrated until two layers formed. These were separated and the bottom layer extracted twice with benzene. The top layer was diluted with benzene, then separated. The combined benzene extract was washed with water, with dilute hydrochloric acid, then with dilute sodium hydroxide solution, and finally with water again. The extract was separated, stirred with anhydrous sodium sulfate, then boiled with Darco, and filtered while hot. Solvent was completely removed on the steam cone, vacuum being applied after the substance became rather viscous. A thick, light brown sirup remained, which solidified to a clear glass when cooled. All attempts to crystallize this substance failed. From 434 g. (1.25 moles) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate, there was obtained 240 g. of this non-crystalline residue.

**1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid (V).**—Two hundred and fourteen grams (0.613 mole, calculated as ethyl 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylate) of the non-crystalline residue from the reduction described above, was dissolved in one liter of 95% ethanol, a solution of 67 g. (1.2 moles) of potassium hydroxide in 100 cc. of water was added, and the mixture refluxed for two hours. The cooled reaction

(11) All microanalyses were done by the Clark Microanalytical Laboratories.

(12) We are indebted to Mrs. J. L. Johnson for the infrared absorption data and its interpretation.

mixture was acidified with concentrated hydrochloric acid, boiled with Norit, filtered and the alcohol removed. The resulting gum was washed with water to remove sodium chloride, and then dissolved in hot benzene. White granular crystals, which deposited out of the cooled solution, were removed on a filter and desiccated under vacuum. There was thus obtained 125 g. of solid, m. p. 189–190° dec., a yield of 63% of theoretical. After two recrystallizations from 25–35% aqueous ethanol, the product melted at 204° dec.

*Anal.* Calcd. for $C_{20}H_{19}O_3N$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.36, 74.99; H, 5.74, 5.50; N, 4.36.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and strong bands at 1750 cm.$^{-1}$ and 3445 cm.$^{-1}$, the carboxyl and hydroxyl regions, respectively. The lower melting product, 189–190° dec., showed extra bands at 2260 cm.$^{-1}$, 1717 cm.$^{-1}$, and 3362 cm.$^{-1}$. Removal of solvent from the mother liquor left a viscous brown oil weighing 61 g.

**Attempted Hydrolysis of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone.** (A).—Two grams (0.007 mole) of the δ-lactone was dissolved in a solution of 10 g. of potassium hydroxide in 100 cc. of ethanol. After being boiled with Norit, the solution was filtered and mixed with 200 cc. of water, cooled and added with stirring to 300 cc. of 1:5 hydrochloric acid. The milky suspension which resulted was allowed to settle overnight in the ice-box. A white solid separated and this was removed on a filter and air-dried. The solid, weighing approximately 1 g., was recrystallized from ethanol, giving well-defined crystals, m. p. 225–226°. A mixed melt with the starting material showed no depression.

In the absence of potassium hydroxide, 2 g. of crystalline δ-lactone failed to dissolve in 100 cc. of ethanol.

(B).—Approximately 1–2 g. of the δ-lactone was powdered and dissolved with stirring in cold concentrated sulfuric acid. Careful dilution of this solution with water gave a white precipitate which was removed on a filter. The solid thus obtained, after being washed with water and air-dried, melted at 225° and showed no depression in a mixed melt with the starting material.

**1-Cyano-2,6-diphenyl-4-hydroxycyclohexane (VI)** (A).—One hundred grams (0.33 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone was refluxed with 1000 g. of 40% aqueous sodium hydroxide for three hours. At the end of the heating period, ammonia was first noted at the top of the reflux condenser. The reaction mixture was allowed to cool and the hardened organic layer was separated and washed with water. The solid was dissolved in ethanol, and the hot solution was treated with Darco, then filtered. Chilling brought out granular crystals which were removed on a filter and dried by vacuum desiccation. Sixty-three grams of solid, melting at 130–135°, and a second crop of 10 g., melting at 140–142°, were obtained. The total of 73 g. represents a yield of 80% of theoretical. Recrystallization of the solid from ethanol gave well-defined crystals, melting at 143–144°.

*Anal.* Calcd. for $C_{19}H_{19}ON$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.20; H, 6.70; N, 5.15.

The infrared absorption spectra showed a weak band at 2260 cm.$^{-1}$, the nitrile region, and a strong band at 3440 cm.$^{-1}$, the hydroxyl region.

Following the above method it was sometimes observed that the product resulting showed a melting range of 120–125°. Thus, in a representative case, there was obtained from 150 g. (0.495 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone, 109 g. of solid melting at 120–125°, a yield of 80%. Recrystallization of this from 95% ethanol gave granular crystals melting at the same temperature. Doubling the volume of ethanol was without effect, so the solution was made alkaline with 2–5 g. of potassium hydroxide, boiled with Darco and filtered. The solid which was deposited melted in the same range, 120–125°.

The investigation of other solvents failed to indicate one better than ethanol.

(B).—A solution of 16 g. (0.05 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, m. p. 202° dec., in 125 cc. of crude quinoline was refluxed for one hour to effect decarboxylation. The cooled reaction mixture, after acidification with 500 cc. of 1:1 hydrochloric acid, was extracted twice with benzene and the resulting benzene extracts combined and treated with Norit. Following filtration, the solvent was removed, leaving a brown oil which was dissolved in ethanol and treated with Norit and Darco, then filtered. From the chilled solution there was obtained 6 g. of crystals, m. p. 142–143°, and a second crop of 1 g., m. p. 122–125°. The total of 7 g. represents a yield of 50% of theoretical.

**2,6-Diphenyl-4-hydroxycyclohexane-1-carboxylic Acid** (VII).—A mixture of 70 g. (0.23 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone, and 1000 g. of 40% aqueous sodium hydroxide was refluxed for thirty-one hours. At the end of the heating period, *i.e.*, when ammonia ceased to be evolved, a gummy upper layer remained in the flask. This solidified when cool and was removed, washed with water and dissolved in ethanol. After being filtered, the warm solution was carefully neutralized with hydrochloric acid, then boiled, and again filtered to remove sodium chloride.

The alkali portion of the original reaction mixture was diluted with an equal volume of water, then carefully acidified with concentrated hydrochloric acid. The resulting solid was removed on a filter, and the wet cake, consisting chiefly of hydrated silica, was extracted with hot ethanol. After removal of the ethanol-insoluble material on a filter, the solution was combined with the one prepared initially.

The alcoholic solution was boiled with Norit, filtered, then concentrated somewhat to insure ease of crystallization. Chilling brought out fine, white needles, which were removed on a filter and dried in a vacuum desiccator. A second crop of crystals was obtained by concentrating and chilling the mother liquor. The first crop, weighing 58 g., melted at 172–173° dec., and the second crop, weighing 6 g., melted at 157–168° dec. The total of 64 g. represents a 94% yield.

After two recrystallizations from water containing 10% ethanol, the solid melted at 173–174° dec.

*Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.97; H, 7.00.

The infrared absorption spectra showed strong bands at 1708 cm.$^{-1}$, the carboxyl region, and at 3365 cm.$^{-1}$, the hydroxyl region.

**2,6-Diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone** (VIII).—Twenty-five grams (0.084 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid was warmed at 135° under reduced pressure for approximately thirty minutes. The temperature was then raised to 170° for about twenty minutes (*i.e.*, until effervescence had ceased). After the light brown product had cooled somewhat, it was taken up in ethanol, decolorized with Darco, filtered and cooled until crystals formed. The white needles which deposited were removed on a filter, and the mother liquor concentrated to recover a second crop. By this means there was obtained a total of 18.5 g. of solid, m. p. 125–126°, 79% of theoretical.

After two recrystallizations from absolute ethanol, the solid melted at 126–127°.

*Anal.* Calcd. for $C_{19}H_{18}O_2$: C, 82.01; H, 6.48. Found: C, 81.95; H, 6.54.

The infrared absorption spectra showed a strong band at 1755 cm.$^{-1}$, the lactone region.

A solution of 6 g. (0.02 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 20 cc. of acetic anhydride was refluxed for five hours. The acetic anhydride was removed under reduced pressure and the solid residue dissolved in ethanol and decolorized with Norit. Fine white needles, m. p. 125°, were obtained from the cooled filtrate. A mixed melt with the δ-lactone, m. p. 125–126°, showed no depression.

To a solution of 5 g. (0.017 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 25 cc. of dry pyridine there was added, with caution, 2.6 cc. (3.84 g., 0.034

mole) of acetyl chloride. The mixture was allowed to stand overnight, then was diluted with water and extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the chloroform was removed and the residual oil dissolved in ethanol and the solution chilled. Crystals, m. p. 123°, were removed on a filter, Recrystallization from ethanol gave a solid melting at 124–125°. A mixed melt with the δ-lactone showed no depression.

To a solution of 5 g. (0.017 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 15 cc. of dry pyridine, there was added 6.85 g. (0.036 mole) of *p*-toluenesulfonyl chloride. The mixture, which became quite hot, was allowed to stand overnight. The crystalline mass which was formed was diluted with ethanol to effect solution, then enough water was added dropwise to induce recrystallization. Two and one-half grams of solid was removed on a filter and recrystallized, giving needles, m. p. 125°. A mixed melt with the δ-lactone showed no depression.

**1-Cyano-2,6-diphenyl-4-methoxycyclohexane (IX).**—The method used by Purdie and Irvine[8] in the alkylation of sugars, was followed with modification. To a solution of 10 g. (0.036 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane, m. p. 142–143°, in 100 cc. of dry benzene in a 500-cc., three-necked, round-bottomed flask, fitted with Hershberg stirrer, and cold finger-type condenser, was added 22.5 cc. (51.3 g., 0.36 mole) of methyl iodide, and 5–10 g. of a 30-g. portion of freshly prepared silver oxide. Two cubic centimeters of methanol was added, the stirrer was started, and the mixture was brought to reflux. The rest of the silver oxide was added in three or four approximately equal-sized batches at two-hour intervals. Reflux was maintained for an over-all period of ten hours.

The hot mixture was filtered to remove the silver residues, and these were washed on the filter with hot benzene, then transferred to a beaker and boiled with fresh benzene. The combined benzene extracts were decolorized with Darco, then evaporated. The residual oil was taken up in absolute ethanol, from which white plates separated immediately. Seven grams of crystalline solid, m. p. 105–106°, was obtained, a yield of 66.5%. The second crop from the concentrated mother liquor weighed less than 0.5 g. A portion of the concentrated mother liquor weighed less than 0.5 g. A portion of the product, after two recrystallizations from absolute ethanol, gave hexagonal plates, m. p. 106–107°.

*Anal.* Calcd. for $C_{20}H_{21}ON$: C, 82.43; H, 7.27; N, 4.81. Found: C, 82.38; H, 7.49; N, 4.85.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and a strong band at 1104 cm.$^{-1}$, the ether C–O region.

**Attempted Hydrolysis of 1-Cyano-2,6-diphenyl-4-methoxycyclohexane. (A).**—A mixture of 2 g. (0.007 mole) of 1-cyano-2,6-diphenyl-4-methoxycyclohexane, m. p. 103–105°, and 50 g. of 40% aqueous sodium hydroxide was refluxed for twenty-four hours. After the mixture was cooled, the organic portion was separated and dissolved in 95% ethanol, treated with Darco, and the solution filtered. The filtrate was acidified with concentrated hydrochloric acid, boiled, again filtered, and finally concentrated. A solid which separated from the chilled solution was collected on a filter, air-dried, and recrystallized from ethanol, giving material melting at 103–104°. A mixed melt with the starting material showed no depression.

(B).—Five grams (0.017 mole) of the methoxynitrile, m. p. 101–103°, was added in small portions to 50 cc. of 75% sulfuric acid at 140–150°. The mixture became orange and all the organic material appeared to disperse after one-half hour. Heating was continued, with frequent shaking, for a total of one hour. The acid mixture, when poured onto cracked ice, deposited a yellow precipitate which was removed on a filter and dissolved in ethanol. After treatment with Norit, the solution was filtered, concentrated, and the resulting oil dissolved in dilute aqueous sodium hydroxide. Acidification of the orange solution with 1:1 hydrochloric acid failed to cause any precipitation.

(C).—A mixture of 2 g. (0.007 mole) of the methoxynitrile and 76 cc. of 50% sulfuric acid was refluxed for five hours. After the mixture had cooled, the solidified organic layer was separated, dissolved in ethanol, treated with Darco and the solution filtered. Crystals which separated from the chilled concentrated solution were collected on a filter and air-dried. In this manner there was obtained approximately 1 g. of material, m. p. 102–104°, which failed to show any depression in a mixed melt with a sample of starting material.

(D).—One gram of the powdered methoxynitrile was added slowly to 50 cc. of cold concentrated sulfuric acid over a period of fifteen to twenty minutes. The solid went into solution, imparting a brown coloration to the acid. While surrounded by ice, the mixture was carefully diluted by dropping in chipped ice until precipitation occurred. The gum which resulted was dissolved in ethanol, from which it failed to crystallize. After removal of the solvent, the concentrate was warmed with dilute aqueous sodium hydroxide, and the solution obtained treated with Darco and filtered. Acidification of the alkaline filtrate failed to cause precipitation.

**2,6-Diphenyl-4-methoxycyclohexane-1-carboxylic Acid (X).**—A solution of 4 g. (0.014 mole) of 1-cyano-2,6-diphenyl-4-methoxycyclohexane in 100 cc. of saturated alcoholic potassium hydroxide was refluxed for forty-eight hours. Ammonia was evolved and a small amount of an insoluble layer formed at the bottom of the flask. The reaction mixture was diluted with an equal volume of water, acidified with concentrated hydrochloric acid, then extracted twice with benzene. After treatment of the benzene extract with Norit and filtering, the solvent was removed completely, leaving a clear yellow oil which was then dissolved in ethanol, again treated with Norit and filtered. The clear yellow solution ultimately deposited crystals which were removed on a filter and air-dried. There was thus obtained 0.5 g. of solid melting at 176–178°. After two recrystallizations from absolute ethanol, crystalline rectangular parallelepipeds melting at 186–187° were obtained.

*Anal.* Calcd. $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.18; H, 7.09.

The infrared absorption spectra showed strong bands at 1730 cm.$^{-1}$, the carboxyl region, and at 1128 cm.$^{-1}$, the ether C–O region.

***p*-Toluenesulfonate of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane.**—The procedure followed was a modification of the method used by Wallis, Fernholz and Gephart[9] for the preparation of cholesteryl *p*-toluenesulfonate. Five grams (0.018 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane was dissolved in 15 cc. of anhydrous pyridine and 6.85 g. (0.036 mole) of *p*-toluenesulfonyl chloride added. The solution immediately became hot and fumes were evolved. After standing at room temperature overnight, large needles had separated and the liquid portion had become sirupy. Absolute ethanol (about 20 cc.) was added dropwise to the stirred solution to induce crystallization again. The crystals were removed on a filter and dried by vacuum desiccation. There was thus obtained 6.5 g. of solid melting at 133–134°, a yield of 84% of theoretical.

Recrystallization from ethanol gave long white needles, melting at 140–142°. A mixture of starting material, m. p. 140–142°, and recrystallized product, showed a melting point depression of 20°. A sodium fusion test for sulfur was clearly positive.

*Anal.* Calcd. for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25. Found: C, 72.52; H, 5.68; N, 3.27.

The infrared absorption spectra showed a very weak band at 2247 cm.$^{-1}$, the nitrile region, and strong bands at 1180 cm.$^{-1}$, and 1193 cm.$^{-1}$, the sulfonyl region.

The ester was recovered unchanged after being refluxed with methanol for three hours.

**Reaction of *p*-Toluenesulfonate of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane with Sodium Methoxide.**—A solution of sodium methoxide, prepared by dissolving 1.5 g. of sodium in 30 cc. of methanol, was added to 8 g.

(0.019 mole) of the *p*-toluenesulfonate in 125 cc. of absolute ethanol, and the mixture refluxed for twenty-three hours. Glistening white plates were deposited during the reflux period. The reaction mixture, after careful acidification with concentrated hydrochloric acid, was chilled and the crystals removed on a filter. Washing of the filtered solid with water left only a small portion of water-insoluble material, which was then dissolved in ethanol and combined with the initial filtrate. As this solution, when chilled, showed a tendency to deposit more water-soluble plates, the solvent was completely removed and the residual semi-solid boiled for one-half hour with dilute aqueous sodium hydroxide solution. The organic material was separated from the cooled mixture and redissolved in ethanol, treated with Darco, filtered and finally chilled. The fine white needles resulting were removed on a filter and after air-drying, weighed approximately 1 g. The material thus obtained sintered at 185° but failed to show a definite melting point. After three recrystallizations from ethanol, a solid melting sharply at 207–208° was obtained.

*Anal.* Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.37; H, 6.44; N, 5.47.

The infrared absorption spectra of the 185° product showed twinned weak bands at 2217 cm.$^{-1}$ and 2247 cm.$^{-1}$, which indicate a conjugated nitrile group. The recrystallized material showed less of the second band at 2217 cm.$^{-1}$ and a more prominent band at 1585 cm.$^{-1}$, the conjugated phenyl frequency.

These data, together with the observation that the product reacted slowly to decolorize bromine in carbon tetrachloride, indicated that the compound was a mixture of $\Delta^1$- and $\Delta^2$-1-cyano-2,6-diphenylcyclohexene.

Similar results were obtained when the *p*-toluenesulfonates were refluxed in ethanol with sodium ethoxide for eighty minutes.

**4-Acetoxy-1-cyano-2,6-diphenylcyclohexane.**—A solution of 20 g. (0.072 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 200 cc. of acetic anhydride was refluxed for six hours. The acetic anhydride was distilled off under reduced pressure and the solid residue dissolved in ethanol, decolorized with Norit and filtered. Chilling brought out long white needles which were removed on a filter and dried by vacuum desiccation. There was thus obtained 19.5 g. of material melting at 141–142°, a yield of 85% of theoretical.

Two recrystallizations from absolute ethanol failed to raise the melting point. A mixed melt with starting material, m. p. 140–141°, showed a depression of 40°.

*Anal.* Calcd. for $C_{21}H_{21}O_2N$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.08; H, 6.55; N, 4.23.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and a strong band at 1723 cm.$^{-1}$, the ester region.

**Hydrolysis of 4-Acetoxy-1-cyano-2,6-diphenylcyclohexane.**—A mixture of 2 g. (0.006 mole) of the acetoxynitrile and 50 g. of 40% aqueous sodium hydroxide was refluxed for twenty-four hours. When the mixture had cooled, the hardened organic layer was separated, washed with water, dissolved in ethanol and the solution treated with Darco and filtered. After acidification with concentrated hydrochloric acid, the solution was boiled and again filtered. Crystals which deposited from the cooled solution were collected on a filter and air-dried. The solid thus obtained melted at 125° and showed no depression in a mixed melt with a sample of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone.

**4-Chloro-1-cyano-2,6-diphenylcyclohexane. (A).**—Four grams (0.019 mole) of phosphorus pentachloride was added to a solution of 5 g. (0.018 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 125 cc. of dry benzene, and the mixture was refluxed for twenty-four hours. The warm reaction mixture was then shaken with an equal volume of water, separated, and shaken with an equal volume of 5% aqueous sodium hydroxide. Following separation, the solution was stirred with anhydrous sodium sulfate, filtered and the solvent removed. The residual oil, after being boiled for one hour with water, was dissolved in ethanol, treated with Norit, and the solution filtered. Chilling caused the deposition of prismatic needles which were then removed on a filter and air-dried. In this manner approximately 1.5 g. of solid was separated, which, after recrystallization from ethanol, melted at 150°. The yield was 26%.

*Anal.* Calcd. for $C_{19}H_{18}NCl$: C, 77.14; H, 6.13; N, 4.74. Found: C, 77.27; H, 5.97; N, 4.68.

(B).—Two cubic centimeters (3.3 g., 0.028 mole) of thionyl chloride was added to a solution of 5 g. (0.018 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 100 cc. of dry benzene and 10 cc. of dry pyridine. A white precipitate formed immediately. During the subsequent reflux period of twenty-four hours, the white precipitate dissolved and sulfur dioxide was evolved. The reaction mixture was shaken twice with water, then filtered and the solvent removed, leaving a brown oil which was warmed with water for one hour, then separated, dissolved in ethanol, treated with Darco and the solution finally filtered. Chilling brought out a white solid which was collected on a filter and air-dried. There was thus obtained 1 g. of material melting at 143–145°, a yield of 19%. After recrystallization from absolute ethanol, the solid melted at 149–150° and showed no depression in a mixed melt with a sample of 4-chloro-1-cyano-2,6-diphenylcyclohexane.

## Summary

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane has been synthesized. An interesting case of *cis–trans* inversion during the hydrolysis and decarboxylation of a cyanolactone has been observed. 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane hydrolyzes with ease but its methyl ether requires rigorous conditions to effect hydrolysis of the nitrile group.

URBANA, ILLINOIS RECEIVED MAY 7, 1948

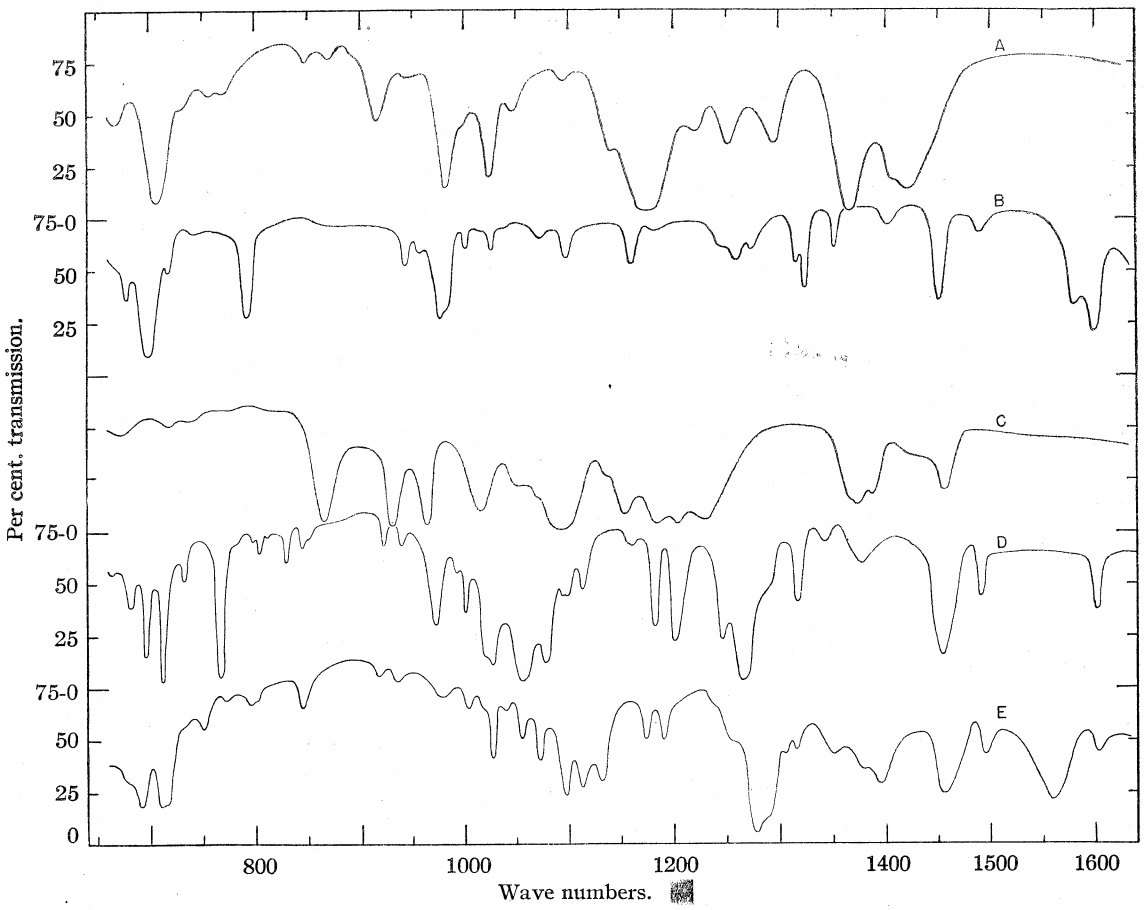
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Benzoyl Cyanide Dimer and the Addition of Benzoyl Cyanide to Aromatic Aldehydes[1]

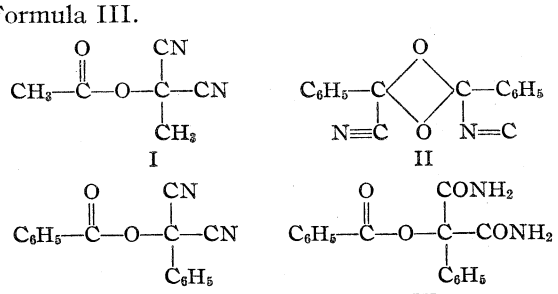
BY C. S. MARVEL, NEAL O. BRACE, FOIL A. MILLER AND AGATHA ROBERTS JOHNSON

While acetyl cyanide and benzoyl cyanide dimers are well characterized compounds, the structure of the latter has not been definitely determined. Brunner[2] assigned Formula I to acetyl cyanide dimer and this structure has been accepted by later workers.[3,4] Diels and Pillow[5] have suggested quite a different type of structure for benzoyl cyanide dimer (Formula II).

We isolated these two dimers as by-products in a reaction we were studying and became interested in their structures and the way in which they were formed. Since the formula for benzoyl cyanide dimer seemed to be less satisfactory than that of the acetyl cyanide dimer, we have re-examined this material and find that it is better described by Formula III.




Figs. 1a and b.—Infrared absorption spectra: A, acetyl cyanide [0.025 mm. liquid cell]; B, benzoyl cyanide [crystalline melt between rocksalt plates]; C, acetyl cyanide dimer; D, benzoyl cyanide dimer; E, diamide from benzoyl cyanide dimer. [These samples were prepared by grinding the crystalline compounds with paraffin oil to reduce light scattering. Absorptions due to the C–H frequencies of the paraffin oil occur at 2920, 2855, 1459 and 1378 cm.$^{-1}$ and partially mask the C–H frequencies of the compounds.]




(1) This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation in connection with the Government Synthetic Rubber Program.

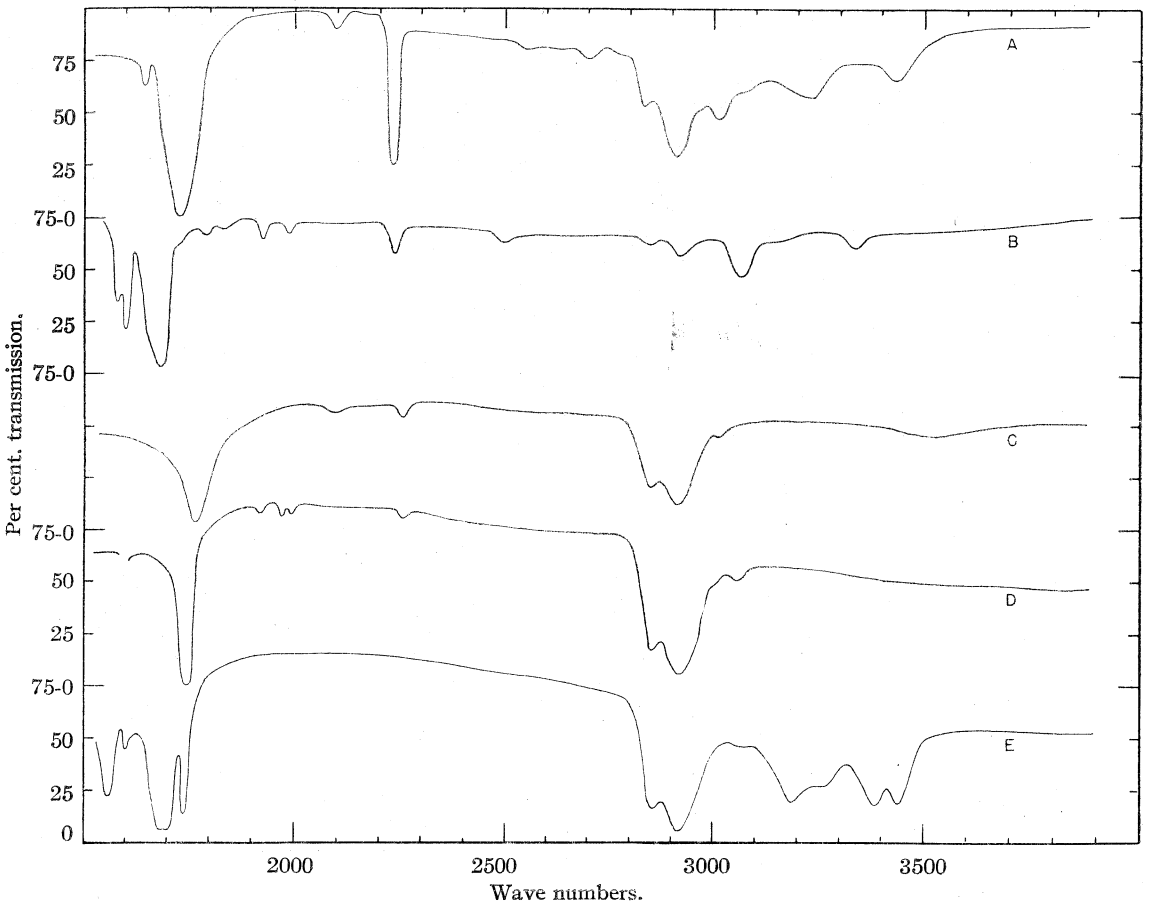
(2) Brunner, *Monatsh.*, **15**, 747 (1894).

(3) Bardroff, *ibid.*, **33**, 859 (1912).

(4) Johnson and Newton, U. S. Patent 2,395,930 (1946); *C. A.*, **40**, 4078 (1946).

(5) Diels and Pillow, *Ber.*, **41**, 1893 (1908).

Diels and Pillow[5] suggested the nitrile–isonitrile structure (II) because they obtained only a monoamide on hydrolysis. We have found that a diamide (IV) can be obtained, and it is a sharper melting compound than the monoamide previously described.[5] Bardroff[3] had similarly prepared the diamide of acetyl cyanide dimer and proved its structure. He recognized that the structure postulated by Diels and Pillow[5] for benzoyl cyanide dimer was not satisfactory, but he did not attempt to relate the structure of this compound to that of acetyl cyanide dimer.

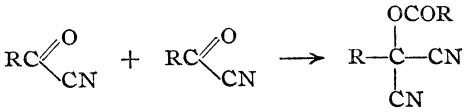



Infrared spectroscopic examination of acetyl cyanide dimer and benzoyl cyanide dimer show they are much alike in structure, and there is no evidence for a four-membered ring containing two oxygen atoms in the latter. Comparison of the spectra (Figs. 1a and b, curves C and D) of the two dimers indicates that they have analogous structures. Both show weak C≡N absorption (2256 cm.$^{-1}$) and strong C=O stretching frequencies (1746 and 1767 cm.$^{-1}$). The fact that the C=O band of the benzoyl cyanide dimer is 20 cm.$^{-1}$ lower than that of the acetyl cyanide dimer indicates that it is conjugated with the phenyl group. In the spectrum of the diamide of the benzoyl cyanide dimer (Figs. 1a and b, curve E) the C≡N absorption is absent and strong amide C=O absorption (1675–1700 cm.$^{-1}$) appears in addition to the C=O frequency found in the original compound. A complex series of N–H stretching frequencies also appear between 3190 and 3450 cm.$^{-1}$. Both these spectra (Figs. 1a and b, curves D and E) show the characteristic carbon-carbon stretching frequencies of the phenyl group, at 1493 and 1602 cm.$^{-1}$. The presence of two strong bands around 700 cm.$^{-1}$, where the mono-substituted phenyl group absorbs, indicates two types of mono-substitution, *e. g.* $C_6H_5C(=O)-$ and $C_6H_5-\underset{|}{\overset{|}{C}}-$. The remainder of the strong absorption bands in the spectra (from 800–1400 cm.$^{-1}$) are due to vibrations of C—O, C—C, C—N linkages and extensive parts of the molecules. These frequencies are too greatly affected by slight changes in structure to be of any value in interpretation.

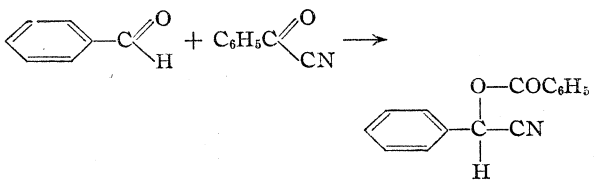
The infrared absorption curves of acetyl (Figs. 1a and b, curve A) and benzoyl (Figs. 1a and b, curve B) cyanide both show a C≡N stretching frequency at 2235 cm.$^{-1}$ and ketone C=O around 1700 cm.$^{-1}$. This is at a lower frequency in the benzoyl where it is more highly conjugated. Characteristic phenyl frequencies appear in curve

B at 1600, 1580, 1490 cm.$^{-1}$ and at 700 cm.$^{-1}$ for the mono-substituted phenyl group. As is typical of methyl ketones, except acetone, the acetyl cyanide absorbs in the $CH_3$ region (1370 cm.$^{-1}$) and has a strong band around 1170 and one between 700 and 800 cm.$^{-1}$.

The dimers thus have the structure that might be expected if one acyl cyanide molecule adds to the carbonyl group of another molecule. A reaction of this general type for acyl halides and aldehydes was reported by Adams and his students[6]



some years ago. It has now been found that benzoyl cyanide will indeed add to the active carbonyl group of an aromatic aldehyde in the presence of catalytic amounts of aqueous potassium hydroxide. This furnishes a convenient method of converting an aromatic aldehyde to the benzoate of the corresponding cyanohydrin.



The reaction works well with benzaldehyde and anisaldehyde, but thus far we have not extended it to aliphatic aldehydes or to any ketone. It is obvious that for the reaction to go well the carbonyl compound used with an acyl cyanide must have a more active carbonyl group than the acyl cyanide itself.

## Experimental

**Acetyl Cyanide Dimer and Benzoyl Cyanide Dimer.**—$\alpha$-Acetoxy-$\alpha$-methylmalononitrile was obtained by high vacuum distillation of the residue of a reaction employing acetic anhydride and aqueous potassium cyanide as clear liquid, b. p. 82° (6 mm.), which on cooling solidified to a white solid, m. p. 69°, having an odor reminiscent of hydrogen cyanide and acetic acid. The solid was crystallized from aqueous alcohol solution. Brunner[2] gives the melting point for acetyl cyanide dimer as 69°.

*Anal.* Calcd. for $C_6H_6O_2N_2$: C, 52.17; H, 4.38; N, 20.29. Found:[7] C, 52.01; H, 4.18; N, 20.28.

Similarly, $\alpha$-benzoyloxy-$\alpha$-phenylmalononitrile was obtained by high vacuum distillation of the residue of a reaction employing benzoyl chloride and aqueous potassium cyanide as a yellow, viscous liquid, b. p. 150° (1 mm.), which solidified on cooling to a white solid, m. p. 95°. The solid was recrystallized from alcohol, m. p. 95°.

*Anal.* Calcd. for $C_{16}H_{10}O_2N_2$: C, 73.30; H, 3.85; N, 10.64. Found: C, 72.76; H, 3.66; N, 10.48.

(6) Adams and Vollweiler, THIS JOURNAL, **40**, 1732 (1918); Adams and French, *ibid.*, **43**, 651 (1921); Adams and Ulich, *ibid.*, **43**, 660 (1921).

(7) We are indebted to Mr. H. S. Clark, Clark Microanalytical Laboratory, for all microanalyses reported in this communication.

**$\alpha$-Phenyl-$\alpha$-benzoyloxymalonamide.**—Two grams of $\alpha$-benzoyloxy-$\alpha$-phenylmalononitrile was placed in a 125-ml. erlenmeyer flask and dissolved in 10 ml. of concentrated sulfuric acid. As a few drops of water were added, the temperature rose to 85°. The flask was cooled in an ice-bath, and a white solid separated out as 100 ml. of water was slowly added with stirring. The solid was collected on a Buchner funnel and washed with cold water. The material was recrystallized from 100 ml. of benzene containing a small amount of alcohol. The recrystallized material, after drying at 55°, melted at 185–190°. After further recrystallization from benzene containing a little alcohol and ether, the solid melted at 203.5–204.5° (uncor.).

*Anal.* Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.60; H, 4.90; N, 9.20.

**Acetyl Cyanide and Benzoyl Cyanide.**—Acetyl cyanide was prepared from cuprous cyanide and acetyl bromide according to the directions given by Migrdichian[8] and benzoyl cyanide by the method given in "Organic Syntheses."[9]

**Benzoate of *p*-Methoxybenzaldehyde Cyanohydrin.**—Three grams (0.023 mole) of benzoyl cyanide and 3 g. (0.023 mole) of anisaldehyde were mixed in a 50-ml. glass-stoppered bottle, and 6 ml. of 10% aqueous potassium hydroxide solution was added. The bottle was shaken about ten minutes. An emulsion formed first, and later a viscous yellow oil settled out. The aqueous layer was decanted and the residual oil crystallized from alcohol. There was obtained 2.8 g. (46%) of a solid, m. p. 64–65°; the mother liquor contained additional material which did not crystallize. Recrystallization of the solid did not change the melting point.

A mixed melting point determination with an authentic sample of the benzoate of *p*-methoxybenzaldehyde cyanohydrin (m. p. 64–65°) prepared by the method of Francis and Davis[10] showed no depression. These authors gave the value of 66–67° for the melting point of this compound.

*Anal.* Calcd. for $C_{16}H_{13}O_3N$: C, 71.91; H, 4.86; N, 5.24. Found: C, 72.09; H, 4.78; N, 5.14.

**Benzoate of Benzaldehyde Cyanohydrin.**—In a 50-ml. glass-stoppered bottle were placed 2 g. (0.015 mole) of benzoyl cyanide, 1.6 g. (0.015 mole) of benzaldehyde and 6 ml. of 5% aqueous potassium hydroxide. The bottle was shaken for about fifteen minutes and a white solid ball formed. The aqueous solution was decanted, and the solid was recrystallized from alcohol. There was obtained 0.45 g. of the benzoate of benzaldehyde cyanohydrin, m. p. 59°, and 0.3 g. of a white solid, m. p. 121° (probably benzoic acid). From the mother liquor there was obtained by further evaporation 1.3 g. of solid, m. p. 54–55°, making a total yield of 49%. Recrystallization of the material melting at 59° did not change its melting point.

*Anal.* Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.03; H, 4.73; N, 5.91.

Francis and Davis[10] report the melting point of the benzoate ester of benzaldehyde cyanohydrin as 63–64°.

## Summary

Benzoyl cyanide dimer has been shown to be $\alpha$-benzoyloxy-$\alpha$-phenylmalononitrile. It is apparently formed by one molecule of benzoyl cyanide adding to the carbonyl group of another. This view is favored by the fact that benzoyl cyanide adds readily to aromatic aldehydes to give the benzoate of the corresponding cyanohydrin.

URBANA, ILLINOIS RECEIVED AUGUST 19, 1948

(8) Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corporation, New York, N. Y., 1947, p. 11.

(9) Drake, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., **24**, 14 (1944).

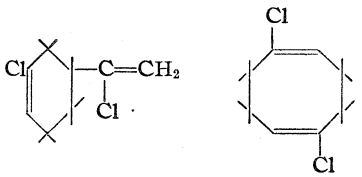
(10) Francis and Davis, *J. Chem. Soc.*, **95**, 1403 (1909).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Dimer of 2-Cyano-1,3-butadiene[1]

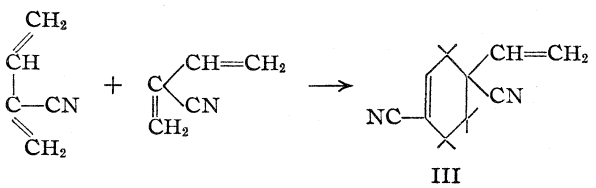
BY C. S. MARVEL AND NEAL O. BRACE

Dimerization is a reaction characteristic of 1,3-butadiene and its derivatives. Thus, it was not surprising to find that 2-cyano-1,3-butadiene on standing in an ice-box, even though picric acid was present, gradually changed to a low-melting solid. The closely related 2-chloro-1,3-butadiene has been shown to yield two dimers, the first a cyclohexene derivative (I)[2,3] and the second a cycloöctadiene derivative (II).[3] Hence we have considered similar possibilities for the structure of the dimer of the cyano derivative.

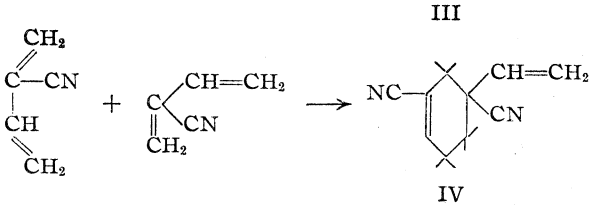


I II

Although there are several possible dimers, the Diels–Alder type of dimerization seems somewhat more probable in the case of 2-cyano-1,3-butadiene since there is present a common dieneophilic group. The Diels–Alder type of self-addition could produce either of two isomeric cyclohexene derivatives III or IV depending on the relative positions of the substituents in the final ring.



III

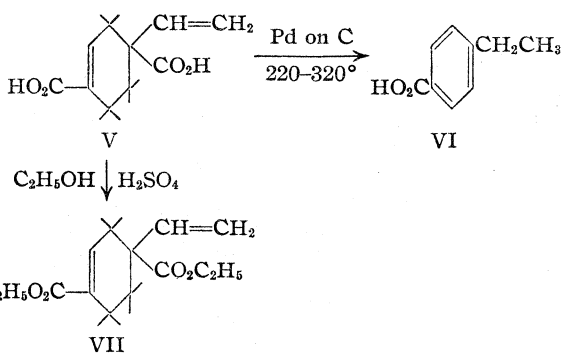


IV

The crude solid obtained from 2-cyano-1,3-butadiene, prepared by cracking the acetate of methyl vinyl ketone cyanohydrin,[4] melted at 30–40°. Purification by evaporation of monomer and crystallization of the solid residue gave long, thin plates which had a melting point of 55°. The melting point was not changed by further purification. Analysis and molecular weight determinations showed this compound was a dimer of the original diene. No other dimer was identified although small amounts may have been present in the residues.

The dimer showed two carbon–carbon double bonds by catalytic hydrogenation. The first mole of hydrogen was absorbed very rapidly and the second mole was added more slowly. Saponification with aqueous alkali gave a single acid (V) with a neutral equivalent of 100.4. This acid also contains two double bonds as shown by catalytic hydrogenation. It gave a diester (VII) with ethyl alcohol. This unsaturated dibasic acid was heated with palladium-on-charcoal containing a little copper chromite catalyst.[5] Carbon dioxide and hydrogen were evolved and a low yield of pure *p*-ethylbenzoic acid (VI) was isolated from the solid residue. No other dehydrogenation product was found.

The isolation of this acid is evidence that the dimer of 2-cyano-1,3-butadiene which we have isolated is best represented by formula III.



V VI VII

Further confirmatory evidence for the structures assigned has been obtained from the infrared spectra[6] of the dimer and of the diester (VII) (see Figs. 1a and b). The infrared absorption curves show two different nitrile absorption maxima, *i. e.*, 2220 (conjugated) and 2243 cm.$^{-1}$ (unconjugated) for the dimer of 2-cyano-1,3-butadiene (III) (curve A), and two different ester carbonyl absorption maxima, 1715 (conjugated) and 1730 cm.$^{-1}$ (unconjugated) for the diester (VII) (curve B) as well as conjugated and unconjugated double bond absorption maxima for both compounds, 1639 and 1649 cm.$^{-1}$ for the dimer (III) and 1636 and 1654 cm.$^{-1}$ for the diester (VII). A structure analogous to either of the 2-chloro-1,3-butadiene dimers (I or II) would have both nitrile groups conjugated with a double bond and would show only one absorption maximum in the nitrile

(1) This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

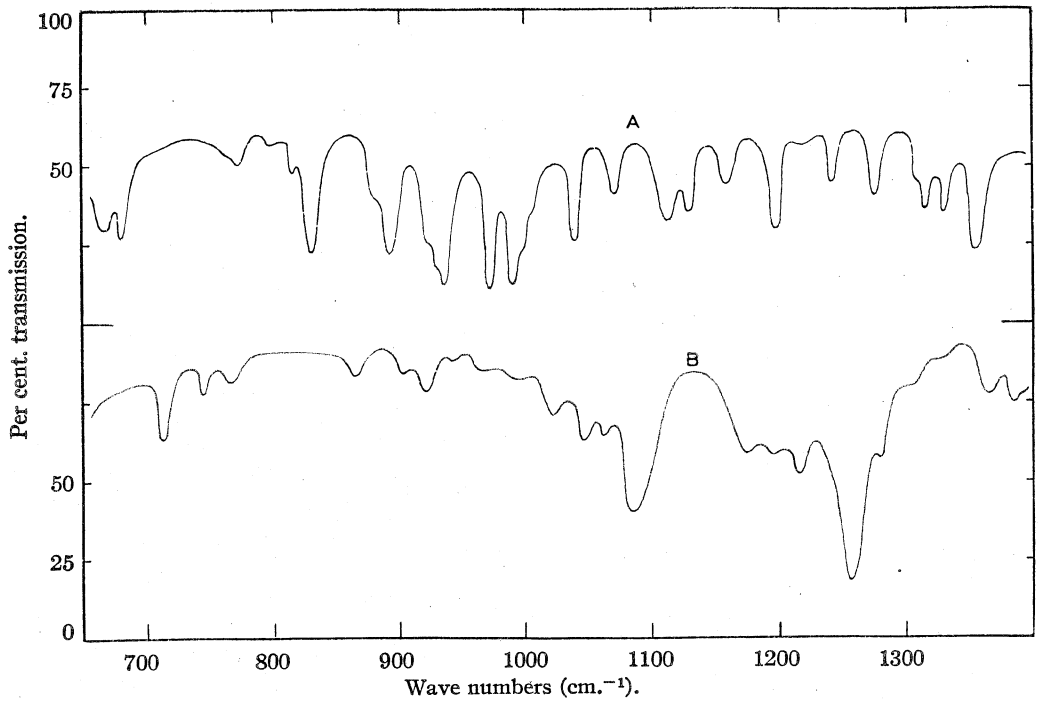
(2) Carothers, Williams, Collins and Kirby, THIS JOURNAL, **53**, 4203 (1931); Carothers, Kirby and Collins, *ibid.*, **55**, 789 (1933).

(3) Brown, Rose and Simonsen, *J. Chem. Soc.*, 101 (1944).

(4) Marvel and Brace, THIS JOURNAL, **70**, 1775 (1948).

(5) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, Boston, Mass., 1941, p. 458.

(6) We are indebted to Dr. Foil A. Miller and Mrs. J. L. Johnson for the infrared absorption curves and for their interpretation.




Infrared absorption spectra: Figs. 1a and b.—Curve A, dimer of 2-cyano-1,3-butadiene (run as crystalline melt between two rocksalt plates); curve B, diester (run as a liquid in an 0.025 mm. rocksalt cell).

frequency band of the infrared absorption spectrum.

The molar refractivity of the diester (VII) as calculated from the physical data is 0.34 higher than the figure obtained using the values given in the tables[7] for atomic refractivities. This exaltation may be attributed to one conjugated ester group but is hardly large enough to indicate two conjugated ester groups.

## Experimental

**Dimer of 2-Cyano-1,3-butadiene.**—A sample of 57 g. of 2-cyano-1,3-butadiene, containing a little picric acid as polymerization inhibitor, when stored at 5° for about three months solidified to the extent of about 75%. When warmed to room temperature the solid dissolved, but after the excess monomer was removed by distillation the residual viscous oil (*ca.* 40 g.) crystallized when cooled, m. p. range 30–40°.

In another instance, the solid residue remaining in a bottle of 2-cyano-1,3-butadiene (containing picric acid as inhibitor) which had been stored in an ice-box for about six months was scraped out and placed in a small ground-glass distilling flask. The dimer was distilled under high vacuum through an 8-in., helix-packed column. There was obtained 4.2 g. of liquid, b. p. 110–112° (1 mm.), which solidified on standing to a white solid, m. p. range 30–40°. A brown, semi-viscous liquid which remained in the flask became spongy when cooled but was interspersed with crystallites. The material darkened on standing. An analysis of the liquid, b. p. 110–112° (1 mm.), was obtained.

*Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found:[8] C, 74.46; H, 5.94; N, 16.74.

This compound was dissolved in alcohol, treated with Darco, and filtered. The filtrate was evaporated and a few milliliters of water added until the solution began to get cloudy at 50°. When cooled to room temperature, the solution was seeded with a small crystal previously isolated and placed in the ice-box. The mass of crystals which formed was collected on a Buchner funnel, washed with very dilute alcohol, and air-dried, m. p. 54–54.5°. Further similar treatment of the filtrate (omitting the Darco) yielded three more crops of crystals. The third crop, which melted over the range of 44–51°, was contaminated with some residual oil, but the fourth crop was colorless and melted at 54–55°. In another experiment crystals were obtained which melted at 55–56°. Analysis of this crystalline material, in contrast to the compound which had merely been distilled, agreed well with the theoretical for a dimer.

*Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71; mol. wt., 158.2. Found: C, 75.92; H, 6.53; N, 17.67; mol. wt. (cryoscopic) in acetic acid, 146; in benzene (ebulloscopic), 141.

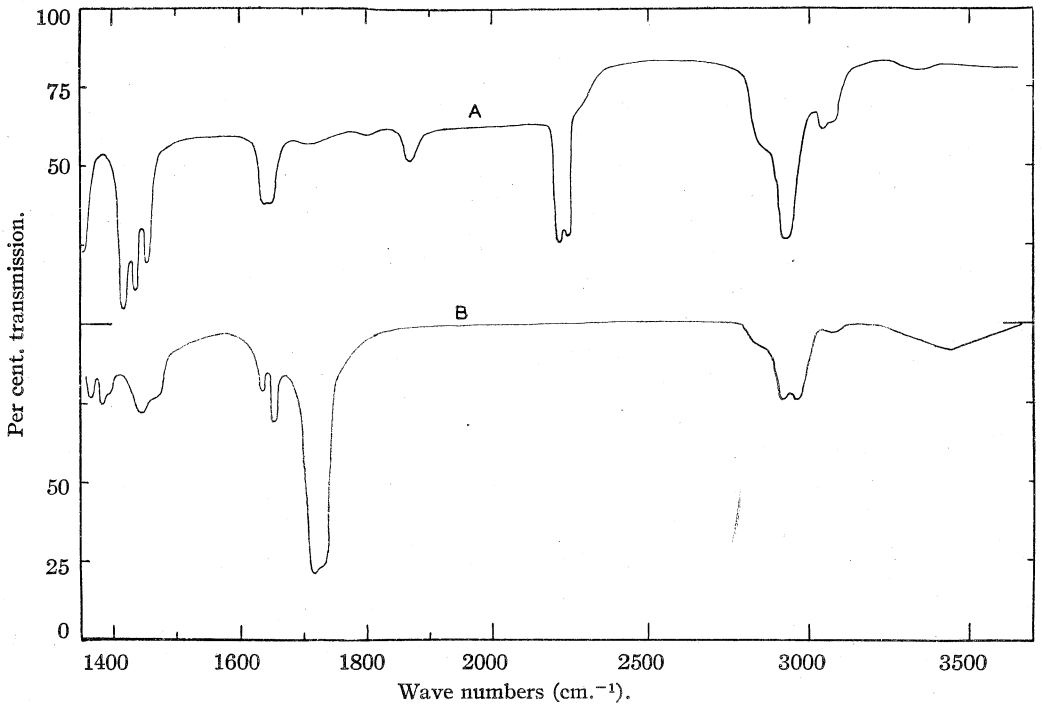
The dimer is soluble in dioxane, absolute ethanol, acetic acid, acetone, benzene and ether, gives a cloudy solution with methanol, and is insoluble in water, cyclohexane and Skellysolve B. The dimer in acetone solution decolorized dilute potassium permanganate solution rapidly.

**Hydrogenation of 2-Cyano-1,3-butadiene Dimer.**—In a ground-glass hydrogenation bottle were placed 0.1547 g. of 10% palladium-on-charcoal and 30 cc. of absolute methanol. The bottle was placed in the quantitative hydrogenation apparatus and evacuated and filled twice with hydrogen. Shaking was begun while the volume, temperature and pressure of the hydrogen was noted. The catalyst absorbed 6 cc. of hydrogen at 27° and 742 mm. pressure in seven minutes but absorbed no more hydrogen with shaking an additional twenty minutes.

The reduced catalyst was collected on a Hirsch funnel with suction and washed with 200 cc. of absolute methanol to remove the last traces of chloride ion, keeping the pyrophoric catalyst moist. The catalyst was transferred to the hydrogenation bottle, 0.3635 g. (0.00230 mole) of

(7) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 107.

(8) The microanalyses reported in this work were done by the Clark Microanalytical Laboratory, Urbana, Illinois.




recrystallized dimer (m. p. 53–55°) was added, and the solid washed down with 30 cc. of absolute methanol. The bottle was placed in the hydrogenation apparatus, evacuated and filled with hydrogen three times, and shaking was begun at 28° and 742 mm. In seven minutes the compound absorbed 58 cc. of hydrogen. This is the amount required by 0.00230 mole for one double bond. The hydrogenation rate then became slower, and a total of 116 cc. of hydrogen (30° and 742 mm.) was absorbed by the compound over a period of seven hours. The amount calculated for 0.00230 mole for two double bonds is 117.0 cc. at 29° and 742 mm.

The catalyst was filtered and the methanol evaporated. The residue was taken up with 95% ethanol and heated on the water-bath at 50° while water was added drop by drop until the solution began to get cloudy. The solution was placed in the ice-box. The reduced material separated as an oil. No crystalline isomer was separated from the mixture.

**Saponification of the Dimer of 2-Cyano-1,3-butadiene.**—Four and one-half grams (0.0286 mole) of the crude solid was heated under reflux with 6.7 g. (0.12 mole) potassium hydroxide in 30 cc. of water. During the heating ammonia was liberated. An additional 0.5 g. of potassium hydroxide was added and refluxing was continued for four hours. No more ammonia could be detected at the top of the reflux condenser. One gram of Darco was added to the resulting orange solution and the mixture was then filtered. The solution was cooled in ice and acidified with 50% sulfuric acid. The precipitated acid was collected on a Buchner funnel, redissolved in 95% ethanol, and concentrated some by evaporation. Then water was added and the solution was allowed to crystallize at room temperature. The first crop of crystals, silvery-white leaflets, amounted to 0.3 g.; m. p. 235–236° (sintered 230°). By further evaporation of the filtrate and crystallization from dilute alcohol solution a total of 2.6 g. of solid (*ca.* 50%), m. p. 235–236°, was collected. A portion of material was lost.

In a second experiment 3.6595 g. of the dimer was saponified by heating with 15 g. of sodium hydroxide in 50 cc. of water over a period of fourteen and one-half hours. The alkaline solution was added slowly with very rapid stirring to a solution of 41.5 cc. of 12 *N* hydrochloric acid and 50 cc. of water in a 250-cc. beaker. The precipitated acid was collected on a Buchner funnel, washed with distilled water and dried in an oven at 55° for two hours, m. p. 231–232° (sintered 229°). The yield was 3.0881 g. or 70.5%. The acid was recrystallized from alcohol–water solution, m. p. 235°.

*Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17; neutral. equiv., 98.1. Found: C, 60.80, 60.73; H, 6.11, 6.34; neutral. equiv., 100.4.

This acid was soluble in alcohol and hot water, and sparingly soluble in ether, benzene and acetone. It decolorized dilute potassium permanganate solution when dissolved in 95% ethanol. It did not decolorize bromine in carbon tetrachloride solution.

**Determination of the Number of Double Bonds in the Unsaturated Acid by Hydrogenation.**—A hydrogenation apparatus designed to measure quantitatively the amount of hydrogen taken up by an unsaturated compound was used in this experiment. There were placed in the reduction bottle 50 cc. of absolute ethanol, 0.5 g. of 10% palladium-on-charcoal and 0.1962 g. (0.001 mole) of the unsaturated acid. The system was evacuated and filled with hydrogen twice, the volume of hydrogen at 737 mm. and 23.8° was noted and shaking begun. In one minute 53.5 cc. of hydrogen was absorbed before stopping the shaker. The gas buret was refilled and shaking was resumed. In the next hour and twenty minutes, 42.9 cc. of hydrogen at 23° and 742 mm. was absorbed, making a total of 96.4 cc. of hydrogen.

In a blank determination, 0.500 g. of 10% palladium-on-charcoal in 50 cc. of absolute alcohol took up 40 ± 2 cc. of hydrogen at 22° and 749 mm. pressure. This is equivalent to 42 cc. at 742 mm. and 23°. In other words, the unsaturated compound itself absorbed 54 ± 2 cc. of hydrogen. The amount calculated for two double bonds is 50.0 cc. at 23.8° and 742 mm.

**Dehydrogenation of the Unsaturated Acid with Palladium-on-Charcoal.**—In an 18 × 150 mm. Pyrex test-tube were placed 1.00 g. (0.00510 mole) of the unsaturated acid, 0.100 g. of 10% palladium-on-charcoal catalyst, and 0.01 g. of copper chromite catalyst. The materials were mixed and the test-tube closed with a one-hole rubber stopper fitted with a 6-in. length of glass tubing. The tube was connected by means of rubber tubing to a U-shaped capil-

lary glass tubing immersed in a pan of water and extending part way up into a 50-cc. buret filled with water and standing in the water.

The evolved gas was collected in the buret and the volume, temperature, and pressure of the gas noted as the dehydrogenation was carried out. As one buret became filled with gas another was put in its place.

The test tube was placed in a Wood's metal-bath heated with a Bunsen burner to an initial temperature of 220°. Gas bubbles began to appear after a few minutes of heating and, as they began to slacken, the temperature of the bath was raised over a period of four hours. The final temperature was 320°. A total volume of 163.5 cc. of gas at standard temperature and pressure (corrected for water vapor pressure) was collected. The theoretical amount of hydrogen at standard temperature and pressure is 114 cc. for 0.00510 mole. An equal amount of carbon dioxide should be evolved, and this explains the excess over the theory for hydrogen. Most of the carbon dioxide was lost by solution in the water over which the gas was collected.

The residue in the test-tube was extracted with ether. The ether solution was filtered and evaporated. The oily residue solidified on cooling. It was dissolved in alcohol, treated with Darco, and filtered. Two successive attempts at crystallization by adding water to the hot solution and cooling yielded only gummy precipitates. The alcohol solution was transferred to a 10-cc. distilling flask, the alcohol removed, and the residue subjected to distillation at reduced pressure. Only a drop or two collected in the side-arm (b. p. 145–150° (19 mm.)), but when the distilling flask cooled, solid crystals appeared on the sides. The crystals, which were removed, amounted to 0.053 g., m. p. 98–105°. After recrystallization from alcohol–water solution, the melting point was 112°. The literature gives 110–111°[9] and 112–113°[10] for the melting point of *p*-ethylbenzoic acid. *m*-Ethylbenzoic acid is reported to melt at 47°.[11]

*Anal.* Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.50; H, 6.99.

**Esterification of the Unsaturated Dibasic Acid.**—In a 50-cc., ground-glass, round-bottom flask attached to a 2-ft., water-cooled condenser were placed 0.98 g. (0.005 mole) of the unsaturated acid (m. p. 235°), 5 cc. of absolute alcohol (0.085 mole) and 2 drops of concentrated sulfuric acid. The reactants were refluxed on the steam-bath for four hours. Then 10 cc. of benzene was added, the water-cooled condenser replaced by a 10-in. Vigreux column and a total reflux-partial take-off head and the solution heated under practically total reflux as the azeotropic mixture of alcohol, benzene, and water was taken off at 65–72° over a period of four and one-half hours. The remaining traces of benzene and alcohol were removed by distillation under water pump pressure.

The residue was dissolved in 50 cc. of distilled ether and washed three times with 15-cc. portions of 5% aqueous potassium hydroxide solution, dried over anhydrous sodium sulfate, filtered, and distilled under reduced pressure in a 10-cc. distilling flask. The ester boiled at 131–133° (3 mm.) and amounted to 15–20 drops; $n^{20}D$ 1.4801[12]; $d^{20}_4$ 1.0639[12]; $M_D$ calcd. 67.04; $M_D$ found 67.38 (exaltation of 0.34).

The ester was soluble in alcohol, ether and chloroform. It was insoluble in dilute potassium hydroxide and 10% sodium bicarbonate solution. The ester decolorized dilute aqueous potassium permanganate solution but did not decolorize bromine in chloroform solution.

*Anal.* Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.54; H, 7.95.

Acidification of the potassium hydroxide wash solution with concentrated hydrochloric acid gave 0.128 g. of recovered acid, m. p. 233–234°.

## Summary

2-Cyano-1,3-butadiene dimerizes on standing at 5° in the presence of a trace of picric acid to yield a solid whose structure is that of the Diels–Alder condensation product, 1-vinyl-1,4-dicyano-$\Delta^4$-cyclohexene. Proof of the six-membered ring structure was obtained by converting the dimer to an unsaturated dibasic acid which was dehydrogenated and decarboxylated to *p*-ethylbenzoic acid.

The infrared absorption spectra of the dimer and of the diester prepared from it indicate the presence of a conjugated and an unconjugated nitrile group and ester group, respectively, thus confirming the structure assigned on the basis of degradation. No evidence for an eight-membered dimer was noted. Smaller amounts of other dimers may have been lost in working up the mixture.

(9) Fittig and König, *Ann.*, **144**, 290 (1867).

(10) Aschenbrandt, *ibid.*, **216**, 218 (1882).

(11) "Handbook of Chemistry and Physics," 29th ed., Chemical Rubber Publishing Company, Cleveland, Ohio, 1945, p. 640.

(12) These data determined by Clark Microanalytical Laboratory, Urbana, Illinois.

Urbana, Illinois Received August 30, 1948

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[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

# Orthoesters and Related Compounds from Malono- and Succinonitriles

By S. M. McElvain and Juel P. Schroeder[1]

The study of the preparation of orthoesters from nitriles, which has been in progress for some time in this Laboratory[2] in connection with work on the ketene acetals, has been extended to malono- and succinonitriles. The present paper reports the preparation and alcoholysis of the various iminoester hydrochlorides that may be obtained from these dinitriles and describes certain related products resulting from these reactions.

(1) Wisconsin Alumni Research Foundation Research Assistant, 1946–47; University Fellow, 1947–48.

(2) McElvain and (a) Nelson, This Journal, **64**, 1825 (1942); (b) Clarke, *ibid.*, **69**, 2661 (1947); (c) Stevens, *ibid.*, **69**, 2663 (1947).

Treatment of each of these dinitriles with equivalent amounts of methanol and hydrogen chloride gave the monoimino salts (I and III) readily and methanolysis of these salts gave good yields of the corresponding cyanoörthoesters (II and IV). In the case of II it was necessary to remove all traces of acid from the reaction product with aqueous sodium carbonate solution before distillation to prevent the pyrolysis of the orthoester to cyanoketene dimethylacetal.

Attempts to convert II to the corresponding iminoester with equivalent amounts of methanol

$$CH_2(CN)_2 \xrightarrow{94\%} CNCH_2C(OCH_3)=NH_2Cl \xrightarrow{65\%} CNCH_2C(OCH_3)_3$$
I II

$$(CH_2CN)_2 \xrightarrow{80\%} CN(CH_2)_2C(OCH_3)=NH_2Cl \xrightarrow{77\%} CN(CH_2)_2C(OCH_3)_3$$
III IV

and hydrogen chloride gave none of the iminoester hydrochloride but instead the corresponding normal esters in the yields shown

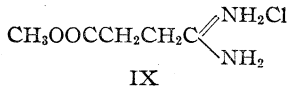
$$II \xrightarrow[HCl]{CH_3OH} \underset{73\%}{CNCH_2COOCH_3} + \underset{21\%}{CH_2(COOCH_3)_2} + \underset{18\%}{NH_4Cl}$$

It appears that most of the hydrogen chloride was consumed in cleavage of II to the cyano-ester, methanol and methyl chloride before it reacted with nitrile and methanol to give the iminoester hydrochloride. The orthoester IV showed a similar tendency to be cleaved by hydrogen chloride prior to reaction of the nitrile group. In an attempt to prepare the diorthoesters directly from the dinitriles, each of the latter was dissolved in sufficient methanol to retain the intermediate salts (I and III) in solution and treated with two equivalents of hydrogen chloride. From these reactions also normal esters were the sole reaction products.

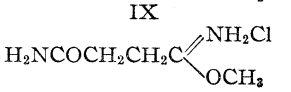
These results indicate that orthoesters of malonic and succinic acids cannot be prepared by a stepwise alcoholysis of the corresponding nitriles. Consequently, their preparation from the di-iminoester hydrochlorides was undertaken. The preparation of diethyl iminomalonate dihydrochloride (VI) in high yields has been reported[3] from the reaction of malononitrile with equivalent amounts of ethanol and hydrogen chloride *in ether solution*. This preparation could not be duplicated in the present work using either methanol or ethanol; instead, the only reaction products obtained were the monohydrochlorides corresponding to I or mixtures of the mono and dihydrochlorides, which precipitated from the reaction mixture. However, the preparation of the di-iminoester salt (VI) in quantitative yield was accomplished by treating the nitrile and alcohol in dioxane solution with a large excess of hydrogen chloride. The melting point of VI (119–120°) so obtained did not correspond to that (138°) previously reported,[3a] but its structure was shown beyond doubt by its halogen content and by its pyrolysis to ethyl chloride (93%) and malonamide (81%). Attempts to prepare the homologous methyl iminoester salt by this procedure gave a mixture of I and V. However, the use of a mixture of chloroform and dioxane as solvent gave V in reasonably pure form. The preparation of the di-iminoester salt VIII from succinonitrile has been reported.[4] Both VII and VIII were readily prepared in practically quantitative yields in the present work using dioxane as a solvent.

$$ClNH_2=(RO)C(CH_2)_nC(OR)=NH_2Cl$$

V. R is $CH_3$, $n$ is 1
VI. R is $C_2H_5$, $n$ is 1
VII. R is $CH_3$, $n$ is 2
VIII. R is $C_2H_5$, $n$ is 2



IX



X

Methanolysis of VII by the procedures used for the cyanoörthoesters II and IV gave dimethyl succinate (45%), ammonium chloride (57%), and β-carbomethoxypropionamidine hydrochloride,[5] IX (36%). The structure of the latter compound was proved by the following synthesis, which eliminates the alternative isomeric structure (X) that might conceivably be a product of this reaction.

$$CH_3OOCCH_2CH_2CN \xrightarrow[HCl]{CH_3OH} CH_3OOCCH_2CH_2C(OCH_3)=NH_2Cl \xrightarrow{NH_3} IX$$

Alkaline hydrolysis converts the amidine salt (IX) to ammonia and succinic acid; acid hydrolysis converts it to β-carboxypropionamidine, which, as the free base, appears to exist as an inner salt, judging from its high melting point and insolubility in water and other inert solvents.

An attempt to prepare the free base from the di-iminoester hydrochloride VII furnished some insight into the mechanism by which IX is formed during the alcoholysis of VII. When VII was treated with an excess of aqueous sodium bicarbonate solution, a clear solution[6] resulted and only one of the hydrochloride functions was decomposed, as shown by the amount of carbon dioxide evolved. When this solution was acidified and subjected to mild hydrolysis for several hours, β-carboxypropionamidine (56%), succinimide (25%) and succinic acid (12%) were isolated. From these results it would appear that the bicarbonate converted VII to a monohydrochloride VIIa, which by loss of methanol passed into the cyclic amidino-ester hydrochloride (VIIb), the structure of which accounts for the failure of the weaker alkali to neutralize but one of the hydrochloride functions of VII as well as the water-solubility of the resulting product. The compounds isolated from the acidic hydrolysis of the half-

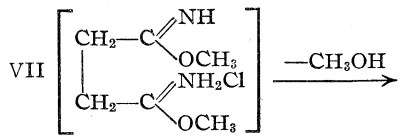
(3) (a) Houben and Blaise, Houben, "Die Methoden der organischen Chemie," 3rd Ed., Vol. VI, p. 436; (b) Kenner, Lythgoe, Todd and Topham, *J. Chem. Soc.*, 574 (1943).

(4) Pinner, *Ber.*, **16**, 352 (1883). No yield of VIII was reported; this method used ether as a solvent and it started with a two-phase system (succinonitrile is sparingly soluble in ether) which was reported to change, as the hydrogen chloride was absorbed, to a homogeneous solution, from which the salt finally precipitated.

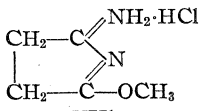
(5) Pinner, ref. 4, noted the concurrent formation of an amidine salt and an ester during the pyrolysis of ethyl iminoformate hydrochloride.

(6) With sodium hydroxide solution a resinous product was precipitated; Pinner (ref. 4), who attempted to isolate the free base of VIII with similar results, assumed that the clear solution obtained was due to the water solubility of the free base.

neutralized solution of VII would be expected from the intermediate cyclic salt VIIb. From these observations it seems reasonable to conclude that IX is formed during the methanolysis of VII *via* the intermediate iminoester VIIb.



VIIa



VIIb

The isolation of normal esters instead of orthoesters in the above alcoholyses indicated that the latter esters were being destroyed during the removal of the alcohol from the alcoholysis solution prior to the alkaline wash. This supposition was confirmed when the two orthoesters XI and XII were obtained by the procedure[2b] in which the solution, resulting from the alcoholysis of VII, was neutralized with sodium methoxide prior to the removal of the alcohol. In this manner methyl ortho-β-carbomethoxypropionate (XI) and methyl orthosuccinate (XII) were obtained in 11 and 15% yields, respectively.

$CH_3OOCCH_2CH_2C(OCH_3)_3$ XI $(CH_3O)_3CCH_2CH_2C(OCH_3)_3$ XII

The ester XI, which may be obtained in much higher yield (63%) from methyl β-cyanopropionate, is a liquid with marked stability to heat; for example, no change was noted in a sample after refluxing (b. p. 210°) for one and one-half hours. This is in marked contrast to the β-cyano-orthoester (IV) which slowly but steadily loses methanol under similar conditions. The di-orthoester XII is a crystalline solid, m. p. 50–51°. It loses methanol slowly on heating and is converted to a high-boiling, viscous oil which was not studied further.

An attempt was made to obtain the diorthoester XII from the trichloroörthoester XIII, which was prepared in good yields from γ,γ,γ-trichlorobutyronitrile. However, XIII failed to undergo a replacement reaction with sodium methoxide; instead it was dehydrohalogenated to a product which gave analytical data approximating those calculated for the structure XIV.

$$\underset{\text{XIII}}{Cl_3CCH_2CH_2C(OCH_3)_3} \xrightarrow{NaOCH_3} \underset{\text{XIV}}{ClC{\equiv}CCH_2C(OCH_3)_3}$$

The preparation of ethyl orthocarbethoxyacetate (XV), a malonic ester corresponding to XI, was accomplished from ethyl cyanoacetate using the same procedure that proved successful for II.[7]

(7) In this connection it is of interest to note that Reitter and Weindel (*Ber.*, **40**, 3358 (1907)) reported that the alcoholysis of ethyl carbiminoethoxyacetate hydrochloride yielded carbethoxyketene diethylacetal instead of the expected orthoester (*cf.* also ref. 10).

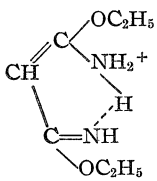
However, the alcoholysis of the diiminoester hydrochloride VI by the procedure that produced XI and XII in the succinic series failed to yield either XV or ethyl orthomalonate (XVI). Instead, ethyl malonate, carbethoxyacetamide, ethyl cyanoiminoacetate (XVII) and ethyl orthocarbiminoethoxyacetate (XVIII) were the products isolated from the reaction.

$C_2H_5OOCCH_2C(OC_2H_5)_3$ XV $(C_2H_5O)_3CCH_2C(OC_2H_5)_3$ XVI

$CNCH_2C(OC_2H_5){=}NH$ XVII $CNCH{=}C(OC_2H_5){-}NH_2$ XVIIa

$HN{=}(C_2H_5O)CCH_2C(OC_2H_5)_3$ XVIII

A singular feature of this alcoholysis was the separation of only 50–55% of the expected ammonium chloride, regardless of the time (twenty to one hundred thirty hours) allowed for the alcoholysis. However, the alcoholic solution from which the ammonium chloride was filtered still contained sufficient hydrochloride salt to require 0.5 of an equivalent of sodium ethoxide (25%) for neutralization after correction for the dissolved ammonium chloride. This fact, the relatively low yield of ammonium chloride, together with the isolation of such products as XVII and XVIII, suggest that a considerable portion of the dihydrochloride VI, which is very insoluble in alcohol, is converted to a more soluble monohydrochloride,[8] which resists alcoholysis by virtue of the resonance stabilization of the ene-amine form of its cation



The neutralization of this cation by sodium ethoxide would produce XVII.[9] The iminoesterorthoester (XVIII) could be formed by the partial alcoholysis of VI and possibly also by the slower alcoholysis of the above cation of the monohydrochloride.

The exaltation of the molar and specific refractivities of ethyl cyanoiminoacetate indicate that it exists in the ene-amine from (XVIIa) as does the corresponding carbiminoethoxyester,[10] $C_2H_5OOC{-}CH{=}C(OC_2H_5)NH_2$.

(8) This conclusion is indicated by the fact that the dihydrochloride (21.5 g.) goes into solution immediately when treated with the same amount (250 ml.) of alcohol containing sufficient pyridine (7.4 g.) to neutralize one of the hydrochloride functions. One reaction by which a monohydrochloride might be formed during alcoholysis is through cleavage of an orthoester by the dihydrochloride: $RC(OC_2H_5)_3 + CH_2(C(OC_2H_5){=}NH_2Cl)_2 \rightarrow RCOOC_2H_5 + C_2H_5Cl + C_2H_5OH + HN{=}(C_2H_5O)CCH_2C(OC_2H_2){=}NH_2Cl$. This reaction is under investigation in this Laboratory.

(9) Neutralization of the dihydrochloride (VI) with sodium ethoxide yields XVII also; with aqueous sodium carbonate, however, VI is converted to diethyl iminomalonate.

(10) Glickman and Cope, This Journal, **67**, 1017 (1945).

TABLE I

IMINOESTER HYDROCHLORIDES, $RC(OR')=NH_2Cl$

| R is | R′ is | Nitrile, moles | Solvent, ml. | | HCl used, moles | Yield, %, in (days) | Formula | Anal., % ionic Cl Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|
| $CNCH_2$ | $CH_3$ (I) | 1.5 | Ether | 850 | 1.6 | 87 (1) | $C_4H_7ClN_2O$ | 26.4 | 26.4 |
| $CNCH_2$ | $C_2H_5$ | 0.05 | Ether | 30 | 0.07 | 98 (1) | $C_5H_9ClN_2O$ | 23.9 | 24.4 |
| $CNCH_2CH_2$ | $CH_3$ (III) | 1.0 | Ether | 700 | 1.2 | 80 (15) | $C_5H_9ClN_2O$ | 23.9 | 24.0 |
| | | | Dioxane | 90 | | | | | |
| $C_2H_5OOCCH_2$ | $C_2H_5$ | 0.35 | None | | 0.44 | 93 (16) | [a] | | |
| $CH_3OOCCH_2CH_2$ | $CH_3$ | 0.34 | Ether | 200 | 1.0 | 93 (3)[b] | $C_6H_{12}ClNO_3$ | 19.5 | 19.9 |
| $Cl_3CCH_2CH_2$ | $CH_3$ | 0.16 | Ether | 100 | 0.21 | 92 (21) | $C_5H_9Cl_4NO$ | 14.7 | 15.0 |
| $ClH_2N{=}(CH_3O)CCH_2$ | $CH_3$ (V) | 0.01 | ..[d] | | ..[e] | 100 (1) | $C_5H_{12}Cl_2N_2O_2$ | 34.9 | 34.2 |
| $ClH_2N{=}(C_2H_5O)CCH_2$ | $C_2H_5$ (VI) | 0.10 | Dioxane | 120 | ..[e] | 95 (1) | $C_7H_{16}Cl_2N_2O_2$ | 30.7 | 30.7 |
| $ClH_2N{=}(CH_3O)C(CH_2)_2$ | $CH_3$ (VII) | 0.20 | Dioxane | 80 | ..[e] | 96 (2) | $C_6H_{14}Cl_2N_2O_2$ | 32.7 | 32.6 |
| $ClH_2N{=}(C_2H_5O)C(CH_2)_2$ | $C_2H_5$ (VIII) | 0.20 | Dioxane | 4[a] | ..[e] | 95 (2) | [f] | | |

[a] Reported by Reitter and Weindel.[7] [b] Product separated as an oil which crystallized after decantation of the supernatant liquid and washing the precipitate with ether. [c] Two moles of the alcohol corresponding to R′ per mole of nitrile used and the solution saturated with hydrochloric acid. [d] A mixture of 15 ml. of chloroform and 15 ml. of dioxane as solvent; when dioxane alone was used as the solvent the product was contaminated with methyl cyanoiminoacetate hydrochloride. [e] This amount of dioxane was required to cause a homogeneous solution of the nitrile in the alcohol. [f] Reported by Pinner, ref. 4.

## Experimental

**Nitriles.**—Malononitrile was prepared by the method of Surrey,[11] succinonitrile by that of Fauconnier,[12] γ,γ,γ-trichlorobutyronitrile by that of Bruson, *et al.*[13] Ethyl cyanoacetate was purchased from the Eastman Kodak Company. Methyl β-cyanopropionate was prepared in the following manner. A mixture of 66.5 g. of methyl β-cyanoiminopropionate hydrochloride (see Table I) and 100 ml. of water was swirled until solution was complete. This process was accompanied by marked cooling; after about two minutes, the solution evolved considerable heat and the ester began to separate. The mixture was allowed to stand at room temperature overnight after which the product was extracted with ether and dried over potassium carbonate. Distillation gave a yield of 38.2 g. (75%) of methyl β-cyanopropionate,[14] b. p. 93–103° (8 mm.), which was collected almost entirely at 95–97°.

**Preparation of the Iminoester Hydrochlorides.**—The general method of preparation described by Pinner[15] was used throughout this work. Strict precautions were always taken to ensure that the reagents were anhydrous and were protected from atmospheric moisture during the reaction. The nitrile and an equimolar quantity of the alcohol were dissolved in an inert solvent, the solution cooled in ice-water, and then treated with dry hydrogen chloride. Pinner and most of the previous workers in this Laboratory used ether as the inert solvent. In the present work anhydrous dioxane was found to be an excellent solvent for the preparation of certain of these salts because of a combination of desirable properties. First, it is a much better solvent for malononitrile and succinonitrile than is ether, *e. g.*, 75 ml. of ether per gram of succinonitrile is necessary to produce a homogeneous solution; however, a mixture of 0.6 ml. of dioxane and 5 ml. of ether dissolves 1 g. of this nitrile. Secondly, the iminoester hydrochlorides precipitate much more slowly from the dioxane than from ether.

The delayed precipitation of the salts from dioxane had two advantages: (a) in the preparation of di-iminoester dihydrochlorides it permitted both nitrile groups to react before any precipitation occurred and (b) it prevented clogging of the gas inlet tube by an early precipitation of the salt. Recently, anhydrous chloroform has been found to exert a similar solvent action on iminoester hydrochlorides and has been used in their preparation.[16] With this solvent, however, these salts often do not precipitate on standing, but must be recovered by evaporation of the solvent. Unfortunately, chloroform is a poor solvent for hydrogen chloride and experience in the present work has shown that a 1:1 mixture of chloroform and dioxane is for this reason a better solvent. This mixed solvent had to be used for the preparation of dimethyl iminomalonate dihydrochloride (V).

The pertinent data concerning the iminoester hydrochlorides prepared in this work are summarized in Table I.

**Ethyl Cyanoiminoacetate.**—To an ice-cooled mixture of 200 ml. of 40% aqueous potassium carbonate and 200 ml. of ether in a separatory funnel was added 26.5 g. (0.178 mole) of ethyl cyanoiminoacetate hydrochloride. The mixture was shaken for one minute and the ether layer separated and poured over anhydrous potassium carbonate. A little ice-water and 100 cc. of cold ether were added to the aqueous layer and the extraction procedure repeated as above. After two additional extractions, the combined extracts were decanted on to a fresh portion of drying agent and allowed to stand several hours. The ether was carefully evaporated on the steam-bath in a stream of dry air and the residue dried to constant weight in the vacuum desiccator. The yield of slightly impure, tan ethyl cyanoiminoacetate, m. p. 75–77°, was 19.4 g. (97%). Recrystallization from ether gave beautiful, white plates, m. p. 78–79°, b. p. 102–103° (10 mm.).

*Anal.* Calcd. for $C_5H_8N_2O$: $C_2H_5O$, 40.2; N, 25.0. Found: $C_2H_5O$, 40.8; N, 24.8.

In order to estimate the molar refraction, the densities and refractive indices at 25° were determined for known mixtures of ethyl cyanoiminoacetate with dioxane and with pyridine. These values were plotted against the corresponding concentrations and the straight lines obtained were extrapolated to 100% iminoester. The values thus obtained were: $n^{25}D$ 1.501 (with dioxane), 1.510 (with pyridine), average 1.506; $d^{25}_4$ 1.063 (with dioxane), 1.060 (with pyridine), average 1.062. $M_D$, calcd. for XVII 28.71, for XVIIa 29.71; found: 31.36. Thus the molar exaltation of XVIIa is 1.65, and the specific exaltation 1.47, which are comparable to the corresponding values of 1.80 and 1.13 reported[10] for ethyl carbethoxyiminoacetate.

Ethyl cyanoiminoacetate also was obtained from diethyl iminomalonate dihydrochloride (VI) in the following manner. To a solution of 4.1 g. (0.06 mole) of sodium ethoxide in 50 ml. of absolute ethanol containing phenolphthalein

(11) "Organic Syntheses," **25**, 63 (1945).

(12) Fauconnier, *Bull. soc. chim.*, **50**, 214 (1888).

(13) Bruson, Niederhauser, Riener and Hester, THIS JOURNAL, **67**, 601 (1945).

(14) Karvonen, *Ann. Acad. Sci. Fennicae*, **20**, no. 9 (1924).

(15) Pinner, "Die Imidoaether und ihre Derivate," Oppenheim, Berlin, 1892; *cf.* also McElvain and Nelson, THIS JOURNAL, **64**, 1825 (1942).

(16) Djerassi and Scholz, *ibid.*, **69**, 1691 (1947).

as an indicator was added 6.9 g. (0.03 mole) of diethyl iminomalonate dihydrochloride. The mixture warmed slightly and the red color of the indicator disappeared. An additional 2 ml. of the sodium ethoxide solution was added to restore the alkalinity of the mixture and the latter was stirred for ten minutes. The precipitated sodium chloride was filtered by suction and the filtrate concentrated. Distillation of the residue gave 1.8 g. (54%) of ethyl cyanoiminoacetate, b. p. 101–102° (10 mm.), which crystallized on cooling. Recrystallization from ether gave the pure iminoester, m. p. 79–80°

When a warm solution of 5.6 g. (0.05 mole) of ethyl cyanoiminoacetate in 20 ml. of anhydrous benzene was mixed with a warm solution of 5.0 g. (0.051 mole) of freshly distilled maleic anhydride in 10 ml. of dry benzene, the mixture heated spontaneously and had to be cooled under the tap; a voluminous precipitate began to separate immediately and after digestion for fifteen minutes on the steam-bath the mixture was cooled and filtered. The yield of crude **ethyl N-(β-carboxyacrylyl)-cyanoiminoacetate**, m. p. 132–134° dec., was 10.4 g. (99%). Recrystallization from either acetone or dioxane gave 5.3 g. of a light yellow product, m. p. 141–142° dec. An additional recrystallization from dioxane yielded 4.1 g. of the pure material, m. p. 152–152.5° dec.; neutral equiv., 203 216 (calcd. 210).

*Anal.* Calcd. for $C_9H_{10}N_2O_4$: N, 13.3; $C_2H_5O$, 21.4. Found: N, 13.2; $C_2H_5O$, 20.4.

**Diethyl Iminomalonate.**—This di-iminoester was obtained in 44% yield by treatment of the salt VI with a cold, saturated aqueous solution of potassium carbonate and immediate extraction with ether. After drying over sodium sulfate, it distilled as a colorless liquid, b. p. 62–63° (0.4 mm.); $n^{25}D$ 1.4530, $d^{25}_4$ 1.011. Houben and Blaise[3a] reported this iminoester to boil at 58° (0.2 mm.), but gave no yield or analytical data for it.

*Anal.* Calcd. for $C_7H_{14}N_2O_2$: N, 17.7. Found: N, 17.9.

On standing this iminoester discolored rapidly and, after several weeks, became a dark brown semi-solid mass.

**Pyrolysis of Diethyl Iminomalonate Dihydrochloride (VI).**—When 2.5 g. of VI was heated in a bath at 150–160°, 1.3 g. (93%) of ethyl chloride, b. p. 12°, was condensed in a trap immersed in a Dry Ice–alcohol mixture. Recrystallization of the pyrolysis residue from absolute alcohol gave 0.9 g. (81%) of malonamide, m. p. 170–172°.

**Attempted Preparation of Dimethyl Iminosuccinate.**—When dimethyl iminosuccinate dihydrochloride was treated with cold, aqueous sodium carbonate or sodium bicarbonate and the mixture shaken with ether, a negligible amount of liquid was found in the ether layer.[6] Stronger bases such as sodium hydroxide or potassium carbonate yielded only resinous material in the ether layer and a dark-colored aqueous phase. The following experiments were performed in order to explain this anomalous behavior.

A mixture of 4.1535 g. of dimethyl iminosuccinate dihydrochloride and 8.0 g. of sodium bicarbonate was placed in a 200-ml. round-bottomed flask immersed in ice-water and equipped with a dropping funnel and delivery tube. On addition of 10 ml. of ice-water from the funnel, carbon dioxide was evolved and collected over mineral oil. The yield of carbon dioxide thus obtained amounted to 42.8% based on complete neutralization of the dihydrochloride. The residue was acidified with dilute nitric acid and the quantity of chloride ion determined. A 6.8% loss of chloride ion indicated the formation of this amount of methyl chloride. The combined yield of carbon dioxide and methyl chloride was, therefore, 49.6%, indicating that only one hydrochloride group per molecule had been neutralized.

To 200 ml. of ice-cooled 10% aqueous sodium carbonate was added 15.5 g. (0.071 mole) of dimethyl iminosuccinate dihydrochloride. The clear solution was acidified with 75 ml. of concentrated hydrochloric acid and evaporated nearly to dryness at a temperature of 50–70° in a stream of dry air. The slightly moist, solid residue was extracted with four 50-ml. portions of boiling acetone. To the acetone-insoluble residue was added 35 ml. of concentrated hydrochloric acid in 100 ml. of water and the evaporative hydrolysis repeated over a period of three hours. After acetone extraction of the residue, the latter was subjected to a third hydrolysis. The amounts of brown, crystalline solid extracted in each of these three acetone treatments were: (1) 10.5 g., (2) 1.5 g. and (3) 0.5 g.

The extracted material was dissolved in water, and sodium bicarbonate added until no further effervescence occurred. The white precipitate which had separated during this neutralization was filtered off and identified as β-carboxypropionamidine, m. p. 255.5° dec.; the yield was 4.6 g. (56%). This product was identical with that prepared from β-carbomethoxypropionamidine hydrochloride (see below). The filtrate was evaporated to dryness and extracted with boiling acetone to yield 1.8 g. (25.5%) of succinimide, m. p. 121.5–124°, which was separated from a small amount of inorganic contaminant by extraction with ether. Recrystallization from absolute ethanol gave the pure imide, m. p. 125–126°. The residue from this acetone extraction was acidified with hydrochloric acid and evaporated to dryness. Extraction with acetone removed a solid, which was recrystallized from water to give 1.0 g. (12%) of succinic acid, m. p. 185–186°.

**Preparation of Orthoesters.**—The following preparation of methyl orthocyanoacetate illustrates the method by which the monoiminoester hydrochlorides of Table I were converted to the corresponding orthoesters; following this preparation are descriptions of procedures used with the di-iminoester dihydrochlorides, VII and VI.

**Methyl Orthocyanoacetate (II).**—A mixture of 385 g. (2.85 moles) of methyl cyanoiminoacetate hydrochloride and 3 l. of absolute methanol was shaken until the salt had dissolved. This process was accompanied by marked cooling. After three hours ammonium chloride began to separate and the reaction appeared to be complete after standing overnight at room temperature. The methanol was removed by distillation through a fifteen-inch Vigreux column. Severe bumping invariably accompanied distillation of the methanol in the conventional manner due to the ammonium chloride that continued to separate. The bumping could be avoided by blowing a gentle stream of *dry* air through the mixture as it was heated on the steam-bath at such a rate that the temperature of the vapors was about 50°. When all the methanol had been removed, the residue was cooled and 500 ml. of dry ether added. The mixture was filtered by suction and the white solid residue washed with 200 ml. of dry ether. Extraction of the solid with hot absolute alcohol dissolved 38.3 g. (16%) of cyanoacetamide, m. p. 110–115°, and left a residue of 114.5 g. (75%) of ammonium chloride. The crude amide was recrystallized from water and the purified material melted at 118–119°.

The ether filtrate and washings from the ether-insoluble solid were combined and washed with a saturated aqueous solution of sodium carbonate. After drying over solid potassium carbonate, the ether layer was distilled to yield 269 g. (65%) of methyl orthocyanoacetate.

**Methyl Orthosuccinate (XII) and Methyl Ortho-β-carbomethoxypropionate (XI).**—A slurry of 38.0 g. (0.175 mole) of dimethyl iminosuccinate dihydrochloride in 250 ml. of absolute methanol was stirred mechanically for forty-two hours while immersed in a bath held at 13–15°. The resulting light green mixture was made alkaline to phenolphthalein with methanolic sodium methoxide and allowed to stand for one hour. The methanol then was distilled under reduced pressure and 200 ml. of anhydrous ether added to the residue. The precipitated solid was filtered and washed with dry ether, after which the filtrate and washings were evaporated to 50 ml. and more solid filtered and washed as before. The filtrate and washings were concentrated and distilled. After collecting a forerun, b. p. 82–104° (5 mm.), a fraction, b. p. 104–108° (5 mm.), which crystallized on standing and melted at 48–50°, was collected. Two recrystallizations from ethyl acetate, which required cooling in a Dry Ice–acetone mixture, gave pure methyl orthosuccinate, m. p. 50–51°. On cooling the forerun, b. p. 82–104° (5 mm.), in ice, additional

TABLE II
ORTHOESTERS $RC(OR')_3$

| R is | R' is | B. p. °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | Yield, % | Formula | Analyses, % Calcd. R'O | N | C | H | Found R'O | N | C | H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CNCH_2$ | $CH_3$ (II) | 98–102 | 13 | 1.4215 | 1.079 | 65 | $C_6H_{11}NO_3$ | 64.2 | 9.7 | | | 64.4 | 9.7 | | |
| $CNCH_2$ | $C_2H_5$ | 83–84 | 2 | 1.4189 | 0.978 | 62[a,b] | $C_9H_{17}NO_3$ | 72.2 | 7.5 | | | 71.9 | 7.5 | | |
| $CNCH_2CH_2$ | $CH_3$ (IV) | 73–74 | 0.5 | 1.4269 | 1.055 | 77[b] | $C_7H_{13}NO_3$ | 58.5 | 8.8 | | | 58.1 | 8.9 | | |
| $C_2H_5OOCCH_2$ | $C_2H_5$ | 120–121 | 18 | 1.4220 | 0.995 | 82 | $C_{11}H_{22}O_5$ | 76.9 | | 56.4 | 9.5 | 75.9 | | 56.0 | 9.3 |
| $CH_3OOCCH_2CH_2$ | $CH_3$ (XI) | 64–65 | 1 | 1.4230 | 1.084 | 63 | $C_8H_{16}O_5$ | 64.6 | | 50.0 | 8.4 | 64.1 | | 49.5 | 8.1 |
| $Cl_3CCH_2CH_2$ | $CH_3$ (XIII) | 91–92 | 4 | 1.4578 | 1.277 | 84 | $C_7H_{13}Cl_3O_3$ | 37.0 | ...[c] | | | 37.5 | ...[c] | | |
| $(CH_3O)_3CCH_2CH_2$ | $CH_3$ (XII) | 104–108 | 5 | 1.4261[d] | ... | 15 | $C_{10}H_{22}O_6$ | 78.1 | | 50.4 | 9.3 | 76.9 | | 50.2 | 9.2 |
| $HN{=}(C_2H_5O)CCH_2$ | $C_2H_5$ (XVIII) | 94–95 | 3 | 1.4272 | 0.979 | 8 | $C_{11}H_{23}NO_4$ | 77.2 | 6.0 | | | 75.9 | 5.6 | | |

[a] Alcoholysis solution neutralized with sodium ethoxide before removal of alcohol; when the alcohol was removed before neutralization as in the preparation of II, the yield was 36%. [b] This orthoester was freed of normal ester by treatment with aqueous ammonia (sp. gr. 0.90). [c] Calcd.: Cl, 42.3. Found: Cl, 42.7. [d] This compound melts at 50–51°; the $n^{25}D$ was determined on the supercooled liquid.

orthoester was obtained and redistillation of the filtrate from this crop provided still more. The total yield of methyl orthosuccinate was 6.4 g. (15%).

From this second distillation of the forerun, b. p. 82–104°, 3.7 g. (11%) of XI, b. p. 91–98° (6 mm.), was obtained.

**Alcoholysis of Diethyl Iminomalonate Dihydrochloride (VI).**—A mixture of 107 g. (0.46 mole) of this salt and 1300 ml. of absolute ethanol was stirred in a bath held at 40°. The salt was quite insoluble in the alcohol and disappeared very slowly. After twenty-one hours, the precipitate of ammonium chloride (18.2 g., 0.34 mole) was filtered off and the filtrate titrated to the phenolphthalein end-point with 168 ml. (0.365 mole) of 2.173 *N* ethanolic sodium ethoxide. Thus the total amount of hydrochloride salts still present in the solution and as precipitated ammonium chloride was 0.705 mole or 77% of the ionic chlorine of the original iminoester hydrochloride. (In a similar run the ionic chlorine in this alcoholic solution was determined by titration with standard silver nitrate; the soluble chloride together with that precipitated as ammonium chloride was found to be 80% of that present in the iminoester salt used, which is in good agreement with the value obtained by neutralization with alkali.) The amount of ammonium chloride which dissolves in 1300 ml. of absolute ethanol is 7.9 g. so that the total yield of that salt was estimated to be 26.1 g. (53%).

The neutralized reaction mixture was made distinctly alkaline by addition of 5 ml. of the alcoholic sodium ethoxide solution and the precipitated sodium chloride removed by filtration. The filtrate was refluxed under a condenser which was connected to a trap immersed in a Dry Ice–alcohol mixture. After fifteen minutes a liquid had collected in the trap; on fractionation it yielded 3.5 g. (6%) of ethyl chloride, b. p. 12–15°, and small amounts of ammonia and ethanol. The alcohol then was distilled at about 100 mm. from the reaction mixture through an efficient column after which the following fractions were collected: (a) 25.0 g. of liquid boiling below 110° (2 mm.) and (b) 12.7 g. (21%) of carbethoxyacetamide, b. p. 130–135° (2 mm.), which was obtained as an oil that crystallized completely on seeding with an authentic sample of the amide. Washing with ether gave white crystals, m. p. 48–49°, which contained 34.5% ethoxyl and 10.8% nitrogen (calcd. 34.4 and 10.7%, respectively). The non-volatile residue from the distillation amounted to 22.0 g.

Fraction (a) was taken up in 400 ml. of 60–68° petroleum ether and the mixture allowed to stand in the refrigerator overnight. Filtration removed 2.4 g. (5%) of crude ethyl cyanoiminoacetate, which after recrystallization from ethyl acetate melted at 78–79°.

The petroleum ether filtrate from the iminoester was fractionated into: (1) 6.9 g. (9%) of diethyl malonate, b. p. 81–90° (4 mm.); (2) 3.4 g., b. p. 90–100° (4 mm.); (3) 8.4 g. (8%) of **ethyl orthocarbiminoethoxyacetate** (XVIII), b. p. 100–105° (4 mm.); and (4) 1.4 g. of residual oil. Redistillation of fraction (3) gave the pure iminoester-orthoester, b. p. 94–95° (3 mm.), the properties and analysis of which are listed in Table II. The identity of this compound was further established by treatment of 1.2 g. of fraction (3) in ice-cooled ether with an ether solution of anhydrous hydrogen chloride of known concentration. The addition of 0.8 mole of hydrogen chloride per mole of nitrogen present caused heat evolution but no precipitation; however, further addition of the reagent up to 2.0 moles per mole of nitrogen caused a separation of a white solid which was not increased by further addition of hydrogen chloride. The precipitate was filtered off and found to be 0.9 g. (90%) of ethyl carbethoxyiminoacetate hydrochloride, m. p. 92–94° dec. (reported,[10] 99–101° dec.), which contained 17.7% chlorine (calcd. 18.1%). Since the melting point did not agree with the value reported in the literature, the salt was further characterized by pyrolysis of a 1.0-g. sample to 0.2 g. (60%) of ethyl chloride, b. p. 11–12°, and 0.7 g. of residual oil which crystallized on seeding with carbethoxyacetamide. Recrystallization from ether gave the pure amide, m. p. 49–50°.

A similar treatment of fraction (2) with hydrogen chloride gave an 80% yield of ethyl carbethoxyiminoacetate hydrochloride indicating that this fraction also was largely XVIII.

Low yields of ammonium chloride were obtained invariably in the alcoholysis of diethyl iminomalonate dihydrochloride. Thus, at 30° the yields were 56, 50 and 53.5% for reaction periods of sixty-five, eighty and one hundred and thirty hours, respectively, while at 50° a yield of only 56% was obtained after twenty-one hours.

**Alcoholysis of Diethyl Iminomalonate Dihydrochloride in the Presence of Pyridine.**—To a solution of 7.4 g. (0.094 mole) of anhydrous pyridine in 250 ml. of absolute ethanol was added 21.5 g. (0.093 mole) of diethyl iminomalonate dihydrochloride (VI). After five minutes of shaking the salt had dissolved completely. The solution was heated under reflux in a bath at 40° for twenty-seven hours. During this time no ethyl chloride was collected in a trap provided for that purpose and only a small amount of crystalline solid precipitated.

The reaction mixture was titrated to the phenolphthalein end-point with 2.173 *N* ethanolic sodium ethoxide and required 78.5 ml. (92%) for neutralization. The precipitated sodium chloride was filtered off and the alcohol distilled from the filtrate through an efficient column at about 100 mm. pressure. Fractionation of the residue gave: (a) 0.9 g. (4%) of XVIII; (b) 0.8 g. (7%) of carbethoxyacetamide; and (c) 6.4 g. of a non-volatile tar. Fraction (a) showed only a slight opalescence in 60–68° petroleum ether, indicating that very little ethyl cyanoiminoacetate was present.

The properties and analyses of the orthoesters prepared by the above procedures are summarized in Table II.

When the alcoholic solution resulting from the methanolysis of dimethyl iminosuccinate dihydrochloride (VII) was distilled without the addition of sodium methoxide, a viscous, yellow oil remained as a residue. After trituration with dry ether, the oil was dissolved in water and this solution extracted with ether. From the combined ether extracts a 45% yield of dimethyl succinate was isolated. The aqueous solution was evaporated to dryness, extracted with boiling absolute ethanol and the insoluble ammonium chlo-

ride filtered off. Evaporation of the alcohol filtrate left a 36% yield of crude **β-carbomethoxypropionamidine hydrochloride (IX)**, which after recrystallization from absolute ethanol melted at 131–132°.

*Anal.* Calcd. for $C_5H_{11}ClN_2O_2$: Cl, 21.3; N, 16.8; $CH_3O$, 18.6. Found: Cl, 21.3; N, 16.7; $CH_3O$, 17.6.

This amidine salt was also prepared in the following manner: A mixture of 16.5 g. (0.091 mole) of methyl β-carbomethoxyiminopropionate hydrochloride and 20 ml. of absolute methanol was placed in a 200-ml. flask and the lumps of the salt broken up with a glass rod. Then a solution of 1.7 g. (0.10 mole) of ammonia in 12 ml. of methanol was added and the mixture swirled. There was an immediate heavy precipitation of a white solid which quickly redissolved. The mixture was kept at room temperature by cooling in an ice-bath. After standing for thirty minutes the solution was evaporated on the steam-bath in a stream of dry air and finally dried in a vacuum desiccator over sulfuric acid. The crystalline product, m. p. 126–128°, weighed 15.1 g. (99%). Recrystallization from absolute ethanol gave pure β-carbomethoxypropionamidine hydrochloride, m. p. 131–132°.

A solution of 0.54 g. of β-carbomethoxypropionamidine hydrochloride in 15 ml. of concentrated hydrochloric acid was heated at 95–100° for one hour. Evaporation of the aqueous acid under diminished pressure left 0.51 g. of crude β-carboxypropionamidine hydrochloride, m. p. 131–137°. Titration of this salt with standard alkali gave 0.305 g. (80%) of β-carboxypropionamidine, m. p. 258–260° dec.

*Anal.* Calcd. for $C_4H_8N_2O_2$: N, 24.1. Found: N, 24.2.

Evaporation of a solution of this amidine in dilute hydrochloric acid left β-carboxypropionamidine hydrochloride, m. p. 138–140°.

*Anal.* Calcd. for $C_4H_9ClN_2O_2$: Cl, 23.3; N, 18.4. Found: Cl, 23.6; N, 18.8.

**Methyl Ortho-β-carbamylpropionate.**—A mixture of 2 g. of methyl ortho-β-carbomethoxypropionate (XI) and 10 ml. of aqueous ammonia (sp. gr. 0.90) was stirred at room temperature until a clear solution was obtained (one-half hour). The resulting solution was extracted with chloroform and dried over Drierite. Evaporation of the solvent left 1.5 g. (82%) of methyl ortho-β-carboxamidopropionate, m. p. 90–94°. After washing with petroleum ether (b. p. 60–68°), this product melted at 94–97°.

*Anal.* Calcd. for $C_7H_{15}NO_4$: N, 7.91. Found: N, 7.85.

This compound is quite sensitive to recrystallization, yielding β-carbomethoxypropionamide when it was recrystallized from the ordinary organic solvents. This product was obtained also when the aqueous ammoniacal solution was evaporated to dryness under diminished pressure.

In contrast to the facile reaction of XI with aqueous ammonia, ethyl orthocarbethoxyacetate did not dissolve in aqueous ammonia even after forty-eight hours of efficient stirring. After this time approximately 75% of the unchanged orthoester was recovered.

**Reaction of Hydrogen Chloride with the Cyano-orthoesters II and IV.**—A solution of 11.6 g. (0.08 mole) of methyl orthocyanoacetate (II) in 2.56 g. (0.08 mole) of anhydrous methanol was cooled in ice while 2.9 g. (0.08 mole) of dry hydrogen chloride was introduced. The clear solution was placed in a refrigerator for one week during which a white solid slowly precipitated. Dry ether was added and the mixture placed in the refrigerator for an additional day. Filtration separated 0.66 g. of ammonium chloride. Distillation of the filtrate yielded 2.2 g. (21%) of dimethyl malonate and 5.8 g. (73%) of methyl cyanoacetate. From the distillation residue an additional 0.11 g. of ammonium chloride was separated, raising the total yield of this product to 0.77 g. (18%).

Dry hydrogen chloride was passed into a 6.2-g. sample of methyl ortho-β-cyanopropionate (IV). The liquid became hot and a small quantity of white solid separated. After saturation with the gas, the liquid was distilled to yield 4.1 g. (93%) of methyl β-cyanopropionate, b. p. 97–99° (9 mm.); 0.7 g. (56%) of methanol was collected in the cold trap.

**Reaction of Sodium Methoxide with Methyl Ortho-γ,γ,γ-trichlorobutyrate (XIII).**—A methanolic solution of sodium methoxide was prepared by dissolving 3.5 g. (0.15 atom) of sodium in 37.5 ml. of absolute methanol. On the addition of 12.6 g. (0.05 mole) of XIII the mixture heated and became dark brown. After standing overnight, 150 ml. of anhydrous ether was added and the white precipitate filtered off. The chloride and titratable alkali contents of this solid indicated that it consisted of 2.9 g. (33% yield) of sodium chloride and a trace of sodium methoxide. The solvents were removed from the filtrate at reduced pressure and the residue was distilled. It boiled over a wide range (44–85° (4–5 mm.)) and all of the fractions collected decolorized a bromine in carbon tetrachloride solution readily indicating that dehydrohalogenation had occurred. The largest fraction (2.4 g.) was a colorless liquid, b. p. 62–73° (5–4 mm.), $n^{25}D$ 1.4550, $d^{25}_4$ 1.1435. This material had the correct analysis and molar refraction for **1-chioro-4,4,4-trimethoxybutyne-1.**

*Anal.* Calcd. for $C_7H_{11}ClO_3$: Cl, 19.9; $CH_3O$, 52.1. Found: Cl, 19.8; $CH_3O$, 53.5.

## Summary

The preparation of cyano-orthoesters from malono- and succinonitriles *via* the mono-iminoester hydrochloride is described. Hydrogen chloride in alcohol solution cleaves each of these orthoesters to the normal ester before it converts the cyano group to the iminoester hydrochloride.

Succinonitrile has been converted *via* the di-iminoester hydrochloride to the ester-orthoester, $(CH_3O)_3CCH_2CH_2COOCH_3$, and the di-orthoester, $(CH_3O)_3CCH_2CH_2C(OCH_3)_3$, of succinic acid. Under the same conditions of reaction, malonitrile yields ethyl orthocarbiminoethoxyacetate. An explanation for this behavior is suggested.

The preparation and properties of a number of related compounds, including ethyl orthocarbethoxyacetate, are described.

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[A CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Ketene Acetals. XX. The Preparation and Properties of Cyanoketene Acetals. Some Novel Benzylation Reactions

BY S. M. MCELVAIN AND JUEL P. SCHROEDER[1]

In previous papers of this series benzylations of ketene diethylacetal[2] (I) and various alkyl- and phenylketene dimethylacetals[3] (VII) with benzyl bromide were reported. In each of these alkylations the reaction proceeded to the formation of disubstituted acetic esters (VI and IX), *i.e.*, the unsubstituted ketene acetal was dibenzylated, presumably through the intermediate ketene acetal IV (R = $C_6H_5CH_2$), while the monosubstituted ketene acetals (VII, X is *n*-propyl, *n*-heptyl or phenyl) yielded only monobenzylated products

$$CH_2{=}C(OC_2H_5)_2 \xrightarrow{RBr} [RCH_2{-}CBr(OC_2H_5)_2] \longrightarrow RCH_2COOC_2H_5 + C_2H_5Br$$
I II III

$$RCH{=}C(OC_2H_5)_2 \xrightarrow{RBr} [R_2CHCBr(OC_2H_5)_2] \longrightarrow R_2CHCOOC_2H_5 + C_2H_5Br$$
IV V VI

$$XCH{=}C(OCH_3)_2 + RBr \longrightarrow [XCHR{-}CBr(OCH_3)_2] \longrightarrow XCHRCOOCH_3 + CH_3Br$$
VII VIII IX

Inasmuch as there appeared to be no tendency for the intermediate VIII to lose hydrogen bromide as did II, even when X is phenyl, it seemed of interest to study the benzylation behavior of a ketene acetal containing the more negative cyano substituent.

Cyanoketene dimethylacetal (XI), as well as the homologous diethylacetal, was prepared by the pyrolysis of the corresponding orthoester (X). This pyrolysis is catalyzed by a trace of acid[4] as is the reverse reaction, the addition of alcohol to the ketene acetal

$$CNCH_2C(OCH_3)_3 \underset{}{\overset{H^+}{\rightleftharpoons}} CNCH{=}C(OCH_3)_2 + CH_3OH$$
X XI

The reaction proceeds to the ketene acetal when X is heated and the alcohol removed by distillation; the orthoester is re-formed from its components at room temperature, but can be isolated only after the removal of all traces of the acid catalyst.[4]

Because of the tendency of ketene diethylacetals to lose ethylene on heating,[5] the reactions subsequently reported were carried out with cyanoketene *dimethyl*acetal (XI). This compound is a solid, m. p. 41–42°, which is surprisingly inert toward water; indeed, it may be recrystallized from this solvent. It dissolves in methanol with noticeable cooling. However, when a drop of hydrochloric acid is added to either an aqueous or methanolic solution of XI, the solution becomes warm and the ketene acetal is converted to methyl cyanoacetate or methyl orthocyanoacetate (X). Also, XI reacts with aniline, in a manner similar to ketene diethylacetal,[6] to yield methyl N-phenylcyanoiminoacetate, $CNCH_2C(OCH_3){=}NC_6H_5$.

A rapid reaction occurred when cyanoketene dimethylacetal (XI) was heated with one equivalent of benzyl bromide at 160–170°. Within thirty minutes, 97% of the halogen of the benzyl bromide was evolved as methyl bromide and distillation of the remaining reaction mixture yielded methyl cyanoacetate (XVI) (31%), methyl benzylcyanoacetate (XIII) (21%) and methyl dibenzylcyanoacetate (XV) (26%). It is apparent

$$[C_6H_5CH_2CHCNCBr(OCH_3)_2] \longrightarrow C_6H_5CH_2CHCNCOOCH_3 + CH_3Br$$
XII XIII

$$C_6H_5CH_2C(CN){=}C(OCH_3)_2 \xrightarrow{C_6H_5CH_2Br} (C_6H_5CH_2)_2CCNCOOCH_3 + CH_3Br$$
XIV XV

from these results that the cyano substituent causes the intermediate (XII), which corresponds to VIII and presumably is formed by the addition of benzyl bromide to XI, to undergo pyrolysis to the disubstituted ketene acetal (XIV) as well as to the monobenzylated ester (XIII). Further benzylation of XIV converts it to the trisubstituted acetic ester (XV). The methyl cyanoacetate (XVI) present in the reaction mixture results from the action of the hydrogen bromide lost by XII on cyanoketene acetal.[7]

$$CNCH{=}C(OCH_3)_2 + HBr \longrightarrow CNCH_2COOCH_3 + CH_3Br$$
XVI

When cyanoketene acetal was heated with *two* equivalents of benzyl bromide at 170–180°, a steady evolution of methyl bromide continued

(1) Wisconsin Alumni Research Foundation Research Assistant, 1946–1947; University Fellow, 1947–1948.

(2) McElvain and Kundiger, THIS JOURNAL, **64**, 254 (1942).

(3) McElvain, Kent and Stevens, *ibid.*, **68**, 1922 (1946).

(4) McElvain and Schroeder, *ibid.*, **71**, 40 (1949).

(5) McElvain, *et al.*, *ibid.*, **64**, 2525 (1942); **68**, 1917 (1946).

(6) Barnes, Kundiger and McElvain, *ibid.*, **62**, 1281 (1940).

(7) Obviously, hydrogen bromide could convert XIV to XIII by a similar reaction, but the ratio of reaction products indicates that it is primarily the ketene acetal XI that combines with this acid.

after one equivalent of this halide had been collected. After five hours of heating the yield of methyl bromide amounted to 82% (of two equivalents); during this time carbon dioxide (30%) also was evolved. As the heating continued, the yield of the latter product increased until it reached (after twenty-six hours) 96% of the theoretical; in this time the yield of methyl bromide rose to 87%. Fractionation of the remaining reaction mixture yielded benzyl bromide (5%), hydrocinnamonitrile XVII (7%), dibenzylacetonitrile XVIII (43%), together with small amounts of toluene and stilbene. All attempts to isolate the expected tribenzylacetonitrile (XIX) from the products of this run were unsuccessful. From another run, which was interrupted after 65% of the theoretical amount of carbon dioxide had been evolved, a 22% yield of benzyl dibenzylcyanoacetate (XX) was obtained.[8] In this run tribenzylacetamide was obtained by treatment of certain of the higher boiling fractions with 50% sulfuric acid.

When the reaction was interrupted before any appreciable evolution of carbon dioxide had occurred (one and one-half hours), 1.24 equivalent (62%) of methyl bromide was collected and benzyl bromide (28%), XVI (20%), XIII (11%), XV (3%), benzyl cyanoacetate (8%), XXI (19%) and XX (10%) were separated from the reaction mixture.

$C_6H_5CH_2CH_2CN$ XVII $(C_6H_5CH_2)_2CHCN$ XVIII $(C_6H_5CH_2)_3CCN$ XIX

$(C_6H_5CH_2)_2CCNCOOCH_2C_6H_5$ XX

$C_6H_5CH_2CHCNCOOCH_2C_6H_5$ XXI

From these results it appeared that the second equivalent of benzyl bromide had reacted further with one or all of methyl esters (XIII, XV and XVI) produced in the initial reaction of the halide with cyanoketene dimethylacetal, converting them to methyl bromide and the corresponding benzyl esters, the latter of which then lost carbon dioxide to yield the nitriles, XVII, XVIII and XIX. The order in which the methyl bromide and carbon dioxide were formed in the reaction together with the isolation of XX from both of the interrupted runs not only seemed to justify this conclusion, but to point to a study of the reaction of benzyl bromide with the individual methyl esters.

A mixture of methyl cyanoacetate (XVI) and benzyl bromide remained apparently unchanged at 170–180° for two hours before any methyl bromide appeared, and after twenty-four hours only a 17% yield of this bromide was collected. After forty-eight hours of heating, an 81% yield of methyl bromide and a 64% yield of carbon dioxide were obtained. However, distillation of the remaining material gave only a small amount of benzyl bromide; the main reaction product was an undistillable tar.

Methyl dibenzylcyanoacetate (XV) gave no evidence of reaction when heated with benzyl bromide; after twenty-two hours, both reactants were recovered unchanged. Methyl benzylcyanoacetate (XIII) had an induction period of one and one-half hours before it reacted with benzyl bromide, but after twenty hours at 170–180°, methyl bromide and carbon dioxide were obtained in 60 and 64% yields, respectively. The other products isolated from this reaction were XVII (19%), XXI (41%) and XX (3%).

The relatively high yield of XXI from XIII indicated that the former ester was probably the key intermediate in the decarboxylation reaction. This supposition was strengthened by the results obtained in an attempt to prepare XXI by an alcohol exchange between an excess of benzyl alcohol and methyl benzylcyanoacetate (XIII). When these reactants were heated together in the presence of a small amount of sodium benzyloxide, the theoretical quantity of methanol distilled out. However, distillation of the remaining reaction mixture was accompanied by loss of carbon dioxide, and XVII (23%), XVIII (39%), XIX (7%) and XX (5%) were the products isolated.[9] When this reaction was repeated and the alkaline catalyst removed after the distillation of the methanol and excess benzyl alcohol, the reaction products were XVIII (14%), the desired ester XXI (13%) and XX (26%).

The presence of XX among the products of this alcohol-exchange reaction indicates that benzyl alcohol functioned as a benzylating agent as did benzyl bromide in certain of the previously described reactions. It appears also that it was the benzyl ester XXI rather than the original methyl ester XIII that was further benzylated, because the yield of XX was much lower in the reaction in which considerable decarboxylation of XXI to XVII—and possibly also to XVIII—had occurred.

From the results described above it is evident that cyanoketene dimethyl acetal reacts with one equivalent of benzyl bromide, probably by an ionic mechanism, to produce the methyl esters XIII, XV and XVI. In the presence of two equivalents of the bromide, however, the reaction apparently takes a different course: the conversion of the primary intermediate XII to XV is suppressed (very little of XV was found among the reaction products although it was shown to be stable to the reaction conditions), and the formation of XIII is favored. This latter ester is then converted by

(8) From one of the earlier runs dibenzyl ether and N-benzylhydrocinnamamide, $C_6H_5CH_2CH_2CONHCH_2C_6H_5$, also were isolated in small amounts. These products, however, were found to be due to the presence of benzyl alcohol in the benzyl bromide, as they did not appear when an alcohol-free bromide was used.

(9) A similar alcohol exchange between benzyl alcohol and ethyl cyanoacetate gave 25% of benzyl cyanoacetate and 5.5% of XXI. During the distillation of these esters, a considerable amount of benzyl alcohol was formed, which, together with the large amount of tar that remained, indicated that benzyl cyanoacetate was suffering intermolecular loss of benzyl alcohol. This reaction is being investigated further.

the excess benzyl bromide to methyl bromide and the benzyl ester XXI, which then undergoes further benzylation and/or decarboxylation, probably *via* a series of free radical interchanges

$$XXI \longrightarrow C_6H_5CH_2CHCNCOO\cdot + \cdot CH_2C_6H_5$$
$$C_6H_5CH_2\cdot + XXI \longrightarrow XX + H\cdot$$
$$C_6H_5CH_2CHCNCOO\cdot \longrightarrow C_6H_5CH_2\dot{C}HCN + CO_2$$
$$C_6H_5CH_2\dot{C}HCN + H\cdot \text{ (or } H{-}C{\equiv}) \longrightarrow XVII$$
$$C_6H_5CH_2\dot{C}HCN + C_6H_5CH_2\cdot \longrightarrow XVIII$$
$$XX \longrightarrow (C_6H_5CH_2)_2CCNCOO\cdot + \cdot CH_2C_6H_5$$
$$(C_6H_5CH_2)_2CCNCOO\cdot \longrightarrow (C_6H_5CH_2)_2\dot{C}CN + CO_2$$
$$(C_6H_5CH_2)_2\dot{C}CN + H\cdot \text{ (or } HC{\equiv}) \longrightarrow XVIII$$
$$(C_6H_5CH_2)_2\dot{C}CN + C_6H_5CH_2\cdot \longrightarrow XIX$$

The presence of toluene and stilbene among the products of this reaction lend further support to the free radical interpretation of this reaction.

It is possible that the nitriles XVII, XVIII and XIX may be formed also by an ionic mechanism involving a concurrent intramolecular rearrangement and loss of carbon dioxide from a benzyl ester, *e.g.*, XXI → XVIII

$$C_6H_5CH_2CH(CN){-}C{=}O \longrightarrow C_6H_5CH_2\underset{C_6H_5CH_2}{\overset{|}{C}}HCN + CO_2$$

However, further work will be required to establish either of these reaction mechanisms.

## Experimental

**Cyanoketene Dimethylacetal (XI).**—In a 50-cc. flask equipped with a six-inch Vigreux column 14.7 g. of methyl orthocyanoacetate[4] was heated in a metal-bath maintained at 220–225°, whereupon 2.7 g. of methanol, b. p. 63–66°, distilled rapidly. The pyrolysis was stopped when the rate of methanol distillation dropped and the residue in the flask became dark. Distillation of this residue under reduced pressure gave an additional 0.25 g. of methanol in the cold trap, bringing the yield to 2.95 g. (90%), 2.65 g. of forerun, b. p. 90–127° (11 mm.), and 7.85 g. of cyanoketene dimethylacetal, b. p. 127–128° (11 mm.), m. p. 41.5–42°, $n^{50}D$ 1.4630, $d^{50}_4$ 1.055.

*Anal.* Calcd. for $C_5H_7NO_2$: N, 12.4; $CH_3O$, 54.9. Found: N, 12.6; $CH_3O$, 54.1.

The residue from the distillation amounted to 1.1 g. of a red tar, which was brittle at room temperature and was completely soluble in concentrated hydrochloric acid.

From the forerun 1.65 g. (17%) of methyl cyanoacetate and an additional 1 g. of XI was obtained on fractionation. The presence of approximately this amount of XI in the lower boiling fraction was indicated by its refractive index.[10] The total yield of XI was 8.85 g. (77%).

The above pyrolysis requires careful attention. Insufficient heating produced low yields of methanol and ketene acetal while an excessively long pyrolysis period resulted in increased tar formation and, consequently, low yields of the desired product. For example, in a run in which a yield of only 78% of methanol was obtained, the amount of tar formed was negligible but, correspondingly, the yield of ketene acetal was 68%. On the other hand, a run in which a quantitative yield of methanol was obtained produced considerably more tar and only 36% of ketene acetal.

(10) In order to make the latter calculation it was necessary to estimate $n^{20}D$ of the ketene acetal, which is a solid at 20° and could not be supercooled to that temperature. The value $n^{20}D$ 1.4774, was obtained by plotting the refractive indices at 20° of known mixtures of dioxane and the ketene acetal against composition and extrapolating the resulting straight line to 100% ketene acetal.

Cyanoketene dimethylacetal crystallizes in beautiful rectangular prisms. It is insoluble in cold water and dilute alkali but is soluble in the ordinary organic solvents and in concentrated sulfuric acid. It readily decolorizes a solution of bromine in carbon tetrachloride. It shows a remarkable inertness toward water as compared to other ketene acetals. For example, a few crystals were shaken with 5 ml. of distilled water for several minutes without apparent change. On warming to about 70°, however, the compound melted and finally dissolved. When the solution was cooled to room temperature an oil separated which quickly crystallized and was filtered off. This proved to be the unchanged ketene acetal, m. p. 41–42°, mixed m. p. 42–42.5°.

The compound dissolved in dilute hydrochloric acid with evolution of heat. Extraction of the solution with ether and evaporation of the extract, after drying over Drierite, left a residue of methyl cyanoacetate, b. p. 210°, $n^{20}D$ 1.4192, which was readily converted by concentrated aqueous ammonia to cyanoacetamide, m. p. 117–119°.

Solution of 4.0 g. of cyanoketene dimethylacetal in 30 ml. of absolute methanol was accompanied by cooling to 17°. When a thermometer moistened with concentrated hydrochloric acid was inserted in the solution the temperature rose immediately to 29°. After several minutes sodium bicarbonate was added and, after stirring, the supernatant liquid was decanted and distilled at reduced pressure. The yield of methyl orthocyanoacetate,[4] b. p. 90–93° (8 mm.), $n^{20}D$ 1.4232, was 4.2 g. (81%).

A solution of 5.2 g. (0.046 mole) of cyanoketene dimethylacetal and 4.3 g. (0.046 mole) of aniline was heated for fifteen hours on the steam-bath under a reflux condenser. Distillation under reduced pressure gave: 0.7 g. (48%) of methanol (cold-trap) and 5.9 g. of liquid which boiled over a wide range. The principal fraction was 3.6 g. (45%) of **methyl N-phenylcyanoiminoacetate**, b. p. 132–136° (4 mm.), $n^{25}D$ 1.5380, $d^{25}_4$ 1.097.

*Anal.* Calcd. for $C_{10}H_{10}N_2O$: N, 16.1; $CH_3O$, 17.8. Found: N, 15.7; $CH_3O$, 17.7.

**Cyanoketene Diethylacetal.**—To 4.00 g. of ethyl orthocyanoacetate[4] was added one drop of 85% phosphoric acid and the mixture distilled. After 0.8 g. of forerun, b. p. 125–145° (20 mm.); $n^{20}D$ 1.4378, 2.0 g. (66%) of cyanoketene diethylacetal, b. p. 145–146° (20 mm.); m. p. 37–38°, $n^{20}D$ 1.4621 (supercooled liquid), $n^{40}D$ 1.4536, was collected.

*Anal.* Calcd. for $C_7H_{11}NO_2$: N, 9.9; $C_2H_5O$, 63.8. Found: N, 9.8; $C_2H_5O$, 63.7.

A yield of 1.05 g. (quantitative) of ethanol was found in the cold-trap after the distillation.

A thermometer moistened with concentrated hydrochloric acid was inserted into a solution of 1.60 g. of this ketene acetal in 3.0 ml. of absolute ethanol. On stirring, the temperature rose from 26 to 39°. Fifty mg. of anhydrous potassium carbonate was added and the mixture distilled, yielding 1.46 g. (69%) of ethyl orthocyanoacetate,[4] b. p. 111–118° (19 mm.), $n^{20}D$ 1.4218.

**The Reaction of Cyanoketene Dimethylacetal with One Equivalent of Benzyl Bromide.**—A mixture of 68.4 g. (0.4 mole) of benzyl bromide and 45.2 g. (0.4 mole) of cyanoketene dimethylacetal was placed in a Claisen flask fitted with a condenser and receiving flask. To the receiving flask was connected a trap protected from atmospheric moisture and immersed in a mixture of Dry Ice and acetone.

The mixture was slowly heated until the bath temperature reached 174°. At this point there was such a vigorous evolution of gas that the bath was cooled to 160°. When ebullition had practically ceased (thirty minutes) the bath was lowered. A total of 39.5 g. of liquid had condensed in the trap of which 37.0 g. (97%) proved to be methyl bromide, b. p. 4°; the remainder was benzyl bromide, which had been swept over by the rapidly evolved methyl bromide.

The residual red oil in the flask was distilled and the following fractions collected: (a) 12.1 g. (31%) of methyl cyanoacetate, b. p. 59–65° (0.5 mm.); (b) 0.2 g., b. p.

65–112° (0.5 mm.); (c) 12.0 g., b. p. 112–129° (0.5 mm.); (d) 8.8 g., b. p. 129–180° (0.5 mm.); (e) 11.8 g., b. p. 180–200° (0.9 mm.); (f) 14.4 g., b. p. 200° (0.9 mm.) –205° (2 mm.). The residual tar weighed 10.4 g.

Redistillation of fractions (c) and (d) gave 14.0 g. of **methyl benzylcyanoacetate** (XIII), b. p. 115–123° (0.5 mm.). Careful refractionation yielded a middle cut of the pure ester, b. p. 114–115° (0.1 mm.), $n^{25}D$ 1.5119, $d^{25}_4$ 1.105.

*Anal.* Calcd. for $C_{11}H_{11}NO_2$: $CH_3O$, 16.4; N, 7.4. Found: $CH_3O$, 15.8; N, 7.2.

The ester was hydrolyzed to benzylcyanoacetic acid, m. p. 101–102°, by the method used[11] for the ethyl ester.

Two smaller, higher-boiling fractions were also collected following the methyl benzylcyanoacetate. The last one and the residue in the distilling flask solidified on cooling. Fraction (e) also solidified on standing to a crystalline mass, m. p. 64–67°. This was combined with the solid products just mentioned and the mixture recrystallized from alcohol to give 11.0 g. of methyl dibenzylcyanoacetate (XV), m. p. 78–79° (reported[12] 78–79°), methoxyl content 11.4% (calcd. 11.1%), nitrogen content 5.2% (calcd. 5.0%). This ester was hydrolyzed in 20% aqueous potassium hydroxide to dibenzylcyanoacetic acid, m. p. 188–189° dec. (reported, 188–189°,[13] 194–195°[12]), neut. equiv., 269 (calcd. 265), nitrogen content 5.4% (calcd. 5.3%). Since one melting point reported in the literature disagreed with the value obtained, the ester was characterized further by hydrolysis in 50% sulfuric acid (by volume) to give ammonia and dibenzylacetic acid, m. p. 87–88°, neut. equiv. 230 (calcd. 240).

The remaining material, *i.e.*, fraction (f), the mother liquor from the recrystallization of (e) and the high boiling liquid obtained in the purification of methyl benzylcyanoacetate, was subjected to a systematic purification scheme involving fractionation followed by recrystallization of those portions boiling in the range 170–200° (0.5 mm.). The process was then repeated on the mother liquors. In this manner an additional 10.0 g. of methyl dibenzylcyanoacetate boiling in the range indicated was obtained. Also an additional 2.0 g. of crude methyl benzylcyanoacetate, b. p. 110–123° (0.2 mm.), $n^{25}D$ 1.5257, was obtained, bringing the total yield of that compound to 16.0 g. (21%).

The material remaining from the above isolations was distilled and two fractions collected: (g) b. p. 192–225° (0.2 mm.) and (h) b. p. 219–250° (0.2 mm.). Fraction (h) solidified and, after recrystallization from ethanol, yielded 0.3 g. of benzyl dibenzylcyanoacetate (see below), m. p. 91–91.5°. The mother liquor from these recrystallizations were combined with (g) and evaporated to a constant weight of 3.7 g. Saponification of this material left 0.7 g. unsaponified. From the alkaline solution 2.1 g. of crude dibenzylcyanoacetic acid was obtained, which calculated as the methyl ester brought the total yield of the latter product to 29.3 g. (26%).

**The Reaction of Cyanoketene Dimethylacetal with Two Equivalents of Benzyl Bromide.**—A mixture of 41.5 g. (0.37 mole) of cyanoketene dimethylacetal and 126.0 g. (0.74 mole) of benzyl bromide was placed in a Claisen flask provided with a condenser and receiving flask. To the latter was connected an absorption train consisting of a wash bottle containing 50% aqueous potassium hydroxide followed by a calcium chloride tube and, finally, a cold trap protected from atmospheric moisture and immersed in a mixture of Dry Ice and alcohol.

The mixture was heated slowly by means of an oil-bath and when the temperature of the bath reached 170° a vigorous evolution of gas began. This subsided after forty-five minutes but mild ebullition continued quite steadily for eight hours. The reaction was allowed to continue for fifteen hours at 170–180°. At this time gas evolution had practically ceased and 47.0 g. (67%) of methyl bromide had collected in the cold-trap. The aqueous alkali had gained in weight by 10.5 g. (65% yield as carbon dioxide). Acidification of a portion of the solution liberated a gas which gave a heavy precipitate when bubbled through lime-water; another portion of this alkaline solution showed no significant content of bromide ion.

The clear, red residue was distilled and the following fractions were collected: (a) 12.3 g., b. p. 50–160° (1 mm.), (b) 25.2 g., b. p. 160–198° (1 mm.), (c) 19.8 g., b. p. 198–252° (1 mm.), (d) 12.9 g., b. p. 252–265° (1 mm.) and (e) 4.6 g. collected at full-oil-pump vacuum but accompanied by so much decomposition that the pressure was too high to measure on a McLeod gage. The tarry residue weighed 10.0 g.

Fraction (a) was refractionated to give (1) 6.1 g. (5%) of benzyl bromide, b. p. 39–45° (0.5 mm.), $n^{25}D$ 1.5639; (2) an intermediate fraction of 0.7 g., b. p. 45–75° (0.5 mm.); (3) 2.8 g. (6%) of hydrocinnamonitrile, b. p. 75–78° (0.4 mm.), $n^{25}D$ 1.5228; and (4) an afterrun of 0.4 g., b. p. 78–85° (0.5 mm.). The residue (2.0 g.) solidified on cooling.

Fractionation of (c) and (d) yielded 6.1 g. of liquid which boiled almost entirely at 160–190° (0.2 mm.) and solidified on cooling. This was combined with (b) which also had solidified and with the solid residue from the distillation of (a), and the resulting mixture was recrystallized from ethanol to give 18.6 g. of dibenzylacetonitrile (XVIII), m. p. 91–91.5° (reported,[14] 89–91°). The major product of the redistillation of (c) and (d) was 24.0 g. of light amber oil which was collected in four fractions boiling at 190–245° (0.2 mm.). All four crystallized on standing and recrystallization of each from ethanol gave **benzyl dibenzylcyanoacetate** (XX), m. p. 91–92°, saponification equiv. 340 (calcd. 355).

*Anal.* Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.9; N, 3.95. Found: C, 81.4; H, 6.1; N, 3.96.

Saponification of this ester in 10% aqueous sodium hydroxide produced benzyl alcohol, b. p. 204°; m. p. of 3,5-dinitrobenzoate, 113.5–114°, and dibenzylcyanoacetic acid,[13] m. p. 189–191°, neut. equiv. 272 (calcd. 265).

A 3.0-g. sample of the ester was hydrolyzed in refluxing 50% (by volume) sulfuric acid, and after making the solution basic it was distilled until the ammonia was removed. Extraction of the remaining alkaline residue with ether gave 1.3 g. of a neutral, semi-crystalline product. Acidification of the aqueous layer gave 1.6 g. of oil, from which dibenzylacetic acid, m. p. 87–88°, neut. equiv. 243, was isolated by distillation at reduced pressure and subsequent recrystallization from petroleum ether. The neutral product was likewise distilled. The light yellow distillate crystallized on cooling and repeated recrystallization from 60–68° petroleum ether gave silky crystals, m. p. 132.5–134°. This compound had the correct analysis for **tribenzylacetamide.**

*Anal.* Calcd. for $C_{23}H_{23}NO$: C, 83.8; H, 7.0; N, 4.25. Found: C, 83.8; H, 7.1; N, 4.68.

This product probably resulted from the hydration of the cyano group of benzyl dibenzylcyanoacetate (XX), followed by loss of carbon dioxide from the resulting amide. It seems unlikely that it was formed directly from tribenzylacetonitrile (XIX), as this compound (see below) was found to be extremely stable to hydration with sulfuric acid.

The deep red residue from the distillation of (c) and (d) was added to (e) and the mixture subjected to vacuum sublimation. A small quantity of solid and 1.2 g. of clear, red oil were obtained. The residue was a dark red tar from which nothing could be isolated. The oil, from its carbon and hydrogen content, appeared to be impure benzyl dibenzylcyanoacetate. The crystalline sublimate after recrystallization from ethanol yielded 0.4 g. of stilbene, m. p. 123–124°; dibromide,[15] m. p. 237–237.5°.

The mother liquor from the recrystallization of dibenzylacetonitrile was distilled and collected in three fractions: (f) b. p. 59–150° (0.4 mm.); (g) b. p. 150–181° (0.4 mm.); and (h) b. p. 181–225° (0.4 mm.). Refractiona-

(11) Hessler, *Am. Chem. J.*, **22**, 176 (1899).
(12) Hessler, This Journal, **38**, 915 (1916).
(13) Cassirer, *Ber.*, **25**, 3027 (1892).
(14) Schneidewind, *ibid.*, **21**, 1328 (1888).
(15) Wislicenus and Seeler, *ibid.*, **28**, 2694 (1895).

tion of (f) gave 0.3 g. of dibenzyl ether, b. p. 111–116° (0.1 mm.), $n^{25}D$ 1.5580, which gave a characteristic heavy precipitate of yellow-green resin with concentrated sulfuric acid. Recrystallization of (g) from ethanol gave 1.3 g. of dibenzylacetonitrile while similar treatment of (h) yielded 0.6 g. of benzyl dibenzylcyanoacetate. The mother liquor from the latter was distilled; the portion boiling at 171–220° (0.5 mm.) solidified and was recrystallized from 60–68° petroleum ether. The yield of N-benzylhydrocinnamamide,[16] m. p. 81–83°, mixed m. p. 81–84°, was 1.2 g. (1%). The yields of both this product and dibenzyl ether were due to benzyl alcohol and were negligible when benzyl bromide,[17] $n^{25}D$ 1.5730, was used.

The remaining mother liquors were subjected to a systematic scheme of purification involving alternate fractionations and recrystallizations. In this manner an additional 2.1 g. of dibenzylacetonitrile, 0.6 g. of benzyl dibenzylcyanoacetate and 8.0 g. of oil, b. p. 187–238° (0.2 mm.), which had a nitrogen content of 5.6%, were obtained. Treatment of this latter fraction with hot 10% aqueous sodium hydroxide for five hours gave 0.6 g. of benzyl alcohol and 2.0 g. of dibenzylcyanoacetic acid; 5.1 g. remained unsaponified (hydrolysis of the same quantity of benzyl dibenzylcyanoacetate under identical conditions left only 5% unsaponified). The unsaponified material was subjected to refluxing 50% (by volume) sulfuric acid. This treatment produced 0.6 g. of a neutral solid, m. p. 122–128°, mixed m. p. with tribenzylacetamide 127–131°. The other products were ammonia and 1.8 g. of ether-soluble, acidic oil which, on sublimation, gave 0.1 g. of hydrocinnamic acid, m. p. 45–47°, neutral equiv. 154 (calcd. 150). The high-boiling residue had a neutral equivalent of 236 and, therefore, appeared to be crude dibenzylacetic acid (neut. equiv. 240).

These results indicated that the 8 g. of oil, which was subjected to saponification, was a mixture of approximately 3 g. of benzyl dibenzylcyanoacetate, 4 g. of dibenzylacetonitrile and 1 g. of tribenzylacetonitrile. Such a mixture would contain 5.2% nitrogen and leave the 5 g. of the alkali-inert nitriles unchanged after saponification of the ester.

The yields of *pure* dibenzylacetonitrile and benzyl dibenzyl cyanoacetate finally obtained were 21.9 g. (27%) and 13.0 g. (10%), respectively. However, since this experiment was designed to give information as to the course of the reaction, the more significant yields are those of the crude materials which make possible a relatively complete material balance. The failure to find but traces of other products in these crudes emphasizes their quantitative significance. The yield of crude dibenzylacetonitrile boiling almost entirely at 160° (0.2 mm.) to 190° (1 mm.) and which solidified on standing was 33.3 g. (41%) and of benzyl dibenzylcyanoacetate, b. p. 190–245° (0.2 mm.), was 29.9 g. less 1.2 g. of N-benzylhydrocinnamamide which was isolated from this fraction, or 28.7 g. (22%). In another run the yield of dibenzylacetonitrile was 43.5%.

**Quantitative Determination of the Carbon Dioxide and Methyl Bromide Evolved in the Reaction of Cyanoketene Acetal and Benzyl Bromide.**—A mixture of 11.3 g. (0.10 mole) of the ketene acetal and 34.2 g. (0.20 mole) of benzyl bromide was heated in a bath maintained at 170–180° and the amounts of methyl bromide (cold-trap) and carbon dioxide (absorption bulbs containing 50% aqueous potassium hydroxide solution) determined periodically. The results are summarized in Table I.

The products obtained from the residue were: (a) 0.9 g. (2.5%) of unchanged benzyl bromide, (b) 0.9 g. (7%) of hydrocinnamonitrile, (c) 9.5 g. (43%) of dibenzylacetonitrile, (d) 5.6 g. of viscous oil, b. p. 220–240° (1 mm.), (e) 0.3 g. of stilbene and (f) 4.1 g. of tarry residue. The condensate in the cold trap was 0.5 g. of toluene, b. p. 100–110°, 2,4-dinitro derivative, m. p. 70–70.5°.

Because of the high yield of carbon dioxide it was thought that (d) was tribenzylacetonitrile, and the fact that saponification of this fraction gave only small quantities of benzyl alcohol also indicated this possibility. However, all attempts to isolate this nitrile from the unsaponified material were unsuccessful.

TABLE I

YIELDS OF METHYL BROMIDE AND CARBON DIOXIDE FROM CYANOKETENE ACETAL (0.10 MOLE) AND BENZYL BROMIDE (0.20 MOLE)

| Time, hr. | $CH_3Br$, mole | $CO_2$, mole |
|---|---|---|
| 1 | 0.091 | 0.004 |
| 3 | .146 | .016 |
| 5 | .164 | .030 |
| 16 | .174 | .085 |
| 23 | .175 | .093 |
| 26 | .176 | .096 |
| 37 | .176 | .103[a] |

[a] A semi-quantitative determination of the carbonate present in the absorption tube was made by acidification of an aliquot of the solution and passing the liberated gas into a barium hydroxide solution. A 90% yield of barium carbonate was obtained. A titration of another aliquot of this solution, after acidification with nitric acid, against silver nitrate showed sufficient bromide ion to account for the discrepancy between the amount of carbon dioxide obtained in the absorption bulbs and that obtained as barium carbonate.

**Interrupted Reaction of Cyanoketene Dimethylacetal with Two Equivalents of Benzyl Bromide.**—A mixture of 31.5 g. (0.28 mole) of cyanoketene dimethylacetal and 96.0 g. (0.56 mole) of benzyl bromide was placed in a Claisen flask connected to the absorption train described above and heated at 170–175° for one and one-half hours. During this time 33.0 g. (62%) of methyl bromide was evolved, but the carbon dioxide-trap did not show any gain in weight. The residue was fractionated into: (a) 31.9 g., b. p. 83–84° (15 mm.); (b) 0.6 g., b. p. 46–108° (0.3 mm.); (c) 9.7 g., b. p. 108–122° (0.3 mm.); (d) 0.7 g., b. p. 122–154° (0.3 mm.); (e) 7.8 g. of a thick oil, b. p. 154–163° (0.3 mm.); (f) 24.6 g. of very viscous amber-colored oil, b. p. 177° (0.6 mm.) to 240° (2.5 mm.). Some decomposition during the distillation of (f) was apparent from the pressure rise and fuming which occurred. The tarry residue amounted to 8.5 g.

The refractive index and nitrogen and methoxyl content showed (a) to consist of 26.5 g. of benzyl bromide and 5.4 g. (19.5%) of methyl cyanoacetate (XVI). Fraction (c) contained 10.0% methoxyl and 7.3% nitrogen and gave a positive test for the benzoxy group with concentrated sulfuric acid. When 3.6 g. of (c) was shaken with 25 ml. of 10% aqueous sodium hydroxide the mixture warmed slightly and the oil dissolved. Extraction with ether gave 1.0 g. of benzyl alcohol; acidification of the aqueous residue gave a liquid acid, which was extracted with ether. After drying and evaporation of the solvent, the acid solidified; recrystallization from benzene gave pure benzylcyanoacetic acid, m. p. 101–102°. The aqueous solution, from which this product had been extracted, was evaporated under 20–30 mm. in a bath at 60–70° to a semi-crystalline residue. This was extracted with ether and the extract evaporated to dryness and allowed to stand over concentrated sulfuric acid in a desiccator overnight. The product was 0.3 g. of hygroscopic crystals which, after drying between filter papers, proved to be cyanoacetic acid, m. p. 60–66°. These results show that (c) was a mixture of methyl benzylcyanoacetate and benzyl cyanoacetate in the proportions 3:2 (based on the methoxyl content of (c)). The nitrogen value is in satisfactory agreement with

(16) Mohr, *J. prakt. Chem.*, [2] **71**, 235 (1905).

(17) Benzyl bromide was prepared by allowing a solution of benzyl alcohol in sufficient 48% hydrobromic acid to contain approximately 2.3 equivalents of hydrogen bromide to stand at room temperature. After two days 83–87% yields of benzyl bromide, $n^{25}D$ 1.5700, were obtained. This product, however, contained sufficient benzyl alcohol to give the products noted. The benzyl bromide, $n^{25}D$ 1.5730, was obtained from an alcohol–acid reaction mixture that had stood for two weeks.

this composition (calcd. N, 7.6; found N, 7.2), but the refractive index of such a mixture is 1.530 instead of the observed 1.515. This indicates the presence in the mixture of still another component of lower refractive index than that of either of these esters. Assuming the methoxyl value to be due solely to methyl benzylcyanoacetate, fraction (c) contained 5.9 g. (11%) of that ester. As to the benzyl cyanoacetate, the data indicate only that the maximum yield of that ester was 3.8 g. (8%).

On standing, fraction (e) partially crystallized. Recrystallization from alcohol gave 2.5 g. of methyl dibenzylcyanoacetate (XV), m. p. 76–79°. Further recrystallization raised the melting point to 79–80°, and a mixed melting point with an authentic sample showed no depression. Fraction (f) also partially crystallized on standing. It was treated with ethanol and the insoluble crystals (4.8 g.) of benzyl dibenzylcyanoacetate (XX), m. p. 90–91°, filtered off.

The alcoholic mother liquors from the recrystallizations of (e) and (f) were combined and distilled. After 1.8 g. of forerun, b. p. 67–165° (1 mm.), there was obtained 14.2 g. (19%) of benzyl benzylcyanoacetate (XXI), b. p. 165–195° (1 mm.), $n^{25}D$ 1.5550, which boiled almost entirely at 182–188° (1 mm.). Following this, 2.1 g. of an intermediate fraction, b. p. 195–205° (1 mm.), and 5.4 g. of benzyl dibenzylcyanoacetate, b. p. 210–240° (1.5 mm.), were collected. The latter ester was obtained as a red oil which was taken up in ethanol, seeded and the mixture allowed to stand overnight in the refrigerator; 2.0 g. of relatively pure ester, m. p. 89–90°, separated. Recrystallization from ethanol raised the melting point to 91–92°. The total yield of crude benzyl dibenzylcyanoacetate was 10.2 g. (10%).

**The Reaction of Methyl Cyanoacetates with Benzyl Bromide.** (a) **Methyl Cyanoacetate.**—A mixture of 10.5 g. (0.11 mole) of this ester and 36.8 g. (0.22 mole) of benzyl bromide was heated in an apparatus similar to the one used for the reaction of cyanoketene dimethylacetal and two moles of benzyl bromide. The heating-bath was held at 170–180° throughout the experiment. During the first two and one-half hours there was no reaction but at the end of that time a very slow evolution of gas commenced. The rate of evolution increased very gradually, finally reached a maximum after thirty hours and then slowly subsided until, after forty-seven hours, no more gas was being given off. The system was swept out for fifteen minutes with nitrogen before the products were examined. The yield of methyl bromide, b. p. 4–5°, condensed in the cold trap was 8.2 g. (81%) (after twenty-four hours the yield was 17%). The aqueous potassium hydroxide had gained 3.0 g., which represented a yield of 64% of carbon dioxide. The residue in the flask was distilled at reduced pressure but underwent decomposition (heavy fuming). The distillate consisted of 6.3 g. of benzyl bromide, b. p. 52–70° (1 mm.), and 5.8 g. of liquid, b. p. 70° (1 mm.), 195° (2 mm.), which was not investigated. The principal product was 16 g. of a black, tarry residue.

(b) **Methyl Dibenzylcyanoacetate.**—A mixture of 11.0 g. (0.04 mole) of this ester and 13.5 g. (0.08 mole) of benzyl bromide was heated at 170–180° for twenty-two hours without any apparent reaction. During this time the flask and contents lost no weight and on distillation there were obtained 11.5 g. of benzyl bromide, b. p. 92–97° (22 mm.), 10.4 g. of the original ester, b. p. 185–205° (0.1 mm.), and 1.6 g. of tar residue.

(c) **Methyl Benzylcyanoacetate.**—A mixture of 10.0 g. (0.053 mole) of this ester and 18.2 g. (0.106 mole) of benzyl bromide was heated at 170–180°. No apparent reaction occurred until one and one-half hours had elapsed when a slow evolution of gas commenced. The rate of evolution increased slowly over a period of several hours but had decreased after eleven hours and after twenty hours had ceased altogether. The yields of methyl bromide and carbon dioxide were 60 and 64%, respectively.

The residue was fractionated and the following fractions collected: (a) 9.3 g. of unreacted benzyl bromide, b. p. 92–102° (23 mm.); (b) 1.3 g. (19%) of hydrocinnamonitrile, b. p. 86–98° (0.1 mm.), $n^{25}D$ 1.5242; (c) 5.8 g. (41%) of benzyl benzylcyanoacetate, b. p. 160–190° (0.1 mm.), $n^{25}D$ 1.5530; (d) 2.9 g. of a viscous oil, b. p. 200–230° (1 mm.); and (e) 1.0 g. of tar as residue.

Fraction (d) was dissolved in ethanol and seeded with a crystal of benzyl dibenzylcyanoacetate (XX). On standing in a refrigerator for several days, 0.6 g. (3%) of crystalline XX separated from the solution.

**The Reaction of Cyanoacetic Esters with Benzyl Alcohol.** (a) **Ethyl Cyanoacetate.**—To a solution of 0.3 g. of metallic sodium in 100 ml. of anhydrous benzyl alcohol was added 20.0 g. (0.18 mole) of ethyl cyanoacetate. The clear solution was heated in an oil-bath and when the bath temperature reached 110° a gelatinous precipitate began to separate. At a bath temperature of 170° a rapid evolution of ethanol began and continued for about ten minutes. Heating at 170–175° (bath temperature) was continued for an additional five minutes, after which time distillation of alcohol had practically ceased. Redistillation of the distillate gave 7.6 g. (92%) of ethanol and 0.2 g. of benzyl alcohol.

The excess benzyl alcohol was distilled from the residue at a pressure of 2 mm. and the residual red oil extracted with two 100-ml. portions of anhydrous ether. Finally, the ether-insoluble semi-solid which remained was taken up in cold water containing sodium chloride to prevent emulsification. This mixture was extracted repeatedly with ether and the ether solution combined with the previous ether extracts. This combined extract was washed repeatedly with the dilute aqueous sodium chloride solution, dried over Drierite, after which the ether was evaporated and the residue distilled. The first fraction collected boiled at 65–152° (1.5 mm.). Further distillation was accompanied by marked decomposition which was apparent from the copious fumes and a rise in pressure. A second fraction was collected during this decomposition at a vapor temperature of 152–200°. The undistillable residue weighed 5.9 g.

Redistillation of the first fraction gave 1.4 g. of forerun, b. p. 60–127° (1 mm.), and 6.7 g. of **benzyl cyanoacetate**, b. p. 127–137° (1 mm.). The latter portion of this fraction was selected for analysis and proved to be the pure ester, b. p. 131–137° (1 mm.); $n^{25}D$ 1.5188; $d^{25}_4$ 1.139.

*Anal.* Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.6; H, 5.4; N, 7.6.

The second fraction was fractionated to yield: 1.7 g. of benzyl alcohol, b. p. 64–65° (1.5 mm.); 0.5 g. of an intermediate fraction, b. p. 65–131° (1.5 mm.); 1.1 g. of benzyl cyanoacetate, b. p. 131–141° (1.5 mm.); and 2.6 g. (5.5%) of benzyl benzylcyanoacetate, b. p. 175–195° (1.5 mm.). The total yield of benzyl cyanoacetate was 7.8 g. (25%). The combined residues from the second distillations weighed only 0.3 g.

Attempts to avoid the formation of large amounts of tar in this reaction by the use of no catalyst or an acid catalyst were unsuccessful. In the former instance, no reaction occurred up to 190°. Catalysts such as sulfuric acid, oxalic acid and sulfosalicylic acid caused only sluggish reaction, the yields of alcohol at the end of two hours heating at 180–200° being of the order of only 50%.

(b) **Methyl Benzylcyanoacetate.**—To a solution of 0.3 g. of metallic sodium in 100 ml. of benzyl alcohol was added 22.2 g. (0.118 mole) of methyl benzylcyanoacetate. The mixture was heated at 180–195° for twenty minutes; 4.0 ml. of methanol was collected. The excess benzyl alcohol was distilled at reduced pressure (1.5 mm.) and during this operation an additional 0.5 ml. of methanol collected in the cold trap (total yield, 94%). To the residue was added 150 ml. of anhydrous ether and the precipitated sodium salt removed by filtration. The filtrate was washed with cold water until the washings were no longer alkaline to phenolphthalein and then dried over Drierite. Fractionation of the ether solution yielded: (a) 2.8 g. of forerun, b. p. 55–93° (1 mm.); (b) 3.7 g. (14%) of dibenzylacetonitrile, b. p. 150–175° (1 mm.); (c) 3.9 g. (12.5%) of benzyl benzylcyanoacetate, b. p. 175–188° (1 mm.); and (d) 10.8 g. (26%) of benzyl dibenzylcyanoacetate, b. p. 220–230° (1 mm.).

Recrystallization of (b) and (d) from ethanol gave pure

dibenzylacetonitrile, m. p. 91–92°, and benzyl dibenzylcyanoacetate, m. p. 91–92°, respectively. A center cut from (c) was pure **benzyl benzylcyanoacetate** (XXI), b. p. 180–183° (1 mm.), $n^{25}D$ 1.5533, $d^{25}_4$ 1.124.

*Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3. Found: C, 77.5; H, 5.7; N, 5.3.

From a similar run of 0.13 mole of methyl benzylcyanoacetate, in which the alkaline catalyst was not removed, a partial decarboxylation occurred during the distillation as indicated by an increase in the pressure and a gain in weight of an Ascarite tube in the system. The products of this run were: (a) 3.9 g. (23%) of hydrocinnamonitrile, b. p. 78–92° (1 mm.); (b) 8.0 g. of dibenzylacetonitrile, b. p. 158–170° (1 mm.); and (c) 8.0 g. of an oil, b. p. 180–220° (1 mm.), which crystallized on cooling. Recrystallization of (b) from ethanol gave pure dibenzylacetonitrile, m. p. 91–92°. Extraction of (c) with ether left 2.9 g. (7%) of **tribenzylacetonitrile** (XIX), m. p. 210–217°, which after recrystallization from a chloroform–alcohol mixture gave white needles, m. p. 222–223.5°.

*Anal.* Calcd. for $C_{23}H_{21}N$: C, 88.7; H, 6.8; N, 4.5. Found: C, 88.1; H, 7.0; N, 4.5.

Tribenzylacetonitrile is insoluble in cold, concentrated sulfuric acid, but dissolves when the acid is warmed to 95–100° to give a pale yellow solution, which yields no precipitate on dilution with water. The nitrile (XIX) is recovered unchanged after heating with 75% (by volume) sulfuric acid at 100–125° for five minutes or with refluxing 50% sulfuric acid for fourteen hours; under the former set of conditions dibenzylacetonitrile (XVIII) is converted in good yield to dibenzylacetamide, which, after recrystallization from ethanol–water, melts at 127–129°.

The ether extract from which XIX was separated was distilled and gave an additional 3.2 g. of dibenzylacetonitrile (total yield, 39%) and 2.5 g. (5%) of benzyl dibenzylcyanoacetate, b. p. 200–220° (0.7 mm.), which crystallized on standing and which after recrystallization from ethanol melted at 91–92°.

## Summary

Cyanoketene dimethyl- and diethylacetals have been prepared by the pyrolysis of the corresponding orthoesters and certain of their properties and reactions reported.

With one equivalent of benzyl bromide the dimethylacetal gives methyl dibenzylcyanoacetate as one of the reaction products, showing that the negative cyano substituent makes possible the replacement of the single methylene hydrogen of the acetal.

In the presence of a second equivalent of benzyl bromide the reaction continues with the methyl esters produced by the first equivalent to yield benzyl esters of mono- and dibenzylcyanoacetates, which lose carbon dioxide to yield mono-, di- and tribenzylacetonitriles.

These novel benzylation reactions are also shown to occur with these methyl esters and benzyl alcohol.

MADISON, WISCONSIN RECEIVED AUGUST 14, 1948

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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

# Ketimines and Acylketimines Related to Amidone[1]

BY L. C. CHENEY, R. R. SMITH AND S. B. BINKLEY

Because of the great importance of morphine and related opium alkaloids in medicine and the associated problem of liability to drug addiction, it is not surprising that information pertaining to the discovery of the potent analgesic drug, amidone (I)[2a,b] has already stimulated rather extensive chemical and clinical investigation.[3–18]

Inasmuch as it has been reported[19] that nuclear substitution of the two phenyl groups in amidone does not enhance analgesic potency or lead to more desirable activity, attention has been focused in this Laboratory on other structural modifications, including the synthesis of certain carbinols, esters,[20] ketimines and acylated ketimines related to amidone. Several examples of the latter class have been described by other investigators[7,12,17] since the completion of this work.

Although ketimines are commonly dealt with as unstable intermediates in the synthesis of ketones by means of the Grignard reagent[21] and the Hoesch and Hoesch–Houben syntheses, few, if any, imines or acylimines of physiologically active ketones appear to have been studied pharmacologically. Our interest was initially aroused in this class of compounds when the remarkably stable isoamidone imine (II)[12,17] was unexpectedly isolated while carrying out the synthesis of amidone in essential accordance

(1) Presented before the Medicinal Division of the American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(2) (a) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of Publication Board, Department of Commerce, Washington, D. C., p. 96; (b) B. I. O. S. Final Report, No. 116, Item No. 24, pp. 51, 56, 65.

(3) Scott and Chen, *J. Pharmacol.*, **87**, 63 (1946).

(4) Scott, Robins and Chen, *Science*, **104**, 587 (1946).

(5) Thorp, *Brit. J. Pharmacol.*, **1**, 113 (1946).

(6) Thorp, Walton and Ofner, *Nature*, **159**, 679 (1947).

(7) Easton, Gardner and Stevens, THIS JOURNAL, **69**, 976, 2941 (1947).

(8) Gentling and Lundy, *Proc. Mayo Clinic*, **22**, 249 (1947).

(9) Elliott, *Fed. Proc.*, **6**, 327 (1947).

(10) Thorp, Walton and Ofner, *Nature*, **160**, 605 (1947).

(11) Blicke and Zambito, paper presented before the Division of Medicinal Chemistry, the American Chemical Society, Atlantic City, N. J., April 16, 1947.

(12) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

(13) Brode and Hill, *ibid.*, **69**, 724 (1947).

(14) Scott, Kohlstaedt and Chen, *Anesthesia & Analgesia*, **26**, 12 (1947).

(15) Hewer and Keele, *Lancet*, **2**, 28 (1947).

(16) Eddy, *J. Am. Pharm. Assoc.*, **8**, 537 (1947).

(17) Easton, Gardner, Evanick and Stevens, THIS JOURNAL, **70**, 76 (1948).

(18) Schultz and Sprague, *ibid.*, **70**, 48 (1948).

(19) Reference 1, p. 93.

(20) Speeter, Byrd and Cheney, *ibid.*, **71**, 57 (1949).

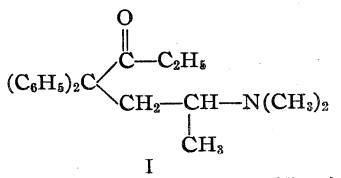
(21) Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft m. b. H., Stuttgart, 1944, pp. 500, 587.

TABLE I

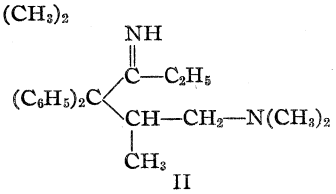
$(C_6H_5)_2RC—C(=NR^1)C_2H_5$ KETIMINES AND ACYL DERIVATIVES

| No. | R | $R^1$ | Formula | M. p. or b. p. °C. |
|---|---|---|---|---|
| 412-10H | $—CH_2—CH_2—NC_4H_8O$ | H | $C_{22}H_{28}N_2O$ | 198–202 (1 mm.) |
| 412-12H | $—CH_2—CH_2—NC_5H_{10}$ | H | $C_{23}H_{30}N$ | 191–193 (1 mm.) |
| C-11912-B | $—CH(CH_3)—CH_2—N(CH_3)_2$ | H | $C_{21}H_{28}N_2\cdot HCl$<br>$C_{21}H_{28}N_2\cdot 2HCl$[c] | 151–152<br>205–206 (dec.) |
| 317-12 | $—CH_2—CH(CH_3)—N(CH_3)_2$ | H | $C_{21}H_{28}N$[d] | 54–56 |
| 489-7H | $—CH_2—CH(CH_3)—N(CH_3)_2$ | $—C(=O)—CH_3$ | $C_{23}H_{30}N_2O$[e]<br>$C_{23}H_{30}N_2O\cdot HCl$[e] | 134–135<br>219–220 |
| C-14719B | $—CH(CH_3)—CH_2—N(CH_3)_2$ | $—C(=O)—CH_3$ | $C_{23}H_{30}N_2O\cdot HCl$[e] | 214–215 |
| 489-16H | $—CH_2—CH_2—NC_4H_8O$ | $—C(=O)—C_2H_5$ | $C_{25}H_{32}N_2O_2\cdot HCl$ | 231–232.5 |
| 489-43H | $—CH_2—CH(CH_3)—N(CH_3)_2$ | $—C(=O)—C_2H_5$ | $C_{24}H_{32}N_2O$<br>$C_{24}H_{32}N_2O\cdot HCl$ | 146–147<br>202–203 |
| 412-16H | $—CH_2—CH_2—NC_5H_{10}$ | $—C(=O)—CH_3$ | $C_{25}H_{32}N_2O\cdot HCl$ | 209–210 |
| 412-11H | $—CH_2—CH_2—NC_4H_8O$ | $—C(=O)—CH_3$ | $C_{24}H_{30}N_2O_2\cdot HCl$ | 202–203 |

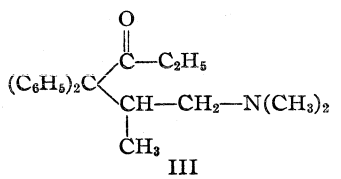
with the original procedure.[1] For the sake of convenience lithium amide was advantageously substituted for sodium amide in the condensation of diphenylacetonitrile with 1-dimethylamino-2 chloropropane. The oily reaction product proved



I



II



III

to be a mixture of isomeric nitriles[12,18] which yielded amidone (I) and isoamidone imine (II) on treatment with ethylmagnesium bromide followed by hydrolysis in accordance with the original directions.[1] In order to ensure complete hydrolysis, the ketimine (II) was refluxed with constant boiling hydrochloric acid for thirty-six hours, whereupon isoamidone (III)[7,8,10,17] was obtained in quantitative yield. The preparation of the dihydrochloride and the acetyl derivative completed the characterization of isoamidone imine.

It is noteworthy that ketimines of the isoamidone series are not appreciably hydrolyzed under the drastic conditions imposed by the German procedure for the preparation of amidone, for sufficient heat is evolved to volatilize practically all of the xylene used as the solvent when the Grignard reaction product is poured into the dilute hydrochloric acid. Other examples of sterically hindered, stable ketimines, however, can be found in the literature. Typical examples are the ketimines of trichloroacetomesitylene[22] and 1,2-diphenyl-2-methyl-1-propanone.[23]

The less sterically hindered and consequently less stable ketimines were isolated in favorable yields by conducting the hydrolysis of the bromomagnesium salt in the cold with ammonium chloride. The imines were then extracted with ether from basic solution and purified by distillation *in vacuo*. They are all low-melting solids or viscous yellow oils, some of which gradually evolve ammonia on standing at room temperature. Precipitation of the ketimines from ethereal solution with hydrogen chloride produced hygroscopic acidic salts which melted over a wide range with the evolution of gas. Cloke[24] has noted a similar phenomenon in working with other ketimines. The acylketimines were prepared by treating a benzene solution of the imine with the appropriate acid chloride or, alternatively, by adopting the general procedure of Moureau and Mignonac[25] and adding dropwise the acid chloride directly to the cold bromomagnesium salt of the ketimine.

(22) Houben and Fischer, *Ber.*, **63**, 2455 (1930).
(23) Bruzau, *Compt. rend.*, **190**, 496 (1930).
(24) Cloke, THIS JOURNAL, **62**, 117 (1940).
(25) Moureu and Mignonac, *Compt. rend.*, **170**, 1353 (1920).

TABLE I (*Continued*)

| Recryst. from | Analyses, % Calculated C | Calculated H | Calculated N | Found C | Found H | Found N | Mouse I. P. $LD/50$[a] | S. C.[a] g. pig anal. dose | Activity[b] index |
|---|---|---|---|---|---|---|---|---|---|
| | 78.6 | 8.39 | 8.33 | 78.5 | 7.85 | 8.38 | 136 ± 15.7 | 15 | 9.1 |
| | 82.7 | 9.04 | 8.38 | 82.4 | 8.96 | 8.30 | 56 ± 11.4 | 12.5 | 4.5 |
| Isopropyl alcohol | 73.2 | 8.48 | 8.13 | 73.2 | 8.65 | 8.26 | 60.5 ± 9 | 15 | 4 |
| Acetone | 66.3 | 7.88 | | 66.2 | 7.71 | | | | |
| Skellysolve A | | | 9.04 | | | 8.7 | 41 ± 3 | 12.5 | 3 |
| Skellysolve B | 78.8 | 8.62 | | 78.7 | 8.63 | | | | |
| Ethyl acetate | 71.4 | 8.08 | | 71.5 | 7.96 | | 151 ± 1.2 | 12.5 | 12 |
| Abs. alcohol–ether | 71.4 | 8.08 | 7.28 | 70.7 | 8.08 | 6.97 | 171 ± 7 | 30 | 5.7 |
| Abs. alcohol–ether | 70.0 | 7.76 | | 70.5 | 7.38 | | 67 ± 8 | 12.5 | 5.4 |
| Abs. alcohol | 79.2 | 8.86 | 7.69 | 79.3 | 9.40 | 7.22 | | | |
| Ethyl acetate | 72.0 | 8.3 | 7.0 | 71.4 | 8.04 | 6.68 | 122 ± 7 | 25 | 4.9 |
| Dioxane | 72.6 | 8.08 | 6.78 | 72.3 | 7.91 | 7.14 | 187 ± 11.7 | 50 | 3.7 |
| Acetone | 69.7 | 7.55 | | 69.2 | 7.35 | | 232.8 ± 33.2 | 75 | 3.1 |

[a] Values expressed with standard error in milligrams per kilogram. [b] Comparative values for amidone: $LD/50$ = 29 ± 1.7, analgesic dose = 12.5, activity index = 2.3; for isoamidone: $LD/50$ = 39 ± 2.8, analgesic dose = 12.5, activity index = 3.1. [c] References 7, 12 and 17. [d] Prepared by Dr. M. E. Speeter. [e] Reference 17.

## Experimental

**Preparation and Separation of 4-Dimethylamino-2,2-diphenyl-3-methylbutyronitrile and 4-Dimethylamino-2,2-diphenylvaleronitrile.**—The following procedure is believed to offer some advantages over the published method.[12] To a well-stirred suspension of 36.3 g. (1.58 moles) of lithium amide in 285 ml. of dry benzene there was added 278 g. (1.44 moles) of diphenylacetonitrile over a period of twenty minutes while the temperature was maintained at 45–50°. After the addition was completed, the mixture was heated at 45–50° for one and one-half hours. It was then cooled to 20–25° and 181.1 g. (1.49 moles) of 1-dimethylamino-2-chloropropane[1] was added. The mixture was stirred for one hour and then heated gradually until a vigorous reaction ensued with the evolution of ammonia. Heating was discontinued until the reaction moderated, whereupon the mixture was refluxed for an additional two hours, then cooled and poured into 800 ml. of water. The benzene layer was separated, washed twice with water and extracted with 6 *N* hydrochloric acid until a precipitate no longer formed in a sample of extract when made basic. The combined extracts were washed once with ether, made strongly alkaline with sodium hydroxide solution and extracted with a total of 700 ml. of ether in three portions. After the combined ether extracts were washed with water and saturated salt solution, they were dried over anhydrous potassium carbonate and the filtered solution was concentrated and cooled to induce crystallization of the higher melting nitrile, which was collected by filtration. Further concentration and cooling led to the total isolation of 187.5 g. (46.8% yield) of 4-dimethylamino-2,2-diphenylvaleronitrile,[12,13] m. p. 90–91°.

The removal of residual ether left a viscous yellow-brown oil which was dissolved in 200 ml. of absolute alcohol, and treated with an excess of absolute alcoholic hydrogen chloride. Small white crystals of the aminonitrile hydrochloride (145.5 g.), m. p. 222–225°, separated. Recrystallization from absolute alcohol (350 ml.) elevated the melting point to 225–226°. The purified hydrochloride (119.4 g.) was dissolved in water, made alkaline with ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried over potassium carbonate, and solvent was removed to obtain 103.2 g. (25.8% yield) of 4-dimethylamino-2,2-diphenyl-3-methylbutyronitrile,[12,13] in the form of a colorless oil which crystallized on scratching and cooling to melt at 67.5–69°. The structure of each isomer has been definitely established.[12]

Repeated attempts to detect the presence of a third aminonitrile, the precursor of Isoamidone I,[7,17] as a product of the alkylation were unsuccessful.

The other alkylations of diphenylacetonitrile were conducted in accordance with the above procedure. When isomeric aminonitriles were not involved, the product was readily purified by distillation through a Vigreux column.

**6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (Isoamidone) (III) Hydrochloride[7,10,17] Monohydrate.**—4-Dimethylamino-2,2-diphenyl-3-methylbutyronitrile was converted into isoamidone imine (II)[12,17] in accordance with the general procedure described for the preparation of ketimines. The product, b. p. 148–153° at 1 mm., was obtained in 76.7% yield. Treatment of an isopropyl alcohol solution of the base with one equivalent of hydrogen chloride followed by dilution with ether precipitated a monohydrochloride monohydrate of II which melted at 89–142°, dec., after being dried in the air. The anhydrous monohydrochloride of II, m. p. 151–152°, was obtained by heating a sample of the hydrate *in vacuo*, first at 61° for two hours, and then at 81° for three hours.

A mixture of 10 g. (0.0275 mole) of the monohydrochloride monohydrate of II was refluxed for thirty-six hours with 90 ml. of concentrated hydrochloric acid. The solution was cooled in ice and made strongly alkaline by the addition of 50 g. of sodium hydroxide dissolved in 145 ml. of water. Prolonged cooling and scratching with a glass rod failed to crystallize the oily base. It was therefore extracted with 400 ml. of ether and the washed extract was dried for four hours over anhydrous potas-

sium carbonate. To the cooled filtered solution there was added an excess of absolute alcoholic hydrogen chloride. After the white hydrochloride which precipitated was collected and dried *in vacuo* overnight over phosphorus pentoxide, it melted at 119–122° and weighed 9.8 g. The melting point was not altered by recrystallization of a sample from dilute hydrochloric acid by the addition of a saturated solution of sodium chloride. Analyses disclosed that the compound, in spite of its subjection to the drying agents, was actually the monohydrate.

*Anal.* Calcd. for $C_{21}H_{28}NOCl \cdot H_2O$: C, 69.4; H, 8.33; N, 3.87. Found: C, 68.9; H, 8.23; N, 3.83.

Following recrystallization of the monohydrate from ethyl acetate and desiccation over phosphorus pentoxide, the salt melted at 155–158° with previous softening but still contained water. The anhydrous material has been reported to melt at 190–193°.[17]

**4,4-Diphenyl-6-(4-morpholinyl)-3-iminohexane (412-10H).**—The general procedure employed for the preparation of the ketimines is illustrated by the following typical example. To the well-stirred solution of ethylmagnesium bromide prepared in the customary manner from 13.4 g. (0.544 mole) of magnesium turnings, 67.9 g. (0.62 mole) of ethyl bromide and 115 ml. of anhydrous ether, there was added during a period of fifteen minutes a solution of 84.9 g. (0.277 mole) of 2,2-diphenyl-4-(4-morpholinyl)-butyronitrile dissolved in 91 ml. of dry xylene. The mixture was stirred and refluxed for four and one-half hours, during which time a greenish gray precipitate formed. A nitrogen atmosphere was provided throughout the reaction. The thick suspension was cooled, diluted with about 100 ml. of ether to facilitate the transfer and poured slowly into a stirred, cooled mixture composed of 150 g. of ice and 300 ml. of water. Following completion of the hydrolysis, 150 ml. of concentrated ammonium hydroxide was added, the ether phase was separated and the aqueous layer extracted twice with 200-ml. portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous potassium carbonate. After the removal of the solvent, distillation through a short Vigreux column afforded 73.8 g. (79.2%) of the ketimine as a pale yellow viscous oil, b. p. 198–202° at less than 1 mm. It separated from ether in the form of colorless crystals, m. p. 85–86.5°.

**6-Dimethylamino-4,4-diphenyl-5-methyl-3-(acetylimino)-hexane Hydrochloride[17] (C-14719B).**—A cold aqueous solution of 3 g. (0.00875 mole) of II monohydrochloride was made alkaline with 20% sodium hydroxide solution and extracted with 50 ml. of benzene. The benzene layer was washed with water, dried over anhydrous potassium carbonate and filtered. Treatment of the solution with 10.5 ml. of a molar solution of acetyl chloride in benzene (a 20% excess) caused a precipitate to form. After refluxing the mixture for two hours, solvent was distilled under reduced pressure and the white residue was boiled with 25 ml. of ethyl acetate, cooled and filtered to obtain 3 g. (89% yield) of fine white crystals, m. p. 214–215°. A sample was dissolved in hot absolute alcohol and precipitated with ether without changing the melting point.

**6-Dimethylamino-4,4-diphenyl-3-(propionylimino)-heptane Hydrochloride (489-43H).**—An ethereal solution of ethylmagnesium bromide prepared from 4.9 g. (0.2 mole) of magnesium, 115 ml. of dry ether and 24.5 g. (0.225 mole) of ethyl bromide in a nitrogen atmosphere was treated with 30 g. (0.108 mole) of 4-dimethylamino-2,2-diphenylvaleronitrile dissolved in 200 ml. of dry xylene and the stirred mixture was refluxed for four and one-half hours. The resulting suspension was chilled in an ice–salt-bath throughout the dropwise addition of 20.8 g. (0.224 mole) of propionyl chloride dissolved in 50 ml. of ether. After standing overnight the yellow-green suspension was stirred into a mixture of 300 g. of ice, 150 g. of ammonium chloride and 150 ml. of water. When all solid had dissolved, the solution was made alkaline with ammonium hydroxide, which caused the precipitation of 5.9 g. of the free acylimine, m. p. 142–145°. Upon treatment of the washed and dried ether layer with hydrogen chloride, 31 g. of hydrochloride precipitated which was dissolved in water and converted into 11.3 g. of the crude base, m. p. 139–144°, by the addition of ammonia. Recrystallization of the combined fractions from 65 ml. of ethanol produced 14.2 g. (35% yield) of the pure base, m. p. 146–147°.

The hydrochloride was prepared by dissolving 13.2 g. of the base in 20 ml. of warm benzene, diluting with 200 ml. of dry ether and bubbling an excess of hydrogen chloride into the solution. The strongly acidic salt (15 g.) which precipitated was boiled under reflux with 140 ml. of anhydrous ethyl acetate until no more hydrogen chloride was evolved. Cooling, filtration and desiccation over phosphorus pentoxide afforded 9.3 g. of small white crystals, m. p. 202–203°.

### Pharmacology

The pharmacological evaluation of these compounds was conducted by Dr. Carl C. Pfeiffer of the University of Illinois Medical School and the preliminary data are presented here with his permission. White mice injected intraperitoneally were used for the toxicity determinations. A modified Wolff–Hardy technique applied to guinea pigs was used to measure minimal subcutaneous analgesic dosage. Activity index is the mouse $LD_{50}$ divided by the guinea pig analgesic dose, a device which serves as an effective basis for comparison.

From the tabulation it can be observed that in both the amidone and isoamidone series the order of decreasing toxicity and increasing activity index is ketone:ketimine:acetylketimine. Owing to comparable potency and significantly lower toxicity, all of the tabulated ketimines and their acyl derivatives possess as high or more favorable activity indices than those of amidone and isoamidone. With reference to the acylated ketimines, the amidone side chain confers highest potency and index when the acyl group is acetyl. Conversely, in the case of the β-morpholinylethyl compounds the propionyl group is more effective than the acetyl.

It should be mentioned that since the *levo*-isomer of amidone has been shown to be the pharmacologically active form,[2,10] one should expect the *l*-isomer of amidone imine and its acyl derivative to be approximately twice as potent as the tabulated values. Since the intermediate nitrile can be resolved without difficulty,[10] the synthesis of these optically active forms appears practicable.

**Acknowledgments.**—The authors are indebted to Dr. Carl C. Pfeiffer for the pharmacological data and to Mr. Richard M. Downing for the microanalyses.

## Summary

Some representative ketimines and acylated ketimines related to amidone have been described. Preliminary pharmacological data indicate that these compounds are potent analgesic drugs which are less toxic than the corresponding ketones.

SYRACUSE, NEW YORK RECEIVED JUNE 3, 1948

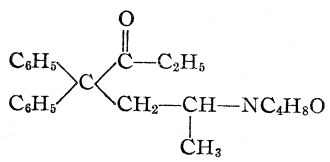
[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

# Analgesic Carbinols and Esters Related to Amidone (Methadon)[1]

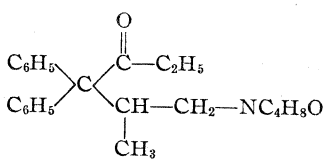
BY MERRILL E. SPEETER, WENDELL M. BYRD, LEE C. CHENEY AND S. B. BINKLEY

A number of ketones and imines related to the potent analgesic Amidone (Methadon) have been prepared[2,3,4,5,6,7,8] but no modifications of the Amidone structure involving other variations in the ketone moiety of the molecule have been reported. The present paper deals with the reduction of Amidone and a number of related ketones, esters and acids to carbinols. Since esterification of the carbinols potentiated the activity in a number of cases, a variety of carbinol derivatives was prepared.

The synthesis of the parent ketones in most cases was carried out using already established procedures.[2,6] When isomers were expected, hydrolysis of the Grignard reaction in the last step paralleled the original German procedure,[2] and isolation of the ketones and imines was accomplished through a combination of recrystallization and distillation methods. The morpholinyl analogs of Amidone and Isoamidone were assigned structures (I) and (II) through consideration of the



I



II

similarities of the isolation procedures for these compounds to the isolation of the corresponding dimethylamino derivatives. The ketone II, isolated in part as the imine, was given the Isoamidone structure while ketone I, which separated as a highly insoluble hydrobromide salt, was assigned the Amidone structure. No degradative studies were carried out to definitely establish the position of the methyl group.[9]

Amidone was readily reduced catalytically by the use of Adams platinum oxide catalyst, but not with palladium. Isoamidone was resistant to all attempts at catalytic hydrogenation under a number of different conditions. The same resistance toward catalytic reduction conditions was shown by the morpholinyl analogs of Amidone I and Isoamidone II. The compound believed to have the structure represented by I was readily reduced by the same conditions employed for Amidone. Compound II was recovered unchanged from all catalytic reduction experiments. This behavior toward reduction of the "iso" forms of these members of the Amidone series is apparently related to steric factors. It was found that lithium aluminum hydride reduces Amidone, Isoamidone and the morpholinyl analogs in good yield.

Reduction of Amidone and the related branched chain compounds introduces a second asymmetric carbon atom in the molecule, making two diastereoisomeric pairs possible. One pure compound was isolated from the reduction of Amidone in sufficiently high yield (98%) to indicate that another isomer, if formed at all, is formed only in small amounts. The same compound was isolated from both the catalytic and lithium aluminum hydride reductions.

The primary alcohols and their esters in the Amidone series were prepared through the lithium aluminum hydride reductions of the appropriate ester or acid. 2,2-Diphenyl-4-(N-morpholinyl)-1-butanol was obtained in 85% yield from the corresponding ethyl $\gamma$-N-morpholinyl-$\alpha,\alpha$-diphenyl butyrate. Reduction of $\gamma$-dimethylamino-$\alpha,\alpha$-diphenylvaleric acid with lithium aluminum hydride proceeded in poor yield because of the low solubility of the acid in ether.

The general method for preparation of the esters involved refluxing of the carbinol in ethyl acetate with an excess of the acyl halide. It was found that some of the esters were hydrolyzed on attempted recrystallization from alcohols although a number of esters in the morpholinyl series, and esters of the higher molecular weight acids were stable in boiling alcohol.

**Pharmacology.**—In Table I physical constants on a number of ketones related to Amidone are given together with pharmacological data. Dr. Pfeiffer and co-workers have found the $LD_{50}$ for

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(2) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of the Publication Board, Department of Commerce, Washington, D. C., pp. 91–98.

(3) Thorpe, Walton and Ofner, *Nature*, **159**, 679 (1947).

(4) Blicke and Zambito, paper presented before the Division of Medicinal Chemistry, American Chemical Society, Atlantic City, N. J., April 16, 1947.

(5) Easton, Gardner and Stevens, THIS JOURNAL, **69**, 976, 2941 (1947).

(6) Easton, Gardner, Evanick and Stevens, *ibid.*, **70**, 76 (1948).

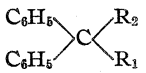
(7) Schultz, Robb and Sprague, *ibid.*, **69**, 2454 (1947).

(8) Cheney, Smith and Binkley, *ibid.*, **71**, 53 (1949).

(9) Since this work was completed P. B. L-70056 (Frames 1229–1232B) reported pharmacological data on compound I although no physical constants or proof of structure were given. The Germans claim I to be a potent analgesic in animals and predict II would have much lower activity through analogy with other series. These data support our structural assignments in view of the pharmacological data for I and II in Table I.

TABLE I[a]

KETONES AND OTHER INTERMEDIATES



| $R_1$ | $R_2$ | M. p., °C. uncor. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | $LD_{50}$ | Analgesic dose | Activity index |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2CH_2NC_4H_8O$ | $C_2H_5CO$ | 229–230 | $C_{22}H_{27}NO_2 \cdot HCl$ | 70.75 | 70.60 | 7.55 | 7.48 | 114 ± 10 | 15 | 7+ |
| $CH_2CH_2NC_4H_8O$ | $C_2H_5CO$ | 114–115 | $C_{22}H_{27}NO_2$ | 78.30 | 78.20 | 8.08 | 7.96 | | | |
| $CH_2CH(CH_3)NC_4H_8O$ | $C_2H_5CO$ | 222–223 | $C_{23}H_{29}NO_2 \cdot HCl$ | 71.18 | 71.50 | 7.78 | 7.64 | 131 ± 7 | 12.5 | 10.5 |
| $CH_2CH(CH_3)NC_4H_8O$ | $C_2H_5CO$ | 230–231 | $C_{23}H_{29}NO_2 \cdot HBr$ | 63.83 | 63.70 | 6.99 | 6.84 | | | |
| $CH(CH_3)CH_2NC_4H_8O$ | $C_2H_5CO$ | 229–230 | $C_{23}H_{29}NO_2 \cdot H_2O \cdot HCl$ | 68.03 | 67.80 | 7.95 | 7.24 | 194 ± 18 | 50 | 4 |
| $CH(CH_3)CH_2NC_4H_8O$ | $C_2H_5CO$ | 139–140 | $C_{23}H_{29}NO_2$ | 78.58 | 78.80 | 8.35 | 8.48 | | | |
| $CH_2CH_2NC_5H_{10}$ | $C_2H_5CO$ | 142–143 | $C_{23}H_{29}NO \cdot HNO_3$ | 69.30 | 69.10 | 7.58 | 7.45 | 79 ± 4 | 15 | 5.3 |
| $CH_2CH_2NC_4H_8O$ | $COOC_2H_5$ | 168–169 | $C_{22}H_{27}NO_2 \cdot HCl$ | 67.90 | 67.80 | 7.25 | 7.38 | 257 ± 6 | 12.5 | 20 |
| $CH_2CH_2NC_4H_8O$ | $COOC_2H_5$ | 68–70 | $C_{22}H_{27}NO_2$ | 74.80 | 74.80 | 7.71 | 7.56 | | | |
| $CH_2CH(CH_3)N(CH_3)_2$ | $CH_3CO$ | 164–165 | $C_{20}H_{25}NO \cdot HBr$ | 64.00 | 64.10 | 6.93 | 7.10 | 57 ± 1 | 20 | 3 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $COOC_2H_5$ | 178–179 | $C_{21}H_{27}NO_2 \cdot HCl$ | 69.80 | 69.70 | 7.80 | 7.87 | 49.3 | 20 | 2.5 |
| $CH_2CH(CH_3)N(CH_3)_2$ | COOH | 200–201 | $C_{19}H_{23}NO_2$ | 76.80 | 76.90 | 7.79 | 8.13 | | | |

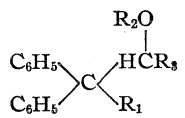
[a] See footnotes to Table II for data on methods of pharmacological evaluation and comparison data with Amidone and Isoamidone.

Amidone intraperitoneally in the mouse to be 28.6 ± 2 mg./kg. while the minimal analgesic dose subcutaneously in the guinea pig is 12.5 mg./kg. It is thus apparent that several of the morpholinyl ketones and esters are nearly as potent as Amidone on a weight basis and much less toxic.

The pharmacological data summarized in Table II establish several generalizations for these series. In all cases the alcohols are less toxic than the corresponding ketones; however, the analgesic activity of the carbinols is unpredictable, being undetectable in some cases. The acetate esters are uniformly more analgesic and more toxic than the parent ketones. The increase in analgesic potency of the acetate esters over the ketones is in all cases sufficient to produce a marked increase in the activity index in spite of the increased toxicity.

TABLE II

CARBINOLS RELATED TO AMIDONE AND THEIR ESTERS



| $R_1$ | $R_2$ | M. p., °C. uncor. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | $LD_{50}$[a] | Analgesic[b] dose | Activity[c] index |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $R_3 = C_2H_5$ | | | | | | | |
| $CH_2CH(CH_3)N(CH_3)_2$ | H | 206–207 | $C_{21}H_{29}NO \cdot HCl$ | 72.47 | 72.20 | 8.68 | 8.56 | 76 ± 1.5 | 12.5 | 6 |
| $CH_2CH(CH_3)N(CH_3)_2$ | H | 101–102 | $C_{21}H_{29}NO$ | 80.95 | 80.80 | 9.37 | 9.34 | | | |
| $CH_2CH(CH_3)N(CH_3)_2$ | $CH_3CO$ | 213–214 | $C_{23}H_{31}NO_2 \cdot HCl$ | 70.70 | 70.30 | 8.28 | 8.38 | 13.8 ± 2.50 | 1.0 | 14 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $CH_3CH_2CO$ | 185–186 | $C_{24}H_{33}NO_2 \cdot HCl$ | 71.34 | 71.10 | 8.48 | 8.55 | 35 ± 6 | 7.6 | 5 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $CH_3CH_2OCO$ | 167–169 | $C_{24}H_{33}NO_3 \cdot HCl$ | 68.70 | 68.70 | 8.17 | 8.15 | 39.6 ± 4.1 | 10.0 | 4 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $C_6H_5CH_2CO$ | 172–173 | $C_{29}H_{35}NO_2 \cdot HCl$ | 74.71 | 74.40 | 7.79 | 7.92 | 76.0 ± 11 | 20.0 | 3.8 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $C_6H_5CO$ | 135–136 | $C_{28}H_{33}NO_2 \cdot H_2O \cdot HCl$ | 71.50 | 71.30 | 7.70 | 7.42 | 206 ± 16 | 50.0 | 4.0 |
| $CH_2CH(CH_3)N(CH_3)_2$ | $C_6H_5NHCO$ | 150–151 | $C_{28}H_{34}N_2O_2 \cdot H_2O \cdot HCl$ | 69.32 | 69.30 | 7.69 | 7.57 | 134 ± 16 | 100.0 | 1.3 |
| $CH(CH_3)CH_2N(CH_3)_2$ | H | 204–205 | $C_{21}H_{29}NO \cdot HCl$ | 72.47 | 71.80 | 8.68 | 8.69 | Inact. 50 mg./kg. | | |
| $CH(CH_2)CH_2N(CH_3)_2$ | H | 109–110 | $C_{21}H_{29}NO$ | 80.95 | 80.80 | 9.37 | 9.59 | | | |
| $CH(CH_3)CH_2N(CH_3)_2$ | $CH_3CO$ | 228–229 | $C_{23}H_{31}NO_2 \cdot HCl$ | 70.70 | 70.80 | 8.28 | 8.40 | 44.5 ± 2.5 | 4.0 | 11.0 |
| $CH_2CH_2NC_4H_8O$ | H | 185–186 | $C_{22}H_{29}NO_2 \cdot HNO_3$ | 65.70 | 65.50 | 7.48 | 7.31 | 182 ± 7 | 15 | 12 |
| $CH_2CH_2NC_4H_8O$ | H | 130–131 | $C_{22}H_{29}NO_2$ | 77.80 | 77.70 | 8.63 | 8.89 | | | |
| $CH_2CH_2NC_4H_8O$ | $CH_3CO$ | 242–243 | $C_{24}H_{31}NO_3 \cdot HCl$ | 68.90 | 69.00 | 7.72 | 7.94 | 106 ± 9 | 4 | 26 |
| $CH_2CH(CH_3)NC_4H_8O$ | H | 225–226 | $C_{23}H_{31}NO_2 \cdot HCl$ | 70.80 | 70.80 | 8.33 | 8.23 | ..... | ..[d] | |
| $CH_2CH(CH_3)NC_4H_8O$ | H | 118–119 | $C_{23}H_{31}NO_2$ | 78.30 | 78.10 | 8.85 | 8.83 | | | |
| $CH_2CH(CH_2)NC_4H_8O$ | $CH_3CO$ | 221–222 | $C_{25}H_{33}NO_3 \cdot HCl$ | 69.46 | 69.50 | 7.94 | 8.22 | 79.8 ± 12 | 2 | 40 |
| $CH_2CH_2CH_2N(CH_3)_2$ | H | 172–173 | $C_{21}H_{29}NO \cdot HCl$ | 72.46 | 72.60 | 8.68 | 8.72 | 185 | 75 | 2.5 |
| $CH_2CH_2CH_2N(CH_4)_2$ | $CH_3CO$ | 183–184 | $C_{23}H_{31}NO_2 \cdot HCl$ | 70.70 | 70.70 | 8.28 | 7.92 | 110.2 ± 3.7 | 25 | 4.5 |
| $CH_2CH_2N(CH_3)_2$ | H | 156–157 | $C_{20}H_{27}NO \cdot HNO_3$ | 66.70 | 66.50 | 7.84 | 7.22 | Inactive 30 mg./kg. | | |
| $CH_2CH(CH_3)N(CH_3)_2$ | H[e] | [f] | $C_{21}H_{35}NO$ | 79.50 | 79.80 | 11.11 | 11.10 | 103 ± 8 | 15 | 7 |
| | | | $R_3 = H$ | | | | | | | |
| $CH_2CH_2NC_4H_8O$ | H | 244–245 | $C_{20}H_{25}NO_2 \cdot HCl$ | 69.00 | 68.90 | 7.54 | 7.66 | Inactive 75 mg./kg. | | |
| $CH_2CH_2NC_4H_8O$ | H | 155–156 | $C_{20}H_{25}NO_2$ | 77.12 | 76.70 | 8.10 | 8.28 | 296 | ..[g] | .. |
| $CH_2CH_2NC_4H_8O$ | $CH_3CO$ | 159–160 | $C_{22}H_{27}NO_3 \cdot HCl$ | 67.74 | 67.20 | 7.24 | 7.02 | 175 | 60 | 3 |
| $CH_2CH(CH_3)N(CH_3)_2$ | H | 210–211 | $C_{19}H_{25}NO \cdot HCl$ | 71.30 | 71.30 | 8.19 | 8.47 | 120 | 50 | 2 |

[a] Intraperitoneal LD/50 in the mouse in mg./kg. The pharmacological data were obtained by Dr. Carl C. Pfeiffer and coworkers of the University of Illinois Medical School. These data were presented in part at the Federation Meetings, Atlantic City, March 15–19, 1948. See *Federation Proceedings*, **7**, 255 (1948). [b] Subcutaneous analgesic dose in the guinea pig in mg./kg. [c] For comparison the activity index for Amidone by the same pharmacological methods is 2.3, for Isoamidone 3.1 (Pfeiffer and co-workers). [d] No analgesia or toxicity found. [e] In this compound one phenyl ring has been reduced to cyclohexyl. [f] The product was obtained as an oil, b. p. 150–153° (1 mm.). [g] Inactive at 75 mg./kg.

**Acknowledgments.**—We wish to express our appreciation to Mr. R. M. Downing for the microanalyses recorded herein. We also wish to thank Dr. Carl Pfeiffer of the University of Illinois Medical School for permission to present the pharmacological data.

## Experimental

**Preparation of Substituted Acetonitriles.**—Diphenylacetonitrile was purchased commercially[10] while the intermediate dialkylaminoalkyl halides were prepared according to literature methods or minor modifications thereof.[2] Published procedures for the preparation of the dialkylaminoalkylacetonitriles[2] were used with the substitution in all cases of lithium amide[11] for sodium amide.

**2,2-Diphenyl-4-(N-morpholinyl)-valeronitrile and 2,2-Diphenyl-3-methyl-4-(N-morpholinyl)-butyronitrile.**—The mixed nitriles were obtained in 90% yield through the condensation of 1-(N-morpholinyl)-2-chloropropane[12] with diphenylacetonitrile. On standing the heavy oil partially crystallized. A portion of these crystals melted at 100–102° after two recrystallizations from ethanol.

*Anal.* Calcd. for $C_{21}H_{24}N_2O$: C, 78.75; H, 7.55. Found: C, 78.60; H, 7.03.

**Preparation of Ketones.**—The ketones were prepared through Grignard reactions on the nitriles or through hydrolysis of imines isolated from the Grignard reactions.[4,8]

**4,4-Diphenyl-6-(N-morpholinyl)-3-heptanone and 4,4-Diphenyl-5-methyl-6-(N-morpholinyl)-3-iminohexane.**—A solution of 320 g. (1.0 mole) of the isomeric nitriles, from the previous reaction, in 400 ml. of dry xylene was added to a solution of ethylmagnesium bromide prepared from 49 g. (2 g. atoms) of magnesium and 218 g. (2 moles) of ethyl bromide in 500 ml. of anhydrous ether. All operations were carried out under nitrogen in a three-necked flask using a mercury-seal stirrer. After the addition of the nitriles the mixture was refluxed for six hours. The green reaction mixture was then poured as rapidly as possible into a 4-liter beaker containing 1 liter of water and 500 ml. of concentrated hydrochloric acid. The hydrolysis was exceedingly vigorous and the ether and xylene were vaporized. When the mixture had cooled somewhat, 500 ml. of benzene was added whereupon three layers separated. In a few hours the heavy, red middle layer sank to the bottom and began to crystallize. After forty-eight hours the brown solid was filtered, and washed with ether; yield 300 g. (calcd. yield of one isomer 216 g.). After recrystallization from 1500 ml. of water, the product weighed 235 g. and after recrystallization from 2500 ml. of isopropanol 171 g.; m. p. 230–231°, yield of ketone I, 79.3%. Analysis established that the compound was the hydrobromide salt of the ketone.

The acid layer from the hydrolysis of the Grignard reaction was made basic and extracted with benzene. The extracts were dried over potassium carbonate and concentrated. The heavy oil which separated was dissolved in hot Skellysolve C; the cooled solution deposited crystals, m. p. 104–105°. From the nitrogen analysis and the rapid reaction of the material with acetyl chloride the compound was considered to be 6-morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane, the imine of II.

*Anal.* Calcd. for $C_{23}H_{30}N_2O$: N, 7.99. Found: N, 8.03.

**Acetylation of 6-Morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane.**—Five grams of the imine was dissolved in 50 ml. of benzene and 5 ml. of acetyl chloride added. After a few minutes the mixture began to deposit crystals. The crystals were filtered after three hours and recrystallized from ethyl acetate. The yield of 6-morpholinyl-5-methyl-4,4-diphenyl-3-acetyliminohexane hydrochloride was 4 g.; m. p. 223–224°.

*Anal.* Calcd. for $C_{25}H_{32}N_2O_2 \cdot HCl$: C, 69.95; H, 7.76. Found: C, 69.50; H, 7.90.

**Hydrolysis of 6-Morpholinyl-5-methyl-4,4-diphenyl-3-iminohexane.**—Two grams of the imine was refluxed for sixteen hours in 50 ml. of constant-boiling hydrochloric acid. The acid was distilled under reduced pressure and the residue made basic. The oil was extracted with ether and the ether solution dried and concentrated. The oily residue was dissolved in hot ethanol. The 6-morpholinyl-5-methyl-4,4-diphenyl-3-hexanone which separated from the cold solution melted at 139–140°.

*Anal.* Calcd. for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.34. Found: C, 78.80; H, 7.90.

**Investigation of Mother Liquors from Ketone I Recrystallization.**—To obtain the ketone II present, the filtrates from the water recrystallization of I were made basic, and the heavy oil which separated dissolved in hot ethanol. The cooled solution deposited crystals which were recrystallized from Skellysolve C, m. p. 139–140°, undepressed with previously obtained ketone II. Additional amounts of ketone II were isolated from isopropyl alcohol recrystallization mother liquors of I. The mother liquors were concentrated, and the oily mixture of ketone and imine hydrolyzed with concentrated hydrochloric acid. The oil liberated through addition of alkali was extracted and distilled, after removal of solvent; b. p. 187–190° (1.6 mm.), m. p. 138–140°. The total yield of ketone II was 75 g. or 42%.

**γ-Dimethylamino-α,α-diphenylvaleric Acid.**—A mixture of 49.5 g. (0.178 mole) of 4-dimethylamino-2,2-diphenylvaleronitrile and 150 ml. of 70% sulfuric acid was heated at 150° for five hours, cooled and poured into water. The precipitated acid was filtered, dissolved in dilute alkali, and the filtered solution made slightly acidic. The precipitated acid was recrystallized from methyl isobutyl ketone and then from water; m. p. 200–201°.

**Carbinols.**—The following preparation illustrates the general method used for the catalytic reduction of the ketones.

Ten grams (0.03 mole) of Amidone hydrochloride was dissolved in 100 ml. of distilled water and 0.5 g. of Adams platinum oxide catalyst[13] added. The compound was then hydrogenated at room temperature under an initial hydrogen pressure of 55 pounds. After two hours the calculated amount of hydrogen was absorbed. The catalyst was filtered, the filtrate made basic and the oil was taken up into ether. The dried ether solution was saturated with dry hydrogen chloride and the oil which first separated soon crystallized. The precipitated material melted at 206–207°. Recrystallization from isopropyl alcohol or methyl isobutyl ketone gave well formed plates or prisms which melted at 195–196°. Prolonged drying at 100° under reduced pressure did not raise this value. The compound is evidently dimorphic.

*Anal.* Calcd. for $C_{21}H_{29}NO \cdot HCl$: N, 4.03. Found: N, 3.99.

**6-Dimethylamino-5-methyl-4,4-diphenyl-3-hexanol.**—This reaction illustrates the general method used for lithium aluminum hydride[14] reductions.[15] A solution of 18.5 g. (0.06 mole) of Isoamidone base in 300 ml. of ether was shaken for three hours with potassium hydroxide pellets to remove last traces of moisture. The dry solution was then added to a solution of 2.5 g. (0.067 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether. The reaction was mildly exothermic, and the mixture refluxed gently. The mixture was refluxed for twelve hours, cooled in an ice-bath, and 200 ml. of 10% aqueous sodium hydroxide added dropwise. The ether layer was decanted and the aqueous layer extracted with ether. The combined ether solutions were washed with water and dried over potassium carbonate. After removal of the ether the oily residue crystal-

(10) Dow Chemical Company, Midland, Michigan.

(11) Metalloy, Inc., Minneapolis, Minnesota.

(12) Prepared from the corresponding alcohol with thionyl chloride.[2] The hydrochloride melted at 172–173°. The alcohol, prepared from morpholine and propylene chlorohydrin, boiled at 85–87° (7 mm.).

(13) American Platinum Company, Newark, New Jersey.

(14) Metal Hydrides, Inc., Beverly, Massachusetts.

(15) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

lized. The crude yield was quantitative. The solid was recrystallized from Skellysolve C and melted at 108–110°.

**6-Dimethylamino-4-cyclohexyl-4-phenyl-3-hexanol.**—Ten grams (0.03 mole) of Amidone was dissolved in 60 ml. of glacial acetic acid and 1 g. of platinum oxide catalyst added. This mixture was shaken at 50–60° with an initial hydrogen pressure of 55 lb. During a seventy-two-hour period, the amount of hydrogen absorbed was somewhat more than that calculated for the complete hydrogenation of one benzene ring and reduction of the ketone to the carbinol. At this stage addition of fresh catalyst caused no additional absorption of hydrogen. The catalyst was filtered, and the filtrate concentrated under reduced pressure. The residue was made basic and extracted into ether. The solvent was removed from the dried extract and the residue distilled; b. p. 150–153° (1 mm.). Although a crystalline phosphate was obtained, all other salts prepared were oils.

**6-Dimethylamino-4,4-diphenyl-3-acetoxyheptane Hydrochloride.**—A mixture of 19 g. (0.061 mole) of Amidone carbinol, 250 ml. of anhydrous ethyl acetate and 7.8 g. (0.100 mole) of acetyl chloride was refluxed for two hours, and then cooled in an ice-bath. The precipitated crystals were recrystallized from ethyl acetate; yield 21.5 g. (90%), m. p. 213–214°.

**6-Dimethylamino-4,4-diphenyl-3-(N-phenylcarbamyloxy)-heptane Hydrochloride**—Ten g. (0.033 mole) of Amidone carbinol was dissolved in ether and 6.7 g. (0.06 mole) of phenyl isocyanate added. After four hours a small quantity of diphenylurea had separated from the reaction mixture. The ether solution was decanted, and the diphenylurea recrystallized from ethanol; mixed m. p. 238–239°. The ether solution was extracted with 300 ml. of 4 *N* hydrochloric acid. After some time the crystalline hydrochloride separated from the extract, m. p. 150–151° after recrystallization from equal parts of methanol and hydrochloric acid.

## Summary

1. Data on a number of ketones related to Amidone are presented.

2. The reduction of the ketones with lithium aluminum hydride and by catalytic hydrogenation is described.

3. Esters, carbonates and carbamates prepared from the carbinols are presented.

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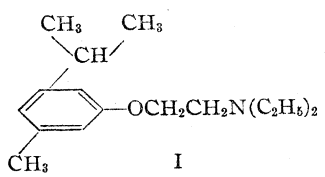
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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

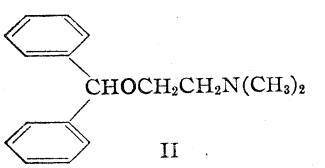
# Alkylaminoalkyl Ethers of the Benzylphenols

BY L. C. CHENEY, RICHARD R. SMITH AND S. B. BINKLEY

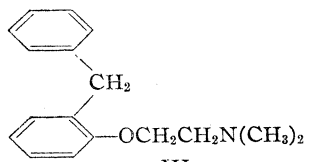
In 1937 Bovet and Staub reported that a series of phenol ethers synthesized by E. Fourneau exerted a protective action against histamine intoxication[1] and anaphylactic shock[2] in guinea pigs. This discovery initiated the ensuing numerous pharmacological investigations of synthetic compounds which have been admirably reviewed by Loew.[3] The more extensive work of Staub[4] suggested that in general the ortho-substituted phenol ethers manifested higher antihistaminic activity than their para and meta isomers. Although the thymol derivative 929F (I) was selected as the most promising compound of this class, toxicity and untoward side-effects militated against its clinical usefulness.




I




II




III

In 1945 Loew and his colleagues[5] announced their discovery of the potent antihistaminic action of benzohydryl β-dimethylaminoethyl ether (Benadryl) (II) synthesized by Rieveschl and Huber.[6]

Inasmuch as none of the Fourneau phenoxyethylamines investigated,[1,2,4] were substituted by a benzyl group, it was considered of interest to prepare 2-benzylphenyl β-dimethylaminoethyl ether (III) for pharmacological evaluation, especially since III is an isomer and vinylog of Benadryl (II). The present paper describes the preparation of II, its 4-isomer, certain homologs and salts thereof.

Pharmacological assays which will be reported elsewhere indicate that III (C-5581H) is to date more promising medicinally than any of the tabulated homologs. Its water-soluble hydrochloride is relatively non-toxic and it elicits a high order of antihistaminic and local anesthetic activity in animals. Clinical tests are in progress.

With the exception of the two hydrogenated derivatives (489-1 and 489-2), all of the com-

(1) Bovet and Staub, *Compt. rend. soc. biol.*, **124**, 547 (1937).
(2) Staub and Bovet, *ibid.*, **125**, 818 (1937).
(3) Loew, *Physiol. Revs.*, **27**, 542 (1947).
(4) Staub, *Ann. inst. Pasteur*, **63**, 400 (1939).
(5) Loew, Kaiser and Moore, *J. Pharmacol.*, **83**, 120 (1945).
(6) Wilson Frederick Huber, Doctoral Dissertation, University of Cincinnati, 1943, Rieveschl, U. S. Patent 2,421,714 (1947).

pounds in Table I were prepared by two general procedures. Method A consisted in condensing sodium benzylphenate with the appropriate aminoalkyl chloride. It is of interest that method A gave a low yield of 518-14 owing to the formation of considerable quantities of low-boiling material which was not investigated. Consequently method B, wherein an ω-bromoalkyl ether of a benzylphenol is caused to react with a particular amine, proved to be the procedure of choice for the synthesis of an ether bearing a secondary amino group.

Because of the marked tendency of the free dialkylaminoalkyl chlorides to polymerize when heated in the presence of polar solvents, the method developed by Dalgliesh[7] for the synthesis of 929F (I) proved less satisfactory than the use of toluene as a solvent. For the same reason sodium or sodium hydride was selected instead of sodium alkoxides for preparing the sodium salts of the phenols. A nitrogen atmosphere guarded against oxidation.

## Experimental[8]

**The Benzylphenols.**—Pure 2-benzylphenol required for this series was first prepared by the method of Claisen[9] in yields ranging from 25 to 35%, a procedure advantageous in the sense that practically none of the 4-isomer is produced. The residues did contain, however, appreciable amounts of the strongly cryptophenolic 2,6-dibenzylphenol,[9,10] which served for the preparation of compound 489-27 (Table I). When larger quantities of 2-benzylphenol were required it proved advantageous to separate the isomeric benzylphenols in commercially available "Santophen 7"[11] by utilizing the marked difference in the water solubility of their barium salts. The procedure is based on a Bayer patent.[12] Another patented method of separating the isomers was not thoroughly investigated. It takes advantage of the remarkably high solubility of the alkali salts of 2-benzylphenol in an inert, non-aqueous organic solvent such as xylene.[13]

**Separation of 2-Benzylphenol from 4-Benzylphenol in "Santophen 7."**[11,12]—To a boiling solution of 1950 g. of technical grade barium hydroxide octahydrate in 7.5 liters of water contained in a 12-l. round-bottom flask was added 1500 g. of molten "Santophen 7." The mixture was boiled for ten to twelve minutes and then cooled to 10–12°. The insoluble barium 4-benzylphenate was collected in a large Büchner funnel and sucked as dry as possible by the use of a rubber dam. The cake was broken up and digested with occasional stirring on the steam-bath for at least two hours with sufficient 6 *N* hydrochloric acid (*ca.* 1300 ml.) to render the medium strongly acidic (*p*H 2). Crude 4-benzylphenol, m. p. 81–84°, crystallized on cooling and stirring. One crystallization from carbon tetrachloride afforded pure 4-benzylphenol, m. p. 84°.

The original filtrate containing the soluble barium 2-benzylphenate was promptly acidified to *p*H 2 (to avoid the formation of purple oxidation products) with about 650 ml. of concentrated hydrochloric acid while cooling and stirring the mixture. It was found expedient to seed the oily product to induce crystallization. When the temperature sank below 8°, the light-brown crystals were collected by suction and dissolved in two liters of hot benzene. The solution was then transferred to a separatory funnel, the water was withdrawn and the benzene layer was washed with two 500-ml. portions of water for the removal of residual inorganic salt. Azeotropic distillation of the water and benzene was then continued until approximately 375 ml. of benzene remained in the flask, whereupon the warm benzene solution was poured into 1500 ml. of petroleum ether (b. p. 77–115°). Cooling and filtration yielded 582 to 654 g. of practically colorless 2-benzylphenol, m. p. 51.5–53°.

**The Dialkylaminoalkyl Chlorides.**—Treatment of the commercially available amino alcohols with thionyl chloride in benzene solution[14] afforded practically quantitative yields of the corresponding chloride hydrochlorides. In general the free bases were not distilled, but rather prepared from a 20 or 30% excess of the salt shortly before use. Dry toluene solutions of the bases appear to be quite stable at room temperature. The Amidone intermediates, 1-dimethylamino-2-propanol and 1-dimethylamino-2-chloropropane, required for 338-19A and B were prepared satisfactorily as originally described[15]; also the I. G. Farbenindustrie procedures[16] for the preparation of β-1-piperidylethyl chloride and the corresponding alcohol produced excellent results.

β-Cyclohexylaminoethyl chloride hydrochloride, m. p. 219–219.5°, an intermediate for 518-14, was prepared in 97.5% yield by Dr. W. B. Wheatley from N-cyclohexylethanolamine.[17] *Anal.* Calcd. for $C_8H_{17}NCl_2$: C, 48.5; H, 8.7; N, 7.1. Found: C, 48.7; H, 8.7; N, 7.0.

**Method A. 2-Benzylphenyl β-Dimethylaminoethyl Ether (C-5581H) (III) Hydrochloride.**—Twelve hundred and ten grams (8.4 moles) of β-dimethylaminoethyl chloride hydrochloride[14] was covered with 1 liter of toluene and cooled in an ice-bath. Into the well-stirred suspension was slowly added a cold solution of 400 g. (10 moles) of sodium hydroxide dissolved in 400 ml. of water. The toluene solution of the base was decanted and the aqueous mixture was extracted further by decantation with 1 liter of toluene divided into five portions. (In the event an emulsion forms at this point, the addition of a relatively large quantity of anhydrous potassium carbonate permits filtration.) The combined extracts were dried overnight (or at least two hours on the mechanical shaker) over anhydrous potassium carbonate. Into a twelve-liter three-neck flask equipped with a sealed stirrer, dropping funnel and reflux condenser were placed 1 liter of dry toluene and 138 g. (6.0 moles) of sodium, and a dry nitrogen atmosphere was provided. A Glas-Col heating mantle was utilized to heat the toluene to boiling. When the sodium had melted the stirrer was started and a solution of 1159 g. (6.3 moles) of 2-benzylphenol (dried over phosphorus pentoxide) in 2360 ml. of dry toluene was added *via* dropping funnel at such a rate as to maintain vigorous boiling without external heating. After the addition was complete the mixture was refluxed and stirred until all of the sodium had dissolved. The previously prepared toluene solution of β-dimethylaminoethyl chloride was then added rapidly through the dropping funnel and the stirred mixture was boiled under reflux for seventeen hours. Steam distillation then served to remove the toluene and to volatilize or polymerize excess β-dimethylaminoethyl chloride. The oily product was extracted from the cooled aqueous phase with approximately 3 liters of ether. Combined ether extracts were washed with 20% sodium hydroxide solution, then with a saturated solution of sodium chloride and dried over anhydrous potassium carbonate. Distillation of the product through a twelve-inch Vigreux column afforded 1444 g. (94.3%

(7) Dalgliesh, *J. Chem. Soc.*, 677 (1944).

(8) All melting points are uncorrected.

(9) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

(10) Short and Stewart, *J. Chem. Soc.*, 556 (1929).

(11) "Santophen 7" is a mixture of 2- and 4-benzylphenol supplied by Monsanto Chemical Company. It is evidently produced by the condensation of benzyl chloride with a large excess of phenol at 150° [McMaster and Bruner, *Ind. Eng. Chem.*, **28**, 505 (1936)].

(12) Kropp, Schranz and Schulemann, U. S. Patent 1,580,052 (1926); [*C. A.*, **20**, 1631 (1926)].

(13) Akimoff, U. S. Patent 2,016,848 (1935); [*C. A.*, **29**, 8008 (1935)].

(14) Slotta and Behnisch, *Ber.*, **65**, 754 (1935).

(15) O. P. B. 981, U. S. Department of Commerce, July, 1945, p. 96.

(16) *Ibid.*, page 41.

(17) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

TABLE I

ALKAMINE ETHERS OF BENZYLPHENOLS AND THEIR HYDROCHLORIDES

| No. | R (R–O–R¹) | R¹ | Method of prepn. | Yield % |
|---|---|---|---|---|
| C-5581H | 2-Benzylphenyl | $-CH_2CH_2-N(CH_3)_2$ | A | 94.3 |
| 338-20 | 4-Benzylphenyl | $-CH_2CH_2-N(CH_3)_2$ | A | 64.5 |
| 338-19A | 2-Benzylphenyl | $-CH(CH_3)-CH_2-N(CH_3)_2$ | A | 58.1 |
| 338-19B | 2-Benzylphenyl | $-CH_2-CH(CH_3)-N(CH_3)_2$ | A | 58.1 |
| 338-22 | 2-Benzylphenyl | $-CH_2CH_2-N(C_2H_5)_2$ | A | 76.8 |
| 546-1 | 2-Benzylphenyl | $-CH_2CH_2CH_2-N$(piperidine) | B | 68.3 |
| 546-2 | 2-Benzylphenyl | $-CH_2CH_2CH_2-N$(3-methylpiperidine) | B | 66.2 |
| 546-3 | 2-Benzylphenyl | $-CH_2CH_2CH_2-N(CH_3)_2$ | B | 86.6 |
| 546-13 | 2-Benzylphenyl | $-CH_2CH_2CH_2-N(C_4H_9\text{-}n)_2$ | A | 98.2 |
| 546-14 | 4-Benzylphenyl | $-CH_2CH_2CH_2-N(C_4H_9\text{-}n)_2$ | A | 75 |
| 612-9 | 2-Benzylphenyl | $-CH_2CH_2-N$(pyrrolidine) | B | 73.5 |
| 612-10 | 2-Benzylphenyl | $-CH_2CH_2-N$(3-methylpiperidine) | B | 75.5 |
| 380-1 | 2-Benzylphenyl | $-CH_2CH_2-N$(morpholine) | A | 85.5[a] |
| 380-3 | 2-Benzylphenyl | $-CH_2CH_2-N$(piperidine) | A | 55.3[a] |
| 489-27 | 2,6-Dibenzylphenyl | $-CH_2CH_2-N(CH_3)_2$ | A | 31.5[a] |
| 489-2 | Hexahydro-2-benzylphenyl[b,c] | $-CH_2CH_2-N(CH_3)_2$ | Hydrogenation | 25.7[a] |
| 489-1 | 2-Cyclohexylmethyl-cyclohexyl[c] | $-CH_2CH_2-N(CH_3)_2$ | Hydrogenation | 38[a] |
| 489-9 | 2-Benzylphenyl | $-CH_2CH_2-NH-CH(CH_3)_2$ | B | 81.2[a] |
| 489-10 | 2-Benzylphenyl | $-CH_2CH_2-NH-CH_3$ | B | 22.3[a,d] |
| 518-14 | 2-Benzylphenyl | $-CH_2CH_2-NH-CH$(cyclohexyl) | A | 34.8 |

[a] Yield of pure hydrochloride. [b] The structure of the selective hydrogenation product was not established. [c] Geometrical isomers were not isolated. [d] The low yield is ascribed to the escape of methylamine from the pressure bottle.

yield based on the sodium) of colorless oil, b. p. 141–144° at less than 1 mm.

The hydrochloride was precipitated quantitatively from ether solution by means of commercial hydrogen chloride. Recrystallization from methyl isobutyl ketone produced 1457 g. (88.3% yield) of colorless crystals, m. p. 119–120°.

**Method B. 2-Benzylphenyl β-Isopropylaminoethyl Ether Hydrochloride (489-9).**—Under an atmosphere of dry nitrogen a solution of 193.4 g. (1.05 moles) of 2-benzylphenol in 200 ml. of dry toluene was added dropwise to a stirred, boiling suspension of 24.0 g. (1.0 mole) of sodium hydride (du Pont) in 100 ml. of dry toluene. After all of the sodium hydride had reacted, 563.6 g. (3 moles) of ethylene bromide was added and the mixture was refluxed for sixty hours. The reaction product, which was still strongly alkaline, was washed successively with water, 20% sodium hydroxide solution, saturated salt solution and then dried over anhydrous magnesium sulfate. After nearly all of the toluene had been distilled under reduced pressure the product crystallized. Recrystallization from isopropyl alcohol produced 142.4 g. (48.8% yield) of crude 2-benzylphenyl β-bromoethyl ether, m. p. 82–85°, which contained a high carbon impurity.

*Anal.* Calcd. for $C_{15}H_{15}BrO$: C, 62.0; H, 5.20. Found: C, 64.4; H, 5.23.

Into a well-cooled solution of 56.3 g. (0.193 mole) of the above crude bromo ether in 80 ml. of dioxane contained in a pressure bottle was slowly poured 34.2 g. (0.58 mole) of isopropylamine. The bottle was sealed and heated in the steam cone overnight (seventeen hours). The light yellow solid which remained after removal of the solvent and excess isopropylamine under reduced pressure was treated with an excess of sodium hydroxide and the liberated base was taken up in ether. Upon shaking the ether extract with 6 *N* hydrochloric acid, the hydrochloride precipitated. After recrystallization from water 47.7 g. (81.2% yield based on the crude bromoethyl ether) of white crystals, m. p. 174–175°, were obtained.

Crude 2-benzylphenyl γ-bromopropyl ether, m. p. 137–163°, was prepared in a 60% yield by the method described for the above β-bromoethyl homolog. For those syntheses involving amines boiling above 100° the use of a pressure bottle was not required. The bromo ether was refluxed overnight with a large excess of the appropriate amine.

TABLE I (*Continued*)

| B. p., °C at 1 mm. | HCl M. p., °C. | Recryst. from | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|
| 141–144 | 119–120 | MeCOBu-*i* | $C_{17}H_{21}NO\cdot HCl$ | 70.1 | 70.0 | 7.6 | 7.7 |
| 152–153 | 179–182 | *i*-PrOH | $C_{17}H_{21}NO\cdot HCl$ | 70.1 | 70.2 | 7.6 | 7.6 |
| 148–152 | 75–80 | EtOAc | $C_{18}H_{23}NO\cdot HCl$ | 70.7 | 70.8 | 7.9 | 8.3 |
| 152–157 | 170–171.5 | $Me_2CO$ | $C_{18}H_{23}NO\cdot HCl$ | 70.7 | 70.7 | 7.9 | 7.9 |
| 160–164 | 158–159 | *i*-PrOH | $C_{19}H_{25}NO\cdot HCl$ | 71.5 | 71.4 | 8.2 | 8.1 |
| 192–198 | 167–168 | *i*-PrOH | $C_{21}H_{27}NO\cdot HCl$ | 73.0 | 72.9 | 8.2 | 8.3 |
| 194.5–197 | 149–150 | *i*-PrOH | $C_{22}H_{29}NO\cdot HCl$ | 73.6 | 73.7 | 8.4 | 8.5 |
| 149–153 | 159–160 | *i*-PrOH | $C_{18}H_{23}NO\cdot HCl$ | 70.8 | 70.6 | 7.9 | 7.8 |
| 174–176 | 86–89 | EtOAc | $C_{24}H_{35}NO\cdot HCl$ | 74.1 | 74.2 | 9.3 | 9.5 |
| 197–200 | 96–98 | EtOAc | $C_{24}H_{35}NO\cdot HCl$ | 74.1 | 73.6 | 9.3 | 9.4 |
| 152–163 | 140–141.5 | $Me_2CO$ | $C_{19}H_{23}NO\cdot HCl$ | 72.1 | 72.1 | 7.6 | 7.7 |
| 151–167 | 139.5–142 | MeCOBu-*i* | $C_{21}H_{28}NO\cdot HCl$ | 72.8 | 73.3 | 8.4 | 8.3 |
| ..... | 184–185 | MeOH | $C_{19}H_{23}NO_2\cdot HCl$ | 68.5 | 68.5 | 7.3 | 7.2 |
| 180–183 | 139–141 | $Me_2CO$ | $C_{20}H_{25}NO\cdot HCl$ | 73.0 | 72.4 | 7.9 | 7.8 |
| ..... | 143–144.5 | MeCOBu-*i* | $C_{24}H_{27}NO\cdot HCl$ | 75.6 | 75.5 | 7.4 | 7.3 |
| ..... | 170 | $Me_2CO$ | $C_{17}H_{27}NO\cdot HCl$ | 68.7 | 68.6 | 9.5 | 9.2 |
| ..... | 128.5–129 | EtOAc | $C_{17}H_{33}NO\cdot HCl$ | 67.0 | 67.1 | 11.6 | 11.1 |
| ..... | 174–175 | $H_2O$ | $C_{18}H_{23}NO\cdot HCl$ | 70.8 | 70.8 | 7.9 | 7.9 |
| ..... | 178.5–179.5 | Abs. EtOH | $C_{16}H_{19}NO\cdot HCl$ | 69.3 | 69.5 | 7.2 | 7.1 |
| 165–171 | 182–183.5 | *i*-PrOH | $C_{21}H_{27}NO\cdot HCl$ | 72.9 | 73.3 | 8.2 | 8.3 |

**2-Benzylphenyl β-Dimethylaminoisopropyl Ether (339-19A) and 2-Benzylphenyl β-Dimethylaminopropyl Ether (338-19B).**—To a solution of sodium methoxide prepared from 6.9 g. (0.3 mole) of sodium and 117 ml. of absolute methanol was added 55.2 g. (0.3 mole) of 2-benzylphenol. Following removal of excess methanol under reduced pressure, the sodium 2-benzylphenate was dissolved in 180 ml. of dry toluene and refluxed with a large excess (59.5 g.) of freshly distilled 1-dimethylamino-2-chloropropane[15] under an atmosphere of nitrogen for five and one-half hours. The basic material was extracted with dilute hydrochloric acid. Combined acid extracts were made strongly basic with alkali and extracted with ether. The ether solution was washed thoroughly with water, dried over potassium carbonate and distilled through a twelve-inch Vigreux column to obtain two fractions: $F_1$, b. p. 148–152°, (27.5 g.) and $F_2$, b. p. 152.5–157°, (19.4 g.) at less than 1 mm. Both fractions were dissolved in ether and precipitated with dry hydrogen chloride. $F_1$ yielded 33.5 g. of hydrochloride, m. p. 80–132°, which afforded 7.4 g. of product, m. p. 168–169°, on recrystallization from acetone. The hydrochloride from $F_2$ weighed 23.5 g. and melted at 73–84°. Treatment with hot acetone produced 5.4 g. of material, m. p. 161–164°. On boiling the two fractions with a large volume of acetone 10.4 g. of the less soluble isomer, m. p. 170–171.5°, was obtained in pure form. The acetone mother liquors were concentrated to dryness and the gummy residue (29.6 g.) was recrystallized twice from ethyl acetate to obtain 23.0 g. of the lower melting isomer, m. p. 75–80°. The structures of these anticipated isomers derived from the halide utilized in the original synthesis of Amidone[15] have been assigned by analogy with the physical properties of Amidone and Isoamidone.[18]

**2-Cyclohexylmethylcyclohexyl β-Dimethylaminoethyl Ether (489-1) Hydrochloride.**—Twenty-five and five-tenths grams (0.10 mole) of 2-benzylphenyl β-dimethylaminoethyl ether was dissolved in 100 ml. of glacial acetic acid. One gram of Adams platinum catalyst and 6 ml. of concentrated sulfuric acid were added and the compound was hydrogenated under a gage pressure of 50 lb. of hydrogen and a temperature of 60° until 0.6 mole of hydrogen was taken up. The catalyst was filtered off and the filtrate was allowed to stand until a duplicate preparation was carried out. After removing the acetic acid from the combined filtrates under reduced pressure, the residue was taken up in 150 ml. of water, made alkaline with 20% sodium hydroxide solution, and extracted into ether. The

(18) For pertinent references see Cheney, Smith and Binkley, THIS JOURNAL, **71**, 53 (1949).

ether solution was washed with water and then dried over anhydrous potassium carbonate. The hydrochloride was precipitated with dry hydrogen chloride to obtain 7.1 g. of product, m. p. 128–129°, which afforded 6.6 g. of material which melted at 128.5–129° after recrystallization from ethyl acetate. On concentrating the ether solution and recrystallizing the residue from ethyl acetate 4.9 g. of additional material was obtained. The over-all yield therefore was 31.5%.

**Hexahydro-2-benzylphenyl β-Dimethylaminoethyl Ether (489-2) Hydrochloride.**—The same quantities and procedure were used as described for 489-1 with the exception that the hydrogenation was interrupted when only one-half as much hydrogen had been taken up. From the partial reduction of 51 g. (0.2 mole) of C-5581H there was obtained 41.9 g. of material melting over the range 117–150°. Two recrystallizations from acetone led to the isolation of 15.3 g. (25.7% yield) of white crystals melting at 169–170°.

**Acknowledgment.**—The authors wish to thank Mr. Richard M. Downing for the microanalyses and the assistance of Messrs. L. E. Lorensen and H. J. Reiche and Dr. W. B. Wheatley is gratefully acknowledged.

## Summary

1. The preparation of 2-benzylphenol and 4-benzylphenol is described.

2. Twenty dialkylaminoalkyl ethers of the benzylphenols and their hydrochlorides are reported.

3. 2-Benzylphenyl β-dimethylaminoethyl ether hydrochloride manifests potent antihistaminic and local anesthetic activity.

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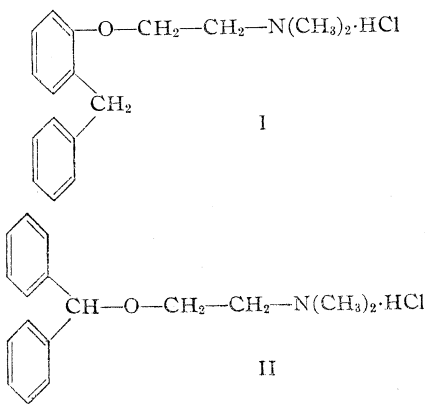
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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

# β-Dimethylaminoethyl Ethers of Substituted 2-Benzylphenols

BY W. B. WHEATLEY, L. C. CHENEY AND S. B. BINKLEY

It has been observed that 2-benzylphenyl β-dimethylaminoethyl ether hydrochloride (I) possesses greater antihistaminic activity when tested




I




II

in guinea pigs than Benadryl (II).[1] Therefore the synthesis of β-dimethylaminoethyl ethers of various substituted 2-benzylphenols was undertaken in order to ascertain whether substitution enhances the antihistaminic activity of the parent compound. In this paper is described a number of new basic ethers related to I, all incorporating the β-dimethylaminoethyl group, but with substitutions in the 2-benzylphenyl portion of the molecule.

In general the basic ethers were prepared by heating together the substituted sodium 2-benzylphenolate and β-dimethylaminoethyl chloride in an inert solvent such as toluene. The products were isolated by standard procedures and converted to the hydrochlorides by saturation of the ether solution of the amines with dry hydrogen chloride. These hydrochlorides are white crystalline compounds, most of which are quite soluble in water.

A survey of the literature reveals that 2-benzylphenol may be prepared in a number of ways. Phenol may be condensed with benzyl chloride alone[2] or with either benzyl chloride or the alcohol in the presence of a variety of catalysts[3] to yield a mixture of 2- and 4-benzylphenols together with traces of benzyl phenyl ether. On the other hand, the use of sodium phenolate and benzyl chloride yields the 2-isomer almost exclusively.[4] A considerable amount of ether is formed, but it can be removed easily by extraction, whereas the separation of 2- and 4-benzylphenols requires more involved procedures.[2,5] For this reason, the method of Claisen, *et al.*,[4] was used to prepare the intermediate substituted 2-benzylphenols (see Table I). Several of those prepared from sodium phenolate and a substituted benzyl chloride were treated with barium hydroxide[5a] in order to insure complete removal of the 4-isomer, but as the amount of 4-isomers appeared to be negligible, this treatment was omitted in later preparations. Sodium hydride, which has recently become available commercially, was employed exclusively to prepare the sodium phenolates, both in the Claisen reaction and in the Williamson ether synthesis. It was found that in the quantities used in the laboratory, sodium hydride is more conveniently handled than sodium, and reacts rapidly and completely with phenolic compounds.

(1) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949).

(2) McMaster and Bruner, *Ind. Eng. Chem.*, **28**, 505 (1936).

(3) (a) Rennie, *J. Chem. Soc.*, **49**, 406 (1886); (b) Huston, THIS JOURNAL, **46**, 2275 (1924); (c) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721 (1929); (d) Andrianov, *J. Gen. Chem.* (*U. S. S. R.*), **6**, 846 (1936).

(4) Claisen, *et al.*, *Ann.*, **442**, 210 (1925).

(5) (a) Kropp, Schranz and Schuleman, U. S. Patent 1,580,053, April 6, 1926; (b) Akimoff, U. S. Patent 2,016,848, Oct. 8, 1945.

TABLE I

SUBSTITUTED 2-BENZYLPHENOLS

| No. | Phenol | Yield, % | B. p., °C. | Mm. | M. p., °C. or $n^{25}D$ | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| III | 4-*t*-Butyl-2-benzyl- | 40 | 157–160 | 2.5 | 1.5624 | $C_{17}H_{20}O$ | 84.9 | 85.0 | 8.4 | 8.8 |
| IV | 4-Cyclohexyl-2-benzyl- | 55 | 188–196 | 2 | 87.5–89.0[b] | $C_{19}H_{22}O$ | 85.7 | 85.7 | 8.3 | 8.2 |
| V | 4-Methoxy-2-benzyl- | 46 | 198–212 | 7 | 103.5–104.5[c] | $C_{14}H_{14}O_2$ | 78.5 | 78.5 | 6.6 | 6.4 |
| VI | 4-Ethoxy-2-benzyl- | 42 | 165–167 | 1 | 1.5820 | $C_{15}H_{16}O_2$ | 78.9 | 79.1 | 7.1 | 7.3 |
| VII | 2-(4′-Isopropylbenzyl)- | 38[a] | 134–137 | 1 | 1.5722 | $C_{16}H_{18}O$ | 84.9 | 84.6 | 8.0 | 7.9 |
| VIII | 2-(4′-Methoxybenzyl)- | 36[a] | 154–157 | 1 | 80.0–81.5[b] | $C_{14}H_{14}O_2$ | 78.5 | 78.3 | 6.6 | 6.6 |
| IX | 2-(2′,3′-Dimethoxybenzyl)- | 49[a] | 148–154 | 1 | 125.5–127.0[b] | $C_{15}H_{16}O_3$ | 73.8 | 73.8 | 6.6 | 6.8 |
| X | 2-(α-Methylbenzyl)- | 37 | 122–126 | 1.5 | 1.5904 | $C_{14}H_{14}O$ | 84.8 | 84.8 | 7.1 | 7.5 |
| XI | 2-(2′,4′-Dichlorobenzyl) | 29 | 142–147 | 1 | 1.6124 | $C_{13}H_{10}OCl_2$ | 61.7 | 61.8 | 4.0 | 4.0 |

[a] The yields in the table represent the once-distilled products, which were treated as described in the experimental reaction to remove any 4-isomer which may have been present. [b] Recrystallized from cyclohexane. [c] Recrystallized from benzene–Skellysolve B.

**Pharmacology.**—Preliminary pharmacological data indicate that none of the compounds herein reported is as active against histamine-induced spasm in guinea pigs as I. A more complete report of the pharmacology of these compounds will be published elsewhere.

## Experimental[6]

**Preparation of Substituted 2-Benzylphenols.**—In a typical experiment, a solution of 138 g. (1.0 mole) of *p*-ethoxyphenol in 250 cc. of warm toluene was added gradually to a stirred suspension of 24 g. (1.0 mole) of sodium hydride in 150 cc. of toluene, under a nitrogen atmosphere. To the resulting suspension, stirred and maintained at gentle reflux, was added dropwise 140 g. (1.1 moles) of benzyl chloride. After five hours of vigorous refluxing, the reaction mixture was cooled and hydrolyzed with dilute hydrochloric acid. The aqueous layer was discarded and the toluene layer washed in turn with water and saturated sodium bicarbonate solution. The toluene solution was then extracted several times with Claisen alkali; the basic extracts acidified with hydrochloric acid and the liberated phenolic material taken up in ether. Evaporation of the ether left an oil which was distilled *in vacuo*, giving a forerun of recovered *p*-ethoxyphenol, followed by 95.8 g. (42%) of 4-ethoxy-2-benzylphenol, a light yellow oil boiling at 165–167° (1 mm.). In an alternative method of working up the reaction, the toluene solution obtained following hydrolysis was stripped of solvent and the residue taken up in approximately four times its volume of Claisen alkali. The neutral material was removed by extraction with Skellysolve C; acidification of the basic solution gave the phenolic fraction, which was extracted and distilled as described above.

Compounds III–VI, X and XI (Table I) were used in the next step without further purification while VII, VIII and IX were treated with barium hydroxide as described below. In order to separate a mixture of 2- and 4-benzylphenols, one mole of the mixture is dissolved in a boiling solution of 0.75 mole of barium hydroxide octahydrate in 900 cc. of water, boiled ten minutes, then cooled and filtered.[5a] Acidification of the filtrate gives the 2-isomer, which may be distilled or recrystallized. It was found that with substituted 2-benzylphenols, the separation of the insoluble barium salt is best carried out at different temperatures, depending on the particular compound. The temperatures at which the separations were done are as follows: VIII, 50°; IX, 10°. The solution of barium salt of VII formed two layers at 80°; the small lower layer was removed and acidified to give the 2-isomer.

Those compounds with substituents in the phenol ring were prepared from the substituted sodium phenolate and benzyl chloride; the others from sodium phenolate and the substituted benzyl chloride (α-bromoethylbenzene was used to synthesize X). In addition to those phenols listed in Table I, there was prepared a number of other substituted 2-benzylphenols, which have been described in the literature: 2-benzyl-4-cresol,[4] 2-benzohydrylphenol,[4] 2-benzoylphenol,[7] 2-(4′-bromobenzyl)-phenol,[8] 4-chloro-2-benzylphenol,[9] 6-chloro-2-benzylphenol,[9] 4-chloro-2-(4′-chlorobenzyl)-phenol,[9] 4,6-dichloro-2-benzylphenol[10] and 2-(2′,3′ and 4′-chlorobenzyl)-phenols.[2]

In one case it was shown that an increase in reaction temperature increased the yield of benzylated phenol. The reaction of 4-chlorobenzyl chloride with sodium phenolate in toluene gave the desired 2-(4′-chlorobenzyl)-phenol in 29% yield; in xylene, 40% yield.

**Preparation of Substituted 2-Benzylphenyl β-Dimethylaminoethyl Ethers.**—The following is a typical example. To a well-stirred, ice-cold suspension of 37 g. (0.26 mole) of β-dimethylaminoethyl chloride hydrochloride[11] in 50 cc. of toluene were added slowly 30 cc. of a 56% potassium hydroxide solution; the mixture was stirred for about fifteen minutes, then the toluene layer decanted. The aqueous sludge was stirred with two successive 50-cc. of portions of toluene and the combined toluene decantates dried by shaking over anhydrous potassium carbonate for four hours. To a suspension of 4.8 g. (0.2 mole) of sodium hydride in 200 cc. of toluene, under a nitrogen atmosphere, was added gradually a solution of 39.6 g. (0.2 mole) of 2-benzyl-4-cresol in 100 cc. of toluene. After completion of the addition, the mixture was refluxed for thirty minutes. To the resulting clear yellow solution, maintained at gentle reflux, was added dropwise the above-described toluene solution of β-dimethylaminoethyl chloride. Precipitation of sodium chloride began almost immediately. After seven hours of refluxing, the mixture was cooled and water added. The toluene layer was washed with 10% potassium hydroxide solution, dried, stripped and the residue distilled *in vacuo*, giving 47.8 g. (89% yield) of 2-benzyl-4-tolyl β-dimethylaminoethyl ether, b. p. 168–174° (3 mm.). The basic ether was converted to its hydrochloride by saturating an ice-cold ether solution of the amine with dry hydrogen chloride. The insoluble hydrochloride was collected by filtration, and recrystallized from isopropyl alcohol–Skellysolve B.

Since crystalline hydrochlorides of 518–19 and 551–43 (Table II) could not be obtained readily, the basic ethers were dissolved in cold 95% ethanol and ethyl acetate, respectively, and the calculated amount of concentrated nitric acid added. Dilution with ether caused precipitation of the crystalline nitrates, which were collected and recrystallized.

(6) All melting points are uncorrected.

(7) Morgan and Plummer, *Rec. trav. chim.*, **56**, 629 (1937).

(8) Huston, *et al.*, THIS JOURNAL, **55**, 2146 (1933).

(9) Huston, *et al.*, *ibid.*, **55**, 4639 (1933).

(10) Huston and Eldridge, *ibid.*, **53**, 2260 (1931).

(11) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

TABLE II

SUBSTITUTED 2-BENZYLPHENYL β-DIMETHYLAMINOETHYL ETHERS, R—O—$CH_2$—$CH_2$—$N(CH_3)_2$

| No. | R | Yield, % | B. p., °C. | Pressure, mm. | M. p., °C. | Formula | Hydrochlorides: Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 446-24 | 2-Benzyl-4-tolyl | 89 | 168–174 | 3 | 126.5–128.0[b] | $C_{18}H_{24}ONCl$ | 70.7 | 70.7 | 7.9 | 8.2 | 4.6 | 4.5 |
| 480-6 | 4-*t*-Butyl-2-benzylphenyl | 87 | 137–140 | 1 | 162.5–164.0[b] | $C_{21}H_{30}ONCl$ | 72.5 | 72.6 | 8.7 | 8.8 | 4.0 | 3.8 |
| 446-44 | 4-Cyclohexyl-2-benzylphenyl | 87 | 186–190 | 1 | 152.5–154.0[b] | $C_{22}H_{32}ONCl$ | 73.9 | 72.8 | 8.6 | 8.4 | 3.7 | 3.7 |
| 446-15 | 4-Methoxy-2-benzylphenyl | 86 | 174–177 | 1 | 131.0–132.0[a] | $C_{18}H_{24}O_2NCl$ | 67.2 | 67.3 | 7.5 | 7.6 | 4.4 | 4.6 |
| 446-28 | 4-Ethoxy-2-benzylphenyl | 79 | 167–171 | 1 | 136.0–137.0[b] | $C_{19}H_{26}O_2NCl$ | 67.9 | 67.7 | 7.8 | 7.6 | 4.2 | 4.1 |
| 446-21 | 4-Chloro-2-benzylphenyl | 82 | 172–176 | 1 | 173.5–175.5[b,g] | $C_{17}H_{21}ONCl_2$ | 62.6 | 62.7 | 6.5 | 6.5 | 4.3 | 4.4 |
| 551-43 | 6-Chloro-2-benzylphenyl | 76 | 160–164 | 1 | 93.0–95.0[c,h] | $C_{17}H_{21}O_4N_2Cl$ | 57.9 | 57.9 | 6.0 | 6.1 | 7.9 | 8.0 |
| 480-25 | 2-(4′-Isopropylbenzyl)-phenyl | 90 | 151–152 | 1 | 144.0–145.5[b] | $C_{20}H_{28}ONCl$ | 71.9 | 72.1 | 8.5 | 8.5 | 4.2 | 4.2 |
| 446-34 | 2-(4′-Methoxybenzyl)-phenyl | 89 | 149–152 | 1 | 123.0–126.0[b] | $C_{18}H_{24}O_2NCl$ | 67.2 | 67.0 | 7.5 | 7.5 | 4.4 | 4.4 |
| 480-38 | 2-(2′,3′-Dimethoxybenzyl)-phenyl | 90 | 164–166 | 1 | 1.5560[f] | $C_{19}H_{25}O_3N$ | 72.3 | 72.2 | 8.0 | 8.2 | 4.4 | 4.3 |
| 518-35 | 2-(2′-Chlorobenzyl)-phenyl | 80 | 155–167 | 1 | 139.5–142.5[b] | $C_{17}H_{21}ONCl_2$ | 62.6 | 62.5 | 6.5 | 6.5 | 4.3 | 4.2 |
| 551-13 | 2-(3′-Chlorobenzyl)-phenyl | 82 | 146–152 | 1 | 120.0–121.5[b] | $C_{17}H_{21}ONCl_2$ | 62.6 | 62.3 | 6.5 | 6.6 | 4.3 | 4.5 |
| 446-48 | 2-(4′-Chlorobenzyl)-phenyl | 81 | 179–185 | 3 | 152.0–153.0[b] | $C_{17}H_{21}ONCl_2$ | 62.6 | 62.3 | 6.5 | 6.9 | 4.3 | 4.2 |
| 570-26 | 2-(4′-Bromobenzyl)-phenyl | 92 | 162–165 | 1 | 158.0–160.5[b] | $C_{17}H_{21}ONBrCl$ | 55.1 | 55.1 | 5.7 | 5.9 | 3.8 | 3.8 |
| 518-39 | 4-Chloro-2-(4′-chlorobenzyl)-phenyl | 86 | 177–182 | 1 | 150.0–152.0[b] | $C_{17}H_{20}ONCl_3$ | 56.6 | 56.6 | 5.6 | 5.8 | 3.9 | 3.9 |
| 570-31 | 2-(2′,4′-Dichlorobenzyl)-phenyl | 91 | 149–152 | 1 | 139.5–141.0[b] | $C_{17}H_{20}ONCl_3$ | 56.6 | 56.7 | 5.6 | 5.7 | 3.9 | 3.8 |
| 570-35 | 4,6-Dichloro-2-benzylphenyl | 85 | 159–163 | 1 | 137.5–140.5[b] | $C_{17}H_{20}ONCl_3$ | 56.6 | 56.4 | 5.6 | 5.6 | 3.9 | 3.8 |
| 490-12 | 2-Benzoylphenyl | 95 | 180–181 | 1 | 144.0–145.5[b] | $C_{17}H_{20}O_2NCl$ | 66.8 | 66.6 | 6.6 | 6.8 | 4.6 | 4.4 |
| 490-15 | 2-(α-Hydroxybenzyl)-phenyl | 70 | ..... | ... | 153.0–154.0[d] | $C_{17}H_{22}O_2NCl$ | 66.3 | 66.3 | 7.2 | 7.4 | 4.6 | 4.7 |
| 518-49 | 2-(α-Methylbenzyl)-phenyl | 78 | 142–146 | 1 | 141.0–142.5[b] | $C_{18}H_{24}ONCl$ | 70.7 | 70.7 | 7.9 | 8.1 | 4.6 | 4.3 |
| 518-19 | 2-Benzohydrylphenyl | 88 | 189–192 | 1 | 184.0–186.5[e,h] | $C_{23}H_{26}O_4N_2$ | 70.0 | 70.3 | 6.6 | 6.9 | 7.1 | 7.0 |

[a] Recrystallized from isopropyl alcohol–ether. [b] Recrystallized from isopropyl alcohol–Skellysolve B. [c] Recrystallized from ethyl acetate–ether. [d] Recrystallized from isopropyl alcohol–methyl isobutyl ketone. [e] Recrystallized from 95% ethanol. [f] $n^{23}$, formula and analysis of the free base. [g] A double melting point was observed, the lower at 141.0–143.0°. The lower melting form was converted to the higher by fusion and seeding with a crystal of the higher melting form. [h] Melting point, formula and analysis of the nitrate.

**2-(α-Hydroxybenzyl)-phenyl β-Dimethylaminoethyl Ether Hydrochloride.**—Twenty grams (0.075 mole) of the hydrochloride of 490-12 was dissolved in 100 cc. of absolute ethanol and hydrogenated over Adams platinum oxide catalyst at three atmospheres pressure. After 2.75 hours, the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, the filtrate diluted with ether and the precipitated amine salt (14.0 g., 70% yield) recrystallized from a mixture of isopropyl alcohol and methyl isobutyl ketone.

**Acknowledgment.**—Dr. E. C. Horning of the University of Pennsylvania kindly supplied samples of *p*-isopropylbenzyl chloride and 2,3-dimethoxybenzyl alcohol. Microanalyses were performed by Mr. Richard M. Downing. Mr. William E. Fitzgibbon carried out certain reactions reported herein.

## Summary

1. The synthesis of a number of new substituted 2-benzylphenols is reported.

2. The synthesis of a series of β-dimethylaminoethyl ethers of substituted 2-benzylphenols is reported.

3. Preliminary pharmacological data indicate that some of these basic ether hydrochlorides prevent histamine-induced asthma in guinea pigs.

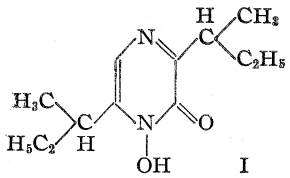
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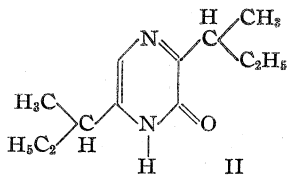
# Analogs of Aspergillic Acid. I. The Tautomerism of the Hydroxypyridine-N-oxides[1]

BY ELLIOTT SHAW

A structural study of aspergillic acid, an antibiotic produced by the mold, *Aspergillus flavus*,[2] led to the conclusion[3] that the substance is a 1-hydroxy-3,6-dialkyl-2-pyrazone (I). The acidic properties are thus attributable to a cyclic hydroxamic grouping. Like the more familiar acyclic hydroxamic acids, aspergillic acid can be reduced



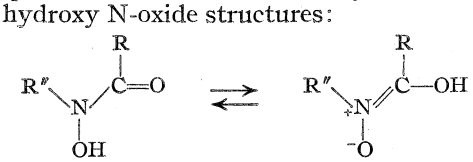
I



II

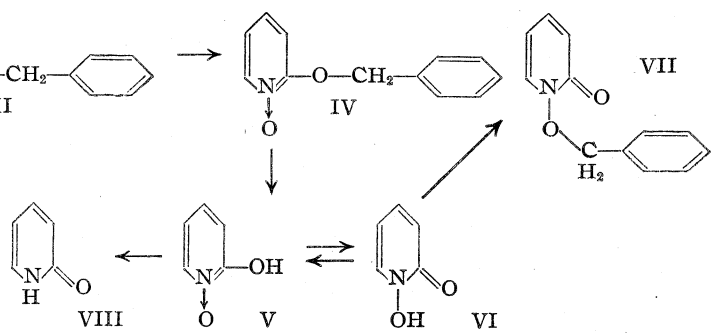
by chemical agents with loss of one oxygen atom to a neutral substance (II) which no longer gives a deep red color with ferric chloride and does not form a copper salt. Of considerable importance is the fact that this change is also accompanied by loss of antibacterial properties. The hydroxamic acid grouping, therefore, seems to be an essential feature of the molecule for biological activity, a conclusion supported by the observation that certain simpler hydroxamic acids not related to pyrazine derivatives also inhibit bacterial growth.[4]

This novel occurrence of a hydroxamic acid grouping in a natural product, together with the possibility of developing synthetically a new series of antibacterial agents, led us to undertake the preparation of cyclic hydroxamic acids. The only examples of this type encountered in the literature are a few N-hydroxy-2-quinolones obtained by a synthesis of quite limited application, *i. e.*, partial reduction of ethyl *o*-nitrocinnamates with cyclization taking place at the *o*-hydroxylamino ester stage.[5,6] It seemed likely that more general methods of preparation might be developed by a study of a postulated tautomerism of hydroxamic acid and hydroxy N-oxide structures:

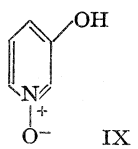


The existence of such a tetrad system has been indicated[7] in the case of N-hydroxyphthalimidine by the formation of the isomeric O-ethers.

The pyridine series was chosen for the initial studies because of the accessibility of intermediates. 2-Benzyloxypyridine (III) was prepared and, by means of perbenzoic acid, converted to its N-oxide (IV), an ether of tautomeric structure (V). The oxide dissolves in aqueous hydrochloric acid with rapid separation of benzyl chloride, and a crystalline acid, $pK = 5.9$, corresponding to (V) or (VI) can be isolated from the solution. The acid forms a copper salt and gives a deep red color with ferric chloride—characteristic, classic properties of hydroxamic acid. However, similar behavior could be expected of the tautomeric hydroxypyridine N-oxide (V) in which the positively charged nitrogen in the amine oxide semi-polar bond would facilitate ionization by an inductive effect. For example, 3-hydroxypyridine N-oxide (IX) was prepared and found to be quite acidic, $pK = 6.4$ compared to $pK = 8.6$ for 3-hydroxypyridine itself. For this isomer, no tautomeric structure comparable to a hydroxamic acid (as in VI) can be formulated.



III IV V VI VII VIII



IX

However, in the 2-pyridyl series it is necessary to conclude from the spectroscopic data described below that the acid obtained on debenzylation of the amine oxide (IV) is not the corresponding hydroxyoxide (V) but a hydroxamic acid (VI). The tautomeric system involved was defined chemically by the preparation of the benzyl ethers corresponding to both forms, (IV) and (VII), and by their conversion on reductive debenzylation to a single acid m. p. 150° (VI).

The N-benzyloxy ether (VII) was formed as the only non-acidic product when the sodium

(1) Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September, 1947.

(2) White and Hill, *J. Bact.*, **45**, 433 (1943).

(3) Dutcher and Wintersteiner, *J. Biol. Chem.*, **155**, 359 (1944).

(4) Dutcher, *J. Biol. Chem.*, **171**, 321 (1947).

(5) Friedlander and Ostermaier, *Ber.*, **14**, 1916 (1881); **15**, 332 (1882).

(6) Heller and Wunderlich, *ibid.*, **47**, 2889 (1914).

(7) Griffiths and Ingold, *J. Chem. Soc.*, **127**, 1689 (1925).

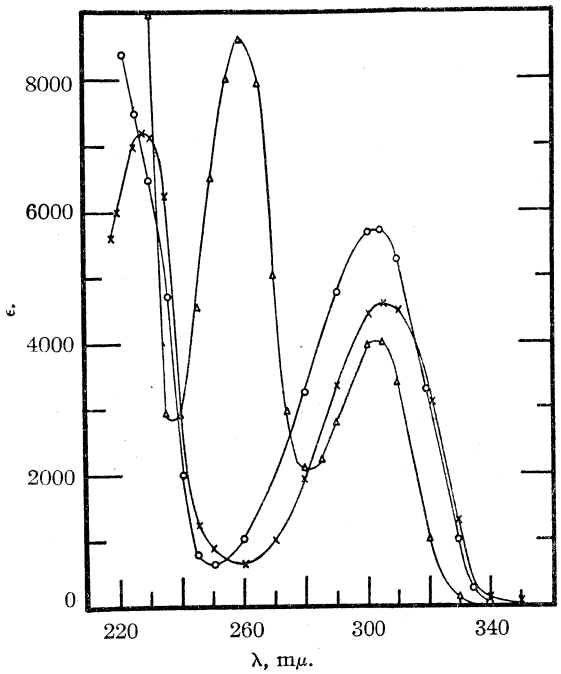



Fig. 1.—Ultraviolet absorption spectra in ethanol: -Δ-Δ-Δ-, 2-benzyloxypyridine N-oxide; -X-X-X, N-hydroxy-2-pyridone; -O-O-O-, N-benzyloxy-2-pyridone.

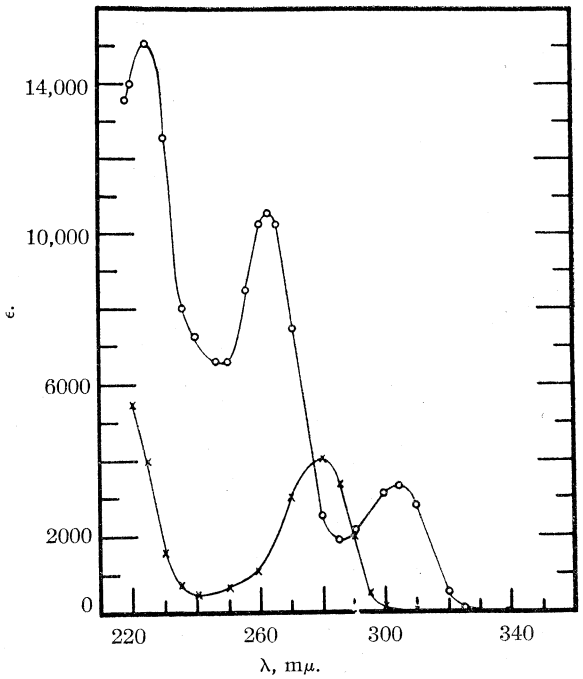
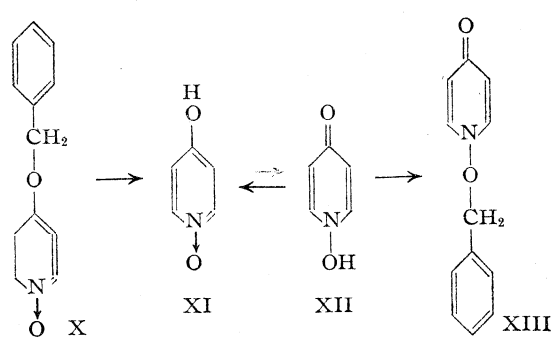



Fig. 2.—Ultraviolet absorption spectra in ethanol: -X-X-X, 3-hydroxypyridine; -O-O-O-, 3-hydroxypyridine N-oxide.

salt of the acid m. p. 150° was treated with benzyl chloride. This ether differs from its isomer (IV) not only in lack of basicity, but also in its resistance to hot, aqueous hydrochloric acid. That it is the more stable isomer is indicated by its isolation, in small quantities, from the hydrochloric acid debenzylation of (IV) apparently due to an isomerization of (IV) to (VII).

In the ultraviolet region, the spectra of the acids (V–VI) in ethanol shows two maxima ($\lambda$ = 228 m$\mu$, $\epsilon$ = 7,200 and $\lambda$ = 305 m$\mu$, $\epsilon$ = 4,600) corresponding rather well to those in the spectrum of 2-pyridone ($\lambda$ = 227 m$\mu$, $\epsilon$ = 7,300 and $\lambda$ = 300 m$\mu$, $\epsilon$ = 5,000). 2-Pyridone is itself considered[8,9] to be in the amide rather than in the hydroxypyridine form, preferably expressed[9] as a dipolar modification. Additional evidence in favor of a hydroxamic acid structure (VI) for the acid is found in a comparison of its spectrum with those of the benzyl ethers of the tautomeric forms shown in Fig. 1. The absorption characteristics for the acid differ markedly from those of the amine oxide (IV) and are in better agreement with the spectrum of the N-benzyloxy isomer (VII). The maximum at 260 m$\mu$ for 2-benzyloxypyridine N-oxide (Fig. 1) is apparently related to the N-oxide configuration. A similar peak is found in the spectrum of 3-hydroxypyridine N-oxide (Fig. 2) at 263 m$\mu$, both substances in ethanol. Further, pyridine N-oxide, measured conveniently in water by neutralizing the hydrochloride prepared by the method of Meisenheimer[10] absorbs mainly at 255 m$\mu$, $\epsilon$ = 9,000; when measured also in water, the spectrum of 3-hydroxypyridine N-oxide shows a shift of the maximum at 263 m$\mu$ (ethanol) to 255 m$\mu$ and, like pyridine N-oxide, exhibits diminishing intensity, as the *p*H drops from 5 to 1, without a change in the wave length of the maximum. Specific absorption in this region is significantly absent from the spectrum in water or ethanol of the acid m. p. 150°, on observation in agreement with the assignment of a hydroxamic acid (VI) rather than a pyridine oxide structure (V) to the substance.

To complete the study of the isomeric hydroxypyridine N-oxides, the 4-pyridyl analog was prepared. As in the 2-pyridyl series, tautomerism with a hydroxamic acid structure was anticipated (XI–XII). 4-Benzyloxypyridine was converted to the N-oxide (X) which, when reduced cata-




(8) Specker and Gawrosch, *Ber.*, **75**, 1345 (1942).
(9) Arndt and Kalischek, *ibid.*, **63**, 587 (1930).
(10) Meisenheimer, *ibid.*, **59**, 1848 (1926).

lytically, gave an acid m. p. 238–240°, $pK = 5.9$. A new benzyl ether, undoubtedly XIII was obtained from the sodium salt of the acid on treatment with benzyl chloride. A comparison of the ultraviolet absorption spectra of the acid (XI–XII) and the isomeric benzyl ethers offers no information as to the state of the tautomerism since all three substances show maximum absorption in the same region, 268–270 mμ (Fig. 3).[11]

Of the three isomeric pyridine acids described, only N-hydroxy-2-pyridone has significant antibacterial activity.

## Experimental[12]

**2-Benzyloxypyridine N-Oxide (IV).**—2-Benzyloxypyridine (37 g.) was added to a chloroform solution of perbenzoic acid (1.5 equivalents) and the mixture left standing at room temperature in a loosely stoppered flask. After three days the solution was washed successively with aqueous sodium carbonate and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crystalline residue was thinned with a mixture of ethyl acetate and hexane for filtration, yielding 18 g. (45%) of product m. p. 99–102°. This material was satisfactory for the next step. An analytical sample was obtained by recrystallization from ethyl acetate and hexane and melted at 103–106°.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.66; H, 5.74; N, 6.88.

**N-Hydroxy-2-pyridone (VI).**—(A) By hydrochloric acid debenzylation: 2-Benzyloxypyridine N-oxide (4.3 g.) was boiled for ten minutes with 15 ml. of 20% hydrochloric acid under a reflux condenser provided with a take-off to remove benzyl chloride. The turbid solution was then taken to dryness *in vacuo* and recrystallized from benzene containing a small amount of methanol. There was obtained 1.6 g. (68%) of product melting at 145–147°. A recrystallization from ethyl acetate brought the m. p. to 149–150°.

*Anal.* Calcd. for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.94; H, 4.62; N, 12.55.

N-Hydroxy-2-pyridone gives a deep red color with ferric chloride in alcohol solution or a precipitate in aqueous solution. The copper salt melts at 298° (dec.).

*Anal.* Calcd. for $(C_5H_4O_2N)_2Cu$: N, 9.87. Found: N, 9.73.

From the mother liquor in the above debenzylation a small neutral fraction was obtained by combining the benzene and ethyl acetate filtrates, extracting acidic material with aqueous alkali, and concentrating the organic layer. Colorless crystals were obtained, m. p. 83–84°, isomeric with the starting material.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.56; H, 5.60; N, 6.97.

(B) By catalytic reduction: 2-Benzyloxypyridine N-oxide (25 g.) was shaken in 100 ml. of ethanol with 750 mg. of palladium catalyst (5% on charcoal) at an initial pressure of 50 lb. of hydrogen. The reduction was complete in about five minutes. Concentration of the filtered solution gave 9.5 g. (69%) of N-hydroxy-2-pyridone, m. p. 150°.

**N-Benzyloxy-2-pyridone (VII).**—N-Hydroxy-2-pyridone (3.25 g.) was added to a solution of sodium (0.75 g.) in 45 ml. of ethanol. The resultant suspension of sodium salt was refluxed with benzyl chloride (4.18 g.) for three hours. The filtrate was concentrated to a small volume, taken up in chloroform, and washed with dilute sodium hydroxide solution to remove unreacted starting acid. The dried organic layer on evaporation left a crystalline neutral residue of 3.8 g. (70%) melting at 85–86°. The melting point was unchanged by recrystallization from ethyl acetate and hexane. This material is identical with that obtained from the mother liquors of the hydrochloric acid debenzylation of 2-benzyloxypyridine N-oxide as described above.

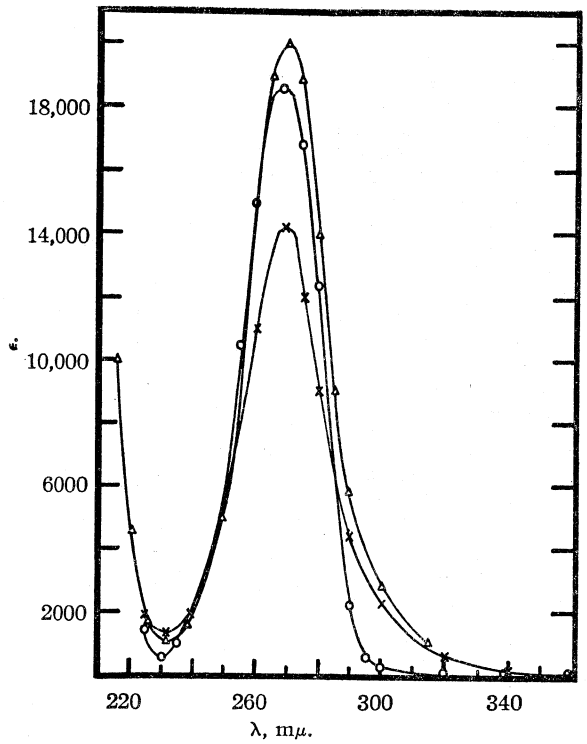



Fig. 3.—Ultraviolet absorption spectra in ethanol: -Δ-Δ-Δ-, 4-benzyloxypyridine N-oxide; X-X-X, N-hydroxy-γ-pyridone or tautomer; -O-O-O, N-benzyloxy-γ-pyridone.

**Reduction of N-Hydroxy-2-pyridone to 2-Pyridone.**—Red phosphorus (1 g.) and iodine (0.5 g.) were left standing for ten minutes in 25 ml. of glacial acetic acid. N-Hydroxy-2-pyridone (2 g.) in 30 ml. of glacial acetic acid was added and the solution refluxed for two and one-half hours. The reaction was worked up although the reduction was not yet complete judging by the persistence of a ferric chloride color test. The filtrate was taken to dryness and the residue extracted with boiling ethyl acetate. The addition of picric acid (5.5 g. in 50 ml. of alcohol) precipitated 2.5 g. of picrate (43%) identical with the picrate prepared from an authentic sample of 2-pyridone and melting at 170–172°.

*Anal.* Calcd. for $C_{11}H_8O_8N_4$: C, 40.75: H, 2.49; N, 17.28. Found: C, 40.75; H, 2.60; N, 17.31.

**3-Hydroxypyridine N-Oxide (IX).**—3-Hydroxypyridine oxidized quite readily with perbenzoic acid (1.5 equivalents in chloroform), the product crystallizing out overnight, m. p. 188–190°, (65%). Recrystallization from methanol raised the m. p. slightly to 189–191°.

*Anal.* Calcd. for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.93; H, 4.68; N, 12.54.

**4-Benzyloxypyridine.**—4-Pyridylpyridinium dichloride[13] (65 g.) was dissolved in 150 ml. of hot benzyl alcohol and added to a solution of sodium (13 g.) in 250 ml. of benzyl alcohol. The suspension was refluxed for four hours, poured into water, and extracted with ether. Fractionation of the residue obtained from concentration of the dried ether extract gave an oil b. p. 147–160° (4 mm.). On redis-

(11) The coöperation of Dr. Nettie H. Coy of the Division of Development, E. R. Squibb and Sons, in providing the spectroscopic measurements cited in this paper is acknowledged.

(12) All melting points are uncorrected. Microanalyses were carried out by Mr. J. F. Alicino.

(13) Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).

tillation there was obtained 11.5 g. (22%) of product, b. p. 155–160° (4 mm.). The free base could be crystallized from hexane, m. p. 55–56°.

*Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.98; N, 7.56. Found: C, 78.22; H, 5.84; N, 7.42.

A picrate of the base melted at 150–151°.

*Anal.* Calcd. for $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$: C, 52.18; H, 3.45. Found: C, 52.22; H, 3.40.

**4-Benzyloxypyridine N-Oxide (X).**—The oxide was prepared from the base by means of perbenzoic acid as described above for the 2-isomer and melted at 178–179°.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.42; N, 6.62.

The amine oxide formed a picrate readily in alcoholic solution, m. p. 123–124°.

*Anal.* Calcd. for $C_{12}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 50.24; H, 3.30. Found: C, 49.84; H, 3.29.

**N-Hydroxy-4-pyridone (XI–XII).**—4-Benzyloxypyridine N-oxide (1 g.) was catalytically reduced with 150 mg. of palladium (5% on charcoal) as described for the 2-isomer. The filtrate was concentrated to a small volume, depositing 345 mg., 68%, m. p. 243–244°. The acid gives no precipitate with ferric chloride but produces an orange color. The preparation of this compound by another method has been described[14] but no m. p. is given.

*Anal.* Calcd. for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.47; H, 4.81; N, 12.20.

(14) Ost, *J. prakt. Chem.*, [2] **29**, 379 (1884).

**N-Benzyloxy-4-pyridone (XIII).**—N-Hydroxy-4-pyridone (47 mg.) was added to a solution of sodium (9.7 mg.) in alcohol and refluxed with benzyl chloride (53.6 mg.) for one hour. The mixture was partitioned between ethyl acetate and alkali. The organic layer on evaporation left a residue of 73 mg. After recrystallization from ethyl acetate and hexane, the material melted 112–113°.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.80; H, 5.60.

The picrate of this benzyl ether melted at 164° and depresses the melting point of the picrate of 4-benzyloxypyridine N-oxide.

*Anal.* Calcd. for $C_{12}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 50.24; H, 3.30. Found: C, 50.33; H, 3.65.

**Acknowledgment.**—The author is indebted to Mr. W. A. Lott for his interest and encouragement.

## Summary

The synthesis of N-hydroxy-2-pyridone, a cyclic hydroxamic acid, is described. The acid is in tautomeric relationship with 2-hydroxypyridine N-oxide.

Isomeric acids of the 3- and of the 4-pyridyl series also have been prepared.

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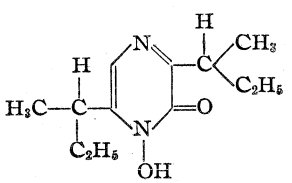
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[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Analogs of Aspergillic Acid. II. Various Antibacterial Heterocyclic Hydroxamic Acids[1]

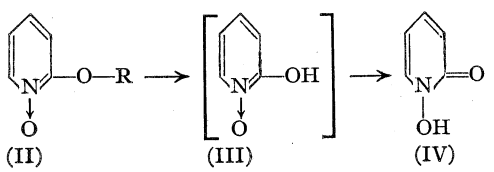
BY W. A. LOTT AND ELLIOTT SHAW

Attempts to develop synthetic methods for introducing into heterocyclic rings the hydroxamic acid grouping present in aspergillic acid (I) led to a



(I)

preparation for N-hydroxy-2-pyridone (IV).[2] The



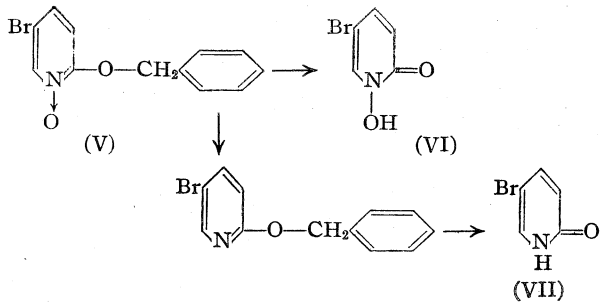
(II) (III) (IV)

synthesis was achieved by conversion of a 2-pyridyl ether to its N-oxide (II), followed by de-alkylation. The 3- and 4-pyridyl derivatives were also prepared[2] but, of these position isomers, only N-hydroxy-2-pyridone showed antibacterial activity, an observation which encouraged the extension of synthetic work to the preparation of additional heterocyclic hydroxamic acids. New methods have been developed. The synthetic acids exceed, in some instances, the *in vitro* antibacterial activity of aspergillic acid.

The hydroxamic acid grouping in N-hydroxy-2-pyridone (IV) is quite stable chemically, resisting the action of boiling aqueous acid or cleavage of the N–O bond by catalytic reduction (Pd), ammonium sulfide, or stannous chloride. In these respects, the grouping bears no resemblance to N-oxides. It is apparent that the amine oxide (II, R = benzyl) is converted to the hydroxamic acid (IV) successfully due to a more rapid initial attack at the ether linkage, by hydrochloric acid or catalytic reduction, than at the N–O bond which subsequently gains increased resistance to reduction by a tautomeric shift (III → IV) to the hydroxamic acid structure.[2] A similar series of reactions led to a 4-methyl derivative of (IV) in good yields. However, when the substituent was bromine in the 5-position, reduction or treatment of the N-oxide (V) with hydrochloric acid led to 5-bromopyridone (VII) as the main product. In the hydrochloric acid debenzylation, for example, the ratio of pyridone to hydroxamic acid isolated (VI) was 3:1. In this case, in contrast to

(1) Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September, 1947.

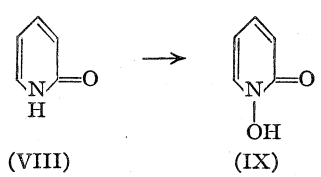
(2) Shaw, THIS JOURNAL, **71**, 67 (1949).



those cited above, the initial attack is mainly at the amine oxide bond.

When attempts were made to apply the above synthesis to the preparation of cyclic quinoline hydroxamic acids, difficulty was encountered in the formation of the intermediate amine oxides. Treatment of 2-benzyloxyquinoline and 2-benzyloxy-4-methylquinoline with perbenzoic acid did not lead to satisfactory oxidations. The problem has been attacked by other methods, to be reported later.

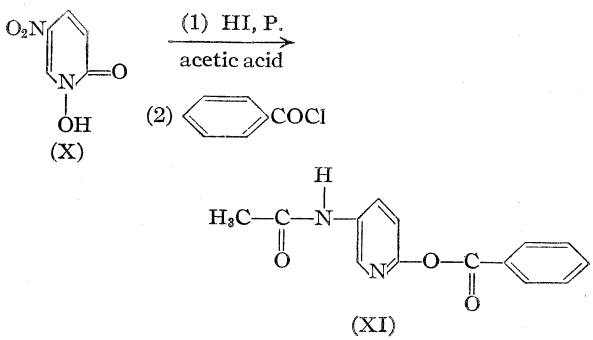
The direct oxidation of amides to hydroxamic acids by means of hydrogen peroxide and ferric chloride has been reported.[3] The conversion of



(VIII) (IX)

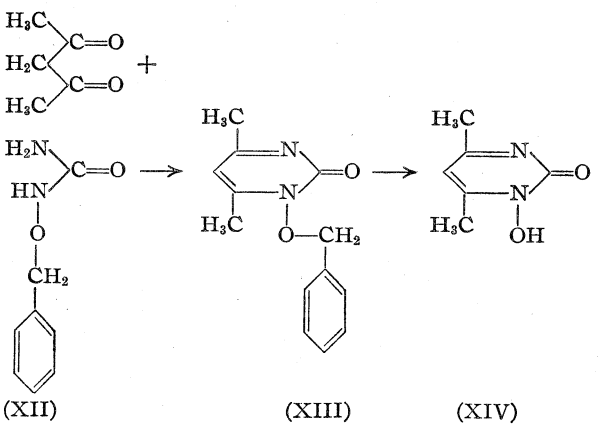
2-pyridone (VIII) to N-hydroxy-2-pyridone (IX) bears a formal resemblance to such a change. This oxidation has been achieved. Persulfuric acid, perbenzoic acid, and performic acid have been tried, but of these only perbenzoic acid gave satisfactory results. 5-Bromopyridone (VII) was also conveniently oxidized in yields of 15–20% to the corresponding hydroxamic acid (VI) and, in view of the poor results obtained in the initial synthetic approach to this acid (V → VI), the direct oxidation offers the best method of preparation. In the quinoline series, however, less than a 1% yield of N-hydroxy-2-quinolone was obtained on treatment of carbostyril with perbenzoic acid.

The stability of the hydroxamic acid grouping in N-hydroxy-2-pyridone (IV) has been described above. It was found that the nucleus in this compound undergoes substitution with ease. Nitration in glacial acetic acid gave a nitro compound identified as N-hydroxy-5-nitro-2-pyridone (X). Reduction with hydriodic acid in glacial acetic acid followed by benzoylation of the product led to the same acetamidopyridyl benzoate (XI) produced from 5-nitro-2-pyridone under similar conditions. Bromination gave a mixture of brominated acids from which was isolated a monobromo derivative different from the known 5- and 6-bromo acids and which is considered to be N-hydroxy-3-bromopyridone. 2-Pyridone itself undergoes substitution in the 3- and 5-positions.[4,5]



(X) (XI)

For the preparation of a hydroxamic acid in the pyrimidine series, benzyloxyurea (XII) was condensed with acetylacetone and the resultant N-benzyloxypyrimidone (XIII) cleaved by catalytic hydrogenation to 1-hydroxy-4,6-dimethyl-2-pyrimidone (XIV).



(XII) (XIII) (XIV)

The *in vitro* antibacterial activities of a group of the synthetic hydroxamic acids are compared with aspergillic acid in Table I.

The values given indicate the concentrations necessary to prevent growth of the organisms.[6] It is significant that the common structural feature of these antibacterial agents is the cyclic hydroxamic acid grouping capable of chelating metals. A number of structurally related compounds have been tested which have some of the features of the active compounds but are incomplete as hydroxamic acids, *viz.*, pyridine N-oxide and 2-pyridone; these are not active *in vitro*. Furthermore, "vinylogs" of hydroxamic acids such as N-hydroxy-4-pyridone[2] (XV) and N-hydroxy-7-chloro-4-quinolone (XVI) which have an acidity comparable to their isomeric N-hydroxy-2-pyridone and -2-quinolone derivatives but, unlike the latter, do not form precipitates with metallic ions are inactive

(3) Oliveri-Mandala, *Gass. chim. ital.*, **52**, I, 107 (1922).

(4) Tschitschibabin and Schapiro, *J. Russ. Phys.-Chem. Soc.*, **53**, 233 (1921).

(5) Binz and Maier-Bode, *Angew. Chem.*, **49**, 486 (1936).

(6) We are indebted to Drs. Rake and Donovick of the Division of Microbiology, The Squibb Institute for Medical Research, for these results. The activities were measured by a dilution method accurate to ±15%.

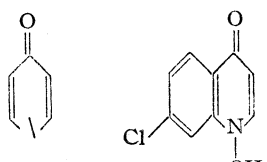
TABLE I

THE *in vitro* ANTIBACTERIAL ACTIVITIES OF SOME SYNTHETIC HYDROXAMIC ACIDS AND THE ANTIBIOTIC, ASPERGILLIC ACID

| | Minimal inhibiting concentration mg./ml. | | |
|---|---|---|---|
| | *Staphylococcus aureus* P209[a] | *Klebsiella pneumoniae*[a] | *Mycobacterium smegmatis*[b] |
| Aspergillic acid | 0.021 | 0.030 | 0.023 |
| N-Hydroxy-2-pyridone | .003 | .043 | .035 |
| N-Hydroxy-4-methyl-2-pyridone | .041 | .045 | .041 |
| N-Hydroxy-3-bromo-2-pyridone | .013 | > .25 | .05 |
| N-Hydroxy-5-bromo-2-pyridone | .005 | .09 | .017 |
| N-Hydroxy-6-bromo-2-pyridone | .011 | .19 | .19 |
| N-Hydroxy-5-nitro-2-pyridone | .14 | .90 | .45 |
| N-Hydroxy-2-quinolone | .0012 | .019 | .013 |
| N-Hydroxy-4,6-dimethyl-2-pyrimidone | .21 | .95 | .44 |

[a] Tested in yeast beef broth. [b] Tested in modified Kirchner's medium.

*in vitro*. It seems probable, therefore, that the compounds in Table I are antibacterial due to their ability to combine with, and deprive microorganisms of, metabolically essential metals. A




(XV) (XVI)

correlation between antibacterial activity and chelating power has been demonstrated[7] in a series of 8-hydroxyquinoline derivatives. With respect to aspergillic acid, Goth has observed that the addition of ferric ion diminishes the *in vitro* activity of the antibiotic.[8]

## Experimental[9]

**2-Bromo-4-methylpyridine and 2,5-Dibromopyridine.**—The 2-bromopyridines were prepared from the corresponding 2-aminopyridines by an adaptation of the method of Craig.[10] In an externally cooled 3-neck flask provided with stirrer, thermometer and dropping funnel, 2-amino-4-methylpyridine (81 g.) was dissolved with cooling in 48% hydrobromic acid (630 ml.). After the addition of 115 ml. of bromine, a solution of sodium nitrite (130 g.) in water (190 ml.) was gradually introduced below 0°. Stirring was then continued for an hour after which the solution was made alkaline with 50% sodium hydroxide and treated with sodium sulfite (100 g.). The mixture was steam distilled, and the oily 2-bromo-4-methylpyridine extracted from the distillate with ether. Fractionation of the dried extract gave 99 g., 77%, b. p. 220–222°.[11] When 2-amino-5-bromopyridine[12] was treated in the same way, 2,5-dibromopyridine, m. p. 92–96°, was obtained as a white solid in the steam distillate, 40%.

**Pyridyl and Quinolyl Benzyl Ethers.**—In the formation of N-hydroxy-2-pyridone (IV) from the N-oxide of a 2-pyridyl ether (II), the ethyl ether was as easily cleaved with hydrochloric acid as the benzyl ether. However, in subsequent applications of the method, the benzyl ether was used because of the additional method of cleavage by hydrogenolysis. The benzyl ethers were prepared from the corresponding bromopyridines and chloroquinolines essentially by the method of Renshaw and Conn.[13] The halogen derivatives were refluxed for two hours with a slight excess of sodium benzylate in benzyl alcohol, poured into water, and extracted with ether. The dried ether–benzyl alcohol layer was concentrated and fractionated *in vacuo*. In those cases resulting in a crystalline product, hexane was used for recrystallization before analysis.

**2-Benzyloxy-4-methylpyridine,** 50% yield, b. p. 142–145° at 5 mm. *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.39; H, 6.53; N, 7.03. Found: C, 78.03; H, 6.85; N, 7.18.

**A picrate formed in alcohol,** m. p. 140–141°. *Anal.* Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.73; N, 13.08. Found: C, 53.63; H, 3.68; N, 12.99.

**2-Benzyloxy-5-bromopyridine,** 71% yield, b. p. 178–185° at 14 mm., m. p. 56–58°. *Anal.* Calcd. for $C_{12}H_{10}ONBr$: C, 54.50; H, 3.79; N, 5.30. Found: C, 54.10; H, 3.85; N, 5.30.

**A picrate** was obtained, m. p. 107–109°. *Anal.* Calcd. for $C_{18}H_{13}O_8N_4Br$: N, 11.34. Found: N, 11.72.

**2-Benzyloxyquinoline,** 86% yield, b. p. 196–197° at 2 mm., m. p. 46–47°. *Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.67; H, 5.57; N, 5.95. Found: C, 82.04; H, 6.10; N, 5.76.

**2-Benzyloxy-4-methylquinoline,** 68% yield, b. p. 174–176° at 1 mm., m. p. 52–56°. *Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.85; H, 6.02; N, 5.62. Found: C, 81.37; H, 5.94; N, 5.46.

**The base gave a picrate,** m. p. 149–150°. *Anal.* Calcd. for $C_{23}H_{18}O_8N_4$: C, 57.70; H, 3.76; N, 11.72. Found: C, 57.32; H, 4.04; N, 11.70.

**4-Benzyloxy-7-chloroquinoline,** 57% yield, m. p. 100–101°, recrystallized from benzene. *Anal.* Calcd. for $C_{16}H_{12}ONCl$: C, 71.24; H, 4.49; N, 5.19. Found: C, 70.92; H, 4.54; N, 5.17

**N-Oxides.**—The pyridyl and quinolyl benzyl ethers were left standing at room temperature with a chloroform solution containing 1.5 equivalents of perbenzoic acid.[14] After several days, when potassium iodide titration showed disappearance of most of the perbenzoic acid, the solution was washed with aqueous sodium carbonate and water. The chloroform layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a small volume. The resultant crystals were drained from adhering oil on a filter and recrystallized from ethyl acetate.

**2-Benzyloxy-4-methylpyridine N-oxide** was thus obtained in a yield of 53%, m. p. 81–82°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.53; H, 6.08; N, 6.51. Found: C, 72.61; H, 6.14; N, 6.72.

**2-Benzyloxy-5-bromopyridine N-oxide,** 25% yield, m. p. 127–128°. *Anal.* Calcd. for $C_{12}H_{10}O_2NBr$: C, 51.40; H, 3.57; N, 5.00. Found: C, 51.59; H, 4.03; N, 5.02.

**4-Benzyloxy-7-chloroquinoline N-oxide** required a modification of the above procedure for its isolation. Concentration of the carbonate-washed chloroform solution gave a benzoic acid salt from which the oxide was obtained by trituration with dilute sodium hydroxide and extraction with chloroform, m. p. 163°, 65% yield. *Anal.* Calcd. for $C_{16}H_{12}O_2NCl$: C, 67.25; H, 4.24; N, 4.89. Found: C, 67.11; H, 4.35; N, 5.11.

**N-Hydroxy-4-methyl-2-pyridone.**—The benzyl ether N-oxide was treated with aqueous hydrochloric acid as previ-

(7) Albert, Rubbo, Goldacre and Balfour, *Brit. J. Exp. Path.*, **28**, 69 (1947).

(8) Goth, *J. Lab. Clin. Med.*, **30**, 899 (1945).

(9) Melting points are uncorrected. Microanalyses were carried out by Mr. J. F. Alicino.

(10) Craig, THIS JOURNAL, **56**, 231 (1934).

(11) Case, THIS JOURNAL, **68**, 2574 (1946).

(12) Tschitschibabin and Tjashelowa, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

(13) Renshaw and Conn, THIS JOURNAL, **59**, 297 (1937).

(14) "Organic Syntheses," Coll. Vol. I, 431 (1941).

ously described[2] and led to the hydroxamic acid, m. p. 129–130°, 75% yield. *Anal.* Calcd. for $C_6H_7O_2N$: C, 57.58; H, 5.63; N, 11.18. Found: C, 57.51; H, 5.89; N, 11.17.

**Action of Aqueous Hydrochloric Acid on 2-Benzyloxy-5-bromopyridine N-Oxide.**—The oxide (7 g.) was refluxed for ten minutes with 20% hydrochloric acid (35 ml.) during which time the benzyl chloride formed was condensed and removed. The aqueous residue was taken to dryness *in vacuo* and the resultant crystalline mixture, dissolved in ethyl acetate–butanol (1:1), was extracted with aqueous sodium carbonate. When the aqueous layer was acidified and taken to dryness, extraction with absolute alcohol gave the hydroxamic acid, N-hydroxy-5-bromo-2-pyridone, m. p. 137–139°, 13%. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 31.65; H, 2.59; N, 7.35.

The ethyl acetate–butanol fraction from the above partition on concentration led to 5-bromo-2-pyridone, 40%, m. p. 179–181°, identical with an authentic sample.[15]

**N-Hydroxy-7-chloro-4-quinolone.**—4-Benzyloxy-7-chloroquinoline N-oxide (10 g.) was reduced with hydrogen at fifty pounds initial pressure in 100 ml. of absolute ethanol and 0.5 g. 5% palladium-on-carbon. The product crystallized out and was separated from the catalyst by solution in dilute sodium hydroxide and reprecipitation with acid, 5 g., m. p. 262°, 73%. Recrystallization from glacial acetic acid did not alter the melting point. The acid gives an orange color with ferric chloride but forms no precipitate. *Anal.* Calcd. for $C_9H_6O_2NCl$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.53; H, 3.32; N, 7.37.

**Direct Oxidation of 2-Pyridones to Hydroxamic Acids.**—The 2-pyridone was left standing at room temperature with a chloroform solution of perbenzoic acid containing a 50% excess of the oxidizing agent. After about one week at room temperature, the solution was taken to dryness and desiccated to a dry powder. This residue was triturated with ether and filtered several times to remove benzoic acid. The insoluble portion was recrystallized from benzene. N-Hydroxy-2-pyridone and N-hydroxy-5-bromo-2-pyridone were obtained in this way in yields of 15 and 18%, respectively, and were identical with the acids obtained from the 2-benzyloxypyridyl N-oxides. 6-Bromo-2-pyridone[16] under the above conditions produced N-hydroxy-6-bromo-2-pyridone, m. p. 155–157°, 19% yield. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 32.02; H, 2.22; N, 7.17.

5-Nitro-2-pyridone was not oxidized by perbenzoic acid at room temperature, judging by the absence of a ferric chloride coloration. Carbostyril (7 g.) produced 0.2 g. of N-hydroxy-2-quinolone, m. p. 189–191°, isolated as the fraction insoluble in aqueous bicarbonate and soluble in carbonate. The acid did not depress the melting point of the material prepared by the method of Friedländer.[17]

**N-Hydroxy-5-nitro-2-pyridone.**—N-Hydroxy-2-pyridone (3.1 g.) was dissolved in glacial acetic acid (15 ml.); concentrated nitric acid (2 ml., d. 1.42) was added with cooling. The product rapidly crystallized out; 2.8 g., 67% yield, m. p. 198–199°, unchanged on recrystallization from glacial acetic acid. *Anal.* Calcd. for $C_5H_4O_4N_2$: C, 38.47; H, 2.59; N, 17.95. Found: C, 38.09; H, 2.34; N, 17.75.

The nitro derivative (1.5 g.) was refluxed in glacial acetic acid (20 ml.) with concentrated hydriodic acid (1.5 ml., sp. gr. 1.7) and red phosphorus (1 g.). Since the hydroxamic acid grouping was not completely reduced (ferric chloride color) after three hours, a second portion of hydriodic acid was added and the refluxing continued for an hour longer. On concentration of the filtrate, yellow crystals of an hydriodide were obtained, 0.95 g. The hydriodide was dissolved in pyridine (15 ml.) and shaken in a stoppered flask with benzoyl chloride (1 ml.). After fifteen minutes, the mixture was poured into water and concentrated under reduced pressure. The derivative, 0.2 g., was recrystallized from ethyl acetate and hexane and melted at 149–150°.

When 5-nitro-2-pyridone was treated in the same way, an identical benzoate (XI) was obtained, indicating that nitration of the hydroxamic acid had produced a 5-nitro derivative. 5-Amino-2-pyridone forms di-acyl derivatives.[18] *Anal.* Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.77; H, 4.73; N, 10.60.

**N-Hydroxy-3-bromo-2-pyridone.**—To a solution of N-hydroxy-2-pyridone (3 g.) in glacial acetic acid (15 ml.) was added a solution of bromine (4.3 g.) in the same solvent (20 ml.). After two hours at room temperature, the solution was filtered and taken to dryness *in vacuo*. The residue was clearly a mixture from which the initial crop of crystals from ethyl acetate, 0.7 g., m. p. 208–209°, was the only pure fraction isolated. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 31.48; H, 2.27; N, 7.46.

An hydriodic acid reduction was carried out as described above for the nitration product, and led to the pyridone, m. p. 183–184° (alcohol). *Anal.* Calcd. for $C_5H_4ONBr$: C, 34.51; H, 2.30; N, 8.04. Found: C, 34.74; H, 2.58; N, 7.89.

**1-Benzyloxy-4,6-dimethyl-2-pyrimidone.**—N-Benzyloxyurea[19] was dissolved in absolute alcohol (200 ml.) in a flask provided with a stirrer; acetylacetone (12.6 g.) and concentrated sulfuric acid (13.8 ml.) were added. After one hour, crystallization was induced by scratching and chilling. With the addition of ether, a 51% yield of the pyrimidine sulfate was obtained. The free base separated on treatment of the salt with aqueous alkali, m. p. 130–131° (from water). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.80; H, 6.12; N, 12.16. Found: C, 68.03; H, 6.24; N, 12.14.

**N-Hydroxy-4,6-dimethyl-2-pyrimidone.**—The benzyl ether (11.5 g.) was shaken with palladium-on-charcoal-5% (1.0 g.) in the atmosphere of hydrogen at an initial pressure of 50 lb. Reduction was rapid. When the theoretical amount of hydrogen had been taken up, the shaking was stopped. The hydroxamic acid was crystallized from the filtrate with the addition of ether; 6.5 g., 90%, m. p. 185–186°. There was no change in melting point on recrystallization from ether. *Anal.* Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.27; H, 5.88; N, 19.68.

## Summary

The synthesis of a number of heterocyclic compounds containing the hydroxamic acid grouping, —N(OH)—C(=O)—, in the ring is described. Such acids have, in general, antibacterial action *in vitro*.

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(15) Tschitschibabin and Tjashelowa, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

(16) Hertog and Wibaut, *Rec. trav. chim.*, **55**, 126 (1936).

(17) Friedländer and Ostermaier, *Ber.*, **14**, 1916 (1881); **15**, 332 (1882).

(18) Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).

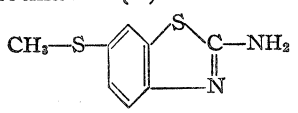
(19) Behrend and Leuchs, *Ann.*, **257**, 207 (1890).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

# Certain Derivatives of 2-Aminobenzothiazole

BY FLAVEN E. JOHNSON[1] AND CLIFF S. HAMILTON

Alkyl aryl and heterocyclic aryl sulfones containing a *p*-amino group have shown marked bacteriostatic[2] and antitubercular[3] activity. This is particularly true of derivatives containing the thiazole ring.[4] Sulfides and sulfoxides have also shown chemotherapeutical activity.[5] The present investigation was undertaken to embody the above characteristics in one compound by synthesizing sulfur containing derivatives of 2-aminobenzothiazole, for example 6-methylmercapto-2-aminobenzothiazole (V).



V

4-Methylmercaptonitrobenzene (II) was prepared by a series of conventional methods, reduced to the amine and converted to 4-methylmercaptophenylthiourea (IV). Oxidation of IV with bromine gave 2-amino-6-methylmercaptobenzothiazole (V) in good yields. After protecting the amino group compound V was oxidized to 2-amino-6-methylsulfonylbenzothiazole (VIII) in excellent yields.

2-Amino-6-methylsulfonylbenzothiazole was also prepared by oxidizing compound II to 4-methylsulfonylnitrobenzene (IX), reducing it to the amine and treating the compound obtained with ammonium thiocyanate, then with bromine to give a low yield of compound VIII. This synthesis proved that the mercapto sulfur and not the ring sulfur was undergoing oxidation.

Conversion of compound VIII to 2-chloro-6-methylsulfonyl-benzothiazole (XI) proceeded smoothly employing a modified Sandmeyer reaction. An attempt to use the same reaction on compound V produced two products, 2-chloro-6-methylsulfinylbenzothiazole (XVI) at 0° and 2-chloro-6-methylmercaptobenzothiazole (XXI) at −20°. Compounds XVI and XXI were later oxidized to XI by means of hydrogen peroxide.

Chloro compounds XI, XVI and XXI were all successfully condensed with benzylamine, piperidine, δ-diethylaminobutylamine and γ-diethylaminopropylamine to produce the remainder of the compounds shown in the accompanying tables.

All of the sulfone derivatives and a representative member of the sulfoxide and sulfide series have been submitted for pharmacological screen testing.

(1) Parke, Davis and Company fellow.

(2) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **127**, 393 (1938); *C. A.*, **32**, 3901 (1938).

(3) Smirnova, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 284 (1947).

(4) Bambas, THIS JOURNAL, **67**, 671 (1945).

(5) Gibbs and Robinson, *J. Chem. Soc.*, 925 (1945).

## Experimental

**Sodium *p*-Nitrothiophenate (I).**—This compound was prepared according to the procedure of Stacy[6] using a 75% ethanol–water solution as the reaction medium. The solution was kept at reflux temperature during the entire reaction to yield 84% of the desired salt.

**4-Methylmercaptonitrobenzene (II).**—The procedure as employed by Waldron and Reid[7] was used to prepare the compound in 70–75% yields; m. p., 68–69°, lit.[7] 67° and 71°.

**4-Methylmercaptoaniline Hydrochloride (III).**—4-Methylmercaptonitrobenzene (45 g., 0.32 mole) was reduced in three runs (15 g. each), by means of hydrogen and Raney nickel in acetone solution. Six hours were required for complete reduction and the product was isolated as a salt by passing dry hydrogen chloride gas through the solution. The product removed by filtration weighed 44.5 g. (94%) and was identified by formation of the benzoyl derivative; m. p. 176–178°, lit.[8] 177–178°.

**4-Methylmercaptophenylthiourea (IV).**—The method used was that of Wertheim[9]; yield 86%, m. p. 200–201°, lit.[9] 198–199°.

**2-Amino-6-methylmercaptobenzothiazole (V).**—4-Methylmercaptophenylthiourea (58 g., 0.29 mole) was suspended in 200 ml. of dry chloroform in a 500-ml. round-bottomed flask. Liquid bromine (58 g., 0.362 mole) in dry chloroform (100 ml.) was carefully added. The reaction flask was placed under a reflux condenser provided with a trap to catch hydrogen bromide vapors and carefully warmed for forty minutes. The solvent was then decanted and fresh chloroform added followed by twenty minutes of heating. The solid which remained was decanted free of solvent and dried. The yellow amorphous material was triturated with sulfurous acid solution and washed with water. The hydrobromide salt obtained was dissolved in 1.5 l. of hot water, filtered free of impurities and made alkaline with ammonium hydroxide. The solid separating on cooling was recrystallized from 50% ethanol–water solution; yield, 51.2 g. (89.5%) of light tan plates melting at 150–151°.

**2-Acetamido-6-methylmercaptobenzothiazole (VI).**—2-Amino-6-methylmercaptobenzothiazole (15 g., 0.8 mole) was dissolved by warming in technical grade acetic anhydride and treated in the conventional manner to obtain 18.1 g. (99%) of cream-colored crystals, which recrystallized from 95% ethanol and had a m. p. of 198–200°.

*Anal.* Calcd. for $C_{10}H_{10}N_2OS_2$: N, 11.75. Found: N, 12.03.

**2-Acetamido-6-methylsulfonylbenzothiazole (VII).**—2-Acetamido-6-methylmercaptobenzothiazole (18.1 g., 0.8 mole) was dissolved in 340 ml. of glacial acetic acid by warming on a steam-bath. Hydrogen peroxide solution (60 ml., 30%) in glacial acetic acid (40 ml.) was added and the mixture warmed to 80° on a steam-bath. After standing at room temperature for one hour the reaction solution was placed in the refrigerator overnight. The white fluffy crystals that separated were removed by filtration, washed with water and dried; yield 15.7 g. (76.5%), m. p. 305–307°.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_3S_2$: N, 10.36. Found: N, 10.52.

**2-Amino-6-methylsulfonylbenzothiazole (VIII) (Method I).**—2-Acetamido-6-methylsulfonylbenzothiazole (15.7 g., 0.6 mole) was heated at reflux temperature with hydrochloric acid (4 *N*, 240 ml.) for thirty minutes. The white

(6) Price and Stacy, THIS JOURNAL, **68**, 498 (1946).

(7) Waldron and Reid, *ibid.*, **45**, 2399 (1923).

(8) Gattermann, *Ann.*, **393**, 230 (1912).

(9) Wertheim, THIS JOURNAL, **53**, 200 (1931).

TABLE I

6-METHYLMERCAPTOBENZOTHIAZOLE DERIVATIVES

| | Compound | Yield, % | Formula | M. p., °C. | Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| V | 2-Amino- | 89.5 | $C_8H_8N_2S_2$ | 150–151 | N 14.27 | 14.16 |
| | | | | | C 48.95 | 49.08 |
| | | | | | H 4.11 | 4.08 |
| XXI | 2-Chloro- | 28 | $C_8H_6ClNS_2$ | 51–52 | C 44.58 | 44.57 |
| | | | | | H 2.80 | 2.83 |
| XXII | 2-(δ-Diethylaminobutylamino)-[a] | 70 | $C_{16}H_{27}Cl_2N_3S_2$ | ..... | C 48.47 | 48.64 |
| | | | | | H 6.86 | 6.92 |
| XXIII | 2-(γ-Diethylaminopropylamino)-[a] | 58 | $C_{15}H_{25}Cl_2N_3S_2$ | ..... | N 10.99 | 10.79 |
| XXIV | 2-(Benzylamino)- | 45 | $C_{15}H_{14}N_2S_2$ | 175–176 | N 9.78 | 9.90 |
| XXV | 2-(Piperidino)- | 40 | $C_{13}H_{16}N_2S_2$ | 75–76 | C 59.05 | 59.13 |
| | | | | | H 6.10 | 6.05 |

TABLE II

6-METHYLSULFINYLBENZOTHIAZOLE DERIVATIVES

| | Compound | Yield, % | Formula | M. p., °C. | Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| XVI | 2-Chloro- | 34 | $C_8H_6ClNO_2S$ | 112–113 | N 6.04 | 6.34 |
| | | | | | C 41.46 | 41.32 |
| | | | | | H 2.61 | 2.62 |
| XVII | 2-(δ-Diethylaminobutylamino)-[a] | 40 | $C_{16}H_{27}Cl_2N_3OS_2$ | ..... | N 10.19 | 10.40 |
| XVIII | 2-(γ-Diethylaminopropylamino)-[a,b] | 21 | $C_{27}H_{29}N_9O_{15}S_2$ | ..... | N 16.08 | 15.91 |
| XIX | 2-(Benzylamino)- | 65 | $C_{15}H_{14}N_2OS_2$ | 158–160 | N 9.27 | 9.41 |
| XX | 2-(Piperidino)- | 23 | $C_{13}H_{16}N_2OS_2$ | 109–110 | N 9.99 | 9.78 |

TABLE III

6-METHYLSULFONYLBENZOTHIAZOLE DERIVATIVES

| | Compound | Yield, % | Formula | M. p., °C. | Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| XI | 2-Chloro- | 48 | $C_8H_6ClNO_2S_2$ | 189–190 | N 5.65 | 5.77 |
| | | | | | C 38.78 | 39.03 |
| | | | | | H 2.44 | 2.42 |
| VIII | 2-Amino- | 91 | $C_8H_8N_2O_2S_2$ | 224–226 | N 12.26 | 12.25 |
| | | | | | C 42.09 | 42.18 |
| | | | | | H 3.53 | 3.57 |
| XII | 2-(δ-Diethylaminobutylamino)-[a] | 44 | $C_{16}H_{27}Cl_2N_3O_2S_2$ | ..... | Cl 16.51 | 16.27 |
| | | | | | N 9.81 | 9.83 |
| XIII | 2-(γ-Diethylaminopropylamino)-[a] | 80 | $C_{15}H_{25}Cl_2N_3O_2S_2$ | ..... | N 10.14 | 10.32 |
| XIV | 2-(Benzylamino)- | 95 | $C_{15}H_{14}N_2O_2S_2$ | 220 | C 56.58 | 56.49 |
| | | | | | H 4.43 | 4.29 |
| XV | 2-(Piperidino)- | 94 | $C_{13}H_{16}N_2O_2S_2$ | 150–151 | C 52.69 | 52.61 |
| | | | | | H 5.44 | 5.31 |

[a] Dihydrochlorides. [b] Analyzed as a dipicrate which has a m. p. of 163–165°.

solid was completely dissolved by this time so the solution was filtered and carefully neutralized with ammonium hydroxide while still hot. The crystals that separated were recrystallized from 95% ethanol; yield 12 g. (91%) of white needles, m. p. 224–226°.

**4-Methylsulfonylnitrobenzene (IX).**—4-Methylmercaptonitrobenzene (2.0 g., 0.012 mole) was placed in glacial acetic acid (15 ml.) and hydrogen peroxide (30%, 10 ml.) was added. The solution was warmed on a steam-bath until all the mercapto compound went into solution. The mixture was allowed to stand at room temperature for one hour and then placed in the refrigerator overnight. The long yellow needles that separated were filtered yielding 1.85 g. (79%), m. p. 142°, lit. 136° and 142.5°.[6]

**4-Methylsulfonylaniline Hydrochloride (X).**—4-Methylsulfonylnitrobenzene (7.1 g., 0.035 mole) was reduced using Raney nickel and hydrogen in acetone solution. After complete reduction the solution was filtered free of catalyst and saturated with dry hydrogen chloride; yield 6.3 g. (86.5%). Some of the hydrochloride was converted to the amine producing a light yellow solid; m. p. 136–137°.[6]

**2-Amino-6-methylsulfonylbenzothiazole (VIII). (Method II).**—4-Methylsulfonylaniline hydrochloride (4.05 g., 0.024 mole) was treated with ammonium thiocyanate (1.8 g., 0.024 mole) in a water solution analogous to the preparation of compound IV. The impure solid thus obtained was treated with bromine and chloroform in a manner analogous to the preparation of compound V; yield 0.5 g. (9.1%), m. p. 223–225°. A mixed melting point determination with compound VIII prepared by Method I gave no appreciable depression of the melting temperature.

**2-Chloro-6-methylsulfonylbenzothiazole (XI).**—2-Amino-6-methylsulfonylbenzothiazole (4 g., 0.02 mole) was dissolved by warming and stirring in 87% phosphoric acid (43 ml.). The solution was cooled externally to 0° and concentrated nitric acid (18 ml.) was added with stirring. A solution of sodium nitrite (1.43 g., 0.02 mole) in water (3.6 ml.) was added to the lower portion of the well-stirred mixture. After standing for ten minutes the viscous diazonium solution was poured in a thin stream into concentrated hydrochloric acid (75 ml.) containing cuprous chloride (3 g., 0.02 mole). After the evolution of

nitrogen had ceased, the mixture was diluted to three times its volume and allowed to stand for one hour. The solid which formed was removed by filtration and recrystallized using charcoal from 95% ethanol (100 ml.); yield 2.4 g. (48%) of white needles, m. p. 189–190°.

**2-Chloro-6-methylsulfinylbenzothiazole (XVI).**—2-Amino-6-methylmercaptobenzothiazole (5 g., 0.03 mole) was dissolved by heating in 87% phosphoric acid (75 ml.). The solution was then cooled to 0° by means of an ice-bath. Cold concentrated nitric acid (25 ml.) was added with rapid stirring. A solution of sodium nitrite (2 g. in 5 ml. of water, 0.03 mole) was then added to the lower portion of the well-stirred acid medium. The deep red viscous diazonium mixture which formed was then poured in a small stream into concentrated hydrochloric acid (100 ml.) containing cuprous chloride (5.0 g., 0.03 mole). As soon as evolution of nitrogen ceased the mixture was stirred for an additional fifteen minutes and diluted to three times its volume. The diluted solution was extracted four times with benzene (100-ml. portions). The benzene was dried over anhydrous sodium sulfate and evaporated to dryness. The resulting orange solid was recrystallized, employing charcoal, from hot water (150 ml.); yield 2 g. (34%) of white fluffy crystals, m. p. 112–113°.

**2-Chloro-6-methylmercaptobenzothiazole (XXI).**—Identical conditions and amounts were employed as in the preparation of compound XVI with the exception that the diazotization was carried out at −20 instead of 0° using an acetone–Dry Ice-bath. The product was extracted with benzene and obtained in the solid form as before. The yellow material was transferred in two portions to a small fractionating column and distilled under reduced pressure. A yellow oil distilled over at 138–142° (3 mm.). This product was recrystallized, using charcoal, from hot petroleum ether; yield 1.5 g. (28%) of white crystals, m. p. 51–52°.

The condensations of amines with chloro compounds were carried out in a slightly over two mole excess of the amine so that the excess amine would form a salt with the hydrogen chloride eliminated. The method employed for isolation of the product was based on the fact that all the amines reacting were more soluble in water than the condensed products. The following preparations illustrate the procedure used.

**2-(Benzylamino)-6-methylsulfonylbenzothiazole (XIV).**—2-Chloro-6-methylsulfonylbenzothiazole (0.75 g., 0.003 mole) and benzylamine (0.86 g., 0.008 mole) reacted together in a 25-ml. round-bottomed flask equipped with a water condenser. Although some heat was evolved at once the mixture was heated at 150° for four hours in an oil-bath to complete the reaction. Upon cooling the reaction mixture solidified. The crystals which formed were washed thoroughly with dilute ammonium hydroxide and water to remove excess benzylamine. The solid that remained was recrystallized from ethyl acetate; yield 0.93 g. of fine white crystals, m. p. 220°.

**2-(δ-Diethylaminobutylamino)-6-methylmercaptobenzothiazole Dihydrochloride (XXII).**—2-Chloro-6-methylmercaptobenzothiazole (0.25 g., 0.001 mole) and δ-diethylaminobutylamine (0.43 g., 0.003 mole) reacted together on a steam-bath for twenty-two hours. The resulting liquid was mixed thoroughly with dilute ammonium hydroxide and extracted with three portions of diethyl ether (25 ml.). The combined solutions were washed three times with water (25 ml.), dried over anhydrous sodium sulfate and dry hydrogen chloride gas added until an oil separated. The oil was recrystallized, using charcoal, from methanol and anhydrous diethyl ether; yield 0.35 g. of a light brown solid.

## Summary

1. 2-Amino-6-methylsulfonylbenzothiazole and 2-amino-6-methylmercaptobenzothiazole have been prepared from *p*-nitrochlorobenzene in good yields.

2. The above compounds were converted to the corresponding 2-chloro compounds producing in addition 2-chloro-6-methylsulfinylbenzothiazole.

3. All three chloro compounds were successfully condensed with benzylamine, piperidine, δ-diethylaminobutylamine and γ-diethylaminopropylamine.

LINCOLN, NEBRASKA RECEIVED AUGUST 5, 1948

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[CONTRIBUTION FROM THE RESEARCH DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

# Some β-Amino-α-chloroacrylonitriles

BY JOHN G. ERICKSON

Except for a few β-aminoacrylonitriles prepared by Moureu and Lazennec,[1] no compounds of this class have been reported. The French workers prepared their compounds by the addition of various primary and secondary amines to several α,β-acetylenic nitriles.

Here we wish to report the preparation of a number of β-amino-α-chloroacrylonitriles (II) by the reaction of α,β-dichloroacrylonitrile (I) with ammonia and aliphatic and aromatic primary and secondary amines.

$$\underset{\text{I}}{\text{ClCH=CCN}} + \text{RR'NH} \longrightarrow \underset{\text{II}}{\text{RR'NCH=CCN}} + \text{HCl}$$

(Cl on the α-carbon in both I and II)

The reactions were carried out in alcohol or benzene solutions at or near room temperature. An acid acceptor, which was either a tertiary amine or an excess of the ammonia or amine being used in the reactions, was always present to neutralize the hydrogen chloride eliminated in the reactions.

The β-amino-α-chloroacrylonitriles are, in general, unstable. Although they may usually be distilled, even at high temperatures, without serious decomposition, those compounds which are liquids at room temperature slowly darken and decompose upon standing. The solid compounds appear to be relatively stable at room temperature. Of the liquid β-amino-α-chloroacrylonitriles, those derived from secondary amines are less stable than those derived from primary amines. The nature of the decomposition is not clear.

Attempts to confirm the structures of these compounds by conversion to known compounds failed, presumably because the chlorine in these

(1) Moureu and Lazennec, *Compt. rend.*, **143**, 553 (1906).

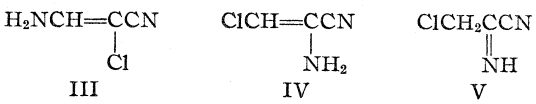
TABLE I

PREPARATION OF SEVERAL β-AMINO-α-CHLORACRYLONITRILES

| Moles of I | Moles of amine | Acid acceptor Formula | Mole | RR'NCH=CCN (Cl) Formula | R | R' | Yield, % | B. p. °C. | B. p. Mm. | M. p., °C. | Index of refr. °C. | Index of refr. $n_D$ | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.00[a] | 4.33 | Excess $NH_3$ | | $C_3H_3N_2Cl$ | H | H | 57 | 98 | 3.5 | 40–43 | | | 27.32 | 27.01 |
| 0.40[b] | 0.85 | Excess amine | | $C_7H_{11}N_2Cl$ | H | $n$-$C_4H_9$ | 92 | 82 | 0.5–1.0 | | 25 | 1.5236 | 17.66 | 17.04 |
| .22[c] | .20 | Pyridine | 0.25 | $C_{13}H_{23}N_2Cl$ | H | $n$-$C_{10}H_{21}$ | 62 | 179–180 | 1 | | 25 | 1.5018 | 11.55 | 11.37 |
| .44[d] | .40 | Pyridine | .50 | $C_{15}H_{27}N_2Cl$ | H | $n$-$C_{12}H_{25}$ | 41 | 175–185 | 1 | 37–40 | | | 10.35 | 10.18 |
| .21[e] | .20 | Pyridine | .25 | $C_9H_6N_2Cl_2$ | H | $p$-$ClC_6H_4$ | 12 | | | 139–140 | | | 13.15 | 12.74 |
| .45[f] | .40 | $(C_2H_5)_3N$ | .50 | $C_{11}H_{19}N_2Cl$ | $n$-$C_4H_9$ | $n$-$C_4H_9$ | 50 | 116–122 | 1 | | 23.5 | 1.5068 | 13.05 | 12.49 |
| .43[g] | .40 | $(C_2H_5)_3N$ | .43 | $C_{10}H_9N_2Cl$ | $CH_3$ | Phenyl | 14 | 127–130 | 1 | | 23.5 | 1.6240 | 14.51 | 14.09 |

[a] Addition carried out over one hour in 320 g. of methanol at 30°. After two hours, part of the solvent was distilled off, benzene was added and the mixture was filtered. The filtrate was distilled. The product was crystallized from hexane. Calcd. for $C_3H_3N_2Cl$: Cl, 34.60. Found: Cl, 34.1. [b] Addition carried out over one hour in 200 cc. of benzene at 50–60°. After twenty-four hours, the mixture was filtered, washed with water and distilled. The product was redistilled. [c] Addition carried out rapidly in 50 cc. of methanol. After twenty hours, the mixture was poured into water and extracted with benzene. The benzene extract was distilled. Calcd. for $C_{13}H_{23}N_2Cl$: iodine number (cg. of $I_2$ per g.), 105. Found: 106. [d] Addition carried out over forty-five minutes in 100 cc. of ethanol at 30–35°. Product washed up as in preceding run and crystallized from ethyl acetate. [e] Addition carried out in 50 cc. of methanol. Little heat was evolved. After twenty hours, the mixture was poured into water. The product was filtered off and crystallized from cold methanol (hot methanol caused decomposition) to give a light orange solid. [f] Addition carried out over two hours in 100 cc. of methanol at 20–30°. Product worked up as in third and fourth runs. Calcd. for $C_{11}H_{19}N_2Cl$: Cl, 16.51; iodine number, 118; found: Cl, 16.05; iodine number, 114. [g] Addition carried out over fifteen minutes in 100 cc. of methanol at 35°. Product worked up as in third, fourth and sixth runs.

compounds is very tightly bound. However, the assigned structures of these compounds are substantiated by a study of the infrared absorption spectrum of β-amino-α-chloroacrylonitrile (II, R=R'=H) which shows, among others, absorption bands at 3500–3200 cm.$^{-1}$, 3070 and 1650 cm.$^{-1}$, and 2210 cm.$^{-1}$, attributable, respectively, to the structural features, —$NH_2$, H—C=C, and —CN. These features are all found in structure III.



III IV V

The isomeric structure, IV, resulting from replacement of the α-chlorine in I, although it possesses the structural features indicated by the infrared absorption spectrum, does not seem likely, since immediate rearrangement to the ketimine structure, V, would be expected. The existence of stable enamine forms, such as III, is also found in the closely related β-aminocrotonic esters. Replacement of the β-chlorine in I rather than the α-chlorine also seems the more likely since I may be regarded as a substituted vinylog of cyanogen chloride and since chlorine atoms alpha to nitrile groups appear to possess lowered activity, at least in certain reactions.[2]

**Acknowledgment.**—The author is indebted to Dr. R. C. Gore of the Physics Division of these Laboratories for the determination and interpretation of the infrared absorption spectrum of β-amino-α-chloroacrylonitrile.

## Experimental

**General Procedure.**—Table I summarizes the results obtained. In each run, α,β-dichloroacrylonitrile (I) was added to a solution of amine and acid acceptor in some suitable solvent. The temperature of the reaction mixture was controlled by the use of a cooling bath. After standing at room temperature for a period of time after the addition, the reaction mixtures were worked up, usually being poured into water, extracted with benzene and distilled. Besides analyses for nitrogen, corroborative chlorine analyses and iodine number determinations were done in several cases.

## Summary

β-Amino-α-chloroacrylonitrile and several of its N-substitution products have been prepared by the reaction of α,β-dichloroacrylonitrile with ammonia and various primary and secondary aliphatic and aromatic amines.

STAMFORD, CONNECTICUT RECEIVED MARCH 19, 1948

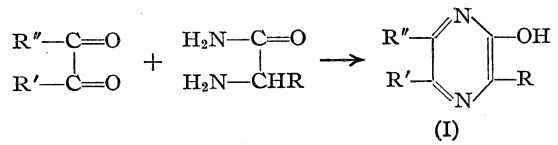
(2) Mowry, *Chem. Revs.*, **42**, 197 (1948).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Pyrazines and Related Compounds. I. A New Synthesis of Hydroxypyrazines

BY REUBEN G. JONES

A new general synthesis of hydroxypyrazines (I) has been devised which involves the condensation of 1,2-dicarbonyl compounds with α-amino acid amides



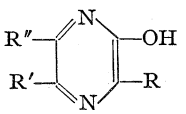
(I)

This appears to be a direct and convenient method for the preparation of hydroxypyrazines which, heretofore, have been obtained in poor yields and by laborious procedures.[1] It also appears to be one of the few satisfactory methods for preparing compounds containing the isolated pyrazine nucleus.[2]

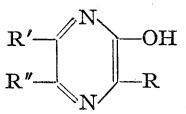
In starting out to explore this reaction the first condensations were carried out with glyoxal and aminomalonamide. When these compounds were mixed in water solution and allowed to stand, or warmed, dark brown reaction products resulted from which no pure materials could be isolated. It was then found that in the presence of base, preferably one equivalent of sodium or potassium hydroxide, glyoxal and aminomalonamide reacted rapidly to form the sodium or potassium salt of 2-hydroxy-3-carboxamidopyrazine. Under these conditions aminomalonamide was also found to condense readily with other 1,2-diketones and ketoaldehydes to give high yields of substituted hydroxycarboxamidopyrazines. Subsequently it was found that diacetyl reacted with aminomalonamide in the absence of any added base to give a practically quantitative yield of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine. In one experiment in which a solid glyoxal polymer was heated in water with aminomalonamide, several drops of aqueous sodium hydroxide was sufficient to bring about condensation.

In order to determine the scope of the reaction glyoxal, methylglyoxal, diacetyl, phenylglyoxal and benzil were condensed with a number of typical α-amino acid amides. The results of these experiments are summarized in Table I. Usually, when the reagents were mixed at room temperature, reaction took place immediately with the evolution of heat and the formation of black intractable tars. The reactions were suitably controlled, however, to yield the desired pyrazine compounds by operating at temperatures of about −10 to −20°. For the most part the reactions were carried out in water or methanol solution and with the use of one equivalent of aqueous sodium hydroxide. However, other solvents and bases may be used. For example, methionine amide and diacetyl were allowed to react in dry chloroform solution using one equivalent of piperidine to give a 70% yield of 2-hydroxy-3-(β-methylmercaptoethyl)-5,6-dimethylpyrazine. Hydroxypyrazine, the parent member of the series, was obtained in good yield by the condensation of glycine amide with glyoxal.

The condensation of an α-amino acid amide with an unsymmetrical dicarbonyl compound might be expected to yield a mixture of the two possible isomeric hydroxypyrazines (II and III).

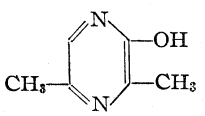


(II)



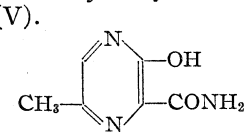
(III)

However, in each case where methylglyoxal or phenylglyoxal has been condensed with an α-amino acid amide, only one compound has been isolated. The melting point of the product from the reaction of methylglyoxal with alanine amide differed from that of the known 2-hydroxy-3,6-dimethylpyrazine.[1b] Therefore, the compound must be 2-hydroxy-3,5-dimethylpyrazine (IV).



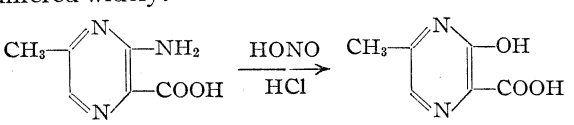
(IV)

Methylglyoxal and aminomalonamide underwent reaction to yield 2-hydroxy-5-methyl-3-pyrazinecarboxamide (V).



(V)

Proof of structure (V) was obtained by hydrolyzing to the acid and comparing the melting point with that of 2-hydroxy-6-methyl-3-pyrazinecarboxylic acid (VI). The latter was synthesized from the known 2-amino-6-methyl-3-pyrazinecarboxylic acid.[3] The melting points of the two acids differed widely.



(VI)

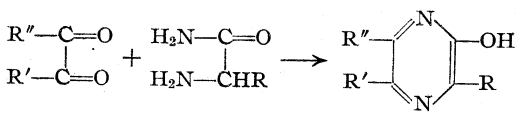
(1) (a) Tota and Elderfield, *J. Org. Chem.*, **7**, 313 (1942); (b) Baxter, Newbold and Spring, *J. Chem. Soc.*, 370 (1947); (c) Newbold and Spring, *ibid.*, 373 (1947); (d) Erickson and Spoerri, THIS JOURNAL, **68**, 400 (1946).

(2) Krems and Spoerri, *Chem. Revs.*, **40**, 279 (1947).

(3) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

TABLE I

2-HYDROXYPYRAZINES



| R | R′ | R″ | Empirical formula | Yield, % | M. p., °C. | Analyses, nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| $CONH_2$ | H | H[a] | $C_5H_5N_3O_2$ | 90 | 265 (dec.) | 30.21 | 29.80 |
| $CONH_2$ | $CH_3$ | H | $C_6H_7N_3O_2$ | 59 | 243–244 (dec.) | 27.46 | 27.60 |
| $CONH_2$ | $CH_3$ | $CH_3$ | $C_7H_9N_3O_2$ | 93 | 231–232 (dec.) | 25.13 | 25.34 |
| $CONH_2$ | $C_6H_5$ | H[b] | $C_{11}H_9N_3O_2$ | 75 | 213–216 | 19.53 | 19.80 |
| $CONH_2$ | $C_6H_5$ | $C_6H_5$ | $C_{17}H_{13}N_3O_2$ | 83 | 174–175 | 14.46 | 14.57 |
| $CH_3$ | H | H | $C_5H_6N_2O$ | 83.7 | 140–142 | 25.44 | 25.12 |
| $CH_3$ | $CH_3$ | H | $C_6H_8N_2O$ | 42 | 145–146 | 22.57 | 22.43 |
| $CH_3$ | $CH_3$ | $CH_3$[c] | $C_7H_{10}N_2O$ | 77.5 | 193–194 | 20.28 | 20.42 |
| $CH_3$ | $C_6H_5$ | H[b] | $C_{11}H_{10}N_2O$ | 56.5 | 212–213 | 15.05 | 14.71 |
| H | $CH_3$ | $CH_3$[d] | $C_6H_8N_2O$ | 11.3 | 199–200 | 22.57 | 22.65 |
| H | $C_6H_5$ | $C_6H_5$ | $C_{16}H_{12}N_2O$ | 97 | 225–227 | 11.29 | 11.22 |
| $CH_2CH_2—S—CH_3$ | H | H | $C_7H_{10}N_2OS$ | 97 | 96–97 | 16.46 | 16.94 |
| $CH_2CH_2—S—CH_3$ | $CH_3$ | $CH_3$ | $C_9H_{14}N_2OS$ | 88 | 128–129 | 14.13 | 13.81 |
| $C_6H_5$ | H | H | $C_{10}H_8N_2O$ | 88.5 | 172–173 | 16.27 | 16.04 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | $C_{12}H_{12}N_2O$ | 45 | 222–226 | 13.99 | 13.91 |
| $p$-$CH_2C_6H_4OH$ | H | H | $C_{11}H_{10}N_2O_2$ | 76 | 212–213 | 13.86 | 13.81 |
| $p$-$CH_2C_6H_4OH$ | $CH_3$ | H[b] | $C_{12}H_{12}N_2O_2$ | 47 | 202–203 | 12.96 | 12.78 |
| $p$-$CH_2C_6H_4OH$ | $CH_3$ | $CH_3$ | $C_{13}H_{14}N_2O_2$ | 77.5 | 236–237 | 12.17 | 11.88 |

[a] Previously prepared by a different method, see McDonald and Ellingson, THIS JOURNAL, **69**, 1034 (1947). [b] Structure not proved. [c] Previously prepared by a different method, see ref. 1c. [d] Previously prepared by a different method, see ref. 1a.

The structures of the hydroxypyrazines obtained from the reaction of phenylglyoxal with alanine amide and with aminomalonamide are now under investigation. It is hoped that these and other studies currently under way will provide an insight into the mechanism of the reaction.

## Experimental

**α-Amino Acid Amides.**—Aminomalonamide,[4] m. p. 187–188° (dec.), separated in 97% yield by allowing a solution of aminomalonic ester[5] in seven volumes of absolute alcohol saturated with ammonia to stand at room temperature seven days. The yellow to orange colored product was pure enough for the condensation with dicarbonyl compounds.

*Anal.* Calcd. for $C_3H_7N_3O_2$: N, 35.88. Found: N, 35.83.

Glycine amide and *dl*-alanine amide were prepared by treating the corresponding amino acid ethyl esters with ten volumes of saturated absolute alcoholic ammonia instead of liquid ammonia as described by Koenigs and Mylo.[6] The reaction with glycine ethyl ester was allowed to proceed for four days and then worked up[6] to give a 38% yield of amide. With a longer reaction time the yield was lower. In the preparation of alanine amide the reaction mixture stood for thirty days before it was worked up to give a 63% yield of amide and 17% of unchanged ester.

A solution of *l*-tyrosine ethyl ester in absolute alcoholic ammonia was allowed to stand for ten days. When the solution was evaporated to dryness, unchanged tyrosine ethyl ester was quantitatively recovered. Tyrosine amide was obtained in 90% yield from tyrosine ethyl ester and liquid ammonia as described by Koenigs and Mylo.[6]

For the preparation of *dl*-methionine amide a solution of 287 g. (1.62 moles) of *dl*-methionine ethyl ester, b. p. 132° (14 mm.), in two liters of absolute alcohol saturated at 0° with ammonia was allowed to stand in a closed flask for thirty days. The clear solution was evaporated in vacuum at about 40° until all alcohol appeared to have been removed. The residual semicrystalline mass was treated with one liter of anhydrous ether and cooled to 0°. The snow-white crystalline product was collected on a filter, washed with dry ether and dried in vacuum: The ether filtrate was distilled to yield 57 g. (20%) of unreacted methionine ethyl ester. The yield of amide was 175 g. (93% based on unrecovered ester); m. p. 48–49°. A sample for analysis was dissolved in chloroform, the solution filtered, and evaporated in vacuum.

*Anal.* Calcd. for $C_5H_{12}N_2OS$: C, 40.51; H, 8.17. Found: C, 40.66; H, 8.14.

α-Aminophenylacetamide was prepared in 88% yield by allowing a solution of ethyl α-aminophenylacetate in seven volumes of absolute alcoholic ammonia to stand at room temperature for two weeks. The product was isolated as described above for methionine amide; m. p. 128–129°.

*Anal.* Calcd. for $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.32.

Samples of the amino acid amides were kept in the refrigerator for several months without decomposition. At room temperature, however, alanine amide and especially glycine amide lost ammonia and changed to the diketopiperazines.

**Condensations with Aminomalonamide.**—To 25 g. (0.166 mole) of 40% aqueous glyoxal solution diluted with 25 ml. of water was added 11.7 g. (0.10 mole) of finely powdered aminomalonamide. The mixture was cooled in an ice–salt-bath, and with stirring 10 ml. (0.125 mole) of 12.5 *N* sodium hydroxide solution was added dropwise while the temperature was maintained below 10°. The resulting solution was allowed to stand at room temperature, and after a few minutes it had set to a semisolid mass of finely-divided crystals (sodium salt of 2-hydroxy-3-carboxamidopyrazine). After several hours, 10 ml. of glacial-acetic acid was added with stirring. The precipitate of 2-hydroxy-3-carboxamidopyrazine was collected on a filter,

(4) Piloty and Nerensheimer, *Ber.*, **39**, 514 (1906).
(5) Locquin and Cerchez, *Compt. rend.*, **186**, 1360 (1928).
(6) Koenigs and Mylo, *Ber.*, **41**, 4427 (1908).

washed with water, then with acetone and air dried. The yield of crude product was 12.5 g. (90% based on aminomalonamide). A sample for analysis was recrystallized from water and dried at 150° for several hours (see Table I).

The yields were lower when the reaction was conducted at higher temperatures or when smaller proportions of glyoxal were used. Potassium hydroxide or diethylamine was used in place of the sodium hydroxide with equally good results. Also, solid glyoxal polymer or glyoxal sodium bisulfite could be substituted for aqueous glyoxal solution.

Diacetyl was condensed with aminomalonamide in the manner described above for glyoxal. Later it was discovered that diacetyl reacted with powdered aminomalonamide in water suspension without any basic catalyst to give a practically quantitative yield of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine. This compound was very sparingly soluble in water, acetic acid or alcohol, but readily soluble in pyridine.

The condensation of aminomalonamide with methylglyoxal proceeded best when an excess of the amide was used.[7] A solution of 36 g. (0.50 mole) of freshly prepared methylglyoxal[8] (b. p. 60–64° at 50 mm.) in 50 ml. of water was cooled to −20° and 60 g. (0.51 mole) of finely powdered aminomalonamide was added. With stirring, 40 ml. (0.50 mole) of 12.5 *N* sodium hydroxide solution was added dropwise while the temperature was kept below 0°. The mixture was then allowed to stand at room temperature for eighteen hours before it was acidified with 50 ml. of 12 *N* hydrochloric acid. After standing for an additional two days, the mixture was chilled, and the 2-hydroxy-3-carboxamido-5-methylpyrazine was collected on a filter, washed with a little water and air dried. The yield was 45 g. (59%). For analysis the compound was recrystallized from water in which it appeared to be appreciably soluble.

A mixture of 21 g. (0.10 mole) of benzil and 11.7 g. (0.10 mole) of powdered aminomalonamide in 350 ml. of 50% aqueous alcohol was heated to about 70° and 10 ml. (0.125 mole) of 12.5 *N* sodium hydroxide solution was added with stirring. A clear brown solution formed and then suddenly it became almost solid with crystalline precipitate. The cooled mixture was filtered, and the solid was washed by suspension in 300 ml. of acetone. This sodium salt was very sparingly soluble in all of the common solvents, including boiling water. It was suspended in 200 ml. of acetone and treated with 20 ml. of concentrated hydrochloric acid. The resulting almost-clear solution was diluted with 500 ml. of water to precipitate 2-hydroxy-3-carboxamido-5,6-diphenylpyrazine as an oil which soon crystallized. The compound was readily recrystallized from acetone–petroleum ether, acetone–water or alcohol–water.

**Condensations with Glycine Amide, Alanine Amide, Methionine Amide and α-Aminophenylacetamide.**—The following typical experiment will illustrate the method used for the preparation of most of the compounds in Table I.

A solution of 8.8 g. (0.10 mole) of alanine amide in 50 ml. of methanol was cooled to −30° and to it was added a solution of 24 g. (0.10 mole) of commercial 30% methylglyoxal in 25 ml. of methanol also precooled to −30°. With stirring, 10 ml. (0.125 mole) of 12.5 *N* aqueous sodium hydroxide solution was added dropwise while the temperature was maintained below −10°. The mixture was allowed to stand in the refrigerator at −5° for two hours, then at room temperature for several hours. To the mixture was added 10 ml. of 12 *N* hydrochloric acid followed by 5 g. of solid sodium bicarbonate to neutralize any excess acid, and the whole was evaporated to dryness in vacuum on the steam-bath. The residue was extracted with three 100-ml. portions of boiling chloroform. Evaporation in vacuum of the chloroform left 8.5 g. of gummy solid. This was recrystallized successively from 25-ml., 15-ml. and 10-ml. portions of ethyl acetate to yield 3.5 g. of white crystals, m. p. 144–146°. The ethyl acetate mother liquors were evaporated and cooled, and after several recrystallizations there was eventually obtained an additional 1.7 g. of pure product making the total yield 5.2 g. (42%). A small sample recrystallized from acetone melted at 145–146° and a sample sublimed in vacuum also melted at 145–146°.

*Anal.* Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.33; H, 6.57; N, 22.42.

The melting point of the known 2-hydroxy-3,6-dimethylpyrazine is reported[1b] to be 210–211°. This difference in melting point in conjunction with the analytical data proves that the present compound must be 2-hydroxy-3,5-dimethylpyrazine.

The condensation of glycine amide with benzil was carried out in *hot* methanol solution.

**Hydroxypyrazine.**—To a solution of 12 ml. of 12.5 *N* sodium hydroxide in 50 ml. of methanol cooled to −20° was added 7.4 g. (0.10 mole) of glycine amide in 20 ml. of methanol. Then with stirring 30 g. (0.15 mole) of 30% aqueous glyoxal was added slowly while the temperature was maintained below −10°. After the solution had stood at room temperature for two hours, 15 ml. of acetic acid was added, and the mixture was evaporated to dryness under vacuum on the steam-bath. The residue was exhaustively extracted with acetone, and after evaporation of the acetone extract there was obtained 8.1 g. (84% yield) of crude hydroxypyrazine, m. p., 140–150°. This product was difficult to purify, but, eventually, after three recrystallizations from absolute alcohol using liberal quantities of activated carbon there was obtained 4.6 g. (48% yield) of pure hydroxypyrazine, m. p. 187–189°, and mixed m. p. with an authentic sample,[3] 187–189°.

**Condensation with Tyrosine Amide.**—The following example is typical. To a suspension of 8.5 g. (0.05 mole) of tyrosine amide in 50 ml. of methanol at −20° was added 12 g. (0.06 mole) of 30% aqueous glyoxal followed by 9 ml. (0.11 mole) of 12.5 *N* sodium hydroxide solution. The mixture was removed from the cooling-bath and allowed to stand overnight at room temperature. With stirring, 10 ml. of 12 *N* hydrochloric acid and 10 ml. of water were added and the solution was chilled to 0°. The white crystalline precipitate of 2-hydroxy-3-(*p*-hydroxybenzyl)-pyrazine (Table I) was collected on a filter, washed with water and air dried. It was recrystallized from methanol–ethyl acetate or methanol–water.

**2-Hydroxy-5,6-dimethyl-3-pyrazinoic Acid.**—A suspension of 11.5 g. (0.069 mole) of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine in 75 ml. of 3 *N* sodium hydroxide solution was heated on the steam-bath for several hours. Ammonia was evolved, and a clear brown solution formed. The solution was acidified with excess (25 ml.) concentrated hydrochloric acid and chilled to 0°. The crystalline precipitate was collected and air dried. It weighed 9.0 g. (79% yield). A sample was recrystallized from water; m. p. 172–174° (dec.).

*Anal.* Calcd. for $C_7H_8N_2O_3$: N, 16.66. Found: N, 16.86.

In the same way 2-hydroxy-3-carboxamidopyrazine was hydrolyzed to 2-hydroxy-3-pyrazinoic acid in 84% yield; m. p. 218–220°. The mixed melting point with a specimen prepared by the method of Weijlard, Tishler and Erickson[3] was also 218–220°.

**2-Hydroxy-5-methyl-3-pyrazinoic Acid.**—A suspension of 20 g. (0.13 mole) of crude 2-hydroxy-3-carboxamido-5-methylpyrazine in 75 ml. of 5 *N* sodium hydroxide solution was heated on the steam-bath for sixteen hours. The resulting solution was acidified and chilled to yield 6.0 g. (30%) of 2-hydroxy-5-methyl-3-pyrazinoic acid. A sample was recrystallized from water, in which it was appreciably soluble.

*Anal.* Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.79; H, 3.99; N, 18.52.

The recrystallized compound melted with decomposition at 155–157°. Authentic 2-hydroxy-6-methyl-3-pyrazin-

(7) Very small yields of the desired 2-hydroxy-3-carboxamide-5-methylpyrazine were obtained when methylglyoxal was used in excess. With commercial 30% methylglyoxal (obtained from Carbide and Carbon Chemicals Corporation) the best yields of pyrazine compound were only 25 to 30%.

(8) Riley, Morley and Friend, *J. Chem. Soc.*, 1875 (1932).

oic acid (see below) melted and decomposed at 182–183°, and a mixture of the two melted and decomposed over the range 150–155°.

**2-Hydroxy-6-methyl-3-pyrazinoic Acid.**—A solution of 3.5 g. (0.023 mole) of 2-amino-6-methyl-3-pyrazinoic acid[3] in 100 ml. of 1.00 *N* hydrochloric acid was cooled to 10° and with stirring 4.5 g. (0.065 mole) of solid sodium nitrite was added in small portions. The solution stood at room temperature for one hour, and then it was heated at 70° for one-half hour. With stirring 3.0 g. (0.035 mole) of sodium bicarbonate was added, and the solution was evaporated to dryness in vacuum. The residue was extracted with 150 ml. of hot absolute alcohol, the alcohol solution was evaporated to 25 ml., and 200 ml. of dry ether was added. The resulting brown hygroscopic precipitate was recrystallized from 20 ml. of water to give 1.2 g. of tan powder. This was recrystallized from 4 ml. of water using carbon to decolorize, and 0.8 g. of light tan crystals were obtained; m. p. 183–184° (dec.).

*Anal.* Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 47.04; H, 4.23; N, 18.65.

## Summary

A new pyrazine synthesis has been evolved in which 1,2-dicarbonyl compounds are caused to condense with α-amino acid amides to yield substituted hydroxypyrazines.

INDIANAPOLIS, INDIANA RECEIVED JULY 26, 1948

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[CONTRIBUTION NO. 59 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# The Catalytic Hydrogenation of the Benzene Nucleus. IV. The Hydrogenation of Methyl-substituted Benzoic Acids

BY HILTON A. SMITH AND JAMES A. STANFIELD

## Introduction

In an earlier paper[1] it was demonstrated that for the polymethylbenzenes the rate of catalytic hydrogenation of the benzene nucleus was governed not only by the number of substituents but also by their position. Those compounds which were symmetrically substituted reacted much faster than did others with the same number of substituents. Evidence that this was a question of symmetrical substitution and not of symmetry in the molecule itself was found in the fact that *p*-cymene hydrogenated more rapidly than did isopropylbenzene.

In order to study this matter further, a number of compounds have now been prepared which have both methyl groups and carboxyl groups attached to a benzene ring. With such compounds it should be possible to confirm the evidence that symmetrical substitution rather than molecular symmetry is the important factor.

## Experimental

**Benzoic, ortho-, meta- and para-toluic acids** were all obtained from the Eastman Kodak Company and were Eastman best grade materials.

**2,3-Dimethylbenzoic acid** was prepared from 3-nitro-1,2-dimethylbenzene. The nitro group was reduced with iron and hydrochloric acid[2] to form the amino compound, which was then converted to 3-iodo-1,2-dimethylbenzene.[3] This was then converted to 2,3-dimethylbenzoic acid using an adaptation of the Grignard reaction.[4]

**2,4-Dimethylbenzoic acid** was prepared by diazotization of the corresponding amino compound followed by treatment of the diazonium salt with potassium iodide.[5] The iodo compound was converted to the acid by treatment of the corresponding Grignard reagent with carbon dioxide.

**2,5-Dimethylbenzoic acid** was prepared by bromination of *p*-xylene[6] which was then converted to the acid by carbonation of the corresponding Grignard reagent.

**2,6-Dimethylbenzoic acid** was prepared from 2-amino-1,3-dimethylbenzene using the same general procedure as that employed in the preparation of the 2,3-dimethylbenzoic acid.

**3,4-Dimethylbenzoic acid** was prepared from *o*-xylene in a manner analogous to that used for the 2,5-dimethylbenzoic acid.

**3,5-Dimethylbenzoic acid** was prepared from mesitylene by oxidation with dilute nitric acid.[7]

**2,3,4-Trimethylbenzoic acid** was prepared; 3-iodo-1,2-dimethylbenzene was treated with magnesium and dimethyl sulfate to form hemimellitene in the same manner as that used in the preparation of isodurene.[8] The hydrocarbon was converted to 2,3,4-trimethylbenzaldehyde through the action of zinc cyanide in the presence of hydrogen chloride gas and aluminum chloride.[9] The aldehyde was then oxidized to the desired acid by means of a 20% permanganate solution.

**2,4,5-Trimethylbenzoic acid** was prepared by bromination of pseudocumene[10] followed by a Grignard reaction similar to that used in the preparation of 2,3-dimethylbenzoic acid.

**2,4,6-Trimethylbenzoic acid** was prepared from bromomesitylene by means of a Grignard synthesis.

**2,3,6-Trimethylbenzoic acid** was prepared from pseudocumene.[10] The pseudocumene was first sulfonated to form pseudocumenesulfonic acid-5[11] which was then brominated. This bromination to form a mixture of 5-bromopseudocumene and 3-bromopseudocumenesulfonic acid-5 has been previously carried out by Smith and Kiess[12] but the procedure was sufficiently modified to warrant description: 136 grams of pseudocumenesulfonic acid-5 ($C_6H_2(CH_3)_3SO_3H \cdot 1.5H_2O$) was suspended in 300 ml. of 20% hydrochloric acid solution; 122 g. of bromine suspended in 56

(1) Smith and Pennekamp, THIS JOURNAL, **67**, 279 (1945).

(2) Mahood and Shaffner, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 160.

(3) Lucas and Kennedy, *ibid.*, p. 351.

(4) Fuson and Kelton, *ibid*, **63**, 1500 (1941).

(5) Smith and Lund, *ibid.*, **52**, 4144 (1930).

(6) Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 95.

(7) Fittig, *Ann.*, **141**, 144 (1867); Snyder, Adams and McIntosh, THIS JOURNAL, **63**, 3280 (1941).

(8) *Cf.* Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 360.

(9) *Cf.* Fuson, Horning, Rowland and Ward, "Organic Syntheses," **23**, 57 (1947).

(10) This was prepared by Mr. Comer Shacklett of this Laboratory by chloromethylation of mixed xylenes followed by a Grignard reaction.

(11) Smith and Cass, THIS JOURNAL, **54**, 1603 (1932).

(12) Smith and Kiess, *ibid.*, **61**, 284 (1939).

ml. of 20% hydrochloric acid was added to the cooled sulfonic acid suspension. The resulting jelly-like mass was stirred for several hours, and then allowed to stand overnight. The 5-bromopseudocumene together with some of the sulfonated material was removed by extraction with ether. The extract was washed with sodium bicarbonate until all acidic materials were removed. The ether was then removed by evaporation and the solid bromopseudocumene recrystallized from ethanol; 60 g. (50%) of white crystals, melting at 71–72° was obtained. In addition, 56 g. (33%) of 3-bromopseudocumenesulfonic acid-5 was recovered.

TABLE I

PHYSICAL CONSTANTS OF ACIDS HYDROGENATED

| Acid | Corr.[a] M. p., °C. | Neutral equivalent Found | Neutral equivalent Theoretical |
|---|---|---|---|
| Benzoic | 121.6–121.8 | 122.2 | 122.0 |
| *o*-Toluic | 106.0–107.0 | 136.2 | 136.1 |
| *m*-Toluic | 114.4–115.0 | 135.8 | 136.1 |
| *p*-Toluic | 182.0–183.0 | 136.3 | 136.1 |
| 2,3-Dimethylbenzoic | 144.5–144.8 | 150.7 | 150.2 |
| 2,4-Dimethylbenzoic | 125.4–125.8 | 150.3 | 150.2 |
| 2,5-Dimethylbenzoic | 133.8–134.1 | 150.4 | 150.2 |
| 2,6-Dimethylbenzoic | 115.8–116.2 | 150.0 | 150.2 |
| 3,4-Dimethylbenzoic | 167.4–168.2 | 149.7 | 150.2 |
| 3,5-Dimethylbenzoic | 171.6–172.0 | 150.2 | 150.2 |
| 2,3,4-Trimethylbenzoic | 166.6–167.4 | 164.5 | 164.2 |
| 2,3,6-Trimethylbenzoic | 102.4–102.8 | 164.4 | 164.2 |
| 2,4,5-Trimethylbenzoic | 150.8–151.2 | 164.6 | 164.2 |
| 2,4,6-Trimethylbenzoic | 157.0–158.0 | 164.4 | 164.2 |
| 2,3,4,6-Tetramethylbenzoic | 169.4–170.0 | 178.5 | 178.2 |
| 2,3,5,6-Tetramethylbenzoic | 179.4–180.0 | 178.3 | 178.2 |
| 2,3,4,5,6-Pentamethylbenzoic | 211.0–211.6 | 192.0 | 192.2 |

[a] All melting points have been corrected for emergent thermometer stem.

**2,3,4,6-Tetramethylbenzoic acid** was prepared using bromomesitylene as a starting material. This was converted to isodurene by the action of dimethyl sulfate on the corresponding Grignard reagent.[8] The isodurene was then brominated to form 4-bromo-1,2,3,5-tetramethylbenzene, which was then converted to 2,3,4,6-tetramethylbenzoic acid by the usual Grignard procedure.

**2,3,5,6-Tetramethylbenzoic acid** was obtained by brominating durene to form 3-bromo-1,2,4,5-tetramethylbenzene which was then converted to the desired acid by a Grignard procedure.

**2,3,4,5,6-Pentamethylbenzoic acid** was prepared by bromination of pentamethylbenzene followed by a Grignard synthesis.[4] The latter was somewhat complicated by the insolubility of both the magnesium complex in ether and the sodium salt of the acid in water. However, good yields (60%) were obtained.

It was necessary that all of these acids be very pure before hydrogenation was attempted. They were recrystallized several times; the solvent for the final crystallization was usually Eastman best grade cyclohexane. Occasionally this solvent was shaken with Raney nickel before use. Neutral equivalents of all acids were determined by titration with standard base. Table I gives the melting points and neutral equivalents of the acids.

As in earlier work, the acetic acid solvent was prepared by fractionation in a five-foot helix-packed still, and the platinum catalyst was either prepared by standard methods[14] or was a commercial sample. The hydrogenations were carried out in a low pressure Parr catalytic reduction apparatus in the manner previously described.[15] For the slower runs, the standard hydrogen reservoir tank (4.02 l.) was replaced by a smaller one (0.875 l.); 50 ml. of glacial acetic acid was used as solvent for each run. This solvent was purified before use by fractionation.

After each hydrogenation was complete, the platinum catalyst was recovered from the solution by filtration. Most of the solvent was then removed by distillation. If the product was a liquid or low-melting solid, it was purified by distillation through a 10-inch Vigreux column. If the product was of sufficiently high melting point so that good crystals could be obtained, the warm liquid from which the excess solvent had been removed was poured into water, and the crystals removed by filtration. The physical constants of the products are given in Table II.

TABLE II

PRODUCTS ISOLATED FROM HYDROGENATION

| Cyclohexanecarboxylic acid derivative | B. p. cor.[a] °C. | Mm. | M. p., cor.[a] | Neutral equivalent Found | Neutral equivalent Theory | $n^{20}D$ | Per cent. recovery |
|---|---|---|---|---|---|---|---|
| 2-Methyl- | 241.7–241.9 | 760 | | 141.9 | 142.1 | .... | 91 |
| 3-Methyl- | 143.5–143.8 | 21 | | 142.4 | 142.1 | 1.4570 | 93 |
| 4-Methyl- | 143.2 | 20.5 | | 142.1 | 142.1 | .... | .. |
| 2,3-Dimethyl-[b] | 138.2–138.3 | 13.5 | | 156.6 | 156.2 | 1.4661 | 87 |
| 2,4-Dimethyl[b] | 143.2–143.4 | 21 | | 156.1 | 156.2 | 1.4590 | 95 |
| 2,5-Dimethyl-[b] | 150.2 | 21 | | 156.0 | 156.2 | 1.4590 | 90 |
| 2,6-Dimethyl- | | | 87.6–88.0 | 155.9 | 156.2 | | 91 |
| 3,4-Dimethyl- | 155.5–155.8 | 20.5 | | 156.7 | 156.2 | 1.4628 | 88 |
| 3,5-Dimethyl- | 137.6–137.7 | 14 | | 155.9 | 156.2 | | 91 |
| 2,3,4-Trimethyl-[b] | | | 63.5–64.4 | 170.4 | 170.2 | | 88 |
| 2,3,6-Trimethyl-[b] | | | 77.8–78.2 | 169.6 | 170.2 | | 85 |
| 2,4,5-Trimethyl-[b] | | | 57.5–58.0 | 170.8 | 170.2 | | 87 |
| 2,4,6-Trimethyl- | | | 103.5–104.3 | 169.7 | 170.2 | | 96 |
| 2,3,4,6-Tetramethyl-[b] | | | 43.8–44.8 | 184.0 | 184.2 | | 85 |
| 2,3,5,6-Tetramethyl-[b] | | | 137.6–138.6 | 184.7 | 184.2 | | 87 |
| 2,3,4,5,6-Pentamethyl-[b] | | | 129.1–130.2 | 198.4 | 198.2 | | 78 |

[a] All melting and boiling points have been corrected for emergent thermometer stem. [b] New compounds.

The 5-bromopseudocumene was converted to 3-bromopseudocumenesulfonic acid-5 by the action of fuming sulfuric acid,[13] and subsequently hydrolyzed to form 3-bromopseudocumene. 2,3,6-Trimethylbenzoic acid was prepared from this bromide by a Grignard synthesis.

(13) Smith and Moyle, THIS JOURNAL, **58**, 1 (1936).

(14) Adams, Voorhees and Shriner, "Organic Syntheses," **8**, 92 (1928).

(15) Smith, Alderman and Nadig, THIS JOURNAL, **67**, 272 (1945).

## Experimental Calculations and Results

It was established, as in previous work, that the hydrogenation reaction was first order with respect to hydrogen pressure, zero order with respect to the hydrogen acceptor, and directly proportional to the amount of catalyst used. This is also true for the compounds studied here, as is shown by Table III. These rate constants are calculated from the equation

$$\log \frac{p^0_{H_2}}{p_{H_2}} = \frac{kt}{2.303\ V}$$

by plotting log $p^0_{H_2}/p_{H_2}$ against $t$, and multiplying the slope of the line thus obtained by 2.303 $V$.[16] These constants all referred to one gram of standard catalyst at 30°[15,17] are given in Table IV. The table also includes constants for corresponding polymethylbenzenes.

TABLE III

EFFECT OF VARIABLES ON RATE OF HYDROGENATION OF METHYL-SUBSTITUTED BENZOIC ACIDS

| Acid | Moles | Grams of catalyst | Initial pressure (p. s. i.) | $k°_{30} \times 10^4$ |
|---|---|---|---|---|
| *o*-Toluic | 0.025 | 0.2000 | 64.7 | 312[a] |
| *o*-Toluic | .025 | .2000 | 17.9 | 319 |
| 2,3,5,6-Tetramethylbenzoic | .05 | .2000 | 64.7 | 35.6 |
| 2,3,5,6-Tetramethylbenzoic | .05 | .1000 | 64.7 | 34.8 |
| 2,4-Dimethylbenzoic | .03 | .2000 | 64.5 | 289 |
| 2,4-Dimethylbenzoic | .01 | .2000 | 65.0 | 291 |

[a] The units of all rate constants are liters × grams$^{-1}$ × min.$^{-1}$.

## Discussion

An examination of Table IV shows at once that the same trend is found in the reaction rate constants for the methyl-substituted benzoic acids as was found in the polymethylbenzenes. In general, the greater the number of substituents found on the benzene ring, the slower is the rate constant. However, whenever the number of substituents is the same, the position of substitution becomes important. In all cases, the most symmetrically substituted molecules hydrogenate faster. This confirms the idea that symmetrical substitution rather than molecular symmetry is the important factor in influencing the rate.

In the last column of Table IV is given the ratio of the rate constants for the corresponding methyl-substituted benzoic acids and polymethylbenzenes. This ratio, which indicates the effect of substitution of a carboxyl group for a methyl group, is fairly constant, the only noteworthy exception being the ratio of the rate constants for pentamethylbenzoic acid and hexamethylbenzene. This acid hydrogenates somewhat more readily than was anticipated. No explanation for this fact can be offered at the present time.

(16) Fuzek and Smith, THIS JOURNAL, **70**, 3743 (1948).

(17) These constants, $k°_{30}$, differ from those previously published by a factor of 4.43.

TABLE IV

COMPARISON OF RATE CONSTANTS WITH PREVIOUS DATA

| Methylbenzene | $k°_{30} \times 10^4$[b] | Corresponding methylbenzoic acid | $k°_{30} \times 10^4$ | Ratio of rate constants[a] |
|---|---|---|---|---|
| Toluene | 1800 | Benzoic | 1120 | 1.6 |
| *o*-Xylene | 932 | 2-Methyl- | 312 | 3.0 |
| *m*-Xylene | 1434 | 3-Methyl- | 813 | 1.8 |
| *p*-Xylene | 1882 | 4-Methyl- | 942 | 2.0 |
| Hemimellitene | 417 | 2,6-Dimethyl- | 200 | 2.1 |
| Hemimellitene | 417 | 2,3-Dimethyl- | 186 | 2.2 |
| Pseudocumene | 847 | 2,5-Dimethyl | 404 | 2.1 |
| Pseudocumene | 847 | 2,4-Dimethyl- | 289 | 2.9 |
| Pseudocumene | 847 | 3,4-Dimethyl | 350 | 2.4 |
| Mesitylene | 1680 | 3,5-Dimethyl- | 641 | 2.6 |
| Prehnitene | 282 | 2,3,4-Trimethyl- | 83.6 | 3.3 |
| Prehnitene | 282 | 2,3,6-Trimethyl- | 77.4 | 3.6 |
| Isodurene | 332 | 2,4,6-Trimethyl- | 209 | 1.6 |
| Durene | 529 | 2,4,5-Trimethyl- | 211 | 2.5 |
| Pentamethylbenzene | 103 | 2,3,4,6-Tetramethyl- | 61.3 | 1.7 |
| Pentamethylbenzene | 103 | 2,3,5,6-Tetramethyl- | 35.2 | 2.9 |
| Hexamethylbenzene | 18 | 2,3,4,5,6-Pentamethyl- | 23.2 | 0.8 |
| | | | Av. | 2.3 |

[a] The ratio of the rate constants is obtained by dividing the constant of the second column by the constant of the fourth column. The units of all rate constants are liters × grams$^{-1}$ × min.$^{-1}$. [b] Calculated from the data of Smith and Pennekamp (ref. 1) by multiplying the rate constants previously reported by 4.43. The value for hexamethylbenzene has been revised due to errors in previous calculation.

## Summary

A study has been made of the kinetics of catalytic hydrogenation of a number of methyl-substituted benzoic acids. The reactions were carried out at low pressures, in acetic acid solution, using Adams platinum catalyst. First-order reaction rate constants, all referred to one gram of standard platinum oxide, are given.

It has been demonstrated that the substitution of a carboxyl group for a methyl group cuts the rate of hydrogenation approximately in half. It has also been demonstrated that compounds with symmetrical substitution generally hydrogenate more readily than corresponding unsymmetrically substituted compounds.

KNOXVILLE, TENNESSEE RECEIVED JULY 28, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# The Ultraviolet Absorption Spectra of Organic Sulfur Compounds. I. Compounds Containing the Sulfide Function[1]

BY EDWARD A. FEHNEL[2] AND MARVIN CARMACK

In connection with a study of the chemistry of certain organic sulfur compounds in this Laboratory, we have frequently had occasion to determine the ultraviolet absorption spectra of compounds containing the sulfide or sulfone functions. Since surprisingly little has been published concerning the absorption spectra of simple organic compounds of this type,[3] we have undertaken an extensive investigation of the absorption spectra of model compounds containing these functions for the purpose of providing data which should prove useful in structure determinations. The present paper describes the results obtained with aliphatic and aromatic sulfides, mercaptals and mercaptoles, alkoxysulfides, ketosulfides and carbalkoxysulfides. Further data on sulfones, nuclearly-substituted aromatic sulfides and sulfones, and heterocyclic sulfur compounds will appear in subsequent publications.

On the basis of the limited information heretofore available on the spectroscopic properties of the sulfide function, it has been stated that —$\ddot{S}$— is a resonance insulator with properties much like those of —$\ddot{O}$— and —$CH_2$—.[4] We have now observed an unusual type of conjugation between chromophores in compounds in which the sulfide function and another function such as a carbonyl, carbalkoxyl, vinyl, phenyl or second sulfide function are both attached to the same carbon atom. These observations lead to some interesting conclusions regarding the correlation of absorption spectra with structure in these types of compounds. A discussion of the theoretical aspects of the problem has been reserved until after a description of the spectra themselves.

**Aliphatic Sulfides.**—Alkyl sulfides in ethanol solution exhibit a narrow absorption band of rather high intensity (log $\epsilon \sim 3$) in the neighborhood of 210 m$\mu$ (Figs. 1–3). A gradual displacement of the maximum toward longer wave lengths and higher intensities is observed as the $\alpha$-hydrogen atoms are successively replaced by methyl groups in the series: methyl sulfide, ethyl sulfide, isopropyl sulfide and *t*-butyl sulfide (Fig. 1). A shoulder which appears on the long wave length side of the curves for methyl sulfide, ethyl sulfide (Figs. 1 and 2), *n*-butyl sulfide (Figs. 3 and 4) and pentamethylene sulfide (Fig. 5) in the region 225–235 m$\mu$ is considerably reduced in the curve for isopropyl sulfide and disappears in the curve for *t*-butyl sulfide. This shoulder is shifted 10 m$\mu$ toward longer wave lengths in the spectrum of tetramethylene sulfide, while the peak at 210 m$\mu$ is broadened and reduced in intensity as compared with the next higher homolog, pentamethylene sulfide (Fig. 5). The differences between the spectra of the latter two compounds presumably have a stereochemical basis and will be considered further in connection with our study of the spectra of heterocyclic sulfur compounds.

**Mercaptals and Mercaptoles.**—The marked optical interaction exhibited by compounds in which two sulfide functions are attached to a common carbon atom is illustrated in Figs. 2 and 3. In the spectra of the mercaptals a new peak (log $\epsilon \sim 2.8$) appears in the region 235–240 m$\mu$. Alkylation of the central carbon atom, as in 2,2-bis-(*n*-butylmercapto)-propane (Fig. 3), has only the effect of intensifying this new absorption band somewhat. As might be expected from the multiplicity of functional units, *sym*-trithiane (Fig. 2) has a spectrum similar to, but uniformly more intense than, those of the simple mercaptals. In contrast to these results, ethanol solutions of trioxane, the oxygen analog of *sym*-trithiane, are completely transparent throughout the region observable with the instrument and solvent used (down to ~208 m$\mu$).

The spectra of bis-(*n*-butylmercapto)-methane and *sym*-trithiane were determined in both ethanol and anhydrous dioxane, and the results, shown in Fig. 6, indicate only a very slight influence of the solvent on the position of the new peak in the region 235–240 m$\mu$. This band is not, therefore, attributable to dissociation or to chemical reaction with a hydroxylated solvent.

That there exists a profound difference in the spectral behavior of sulfur and oxygen was shown by replacing one of the sulfur atoms of a mercaptal with an oxygen atom in the monothioacetal, *n*-$C_4H_9SCH_2OC_2H_5$ (Fig. 4). It will be noted that the replacement of sulfur with oxygen not only results in the disappearance of the peak at 236 m$\mu$ but suppresses the intensity of absorption below that of even the simple alkyl

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society at the Chicago meeting, April, 1948.

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(3) Absorption data for a few simple aliphatic and aromatic thioethers have been reported previously, but much of this is of a semiquantitative nature and permits little more than a rough comparison between the compounds studied in a given investigation. References to the earlier data are included in Table I.

(4) See, for example, Brode, "Chemical Spectroscopy," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 221. Lewis and Calvin (ref. 9a, p. 284) have, however, suggested that sulfur atoms may sometimes join chromophoric groups into single chromophoric units.

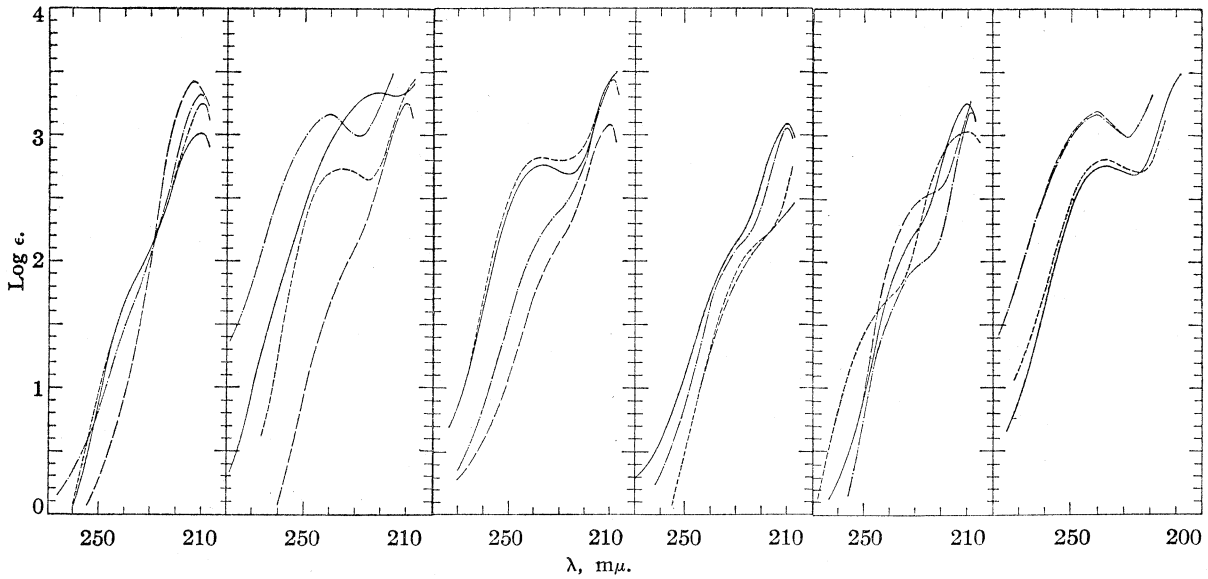



Fig. 1. Fig. 2. Fig. 3. Fig. 4. Fig. 5. Fig. 6.

Fig. 1.—Absorption spectra of $(CH_3)_2S$, —; $(C_2H_5)_2S$, - - - - - -; $[(CH_3)_2CH]_2S$, -·-·-; $[(CH_3)_3C]_2S$, — — —.

Fig. 2.—Absorption spectra of $(CH_2{=}CHCH_2)_2S$, —; $CH_3SCH_2SCH_3$, - - - - - -; *sym*-trithiane, -·-·-; $(C_2H_5)_2S$, — — —.

Fig. 3.—Absorption spectra of *n*-$C_4H_9SCH_2SC_4H_9$-*n*, —; *n*-$C_4H_9SC(CH_3)_2SC_4H_9$-*n*, - - - - - -; *n*-$C_4H_9SCH_2CH_2SC_4H_9$-*n* -·-·-; $(n\text{-}C_4H_9)_2S$, — — —.

Fig. 4.—Absorption spectra of $(n\text{-}C_4H_9)_2S$, —; *n*-$C_4H_9SCH_2OC_2H_5$, - - - - - -; *n*-$C_4H_9SCH_2CH_2OC_2H_5$, -·-·-; $(CH_3OCH_2)_2S$, — — —.

Fig. 5.—Absorption spectra of $(CH_2)_5S$, —; $(CH_2)_4S$, - - - - - -; 1,4-thioxane, -·-·-; 1,4-dithiane, — — —.

Fig. 6.—Absorption spectra of *n*-$C_4H_9SCH_2SC_4H_9$-*n* in ethanol, —, and in dioxane, - - - - - -; *sym*-trithiane in ethanol, -·-·-, and in dioxane, — — —.

sulfides. A similar effect is observed in the spectra of the dimethoxysulfide, $CH_3OCH_2SCH_2OCH_3$, and of *n*-$C_4H_9SCH_2CH_2OC_2H_5$ (Fig. 4).

When two sulfide functions are separated by two methylene groups, as in 1,2-bis-(*n*-butylmercapto)-ethane (Fig. 3), the chromophores are effectively insulated from each other, and the spectrum is similar to that calculated for a simple monosulfide at twice the molar concentration.

A comparison of the relative effect of $-CH_2-$, $-\ddot{O}-$, and $-\ddot{S}-$ in six-membered rings is shown in Fig. 5 in the spectra of pentamethylene sulfide, 1,4-thioxane and 1,4-dithiane. Little difference is observed in the effect of sulfur and oxygen when either of these is separated from a sulfide function by two carbon atoms, in marked contrast to the unique behavior observed when only a single carbon atom intervenes between two sulfide functions.

**Allyl Sulfide.**—An example of the effect of having a vinyl group and a sulfide function attached to the same carbon atom is provided by the spectrum of allyl sulfide (Fig. 2). The curve, which consists of a broad absorption band having a maximum at 221 mμ, differs markedly from those of both non-conjugated alkadienes[5] (*e.g.*, 1,5-hexadiene, $\lambda_{max.} < 200$ mμ) and simple sulfides.

**Aromatic Sulfides.**—The ultraviolet absorption spectra of a number of typical aryl and aralkyl sulfides are illustrated in Figs. 7–11. Considerable interaction between sulfur and an attached benzene ring is evident in the spectra of phenyl sulfide (Fig. 9), benzyl phenyl sulfide (Fig. 9) and the phenyl alkyl sulfides (Figs. 7 and 8), all of which differ markedly from the spectra of simple benzenoid hydrocarbons such as toluene (Fig. 8). A smoothing out of the benzenoid fine structure and a great intensification of the absorption throughout are features which appear to be characteristic of the phenylmercapto group. However, a progressive change in the position of the long wave length maximum is noted when the α-hydrogen atoms in the phenyl alkyl sulfides (Fig. 7) are replaced stepwise by alkyl groups in the series: phenyl methyl sulfide ($\lambda_{max.}$ 254 mμ), phenyl ethyl sulfide ($\lambda_{max.}$ 256 mμ), phenyl isopropyl sulfide ($\lambda_{max.}$ 258 mμ), and phenyl *t*-butyl sulfide ($\lambda_{max.}$ 266 mμ). Simultaneously with the shift of the maxima toward longer wave lengths, a downward trend in intensities is observed (log ε: 3.98, 3.90, 3.75, 3.19, resp.). Progressive changes are likewise noted in the shoulder in the region 270–290 mμ and in the short wave length peaks at 200–220 mμ.

The effect of interposing one or more methylene

(5) Spectra of these and most other comparison compounds mentioned in this paper may be found in the "International Critical Tables," Vol. V, McGraw-Hill Book Co., New York, N. Y., 1929, pp. 359 ff.

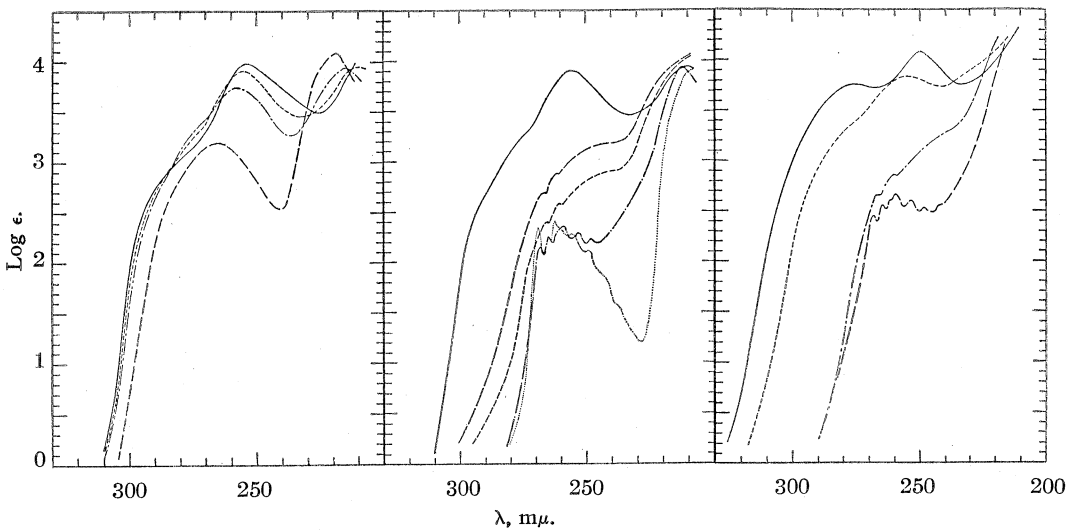



Fig. 7. Fig. 8. Fig. 9.

Fig. 7.—Absorption spectra of $C_6H_5SCH_3$, —; $C_6H_5SC_2H_5$, - - - - - -; $C_6H_5SCH(CH_3)_2$, —·—·—; $C_6H_5SC(CH_3)_3$, — — —.

Fig. 8.—Absorption spectra of $C_6H_5SC_2H_5$, —; $C_6H_5CH_2SC_2H_5$, - - - - - -; $C_6H_5CH_2CH_2SC_2H_5$, —·—·—; $C_6H_5CH(SCH_3)_2$, — — —; $C_6H_5CH_2$, . . . . . .

Fig. 9.—Absorption spectra of $(C_6H_5)_2S$, —; $C_6H_5SCH_2C_6H_5$, - - - - - -; $(C_6H_5CH_2)_2S$, —·—·—; $(C_6H_5CH_2CH_2)_2S$, — — —.

groups between the sulfide function and the benzene ring is illustrated in the curves for the homologous series: phenyl ethyl sulfide, benzyl ethyl sulfide, and phenethyl ethyl sulfide (Fig. 8). Although the spectrum of benzyl ethyl sulfide is less intense than that of phenyl ethyl sulfide, considerable interaction between the sulfur atom and the aromatic nucleus in the former compound is indicated by the development of a prominent shoulder at 235–240 mμ (log ε ~2.9). In this same region a minimum appears in the curve for phenethyl ethyl sulfide, which is essentially a summation of the spectra of an alkyl benzene and an alkyl sulfide. Analogous relationships, on a somewhat higher level of absorption, are observed with the corresponding series of symmetrical aryl-substituted sulfides: phenyl sulfide, benzyl sulfide and phenethyl sulfide (Fig. 9).

In contrast to the striking changes brought about in the absorption spectra of the alkyl sulfides by the attachment of a second alkylmercapto group to an α-carbon atom, there appears to be little evidence of interaction between the sulfide functions in the bis-(phenylmercapto)-methanes, $C_6H_5SCH_2SC_6H_5$ and $C_6H_5SC(CH_3)_2SC_6H_5$ (Fig. 10). The spectrum of the first compound is approximately that of phenyl ethyl sulfide at twice the molar concentration, and the spectrum of the second is similarly related to the curve for phenyl *t*-butyl sulfide. When one of the hydrogen atoms on the central carbon atom of a bis-(alkylmercapto)-methane is replaced by a phenyl group, as in $CH_3SCH(C_6H_5)SCH_3$ (Fig. 8), the resultant spectrum closely resembles that of benzyl ethyl sulfide except that the molar extinction values are uniformly about twice as large (0.3 log unit higher) in the case of the mercaptal.

The effect of substitution of oxygen in the alkyl portion of the aromatic sulfides is shown in the curves for $C_6H_5SCH_2OCH_3$ and $C_6H_5CH_2SCH_2OCH_3$ (Fig. 11). Here again oxygen exerts a suppressive effect on the absorption similar to that observed with the aliphatic alkoxysulfides.

**Ketosulfides.**—The aliphatic β-ketosulfides, ethylmercaptoacetone and α-ethylmercaptoisopropyl methyl ketone (Fig. 12), exhibit absorption maxima in approximately the same regions of the spectrum ($\lambda_{max.}$ 295–300 mμ and 240–245 mμ) as the aliphatic α,β-unsaturated ketones ($\lambda_{max.}$ 310–350 mμ and 230–250 mμ).[6] This conjugative effect disappears when the sulfide function and the carbonyl function are separated by two methylene groups, as in β-ethylmercaptoethyl methyl ketone (Fig. 12), the spectrum of which is essentially a summation of the spectra of a simple ketone and an alkyl sulfide. The presence of a well-developed peak at 235 mμ in the spectrum of tetrahydro-1,4-thiapyrone (Fig. 12) is somewhat surprising, but the absorption curve for this compound is very similar to that of an acyclic γ-ketosulfide at longer wave lengths.

The absorption spectra of several typical phenyl-substituted ketosulfides are shown in Figs. 13 and 14. Attachment of an alkylmercapto group to the α-carbon atom of a phenyl alkyl ketone, as in ω-ethylmercaptoacetophenone (Fig. 13), causes a pronounced bathochromic and hyperchromic displacement of the long wave length

(6) For a discussion of the spectra of the α,β-unsaturated ketones, see Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).

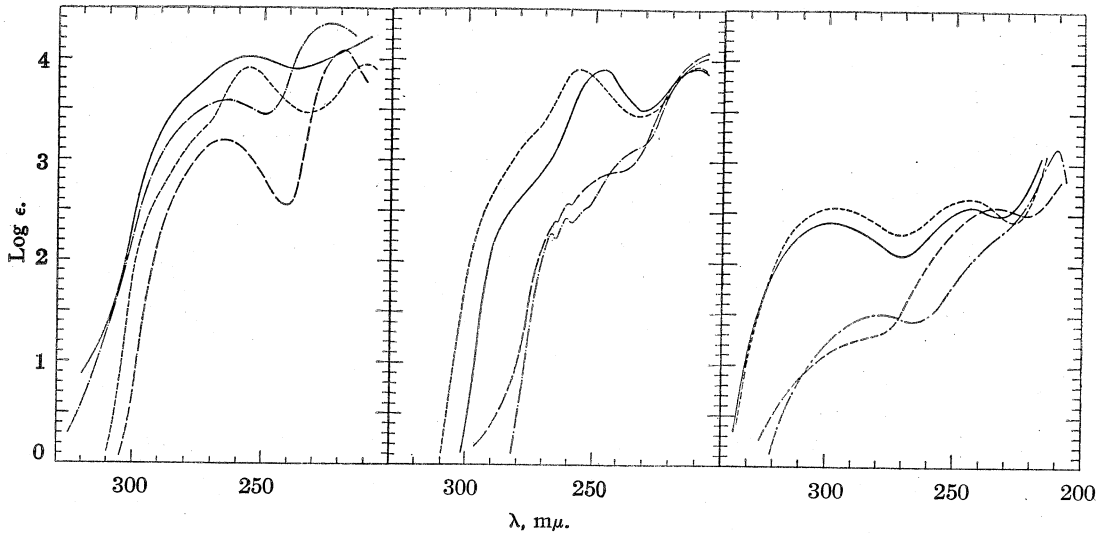



Fig. 10. Fig. 11. Fig. 12.

Fig. 10.—Absorption spectra of $C_6H_5SCH_2SC_6H_5$, —; $C_6H_5SC_2H_5$, - - - - - -; $C_6H_5SC(CH_3)_2SC_6H_5$, -·-·-; $C_6H_5SC(CH_3)_3$, — — —.

Fig. 11.—Absorption spectra of $C_6H_5SCH_2OCH_3$, —; $C_6H_5SC_2H_5$, - - - - - -; $C_6H_5CH_2SCH_2OCH_3$, -·-·-; $C_6H_5CH_2SC_2H_5$, — — —.

Fig. 12.—Absorption spectra of $C_2H_5SCH_2COCH_3$, —; $C_2H_5SC(CH_3)_2COCH_3$, - - - - - -; $C_2H_5SCH_2CH_2COCH_3$, -·-·-; tetrahydro-1,4-thiapyrone, — — —.

portion of the curve. Substitution of an alkylmercapto group on a β-carbon atom, as in β-ethylmercaptopropiophenone (Fig. 13), has little effect upon the characteristic absorption of the benzoyl chromophore, and the resultant spectrum is almost identical with that of a phenyl alkyl ketone. The spectra of the α-phenylmercaptoketones, phenylmercaptoacetone and α-phenylmercaptoisopropyl methyl ketone (Fig. 14), appear to be approximately summations of the spectra of an aliphatic ketone and an appropriately substituted phenyl alkyl sulfide (phenyl ethyl sulfide and phenyl *t*-butyl sulfide, respectively).

**Carbalkoxysulfides.**—The spectra of several α- and β-carbalkoxysulfides are shown in Fig. 15. Strong interaction between the sulfide func-

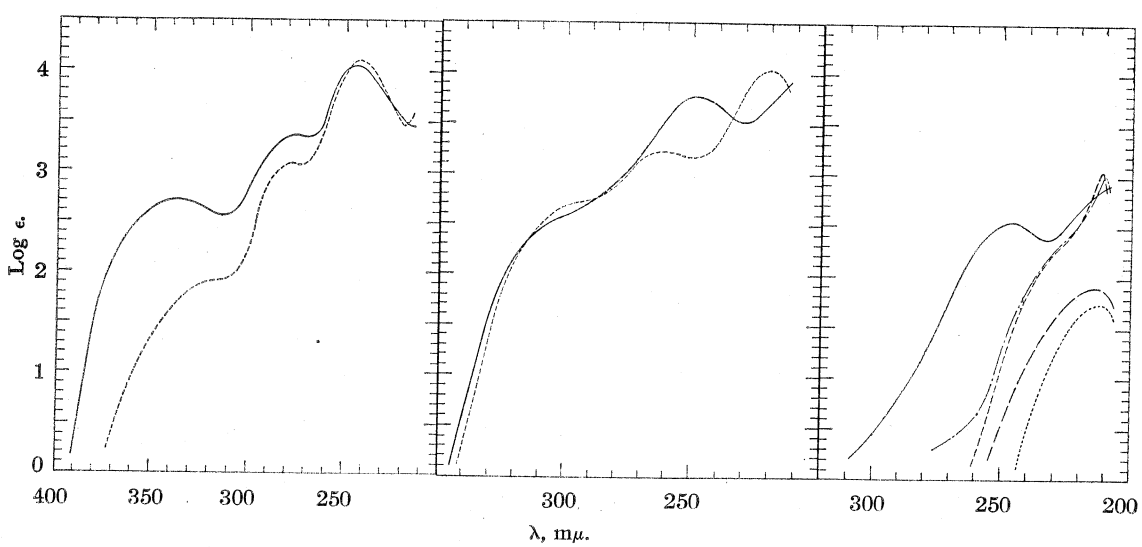



Fig. 13. Fig. 14. Fig. 15.

Fig. 13.—Absorption spectra of $C_2H_5SCH_2COC_6H_5$, —; $C_2H_5SCH_2CH_2COC_6H_5$, - - - - - -.

Fig. 14.—Absorption spectra of $C_6H_5SCH_2COCH_3$, —; $C_6H_5SC(CH_3)_2COCH_3$, - - - - - -.

Fig. 15.—Absorption spectra of *n*-$C_4H_9SCH_2CO_2C_2H_5$, —; *n*-$C_4H_9SCH_2CH_2CO_2CH_3$, - - - - - -; $S(CH_2CH_2CO_2CH_3)_2$, -·-·-; $C_2H_5OCH_2CO_2C_2H_5$, — — —; $CH_3CO_2C_2H_5$, . . . . . .

tion and the carbalkoxyl group in α-carbalkoxysulfides is indicated by the appearance of an absorption band at 247 mμ (log ε 2.54) in the spectrum of ethyl *n*-butylmercaptoacetate. The interpolation of a second methylene group between the sulfide and carbalkoxyl functions, as in methyl β-*n*-butylmercaptopropionate and methyl β-thiodipropionate, effectively insulates the chromophores from each other, with the result that the spectra of β-carbalkoxysulfides differ only slightly from those of simple alkyl sulfides. An ethoxyl group in the α-position of an ester has only a slight bathochromic effect on the absorption of the weakly chromophoric carbalkoxyl group, as shown in the comparison of the spectra of ethyl acetate and ethyl ethoxyacetate (Fig. 15).

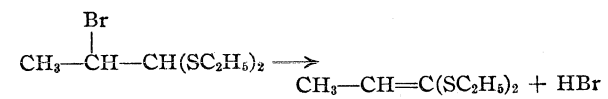
## Discussion

The absorption of visible and near-ultraviolet radiation (800–200 mμ) by organic compounds is usually associated with a separation of electrical charge arising from the polarization of the π-orbital electrons of a system of multiple bonds.[7] A closely related phenomenon is the absorption of radiation in the far-ultraviolet region of the spectrum by molecules containing atoms with unshared pairs of valence electrons, which, like one of the electron pairs in a double bond, enter a π orbital in the molecule and interact more or less readily with electromagnetic vibrations of sufficiently high energy. Although absorption bands due solely to this process can generally be observed only at wave lengths below 200 mμ, the near-ultraviolet bands in the spectra of alkyl derivatives of such highly polarizable atoms as sulfur, bromine and iodine have been attributed to the excitation of these non-bonding electrons.[8] The displacement of these bands toward longer wave lengths with increasing alkyl substitution on the α-carbon atom has been ascribed to the accumulation on the sulfur and halogen atoms of a negative charge induced by the electron-releasing alkyl groups.[8b]

While this interpretation accounts satisfactorily for the absorption bands of the simple alkyl sulfides in the neighborhood of 210 mμ it fails to explain the extensive optical interaction which we have observed in the case of the alkylmercaptals and alkylmercaptoles. The appearance of a new long wave length band in the spectra of these compounds cannot be due to an inductive effect acting through the central carbon atom, since the $-I$ effect of each sulfur atom would be expected to put the π electrons of the other sulfur atom under additional constraint, thereby decreasing the normal absorption associated with each sulfide function. This is the observed result when one of the sulfur atoms is replaced by oxygen in the monothioacetals. The disappearance of the long wave length band and the return of the spectrum to the alkyl sulfide type when a second carbon atom is introduced into the molecule between the two sulfide functions also argues against an interpretation in terms of an inductive effect.

When absorption of visible or ultraviolet light by a polyfunctional molecule differs markedly from a summation of the spectra of the individual chromophores (*i.e.*, by exhibiting large bathochromic and hyperchromic displacements of the absorption bands characteristic of the component chromophores, or by the appearance of entirely new bands), the effect is generally regarded as evidence for the conjugation of the chromophoric groups. Since many of the polyfunctional sulfides show the optical behavior characteristic of conjugated systems, it is of interest from the theoretical point of view to deduce what modes of polarization are possible and probable in these compounds and to evaluate their effects on the optical properties of the system.

Two types of electronic interaction appear to be possible in the mercaptal system: (1) hyperconjugation involving the valence bonds of the central carbon atom, with attendant expansion of the valence shell of the sulfur atoms; and (2) direct interaction of the electronic fields of the two sulfur atoms through space. The hyperconjugation of C–H and C–C bonds with other groups has been discussed in connection with a number of physico-chemical problems, including its effect on absorption spectra.[9] It has been specifically suggested in connection with mercaptals by Rothstein[10] to account for the observed mobility of hydrogen attached to the central carbon atom in these compounds, as for example, in the spontaneous elimination of hydrogen bromide from 2-bromo-1,1-bis-(ethylmercapto)-propane, where the apparent proton-releasing



effect of sulfur is attributed to resonance forms in which sulfur has an expanded valence shell.[11]

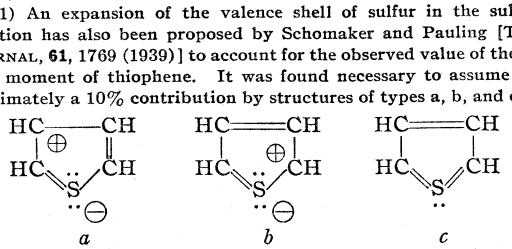
(7) (a) Lewis and Calvin, *Chem. Revs.*, **25**, 273 (1939); (b) Maccoll, *Quart. Revs. (London)*, **1**, No. 1, 16 (1947).

(8) (a) Mulliken, *J. Chem. Phys.*, **3**, 506 (1935); (b) Price, *ibid.*, **4**, 539, 547 (1936); *Ann. Reports Chem. Soc. (London)*, **36**, 47 (1939); *Chem. Revs.*, **41**, 257 (1947).

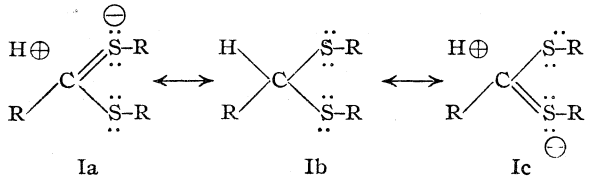
(9) (a) Pauling, Springall and Palmer, THIS JOURNAL, **61**, 927 (1939); (b) Mulliken, *J. Chem. Phys.*, **7**, 339 (1939); (c) Mulliken, Rieke and Brown, THIS JOURNAL, **63**, 41 (1941).

(10) Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558 (1940).

(11) An expansion of the valence shell of sulfur in the sulfide function has also been proposed by Schomaker and Pauling [THIS JOURNAL, **61**, 1769 (1939)] to account for the observed value of the dipole moment of thiophene. It was found necessary to assume approximately a 10% contribution by structures of types a, b, and c, in



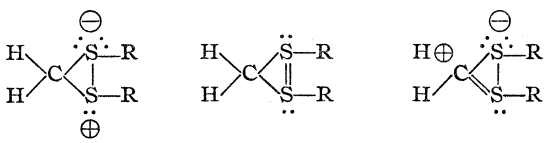
which the sulfur atom expands its valence shell to a decet.



Ia Ib Ic

Woodward and Eastman[12] have recently pointed out that Rothstein's mechanism would also account for the formation of 2-carbomethoxy-3-ketotetrahydrothiophene as the major product in the Dieckmann cyclization of $\alpha,\beta'$-dicarbomethoxymethylethyl sulfide at low temperatures.

The type of polarization represented by structures Ia and Ic might be considered to afford an adequate explanation for the development of a new peak in the region 235–240 m$\mu$ in the spectra of the alkylmercaptals and alkylmercaptoles. It is of interest to note, however, that the possibilities for polarized resonance forms are not exhausted by the structures postulated by Rothstein if one accepts the original assumption that the sulfide function can behave as either a donor or an acceptor of electrons. For example, there seems to be no reason for excluding the possibility of direct interaction of the electronic systems of the two sulfur atoms, involving a transfer of charge from one sulfur atom to the other and giving rise to polarizations along the line of centers of these atoms. Such interactions, illustrated in formulas II and III, imply the existence of transient three-membered rings. In addition, still other resonance forms (formula IV) can be



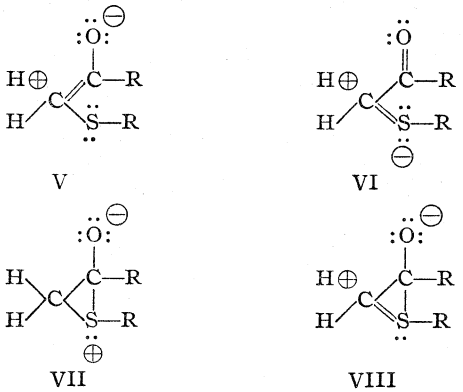
(two forms) (four forms)

II III IV

written which involve the simultaneous operation of this effect and the hyperconjugative effect proposed by Rothstein.[13]

That direct interaction may occur between the two sulfur atoms in the alkylmercaptals and alkylmercaptoles seems to be supported by the resemblance of the spectra of these compounds to those of the alkyl disulfides, RSSR, in which two sulfur atoms are joined by primary valence bonds.[14] The marked difference in the optical behavior of the mercaptals and monothioacetals is also consistent with this interpretation; while the oxygen atom can exert an inductive effect upon the sulfur atom, it cannot be considered to participate in resonance involving expansion of its valence shell to accommodate more than eight electrons.

Resonance forms embodying similar assumptions can be written for the $\beta$-ketosulfides, $\alpha$-carbalkoxysulfides, benzyl sulfides, and allyl sulfides. Thus, contributions from structures such as V–VIII might account for the characteristic absorption spectra of the $\beta$-ketosulfides.



V VI

VII VIII

In 1,2-bis-(alkylmercapto)-ethanes and $\gamma$-ketosulfides, little, if any, direct interaction between the functional groups would be anticipated, since these groups would, on the average, be widely separated in space. Possible exceptions might be found in cyclic compounds, such as 1,4-dithiane and tetrahydro-1,4-thiapyrone, in which the 1,4-atoms are restricted to relatively feeble oscillations between the positions corresponding to "chair" and "boat" forms of the rings and, as a result, are always in close proximity to each other.[15] It is interesting to note that the spectra of 1,4-dithiane and tetrahydro-1,4-thiapyrone differ from those of their acyclic analogs, and it is very probable that these differences are attributable to direct interaction between the 1,4-atoms.

When the sulfide function is attached directly to a benzene ring, a much larger number of modes of polarization are possible than in the case of the aliphatic sulfides. By analogy with the corresponding phenyl ethers, structures in which sulfur behaves as an electron donor with respect to the benzene ring would be expected to contribute heavily to the resonance in all phenylmercapto derivatives. If, however, the sulfur atom is also capable of accepting electrons from the aromatic nucleus, additional resonance structures can be

(12) Woodward and Eastman, THIS JOURNAL, **68**, 2229 (1946).

(13) The possible participation of cyclic structures such as II, III and IV depends not only upon the ability of sulfur to donate *and accept* electrons, but also upon the ability of the two sulfur atoms to approach each other sufficiently closely to interact. That such three-membered rings are not a stereochemical impossibility is indicated by considerable recent work on the role of neighboring groups in nucleophilic displacement reactions [*cf.* Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 176–178; Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942), and succeeding papers; Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 242]. Studies on the mechanism of replacement of halogen in mustard gas have shown specifically that the sulfur atom may be involved in three-membered rings [*cf.* Gilman and Philips, *Science*, **103**, 409 (1946); Fuson, Price and Burness, *J. Org. Chem.*, **11**, 475 (1946)].

(14) Ethyl disulfide has an absorption band with a maximum at 249 m$\mu$ (log $\epsilon$ 2.63) [Ley and Arends, *Z. physik. Chem.*, **B15**, 311 (1932)].

(15) The close approach of the 1,4-atoms of these compounds in all possible configurations of the rings is only fully appreciated after an examination of the scale models; *e. g.*, Stuart or Fisher-Hirschfelder molecular models.

written which are not possible with the analogous oxygen compounds. The progressive changes observed in the spectra of the phenyl alkyl sulfides with increasing alkylation of the $\alpha$-carbon atom might result either from changes in the relative importance of resonance contributions by structures of these two types, or from steric effects, or from a combination of both these factors. A study of the absorption spectra of various nuclearly-substituted phenyl sulfides is being undertaken to provide additional data on this aspect of the problem, and the results will be described in a subsequent communication.

Regardless of the directional character of the polarization within the phenylmercapto group, it is evident that the resonance within this system is considerable, and it is not surprising, therefore, to find that the sulfur atom in this combination shows little or no tendency to interact with other functional groups attached to the $\alpha$-carbon atom. We can thus account for the fact that the attachment of a second phenylmercapto group or an acetyl group in this position on a phenyl alkyl sulfide fails to give rise to new absorption bands or to cause any appreciable displacement of the maxima characteristic of the parent sulfide.

An obvious implication of these concepts is that the unique properties postulated for the sulfide function on spectroscopic grounds should be reflected in the chemical reactivity of compounds containing this function. Several examples of the activation of methylene groups by adjacent alkylmercapto groups have been referred to[10,12] above, and other unusual properties of thio compounds have been reported which might be satisfactorily explained on the basis of these concepts. Further work is planned along chemical and physico-chemical lines suggested by the spectroscopic data.

## Experimental[16]

**Ultraviolet Absorption Measurements.**—The ultraviolet absorption spectra were determined with a Beckman quartz spectrophotometer, Model DU, using an approximately constant spectral band width of *ca.* 1 m$\mu$ down to wave lengths in the neighborhood of 220 m$\mu$. Readings at shorter wave lengths were obtained by using the 0.1 switch position and balancing the galvanometer for 100% transmission with the solvent in position before the phototube. The wave lengths and logarithms of the molar extinction coefficients at the absorption maxima and at prominent points of inflection are listed in Table I.

**Preparation of Compounds.**—Most of the previously known compounds were prepared by methods described in the literature or were obtained from commercial supply houses; source references are given in Table I. With several exceptions which are noted below, all compounds were purified by two or more redistillations or recrystallizations immediately before determination of the spectra. The physical constants for all previously known compounds except phenethyl sulfide (see below) checked those recorded in the literature.

bis-(Phenylmercapto)-methane,[17] 2,2-bis-(phenylmercapto)-propane,[18] and $\alpha,\alpha$-bis-(methylmercapto)-toluene,[19] decomposed so readily on heating that it was not found possible to purify the crude products by distillation, even at very low pressures. To obtain the pure compounds, large excesses of the sulfhydryl intermediates were employed in the preparations, and the crude oils

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF ORGANIC SULFIDES[a]

| Compound | Source[b] | Maxima[c] λ (mμ) | Log ε |
|---|---|---|---|
| **A. Alkyl Sulfides** | | | |
| Methyl sulfide[d] | 1 | (229) | 2.14 |
| | | 210 | 3.01 |
| Ethyl sulfide[e,f] | 2 | (229) | 2.14 |
| | | 210 | 3.25 |
| *n*-Butyl sulfide | 3 | (229) | 2.16 |
| | | 210 | 3.09 |
| Isopropyl sulfide | 4 | 211 | 3.32 |
| *t*-Butyl sulfide | 5 | 213 | 3.42 |
| Allyl sulfide | 2 | 221 | 3.33 |
| Pentamethylene sulfide[g] | 6 | (229) | 2.26 |
| | | 210 | 3.25 |
| Tetramethylene sulfide | 7 | (239) | 1.73 |
| | | 210 | 3.04 |
| **B. Mercaptals and Mercaptoles** | | | |
| bis-(Methylmercapto)-methane | 8 | 235 | 2.73 |
| bis-(*n*-Butylmercapto)-methane | 9 | 236 | 2.76 |
| bis-(*n*-Butylmercapto)-methane[h] | 9 | 236 | 2.81 |
| 2,2-bis-(*n*-Butylmercapto)-propane | 9 | 237 | 2.82 |
| bis-(Phenylmercapto)-methane | 5 | 255 | 4.03 |
| 2,2-bis-(Phenylmercapto)-propane | 5 | 265 | 3.58 |
| | | 224 | 4.36 |
| $\alpha,\alpha$-bis-(Methylmercapto)-toluene | 5 | (266) | 2.69 |
| | | (260) | 2.88 |
| | | (240) | 3.17 |
| *sym*-Trithiane | 10 | 240 | 3.16 |
| *sym*-Trithiane[h] | 10 | 240 | 3.19 |
| **C. 1,2-bis-(Alkylmercapto)-ethanes** | | | |
| 1,2-bis-(*n*-Butylmercapto)-ethane | 9 | (229) | 2.42 |
| | | 209 | 3.44 |
| 1,4-Dithiane[f,g,i] | 11 | (225) | 2.54 |
| **D. Aryl and Aralkyl Sulfides** | | | |
| Phenyl methyl sulfide | 12 | (275) | 3.15 |
| | | 254 | 3.98 |
| Phenyl ethyl sulfide | 13 | (270) | 3.40 |
| | | 256 | 3.90 |
| | | 210 | 3.94 |
| Phenyl isopropyl sulfide | 5 | 258 | 3.75 |
| | | 215 | 3.94 |
| Phenyl *t*-butyl sulfide | 14 | 266 | 3.19 |
| | | 218 | 4.08 |
| Benzyl phenyl sulfide | 15 | 255 | 3.83 |
| Phenyl sulfide[i,j,k] | 16 | 277 | 3.76 |
| | | 250 | 4.08 |

(16) Microanalyses were performed by Mrs. Sarah M. Woods. All melting points are corrected.

(17) Fromm, *Ann.*, **253**, 135 (1889); *cf.* Otto and Tröger, *Ber.*, **25**, 3425 (1892).

(18) Baumann, *ibid.*, **19**, 2803 (1886).

(19) Bongartz, *ibid.*, **21**, 478 (1888).

TABLE I (*Continued*)

| Compound | Source[b] | Maxima[c] λ (mμ) | Log ε |
|---|---|---|---|
| Benzyl sulfide[i,l] | 17 | (266) | 2.66 |
| | | 260 | 2.85 |
| | | (238) | 3.30 |
| Phenethyl sulfide | 5 | 268 | 2.45 |
| | | 265 | 2.55 |
| | | 259 | 2.65 |
| | | 253 | 2.59 |
| | | 248 | 2.52 |
| | | (242) | 2.56 |
| Benzyl ethyl sulfide | 18 | (265) | 2.40 |
| | | (260) | 2.58 |
| | | (240) | 2.90 |
| Phenethyl ethyl sulfide | 5 | 268 | 2.15 |
| | | 265 | 2.23 |
| | | 259 | 2.35 |
| | | 253 | 2.28 |
| | | 248 | 2.22 |
| | | 212 | 3.95 |
| **E. Alkoxysulfides** | | | |
| *n*-Butylmercaptomethyl ethyl ether | 9 | (219) | 2.18 |
| β-*n*-Butylmercaptoethyl ethyl ether | 5 | (226) | 2.19 |
| | | 210 | 3.06 |
| bis-(Methoxymethyl) sulfide | 19 | <210 | >2.38 |
| 1,4-Thioxane[g,j] | 20 | (227) | 2.00 |
| | | 209 | 3.18 |
| Phenylmercaptomethyl methyl ether | 5 | (272) | 2.86 |
| | | 247 | 3.90 |
| | | 210 | 3.92 |
| Benzylmercaptomethyl methyl ether | 5 | 267 | 2.28 |
| | | 261 | 2.43 |
| | | (233) | 3.13 |
| **F. Ketosulfides** | | | |
| Ethylmercaptoacetone | 21 | 299 | 2.41 |
| | | 243 | 2.56 |
| α-Ethylmercaptoisopropyl methyl ketone | 5 | 296 | 2.56 |
| | | 244 | 2.66 |
| β-Ethylmercaptoethyl methyl ketone | 5 | 278 | 1.50 |
| | | (235) | 2.24 |
| | | 210 | 3.15 |
| Tetrahydro-1,4-thiapyrone | 22 | (283) | 1.26 |
| | | 235 | 2.55 |
| ω-Ethylmercaptoacetophenone | 23 | 337 | 2.71 |
| | | 276 | 3.36 |
| | | 245 | 4.07 |
| β-Ethylmercaptopropiophenone | 5 | (315) | 1.91 |
| | | 277 | 3.08 |
| | | 242 | 4.10 |
| Phenylmercaptoacetone | 21 | ~(300) | 2.58 |
| | | 250 | 3.78 |
| α-Phenylmercaptoisopropyl methyl ketone | 5 | (293) | 2.72 |
| | | 262 | 3.22 |
| | | 220 | 4.03 |
| **G. Carbalkoxysulfides** | | | |
| Ethyl *n*-butylmercaptoacetate | 5 | 247 | 2.54 |
| Methyl β-*n*-butylmercaptopropionate | 5 | (225) | 2.37 |
| | | 211 | 3.05 |
| Methyl β-thiodipropionate | 24 | (225) | 2.39 |
| | | 210 | 3.01 |
| **H. Other Compounds** | | | |
| Toluene[m] | 2 | 269 | 2.33 |
| | | 265 | 2.24 |
| | | 262 | 2.40 |
| | | (260) | 2.33 |
| | | 256 | 2.27 |
| | | 249 | 2.11 |
| Ethyl acetate[m] | 2 | 211 | 1.76 |
| Ethyl ethoxyacetate | 25 | 214 | 1.92 |
| Trioxane | 2 | Transparent[n] | |

[a] All spectra were determined in absolute ethanol unless otherwise indicated. [b] Source references: (1) reaction of methyl iodide and sodium sulfide in aqueous ethanol; (2) purified commercial material; (3) Grabowsky and Saizew, *Ann.*, **171**, 253 (1874); (4) Beckmann, *J. prakt. Chem.*, [2] **17**, 459 (1878); (5) see section on "Preparation of Compounds"; (6) Clarke, *J. Chem. Soc.*, **101**, 1805 (1912); (7) Tarbell and Weaver, THIS JOURNAL, **63**, 2939 (1941); (8) Böhme and Marx, *Ber.*, **74B**, 1667 (1941); (9) Whitner and Reid, THIS JOURNAL, **43**, 638 (1921); (10) Bost and Constable, "Organic Syntheses," Coll. Vol. II, p. 610; (11) Masson, *J. Chem. Soc.*, **49**, 233 (1886); (12) Bourgeois and Abraham, *Rec. trav. chim.*, **30**, 413 (1911); (13) Otto, *Ber.*, **13**, 1275 (1880); (14) Ipatieff, Pines and Friedman, THIS JOURNAL, **60**, 2731 (1938); (15) Pummerer, *Ber.*, **43**, 1406 (1910); (16) Mauthner, *ibid.*, **39**, 3593 (1907); (17) Märcker, *Ann.*, **136**, 88 (1865); (18) Märcker, *ibid.*, **140**, 86 (1866); (19) Bloch and Höhn, *Ber.*, **55B**, 53 (1922); (20) Clarke, *J. Chem. Soc.*, **101**, 1788 (1912); (21) Autenrieth, *Ber.*, **24**, 159 (1891); (22) Fehnel and Carmack, THIS JOURNAL, **70**, 1813 (1948); (23) Prelog, Hahn, Brauchli and Beyerman, *Helv. Chim. Acta*, **27**, 1209 (1944); (24) Gershbein and Hurd, THIS JOURNAL, **69**, 241 (1947); (25) Scheibler, Marhenkel and Nikolic, *Ann.*, **458**, 36 (1927). [c] The wave lengths in parentheses refer to inflection points. [d] *Cf.* Hantzsch, *Ber.*, **52**, 1544 (1919); **58**, 612 (1925). [e] *Cf.* ref. 14. [f] *Cf.* Mohler, *Helv. Chim. Acta*, **20**, 1188 (1937); Mohler and Sorge, *ibid.*, **23**, 1200 (1940). [g] *Cf.* Houston, Canning and Graham, *J. Chem. Soc.*, 965 (1935). [h] In dioxane. [i] *Cf.* Gibson, Graham and Reid, *ibid.*, **123**, 874 (1923). [j] *Cf.* Fox and Pope, *ibid.*, **103**, 1265 (1913). [k] *Cf.* Chaix, *Bull. soc. chim.*, [4] **53**, 700 (1933). [l] *Cf.* Purvis, Jones and Tasker, *J. Chem. Soc.*, **97**, 2287 (1910). [m] *Cf.* ref. 5. [n] A 0.1 *M* solution in a 1-cm. cell gave transmission readings above 90% at all wave lengths down to limits of observation (208 mμ).

were then washed repeatedly with water, 10% sodium hydroxide and saturated sodium bisulfite solution. The oils were dried over anhydrous magnesium sulfate, treated with Norit, filtered and used at once for the determination of spectra. Since analytical data for these and several other compounds used in the present investigation have not previously been reported, we have listed our values in Table II.

Phenyl isopropyl sulfide,[20] b. p. 97° at 20 mm., phenylmercaptomethyl methyl ether,[21] b. p. 113–114° at 18 mm., and ethyl *n*-butylmercaptoacetate, b. p. 110–111° at 18 mm., which have previously been prepared by other methods, were conveniently obtained by the action of isopropyl bromide, chloromethyl ether, and ethyl bromoacetate, respectively, on the appropriate sodium mercaptide in ethanol.[22]

(20) Table I, source ref. 14.

(21) de Lattre, *Bull. soc. chim. Belgique*, **26**, 323 (1912); *Chem. Zentr.*, **83**, II, 1192 (1912).

(22) Uyeda and Reid, THIS JOURNAL, **42**, 2388 (1920).

TABLE II

| Compound | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|
| bis-(Phenylmercapto)-methane | $C_{13}H_{12}S_2$ | 67.18 | 67.09 | 5.21 | 5.00 |
| 2,2-bis-(Phenylmercapto)-propane | $C_{15}H_{16}S_2$ | 69.18 | 69.12 | 6.19 | 6.06 |
| α,α-bis-(Methylmercapto)-toluene | $C_9H_{12}S_2$ | 58.64 | 58.65 | 6.57 | 6.42 |
| bis-(*n*-Butylmercapto)-methane | $C_9H_{20}S_2$ | 56.18 | 56.25 | 10.48 | 10.27 |
| 2,2-bis-(*n*-Butylmercapto)-propane | $C_{11}H_{24}S_2$ | 59.94 | 60.09 | 10.98 | 10.91 |
| 1,2-bis-(*n*-Butylmercapto)-ethane | $C_{10}H_{22}S_2$ | 58.19 | 58.03 | 10.74 | 10.52 |
| *n*-Butylmercaptomethyl ethyl ether | $C_7H_{16}OS$ | 56.69 | 56.52 | 10.88 | 10.90 |

***t*-Butyl Sulfide.**[23]—A mixture of 225 g. of concentrated sulfuric acid and 65 g. of water was cooled in an ice-bath, and 50.4 g. (0.60 mole) of *t*-butyl alcohol was added at such a rate that the temperature of the mixture did not exceed 10°. After addition of the alcohol was complete, stirring and cooling were continued while 27.0 g. (0.30 mole) of *t*-butyl mercaptan was added dropwise over a thirty-minute period. The ice-bath was then removed and the mixture was allowed to warm to room temperature. The product was separated by pouring the reaction mixture into 500 g. of ice, extracting with ether, drying the combined extracts over anhydrous magnesium sulfate, and fractionally distilling the ether solution. After removal of the ether, a fraction boiling at 60–65° and consisting mostly of unreacted mercaptan was obtained; recovery, 7.1 g. The crude *t*-butyl sulfide boiled at 144–149°; yield, 27.9 g. (87%, taking the recovered mercaptan into account). Redistillation afforded pure material boiling at 148–149°.

**Phenethyl sulfide** was prepared by a modification of the method of Bermejo and Herrera,[24] using sodium sulfide nonahydrate instead of potassium sulfide. The product was a colorless oil, b. p. 190–192° at 8 mm. (yield, 67%), which crystallized when cooled in a Dry Ice–acetone mixture but remelted again below room temperature[25]; the earlier investigators[24] reported a melting point of 92°.

*Anal.* Calcd. for $C_{16}H_{18}S$: C, 79.27; H, 7.48. Found: C, 79.11; H, 7.35.

**Phenethyl Ethyl Sulfide.**—A solution of 13.6 g. (0.22 mole) of ethyl mercaptan and 8.8 g. (0.22 mole) of sodium hydroxide in 100 ml. of ethanol was heated to boiling, and 31.0 g. (0.22 mole) of phenethyl chloride was added dropwise at such a rate as to maintain refluxing without the application of external heat. The mixture was then refluxed for another thirty minutes after which most of the solvent was removed by distillation, the residue was diluted with several times its volume of water, and the layers were separated. The upper layer was washed with water, dried over anhydrous magnesium sulfate, and distilled under diminished pressure to yield 29.5 g. (81%) of colorless oil, b. p. 96–98° at 4 mm. This material was redistilled and the middle fraction, b. p. 96° at 4 mm., was taken for the spectrum determination.

*Anal.* Calcd. for $C_{10}H_{14}S$: C, 72.22; H, 8.49. Found: C, 72.27; H, 8.54.

**β-*n*-Butylmercaptoethyl Ethyl Ether.**—A solution of 45 g. (0.50 mole) of *n*-butyl mercaptan and 20 g. (0.50 mole) of sodium hydroxide in 200 ml. of ethanol was treated with 76.5 g. (0.50 mole) of 2-bromoethyl ethyl ether and worked up exactly as in the procedure above. Distillation of the crude product at reduced pressure gave 57.8 g. (71%) of colorless oil, b. p. 103–108° at 31 mm. The spectral sample was taken from the middle fraction of a second distillation; b. p. 105–106° at 30 mm.

*Anal.* Calcd. for $C_8H_{18}OS$: C, 59.20; H, 11.18. Found: C, 59.32; H, 11.34.

**Benzylmercaptomethyl Methyl Ether.**—A solution of 52.0 g. (0.42 mole) of benzyl mercaptan and 16.8 g. (0.42 mole) of sodium hydroxide in 200 ml. of ethanol was treated with 33.5 g. (0.42 mole) of chloromethyl methyl ether and worked up as above. Fractional distillation of the crude product afforded 11.7 g. (17%) of colorless oil, b. p. 128–133° at 19 mm. On redistillation most of this sample boiled at 128° at 18 mm.

*Anal.* Calcd. for $C_9H_{12}OS$: C, 64.23; H, 7.19. Found: C, 64.33; H, 7.11.

**α-Ethylmercaptoisopropyl methyl ketone** was prepared by an adaptation of the method for ethylmercaptoacetone,[26] using α-bromoisopropyl methyl ketone instead of chloroacetone. The crude product was obtained as a colorless oil, b. p. 64–67° at 15 mm., yield 73%. On redistillation most of this material boiled at 65–66° at 15 mm.

*Anal.* Calcd. for $C_7H_{14}OS$: C, 57.50; H, 9.65. Found: C, 57.51; H, 9.59.

**β-Ethylmercaptoethyl methyl ketone** was obtained by the dropwise addition of 8.7 g. (0.14 mole) of ethyl mercaptan in which a bit of sodium had been dissolved to 12.8 g. (0.18 mole) of methyl vinyl ketone, and distillation of the crude product at reduced pressure; yield, 10.9 g. (61%) of colorless oil, b. p. 78–79° at 10 mm.

*Anal.* Calcd. for $C_6H_{12}OS$: C, 54.51; H, 9.15. Found: C, 54.58; H, 9.01.

**β-Ethylmercaptopropiophenone** was prepared in a similar manner from 17.5 g. (0.13 mole) of phenyl vinyl ketone and 9.3 g. (0.15 mole) of ethyl mercaptan. The crude product solidified on standing overnight and was recrystallized from aqueous ethanol (Norit) to yield 13.4 g. (53%) of colorless microcrystalline powder, m. p. 46–47°.

*Anal.* Calcd. for $C_{11}H_{14}OS$: C, 67.99; H, 7.26. Found: C, 68.13; H, 7.17.

**α-Phenylmercaptoisopropyl methyl ketone** was prepared by an adaptation of the method for phenylmercaptoacetone,[26] using α-bromoisopropyl methyl ketone instead of chloroacetone. The crude product was obtained as a colorless oil, b. p. 115–117° at 5 mm., yield 65%. On redistillation most of this material boiled at 102° at 3 mm.

*Anal.* Calcd. for $C_{11}H_{14}OS$: C, 67.99; H, 7.26. Found: C, 67.88; H, 7.13.

**Methyl β-*n*-butylmercaptopropionate** was obtained by the cautious addition of 27.9 g. (0.31 mole) of *n*-butyl mercaptan, in which a bit of sodium had been dissolved, to 25.8 g. (0.30 mole) of methyl acrylate, and distillation of the crude product at reduced pressure; yield, 42.8 g. (81%) of almost colorless oil, b. p. 118–119° at 19 mm. Redistillation of this material afforded the pure compound as a colorless oil, b. p. 118° at 19 mm.

*Anal.* Calcd. for $C_8H_{16}O_2S$: C, 54.50; H, 9.15. Found: C, 54.30; H, 9.10.

## Summary

The ultraviolet absorption spectra are reported for forty-four organic compounds containing the sulfide function, including alkyl, aryl and aralkyl sulfides, mercaptals and mercaptoles, 1,2-bis-(alkylmercapto)-ethanes, alkoxysulfides, ketosulfides and carbalkoxysulfides. The prepara-

(23) Jones and Reid, *ibid.*, **60**, 2452 (1938), obtained a 6% yield of this compound as a by-product in the addition of hydrogen sulfide to isobutylene at 180° in the presence of sulfur.

(24) Bermejo and Herrera, *Congr. intern. quim. pura y aplicada 9th Congr., Madrid*, **4**, 238 (1934); *C. A.*, **30**, 3418 (1936).

(25) Oxidation of this product with excess 30% hydrogen peroxide in acetic acid gave the sulfone as colorless leaflets, m. p. 99–100° after recrystallization from aqueous ethanol; reported[24] m. p. for phenethyl sulfone 101°.

(26) Table I, source ref. 21.

tion of a number of new sulfides and a greatly improved method for the preparation of *t*-butyl sulfide are described.

Considerable optical interaction is observed when the sulfide function is attached to a benzene ring or to a carbon atom bearing a carbonyl, carbalkoxyl, phenyl, vinyl or alkylmercapto group. The apparent conjugative effect of the sulfide function in these compounds is not destroyed by alkylation of the central carbon atom, but when two methylene groups intervene between the functional groups, the absorption spectra are essentially summations of the spectra of the component chromophores.

An attempt is made to account for the interaction of the sulfide function with a second similar function or with an unsaturated group attached to the same carbon atom by assuming the formation of three-membered rings stabilized by resonance among forms in which sulfur has an expanded valence shell.

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[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

# Ultrasonic Investigation of Molecular Properties of Liquids. III.[1] Linear Polymethylsiloxanes[2]

BY ALFRED WEISSLER

Certain aspects of the relation between molecular structure and sound velocity in liquids may be studied by means of a polymer series. This has already been done (using four or five members of each series) in the cases of the polyethylene glycols,[3] polychlorotrifluoroethylene,[4] and polyisobutylenes.[5] The last is of special interest because it was in highly viscous polyisobutylenes that Mason found the first unquestionable example of sound velocity dispersion in liquids.

A polymer series in which the liquid state persists up to high molecular weights is the linear polydimethylsiloxanes,[6,7] of type formula

$$(CH_3)_3Si-\left[-O-\underset{CH_3}{\overset{CH_3}{Si}}-\right]_n-O-Si(CH_3)_3$$

where $n$ may vary from zero up to several hundred. These materials offer an opportunity for more extensive investigations than the three series mentioned above, where members of moderate molecular weight are already solids. In the present work, the velocity of sound, density and refractive index (D light) at 30° were measured for fourteen linear polydimethylsiloxanes, and the results were used to calculate adiabatic compressibility, ratio of specific heats and molecular weight.

## Experimental

The polymers used were those sold by Dow Corning under the name Silicone Fluids DC 500 and 200, viscosity grades from 0.65 to 1000 centistokes. Higher members are polymerization mixtures with the volatiles removed, but the first four fluids are chemical individuals—the dimer, trimer, tetramer and pentamer, respectively. A few measurements were also made on two partially phenylated polymethylsiloxane fluids, of the DC 700 and 702 series.

Sound velocity in these liquids was measured by means of the one-megacycle ultrasonic interferometer previously described.[1] Refractive indices were determined with an Abbe refractometer.

## Results and Discussion

The values of sound velocity listed in Table I are lower than for most organic liquids, except that replacing methyl groups by phenyls raises the velocity, as in the 700 and 702 fluids. Figure 1 is a semilogarithmic plot of the data, which shows

TABLE I

PHYSICAL PROPERTIES OF LINEAR POLYMETHYLSILOXANES (DOW CORNING SILICONE FLUIDS)

| Fluid | Velocity (meters/sec.) at 30.0° | Velocity (meters/sec.) at 50.7° | Temp. coeff. (meters/second/degree) | Refractive index (D) | Density, g./ml. |
|---|---|---|---|---|---|
| DC 500–0.65 cs | 873.2 | 795.3 | −3.8 | 1.3724 | 0.7535 |
| 1.0 | 901.3 | 828.5 | −3.5 | 1.3810 | .8114 |
| 1.5 | 919.0 | 849.8 | −3.3 | 1.3856 | .8434 |
| 2.0 | 931.3 | 863.0 | −3.3 | 1.3883 | .8652 |
| 3.0 | 942.2 | 875.2 | −3.2 | 1.3916 | .8874 |
| 5.0 | 953.8 | 892.1 | −3.0 | 1.3943 | .9083 |
| 10 | 966.5 | 909.4 | −2.8 | 1.3972 | .9295 |
| 20 | 975.2 | 918.0 | −2.8 | 1.3992 | .9423 |
| 50 | 981.6 | 925.3 | −2.7 | 1.4007 | .9540 |
| 200–100 | 985.2 | 929.6 | −2.7 | 1.4015 | .9579 |
| 200 | 985.7 | 931.5 | −2.6 | 1.4017 | .9611 |
| 350 | 986.2 | 932.0 | −2.6 | 1.4018 | .9628 |
| 500 | 986.4 | 932.1 | −2.6 | 1.4019 | .9632 |
| 1000 | 987.3 | 933.3 | −2.6 | 1.4020 | .9636 |
| 702–27 | 1236.4 | | | | |
| 700–50 | 1054.0 | | | | |

(1) Weissler, Part II, THIS JOURNAL, **70**, 1634 (1948).

(2) The opinions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the navy service at large.

(3) Weissler, Fitzgerald and Resnick, *J. Appl. Phys.*, **18**, 434 (1947).

(4) Lagemann, Woolf, Evans and Underwood, THIS JOURNAL, **70**, 2994 (1948).

(5) Mason, Baker, McSkimin and Heiss, *Phys. Revs.*, **73**, 1074 (1948).

(6) Hunter, Warrick, Hyde and Currie, THIS JOURNAL, **68**, 2284 (1946).

(7) Patnode and Wilcock, *ibid.*, **68**, 358 (1946).

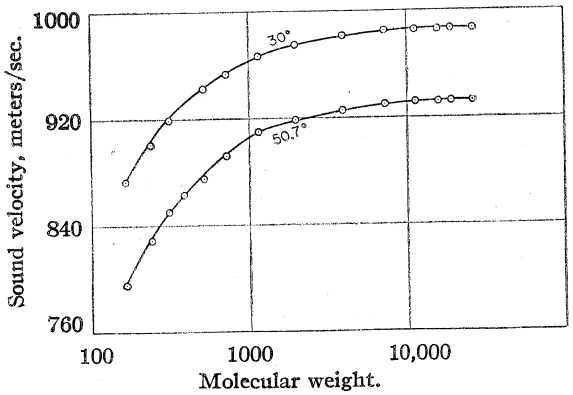



Fig. 1.—Sound velocity in the polydimethylsiloxane fluids.

that the velocity in polydimethylsiloxanes at first increases rapidly with molecular weight, but then levels off in the region of molcular weight 20,000. A similar leveling-off for the higher members is apparent in the refractive indices and densities.

Supplementary measurements at 50.7° showed that the rate of change of sound velocity with temperature decreases from −3.8 to −2.6 meters/second/degree as one goes from the lowest to the highest member (Table I). Such slopes are normal for liquids,[8] in contrast to the unusually flat viscosity–temperature slopes for which these silicone fluids are noted.

**Adiabatic Compressibility.**—From the sound velocity $v$ and density $d$, the adiabatic compressibility $K_{ad}$ is readily calculated by means of the equation

$$K_{ad} = 1/v^2d \qquad (1)$$

Table II reveals that the compressibilities so obtained are unusually high. This correlates with other characteristic properties of the silicones: low cohesive forces, low boiling points, and X-ray evidence[9] for large-amplitude oscillations of the methyl groups which sweep out umbrella-like surfaces.

The densities at 50.7°, required in eqn. (1), were computed with the aid of the thermal expansion coefficients supplied by the manufacturer.[10]

**Ratio of Specific Heats.**—The isothermal compressibility $K_{is}$ can be calculated from the relation

$$K_{is} = K_{ad} + T\alpha^2/c_pd \qquad (2)$$

where $T$ is the absolute temperature, $\alpha$ the coefficient of thermal expansion, and $c_p$ the specific heat at constant pressure. The values of $c_p$ at 30° for the first nine fluids were determined by electrical heating in a simple vacuum-bottle calorimeter,[11] with no attempt at high precision; they ranged from 0.45 calorie/gram for the 0.65 cs. fluid, to 0.39 calorie/gram for the 50 cs. fluid.

In Table II, the isothermal compressibilities calculated in this way are seen to be unusually high. A novel use of this property is in an aircraft landing gear developed in Great Britain, in which the spring action results from the compressibility of a silicone fluid.[12]

TABLE II

COMPRESSIBILITY OF LINEAR POLYMETHYLSILOXANES

| Fluid | Adiabatic compressibility ($10^{-12}$ sq. cm./dyne) at 30° | Adiabatic compressibility ($10^{-12}$ sq. cm./dyne) at 50.7° | Isothermal compressibility at 30° ($10^{-12}$ sq. cm./dyne) | Ratio of specific heats |
|---|---|---|---|---|
| 500–0.65 cs. | 174.1 | 219.5 | 228.7 | 1.31 |
| 1.0 | 151.7 | 186.4 | 196.4 | 1.29 |
| 1.5 | 140.4 | 169.7 | 176.6 | 1.26 |
| 2.0 | 133.3 | 160.0 | 165.9 | 1.24 |
| 3.0 | 126.4 | 151.2 | 155.5 | 1.22 |
| 5.0 | 121.0 | 141.9 | 145.6 | 1.20 |
| 10 | 115.2 | 133.2 | 136.6 | 1.19 |
| 20 | 111.6 | 128.8 | 132.3 | 1.18 |
| 50 | 108.8 | 125.1 | 128.3 | 1.18 |
| 200–100 | 107.6 | 123.4 | | |
| 200 | 107.1 | 122.5 | | |
| 350 | 106.8 | 122.1 | | |
| 500 | 106.7 | 122.0 | | |
| 1000 | 106.5 | 121.7 | | |
| 702–27 | 61.5 | | | |
| 700–50 | 91.3 | | | |

Also listed in Table II is the ratio of specific heats $\gamma$, which is equal to the ratio of isothermal to adiabatic compressibilities

$$\gamma = c_p/c_v = K_{is}/K_{ad} \qquad (3)$$

This ratio decreases monotonically as the molecular weight increases. Such a result is expected, because of the greater number of degrees of freedom in more complex molecules.

**Molecular Weight.**—An empirical method[3] for determining molecular weight $M$ within a polymer series (from sound velocity, density, and refractive index $n$) utilizes the equation

$$M = \frac{Bd}{v^{1/3} - A\left(\frac{n^2-1}{n^2+2}\right)} \qquad (4)$$

where $A$ and $B$ are two empirical constants characteristic of the series. For the polydimethylsiloxanes, these constants were evaluated at 40.885 and 48.10, respectively.

Equation (4) yielded the molecular weights listed in Table III, which have an average accuracy[13] of 5% for the first twelve of the fluids. It is

(8) Bergmann, "Der Ultraschall," 3rd ed., Edwards Brothers, Ann Arbor, Mich., 1944, p. 181.

(9) Roth, THIS JOURNAL, **69**, 474 (1947).

(10) Dow Corning Corporation, "New Engineering Materials—DC Silicones," Midland, Michigan, 1946, p. 6.

(11) Sturtevant, in "Physical Methods of Organic Chemistry," edited by A. Weissberger, Interscience Publishers, New York, N. Y., 1945, p. 365.

(12) T. K. Cordes, *Engineer's Digest*, March, 1946.

(13) The "theoretical" molecular weights are those kindly furnished by Dr. A. J. Barry of the Dow Chemical Co. in a personal communication. See also *J. Appl. Phys.*, **17**, 1020 (1946). Dr. Barry points out that his figures are not to be regarded as precise standards, because two fluids may have identical viscosities but different number average molecular weights, due to variations in polymerization technique.

evident that the results fall off in accuracy for values above about 15,000, because the computation then involves a very small difference between the two terms in the denominator of eqn. (4).

TABLE III

DETERMINATION OF MOLECULAR WEIGHTS OF POLYDIMETHYLSILOXANES BY THE SOUND VELOCITY METHOD

$$M = \frac{48.10d}{v^{1/3} - 40.855\left(\frac{n^2-1}{n^2+2}\right)}$$

| Fluid | Theoretical molecular weight | Found molecular weight | Deviation, % |
|---|---|---|---|
| 0.65 cs. | 162.2 | 141.0 | −13.1 |
| 1.0 | 236.3 | 233.7 | − 1.1 |
| 1.5 | 310.4 | 316.9 | + 2.1 |
| 2.0 | 384.5 | 371.6 | − 3.3 |
| 3.0 | 520 | 554 | + 6.5 |
| 5.0 | 720 | 753 | + 4.6 |
| 10 | 1,160 | 1,208 | + 4.1 |
| 20 | 1,970 | 1,971 | + 0.1 |
| 50 | 3,900 | 4,170 | + 6.9 |
| 100 | 7,100 | 7,680 | + 8.2 |
| 200 | 11,200 | 11,560 | + 3.2 |
| 350 | 15,800 | 15,440 | − 2.3 |
| 500 | 19,000 | 23,100 | +21.5 |
| 1000 | 26,500 | 23,200 | −12.5 |

In a paper that came to attention after this work was completed, Warrick[14] has shown how similar results may be obtained from refractive index and density data alone.

**Molar Sound Velocity Increments.**—Just as in the familiar case of molar refraction, the molar sound velocity $R = v^{1/3}M/d$ of a compound may be calculated by summing the increments[15] for each atom in the molecule, or alternatively for each bond in the molecule. No velocity increment involving silicon has previously been reported. Using the present data on the first four polymers and a value of 95.2 for the C–H bond, the bond increment for silicon–carbon is here determined as 35.4, and that for silicon–oxygen as 61.5. These figures give truly additive molar sound velocities, in which the deviations from experimental values are only a few tenths of a per cent.

Attempts to calculate an atomic increment for silicon gave values of 129, 122, 120 and 117, respectively, for the first four liquids. A corresponding lack of constancy in the atomic *refraction* increments for silicon in these same compounds has been reported[14]; it was necessary to use *bond* refraction increments, again, in order to attain an additive system. This situation was tentatively attributed to wide variations in the ionic character of the bonds in organosilicon compounds.

**Acknowledgment.**—The assistance of Patricia E. Mortell in the measurements of sound velocity is hereby gratefully acknowledged.

## Summary

The variation of sound velocity with molecular weight has been studied in a series of 14 polydimethylsiloxanes, at 30 and 50.7°. These fluids were found to possess remarkably high compressibilities.

Bond increments for the molar sound velocity have been determined for the silicon–carbon and silicon–oxygen bonds.

(14) Warrick, THIS JOURNAL, **68**, 2455 (1946).

(15) Lagemann and Dunbar, *J. Phys. Chem.*, **49**, 428 (1945).

WASHINGTON, D. C. RECEIVED JULY 2, 1948

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[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY OF BROWN UNIVERSITY]

# Properties of Electrolytic Solutions. XXXVI. Effect of Addition Agents on the Conductance of Long Chain Salts[1]

BY GEORGE L. BROWN,[2] PHILIP F. GRIEGER[3] AND CHARLES A. KRAUS

## I. Introduction

In previous papers of this series, it has been shown that the addition of methanol to aqueous solutions of long chain salts has marked effect on their properties in the critical region and at higher concentrations.[4]

The present study was undertaken for the purpose of determining the effect of additives in somewhat greater detail in order to ascertain the generality of the phenomena and some of the underlying factors that influence observed results. The present, like the several preceding investigations, has been exploratory in nature. A high precision is not claimed for the results; nevertheless, it is believed that, in the critical region, they are not seriously in error. Precision measurements in the dilute region are now under way in this Laboratory, and the results will be communicated in due course.

The effect of additions of methanol, isopropyl alcohol and *t*-butanol on the conductance of dodecylammonium chloride in water was measured at several concentrations of the additives.

(1) This paper is based on a portion of a thesis presented by G. L. Brown in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Brown University, October, 1947.

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(4) Evers and Kraus, THIS JOURNAL, **70**, 3049 (1948); Grieger and Kraus, *ibid.*, **70**, 3803 (1948); see also Ward, *J. Chem. Soc.*, I, 522 (1939); *Proc. Roy. Soc. (London)*, **176A**, 412 (1940).

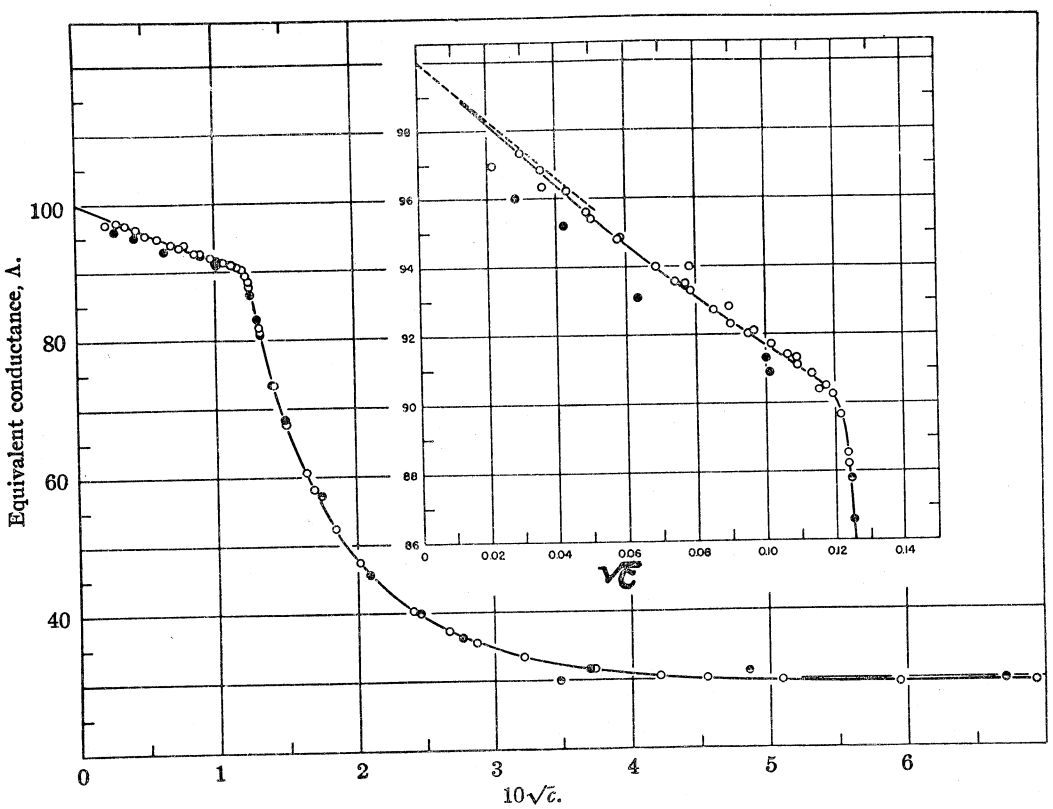



Fig. 1.—Dodecylammonium chloride in water at 25°: ○, this investigation; ●, Ralston and Eggenberger; ◓, Ralston, Hoerr and Hoffman. Dotted line on insert has theoretical slope.

More interesting, perhaps, are the results upon addition of methanol and tertiary butanol to solutions of octadecylpyridonium iodate and hexadecylpyridonium iodate; each of these two salts exhibits a maximum in pure water.[5]

Measurements were also carried out with dodecylammonium chloride in a 24.65% methanol–water mixture to which were added varying proportions of dodecanol: from 0.044 to 0.651 mole of dodecanol per mole of salt. The reason for carrying out the measurements in a methanol–water mixture was to increase the solubility of dodecanol.

The conductance of aqueous solutions of the hydrochlorides of two diamines having ten carbon atoms connecting the ammonium groups was measured for the purpose of determining whether or not they exhibit the usual properties of long chain salts.

## II. Experimental

**1. Apparatus and Procedure.**—These were substantially the same as those described in earlier papers of this series.[4] All measurements were carried out at 25 ± 0.01°.

**2. Solvents.**—Freshly distilled water was employed having a specific conductance of $1 \times 10^{-6}$ mho, or lower.

Methanol, after standing over lime, was decanted onto activated alumina pellets and, after refluxing, was distilled in a packed column. Middle and later fractions, excepting the last, had a conductance varying from $1 \times 10^{-7}$ to $0.3 \times 10^{-7}$.

Isopropyl alcohol, commercial Petrohol, was treated after the manner of methanol. Solvent having a specific conductance of $4 \times 10^{-9}$ was readily obtained. The density at 25° was found to be 0.7856 as against 0.7805 as given in the literature.[6] This may indicate the presence of some higher alcohols as impurities. For the purpose in hand, these could have little effect on the results obtained.

*t*-Butanol was purified by distillation. Its refractive index, $n^{25}D$, was found to be 1.3865.

Dodecanol was used as supplied by the dealer, without purification; it had a negligible specific conductance.

**3. Salts: Dodecylammonium Chloride.**—Hydrogen chloride was passed through a solution of the amine (purified by distillation, m. p., 27.9–28.2°) in diethyl cellosolve. The product, after filtration, was twice recrystallized from diethylcellosolve. It was finally recrystallized from absolute ethanol and washed with acetone; m. p. (sealed tube) 182.3°; chlorine: found, 15.95 ± 0.02; theory, 15.985%.

Hexadecylpyridonium iodate was prepared by metathesis of the iodide with freshly prepared silver iodate in ethanol. After filtration, the salt was precipitated by addition of acetone and recrystallized four times from an acetone–ethanol mixture; iodate: found, 36.6 and 37.2%; calcd., 36.5%. Difficulty was experienced in the analyses due to absorption of iodine by the hexadecylpyridonium iodide which precipitated upon addition of potassium iodide.

Octadecylpyridonium iodate was prepared like the corresponding hexadecyl compound; iodate: found, 34.31 and 34.68%; calcd., 34.49%.

1-N-Morpholino-10-N′-piperidinodecane dihydrochloride and di-*n*-propylamino-10-N-piperidinodecane dihydrochloride were made from the corresponding amines which were kindly furnished by Dr. N. J. Leonard, of the Univer-

(5) Brown, Grieger, Evers and Kraus, THIS JOURNAL, **69**, 1835 (1947).

(6) Brunel, *ibid.*, **45**, 1334 (1923).

sity of Illinois. Preparation and analysis of the amines are described by Price, Guthrie, Herbrandson and Peel.[7] Analyses of the salts are as follows: morpholino salt, chlorine: found, 18.55%; calcd., 18.50%; dipropyl salt, chlorine: found, 17.85%; calcd., 17.85%.

## III. Results

The results of measurements with dodecylammonium chloride in water and mixtures containing varying amounts of tertiary butanol, isopropyl alcohol and methanol, respectively, are presented in Table I. The square root of concentration, in moles per liter of solution, appears in the first column and the corresponding value of the equivalent conductance in the second column. Results are shown graphically in Figs. 1, 2 and 3.

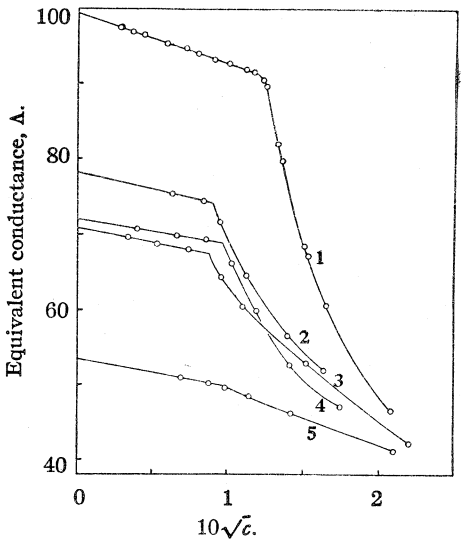



Fig. 2.—Dodecylammonium chloride in alcohol–water mixtures at 25°: (1) water, (2) 5.66% *t*-butanol, (3) 7.88% *t*-butanol, (4) 8.00% isopropanol, (5) 16.19% isopropanol.

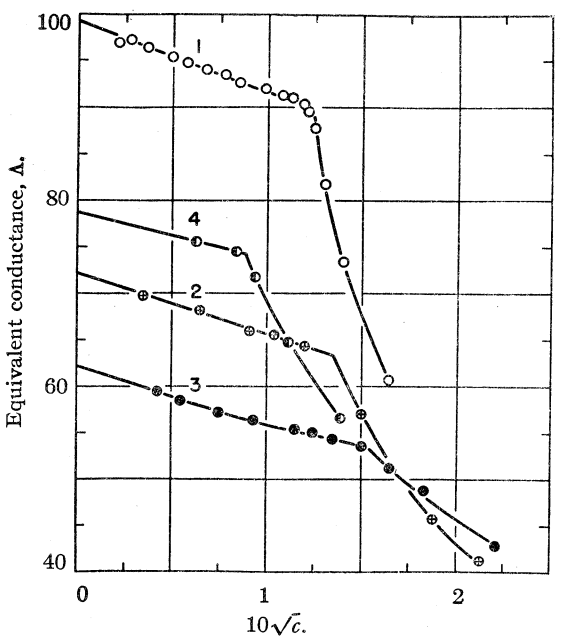



Fig. 3.—Dodecylammonium chloride in methanol–water mixtures at 25°: methanol, %: (1) 0.0, (2) 16.19, (3) 24.65; butanol, %, (4) 5.66.

(7) Price, Guthrie, Herbrandson and Peel, *J. Org. Chem.*, **11**, 281 (1946).

The results for octadecylpyridonium iodate in pure water and in the presence of methanol and *t*-butanol, and for hexadecylpyridonium iodate in water and in the presence of *t*-butanol, are similarly given in Table II. The results are shown graphically in Fig. 4.

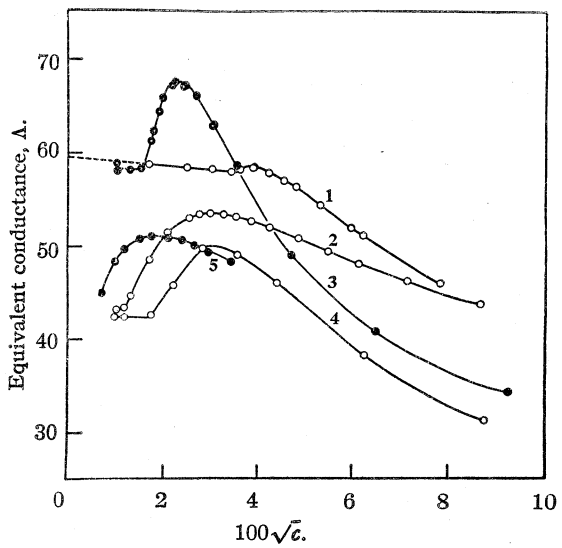



Fig. 4.—Hexadecylpyridonium iodate in: (1) water, (2) 7.94% *t*-butanol; octadecylpyridonium iodate in: (3) water, (4) 16.18% methanol, (5) 10.15% *t*-butanol.

In Table III are presented the results for dodecylammonium chloride in a 24.65% methanol–water mixture to which were added 0.110, 0.261 and 0.651 mole of dodecanol per mole of salt, respectively. Measurements were also carried out with mixtures containing, respectively, 0.044 and 0.246 mole of dodecanol per mole of salt. These values are shown in Fig. 5 along with those for which numerical data are given in the table.

The results for the diammonium salts are shown graphically in Fig. 6.

Except in the case of solutions of dodecylammonium chloride and the diammonium salts in water, solution densities were taken equal to solvent densities. The densities of aqueous solutions of dodecylammonium chloride at 25° were computed from the equation of Ralston and Hoerr.[8]

Values of the specific conductance, $\kappa_0$, the density, $d$, and the dielectric constant, $D$, for the solvent mixture are given at the head of each table. The composition of the solvent mixtures is given in weight per cent. of additive.

(8) Ralston and Hoerr, THIS JOURNAL, **64**, 772 (1942).

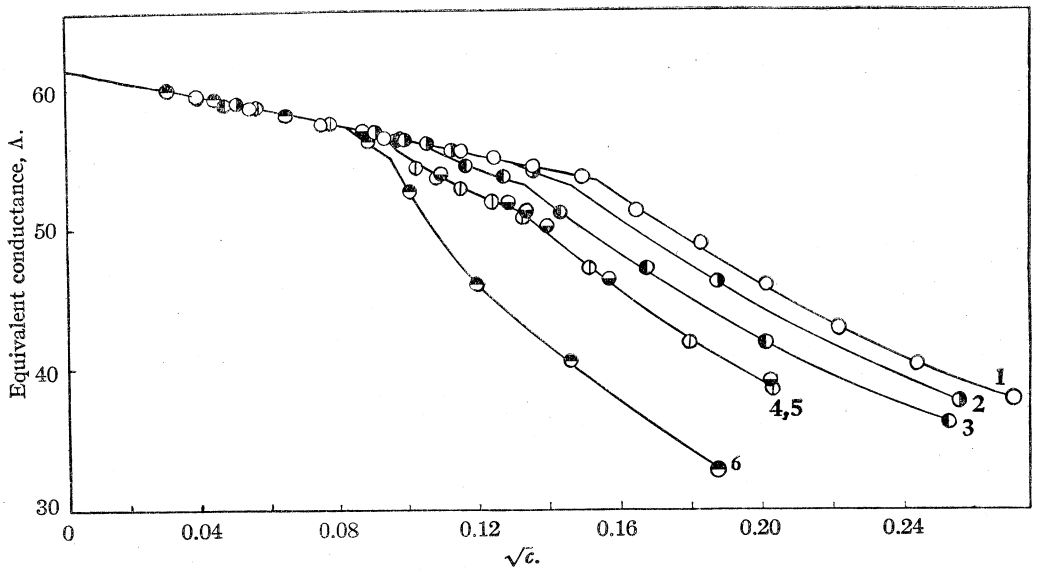



Fig. 5.—Dodecylammonium chloride in 24.65% methanol on addition of following moles of dodecanol per mole salt: (1) 0.0, (2) 0.044, (3) 0.111, (4) 0.246, (5) 0.261, (6) 0.651.

## IV. Discussion

**1. Conductance of Dodecylammonium Chloride in Water at 25°.**—In Fig. 1, the equivalent conductance of dodecylammonium chloride is plotted as a function of the square root of concentration. The results of Ralston and his coworkers are also shown for comparison. As may be seen from inspection of the figure, our results are in excellent agreement with those of Ralston and Eggenberger[9] at concentrations higher than the critical and are in fair agreement at lower concentrations. Our results are also in fair agreement with those of Ralston, Hoerr and Hoffman[10] at concentrations greater than critical.

The results of the present investigations are not sufficiently precise to establish definitely the form of the conductance curve below the breakpoint. For example, the solvent correction is about 1 and 10% at concentrations of $10^{-3}$ and $10^{-4}$, respectively. They indicate, however, that Λ is not a linear function of $\sqrt{c}$ up to the breakpoint, since an upward curvature is noticeable. Below $3 \times 10^{-3}$, the curve approximates the Onsager slope (*viz.*, 83) within the experimental error.

TABLE I

CONDUCTANCE OF DODECYLAMMONIUM CHLORIDE IN WATER AND IN MIXTURES WITH TERTIARY BUTANOL, ISOPROPANOL AND METHANOL AT 25°

| $10\sqrt{c}$ | Λ | $10\sqrt{c}$ | Λ | $10\sqrt{c}$ | Λ | $10\sqrt{c}$ | Λ | $10\sqrt{c}$ | Λ | $10\sqrt{c}$ | Λ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Water | | 5.66% *t*-Butanol | | 7.88% *t*-Butanol | | 8.00% Isopropyl alcohol | | 16.19% Isopropyl alcohol | | 16.19% Methanol | | 24.65% Methanol | |
| $\eta_0 = 1.0$ to $1.3 \times 10^{-6}$ | | $\kappa_0 = 0.69 \times 10^{-6}$, $d = 0.9881$, $D = 73.8$ | | $\kappa_0 = 0.70 \times 10^{-6}$, $d = 0.9845$, $D = 72.0$ | | $\kappa_0 = 0.80 \times 10^{-6}$, $d = 0.9837$, $D = 72.8$ | | $\kappa_0 = 0.57 \times 10^{-6}$, $d = 0.9724$, $D = 66.8$ | | $\kappa_0 = 0.62 \times 10^{-6}$, $d = 0.9703$, $D = 71.6$ | | $\kappa_0 = 0.50 \times 10^{-6}$, $d = 0.9568$, $D = 68.0$ | |
| 0.4317 | 96.22 | 6.243 | 75.56 | 3.365 | 69.09 | 3.952 | 70.84 | 6.896 | 51.08 | 3.723 | 69.70 | 4.002 | 59.44 |
| .4951 | 95.40 | 8.333 | 74.61 | 5.228 | 68.16 | 6.539 | 70.03 | 8.729 | 50.36 | 6.272 | 68.50 | 5.504 | 58.53 |
| .6846 | 94.01 | 9.403 | 71.82 | 7.345 | 67.56 | 8.409 | 69.46 | 9.785 | 49.73 | 9.121 | 65.98 | 7.500 | 57.28 |
| .9004 | 92.32 | 11.13 | 64.75 | 9.110 | 63.89 | 10.19 | 66.39 | 11.35 | 48.55 | 10.37 | 65.50 | 9.334 | 56.38 |
| 1.193 | 90.25 | 13.90 | 56.61 | 10.89 | 59.92 | 11.81 | 60.04 | 14.15 | 46.24 | 12.02 | 64.35 | 11.52 | 55.38 |
| 1.215 | 89.46 | 16.30 | 52.01 | 15.12 | 52.45 | 14.07 | 52.68 | 20.90 | 41.19 | 14.99 | 57.00 | 12.45 | 54.99 |
| 1.312 | 81.80 | | | 21.97 | 46.00 | 17.38 | 47.23 | | | 18.75 | 45.72 | 13.59 | 54.21 |
| 1.635 | 60.68 | | | 32.33 | 41.74 | | | | | 21.25 | 41.24 | 14.95 | 53.61 |
| 2.018 | 47.46 | | | | | | | | | 25.37 | 36.13 | 16.48 | 51.20 |
| 3.217 | 33.57 | | | | | | | | | | | 18.28 | 48.88 |
| 4.205 | 30.74 | | | | | | | | | | | 20.10 | 45.92 |
| 6.938 | 29.46 | | | | | | | | | | | 22.15 | 42.84 |
| | | | | | | | | | | | | 27.14 | 37.81 |

(9) Ralston and Eggenberger, THIS JOURNAL, **70**, 436 (1948).

(10) Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).

TABLE II

CONDUCTANCE OF HEXADECYLPYRIDONIUM IODATE AND OCTADECYLPYRIDONIUM IODATE IN WATER AND WATER–ALCOHOL MIXTURES AT 25°

| $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ |
|---|---|---|---|---|---|---|---|---|---|
| Hexadecylpyridonium iodate in water | | Hexadecylpyridonium iodate in 7.94% *t*-butanol | | Octadecylpyridonium iodate in water | | Octadecylpyridonium iodate in 16.18% methanol | | Octadecylpyridonium iodate in 10.15% *t*-butanol[11] | |
| $\kappa_0 = 1.04 \times 10^{-6}$ | | $\kappa_0 = 0.64 \times 10^{-6}$, $d = 0.9844$, $D = 71.9$ | | $\kappa_0 = 1.01 \times 10^{-6}$ | | $\kappa_0 = 0.60 \times 10^{-6}$, $d = 0.9700$, $D = 71.8$ | | $\kappa_0 = 0.70 \times 10^{-6}$, $d = 0.9815$, $D = 69.8$ | |
| 1.457 | 58.76 | 1.001 | 43.27 | 1.054 | 58.13 | 0.9834 | 42.45 | 0.6977 | 45.0 |
| 1.700 | 58.78 | 1.163 | 43.43 | 1.287 | 59.06 | 1.182 | 42.40 | 0.9777 | 48.4 |
| 2.512 | 58.44 | 1.342 | 44.70 | 1.347 | 58.21 | 1.747 | 42.59 | 1.513 | 50.8 |
| 3.037 | 58.30 | 1.693 | 48.27 | 1.809 | 62.37 | 2.216 | 45.80 | 1.764 | 51.08 |
| 3.452 | 58.00 | 1.716 | 48.62 | 2.008 | 65.87 | 2.841 | 49.77 | 2.134 | 50.94 |
| 3.639 | 58.25 | 2.096 | 51.51 | 2.275 | 67.62 | 3.583 | 49.11 | 2.663 | 50.10 |
| 3.917 | 58.43 | 2.551 | 53.11 | 2.480 | 67.27 | 4.412 | 46.06 | 3.437 | 48.39 |
| 3.952 | 58.59 | 2.773 | 53.48 | 2.707 | 66.09 | 6.272 | 38.29 | | |
| 4.251 | 57.87 | 2.986 | 53.58 | 3.081 | 63.04 | 8.767 | 31.26 | | |
| 4.570 | 57.08 | 3.276 | 53.49 | 3.578 | 58.68 | | | | |
| 4.825 | 56.40 | 3.537 | 53.22 | 4.719 | 49.11 | | | | |
| 5.338 | 54.45 | 3.868 | 52.77 | 6.505 | 40.85 | | | | |
| 6.252 | 51.15 | 4.262 | 52.12 | 9.261 | 34.33 | | | | |
| 7.851 | 45.97 | 4.867 | 50.97 | | | | | | |
| 9.140 | 42.80 | 5.522 | 49.56 | | | | | | |
| 14.16 | 35.75 | 6.149 | 48.21 | | | | | | |
| | | 7.169 | 46.29 | | | | | | |
| | | 8.687 | 43.77 | | | | | | |

TABLE III

CONDUCTANCE OF DODECYLAMMONIUM CHLORIDE IN 24.65% METHANOL WITH DODECANOL ADDED AT 25°

| $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ | $10^2\sqrt{c}$ | Λ |
|---|---|---|---|---|---|
| 0.110 Mole dodecanol per mole salt | | 0.261 Mole dodecanol per mole salt | | 0.651 Mole dodecanol per mole salt | |
| $\kappa_0 = 0.62 \times 10^{-6}$ | | $\kappa_0 = 0.77 \times 10^{-6}$ | | $\kappa_0 = 0.77 \times 10^{-6}$ | |
| 4.781 | 58.70 | 3.170 | 59.74 | 4.291 | 59.20 |
| 9.797 | 56.28 | 5.629 | 58.58 | 6.495 | 57.97 |
| 11.66 | 54.37 | 7.770 | 57.35 | 8.885 | 56.14 |
| 12.72 | 53.58 | 10.22 | 54.19 | 10.06 | 52.60 |
| 14.34 | 51.02 | 10.81 | 53.51 | 11.92 | 45.92 |
| 16.76 | 47.06 | 11.48 | 52.76 | 14.60 | 40.48 |
| 20.12 | 41.76 | 12.37 | 51.79 | 18.75 | 32.74 |
| 25.28 | 36.17 | 13.27 | 50.66 | | |
| | | 15.11 | 47.03 | | |
| | | 17.94 | 41.76 | | |
| | | 20.29 | 38.49 | | |

The critical concentration lies between 1.42 and $1.44 \times 10^{-2}$. Ralston, Hoerr and Hoffman[11] give $1.30 \times 10^{-2}$. Corrin and Harkins,[12] using the indicator method, found values ranging between 1.24 and $1.36 \times 10^{-2}$, depending upon the dye used.

**2. Effect of Alcohols on Dodecylammonium Chloride in Aqueous Solution.**—As appears from the earlier work of Evers[4] and of Grieger,[4] the hexadecyl and octadecyl quaternary ammonium salts, as used by them, show a marked shift of the breakpoint toward higher concentrations on addition of methanol. The same is true of solutions of dodecylammonium chloride as appears from Fig. 3. Whether or not there is an initial recession of the break point concentration on addition of small amounts of methanol is uncertain, but it may be inferred that, if it occurs at all, it is very small.

The effect of different alcohols on the breakpoint concentration of dodecylammonium chloride is of interest. The effect is shown graphically in Figs. 2 and 3 and the values are given in Table IV.

TABLE IV

EFFECT OF ALCOHOLS ON BREAKPOINT CONCENTRATION, $C_b$, OF DODECYLAMMONIUM CHLORIDE IN WATER

| Alcohol | % Alcohol | $C_b \times 10^2$ |
|---|---|---|
| ..... | 0.0 | 1.4 |
| Methanol | 16.2 | 3.1 |
| Methanol | 24.7 | 5.2 |
| Isopropyl | 8.0 | 0.92 |
| Isopropyl | 16.2 | 1.04 |
| *t*-Butanol | 5.7 | 0.79 |
| *t*-Butanol | 7.9 | 0.74 |

It will be noted that for dodecylammonium chloride, as for quaternary hexadecyl and octadecyl compounds, the addition of methanol causes an increase in the breakpoint concentration. Isopropyl alcohol, on the other hand, causes a marked decrease of the critical concentration. Thus, 16% of methanol raises the breakpoint from $1.4 \times 10^{-2}$ to $3.1 \times 10^{-2}$, while 16% of isopropyl lowers it to $1.04 \times 10^{-2}$. The decrement, in the case of *t*-butanol, is even greater the breakpoint falling to $0.74 \times 10^{-2}$ for 8% of this alcohol as against $0.92 \times 10^{-2}$ for 8% of isopropyl alcohol.

(11) Measurements by P. F. Grieger.

(12) Corrin and Harkins, THIS JOURNAL, 69, 683 (1947).

The breakpoint concentration passes through a minimum on addition of isopropyl alcohol but in the case of *t*-butanol, the concentration is still decreasing as far as the highest content of alcohol measured. Ralston and Hoerr[13] have determined the effect of ethanol on the breakpoint of dodecylammonium chloride. They found little change on initial addition and a marked shift toward higher concentration for larger additions.

It is, thus, evident that the effect of an added alcohol on the breakpoint concentration is markedly dependent on the number of carbon atoms in the alcohol.

**3. Hexadecyl- and Octadecylpyridonium Iodate.**—These two salts are remarkable in that both exhibit a maximum in their conductance curves in pure water.[14] The results are shown graphically in Fig. 4, curves 1 and 3. In curves 2, 4 and 5 are shown the results obtained on adding tertiary butanol and methanol.

For convenience in discussion, numerical values are given in Table V for some of the variables that characterize the curves of Fig. 4. The concentration at which the curve begins to rise above the straight line in dilute solution is termed the "risepoint."

TABLE V

CHARACTERISTIC VALUES FOR CURVES OF FIGURE 4

| Solvent mixture | Λ Risepoint | Λ Max. | Rise, % | $c \times 10^4$ Risepoint | $c \times 10^4$ Max. |
|---|---|---|---|---|---|
| **Hexadecylpyridonium Iodate** | | | | | |
| Water | 58.0 | 58.6 | 1 | 9.9 | 16 |
| 7.9% Butanol | 43.3 | 53.5 | 24 | 1.35 | 9 |
| **Octadecylpyridonium Iodate** | | | | | |
| Water | 57.8 | 67.6 | 17 | 0.9 | 5 |
| 16.2% Methanol | 42.6 | 49.8 | 16 | 2.9 | 8 |

These two salts are of particular interest in that they enable us to study the effect of various factors on the maximum phenomenon in water. The addition of two carbon atoms to the hexadecyl chain decreases the risepoint concentration to one-tenth that of the hexadecyl compound. The rise at the maximum is increased from 1 to 17% and the concentration of the maximum is reduced in the ratio of 3 to 1. It is apparent that the maximum phenomenon is very sensitive to the length of the hydrocarbon chain.

On addition of 16% methanol to the solution of the octadecyl compound, no great change occurs; the conductance increase at the maximum is not appreciably altered, the risepoint and the maximum are shifted toward higher concentrations. In 10% *t*-butanol, the risepoint concentration could not be determined but it appears from curve 5 that it is not far from $0.5 \times 10^{-4}$. The value of Λ at the maximum is 51 and the limiting conductance of octadecylpyridonium iodate, based on the conductance of this salt in water and potassium iodate in water and in the butanol–water mixture[15] is 40. Thus, the height of the maximum in water and in the 10% *t*-butanol mixtures is approximately the same. Although the measurements were carried to a concentration of only $10^{-3}$, it is evident that the bow of the maximum is much broader in 10% *t*-butanol than in water.

On addition of *t*-butanol to a solution of the hexadecyl compound, the conductance curve is greatly altered. The increase of κ at the maximum rises from 1 to 24% and the bow of the maximum is widened toward both lower and higher concentrations. The risepoint is shifted to lower concentration in the ratio of 7 to 1 and the maximum is shifted in the same direction in the ratio of 2 to 1.

**4. Dodecylammonium Chloride on Addition of Dodecanol.**—Measurements were carried out with five different proportions of dodecanol to salt in a 25.64% methanol–water mixture; the results for three of them are presented in Table III, while all are shown graphically in Fig. 5. Two series were carried out for nearly the same proportion of alcohol to salt; the results are in good agreement as may be seen from curves 4 and 5 of the figure.

With increasing proportion of dodecanol, the breakpoint recedes to lower concentration. Breakpoint values are presented in Table VI.

TABLE VI

BREAKPOINT CONCENTRATIONS FOR DODECYLAMMONIUM CHLORIDE ON ADDITION OF DODECANOL IN 25.64% METHANOL–WATER MIXTURE

| Moles dodecanol per mole salt | 0.0 | 0.044 | 0.111 | 0.261 | 0.651 |
|---|---|---|---|---|---|
| Breakpoint concn. $\times 10^2$ | 2.37 | 1.69 | 1.08 | 0.83 | 0.69 |

The breakpoint concentration is markedly lowered (to 1/3) on addition of 0.651 mole of dodecanol per mole of salt. More significant, perhaps, is the fact that at concentrations below the breakpoint, the conductance values are the same as in the pure solvent mixture, regardless of the proportion of dodecanol. This indicates that below the breakpoint, the salt behaves like a normal electrolyte and is unaffected by the dodecanol. This result is at variance with those obtained by Ralston and Hoerr[16] for dodecylammonium chloride in aqueous solutions on addition of methyllauramide, dodecane and lauronitrile. These authors found only a slight depression in the breakpoint concentration on making the additions, while they found the conductance to be strongly (and rather uniformly) depressed at all salt concentrations, even below the breakpoint. For a given addition agent, the conductance was found to be independent of the amount of non-electrolyte added.

(13) Ralston and Hoerr, THIS JOURNAL, **68**, 2460 (1946).

(14) Recently, Ralston, Eggenberger and Du Brow, *ibid.*, **70**, 977 (1948), found that the equivalent conductance of didodecyldimethylammonium chloride in water passes through a maximum in the neighborhood of $C = 10^{-4}$.

(15) Unreported measurements by P. F. Grieger.

(16) Ralston and Hoerr, THIS JOURNAL, **69**, 883 (1947).

More recently, Ralston and Eggenberger[17] have reported that the equivalent conductance of dodecylammonium chloride in water and in water saturated with a number of sparingly soluble organic non-electrolytes (hydrocarbons, alcohols, etc.) is the same at concentrations less than the critical.

As the concentration of dodecylammonium chloride is increased above that of the breakpoint in the presence of dodecanol, there occurs a change in the character of the curves which may be of the nature of a second breakpoint. This is best shown by curves 4 and 5 for 0.246 and 0.261 mole of dodecanol per mole of salt. The two series are in good agreement, and there is little doubt that, at a certain concentration, the course of the curves undergoes a marked change. At concentrations above the "second breakpoint," the curves are all convex to the concentration axis, and they parallel one another rather closely.

It is of interest to note that for 0.044 and 0.111 mole of dodecanol per mole of salt, the solutions remained homogeneous over the entire range of concentration. For 0.26 mole of dodecanol, the solution became cloudy at the second breakpoint, the cloudiness increasing up to the first breakpoint; thereafter, the cloudiness decreased with dilution. For 0.65 mole of dodecanol, the solution was cloudy, although stable, over the whole range of concentration. The reproducibility of the results leaves little doubt that, in these solutions, we are dealing with a system in equilibrium. The fact that below the breakpoint the curves coincide for all proportions of alcohol to salt is strong evidence that under these conditions the two (alcohol and salt) are not associated.

**5. Salts of Doubly Charged Long Chain Ions.**—It was of interest to determine whether salts with two ions connected by a hydrocarbon chain would exhibit properties similar to those of uni-univalent long chain salts. Measurements were carried out with 1-N-morphine 10-N′-piperidinodecane dihydrochloride and di-N-propyl-10-N-piperidinodecane dihydrochloride. The results are shown graphically in Fig. 6 along with the conductance curve for decylammonium chloride at 20° as determined by Ralston and Hoerr.[18] As may be seen from the figure, the conductance curves for the diammonium salts exhibit no singularities up to 0.25 *N*. It may be concluded that these salts do not exhibit the properties of ordinary long chain electrolytes over the concentration range measured, at least not so far as conductance is concerned.

(17) Ralston and Eggenberger, THIS JOURNAL, **70**, 983 (1948).
(18) Ralston and Hoerr, *ibid.*, **64**, 772 (1942).

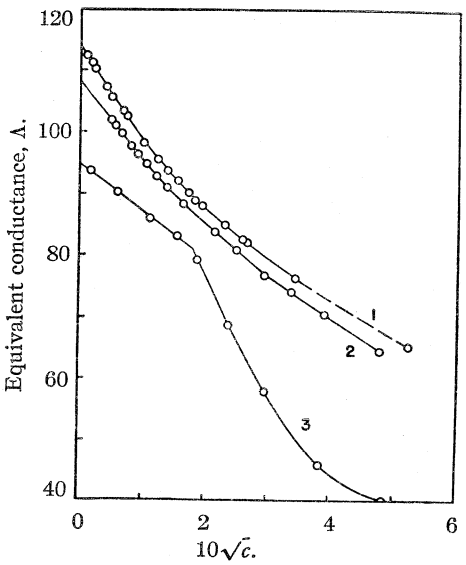



Fig. 6.—Diammonium salts in water at 25°: (1) 1-N-morpholino-10-N′-piperidinodecane dihydrochloride; (2) di-N-propyl-10′N′-piperidinodecane dihydrochloride; (3) decylammonium chloride at 20° (Ralston and Hoerr).

## V. Summary

1. The effect of isopropyl alcohol and *t*-butanol on the conductance of dodecylammonium chloride in aqueous solution has been determined and compared with that of methanol.

2. It has been found that octadecylpyridonium and hexadecylpyridonium iodate exhibit a maximum in their conductance curves in aqueous solution; the maximum is much the more pronounced for the octadecyl compound.

3. The effect of methanol and *t*-butanol on the conductance of the octadecyl compound in aqueous solution has been determined as has also that of *t*-butanol on solutions of the hexadecyl compound. The effect of butanol in the case of the latter compound is very pronounced.

4. The effect of dodecanol on the conductance of solutions of dodecylammonium chloride in a 25.64% methanol–water mixture has been studied. The breakpoint concentration is lowered on addition of dodecanol; at concentrations below the breakpoint, the conductance is unaffected by addition of dodecanol. There are indications of a second break at concentrations above that of the normal breakpoint.

5. The conductance of the two diammonium salts with ten carbon atoms between the ionic groups follows the course of a normal electrolyte as far as measured (0.25 *N*).

PROVIDENCE, R. I. RECEIVED AUGUST 14, 1948

[CONTRIBUTION FROM THE MALLINCKRODT LABORATORY, HARVARD UNIVERSITY]

# Activity of Cadmium Iodide in Deuterium Oxide

BY EVAN C. NOONAN[1]

Many salts have been found to be less soluble in deuterium oxide than in protium oxide. Provided the solid phase is not hydrated the activities of the electrolyte in both solvents must be identical at saturation, *i. e.*

$$(A) \qquad m_H\gamma_H = m'_D\gamma'_D$$

In this expression $m_H$ and $m'_D$ represent the concentrations in terms of moles of salt per 55.507 moles of solvent, $\gamma_H$ is the conventional stoichiometric mean ionic activity coefficient in water whose value is unity at infinite dilution, while $\gamma'_D$ is a relative activity coefficient defined by the above equation. The value $\gamma'_D$ at infinite dilution in $D_2O$ is not unity; it combines the change in standard state in passing from $H_2O$ to $D_2O$ with the conventional activity coefficient in $D_2O$. Although $\gamma'_D$ was termed an absolute activity coefficient by La Mer and Noonan[2] this designation is somewhat misleading since it is not referred to an absolute standard state. While the relative activity coefficient defined in this way could be used to describe the behavior of a given salt in any pair of solvents it is of particular value in the case of protium and deuterium oxides since the molecular volumes and dielectric constants of these solvents are nearly identical, and contributions to the change in standard state from these sources may usually be neglected. Any pronounced differences in activity effects between $H_2O$ and $D_2O$ can be directly compared, and are of interest since important factors of electrolytic behavior may be revealed which are not accounted for by present theories.

It has been suggested[3] that the macromolecular structure of water is responsible for solubility differences of salts in $H_2O$ and $D_2O$. The greatest effects should therefore be observed at the highest dilutions, since the structure of the solution would then approach that of the undisturbed solvent. Only limited information is obtainable from solubility determinations in this region; activity data for salts in heavy water as a function of concentration are therefore desirable.

Eddy and Menzies[4] found that cadmium iodide was 26% less soluble in heavy water than in light water at 25°, indicating that further study of this salt might prove profitable. Bates[5] determined thermodynamic properties of cadmium iodide using the cell

$$(B) \qquad Cd\text{–}Hg(2\ phase)/CdI_2(m\ in\ H_2O)/AgI\text{–}Ag$$

Information obtained from measurements on a similar cell using $H_2O$–$D_2O$ mixtures as the solvent is the subject of this paper.

## Experimental

**A. Preparation of Materials: Deuterium oxide** was purified before each determination by consecutive vacuum distillation from alkaline permanganate and then from a crystal of potassium dichromate or chromic anhydride. Water treated in this manner was found to have a conductance of $2 \times 10^{-6}$ mho or better.

**Cadmium iodide** was purified by the method of Baxter and Hartman for cadmium chloride.[6] A C.P. grade of cadmium iodide was fused in a glass vessel, cooled, dissolved in distilled water and filtered from an insoluble residue. The solution was then evaporated and the process repeated for a total of five times. The resulting salt was recrystallized twice.

**Cadmium Amalgam.**—An 800-g. sample of cadmium metal was distilled three times in vacuum using an all glass apparatus. The distillate amounted to 300 g. and carefully purified mercury was distilled upon it to give a saturated amalgam. During the course of the experiments, this amalgam was found to be awkward to use with the micro equipment involved and became contaminated with stopcock grease. It was then filtered through sintered glass and divided into two portions, one of which was diluted with mercury to yield a single phase amalgam. All these operations were carried out in vacuum or under an atmosphere of nitrogen.

**Silver Iodide Electrodes.**—These were made by the thermal method recommended by Bates.[5]

**B. Apparatus and Procedure.**—A 16-ml. pyrex pycnometer fitted with platinum electrodes was used to determine the density and conductivity of heavy water. Ground glass joints were used on the pycnometer, cell, weighing flasks and on all parts which came into contact with the heavy water solutions. All apparatus other than the pycnometer was carefully cleaned, steamed and dried before use. All parts of the apparatus were pyrex except the silver iodide electrode supports which were made of hard Jena glass.

Solutions for each cell were made up from 16 ml. of heavy water and the appropriate amount of dry salt. For the 0.1 molal solutions, the amount of water was adjusted with a 0.25-ml. hypodermic syringe calibrated to 0.01 ml. The three least concentrated solutions were made by diluting a stock solution. All solutions were evacuated to remove dissolved air and a nitrogen atmosphere substituted in the weighing flasks. The usual corrections were applied for the buoyancy of air.

The cell employed was equipped with two silver iodide and two cadmium-amalgam electrodes. Total volume of the cell was about 10 ml., and it was filled using vacuum technique. Voltage readings were taken over a six–twelve hour period with a suitably equipped Leeds and Northrup Type K potentiometer. Temperature was controlled at $25 \pm 0.01°$ as measured with a B. S. calibrated thermometer.

A special cell was built to measure the e. m. f. of the 2-phase cadmium amalgam *versus* the dilute amalgam actually employed for the cadmium iodide cells. Two electrodes for each amalgam concentration were used, and the cell was filled with an aqueous solution of purified cadmium sulfate of undetermined concentration.

**C. Experimental Results.**—Deuterium contents of the heavy water mixtures were computed from the density increment over unity at

(1) Present address: University of Tennessee, Knoxville, Tennessee.

(2) La Mer and Noonan, THIS JOURNAL, **61**, 1489 (1939).

(3) Shearman and Menzies, *ibid.*, **59**, 185 (1937).

(4) Eddy and Menzies, *J. Phys. Chem.*, **44**, 207 (1940).

(5) Bates, THIS JOURNAL, **63**, 399 (1941).

(6) Baxter and Hartman, *ibid.*, **37**, 120 (1915).

25° and the $d^{25}_{25}$ value for heavy water of 1.10764 as determined by Stokland, Ronaess and Tronstad.[7] The total moles of water species were used to compute the molality which is uniformly expressed as moles of salt per 55.507 moles of water.

All cells were made using a single phase amalgam which was 0.00239 volt positive to a 2-phase cadmium amalgam at 25° and observed values were increased by this figure to give the e. m. f. of the cell

(C) Cd–Hg(2 phase)/$CdI_2(m'$ in $H_2O$, $D_2O$)/AgI–Ag

Results of measurements of the e. m. f. of the above cell at 0.1 $m'$ (moles of salt per 55.507 moles of total water species) as a function of deuterium content are presented in Table I. Values for light water were interpolated from the data of Bates[5] using large-scale plots of $-\log\gamma_H$ *vs.* $m^{1/2}$ and the electromotive force equation at 25° given as (D).

$$(D) \qquad E = 0.18280 - 0.088716 \log \gamma_H m_H$$

Good agreement was obtained between the check runs in protium water and the original data of Bates. The voltage decrease of the cells made with deuterium water is nearly a linear effect of the deuterium content. Deviations from linear variation are given in the last column of Table I, and it appears that there may be a slight sag just beyond the experimental error. A slightly sagged curve was observed in a similar study of the thermodynamics of potassium chloride in protium and deuterium oxide.[2] For this work cells involving liquid junctions were employed and isotopic water species may have been transferred across the boundary. Apparently, whatever the nature of the solvation effects on cadmium iodide in protium-deuterium oxide mixtures, the amount of HDO present is not important. This is decidedly not true for the hydrochloric acid cell made in heavy water, for the value of $E_H - E_D$ passes through a maximum,[8] the effect being associated with the various isotopic hydronium ions formed.

TABLE I

ELECTROMOTIVE FORCE OF THE CELL Cd–Hg(2 PHASE)/$CdI_2(0.1m')$/AgI–Ag AT 25° AS A FUNCTION OF THE DEUTERIUM CONTENT OF THE SOLVENT

| $D_2O$, % | $m'$ | $E_{H_2O,\ D_2O}$ obs., volts | $E_{H_2O} - E_{H_2O,\ D_2O}$ volts | Deviation from linearity, millivolts |
|---|---|---|---|---|
| 0.02 | 0.09989 | 0.35766 | −0.00004 | −0.01 |
| 0.02 | .09996 | .35765 | − .00003 | .00 |
| 18.76 | .09991 | .35620 | .00142 | − .17 |
| 44.15 | .09971 | .35391 | .00372 | − .07 |
| 89.33 | .10000 | .34994 | .00768 | − .02 |
| 89.46 | .10003 | .34989 | .00773 | + .02 |

## Discussion of Results

The data obtained in heavy water are not sufficiently comprehensive to permit the evaluation of the standard molal potential in pure $D_2O$ nor the calculation of conventional activity coefficients in this solvent. However, the relative activity coefficient, $\gamma'_D$, defined in equation (A) may be obtained in the following manner. For the light water cell the e. m. f. is represented as

$$(E) \qquad E_H = E^0_H - RT/2F \ln 4(m_H\gamma_H)^3$$

(E) while for the deuterium oxide cell on the modified molal scale, $m'$, (F) holds. If $E^0_H$ is arbitrarily

$$(F) \qquad E_D = E'^0_D - RT/2F \ln 4(m'_D\gamma'_D)^3$$

set equal to $E'^0_D$ and if $m_H = m'_D$ then equations (E) and (F) can be combined to give (G). At

$$(G) \qquad E_H - E_D = 3RT/2F \ln (\gamma'_D/\gamma_H)$$

25° this equation can be further simplified to (H).

$$(H) \qquad (E_H - E_D)/0.0088716 + \log \gamma_H = \log \gamma'_D$$

Table II summarizes the results obtained at various concentrations, $m'$, of cadmium iodide for cell (C). In all cases $m'$ is given as the moles of salt per 55.507 moles of total water species. The observed potential of cell (C) is listed in the column headed $E_{H_2O,\ D_2O}$, obs. The heading $E_{H_2O} - E_{D_2O}$ refers to the difference between the e. m. f. of cell (B) in water (data of Bates) and the observed value of cell (C) extrapolated to pure deuterium oxide. Stoichiometric mean ionic activity coefficients, $\gamma_H$, taken from the data of Bates, were used to compute the listed values of $\gamma'_D$.

TABLE II

ELECTROMOTIVE FORCE OF THE CELL: Cd–Hg(2 PHASE)/$CdI_2(m')$/AgI–Ag IN DEUTERIUM OXIDE AS A FUNCTION OF CONCENTRATION AT 25°

| $D_2O$, % | $m'$ | $E_{H_2O,D_2O}$, obs., volts | $E_{H_2O} - E_{D_2O}$, volts | $\gamma_H$ | $\gamma'_D$ |
|---|---|---|---|---|---|
| 90.68 | 0.005729 | 0.39955 | 0.01247 | 0.469 | 0.649 |
| 90.82 | .010008 | .38697 | .01139 | .382 | .513 |
| 90.48 | .015542 | .37823 | .00998 | .319 | .413 |
| 90.33 | .02836 | .36767 | .00926 | .234 | .298 |
| 90.78 | .05961 | .35669 | .00878 | .149 | .188 |
| 90.34 | .06019 | .35674 | .00862 | .149 | .186 |
| 89.33 | .10000 | .34994 | .00860 | .107 | .134 |
| 89.46 | .10003 | .34989 | .00864 | .107 | .134 |
| 89.46 | .14385 | .34511 | .00860 | .0843 | .105 |
| 89.23 | .50831 | .32828 | .00913 | .0365 | .0463 |
| 90.34 | .83077 | .32066 | .00826 | .0277 | .0343 |
| 90.87 | 1.3593 | .31186 | .00796 | .0214 | .0263 |

Figure 1 is a plot of the activity ratio, $a_D/a_H$ (which is equivalent to $(\gamma'_D)^3/(\gamma_H)^3$), *versus* the square root of molality, $m'$. It may be seen that there is a slight linear change with molality down to 0.06 $m'$; below that concentration the activity ratio rises sharply. Although the experimental error increases in this region the results indicate a very real trend. The most interesting area appears to be at dilutions beyond those reported in this paper (0.006 $m'$).

At 0.1 $m'$ the value for the partial molal free energy change when 1 mole of cadmium iodide

(7) Stokland, Ronaess and Tronstad, *Trans. Faraday Soc.*, **35**, 312 (1938).

(8) Noonan and La Mer, *J. Phys. Chem.*, **43**, 247 (1939).

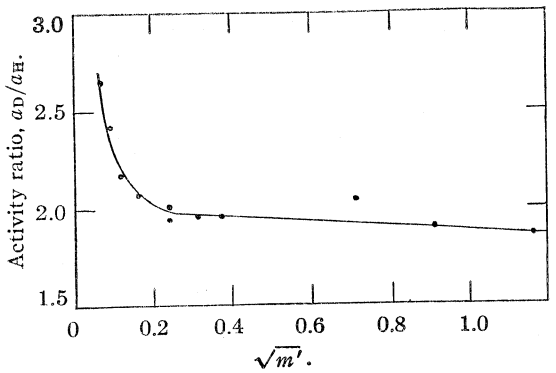



Fig. 1.—Activity ratio of cadmium iodide in heavy and light water at 25° as a function of concentration.

is transferred isothermally and reversibly from pure deuterium oxide solution to pure protium oxide solution is −398 cal. This may be compared with about −225 cal. for a similar transfer of potassium chloride.[2]

**Correction for Differences in Molar Volume.**—Because a mole of $D_2O$ occupies 0.36% more volume than a mole of $H_2O$ at 25° a correction should be applied for the electrical work obtained on isothermally and reversibly expanding the ionic assembly in light water to the volume it would occupy in heavy water. Using the appropriate e.m.f. equation for a cadmium iodide concentration cell, and assuming that the density and activity coefficients of the solutions do not change over a range of 0.36% variation in molality, it will be found that the value is 0.00014 volt. This correction should be added to the difference, $E_H - E_D$. It is about the order of the experimental error in measuring the most concentrated solutions and was neglected in treating the results.

## Summary and Conclusions

1. The e.m.f. of cell (C) has been determined

(C) Cd–Hg(2 phase)/$CdI_2$($m'$ in $H_2O$, $D_2O$)/AgI–Ag

at 25° as a function of concentration, $m'$, of cadmium iodide in terms of moles of salt per 55.507 moles of total water species. By combining the results with light water data, relative stoichiometric mean ionic acitivity coefficients, $\gamma_D$, in deuterium oxide have been computed. The value of this activity coefficient is not unity at infinite dilution, but it affords a comparison of the activity behavior of cadmium iodide in the isotopic solvents.

2. At 0.1 $m'$ the e.m.f. of cell (C) was found to be nearly a linear function of the deuterium content of the solvent.

KNOXVILLE, TENN. RECEIVED JUNE 9, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, HARVARD UNIVERSITY]

# Adsorption of Gas Mixtures. Nitrogen–Oxygen on Anatase

BY JAMES R. ARNOLD[1]

The data on multilayer adsorption of gas mixtures[2] are limited in quantity compared to those available on single gases. Moreover, the studies which have been made have employed chiefly charcoal and silica gel as adsorbents. These substances, while industrially important, are not suitable for fundamental studies, since the phenomena of multilayer adsorption and capillary condensation occur simultaneously on their surfaces. A further limitation of some of the studies[3] is the choice of pairs of adsorbates for which large deviations from additive properties, *e. g.*, Raoult's law, are to be expected. Such data are peculiar to the system studied, and cannot yield generally useful information.

Hill[4] has recently generalized the Brunauer–Emmett–Teller (BET) theory[2,5] to mixtures of gases, for which no or moderate deviations from Raoult's law occur. This extension brings out the important fact that any statistical theory of adsorption can be generalized to give adsorption isotherms for such mixtures. Since the added assumption involved in the generalization will not introduce a large error, for a well-chosen pair of gases, the degree of agreement obtained between gas mixture data and the extended theory will provide evidence for or against the original theory. It will be shown below that the present study provides strong evidence against at least one of the postulates of the BET theory, and indications in favor of a quite different model.

The system chosen for this study was the gas pair nitrogen–oxygen on the adsorbent anatase ($TiO_2$). The two gases have convenient vapor pressures at liquid nitrogen temperature, and their phase diagrams at this temperature show small deviations from Raoult's law. The analysis can be made readily by a direct method. The adsorbent is one which has been extensively studied,[6,7] and consists of single crystals, free from

(1) Present address: Institute for Nuclear Studies, University of Chicago, Chicago 37, Illinois.

(2) Brunauer, "The Adsorption of Gases and Vapors," Princeton University Press, Princeton, N. J., 1943, pp. 474–497.

(3) Rao, *J. Phys. Chem.*, **36**, 616 (1932); Tryhorn and Wyatt, *Trans. Far. Soc.*, **22**, 139 (1926).

(4) Hill, *J. Chem. Phys.*, **14**, 268 (1946).

(5) Hill, *ibid.*, **14**, 263 (1946).

(6) Jura and Harkins, THIS JOURNAL, **66**, 1356 (1944); Harkins and Jura, *ibid.*, **66**, 1362, 1366 (1944).

(7) Beebe, Beckwith and Honig, *ibid.*, **67**, 1557 (1945).

microscopic flaws and fissures, so that capillary condensation is minimized.

The usual technique for taking mixture adsorption data consists of varying gas composition at constant pressure in a static system. A flow method, in which data are taken over a range of pressures for a few definite gas compositions, has a double advantage. First, the time taken to reach equilibrium is greatly reduced by the elimination of diffusion block and, second, the isotherm equations come out in particularly simple form. This method was used in the present work.

## Experimental

**Materials.**—The anatase used in this study was supplied through the kindness of Professor W. D. Harkins. It was degassed under high vacuum at 300° before each run, and as frequently as necessary during the course of a run. Measurement of the area of a 3-g. sample, using nitrogen as adsorbate, in a multibulb apparatus of standard type[8] gave a value of 13.73 sq. meters/gram for its specific area, in good agreement with values obtained elsewhere.[6,7] The area of a 1.294-g. sample measured with the flow apparatus described below was 13.81 sq. meters/gram.

Five tanks of nitrogen–oxygen mixtures, containing 14.9, 29.8, 50.2, 70.2 and 85.3% oxygen, respectively, were obtained from the Linde Air Products Co. They were certified to contain less than 0.1% argon, and only traces of other non-condensable impurities. The nitrogen and oxygen used for the single gas isotherms were Air Reduction Co. Prepurified and Electrolytic grades, respectively.

The gases were passed over "Dehydrite" (magnesium perchlorate) to remove water, and used without further purification.

**Apparatus and Procedure.**—The measurements were made in the flow apparatus shown in Fig. 1. The detachable sample cell F has 2-mm. capillary leads to cut down dead space; the sample itself is about six inches below the surface of a liquid nitrogen bath. The anatase powder is prevented from blowing over by a loose-fitting glass ball-socket valve at the base of the bulb. The pretrap C consists of an identical sample of anatase in a liquid nitrogen bath, and serves to remove condensible impurities.

In operation, gas flows at the rate of 20 cc./min. through the capillary flowmeter A (maintained at slightly above atmospheric pressure), through the Hoke needle valve B, the pretrap C, the cell F, the Hoke needle valve H, and finally through the stopcock P to a Nelson roughing pump. The needle valves B and H allow the pressure in the cell system to be set at any desired value (as read on the manometer D). The time necessary for the adsorbed gas to come into equilibrium with the given mixture at a given pressure was tested in a series of preliminary experiments. A running time of eight to ten minutes was found to be sufficient, except at very low pressures, where the flow rate had to be decreased to prevent excessive pressure drops in the line, and at pressures near the condensation pressure, where especially large volumes of gas were taken up. The running time used in the actual measurements was approximately thirty minutes.

At the end of this period valves B and H are closed simultaneously, and the pressure read on manometer D. The temperature was read on a nitrogen vapor pressure thermometer[9] with bulb immersed in the bath surrounding F. Data used for calibration were those of Dodge and Dunbar.[10] Stopcocks E and G are then closed, valve H opened, and the system evacuated through stopcock N. The analytical train, consisting of Toepler pump K, measuring bulb L, and reaction bulb M, is also evacuated.

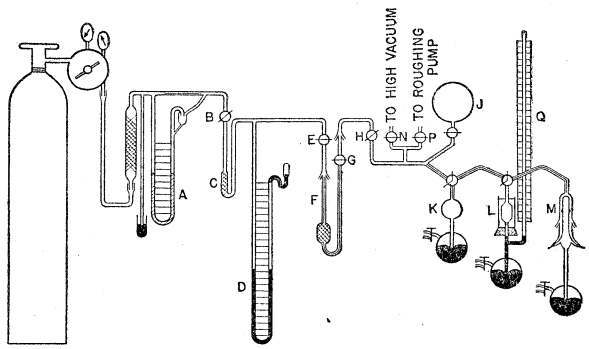



Fig. 1.—Diagram of flow apparatus.

Stopcock N is then closed, G opened, the liquid nitrogen bath removed, and the gas in the cell transferred with the Toepler pump to the measuring bulb L. The gas pressure, measured with manometer Q, the known volume of bulb L, and dead space of the cell F, permit the calculation of the total amount adsorbed at the given pressure and gas composition. After mixing to insure homogeneity, an aliquot of the gas is measured in L and transferred to the analytical bulb M. Smaller samples of gas are used entire.

The reactive element in M is an iron-plated platinum wire (after Lambert and Peel[11]), heated electrically to bright red heat. Two one-minute passes usually suffice for complete reaction, after which the gas is transferred back to bulb L, the residual pressure representing the nitrogen content of the sample. From this value the amount of each gas adsorbed can be calculated. After several analyses the wire is restored to activity by reduction with hydrogen. This method of analysis is quite satisfactory in practice, though a small correction (a few tenths per cent.) was necessary for residual gases in the electrolytically plated iron. The method is reproducible to 0.1%. It is necessary to replace the plated wire occasionally, as it burns out after prolonged use.

To begin a new point, stopcock G is closed, and the liquid nitrogen bath placed around cell F. Stopcock E is then opened. As points on an isotherm of a given gas composition are taken in more or less random order, the pressure in the cell might now be either greater or less than the final running pressure. Thus the points on the isotherm include indiscriminately "adsorption" and "desorption" points. The fact that the isotherm points showed no scatter due to this effect was a further check that the points represent equilibrium. Valves B and H are then roughly adjusted, stopcock P opened, followed by stopcock G, and the valves adjusted until the desired pressure is reached.

Each mixture isotherm consists of 40 to 50 points taken as described above. The pure gas isotherms were determined in the same way, omitting the analysis. The lowest pressure at which the apparatus gave reliable results was 2–3 mm.

The points on the pure gas isotherms below 1 mm. pressure were measured in a static system, using a three-range calibrated McLeod gage in place of the usual gas buret, with the sample contained in the detachable cell F. Thermal transpiration causes an error in pressure readings at these low pressures; the maximum possible error is a factor of $\sqrt{T_1/T_2} = \sqrt{298/78} = 1.95$. Correction for this effect was made according to Loeb.[12] The theory given is not exact, so that residual errors in pressure of 10–20% may be expected. The resulting errors in amount adsorbed are negligible.

## Results and Discussion

The isotherms obtained for the two pure gases and the five mixtures are shown in Figs. 2–8. The

(8) See, for example, Deitz and Gleysteen, *J. Research Natl. Bur. Standards*, **29**, 191 (1942).

(9) Farkas and Melville, "Experimental Methods in Gas Reactions," Macmillan and Co., London, 1939, p. 104.

(10) Dodge and Dunbar, THIS JOURNAL, **49**, 610 (1927).

(11) Lambert and Peel, *Proc. Roy. Soc.* (*London*), **A144**, 205 (1934).

(12) Loeb, "Kinetic Theory of Gases," McGraw-Hill Book Co., New York, N. Y., 1934, pp. 352–363.

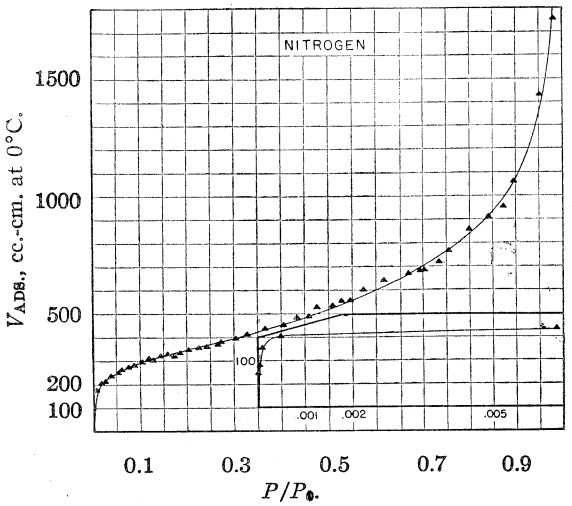



Fig. 2.—Pure nitrogen isotherm.

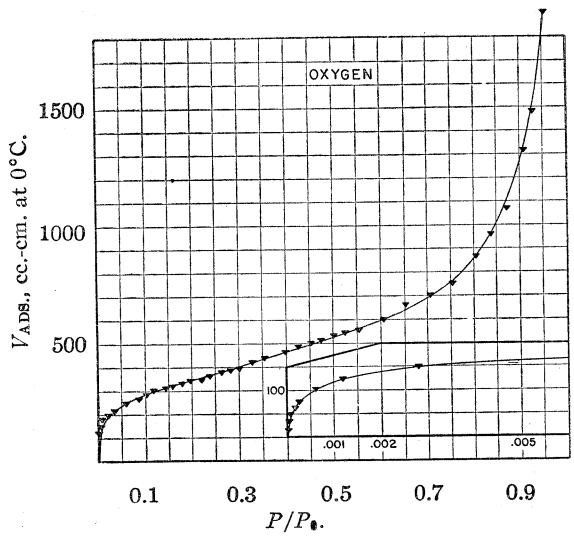



Fig. 3.—Pure oxygen isotherm.

pressure $p_0$ is the saturation vapor pressure of the liquid phase in equilibrium with gas of the given composition at 78.2°K. The composition and vapor pressure of these liquid phases are given in Table I. It may be seen that Raoult's law is obeyed in this system within a few per cent.

In examining the pure gas isotherms, we note that in the region of moderate to high $p/p_0$, the two curves are nearly superimposable. In the low pressure region, however (inserts, Figs. 2 and 3), the adsorption of nitrogen greatly exceeds that of oxygen.

The mixed adsorption isotherms show a number of striking features. First, we note the close resemblance between the total gas isotherms and those for the pure gases. In fact, except for a small difference in scale, all seven total gas isotherms can be nearly superposed (except below $p/p_0$ = 0.01, where there are no mixture data). At the highest pressures, the adsorbed phase is much

TABLE I

GAS-LIQUID EQUILIBRIUM AT 78.2°K.[a]

| $y_2$, % | $r_2$, % | $p_0$, mm. | $r_2'$, % | $p_0'$, mm. |
|---|---|---|---|---|
| 0 | 0 | 840 | 0 | 840 |
| 14.9 | 43.4 | 581 | 45.1 | 543 |
| 29.8 | 67.7 | 418 | 66.5 | 401 |
| 50.2 | 84.6 | 296 | 82.5 | 295 |
| 70.2 | 93.1 | 232.4 | 91.7 | 234.6 |
| 85.3 | 97.1 | 202.1 | 96.4 | 203.2 |
| 100 | 100 | 179.7 | 100 | 179.7 |

$y_2$ = mole per cent. $O_2$ in gas phase.
$r_2$ = mole per cent. $O_2$ in liquid phase.
$r_2'$ = mole per cent. $O_2$ in liquid phase in Raoult's law.
$p_0$ = vapor pressure of liquid of composition $r_2$
$p_0'$ = vapor pressure of liquid of composition $r_2'$, from Raoult's law.

[a] Dodge and Davis, THIS JOURNAL, 49, 591 (1927).

richer in oxygen, the more condensable gas, than is the gas phase, its composition approaching that of the bulk liquid asymptotically as $p$ approaches $p_0$. This behavior is to be expected unless there is a first order phase transition at $p_0$ between the adsorbed and liquid phases. At low pressures, corresponding to low surface coverage, the adsorbed phase becomes poorer in oxygen than the gas phase. This characteristic may be seen most readily in Fig. 6. At the lowest pressure measured, the adsorbed phase contains 23% nitrogen, compared to 77% at the highest pressure. Considering the generally parallel features of the two pure gas isotherms, the specificity of the surface for nitrogen adsorption is an apparent anomaly.

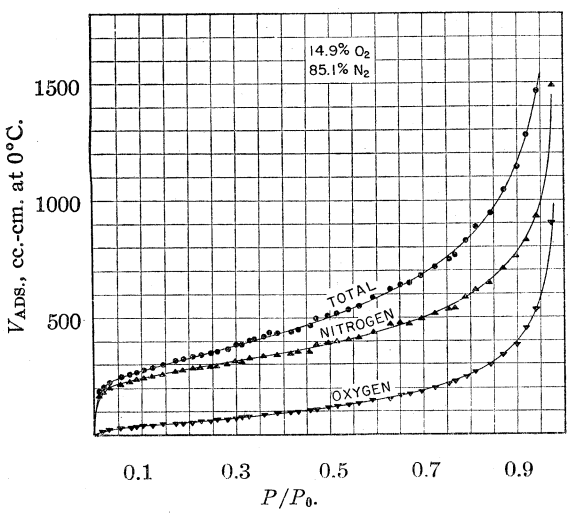



Fig. 4.—14.9% oxygen, 85.1% nitrogen isotherms. ▲, nitrogen; ▼, oxygen; ●, total gas adsorbed. The designations are the same in succeeding figures.

Another qualitative feature may be noted in the oxygen-rich mixtures, Figs. 7 and 8. In these isotherms the adsorption of nitrogen is almost independent of pressure over a considerable range of pressure.

**Comparison with Extended BET Theory. The Total Gas Isotherms.**—We shall use

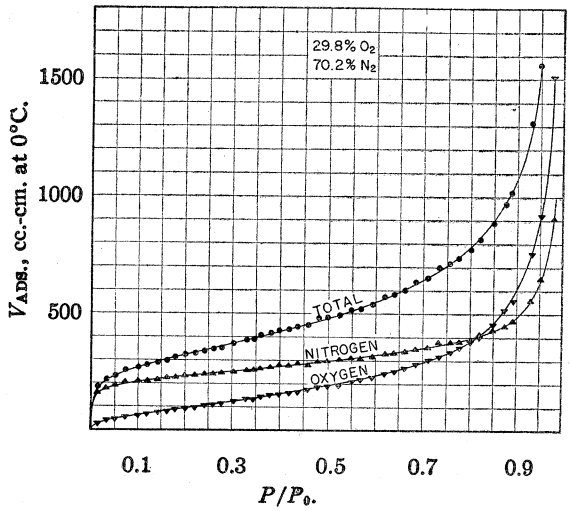



Fig. 5.—29.8% Oxygen, 70.2% nitrogen isotherm.

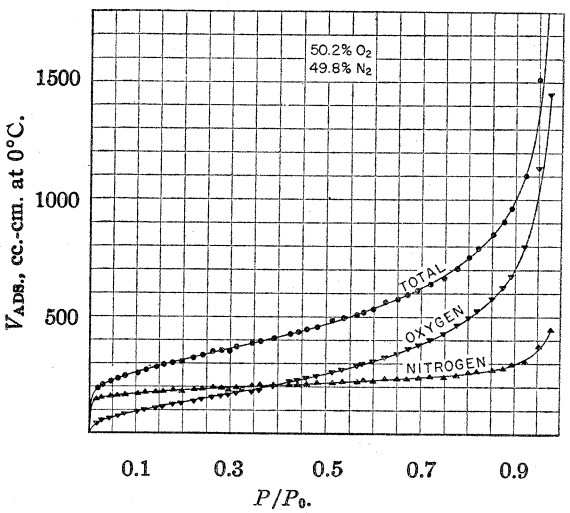



Fig. 6.—50.2% Oxygen, 49.8% nitrogen isotherm.

Hill's[4] eqn. (38), under the condition that Raoult's law is obeyed. Raoult's law, it may be noted, can be derived rigorously from statistical mechanics only on the assumption that the molecular area (or volume) is the same.[13] The error introduced by moderate differences in molecular size is small, however. We shall restate the equation in the form

$$\frac{v_1}{v_m} = \frac{cxX}{1 + cxY} \qquad (1)$$

letting

$$c = \frac{x_1c_1 + x_2c_2}{x_1 + x_2},\ x = x_1 + x_2,\ x_1 = y_1p/p_{10}$$

where

$p$ = gas pressure
$y_1$ = mole fraction of component 1 in gas phase
$p_{10}$ = vapor pressure of (pure) component 1

(13) Fowler, "Statistical Mechanics," Cambridge Univ. Press, Cambridge, England, 1936, p. 532.

$c_1$ = $c$ (after Brunauer, Emmett and Teller) for component 1, as determined from the pure gas isotherm
$v_1$ = volume of component 1 adsorbed from the mixture
$v_m$ = volume adsorbed corresponding to one monolayer

with similar definitions for component 2.

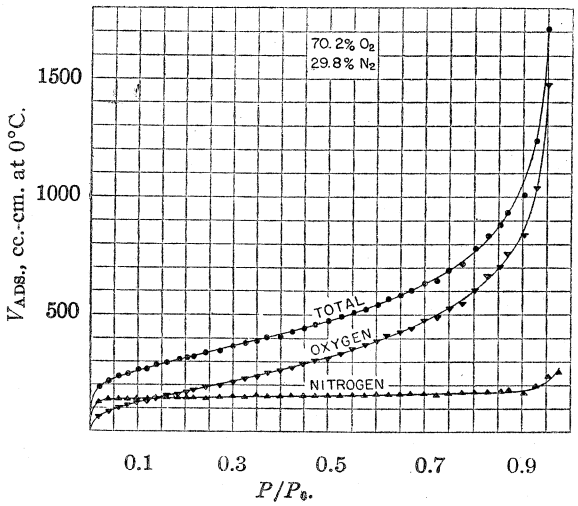



Fig. 7.—70.2% Oxygen, 29.8% nitrogen isotherm.

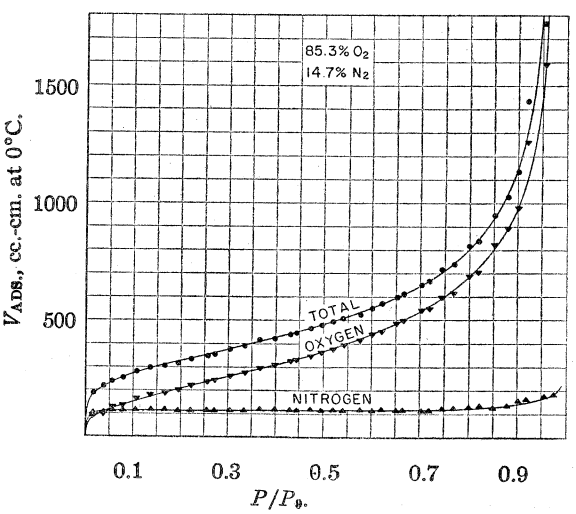



Fig. 8.—85.3% Oxygen, 14.7% nitrogen isotherm.

The two functions $X$ and $Y$ are given by Hill's eqns. (29) and (30), which we can restate as

$$X = \left[\frac{c_1x_1}{cx} + \frac{x_1}{(1 - x)}\right]\frac{1}{(1 - x)} \qquad (2)$$

$$Y = 1/(1 - x) \qquad (3)$$

Combining and simplifying

$$\frac{v_1}{v_m} = \frac{cx}{(1 - x)(1 - x + cx)}\left[\frac{c_1x_1(1 - x)}{cx} + x_1\right] \qquad (4a)$$

Likewise for component 2

$$\frac{v_2}{v_m} = \frac{cx}{(1 - x)(1 - x + cx)}\left[\frac{c_2x_2(1 - x)}{cx} + x_2\right] \qquad (4b)$$

The total gas adsorbed will then be

$$\frac{v_1 + v_2}{v_m} = \frac{cx}{(1 - x)(1 - x + cx)} \qquad (5)$$

This equation has the same form as the BET isotherm for a single gas.[5] That the terms have substantially the same significance may be seen by the following transformations. If the gas composition $y_1$ is held constant, the condensation pressure of the gas mixture will be given by

$$1/p_0 = y_1/p_{10} + y_2/p_{20} \qquad (6)$$

and

$$x = y_1 p/p_{10} + y_2 p/p_{20} = p/p_0 \qquad (7)$$

while $c$, the weighted mean of the $c$ values for the pure components, is likewise a constant over the whole pressure range.

It is apparent from Figs. 2 to 8 that the total gas isotherms for the various mixtures fit the BET eqn. (5) about as well as those for the pure gases. The BET constants, calculated from the isotherms by least squares, are given in Table II.

TABLE II

BET CONSTANTS FOR ISOTHERMS

| $y_2$, % | $v_m$, cc.-cm. | Mol. area, sq. Å. | $c$ | $c$ (from eqn. 1) |
|---|---|---|---|---|
| 0 | 312[a] | 16.2 | 143 | 143 |
| 14.9 | 273 | 18.5 | 94 | 112 |
| 29.8 | 266 | 19.0 | 92 | 95 |
| 50.2 | 261 | 19.4 | 86 | 83 |
| 70.2 | 261 | 19.4 | 90 | 77 |
| 85.3 | 267 | 18.9 | 83 | 74 |
| 100 | 288 | 17.5 | 72 | 72 |

[a] This value is somewhat uncertain due to non-linearity of the BET plot for this isotherm. $V_m$ may be as low as 288 cc.-cm.

The $p_0$'s used in calculating the constants, and in plotting Figs. 4 to 8, are the actual saturation pressures, not those calculated from Raoult's law. The difference in $c$ values by the two methods of calculation is at most 6%; the difference in molecular areas is negligible. The last column lists the $c$ values calculated from eqn. (1).

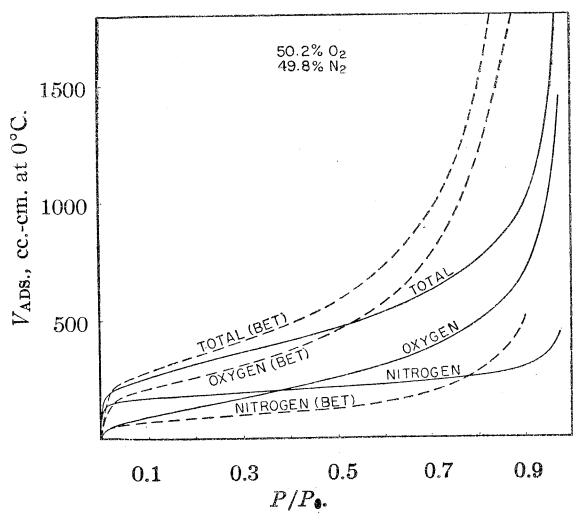



Fig. 9.—50.2% Oxygen isotherm: —, observed; - - - -, calculated from extended BET theory.

The range over which eqn. (5) holds for the mixtures is the same as that for the pure gases, namely, from $p/p_0 = 0.05$ to 0.30. The difference between the two sets of $c$ values is probably outside experimental error; it is too small, however, to cause more than minute deviations in the observed isotherms.

The $v_m$ values show strikingly the effect of molecular environment on molecular area in films of moderate thickness. We note that the observed value of the molecular area of oxygen on anatase (taking 16.2 sq. Å. for nitrogen as a reference value) is 17.5 sq. Å., compared with 13.2 sq. Å. calculated for liquid packing. This greater apparent area is common when other adsorbates are compared to nitrogen.[6,7] It has the fortunate effect, from our point of view, of bringing the two molecular areas into closer agreement. The areas for the mixtures are average areas per molecule of whatever species, it being impossible to treat the average molecular areas of nitrogen and oxygen separately. These areas turn out to be greater in every case than the molecular areas of either pure gas, and to pass through a smooth maximum between the 50.2 and 70.2% oxygen mixtures. The effect is far outside the experimental error, estimated at 0.5 to 1%. Moreover, it is independent of the correctness of the extended BET theory, since, as pointed out above, the isotherms are nearly superimposable except for a scale factor. Thus whatever point on the isotherm represents complete coverage of a monolayer, the relative values of $v_m$ in Table II will be preserved.

This effect is presumably associated with other signs of non-ideal behavior in these systems (see below).

**Component Isotherms.**—Figure 9 gives a comparison between the 50.2% oxygen isotherm (Fig. 6) and the isotherm predicted by the extended BET theory. Between $p/p_0 = 0.05$ and 0.30 the observed and calculated total gas isotherms run parallel, differing only by the scale factor discussed above. Above $p/p_0 = 0.30$ the predicted isotherm diverges increasingly in the direction of increased adsorption. This behavior exactly parallels that for the pure gas isotherms. When we compare the isotherms of the component gases in the moderate pressure region, however, we find a sharp discrepancy between theory and experiment. *The observed isotherms for the individual components, oxygen and nitrogen, differ from those calculated from the extended BET theory by more than a factor of two.* Instead of the observed highly selective adsorption of nitrogen at low pressures, the theory predicts only a small difference between the composition of the adsorbed phase below one monolayer surface coverage, and that of the bulk liquid. This discrepancy is equally apparent in all five mixture isotherms.

Returning to equations (4a) and (4b), we note that in the special case $c_1 = c_2 = c$

$$v_1/(v_1 + v_2) = x_1/(x_1 + x_2) = \frac{(y_1/p_{10})}{(y_1/p_{10} + (y_2/p_{20})} \quad (8)$$

That is, the composition of the adsorbed phase is equal to that of the bulk liquid, and is independent of $c$ and $x$. We can see from Table II that the difference between $c_1$ and $c_2$ is small, although in the right direction. In fact, the theory predicts a minimum oxygen concentration of 71% in the adsorbed phase, compared with 85% in the bulk liquid and 23% actually observed at $p/p_0 = 0.017$.

**Theoretical Discussion. The "Liquid Entropy" Model.**—Since the adsorbed phase is in equilibrium with gas at a lower pressure than the vapor pressure, we have from elementary thermodynamics

$$(\mu_A - \mu_L) = RT \ln (p/p_0) \quad (9)$$

that is, the partial molal free energy of the adsorbed phase is always less than that for the bulk liquid. This free energy difference (henceforth written $\Delta\mu_A$) can be considered as the sum of two terms

$$\Delta\mu_A = \overline{\Delta H}_A - T\overline{\Delta S}_A \quad (10)$$

In the simplest possible case of the BET theory, where $c = 1$, and $\Delta H_1 = 0$, $\overline{\Delta H}_A = 0$ over the whole isotherm and equation (10) reduces to

$$\Delta\mu_A = -T\overline{\Delta S}_A \quad (11)$$

That is, the partial molal entropy of the adsorbed phase is greater than that of the bulk liquid. In the usual type II BET isotherm $H_1 < H_L$ (these are negative quantities; the heat content of the adsorbed phase decreases with increasing heat of adsorption). $\overline{\Delta H}_A$ has its minimum value $\Delta H_1$ at zero pressure and coverage, and increases to zero at high coverage. Thus both heat and entropy contribute to adsorption in this case, but at least at high coverage, where the family of BET isotherms approach one another, the entropy term is the major contributor to the decreased free energy of the adsorbed phase, according to this theory. This entropy term may be loosely spoken of as "configurational entropy," thought of as arising from the large number of possible states for a BET adsorbed phase (see Hill's eqn. (4)), or the large amount of "disorder" in such a phase.

One of the basic assumptions of the BET theory is that a molecule may be adsorbed on another molecule with equal probability whether or not the lower or upper molecules have any nearest neighbors, *i. e.*, horizontal interactions are neglected. Thus the physical picture of the BET adsorbed phase at high coverage is of columns of molecules of various heights scattered at random, so that occasional columns of many molecules arise out of nearly bare areas. It has been pointed out, for example by Cassel,[14] that the van der Waals forces, which produce surface tension in liquids, will tend to draw these columns down and produce a smooth, ordered film. Hill's[15] calculations have shown the importance of this effect. This assumption, of the BET theory, together with the assumption of a constant $E_1$ which stands or falls with it, is its most obvious weakness.

The recent accurate heat measurements of Beebe and Kington[16] have permitted the calculation of the partial molal entropies of adsorption in a number of gas–solid systems, including the systems nitrogen–anatase and oxygen–anatase. In the systems studied the partial molal entropy of the adsorbed phase is uniformly *less* than that of the bulk liquid, approaching it closely at about $v/v_m = 1$ and above. The observed entropies have a minimum value about 4–5 e. u. less than that of the bulk liquid.

In light of these observations, a model is proposed based on the following assumptions: (1) the partial molal entropy of the adsorbed phase is constant and equal to that of the bulk liquid, for the pure gas isotherms; (2) if the sites for adsorption are arranged in order of decreasing heat of adsorption for component 1, they will also be in decreasing order for component 2; (3) for sites of a given heat of adsorption Raoult's law is obeyed. Assumption (1) is an approximation to the observed entropies of Beebe and Kington. Assumption (2) is a pure assumption in the region of low coverage, so long as the reason for the varying heat of adsorption is not known. In the region of multilayer adsorption, it must be approximately valid on purely geometrical grounds, since here the concept of "sites" gives way to that of "layers," the order of filling of which must be the same. The physical picture here, one frequently proposed before,[2] is of a smooth liquid-like film, the van der Waals field of the solid being superimposed on the liquid forces, and falling off fairly slowly with distance from the surface. Halsey, in a fundamental paper on the theory of adsorption,[17] has discussed this assumption extensively. As a consequence of assumptions (1) and (2), all sites of heat of adsorption $\Delta H_A$ fill at the pressure given by $\Delta H_A = RT \ln (p/p_0)$. If the first two assumptions are granted, the third becomes subject to experimental test. We shall refer to this set of assumptions as the "liquid entropy" (LE) model.

Calculation of a mixed adsorption isotherm then proceeds as follows. For any given set of sites, let the heats of adsorption for the two components be $\Delta H_{A1}$ and $\Delta H_{A2}$, and let the equilibrium pressures on the two pure gas isotherms be $p_1'$ and $p_2'$. Then the composition of the gas adsorbed on these sites is

$$r_1(v) = \frac{(y_1/p_1')}{(y_1/p_1') + (y_2/p_2')} \quad (12)$$

(14) Cassel, *J. Phys. Chem.*, **48**, 195 (1944).

(15) Hill, *J. Chem. Phys.*, **15**, 767 (1944).

(16) Beebe and Kington, THIS JOURNAL (in press). The author is greatly indebted to Drs. Beebe and Kington for making their data available to him before publication.

(17) Halsey, *J. Chem. Phys.*, **16**, 931(1948).

The equilibrium pressure is determined by

$$1/p = y_1/p_1' + y_2/p_2' \qquad (13)$$

The composition of the whole film at volume adsorbed $v$ and pressure $p$ is given by

$$R_1(v) = \frac{1}{v}\int_0^v r_1(v)\,dv \qquad (14)$$

$r_1(v)$ and $p(v)$ may be determined from the pure gas isotherms. These isotherms must be determined down to very low surface coverage. The integration of eqn. (14) is performed numerically.

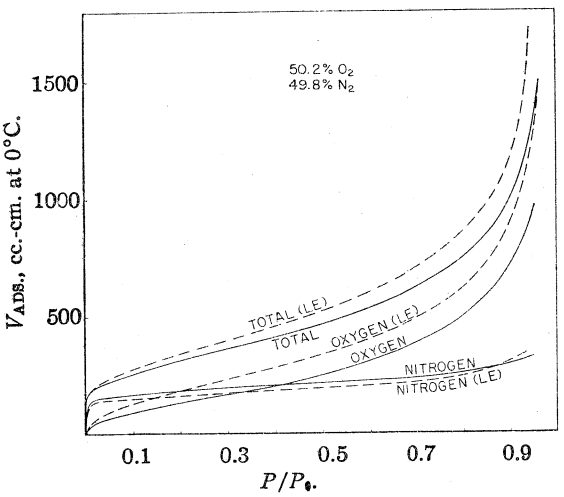



Fig. 10.—50.2% Oxygen isotherm: —, observed; - - - -, calculated from "liquid entropy" (LE) model.

The result of such a calculation for the 50.2% oxygen isotherm is shown in Fig. 10. The agreement is seen to be much better than that in Fig. 9. That this is so for the total gas isotherm reflects no credit on our model since the functions $p'(v)$ and $p_2'(v)$ are the observed isotherms (Figs. 2 and 3), while the pure gas isotherms used in eqns. (4) and (5) are the BET isotherms, which fit the experimental data only between $p/p_0 = 0.05$ and 0.30. For the component isotherms a real improvement is apparent. The composition of the adsorbed phase at $p/p_0 = 0.017$ is now 29% oxygen, compared to 71% on the BET model, and 23% actually observed. The discrepancy between calculated and observed isotherm is greater for oxygen than for nitrogen, the scale factor of the total gas isotherm tending to increase the discrepancy in the oxygen case, and reduce it in the nitrogen case.

Semi-quantitative agreement is likewise obtained with the isotherms for the other four gas mixtures.

In testing assumption (3) of our model, given the other two, we again encounter the scale factor of the total gas isotherm, as a positive deviation from Raoult's law, *i. e.*, greater pressure corresponding to a given surface coverage. The assumption of "regular solution" behavior, and the introduction of the scale factor as a measure of departure from ideality, would undoubtedly improve the calculations somewhat, bringing the total gas isotherms closely into line with predictions.

The use of the measured entropies of Beebe and Kington, instead of assumption (1), is also possible. The calculations become tedious, and assumption (3) can no longer hold at more than one temperature, or even at one temperature except by fortuitous cancellation of effects. Rough approximate calculations show improved agreement; more accurate entropy data, especially at low coverage, would probably be necessary for a real test of this method.

We may conclude that in this system, and probably in others where small deviations from Raoult's law are to be expected, the "liquid entropy" model gives semi-quantitative agreement with experiment. The data required for this model are simply the pure gas isotherms, over the whole range from low coverage to many-layer coverage. Determination of the total gas isotherms at constant gas composition will improve the agreement by allowing for "regular solution" behavior. Measurement of heats of adsorption, and use of observed rather than liquid entropies, will give further improvements. Since determination of the two pure gas isotherms is much less difficult and time-consuming than measurement of a series of gas mixture isotherms, the "liquid entropy" model will be a practical tool for predicting mixed adsorption behavior. The more exact methods, requiring data more difficult to determine, probably will not.

**Acknowledgments.**—The author is indebted to the National Research Council for the grant of a fellowship to pursue these studies, and to Harvard University for the generous provision of facilities and equipment. He is grateful to Professor George B. Kistiakowsky for his continued support and encouragement, and to Dr. Kistiakowsky, Professor Ralph A. Beebe, Dr. Henry A. Kierstead and Dr. George Halsey for a number of illuminating discussions, at various times and places.

## Summary

Adsorption isotherms at constant gas composition have been determined at 78.2°K. for five nitrogen–oxygen mixtures on Harkins' anatase. Isotherms for the two pure gases have also been determined. The isotherms show selective adsorption of nitrogen by this surface at low coverage.

Comparison with the extended BET theory shows qualitative disagreement, and provides evidence against at least one of the assumptions of the BET theory.

Use of a "liquid entropy" model gives semi-quantitative agreement with experiment.

This model allows the prediction of mixed adsorption behavior from the pure gas isotherms, for pairs of gases for which Raoult's law holds approximately.

CAMBRIDGE, MASS. RECEIVED MARCH 12, 1948

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# The Electric Moments of Some Aromatic Fluorine Compounds[1]

BY HENRY FREISER,[2] MARCUS E. HOBBS AND PAUL M. GROSS

The unusual and in some cases unique properties of organic fluorine compounds make an interpretation of these properties in terms of molecular structure of importance both because of the end use to which the compounds may be put and because of the insight that such an interpretation may lend to the relations of structure and properties. The present paper gives the results of determinations of the polar properties of a series of organic fluorine compounds in terms of the dipole moments and polarizabilities of the molecules and relates these values to the molecular structures involved.

TABLE IA

SUMMARY OF PHYSICAL PROPERTIES OF COMPOUNDS

| Compound | B. p. (cor.) °C. | Mm. | $n^{30}D$ | $d^{30}_4$ | | Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| Fluorobenzene | 84.8 | | 1.4610 | 1.0066 | *a* | | |
| Chlorobenzene | 132.1 | | 1.5197 | 1.1013 | *a* | | |
| Benzotrifluoride | 102.7 | | 1.3918 | 1.1719 | *c* | | |
| Benzotrichloride | 95.4 | 14 | 1.5540 | 1.3769 | *a* | | |
| *o*-Fluorochlorobenzene | 137.6 | | 1.4968 | 1.2233 | *a* | | |
| *m*-Fluorobenzotrifluoride | 100.9 | | 1.3970 | 1.2769 | *b* | | |
| *m*-Chlorobenzotrifluoride | 137.2 | | 1.4432 | 1.3345 | *b* | | |
| *m*-Fluorobenzotrichloride | 119.4 | 45 | 1.5310 | 1.4408 | | | |
| 1,3-bis-(Trifluoromethyl)-benzene | 116.1 | | 1.3759 | 1.3721 | | 53.24 F | 53.0 |
| *p*-Chlorobenzotrifluoride | 138.9 | | 1.4430 | 1.3278 | *b* | | |
| *p*-Fluorobenzotrichloride | 93.7 | 14 | 1.5311 | 1.4385 | | | |
| *p*-Chlorobenzotrichloride | 104.5 | 4 | 1.5690 | 1.4947 | | | |
| 2-Chloro-1,4-bis-(trifluoromethyl)-benzene | 148.6 | | 1.4090 | 1.5043 | | 14.27 Cl | 14.31 |
| 5-Chloro-1,3-bis-(trifluoromethyl)-benzene | 134.9 | | 1.4028 | 1.4722 | | 14.27 Cl | 14.33 |
| 4,5-Dichloro-1,3-bis-(trifluoromethyl)-benzene | 174.2 | | 1.4372 | 1.5958 | | | |
| 4-Fluoro-1,3-bis-(trifluoromethyl)-benzene | 159 | 11 | 1.5661 | 1.6464 | | 64.30 Cl | 64.48 |
| 1,3-bis-(Trichloromethyl)-benzene | F. p. 38.8–38.0° | | .... | .... | | 68.1 Cl | 68.0 |

[a] Best grade obtained from Eastman Kodak Company. [b] No analysis data available, but physical properties check with those described by H. S. Booth, H. M. Elsey and P. E. Burchfield, THIS JOURNAL, **57**, 2066 (1935). [c] Obtained from Hooker Electrochemical Company and treated with boiling sodium bicarbonate solution until no tests for $Cl^-$ were obtained in the solution. This was followed by fractional distillation.

## Materials and Experimental Details

Most of the compounds used in these measurements were made in the Duke University Laboratories in connection with the research being carried on by Messrs. P. Tarrant, L. Rapoport, R. Kittila and G. West under the direction of Drs. L. A. Bigelow and C. K. Bradsher. Their syntheses will be described in other publications. The analyses reported in this section were made by Dr. Rose Davis.

Both the solvents and compounds to be measured were carefully purified. Liquids were purified by careful fractionation while solids were fractionally crystallized. In the absence of other data, constancy of boiling point or freezing point was used as a criterion of purity.

**Benzene.**—Jones and Laughlin best grade of benzene (did not discolor concentrated sulfuric acid) was dried over anhydrous sodium sulfate, then refluxed over sodium wire for six hours and finally distilled from sodium. Fractions boiling over 0.02° range were used in the measurements. After the benzene had been used for a measurement it was recovered by repeated fractionation from the higher boiling solute and finally redistilled from sodium until

TABLE IB[a]

| Compound | 30.0° C. $V$, cc. | $R_D$ obs., cc. | $R_D$ calcd., cc. | $\Delta R_{D_{o-c}}$ |
|---|---|---|---|---|
| Fluorobenzene | 95.37 | 26.17 | 26.09 | +0.08 |
| Chlorobenzene | 112.35 | 31.03 | 31.06 | − .03 |
| Benzotrifluoride | 124.58 | 29.65 | 30.50 | − .85 |
| Benzotrichloride | 141.99 | 45.49 | 45.41 | + .09 |
| *o*-Fluorochlorobenzene | 106.68 | 31.20 | 30.96 | + .24 |
| *m*-Fluorobenzotrifluoride | 128.44 | 30.93 | 30.40 | + .53 |
| *m*-Chlorobenzotrifluoride | 135.26 | 35.87 | 35.37 | + .50 |
| *m*-Fluorobenzotrichloride | 148.18 | 45.85 | 45.31 | + .54 |
| 1,3-bis-(Trifluoromethyl)-benzene | 155.97 | 35.77 | 34.81 | + .96 |
| 1,3-bis-(Trichloromethyl)-benzene | .... | ... | 64.63 | .... |
| *p*-Chlorobenzotrifluoride | 135.94 | 36.04 | 35.37 | + .67 |
| *p*-Fluorobenzotrichloride | 148.41 | 45.92 | 45.31 | + .61 |
| *p*-Chlorobenzotrichloride | 153.88 | 50.41 | 50.28 | + .13 |
| 2-Chloro-1,4-bis-(trifluoromethyl)-benzene | 165.19 | 40.84 | 39.68 | +1.16 |
| 5-Chloro-1,3-bis-(trifluoromethyl)-benzene | 168.80 | 41.17 | 39.68 | +1.49 |
| 4,5-Dichloro-1,3-bis-(trifluoromethyl)-benzene | 177.34 | 46.48 | 44.55 | +1.93 |
| 4-Fluoro-1,3-bis-(trichloromethyl)-benzene | 210.04 | 65.60 | 64.53 | +1.07 |

[a] For this table $R_D = \frac{n_D^2 - 1}{n_D^2 + 2} \cdot \frac{M}{d}$. Values of refractivities used were $Benzene_D$ 26.19, $H_D$ 1.100, $F_D$ 0.997, $Cl_D$ 5.967 and $C_D$ 2.418. Values were taken from Fuchs and Wolf, "Dielektrische Polarisation," Akademische Verlagsgesellschaft, Leipzig, 1935, p. 258. $V$ is the molar volume.

(1) Presented at the Fluorine Symposium at the American Chemical Society Meeting, New York, N. Y., September 17, 1947.

(2) (a) Present address, University of Pittsburgh, Pittsburgh, Pennsylvania. (b) Part of a thesis of Henry Freiser submitted in partial fulfillment of the requirements of the Ph.D. degree in Chemistry at Duke University, June, 1944.

its b. p. was constant. This recovered benzene was also used for some of the measurements: b. p. 80.10–80.12° (cor.); $d^{30}_4$ 0.868143 (av.); $n^{30}D$ 1.49483.

**Heptane.**—"Technical" *n*-Heptane from the Phillips Petroleum Company was described by them as "possibly containing up to 4% branched hydrocarbons. The sulfur content is about 0.004% and no olefins are present." The heptane was purified by shaking it with successive portions of concentrated sulfuric acid until the acid remained colorless after four hours of shaking. The product was then washed with dilute sodium hydroxide and finally with water. It was dried over calcium chloride, refluxed for six hours over sodium wire from which the heptane was finally distilled. Fractions boiling over a 0.02° range were used. The heptane was recovered after each measurement in the same manner employed in benzene recovery and was used again in some of the measurements: b. p. 98.52–98.54° (cor.), $d^{30}_4$ 0.677431 (av.).

**1,3-bis-(Trichloromethyl)-benzene.**—Crystals already partly purified by Mr. G. West were further recrystallized from carbon tetrachloride and a cooling curve obtained: f. p. 38.8–39.0°.

*Anal.* Calcd.: Cl, 68.1. Found: Cl, 68.0.

All the other compounds used were liquids under ordinary conditions and were purified in the following manner. They were dried over drierite and then fractionally distilled through a nichrome wire-wound spiral column. A summary of their physical properties is given in Tables IA and IB. Where the analysis data are available, they are included.

The procedure has been described previously.[3] The dielectric constant measurements were made with an apparatus of the heterodyne beat type which has been described recently.[4]

## Results and Discussion

The experimental results of the electric moment determination are summarized in Table II. In this table $\mu_D$ is the value of the moment obtained by means of the usual Debye expression and $\mu_0$ is obtained from the Onsager equation[5] for a polar solute in a dilute solution of a non-polar solvent. The latter equation is

$$\lim \frac{\Delta\epsilon}{f_2} = \frac{M_2 d_1}{M_1 d_2}\frac{3\,\epsilon_1(n_2^2-\epsilon_1)}{(2\,\epsilon_1+n_2^2)} + \frac{4\pi N_A d_1}{3kTM_1}\left[\frac{\epsilon_1(n_2^2+2)\,\mu_0}{(2\,\epsilon_1+n_2^2)}\right]^2 \quad (1)$$

In this expression the subscripts 1 and 2 refer to solvent and solute, respectively. $\Delta\epsilon$ is the increment in the dielectric constant of the solution over that of the solvent, $f_2$ the mole fraction of the solute, $d$ the density, $n$ the refractive index which was taken for the sodium D lines, $M$ the molecular weight and the other symbols have the usual meaning. Since, in the low concentrations employed, the value of $\Delta\epsilon/f_2$ was constant within experimental error, the average value was employed in the calculations. $\mu_M$ was calculated using the empirical extrapolation equation of Müller[6] by insertion of the value $\mu_D$ calculated from the Debye dilute solution equation as the value of $\mu_{soln.}$

It can be seen from Table II that agreement between the dipole moment values calculated by the different methods is rather close in most cases, although the Müller value is always somewhat higher than $\mu_D$ as would be necessary because of the form of the Müller equation.[6]

TABLE II

| Compound | Solvent | Moments (× $10^{18}$) $\mu_D$ | $\mu_0$ | $\mu_M$ |
|---|---|---|---|---|
| Fluorobenzene | Benz. | 1.47 | 1.49 | 1.57 |
| Chlorobenzene | Benz. | 1.58 | 1.57 | 1.68 |
| | Hep. | 1.58 | 1.54 | 1.63 |
| Benzotrifluoride | Benz. | 2.56 | 2.62 | 2.73 |
| | Hep. | 2.63 | 2.60 | 2.72 |
| Benzotrichloride | Benz. | 2.04 | 2.01 | 2.17 |
| | Hep. | 2.14 | 2.06 | 2.21 |
| *o*-Fluorochlorobenzene | Benz. | 2.38 | 2.38 | 2.54 |
| | Hep. | 2.40 | 2.34 | 2.48 |
| *m*-Fluorobenzotrifluoride | Benz. | 2.19 | 2.25 | 2.33 |
| | Hep. | 2.24 | 2.23 | 2.32 |
| *m*-Chlorobenzotrifluoride | Benz. | 2.22 | 2.26 | 2.37 |
| *m*-Fluorobenzotrichloride | Benz. | 1.78 | 1.77 | 1.90 |
| | Hep. | 1.84 | 1.78 | 1.90 |
| 1,3-bis-(Trifluoromethyl)-benzene | Benz. | 2.43 | 2.51 | 2.59 |
| 1,3-bis-(Trichloromethyl)-benzene | Benz. | 1.99 | 1.90 | 2.12 |
| *p*-Chlorobenzotrifluoride | Benz. | 1.15 | 1.17 | 1.23 |
| | Hep. | 1.22 | 1.20 | 1.26 |
| *p*-Fluorobenzotrichloride | Benz. | 0.68 | 0.68 | 0.72 |
| *p*-Chlorobenzotrichloride | Benz. | 0.78 | 0.76 | 0.83 |
| 2-Chloro-1,4-bis-(trifluoromethyl)-benzene | Benz. | 1.14 | 1.17 | 1.22 |
| 5-Chloro-1,3-bis-(trifluoromethyl)-benzene | Benz. | 1.29 | 1.33 | 1.38 |
| 4,5-Dichloro-1,3-bis-(trifluoromethyl)-benzene | Benz. | 1.51 | 1.54 | 1.61 |
| 4-Fluoro-1,3-bis-(trichloromethyl)-benzene | Benz. | 1.91 | 1.88 | 2.04 |

A comparison of the values obtained in this work with those available in the literature is given below. In general the agreement is satisfactory.

| Substance | Present work | Others | |
|---|---|---|---|
| $C_6H_5Cl$ | 1.58 | 1.56[a,b] | 1.57[c] |
| $C_6H_5F$ | 1.47 | 1.45[a,d] | 1.46[e] |
| $C_6H_5Cl_3$ | 2.04 | 2.07[f] | 2.15[g] |
| *o*-$C_6H_4ClF$ | 2.38 | 2.33[a] | |

[a] Bergmann, Engel and Sandor, *Z. physik. Chem.*, **B10**, 106 (1930). [b] L. Tiganik, *ibid.*, **B13**, 425 (1931). [c] A. A. Maryott, Ph.D. Thesis, Duke University, 1940. [d] A. Nukada, *Nia Kemio*, **5**, 41 (1932). [e] Brown, de-Bruyne and Gross, THIS JOURNAL, **56**, 1291 (1934). [f] L. E. Sutton, *Proc. Roy. Soc.* (*London*), **133**, 668 (1931). [g] A. Parts, *Z. physik. Chem.*, **B13**, 312 (1931).

The results of the Onsager calculations were in no better agreement with the gas values, where these were known, than were the Debye values. The Müller equation was somewhat better in this regard. Specifically, a comparison[7] may be made for the chlorobenzene gas value of 1.70*D* and the fluorobenzene gas value of 1.57*D*. While the Onsager moments deviated from the gas moments by about 0.10 debye unit, the Müller values agreed with those obtained from gas measure-

(3) Maryott, Hobbs and Gross, THIS JOURNAL, **62**, 2320 (1940).
(4) Weith, Hobbs and Gross, *ibid.*, **70**, 805 (1948).
(5) L. Onsager, THIS JOURNAL, **58**, 1486 (1936).
(6) H. Müller, *Physik. Z.*, **34**, 689 (1933).
(7) MacAlpine and Smyth, *J. Chem. Phys.*, **3**, 55 (1935).

ments within experimental error. For the Müller equation good agreement is usually obtained in the cases of compounds measured in both solvents. This would indicate the internal consistency of Müller's equation but not its validity and it must be remembered that Müller's equation is empirical. Because of its empirical nature and consequent limitations it should be used only as an expedient for calculating moments when gas values are not available.

In many structural problems, the difference between the observed dipole moment of a molecule and the moment calculated on the basis of vector additivity of the group moments is of considerable interest. For the compounds measured in this study, these differences are fairly independent of the method of calculation used, provided that the same method is used for each molecule considered. Table III lists the results of such a computation.

TABLE III

DEVIATIONS FROM VECTOR ADDITION

| Compound | Δ Debye, *D* | Δ Onsager, *D* | Δ Müller, *D* |
|---|---|---|---|
| *o*-Fluorochlorobenzene | −0.07 | −0.09 | −0.29 |
| *m*-Fluorobenzotrifluoride | − .03 | − .03 | − .04 |
| *m*-Chlorobenzotrifluoride | − .02 | − .01 | − .01 |
| *m*-Fluorobenzotrichloride | − .04 | − .05 | − .06 |
| 1,3-bis-(Trifluoromethyl)-benzene | − .13 | − .10 | − .14 |
| 1,3-bis-(Trichloromethyl)-benzene | − .05 | − .17 | − .11 |
| *p*-Chlorobenzotrifluoride | .17 | .14 | .18 |
| *p*-Fluorobenzotrichloride | .11 | .13 | .10 |
| *p*-Chlorobenzotrichloride | .32 | .24 | .25 |
| 2-Chloro-1,4-bis-(trifluoromethyl)-benzene | − .44 | − .39 | − .44 |
| 5-Chloro-1,3-bis-(trifluoromethyl)-benzene | .31 | .28 | .29 |
| 4,5-Dichloro-1,3-bis-(trifluoromethyl)-benzene | .13 | .16 | .15 |
| 4-Fluoro-1,3-bis-(trichloromethyl)-benzene | .09 | .05 | .09 |

The dipole moment of each molecule listed in Table III was calculated by vector addition of the bond moments using as component moments values obtained in the following manner: (1) the Debye value obtained in benzene, since for better comparison, measurements in the same solvent were chosen, (2) the average Onsager value and (3) the average value obtained by calculation using Müller's equation. In all cases, the values of the moments of chlorobenzene, fluorobenzene, benzotrifluoride and benzotrichloride were taken as being those of the C–Cl, C–F, C–$CF_3$, C–$CCl_3$ bonds, respectively. The values of the moments obtained in this manner were compared to the actual moments and the deviations listed in Table III. A positive deviation signifies that the measured moment is larger than that calculated by vector addition of the component bond moments. As shown in the table good agreement between the deviations is obtained in most of the cases. The lack of agreement for *o*-fluorochlorobenzene where the value of the deviation calculated by Müller's method is quite different from the other two is the only case where a serious discrepancy is noted. The reason for this discrepancy is not understood.

A general consideration of the origins within the solute molecule of such deviations as shown in Table III have been discussed elsewhere.[8] A cause for deviation extraneous to the solute molecule itself may arise from solvent effects. The theoretical aspects of this effect have been discussed by Frank and Sutton and others.[9] To illustrate the nature of the effect as discussed by Frank and Sutton consider a molecule in which the electric moments completely compensate; *i. e.*, *p*-dichlorobenzene. On the average, in the absence of a field, the solvent molecules arrange themselves in the vicinity of the polar bonds in such a way as to have the moments induced in them by the polar bonds completely cancel one another. In case the moments induced in the solvent molecules by the polar bonds lie in the direction of an imposed field these molecules will be bound more tightly to the solute molecule whereas the solvent molecules with their induced moment directions opposing the field are bound to the solute molecule less tightly than if the field were absent. The net effect of the above is that the solvated solute molecule shows an average electric moment in the direction of the field, *viz.*, an increased polarizability. Such an increased polarizability will, in the usual method of calculation of electric moments from solution measurements, lead to a calculated real dipole moment of the solute molecule. For future reference we will refer to this type of effect as a deviation originating from solvent effects.

Examination of Table III shows that for all of the disubstituted cases the para compounds exhibit a positive deviation and all ortho and meta substituted compounds show negative deviations from vector additivity. The explanation of this difference in sign may well lie in differences in the origins of the observed deviations. It is suggested that the para compounds show positive deviations because the predominating deviation effect is one originating in the solvent effects discussed above. The negative deviations for the ortho and meta cases may be most simply attributed to a preponderance of deviation effects arising from the inductive and space induction effects. However, it may be noted that both the space induction and inductive effects through the ring are expected to be rather small for the meta cases. The distance of separation of the groups minimizes the space effect and the inductive effects through the ring would probably be small if the

(8) Hobbs and Weith, THIS JOURNAL, **65**, 925 (1943).

(9) (a) Frank and Sutton, *Trans. Faraday Soc.*, **33**, 1307 (1937); (b) S. H. Bauer, *J. Chem. Phys.*, **4**, 458 (1936); (c) H. O. Jenkins, *J. Chem. Soc.*, 910 (1936).

effect is considered to be distributed equally on all carbon atoms of the ring. In the disubstituted cases the electric moments in general corroborate the structure of the isomers considered.

The cause for the observed deviations in the tri- and tetra-substituted compounds is difficult if not impossible to locate because of the complexity and undetermined magnitude of the factors which might cause such deviations. A rather simple consideration of the other reasonable isomers that might have been obtained in the method of preparation leads one to conclude that, in general, the observed moments, considered in light of the deviations from additivity are such as to corroborate the identity of the molecule involved.

In considering the influence of the polar substituents on physical characteristics one of the simplest evidences of this influence is found in Table IB where the values of the molar refraction, $R_D$, for the sodium D lines are shown. The calculated values are obtained by summing the atomic and bond components of the molecule and this value is compared with the observed value as calculated from the Lorenz–Lorentz expression, *viz.*

$$R_D = \frac{n^2_D - 1}{n^2_D + 2}\frac{M}{d}$$

The difference between $R_D$(obs.) and $R_D$(calcd.) might originate in an effect of the substituents on either the electrical volume fraction term, $(n^2 - 1)/(n^2 + 2)$, or the molar volume term, $M/d$ or on both terms. Thus the electronic transitions responsible for the refractive index may either increase or decrease their strengths, and/or new transitions may become accessible when substituents are attached to the ring. The effect of any of these potential changes on the value of $R_D$ would probably appear most prominently in the $(n^2 - 1)/(n^2 + 2)$ term. If, because of the repulsive or attractive fields of the substituents, the molar volume changes disproportionately to the $(n^2 - 1)/(n^2 + 2)$ term the value of $R_D$ will be affected in direct proportion to the lack of compensatory changes in these terms.

The only data presented which allow a simple evaluation of the relative effects of the above two terms are (1) *m*-chlorobenzotrifluoride and *p*-chlorobenzotrifluoride and (2) *m*-fluorobenzotrichloride and *p*-fluorobenzotrichloride. If we denote $(n^2 - 1)/(n^2 + 2)$ as $B$, then the following approximate expression may be derived from the equation for $R$ for the meta and para cases

$$(R_p - R_m) = B_pV_p - B_mV_m$$
$$\simeq B_p(V_p - V_m) + V_p(B_p - B_m) \qquad (2)$$

With division by $R_p$ we obtain

$$\frac{\Delta R_{p-m}}{R_p} \simeq \frac{\Delta V_{p-m}}{V_p} + \frac{\Delta B_{m-m}}{B_p} \qquad (3)$$

The values of $R$, $V$ and $B$ are given for the above compounds in Table IV.

TABLE IV

| | $R$, cc. | $V$, cc. | $B$ |
|---|---|---|---|
| *m*-Chlorobenzotrifluoride | 35.87 | 135.26 | 0.26521 |
| *p*-Chlorobenzotrifluoride | 36.04 | 135.94 | .26520 |
| *m*-Fluorobenzotrichloride | 45.85 | 148.18 | .30939 |
| *p*-Fluorobenzotrichloride | 45.92 | 148.41 | .30944 |

The values for the terms of eq. (3) taken from the experimental data are shown directly below.

| | $\frac{\Delta R_{p-m}}{R_p}$ | $\frac{\Delta B_{p-m}}{B_p}$ | $\frac{\Delta V_{p-m}}{V_p}$ |
|---|---|---|---|
| (*p*-*m*)-Chlorobenzotrifluoride | $4.7 \times 10^{-3}$ | $-0.6 \times 10^{-3}$ | $+5.0 \times 10^{-3}$ |
| (*p*-*m*)-Fluorobenzotrichloride | $1.5 \times 10^{-3}$ | $+0.2 \times 10^{-3}$ | $+1.6 \times 10^{-3}$ |

The discrepancy between $\Delta R_{p-m}/R_p$ and the sum of the other two terms is attributable to lack of precision in the value from which the various terms were obtained and to the approximations used in eq. (3). It is evident from these results that the major fraction of the difference in the $R$ values for the para and meta compounds resides in the molar volume term and as would be expected on the basis of the interdependence of $n$ and $V$ the two terms $\Delta V/V$ and $\Delta B/B$ may be of opposite sign. In general it may be concluded from these results that the repulsive fields of the electronegative atoms cause a volume change that is not compensated for by a corresponding change in $n$. In view of these results it may be suggested that the probable cause of the other large + $\Delta R_D$ values in Table IB lies in volume changes rather than changes in $B$.

Table IB contains only one serious negative $\Delta R_D$. This value of $-0.85$ for benzotrifluoride probably shows how significantly the large electronegativity of the $-CF_3$ group can influence the polarizability of the benzene ring. Some evidence for this may be obtained from the data shown for toluene and benzotrifluoride in Table V.

TABLE V

| Substance | 30°C. $R_D$ | 30°C. $V$ | $\frac{\Delta V(100)}{V}$ | $\frac{\Delta B(100)}{B}$ |
|---|---|---|---|---|
| Toluene | 31.06 | 107.58 | 0 | 0 |
| Benzotrifluoride | 29.65 | 124.58 | +15.8 | −17.6 |
| *m*-Xylene | 35.90 | 124.03 | 0 | 0 |
| 1,3-bis-(Trifluoromethyl)-benzene | 35.77 | 155.97 | +25.8 | −20.8 |

The $\Delta V/V$ and $\Delta B/B$ column data are obtained by using toluene as a reference for the first two cases and *m*-xylene for the latter two. It is evident from the data on toluene and benzotrifluoride that the negative value of $\Delta R_D$ for benzotrifluoride probably arises from the overcompensation of the positive volume change by a negative change in the $B$ term. This may be taken as indicative of a tightening of the ring electron

system in the benzotrifluoride molecule. This situation is apparently reversed when the cases of *m*-xylene and the 1,3-bis-(trifluoro)-compounds are considered, *viz.*, the fractional positive volume change exceeds the fractional negative change in *B*. It will be noted in Table IB that the values of $\Delta R_D$ are roughly constant for the *m*-fluoro and *m*-chloro compounds and the same applies to the *p*-compounds except for *p*-chlorobenzotrichloride. The latter compound has a rather low $\Delta R_D$ in view of the data on the other compounds of similar nature. It is notable that in all cases of the disubstituted compounds in which large + $\Delta R_D$ deviations occur one of the substituents is fluorine. This atom because of its small size, large electronegativity and low polarizability would give rise to a large coulombic repulsion for other bonded electronegative atoms and would have low compensatory attraction arising from dispersion forces. The larger chlorine atom has a lower electronegativity and a higher polarizability and as such might give rise to a smaller *relative* volume increment than would the fluorine atom.

The bonded fluorine atom should contribute to the London[10] dispersion forces about the same as bonded hydrogen atoms and yet in spite of the large dipole moment of benzotrifluoride and 1,3-bis-(trifluoromethyl)-benzene the boiling point of the former is roughly 8° lower than that of toluene and of the latter roughly 23° lower than that of *m*-xylene. The first order factor in determining boiling points in normal liquids is the force arising from the interaction of instantaneous atomic dipoles with dipoles induced in neighboring polarizable systems. Since in first approximation this force varies as $1/r^6$, it is evident that a very small change in *r* will have a considerable influence on the interaction energy, and in cases of systems of essentially the same distribution and magnitude of polarizability within a molecule it may be generally expected that the substance with largest intermolecular distances will have the lower boiling point. In the cases of *m*-xylene and 1,3-bis-(trifluoromethyl)-benzene the ratio of the average intermolecular separations at 30° is about 1/1.15 and for toluene and benzotrifluoride at 30° the ratio is about 1/1.10. The molar volume at the respective boiling points of the compounds would be more instructive in the above connection than the data at 30°; however, to the knowledge of the authors, such data are not available for the fluorine compounds. The fact that the substances listed with largest intermolecular distances are the lowest boiling of the pairs considered can hardly be regarded as coincidence although it is recognized that the entire line of reasoning relating to the boiling point and intermolecular distance has serious quantitative limitations.

(10) F. London, *Trans. Faraday Soc.*, **33**, 8 (1937).

## Summary

The electric moments of a number of organic fluorine compounds have been measured and discussed in relation to the structure of the molecules. The effect of fluorine on some physical characteristics of molecules is briefly considered.

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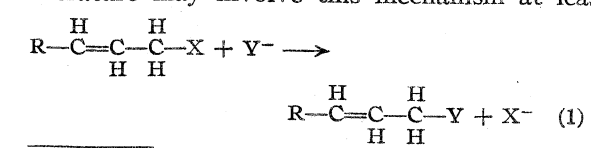
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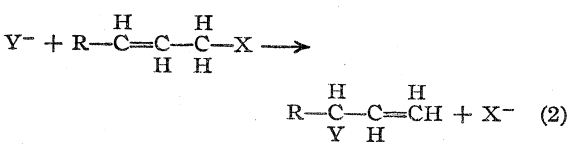
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

# Allylic Rearrangements. XXIV. Abnormal Bimolecular Substitution. The Condensation of Butenyl and Pentenyl Chlorides with Sodium Malonic Ester

BY RICHARD E. KEPNER,[1a] S. WINSTEIN AND WILLIAM G. YOUNG

Recent work[1b,c] on nucleophilic displacement reactions of allylic systems has indicated that bimolecular ($S_N2$) reactions produce unrearranged products (eqn. 1). An abnormal bimolecular ($S_N2'$) mechanism (eqn. 2) has been proposed[2] and, while some of many conversions in the literature may involve this mechanism at least partly, no completely satisfactory evidence for its operation has so far appeared.





Thus many reported cases of reactions of allylic halides with nucleophilic reagents such as sodium malonic ester,[3] sodium acetoacetic ester,[4] sodium allyl benzene,[5] potassium phthalimide,[6] sodium

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(1) (b) Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942); (c) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

(2) (a) Winstein, Dissertation, California Institute of Technology, 1938; (b) Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938); (c) Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(3) (a) Staudinger, Kries and Schilt, *Helv. Chim. Acta*, **5**, 743 (1922); (b) Braun and Schirmacher, *Ber.*, **56**, 538 (1923); (c) Doran and Shonle, THIS JOURNAL, **60**, 2880 (1938).

(4) (a) Fischer and Lowenberg, *Ann.*, **475**, 183 (1929); (b) Ruzicka and Firmenich, *Helv. Chim. Acta*, **22**, 392 (1939).

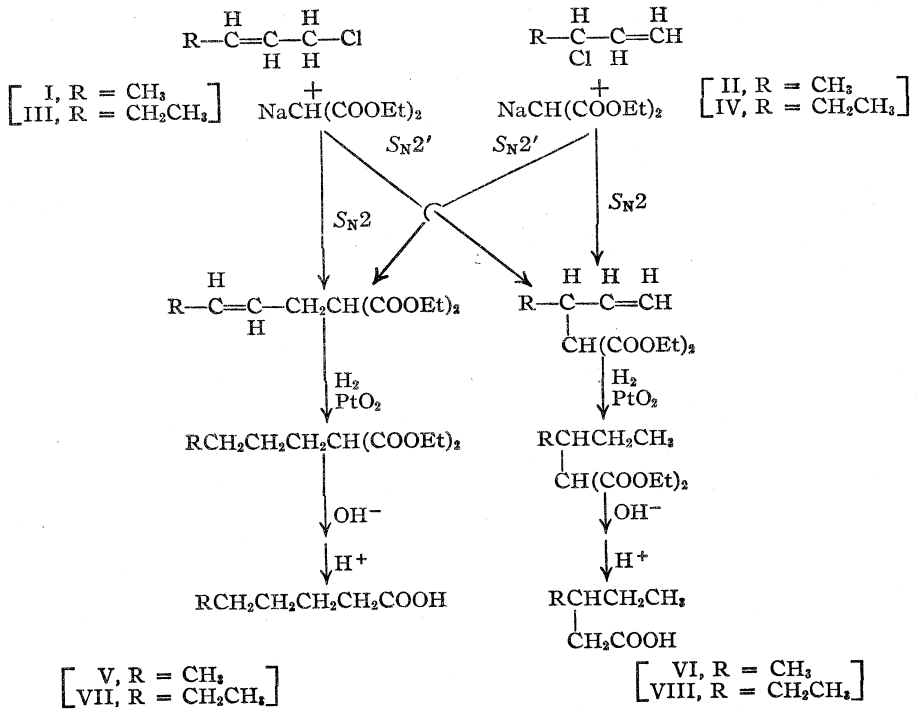
(5) Cope and Levy, THIS JOURNAL, **66**, 1684 (1944).

(6) Meisenheimer and Link, *Ann.*, **479**, 211 (1930).

phenoxide[7] or the sodium enolates of ethyl isopropylidenemalonate and ethyl (1-methyl-propylidene)-cyanoacetate[8] afford no evidence for the operation of the $S_N2'$ mechanism because of either the lack of kinetic evidence, the use of impure allylic halides, the probability of allylic rearrangement during the reaction, or extreme difficulty in detecting the presence of small amounts of abnormal product in certain cases.

The reactions of allylidene chlorides[9] seemingly offered an example of the mechanism at first sight, but later work[10] has indicated that these reactions can best be explained by other means. Carroll[11] reported the formation of $CH_3COCH_2$-$CH_2CH{=}CHC_6H_5$ in the treatment of $\alpha$-phenylallyl alcohol with acetoacetic ester, and Wilson[12] has suggested that this rearranged product may result from the $S_N2'$ mechanism. However, Kimel and Cope[13] found that the observed product was formed by successive ester interchange and cyclic rearrangement of the unsaturated ester.

Bergmann[2c] claims that the abnormal bimolecular mechanism operates in the reaction of optically active $\alpha,\gamma$-dimethylallyl chloride with sodium malonic ester or sodium diphenylmethide, in this way accounting for the complete loss of optical activity. The same product results from either a normal or abnormal bimolecular attack on $\alpha,\gamma$-dimethylallyl chloride, and thus it was impossible for Bergmann to prove the operation of the $S_N2'$ mechanism from the structure of the product. In this article is reported some further work on displacement reactions of allylic halides which is pertinent to the question of the operation of an abnormal bimolecular mechanism. The conversions in question involved the action of sodium malonic ester on $\gamma$-methylallyl (I), $\alpha$-methylallyl (II), $\gamma$-ethylallyl (III) and $\alpha$-ethylallyl (IV) chlorides. These chlorides are similar to the one employed by Bergmann[2c] but normal and abnormal bimolecular mechanisms give different products.




The products of the displacement reactions were directly hydrogenated, saponified and decarboxylated to yield saturated monocarboxylic acids. The acids which may result from the butenyl chlorides are *n*-caproic acid (V) and $\beta$-methylvaleric acid (VI), and from the pentenyl chlorides are *n*-heptanoic acid (VII) and $\beta$-ethylvaleric acid (VIII). The acid product from each halide was carefully fractionated and various of the distillation fractions converted to benzyl amine salts to yield a semiquantitative estimate of the composition. The estimates thus obtained indicated less than 1% of abnormal product from each of the primary chlorides (I and III). With $\alpha$-methylallyl chloride (II), there was estimated 10% of abnormal product when the condensation with sodium malonic ester was carried out at the reflux temperature of the alcoholic solution and 6% when the condensation was carried out at room temperature. With $\alpha$-ethylallyl chloride (IV) the abnormal product was estimated at 23%.

The original chlorides (I–IV) were very carefully purified so that the production of abnormal products cannot be due to impurity of starting materials. Also, the chlorides are quite stable to thermal rearrangement, so this possible cause for production of abnormal products can be eliminated. It was shown by refractive index measurements that the pure chlorides without a solvent are unchanged after three hours at 80°. Actually, we should be concerned about rearrangements in ethanol, the solvent employed for the condensa-

(7) (a) Claisen and Tietze, *Ber.*, **59B**, 2344 (1926); (b) Reichstein and Trivelli, *Helv. Chim. Acta*, **16**, 968 (1933).

(8) Cope, Hoffman and Hardy, THIS JOURNAL, **63**, 1852 (1941).

(9) (a) Strauss and Berkow, *Ann.*, **401**, 121 (1913); (b) Kirrmann, *Compt. rend.*, **199**, 1228 (1934); (c) Kirrmann and Grard, *ibid.*, **190**, 876 (1930); (d) Kirrmann, Pacaud and Dosque, *Bull. soc. chim.*, [5] **1**, 860 (1934).

(10) Andrews, THIS JOURNAL, **69**, 3062 (1947).

(11) Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941).

(12) Wilson, *Trans. Faraday Soc.*, **37**, 631 (1941).

(13) Kimel and Cope, THIS JOURNAL, **65**, 1992 (1943).

tions. However, we should expect rearrangement in ethanol to be accompanied by very extensive solvolysis and this, as will be discussed shortly, is quite slow relative to the rate of the reaction with sodium malonic ester.

Ruling out impurity and rearrangement of the halides, there is still another conceivable mode of production of abnormal products besides the $S_N2'$ mechanism. This would be by way of a rate-determining ionization of the halide followed by very successful competition by malonic ester anion for the allyl carbonium ion. This we are able to rule out on the basis of kinetic experiments with α-ethylallyl chloride (IV), the halide which gave rise to the most abnormal product. The rate of solvolysis of this chloride in absolute ethanol and the rate of the condensation with diethyl malonate ion in absolute ethanol were both determined at 50.00°. The first order constant, $k_1$, observed for solvolysis of *ca.* 0.3 *M* chloride was $4.96 \times 10^{-4}$ hr.$^{-1}$, the same order of magnitude as that previously observed for α-methylallyl chloride,[14] $2.11 \times 10^{-4}$ hr.$^{-1}$ at 40°. The condensation of α-ethylallyl chloride with diethyl malonate ion gave excellent second-order kinetics, the results of a typical run being summarized in Table I and the results of several runs in Table II.

TABLE I

CONDENSATION OF α-ETHYLALLYL CHLORIDE WITH SODIUM MALONIC ESTER IN ABSOLUTE ETHANOL AT 50.00°

α-EA-Cl = 0.6461 *M* NaCH(COOEt)$_2$ = 0.1625 *M*

| *t*, hr. | NaCH(COOEt)$_2$ at time, *t*, mole/liter | α-EA-Cl reacted at time, *t*, mole/liter | $k_2$ |
|---|---|---|---|
| 0.0 | 0.1625 | 0.0 | ... |
| 0.25 | .1470 | .0155 | ... |
| 0.75 | .1312 | .0313 | 0.353 |
| 2.00 | .1002 | .0623 | .362 |
| 2.75 | .0851 | .0774 | .368 |
| 3.75 | .0711 | .0914 | .353 |
| 4.75 | .0581 | .1044 | .357 |
| 6.75 | .0410 | .1215 | .348 |
| | | Mean 0.357 ± .005 | |

TABLE II

SUMMARY OF RATE CONSTANTS FOR THE REACTION OF α-ETHYLALLYL CHLORIDE WITH SODIUM MALONIC ESTER

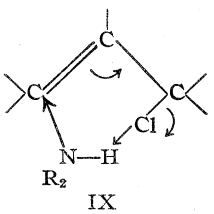
| Run | α-EA-Cl, mole/liter | NaCH(COOEt)$_2$, mole/liter | $k_2$ |
|---|---|---|---|
| 1 | 0.3391 | 0.3586 | 0.349 |
| 2 | .3495 | .3268 | .366 |
| 3 | .1655 | .6279 | .325 |
| 4 | .6461 | .1625 | .357 |

From the second-order rate constant, $k_2$, listed in Tables I and II, it is clear that the bimolecular reaction with malonic ester anion is much faster than the first-order solvolysis. In fact, one can calculate[1a] for an experiment at 50° with initially 2 *M* reagents that at complete reaction only 0.5% of the α-ethylallyl chloride has reacted by a solvolytic first-order mechanism. Thus, even if solvent does not compete with malonic ester anion, a maximum of 0.5% abnormal product could be accounted for by a solvolytic mechanism.

It is clear from the above arguments that the abnormal product observed in the case of the secondary chlorides (II and IV) arises from a bimolecular displacement process involving attack on the γ-carbon atom. Similarly this must have contributed to the reaction of α,γ-dimethylallyl chloride studied by Bergmann, but one would hardly anticipate sufficient contribution to account for complete racemization.

Other pertinent cases of nucleophilic displacements with allylic compounds involve the action of amines on halides. Thus Meisenheimer and Link[15] found that α-ethylallyl chloride (IV) on treatment with diethylamine or methylaniline yielded abnormal products, the same ones derived from γ-ethylallyl chloride (III). Also, Webb has found in these laboratories that α-methylallyl chloride II yields, on reaction with diethylamine, an abnormal product identical with the one from γ-methylallyl chloride (I). While these reactions are being scrutinized further, the indications are that abnormal product arises from bimolecular processes involving attack on the γ-carbon atom.

In the case of the abnormal displacement reactions, it is still not clear to what extent a mechanism of the type symbolized in IX contributes.




IX

Just as this manuscript was being completed, Jones, Lacey and Smith[16] reported the formation of an abnormal product from the action of diethylamine on the halides X (R = H or *n*-$C_4H_9$).

$RC{\equiv}CCH{=}CHCHClCH_3$ X $\quad$ $RC{\equiv}CCH{=}CHCH_2Cl$ XI

Normal products were obtained with aniline, ammonia and ethylamine. The halides XI (R = H or *n*-$C_4H_9$) yielded normal products even with diethylamine. The case of the abnormal product may be analogous to the cases of Meisenheimer and Link and Webb. However, abnormal product from X may arise from isomerization of normal product since treatment of normal product from X (R = H) and ethylamine with ethyl bromide gives the abnormal product.

Among the factors favoring abnormal product formation, Jones, Lacey and Smith emphasize basic strength of the nucleophilic reagent, in this way accounting for the formation of abnormal product with only diethylamine (and not $NH_3$

(14) Young and Andrews, THIS JOURNAL, **66**, 421 (1944).

(15) Meisenheimer and Link, *Ann.*, **479**, 211 (1930).

(16) Jones, Lacey and Smith, *J. Chem. Soc.*, 940 (1946).

$C_2H_5NH_2$ or $C_6H_5NH_2$). We feel that in cases of competing modes of attack (in this case $\alpha$ *vs.* $\gamma$) by a *limited* series of reagents, the dependence of rate on basic strength for each mode will be different. Thus a correlation of the ratio of the two rates with basic strength may become possible for a *limited* series of reagents. However, on this basis we do not expect a sharp difference between diethylamine and the other amines employed by Jones and co-workers, for the gap in basic strength is large between aniline and ethylamine and small between ethylamine and diethylamine.

One factor which is certain to be serious in a case of competing attacks such as the present competition between $\alpha$- and $\gamma$-attacks is the steric one. Thus, primary halides will suffer $\alpha$-attack more rapidly than the secondary halides, at least partly or largely for steric reasons. It is interesting that on this basis alone, without considering resonance effects and steric effects in the $\gamma$-attacks, the general behavior of the various halides can be correlated. The primary halides I, III and XI (R = H or *n*-$C_4H_9$) give normal products and similarly Meisenheimer and Link[15] obtained normal product from cinnamyl chloride and ethylaniline. On the other hand, the secondary halides II, IV and X (R = H or *n*-$C_4H_9$) give partly or largely abnormal products with certain reagents.

## Experimental

**$\alpha$- and $\gamma$-Methylallyl Chlorides.**—A mixture of the chlorides was prepared from a mixture of the alcohols and purified by standard methods.[17] The chlorides used had the following properties: $\alpha$-methylallyl chloride, b. p. 63.2–63.5° (750 mm.), $n^{20}D$ 1.4151, and $\gamma$-methylallyl chloride, b. p. 58.5–59.0° (300 mm.), $n^{20}D$ 1.4351.

**$\alpha$- and $\gamma$-Ethylallyl Chlorides.**—The $\alpha$-ethylallyl alcohol, b. p. 113–113.5° (750 mm.), $n^{25}D$ 1.4223, $d^{25}_4$ 0.8344, used as a source of the allylic chlorides was prepared from ethylmagnesium bromide and acrolein according to the method of Delaby[18] as modified by Prevost.[19] The pentenyl chlorides were prepared from the $\alpha$-ethylallyl alcohol by means of phosphorus trichloride and pyridine at 0° using standard methods[17] and were fractionated through a 1.5 × 135 cm. helices packed column under reduced pressure. The properties of the chlorides[20] used were as follows: $\alpha$-ethylallyl chloride, b. p. 55.0° (200 mm.), $n^{20}D$ 1.4253, $n^{25}D$ 1.4229, $d^{25}_4$ 0.8933, $M_D$, obs. 29.81, calcd. 29.69, equiv. wt., obs. 104.6, 104.9, calcd. 104.6; $\gamma$-ethylallyl chloride, b. p. 71.8° (200 mm.), $n^{20}D$ 1.4404, $n^{25}D$ 1.4380, $d^{25}_4$ 0.9089, $M_D$, obs. 30.20, calcd. 29.69, equiv. wt., obs. 105.2, 105.7, calcd. 104.6.

***n*-Caproic Acid.**—This material was redistilled Eastman Kodak Company White Label material, b. p. 97.5–98.0° (10 mm.), $n^{20}D$ 1.4163. The benzylamine derivative was prepared according to the method of Buehler, Carson and Edds[21] and recrystallized from anhydrous ethyl acetate; m. p.[22] 71–71.5° (cor.).

*Anal.* Calcd. for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.48. Found: C, 69.97; H, 9.64.

**$\beta$-Methylvaleric Acid.**—Secondary butyl bromide, b. p. 89–90° (750 mm.), $n^{25}D$ 1.4345, prepared from redistilled Eastman Kodak Company White Label 2-butanol, b. p. 99.0° (750 mm.), by means of phosphorus tribromide and pyridine at 0°, was condensed with malonic ester, b. p. 104–5° (25 mm.), in absolute ethanol according to the general method of Gilman and Blatt.[23] The condensation product was isolated but not purified and then hydrolyzed and decarboxylated as described by Blatt[24] to give $\beta$-methylvaleric acid, b. p. 93–94° (13 mm.), $n^{20}D$ 1.4158. The benzylamine derivative was somewhat hygroscopic and melted at 66–67° (cor.) after several recrystallizations from a mixture of anhydrous ethyl acetate and low-boiling petroleum ether.

*Anal.* Calcd. for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.48. Found: C, 70.44; H, 9.52.

***n*-Heptanoic Acid.**—Hydrolysis of Eastman Kodak Company White Label heptanoic anhydride yielded *n*-heptanoic acid, b. p. 109–110° (10 mm.), $n^{20}D$ 1.4225. The benzylamine derivative, recrystallized from a mixture of anhydrous ethyl acetate and low boiling petroleum ether, melted at 66.0–66.5° (cor.).

*Anal.* Calcd. for $C_{14}H_{23}O_2N$: C, 70.85; H, 9.77. Found: C, 71.72; H, 9.88.

**$\beta$-Ethylvaleric Acid.**—Diethylcarbinol, b. p. 115–115.2° (750 mm.), $n^{15}D$ 1.4126, prepared by the reaction of ethylmagnesium bromide with propionaldehyde, was converted to 3-bromopentane by treatment with phosphorus tribromide and pyridine at 0°. The 3-bromopentane, b. p. 116.5–116.8° (750 mm.), $n^{20}D$ 1.4444, was condensed with malonic ester[23] and the condensation product hydrolyzed and decarboxylated[24] to $\beta$-ethylvaleric acid, b. p. 104–105° (13 mm.), $n^{20}D$ 1.4250, in 40% over-all yield. The benzylamine derivative of $\beta$-ethylvaleric acid crystallized slowly from low boiling petroleum ether at room temperature. Since the derivative was extremely hygroscopic and difficult to handle the best melting point which could be obtained was 51–53°.

*Anal.* Calcd. for $C_{14}H_{23}O_2N$: C, 70.85; H, 9.77. Found: C, 70.63; H, 10.11.

**Condensation of $\alpha$- and $\gamma$-Methylallyl and $\alpha$- and $\gamma$-Ethylallyl Chlorides with Sodium Malonic Ester.**—To a stirred solution of sodium ethoxide, prepared by adding 0.50 mole of freshly cut sodium to 250 ml. of absolute ethanol (99.96%), was added 0.50 mole of diethyl malonate, b. p. 104–105° (25 mm.), over a one-half hour period. To this stirred sodium malonic ester solution was added 0.50 mole of the allylic chloride over a one-half hour period and the mixture then refluxed for two hours to complete the condensation. The cooled reaction mixture was poured into 800 ml. of water, neutralized with carbon dioxide gas, and the condensation product isolated by extraction with diethyl ether. The diethyl ether was removed by distillation and the condensation product added to 100 ml. of 95% ethanol and reduced at atmospheric pressure using platinum oxide catalyst. The catalyst was removed by filtration and the reduction product hydrolyzed and decarboxylated as described by Blatt.[24] The organic acids were isolated by extraction with diethyl ether and then completely removed from the ether layer by extraction with sodium carbonate solution. The aqueous solution of the sodium salts was decolorized with carbon, filtered, and the resulting colorless solution acidified with sulfuric acid. The organic acids were again isolated by extraction with diethyl ether. The diethyl ether was removed by distillation and the organic acids were carefully fractionated into 2–3 g. fractions. A second run was made using $\alpha$-methylallyl chloride (Method 2) in which the condensation of the chloride with sodium malonic ester was completed by allowing the mixture to stand at room temperature for one week instead of refluxing for two hours.

(17) Young and Lane, THIS JOURNAL, **59**, 2051 (1937).

(18) Delaby, *Compt. rend.*, **175**, 967 (1922).

(19) Prevost, *Ann. chim.*, [10] **10**, 113, 147 (1928).

(20) Prevost [*Compt. rend.*, **187**, 1052 (1928)] reported the following properties: $\alpha$-ethylallyl chloride, $n^{23}D$ 1.4224, $d^{23}_4$ 0.8966; $\gamma$-ethylallyl chloride, $n^{23}D$ 1.4347, $d^{23}_4$ 0.9095.

(21) Buehler, Carson and Edds, THIS JOURNAL, **57**, 2181 (1935).

(22) Buehler, Carson and Edds[21] reported the melting point of the benzylamine salt of *n*-caproic acid to be 51.7–52.7°.

(23) Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

(24) Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 416.

The products from the condensations with α-methylallyl chloride (Method 1), α-methylallyl chloride (Method 2), γ-methylallyl chloride, α-ethylallyl chloride and γ-ethylallyl chloride absorbed 92, 88, 93.5, 93.5 and 100%, respectively, of the theoretical amount of hydrogen, and the over-all yields of the saturated monocarboxylic acids were 89, 76, 80, 80 and 74%, respectively.

Fractionation of the saturated acids from the first condensation with α-methylallyl chloride with the aid of an estimated 25-plate 0.9 × 85 cm. platinum gauze-packed column similar to one described by Bower and Cooke[25] yielded 22 fractions (2–3 g. each) with a distillation temperature variation of 89–91° (10 mm.) and refractive index variation of $n^{20}D$ 1.4155–1.4157. Benzylamine derivatives of various distillation fractions were prepared by addition of approximately 0.25 ml. of benzylamine to 0.25 ml. of the acid. The resulting solid mass of crystals was recrystallized from a minimum volume (approximately 1 ml.) of a 50% mixture of anhydrous ethyl acetate and low boiling petroleum ether. From the melting point data for these derivatives, summarized in Table III, the amount of *n*-caproic acid, the abnormal product, was estimated to be 10 ± 3% of the total acid obtained. The loss of benzylamine derivative in the small amount of mother liquor was low but some difference in the solubility of the derivative of the normal and the abnormal products was a source of some uncertainty in the analysis, estimated at ±3%.

TABLE III

MELTING POINTS OF BENZYLAMINE DERIVATIVES OF α-METHYLALLYL CHLORIDE PRODUCTS

| Distillation fraction | M. p., of benzylamine salt, °C. | Mixed m. p. with β-methylvaleric acid salt, m. p. 66–67° | Mixed m. p. with *n*-caproic acid salt, m. p. 71–71.5° |
|---|---|---|---|
| 2 | 66–67 | 66–67 | |
| 4 | 65–67 | 66–67 | |
| 12 | 66–67 | 66–67 | |
| 18 | 65.5–67 | 66–67 | 50–56 |
| 19 | 66–67 | 66–67 | 53–57 |
| 20 | 47–51 | 50–55 | 42–45 |
| 21 | 65–68 | 54–57 | 66–69 |
| 22 | 70–71 | 55–57 | 70–71 |

The second condensation with α-methylallyl chloride (Method 2) gave similar results and the amount of abnormal product was estimated by means of benzylamine derivatives to be 6 ± 3% of the total acid obtained.

Fractionation of the saturated acids from the condensation with α-ethylallyl chloride gave 21 fractions (2–3 g. each) with a distillation temperature variation of 100–108° (10 mm.). The refractive index of fractions 1–14 varied from $n^{20}D$ 1.4250–1.4254 and then decreased for fractions 15–17 until fractions 18–21 were constant at 1.4226. In this fractionation, the refractive indices, the boiling points and the odor all indicated the presence of *n*-heptanoic acid, the abnormal product, in fractions 15–21, inclusive. Benzylamine derivatives of various distillation fractions were prepared and recrystallized once from low-boiling petroleum ether and the minimum amount of anhydrous ethyl acetate necessary to dissolve the solid. From the melting point data for these derivatives, summarized in Table IV, the amount of *n*-heptanoic acid, the abnormal product, was estimated to be 23 ± 3% of the total acid obtained.

Investigation of the fractionated acids from the condensations with γ-methylallyl and γ-ethylallyl chlorides in a similar manner indicated that a generous estimate of the amount of abnormal product present in each case would be 1% of the total acid obtained.

**Kinetic Studies.**—The presence of a small amount of acidic impurity in the solutions resulted in a fast initial rate so that in each run the first determination was taken as a blank and the rate constants calculated assuming this to be zero time.

TABLE IV

MELTING POINTS OF BENZYLAMINE DERIVATIVES OF α-ETHYLALLYL CHLORIDE PRODUCTS

| Distillation fraction | M. p., of benzylamine salt °C. | Mixed m. p. with β-ethylvaleric acid salt, m. p. 51–53° | Mixed m. p. with *n*-heptanoic acid salt, m. p. 66.0–66.5° |
|---|---|---|---|
| 3 | 51–53 | | 30–38 |
| 14 | 50–53 | | 40–44 |
| 15 | Obtained crystals at 0° which melted at room temp. | | |
| 16 | Viscous oil | | |
| 17 | 60–63 | 37–41 | 63–65 |
| 18 | 65–66 | 38–41 | 65.5–66.5 |
| 19 | 66–66.5 | 37–42 | 66–66.5 |
| 20 | 66–66.5 | 37–40 | 66–66.5 |
| 21 | 65–66 | 36–40 | 65.5–66.5 |

**(A) Solvolysis of α-Ethylallyl Chloride in Absolute Ethanol.**—A sample of α-ethylallyl chloride was weighed into a 100-ml. volumetric flask and diluted to volume with absolute ethanol (99.96%). Approximately 13 ml. of this solution was sealed into each of a series of tubes which were maintained at 50.00°. At certain time intervals tubes were withdrawn from the thermostat, cooled quickly in an ice-bath and 10.00-ml. aliquots titrated to the first definite phenolphthalein end-point with standard sodium hydroxide solution.

**(B) Condensation of α-Ethylallyl Chloride with Sodium Malonic Ester in Absolute Ethanol.**—To a weighed sample (approximately 0.034 mole) of α-ethylallyl chloride in a 100-ml. volumetric flask was added 85 ml. of 0.44 *M* alcoholic sodium malonic ester solution and the resulting mixture diluted to volume with absolute ethanol (99.96%). The solution was mixed thoroughly and 10.00-ml. aliquots sealed in test-tubes and placed in a thermostat at 50.00° as rapidly as possible. The samples were removed from the thermostat at intervals, cooled rapidly in an ice-bath and the contents of the tube washed quantitatively into an excess of standard alcoholic hydrochloric acid. The excess hydrochloric acid was then titrated with standard sodium hydroxide solution using brom thymol blue indicator. Determinations of the initial concentration of the sodium malonic ester in the reaction mixture by analyzing one aliquot when the samples were immersed in the thermostat and by analyzing another aliquot which had been heated fifteen hours at 80° to complete the reaction agreed within 0.3%.

## Summary

The products resulting from the condensation of sodium malonic ester with α- and γ-methylallyl and α- and γ-ethylallyl chlorides have been investigated. γ-Methylallyl and γ-ethylallyl chlorides reacted entirely to give products which would result from a normal bimolecular displacement. α-Methylallyl and α-ethylallyl chlorides reacted to give 10 and 23%, respectively, of the product which would result from an abnormal bimolecular displacement involving attack on the γ-carbon atom. Kinetic studies with α-ethylallyl chloride indicated that the abnormal product arises from a second-order reaction.

Abnormal bimolecular displacements are briefly discussed.

LOS ANGELES 24, CALIF. RECEIVED[26] AUGUST 4, 1948

(25) Bower and Cooke, *Ind. Eng. Chem., Anal. Ed.*, **15**, 291 (1943).

(26) Original manuscript received June 11, 1947.

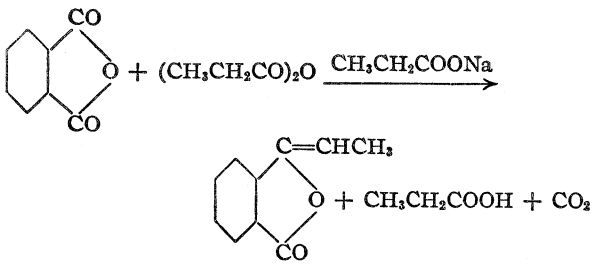
[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE MONSANTO CHEMICAL COMPANY]

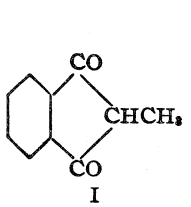
# Vinyl Aromatic Compounds. VI. Alkylidenephthalides and Related Compounds[1]

BY DAVID T. MOWRY, EUGENE L. RINGWALD AND MARY RENOLL[2]

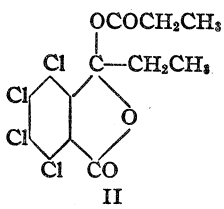
The Gabriel modification of the Perkin reaction, in which phthalic anhydride is substituted for benzaldehyde, has been reviewed briefly.[3]

We have selected the preparation of 3-ethylidenephthalide from phthalic anhydride, propionic anhydride and sodium propionate,[4,5] for study as representative of the Gabriel method of alkylidenephthalide formation. Although Gottlieb[4] reported an 88% crude yield, we have found that only 40–50% could be isolated as a pure product having a melting point of 64–65°. 2-Methyl-1,3-indandione (I), m. p. 84°, has been identified as one of the by-products and was easily separated by virtue of its solubility in cold aqueous alkali. The principal impurity, however, was an oil which could not be satisfactorily separated and purified by crystallization or distillation.





I



II

In order to elucidate the nature of this by-product, tetrachlorophthalic anhydride was condensed with a 200% excess of propionic anhydride under similar conditions to give a mixture of products from which 10% of 3-ethylidene-4,5,6,7-tetrachlorophthalide, m. p. 161°, and 14% of a neutral substance, $C_{13}H_{10}O_4Cl_4$, m. p. 107–108°, were isolated by fractional crystallization. The neutral by-product was easily saponified to 2-propionyl-3,4,5,6-tetrachlorobenzoic acid, m. p. 178–180°, which was independently prepared from 3-ethylidene-4,5,6,7-tetrachlorophthalide. Hence, the by-product is probably 3-propionoxy-3-ethyl-4,5,6,7-tetrachlorophthalide (II) which may have been formed by the addition of propionic acid to the ethylidenephthalide. The oily by-product formed in the preparation of 3-ethylidenephthalide probably has an analogous structure.

The phthalic anhydride–propionic anhydride reaction conditions have been varied with respect to catalyst, reagent ratios, and reaction times. Using 1.1 moles of propionic anhydride, 0.5 mole of sodium propionate and a reaction time of five hours at 180° there was obtained an 80% yield of crude distilled product, b. p. 154–162° (11 mm.) and a 58% yield of pure 3-ethylidenephthalide, m. p. 64–65°. The use of potassium propionate gave similar results, while sodium acetate was markedly inferior. Pyridine did not catalyze the reaction, although this catalyst recently has been reported,[6] to be satisfactory for the condensation of phthalic anhydride with malonic acid. No improvement in yield was obtained by increasing the reaction time.

On standing for several months 3-ethylidenephthalide is slowly transformed to a sticky resinous material.[7] This appears to be a low molecular weight polymer, $(C_{10}H_8O_5)_x$, of considerably higher oxygen content than the monomeric substance. It forms phthalic anhydride on destructive distillation. This transformation is caused by atmospheric oxygen since samples of ethylidenephthalide stored for six months in sealed evacuated ampoules showed no evidence of change.

By similar techniques, phthalic anhydride has been condensed with butyric anhydride and heptanoic anhydride to give propylidene- and *n*-hexylidene-phthalides. Attempts to prepare cyanomethylenephthalide from cyanoacetic acid and phthalic anhydride have been unsuccessful.[8] Thiophthalic anhydride reacted normally with propionic anhydride to give 3-ethylidenethiophthalide, but maleic and dichloromaleic anhydride gave only intractable tars. 3-Benzal-4,5,6,7-tetrachlorophthalide has been prepared from phenylacetic acid and tetrachlorophthalic anhydride in 60% yield.

We have attempted to prepare the ethyl ester of phthalideneacetic acid by direct esterification using acid catalysts. However, a hydration and decarboxylation took place with the formation of ethyl *o*-acetylbenzoate. A similar hydration and decarboxylation is reported by Yale,[6] who prepared *o*-acetylbenzoic acid directly from phthalic anhydride and malonic acid in pyridine

(1) Preceding paper of this series: THIS JOURNAL, **70**, 1916 (1948).

(2) Present address: Department of Chemistry, The Ohio State University, Columbus, Ohio.

(3) Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 222–223.

(4) Gottlieb, *Ber.*, **32**, 958 (1899).

(5) Kohlrausch and Seka, *ibid.*, **77**, 469 (1944).

(6) Yale, THIS JOURNAL, **69**, 1547 (1947).

(7) Auwers and Auffenberg, *Ber.*, **51**, 1109 (1918).

(8) Pascual Vila and Ballester, *Anales fis. y quim.* (*Madrid*), **42**, 1097 (1946); *C. A.*, **41**, 6549 (1947), also failed to obtain a condensation product from 3,3-diethoxy-4,5,6,7-tetrachlorophthalide and cyanoacetic ester.

solution. 3-Methylenephthalide may have been the intermediate since the crude distillate on some runs formed a glassy polymer on standing. The desired esters of phthalideneacetic acid were prepared in satisfactory yields by treating phthalideneacetyl chloride with methyl, ethyl and *n*-hexyl alcohols. However, an attempted esterification of the acid chloride with phenol by the Schotten–Baumann technique was unsuccessful.

## Experimental Part[9]

**3-Ethylidenephthalide.**—The following is a typical procedure for the preparation of ethylidenephthalide.[4,5] Phthalic anhydride (296 g., 2.0 moles) and propionic anhydride (286 g., 2.2 moles) were placed in a two-liter three-necked flask equipped with a stirrer, thermometer, reflux condenser and funnel for addition of solids. After heating to 150–160°, 96 g. (1.0 mole) of dry sodium propionate was added in four portions over a period of thirty minutes, taking care to allow the evolution of carbon dioxide to subside after each addition. After heating at slow reflux (170–180°) for five hours, the reaction was cooled somewhat and stirred vigorously with 700 cc. of hot water. The organic layer was taken up in 200 cc. of carbon tetrachloride and separated and washed with warm water. The product was then distilled to give 256 g. (80%) of crude ethylidenephthalide, b. p. 154–162° (11 mm.). Two recrystallizations from a mixture of benzene and hexane gave 130 g. of white crystals, m. p. 64–65°. An additional 55 g., m. p. 62–63° was obtained from the mother liquors, giving a total yield of 58%.

Extraction of the yellow oil remaining in the mother liquors with sodium hydroxide gave, after acidification, 12 g. (4%) of white crystals, b. p. 150° (17 mm.), m. p. 84–85°. This was 2-methyl-1,3-indandione, which Nathanson[10] prepared from sodium methylate and ethylidenephthalide.

The following table gives the crude (distilled) and pure (fraction melting above 60°) yields of ethylidenephthalide based on phthalic anhydride which were obtained under various conditions of catalyst concentration, reagent ratios, and reaction times at 170–180°.

| Phthalic anhydride, moles | Propionic anhydride moles | Sodium propionate, moles | Time, hr. | Crude yield, % | Pure yield, % |
|---|---|---|---|---|---|
| 1.0 | 1.1 | 0.1 | 5 | <5 | .. |
| 1.0 | 1.1 | .5 | 2 | 71 | 43 |
| 1.0 | 1.1 | .5 | 5 | 80 | 58 |
| 1.0 | 1.1 | .5[a] | 6 | 43 | 25 |
| 1.0 | 1.1 | .5[b] | 3 | 65 | 50 |
| 1.0 | 1.1 | .5[c] | 5 | 0[d] | .. |
| 1.0 | 1.1 | 1.0 | 5 | 75 | 50 |
| 1.0 | 1.1 | 1.0 | 24 | 78 | 46 |
| 1.0 | 1.5 | 0.5 | 3 | .. | 45 |
| 1.2 | 1.0 | 0.5 | 3 | 62 | 41 |

[a] Sodium acetate. [b] Potassium propionate. [c] Pyridine. [d] Essentially all the phthalic anhydride was recovered unchanged.

The gummy resinous material formed by ethylidenephthalide[7] on standing in contact with air at room temperature for several months was washed with hot benzene. The insoluble portion was a white powder which melted at 196–199°, and a 2% solution in dioxane had a specific viscosity at 25° of 0.067 compared to 0.018 for unchanged ethylidenephthalide. Analysis indicated that this low polymer contained considerably more oxygen than the monomer.

*Anal.* Calcd. for $(C_{10}H_8O_5)_x$: C, 57.7; H, 3.8. Calcd. for $(C_{10}H_8O_4)_x$: C, 62.5; H, 4.6. Found: C, 58.5; H, 3.97.

Destructive distillation of the crude gummy material was effected under vacuum using an open flame. About fifty weight per cent. of phthalic anhydride, m. p. 129–131° after recrystallization, was obtained in the distillate.

**3-Ethylidene-4,5,6,7-tetrachlorophthalide and 3-Ethyl-3-propionoxy-4,5,6,7-tetrachlorophthalide.**—One mole (286 g.) of tetrachlorophthalic anhydride and 390 g. (3.0 moles) of propionic anhydride were heated with stirring to 160°. Then 60 g. (0.63 mole) of sodium propionate was added in five portions over a period of one hour. The reaction was then refluxed for five hours before distilling off the excess propionic anhydride and propionic acid under reduced pressure. The residue was washed with 500 cc. of water at reflux, dissolved in a little carbon tetrachloride and separated. The organic layer was distilled and a fraction boiling at 210–230° (5–8 mm.) was collected. This was dissolved in hot acetone and cooled to give white crystals which were recrystallized once from acetone and again from a mixture of benzene and hexane. There was obtained 29 g. (10%) of 3-ethylidene-4,5,6,7-tetrachlorophthalide, m. p. 161–162°.

*Anal.* Calcd. for $C_{10}H_4O_2Cl_4$: C, 40.3; H, 1.34; Cl, 46.7. Found: C, 40.5; H, 1.54; Cl, 48.2.

The filtrate from the first acetone recrystallization was diluted with water and the resultant solid collected and recrystallized several times from dilute ethanol to give 51 g. (14%) of 3-ethyl-3-propionoxy-4,5,6,7-tetrachlorophthalide, white crystals, m. p. 107–108°.

*Anal.* Calcd. for $C_{13}H_{10}Cl_4O_4$: C, 42.0; H, 2.70; Cl, 38.2; mol. wt., 372. Found: C, 42.26; H, 2.78; Cl, 38.33; mol. wt. (Rast), 395.

Although this material was not soluble in aqueous alkali it instantly formed a reddish yellow solution in alcoholic sodium hydroxide. After warming for fifteen minutes it was acidified and the solid was recrystallized from dilute alcohol to give yellow crystals, m. p. 178–180°, which were soluble in sodium bicarbonate. This was 2-propionyl-3,4,-5,6-tetrachlorobenzoic acid and was identical with a sample prepared by the saponification of 3-ethylidene-4,5,6,7-tetrachlorophthalide.

*Anal.* Calcd. for $C_{10}H_6O_3Cl_4$: C, 38.0; H, 1.90. Found: C, 38.2; H, 2.09.

**3-Propylidenephthalide.**—Phthalic anhydride (296 g., 2.0 moles) was treated with butyric anhydride (348 g., 2.2 moles) in the presence of sodium butyrate (110 g., 1.0 mole) at 150–180° for five hours. The product was recovered as described above to give 217 g. (62%) of 3-propylidenephthalide, b. p. 142–145° (4.0 mm). Careful refractionation through a one-meter column packed with glass helices gave an analytical sample b. p. 143° (4 mm.), $n^{25}D$ 1.5859, f. p. 5°. Bromberg[11] reported b. p. 169–170° (12 mm.) for a product obtained in 41% yield.

**3-*n*-Hexylidenephthalide.**—This compound was prepared from 1.0 mole of phthalic anhydride, 1.1 moles of heptanoic anhydride and 0.5 mole of sodium heptanoate in the same manner as described for ethylidenephthalide. There was obtained a 54% yield of 3-*n*-hexylidenephthalide, b. p. 175–176° (5 mm.), $n^{25}D$ 1.5585, f. p. 5–6°.

*Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.7; H, 7.41. Found: C, 77.42; H, 7.42.

**3-Ethylidenethiophthalide.**—Thiophthalic anhydride[12] (91 g., 0.55 mole, m. p. 108°) was treated with 170 g. (1.3 moles) of propionic anhydride and 53 g. (0.55 mole) of sodium propionate at 160° for three hours. The product was recovered in the usual fashion and boiled at 155–160° (6 mm.) with slight decomposition. The crude product was recrystallized twice from hexane to give 3-ethylidenethiophthalide, m. p. 56–57°, in 31% yield. The white crystals assumed an orange color on exposure to light.

*Anal.* Calcd. for $C_{10}H_8OS$: S, 18.2. Found: S, 18.43.

(9) Analyses by Oakwold Laboratories, Alexandria, Va. All melting points corrected.

(10) Nathanson, *Ber.*, **26**, 2581 (1893).

(11) Bromberg, *Ber.*, **29**, 1436 (1896).

(12) Reissert and Holle, *Ber.*, **44**, 3029 (1911).

**3-Benzal-4,5,6,7-tetrachlorophthalide.**—The procedure of Weiss[13] for benzalphthalide was used. Phenylacetic acid (136 g., 1.0 mole), tetrachlorophthalic anhydride (238 g., 0.84 mole) and 3 g. of sodium acetate were heated at 230 to 260° for several hours using a short column and downward condenser to remove the water formed. The molten residue was then poured out and recrystallized from five liters of xylene. The product, 173 g. (53%) melted at 300°.

*Anal.* Calcd. for $C_{15}H_6O_2Cl_4$: C, 50.0; H, 1.67; Cl, 39.5. Found: C, 50.6; H, 2.26; Cl, 39.40.

**Ethyl Phthalideneacetate.**—Phthalideneacetic acid[14] (170 g., 0.9 mole) and 225 cc. of thionyl chloride were refluxed for four hours and the excess thionyl chloride was evaporated under water-pump vacuum. The resultant crystalline solid was broken up and treated with 300 cc. of cold absolute ethanol. After stirring for several hours the yellow solid was filtered and recrystallized from a mixture of benzene and hexane to give 90 g. (46%) of yellow crystals, m. p. 131–133°. The analytical sample after two more recrystallizations melted at 134–135°.

*Anal.* Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62; sapn. no., 218. Found: C, 66.33; H, 4.62; sapn. no., 212.

Earlier attempts to esterify phthalideneacetic acid directly with an excess of ethanol using sulfuric acid as a catalyst gave a good yield of ethyl *o*-acetylbenzoate, b. p. 112–115° (2 mm.), $n^{25}D$ 1.5122.

*Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.8; H, 6.32; sapn. no., 192. Found: C, 68.92; H, 6.55; sapn. no., 199.

Saponification of a small sample with alcoholic potassium hydroxide gave *o*-acetylbenzoic acid,[15] m. p. 115°. In one esterification run the crude distilled product having $n^{25}D$ 1.5238 was thought to contain some methylenephthalide since the material polymerized to an insoluble incompatible mass on standing at room temperature for several days.

**Methyl Phthalideneacetate.**—Treatment of phthalideneacetyl chloride with methanol at 5–10° in a similar fashion gave a 61% yield of the methyl ester, yellow crystals, m. p. 171–172° cor., after recrystallization from a mixture of benzene and hexane.

*Anal.* Calcd. for $C_{11}H_8O_4$: C, 64.7; H, 3.92. Found: C, 64.78; H, 4.12.

***n*-Hexyl Phthalideneacetate.**—Seventy grams of crude phthalideneacetyl chloride was treated with 250 cc. of *n*-hexanol at room temperature and warmed to 60° with stirring. The resultant oil was distilled twice to give 54 g. (59%) of a pale yellow oil, b. p. 208–210° (3 mm.).

*Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.2; H, 6.58. Found: C, 69.92; H, 6.96.

## Summary

The preparation of 3-ethylidenephthalide from phthalic anhydride and propionic anhydride in the presence of sodium acetate has been studied and 2-methyl-1,3-indanedione has been isolated as a by-product. The formation of a second by-product, 3-ethyl-3-propionoxyphthalide, is inferred since an analogous compound has been isolated from a similar reaction using tetrachlorophthalic anhydride. 3-Propylidenephthalide, 3-*n*-hexylidenephthalide, 3-ethylidenethiophthalide, 3-ethylidene- and 3-benzal-4,5,6,7-tetrachlorophthalides, and the methyl, ethyl and hexyl esters of phthalideneacetic acid have been prepared and characterized.

DAYTON, OHIO RECEIVED AUGUST 5, 1948

(13) Weiss, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 61.

(14) Gabriel and Newman, *Ber.*, **26**, 951 (1893).

(15) Karslake and Huston, THIS JOURNAL, **31**, 479 (1909).

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

# Reduction of Aldehydes, Ketones and Acid Chlorides by Sodium Borohydride

BY SAUL W. CHAIKIN AND WELDON G. BROWN

The successful use of lithium aluminum hydride as a reducing agent for organic compounds[1] has prompted the investigation of the reducing properties of other complex hydrides. The borohydrides of aluminum,[2] gallium,[3] beryllium,[4] lithium[5] and sodium[6] have been described. Of these, the sodium compound appeared to be of the greatest practical interest because it is potentially a cheaper material than lithium aluminum hydride and because a convenient preparative method is available.[6]

The reduction of various inorganic substrates by sodium trimethoxyborohydride, $NaBH(OCH_3)_3$, in aqueous solution has been studied by Sheft,[7] who also effected the reduction of carbon dioxide to formate. Previous studies on sodium borohydride, $NaBH_4$, as a reducing agent by Schlesinger, Schaeffer and collaborators[8] have been concerned with applications in the fields of inorganic and analytical chemistry, but have nevertheless served to indicate the potential value of the reagent in organic synthesis.

We find that the reduction of aldehydes and ketones by sodium borohydride follows the same pattern as with lithium aluminum hydride. The reactions occur rapidly at room temperature in most cases, although occasionally heating is required, and the corresponding alcohols are formed in comparable yields. Unsaturated aldehydes and ketones, in three examples studied, furnish the unsaturated alcohols.

(1) Nystrom and Brown, THIS JOURNAL, **69**, 1197, 2548 (1947).

(2) Schlesinger, Sanderson and Burg, *ibid.*, **62**, 3421 (1940).

(3) Schlesinger, H. C. Brown and Schaeffer, *ibid.*, **65**, 1786 (1943).

(4) Burg and Schlesinger, *ibid.*, **62**, 3425 (1940).

(5) Schlesinger and H. C. Brown, *ibid.*, **62**, 3429 (1940).

(6) (a) Albert E. Finholt, Ph.D. Dissertation, The University of Chicago, June, 1946; (b) Schlesinger, "Final Report on Contract W.3434-SC-174," Official Publications Board, PB 6331, Department of Commerce, Washington, 1946.

(7) Irving Sheft, M.S. Dissertation, The University of Chicago, March, 1944.

(8) (a) Henry R. Hoekstra, Ph.D. Dissertation, The University of Chicago, August, 1946; (b) Albert C. Stewart, M.S. Dissertation, The University of Chicago, March, 1948; (c) Schaeffer and Frank, unpublished work.

The experimental techniques are quite different, for whereas lithium aluminum hydride must be used in non-hydroxylic solvents and must be rigorously protected from moisture, the reductions with sodium borohydride may be carried out in water or methanol solution. This represents a gain in convenience and economy, and suggests a possible further advantage in the reduction of ether-insoluble compounds, such as the sugars, for which lithium aluminum hydride is unsuitable.

However, a limitation is imposed by the difficultly hydrolyzable nature of the intermediate alkyl borates in certain cases. The *n*-alkyl borates are very rapidly hydrolyzed and thus, where the reduction of an aliphatic aldehyde is carried out in an aqueous solution of sodium borohydride, hydrolysis of the intermediate boron ester takes place concurrently. Other types undergo hydrolysis less readily,[9] and in the reduction of aromatic aldehydes and some of the ketones studied subsequent heating with alkali was necessary in order to liberate the alcohols. Stable complexes with boric acid are formed by α-hydroxy-acids[10] and by many polyhydroxy compounds[11] and the isolation of such products presents a problem which has not been satisfactorily solved. Thus pyruvic acid and glucose, although evidently reduced by sodium borohydride, form complexes from which boron-free reduction products could not be isolated.

The reduction of the carboxylate group of acids by sodium borohydride does not occur to any appreciable extent under the conditions described above for the reduction of carbonyl groups. Moreover, these conditions are not appropriate, because of the alkaline medium, for the reduction of easily hydrolyzable derivatives of carboxylic acids. Acid chlorides may be successfully reduced however by employing a suspension of sodium borohydride in dioxane or other inert solvent. The reaction is vigorous with aliphatic acid chlorides but aromatic acid chlorides require heating. Simple acid chlorides are converted to the alcohols in good yields but the results for unsaturated and other polyfunctional acid chlorides are less clean-cut.

Crotonyl chloride and cinnamoyl chloride evidently undergo reaction at the carbon–carbon double bonds as is shown by the isolation, in the latter case, of some hydrocinnamyl alcohol, and by the fact that in neither case was it possible to isolate any of the unsaturated alcohol. Analogous reactions of lithium aluminum hydride are known[1,12] and on the basis of this analogy it is assumed that the borohydride adds to the double bond forming a carbon–boron bond with the β-carbon atom. This bond, in contrast with the analogous aluminum compounds, is evidently highly resistant to hydrolytic fission. It is noteworthy that the reduction of cinnamaldehyde by sodium borohydride in methanol solution could not be forced beyond the cinnamyl alcohol state.

Under conditions favorable for the reduction of acid chlorides, sodium borohydride is without action on the esters and nitriles tested. Acids and acid anhydrides show only slight reduction on prolonged heating of the mixtures. It is with respect to these types that the milder reducing action of sodium borohydride, as compared with lithium aluminum hydride, is most clearly evident.

The lower reactivity of the borohydride is advantageous in permitting the selective reduction of acid chloride or carbonyl groups in the presence of other functional groups which, with lithium aluminum hydride, would also be reduced. This special application is perhaps most strikingly illustrated in the present work by the selective reduction at the carbonyl groups in levulinic acid, ω-bromoacetophenone[13] and *m*-nitrobenzaldehyde.

Although precise determinations of the stoichiometrical relationships have not been carried out the end-point in the strongly exothermic reaction of most aldehydes and ketones with sodium borohydride is easily recognizable. Semi-quantitative observations of this kind leave no doubt that four moles of the aldehyde or ketone react with one of the borohydride and the course of the reactions may be formulated as

$$4R_2CO + NaBH_4 = NaB(OCHR_2)_4 \quad (1)$$

$$NaB(OCHR_2)_4 + 2NaOH + H_2O = Na_2BO_3 + 4R_2CHOH \quad (2)$$

## Experimental

**Sodium Borohydride.**—The sodium borohydride used in this work was supplied to us through the kindness of Professor H. I. Schlesinger. Analysis, by measurement of the hydrogen gas evolved upon acidification of an aqueous solution, showed 90% sodium borohydride. It was kept in a screw-cap bottle which was opened intermittently with no special precautions to prevent access of atmospheric moisture; the rate of deterioration was less than 2% per year. Aqueous or methanolic solutions were prepared for immediate use by dissolving the required quantity to make a 10–15% solution. Aqueous solutions, stabilized by the addition of sodium hydroxide (0.2 *N*), showed less than 5% loss of activity in two weeks. A solution 6 *N* in sodium hydroxide showed only slight decomposition at 100°.

**Reduction of Aldehydes and Ketones.**—The order in which the reactants were combined was largely arbitrary except where special considerations indicated a preference. Alkali-sensitive compounds, *e. g.*, crotonaldehyde, were reduced by addition of the compound, dissolved in water or methanol, to a solution of the hydride in order to avoid prolonged contact of unreduced compound with alkali. Compounds of very low solubility, *e. g.*, benzil and dicyclohexyl ketone, were more conveniently reduced by adding a solution of the hydride to a suspension of the compound in methanol; in such cases the reaction mixtures became homogeneous as the reactions proceeded.

Two ketones, mesityl oxide and dicyclohexyl ketone, required heating to 60–70° to initiate reaction. More com-

(9) Scattergood, Miller and Gammon, THIS JOURNAL, **67**, 2150 (1945), have reported qualitative observations on the ease of hydrolysis of alkyl borates and have noted that a wide variation exists, secondary alkyl borates hydrolyzing less rapidly than primary with pronounced chain-branching effects in both types.

(10) Kolthoff, *Rec. trav. chim.*, **45**, 607 (1926).

(11) Hermans, *Z. anorg. Chem.*, **142**, 83 (1925).

(12) Hochstein and Brown, THIS JOURNAL, **70**, 3484 (1948).

(13) This compound is reduced to methylphenylcarbinol by lithium aluminum hydride (unpublished work by Mr. Lloyd Trevoy).

monly, cooling was necessary to moderate the reactions and to maintain the temperature in the range 20–30°.

In order to avoid the acid-catalyzed decomposition of hydride which would otherwise be caused by the free acidic groups, the solutions of levulinic acid and of *m*-hydroxybenzaldehyde were neutralized by the addition of sodium hydroxide prior to reduction.

When necessary, to establish completeness of reaction, the presence of excess sodium borohydride was detected by adding one drop of the reaction mixture to 1 ml. of dilute acid, the immediate evolution of hydrogen constituting a positive test.

Striking color phenomena were observed during the course of the reduction of benzil. A reddish-purple color appeared on the first addition of hydride solution and persisted until about one third of the required amount of hydride had been added. Thereafter, until nearly the end of the addition of hydride, the color was discharged on each fresh addition of hydride, leaving the yellow color of benzil, and then slowly returned. After all of the hydride solution had been added the color was still yellow; on warming the mixture to 60° it became colorless. The crude product from this reduction melted over the range 124–131° and was evidently a mixture of *meso*- and *dl*-hydrobenzoin. By multiple recrystallizations from carbon tetrachloride and from mixtures of carbon tetrachloride and chloroform, following the procedure of Böeseken and Elsen,[14] ***meso***-hydrobenzoin, m. p. 137°, was isolated in 56% yield.

In the reduction of diacetyl no comparable color phenomena were observed. The yellow color of diacetyl disappeared when a quantity of hydride had been added which was sufficient to reduce one carbonyl group.

Our results for aldehydes and ketones are summarized in Table I.

**Reduction of Acid Chlorides.**—Dioxane, used in the reduction of acid chlorides, was purified by refluxing for twenty-four hours over calcium hydride followed by distillation, rejecting the forerun until a 1-ml. test sample showed no gas evolution when treated with a few milligrams of sodium borohydride. Diethyl carbitol was used instead of dioxane in those cases where the boiling point of the reduction product is near that of dioxane. The diethylcarbitol was a technical grade, purified by distillation.

The reduction of aliphatic acid chlorides was carried out by the regulated addition of the acid chloride, dissolved in dioxane if necessary, to a cooled suspension of sodium borohydride, in excess, in dioxane. The mixtures were heated on the steam-bath for a short time following the addition and then, after cooling, water was added. The addition of water invariably resulted in a vigorous exothermic reaction accompanied by the evolution of hydrogen gas in the amount of approximately four moles per mole of acid chloride taken. The evolution of hydrogen was probably caused by the acid, liberated in the hydrolysis of the intermediate complexes, acting upon the excess sodium borohydride. Isolation of the reduction products was accomplished by appropriate methods with the results shown in Table II.

TABLE I

REDUCTION OF ALDEHYDES AND KETONES

| Compound | Product | Yield, % | $n_D$ or m. p.,[a] °C. |
|---|---|---|---|
| **A. Reductions in Aqueous Solution** | | | |
| Acetonylacetone | Hexanediol-2,5 | 86 | 1.4453 |
| *n*-Butyraldehyde (C)[b] | *n*-Butanol | 85 | 1.3977 |
| Chloral hydrate | 2,2,2-Trichloroethanol | 61 | |
| Crotonaldehyde (C) | Crotyl alcohol | 85 | 1.4249 |
| Cyclopentanone | Cyclopentanol | 90 | 1.4520 |
| Diacetyl | Butanediol-2,3 | 62 | 1.4336 |
| Levulinic acid | γ-Valerolactone | 81 | 1.4319 |
| Mesityl oxide (C)[c] | 4-Methyl-3-pentenol-2[d] | 77 | 1.4310 |
| Methyl ethyl ketone | *s*-Butanol | 87 | 1.3956 |
| **B. Reductions in Methanol Solution** | | | |
| Anisaldehyde (C) | Anisyl alcohol | 96 | 24 |
| Benzil | Hydrobenzoin[e] | 89 | 124–131 |
| ω-Bromoacetophenone | Styrene bromohydrin | 71 | 1.5751 |
| Cinnamaldehyde | Cinnamyl alcohol | 97 | 32.5 |
| Dicyclohexyl ketone | Dicyclohexylcarbinol | 88 | 62 |
| *p*-Dimethylaminobenzaldehyde (C) | *p*-Dimethylaminobenzyl alcohol | 96 | 1.5775 |
| *m*-Hydroxybenzaldehyde (C) | *m*-Hydroxybenzyl alcohol | 93 | 64 |
| *m*-Nitrobenzaldehyde | *m*-Nitrobenzyl alcohol[f] | 82 | 30.5 |

[a] Melting points are given for solid products, refractive indices (at 25°) for liquid products. Other data pertaining to characterization are omitted except in special cases noted below. [b] The letter "C" designates the order of addition to be: compound added to solution of the borohydride, except where thus designated the order of addition was the opposite. [c] Mesityl oxide was purified by the procedure of Stross, Monger and de V. Finch [THIS JOURNAL, 69, 1627 (1947)]; b. p. 128.8–129°, $n^{24}D$ 1.4435. The reduction was carried out in a 2:1 water–methanol mixture. [d] B. p. 138–140°. Doeuvre [*Bull. soc. chim.*, 10, 371 (1943)] who prepared this compound in 25% yield by the Meerwein–Ponndorf reduction of mesityl oxide, reported b. p. 138–140°, $n^{15}D$ 1.4377. The 63% yield, given by Wilds ["Organic Reactions," Vol. II, Wiley & Sons, New York, N. Y., 1944, p. 209], is incorrectly quoted from earlier literature. [e] The stated yield pertains to a mixture of isomers (*cf.* text). [f] The compound was observed in two allotropic modifications, one melting at 15° and a stable form melting at 30.5°. The literature melting point is 27° [Staedel, *Ber.*, 27, 2112 (1894)].

TABLE II

REDUCTION OF ACID CHLORIDES

| Compound | Product | Yield, % | $n_D$ or m. p.[a] °C. |
|---|---|---|---|
| Benzoyl chloride | Benzyl alcohol | 76 | 1.5371 |
| *n*-Butyryl chloride | *n*-Butanol | 81 | 1.3979 |
| Cinnamoyl chloride | Hydrocinnamyl alcohol[b] | 12 | 1.5248 |
| Monoethyl succinate acid chloride | Butyrolactone[c] | 40 | |
| Palmitoyl chloride | Cetyl alcohol[d] | 87 | 47.5–49 |
| *o*-Phthalyl chloride | Phthalide[e] | 49 | 72 |
| | Phthalyl alcohol[e] | 15 | 59 |

[a] See footnote (*a*), Table I. [b] Identified through the 3,5-dinitrobenzoate, m. p. 91°. A major portion of the product consisted of an organic material containing boron not decomposed by hot alkali. [c] B. p. 87–87.5° (12 mm.). Chromic acid oxidation furnished succinic acid, m. p. 183–184.5°. [d] Reaction product hydrolyzed in hot dilute acid. [e] Identity of products verified by mixed melting points with authentic specimens.

In the case of aromatic acid chlorides, which were found not to react at room temperature, a modified procedure was followed in which the mixtures were heated on the steam-bath for one to two hours, and then were cooled in an ice-bath before adding water. Some difficulty with foaming during the first addition of water was experienced.

**Miscellaneous Experiments.**—The following compounds, heated with a dioxane or diethylcarbitol suspension of sodium borohydride for one hour, showed no evidence of reduction: ethyl butyrate, ethyl phenylacetate, benzyl cyanide, maleic acid. Partial reduction was observed under similar conditions with butyric acid, phthalic anhydride and succinic anhydride. Cinnamyl alcohol, refluxed for one hour with an alkaline methanol solution of sodium borohydride, was recovered unchanged.

The isolation of boron-free products was unsuccessful, although reduction obviously occurred, with pyruvic acid,

(14) Böeseken and Elsen, *Rec. trav. chim.*, 47, 694 (1928).

glucose, anthraquinone and crotonyl chloride. Acetylacetone evidently suffered cleavage prior to or during the reduction; isopropyl alcohol was isolated in 63% yield.

Solutions of benzene diazonium chloride exhibited a rapid and strongly exothermic reaction with sodium borohydride. Benzene, aniline and phenylhydrazine were isolated in relatively small yields. The course of the reaction was qualitatively similar in neutral and in strongly alkaline solutions.

**Acknowledgment.**—The support afforded by the Lindsay Light and Chemical Company through the award of a Fellowship to the junior author (S. W. C.) is gratefully acknowledged.

## Summary

Sodium borohydride, in water or methanol solution, is an effective reagent for the conversion of aldehydes and ketones to the corresponding alcohols. Its properties are compared with those of lithium aluminum hydride and it is shown to be superior in selective reductions. Acid chlorides are reduced to primary alcohols in non-aqueous media, but carboxylic acids, anhydrides, esters and nitriles are practically unaffected.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

# Crystalline Derivatives of Isomaltose[1,2]

BY M. L. WOLFROM, L. W. GEORGES[3] AND I. L. MILLER[4]

In the course of our studies on the structure of starch it became desirable to have a reference compound made up of two D-glucose residues combined by a 6-$\alpha$-D-glucosyl linkage. Musculus,[5] Grimaux and Lefèvre[6] and Gautier[7] had prepared weakly reducing non-fermentable sirupy disaccharides by condensing D-glucose in the presence of acids. E. Fischer[8] in attempts to synthesize maltose, obtained a similar material which he called "isomaltose" and characterized as its phenylosazone (m. p. 158°). Georg and Pictet[9] prepared isomaltose according to the procedure of Fischer as modified by Friedrichs[10] and obtained a sirup which produced an amorphous acetate upon hot acetylation with acetic anhydride and sodium acetate. By means of a fractional precipitation procedure from ethanol the crude acetate was separated into three fractions: octaacetylgentiobiose, m. p. 190–195°; $\beta$-octaacetylisomaltose, amorphous, fusing at 72–77° and showing a rotation of $[\alpha]^{20}D$ +93.7° ($c$ 4.8); a small amount of a third fraction, amorphous and fusing at 115–123°. The $\beta$-octaacetylisomaltose was converted into amorphous $\alpha$-octaacetylisomaltose by heating with acetic anhydride and zinc chloride, $[\alpha]^{19}D$ +115.5° ($c$ 4.2). The free sugar exhibited a rotation of $[\alpha]^{23}D$ +104.6° (ten minutes), +99.7° (twenty-four hours) ($c$ 5.1, water), and produced a phenylosazone which melted at 160° and had a rotatory value of $[\alpha]^{23}D$ +23.1° ($c$ 1.2, methanol). Upon methylation of the free sugar with subsequent hydrolysis, Georg[11] obtained 2,3,-4-trimethyl-D-glucose and 2,3,4,6-tetramethyl-D-glucose indicating a 6-D-glucopyranosyl structure. Myrbäck[12] prepared "isomaltose" as a reversion product of D-glucose by the action of hydrochloric acid and by methylation studies confirmed Georg's observation that it is 6-$\alpha$-D-glucosyl-D-glucose. Berlin[13] has been able to isolate gentiobiose octaacetate from the "isomaltose" of Fischer. He believes that this preparation is a gross mixture containing gentiobiose. His observation is supported by Isaiev.[14] By acid hydrolysis and by Taka diastase treatment, Ahlborg and Myrbäck[15] obtained from corn starch a sirupy disaccharide which on methylation and hydrolysis yielded 2,3,4,6-tetramethyl-D-glucose and 2,3,4-trimethyl-D-glucose. It was thus established as an "isomaltose" derivative. Following the publication of our preliminary notice,[1] Montgomery, Weakley and Hilbert[16] hydrolyzed amylopectin (waxy corn starch) with a Taka diastase type of enzyme and isolated a disaccharide characterized by a crystalline octa-$p$-nitrobenzoate and by two isomeric crystalline octaacetates. One of the latter was shown to be identical with the product described herein by a direct comparison involving mixed melting point and comparative X-ray powder diffraction diagrams.

For a source of this disaccharide we turned to the synthetic polysaccharide dextran which is made from sucrose by the action of *Leuconstoc dextranicum*. Methylation studies[17,18] have shown that

(1) A preliminary communication by the present authors describing the crystalline octaacetate of 6-$\alpha$-D-glucosyl-$\beta$-D-glucose appeared in THIS JOURNAL, **69**, 473 (1947).

(2) In the present communication we will employ provisionally the term isomaltose to designate 6-$\alpha$-D-glucopyranosyl-D-glucose.

(3) Corn Industries Research Foundation Associate of The Ohio State University Research Foundation (Project 203).

(4) Corn Industries Research Foundation Fellow of The Ohio State University Research Foundation (Project 203).

(5) Musculus, *Bull. soc. chim. France*, [2] **18**, 66 (1872).

(6) E. Grimaux and L. Lefèvre, *Compt. rend.*, **103**, 146 (1886).

(7) A. Gautier, *Bull. soc. chim. France*, [2] **22**, 145 (1874).

(8) E. Fischer, *Ber.*, **23**, 3687 (1890); **28**, 3024 (1895).

(9) A. Georg and A. Pictet, *Helv. Chim. Acta*, **9**, 612 (1926).

(10) O. v. Friedrichs, *Arkiv Kemi Mineral. Geol.*, **5**, No. 4, 1 (1913); *Chem. Centr.*, **85**, I, 763 (1914).

(11) A. Georg, *Compt. rend. soc. phys. hist. nat. Genève*, **47**, 94 (1930).

(12) K. Myrbäck, *Svensk Kem. Tid.*, **53**, 67 (1941); **53**, 264 (1941).

(13) H. Berlin, THIS JOURNAL, **48**, 1107 (1926).

(14) B. J. Isaiev, *Chem. Listy*, **20**, 251 (1926); *C. A.*, **20**, 3159 (1926).

(15) K. Ahlborg and K. Myrbäck, *Biochem. Z.*, **308**, 187 (1941).

(16) Edna M. Montgomery, F. B. Weakley and G. E. Hilbert, THIS JOURNAL, **69**, 2249 (1947).

(17) E. C. Fairhead, M. J. Hunter and H. Hibbert, *Can. J. Research*, **B16**, 151 (1938).

(18) S. Peat, E. Schlüchterer and M. Stacey, *J. Chem. Soc.*, 581 (1939).

this polysaccharide is bound at least to the extent of 90% by 6-α-D-glucopyranosyl linkages.

In this work we report the preparation of a disaccharide, isolated as its crystalline β-D-octaacetate (Fig. 1), by controlled acid hydrolysis of dextran under conditions which do not favor the production of reversion products. The isolation was effected by application of the acetate chromatographic techniques established in this Laboratory.[19] Molecular weight and acetyl determinations together with elementary analyses showed the acetate to be a disaccharide.

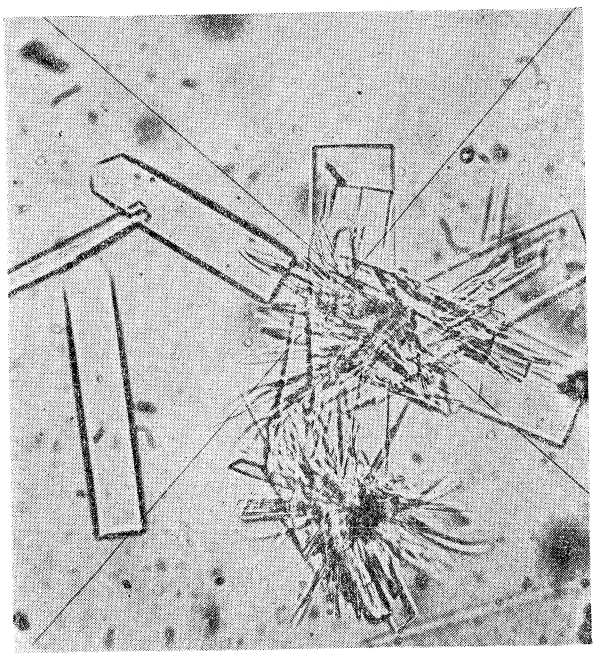


Fig. 1.—β-D-Isomaltose octaacetate.

The determined rotation of the disaccharide octaacetate is in close agreement with that of the amorphous acetate of Georg and Pictet[9] and with that predictable for a 6-α-D-glucopyranosyl disaccharide linkage by application of Hudson's rules of isorotation. The value may be calculated from the rotations of three known octaacetates containing 6-D-glycosyl linkages as follows

| | | |
|---|---|---|
| Gl + L + Gal | = 69,560 | (6-α-D-galactosyl-β-D-glucose octaacetate) (β-melibiose octaacetate) |
| −(Gl − L + Gal) | = 0 | (6-β-D-galactosyl-β-D-glucose octaacetate) |
| 2L | = 69,560 | |
| L | = 34,780 | |
| Gl − L + Gl′ | = −3,590 | (6-β-D-glucosyl-β-D-glucose octaacetate) (β-gentiobiose octaacetate) |
| + L | = 34,780 | |
| Gl + Gl′ | = 31,190 | |

(19) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

| | | |
|---|---|---|
| Gl + L + Gl′ | = 31,190 + 34,780 = 65,970 | = (6-α-D-glucosyl-β-D-glucose octaacetate) (β-isomaltose octaacetate) |

$$[\alpha]_D = \frac{65,970}{678.6} = +97°$$

in which L, Gl, Gl′ and Gal represent portions of the molecular rotation due to the glycosyl carbon atom binding the disaccharide, the two acetylated pyranoid D-glucose entities and the pyranoid D-galactose entity, respectively.

Deacetylation of this crystalline acetate yielded the free reducing disaccharide in amorphous form with a specific rotation of $[\alpha]^{24}D$ +103.2° (water) in good agreement with the value of 104.6° cited by Georg and Pictet.[9] The disaccharide was not fermentable by yeast.

The crystalline disaccharide octaacetate was converted to the crystalline 6-α-D-glucopyranosyl-α-D-glucopyranosyl bromide heptaacetate and this in turn was transformed into the crystalline methyl 6-α-D-glucopyranosyl-β-D-glucopyranoside heptaacetate. Deacetylation of the latter compound yielded an amorphous glycoside which on periodate oxidation produced the data shown in Table I, which table also cites comparative oxidation data with the corresponding glycosides of the β-1,4-linked cellobiose and the β-1,6-linked gentiobiose. These data definitely establish the new glycoside as a methyl 6-α-D-glucopyranosyl-β-D-glucopyranoside. The ring structure in the nonreducing portion of the disaccharide and in both the D-glucose entities in the glycoside, octaacetate, and acetohalogen compound can be considered as established.

TABLE I

PERIODATE OXIDATION AT 25° OF THE METHYL GLYCOSIDES OF β-D-FORMS OF CELLOBIOSE, GENTIOBIOSE AND ISOMALTOSE

| Substance | Time, hr. | Oxidant consumed[a] | Formic acid formed |
|---|---|---|---|
| Methyl β-D-cellobiopyranoside | 8 | 3.01 | |
| | 10 | 3.02 | 1.05 |
| Methyl β-D-gentiobiopyranoside | 3 | 4.06 | |
| | 4.5 | 4.08 | 1.95 |
| Methyl 6-α-D-glucopyranosyl-β-D-glucopyranoside (Methyl β-D-isomaltoside)[b] | 3 | 4.02 | |
| | 4 | 4.04 | 1.91 |

[a] Eighteen:one (moles periodate:glycoside). [b] Prepared through its crystalline acetate and chromatographically homogeneous.

## Experimental

**6-α-D-Glucopyranosyl-β-D-glucopyranose Octaacetate.**—An amount of dextran (100 g.), prepared by the action of *Leuconostoc dextranicum* on sucrose[19] (rotation $[\alpha]_D$ +180° (*c* 1, water)), which is in agreement with the value reported by Peat[18]) was dissolved by shaking in 3 liters of 30% hydrochloric acid. The mixture was held at 24–26° and polarimetric readings were taken at intervals. When the rotation had dropped to $[\alpha]_D$ +105°, which required about twelve hours, the solution was poured into 15 liters of water, and the acid neutralized with basic lead carbonate. The precipitate was filtered and washed with

500 ml. of water. The lead ion was precipitated from the combined filtrate and washings with hydrogen sulfide and after filtration the solution was neutralized to a *p*H of 7.0 by the addition of sodium bicarbonate. The solution was concentrated to about 700 ml. under reduced pressure at 50°. The remainder of the ionic material was removed by passing the solution successively over Amberlite[20] resins IR-100 and IR-4. The solution and washings were concentrated to a sirup at 50° and this was dried to an amorphous powder by azeotropic distillation with absolute ethanol under reduced pressure.

Twenty grams of the amorphous hydrolyzate, 20 g. of freshly fused sodium acetate and 200 ml. of acetic anhydride were placed in a liter flask fitted with a reflux condenser and heated gradually by means of an oil-bath to 110–120° and held there until completion of the vigorous reaction. The reaction mixture was then cooled and poured into 2 liters of ice and water. When the oily layer had hardened to an amorphous solid, it was filtered and washed free of acetic acid with water; yield *ca.* 25 g.

Five grams of the above-described amorphous acetylated hydrolyzate of dextran was dissolved in 100 ml. of benzene and placed on a column of Magnesol[21]–Celite[22] (5:1 by wt.) (240 × 80 mm. in diam.[23]) and developed with 3000 ml. of benzene–ethanol (100:1 by vol.). The first zone near the bottom of the extruded column, as located by means of streak indicator (1 part of potassium permanganate, 10 parts of sodium hydroxide and 100 parts of water) contained β-D-glucose pentaacetate. The second zone located about one-third of a column length from the bottom contained the disaccharide octaacetate. It was cut out, eluted with 750 ml. of acetone and evaporated to a sirup; yield 0.5 g. Material (1.6 g.) obtained in this manner was dissolved in 50 ml. of benzene and placed on a column of Magnesol[21]–Celite[22] (5:1 by wt.) (240 × 43 mm.[23]) and developed with 1200 ml. of benzene–ethanol (100:1). The first significant zone from the bottom of the column was sectioned and eluted with 750 ml. of acetone to produce a sirup on solvent removal; yield 0.9 g. This material was crystallized from ethanol and was recrystallized from the same solvent; yield 0.7 g., m. p. 143–144°, $[\alpha]^{25}D$ +96.9° (*c* 2.7, chloroform).

*Anal.* Calcd. for $C_{12}H_{14}O_{11}(CH_3CO)_8$: C, 49.56; H, 5.63; $CH_3CO$, 11.78 ml. of 0.1 *N* NaOH per 100 mg.; mol. wt., 679. Found: C, 49.74; H, 5.67; $CH_3CO$, 11.86 ml.; mol. wt. (Rast), 680.

**6-α-D-Glucopyranosyl-D-glucose.**—Two grams of 6-α-D-glucopyranosyl-β-D-glucopyranose octaacetate was deacetylated according to the method of Isbell.[24] The acetate was dissolved in 40 ml. of absolute methanol and cooled to 0°. Barium methoxide (2.4 ml. of 0.4 *N*) was added to the solution and the whole kept at 0° for twenty-four hours. It was then diluted with 200 ml. of cold water and the ionic material removed by passing over Amberlite resins IR-100 and IR-4.[20] The effluent from the ion exchange columns was concentrated to a sirup under reduced pressure. The residual water was removed by repeatedly stirring with ethanol and evaporating to dryness in a vacuum desiccator. All attempts to crystallize the substance failed. It is a very hygroscopic solid; $[\alpha]^{24}D$ +103.2° (*c* 3.85, water). This material displayed only one zone when placed on Silene[25]–Celite[22] (5:1 by wt.) (240 mm. × 43 mm.[23]) and developed with 120 ml. of 90% dioxane. The free sugar is not fermented by bakers' yeast.

*Anal.* Calcd. for $C_{12}H_{22}O_{11}$: C, 42.10; H, 6.48. Found: C, 42.73; H, 7.10.

(20) A product of The Resinous Products and Chemical Co., Philadelphia, Pennsylvania.

(21) A product of Westvaco Chlorine Products Corp., South Charleston, West Virginia.

(22) No. 535, a product of Johns–Manville Co., New York, N. Y.

(23) Dimensions of the adsorbent.

(24) H. S. Isbell, *Bur. Standards J. Research*, **5**, 1185 (1930).

(25) A product of Columbia Chemical Division, Pittsburgh Plate Glass Co., Barberton, Ohio.

**6-α-D-Glucopyranosyl-α-D-glucopyranosyl Bromide Heptaacetate.**—Two grams of 6-α-D-glucopyranosyl-β-D-glucopyranose octaacetate was dissolved in 20 ml. of dry, freshly prepared, and ethanol-free chloroform. The solution was cooled in an ice–salt-bath and to it was added 5.2 ml. of dry glacial acetic acid containing 30–32% of hydrogen bromide. The mixture was allowed to stand at 0° for two hours after which it was poured into a separatory funnel containing cracked ice. The chloroform solution was washed four times with cold water and dried over anhydrous sodium sulfate. A sirup was obtained on solvent removal that was crystallized from absolute ethanol; m. p. 131–133°, $[\alpha]^{24}D$ +202° (*c* 1.75, chloroform).

*Anal.* Calcd. for $C_{26}H_{35}O_{17}Br$: C, 44.64; H, 5.04; Br, 11.41. Found: C, 44.74; H, 5.01; Br, 10.98.

**Methyl 6-α-D-Glucopyranosyl-β-D-glucopyranoside Heptaacetate.**—An amount of 0.19 g. of crystalline 6-α-D-glucopyranosyl-α-D-glucopyranosyl bromide heptaacetate was dissolved in 3 ml. of absolute methanol containing 0.2 g. of powdered Drierite, 0.2 g. of silver carbonate, 2 ml. of alcohol-free chloroform and a trace of iodine. The mixture was shaken overnight, filtered and evaporated to a sirup. The sirup was crystallized from ethanol–water and was recrystallized in the same manner; yield 0.06 g., m. p. 114–116°, $[\alpha]^{25}D$ +88.5° (*c* 2.0, chloroform).

*Anal.* Calcd. for $C_{26}H_{35}O_{17}(OCH_3)$: C, 49.84; H, 5.89; $OCH_3$, 4.77. Found: C, 49.97; H, 6.17; $OCH_3$, 4.96.

**Methyl 6-α-D-Glucopyranosyl-β-D-glucopyranoside.**—Methyl 6-α-D-glucopyranosyl-β-D-glucopyranoside heptaacetate (0.45 g.) was dissolved in 2.5 ml. of absolute methanol and heated under reflux for fifteen minutes with 0.2 ml. of 0.1 *N* sodium methoxide according to the method of Zemplén and Pacsu.[26] The reaction mixture was cooled and the methanol was removed under reduced pressure at 50–55°. The resulting sirup was dissolved in 5 ml. of water and the ionic material removed by passing the solution over Amberlite resins IR-100 and IR-4.[20] The effluent from the ion exchange columns was concentrated to a viscous sirup and the product was obtained as an amorphous solid by stirring in dioxane and concentrating under reduced pressure in a vacuum desiccator. This operation was repeated several times; yield 0.2 g., $[\alpha]^{24}D$ +50° (*c* 5.8, water).

*Anal.* Calcd. for $C_{12}H_{21}O_{10}(OCH_3)$: C, 43.82; H, 6.79; $OCH_3$, 8.71. Found: C, 44.11; H, 6.83; $OCH_3$, 8.68.

**Acknowledgment.**—We are pleased to acknowledge the advice of Professor Grant L. Stahly of the Department of Bacteriology of this University, in the preparation of the dextran.

## Summary

1. 6-α-D-Glucopyranosyl-β-D-glucopyranose octaacetate has been separated in crystalline condition by chromatographic methods from the acetylated hydrolyzate of dextran (from *Leuconostoc dextranicum*). This acetate was converted to the crystalline 6-α-D-glucopyranosyl-α-D-glucopyranosyl bromide heptaacetate.

2. 6-α-D-Glucopyranosyl-D-glucose and methyl 6-α-D-glucopyranosyl-β-D-glucopyranoside have been prepared in amorphous but chromatographically pure condition through their crystalline acetates and the 1,6-linkage established by periodate oxidation of the latter compound.

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(26) G. Zemplén and E. Pacsu, *Ber.*, **62**, 1613 (1929).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

# Further Studies of the Action of Pancreatic Amylase: A Differentiation of the Products of the Hydrolysis of Potato Starch and of a Linear Fraction from Corn Starch[1]

BY ROSLYN B. ALFIN[1a] AND M. L. CALDWELL

Considerable information concerning the mechanism of the enzymic hydrolysis of starch may be obtained from investigations of the action of purified amylases upon different substrates. The work reported briefly here deals with studies of the action of highly purified maltase-free pancreatic amylase[1,2] upon unfractionated potato starch, Lintner soluble potato starch, and upon a linear fraction from corn starch. The linear substrate was kindly supplied by Dr. T. J. Schoch. It was hydrolyzed completely to fermentable sugar by beta amylase and corresponded to 94% "amylose"[3] by potentiometric titration.[4] The studies included comparisons of the rates of the hydrolysis of the different substrates as well as of the products formed from them.

## Experimental

The hydrolyses were carried out at 40° as previously described.[2] Portions of the reaction mixtures were removed at intervals during the hydrolyses and examined for total reducing value by iodometric titration.[5] The reducing values were converted into their equivalents of maltose or of glucose and are reported in terms of the percentage yield of maltose or of glucose that could be obtained theoretically from the substrate. Because they give stoichiometric values, iodometric titrations give a measure of the number of glucosidic linkages of the substrate that have been ruptured. Portions of the reaction mixtures were also examined at intervals during the hydrolyses for maltose and for glucose by a modification of the method of Somogyi[6,7] for the selective fermentation of these sugars by washed bakers yeast. Examination of mixtures of known concentrations of glucose and of maltose in the presence of starch showed that these sugars could be accounted for under the conditions of these experiments to within 2%. The reducing value of the reaction mixtures in excess of that due to glucose and maltose was attributed to unfermented reducing dextrins. According to Myrbäck,[8,9] conditions which permit the fermentation of maltose also permit some fermentation of any straight-chain trisaccharide which may be present. No attempt was made in this work to distinguish between maltose and such a trisaccharide.

Average degrees of polymerization have been calculated for the reducing dextrins from their weights and reducing values. In the early stages of the hydrolyses, the values for the average degrees of polymerization of the dextrins cannot be taken as absolute values. Iodometric methods are stoichiometric for reducing sugars of low molecular weights. The application of the method to dextrins formed in the earlier stages of the hydrolyses may introduce certain errors. However, this method seems to be the most satisfactory of those at present available by which to obtain an indication of the breakdown of the substrates.

No evidence of maltase activity was found in composite mixtures of the preparations of purified pancreatic amylase even when the highest concentrations used here reacted for twenty-four hours at 40° with 1% maltose under the conditions used for the hydrolysis of starch.[10] Similarly, attempts to cause the selective inactivation of amylase and of glucosidase (dextrinase) activities failed to give evidence of the presence of traces of carbohydrases other than amylase in the preparations of purified pancreatic amylase.[2] Therefore, the results reported here do not appear to be influenced to any significant extent by the action of contaminating carbohydrases.

## Results

**Rates of Hydrolysis.**—The typical data summarized in Table I show that Lintner soluble

TABLE I

A COMPARISON OF THE ACTION OF PANCREATIC AMYLASE ON POTATO STARCH AND ON LINTNER SOLUBLE POTATO STARCH

| | Relative concentrations of amylase[b] | | | | | |
|---|---|---|---|---|---|---|
| | 1 | | 8 | | 32 | |
| | Reducing values as per cent. theoretical maltose, % | | | | | |
| Reaction[a] time, min. | Potato starch | Lintner soluble potato starch | Potato starch | Lintner soluble potato starch | Potato starch | Lintner soluble potato starch |
| 15 | 67 | 69 | 74 | 77 | 83 | 84 |
| 30 | 71 | 71 | 75 | 79 | 86 | 86 |
| 60 | 73 | 71 | 79 | 80 | 89 | 91 |
| 180 | 76 | 73 | 85 | 84 | 99 | 100 |
| 300 | 77 | 74 | 89 | 86 | 105 | 107 |

[a] Starch, 1%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2; 40°.[10] [b] Amylase preparation 1, 8 or 32 mg. per 1000 mg. starch.

TABLE II

A COMPARISON OF THE ACTION OF PANCREATIC AMYLASE ON LINTNER SOLUBLE POTATO STARCH AND ON A LINEAR FRACTION FROM CORN STARCH

| | Reducing value as per cent. theoretical maltose | |
|---|---|---|
| Reaction[a] time, min. | Lintner soluble potato starch | Linear fraction from corn starch |
| 15 | 74 | 95 |
| 30 | 77 | 96 |
| 60 | 79 | 99 |
| 120 | 85 | 100 |
| 180 | 90 | 108 |
| 360 | 94 | 111 |

[a] Starch or linear substrate, 0.5%; 0.01 *M* phosphate; 0.02 *M* chloride, *p*H 7.2; 40°.[10] Amylase preparation 8 mg. per 1000 mg. of carbohydrate.

(1) (a) The authors wish to thank the Corn Industries Research Foundation for generous grants in aid of this investigation. (b) The data reported here are taken from a dissertation submitted by Roslyn B. Alfin in partial fulfillment of the requirements for the degree Doctor of Philosophy in Chemistry under the Faculty of Pure Science of Columbia University.

(2a) H. C. Sherman, M. L. Caldwell and M. Adams, *J. Biol. Chem.*, **88**, 295 (1930); (2b) R. B. Alfin and M. L. Caldwell, THIS JOURNAL, **70**, 2534 (1948).

(3) R. W. Kerr and G. M. Severson, *ibid.*, **65**, 193 (1943).

(4) F. L. Bates, D. French and R. E. Rundle, *ibid.*, **65**, 142 (1943).

(5) M. L. Caldwell, S. E. Doebbeling and S. H. Manian, *Ind. Eng. Chem., Anal. Ed.*, **8**, 181 (1936).

(6) M. Somogyi, *J. Biol. Chem.*, **119**, 741 (1937).

(7) M. Somogyi and I. E. Stark, *ibid.*, **142**, 579 (1942).

(8) B. Örtenblad and K. Myrbäck, *Biochem. Z.*, **303**, 335 (1940).

(9) K. Myrbäck, *ibid.*, **304**, 147 (1940).

(10) H. C. Sherman, M. L. Caldwell and M. Adams, THIS JOURNAL, **50**, 2529, 2535, 2538 (1928).

TABLE III

A COMPARISON OF THE HYDROLYSIS OF POTATO STARCH AND OF A LINEAR FRACTION FROM CORN STARCH BY PURIFIED MALTASE-FREE PANCREATIC AMYLASE

| Reaction[a] time, min. | Reducing values as per cent. theoretical maltose: Total, Potato starch | Total, Linear substrate | Maltose[b], Potato starch | Maltose[b], Linear substrate | Glucose[b] as per cent. of theoretical glucose: Potato starch | Glucose[b] as per cent. of theoretical glucose: Linear substrate | Dextrins: Per cent. of total products by weight, Potato starch | Dextrins: Per cent. of total products by weight, Linear substrate | Dextrins: Average degree of polymerization, DP[c], Potato starch | Dextrins: Average degree of polymerization, DP[c], Linear substrate |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 2.94 | 1.55 | 1.57 | 1.32 | | | 98.4 | 98.7 | 144 | 860 |
| 10 | 4.08 | 3.34 | 1.92 | 2.29 | | | 98.1 | 97.7 | 89 | 464 |
| 15 | 5.36 | 5.27 | 2.12 | 3.56 | | | 97.9 | 96.4 | 60 | 113 |
| 20 | 6.40 | 6.64 | 2.53 | 3.83 | | | 97.5 | 96.2 | 51 | 68 |
| 25 | 7.49 | 8.19 | 2.94 | 4.09 | | | 97.1 | 95.9 | 43 | 47 |
| 30 | 8.58 | 9.97 | 3.46 | 5.27 | | | 96.5 | 94.7 | 38 | 40 |
| 45 | 12.8 | 14.8 | 4.50 | 6.42 | 0.24 | | 95.3 | 93.6 | 24 | 22 |
| 60 | 16.6 | 19.3 | 6.00 | 8.00 | .55 | 0.15 | 93.5 | 91.9 | 20 | 17 |
| 90 | 23.2 | 27.9 | 7.92 | 10.5 | .89 | .65 | 91.2 | 88.9 | 13 | 11 |

[a] Potato starch, 1% or linear substrate, 0.25%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2; 40°.[10] Amylase preparation, 0.01 mg. per 1000 mg. carbohydrate. [b] Glucose or maltose by selective fermentation with washed bakers yeast; dextrins by difference.[6,7] [c] Average degrees of polymerization of dextrins, calculated from their reducing values (maltose equivalents) as follows:

$$DP = \frac{\text{weight of dextrins (mg.)}}{\text{reducing value as maltose (mg.)}} \times 2$$

potato starch and unfractionated potato starch were hydrolyzed at practically the same rates when treated with the same concentrations of pancreatic amylase under comparable conditions. On the other hand, the data given in Tables II and III show significant differences in the rates of the hydrolysis of the linear substrate and of unfractionated potato starch.

In the very early stages of the hydrolyses, in the presence of relatively low concentrations of amylase (Table III), unfractionated potato starch was hydrolyzed more rapidly than the linear substrate. However, after approximately 3% of the glucosidic linkages of the substrates had been broken, the linear substrate was hydrolyzed more rapidly than the unfractionated starch (Tables II and III). These results suggest that there are more points for attack by pancreatic amylase in the branched chain than in the straight-chain components of starch, but that the reducing dextrins formed from the branched chain components are hydrolyzed less rapidly by the amylase than are the reducing dextrins formed from the straight chain components.

Further study of the data given in Table III shows not only that pancreatic amylase hydrolyzes

TABLE IV

PRODUCTS FORMED FROM POTATO STARCH AND FROM THE LINEAR SUBSTRATE BY PURIFIED MALTASE-FREE PANCREATIC AMYLASE[a]

| Reducing values as per cent. theoretical maltose: Total | Reducing dextrins[b], Potato starch | Reducing dextrins[b], Linear substrate | Maltose[b], Potato starch | Maltose[b], Linear substrate | Glucose[b] as per cent. of theoretical glucose: Potato starch | Glucose[b] as per cent. of theoretical glucose: Linear substrate | Dextrins[b]: Per cent. of total products by weight, Potato starch | Dextrins[b]: Per cent. of total products by weight, Linear substrate | Dextrins[b]: Average degrees of polymerization[c], Potato starch DP | Dextrins[b]: Average degrees of polymerization[c], Linear substrate DP |
|---|---|---|---|---|---|---|---|---|---|---|
| 2.9 | 1.33 | 0.5 | 1.57 | 2.0 | | | 98.4 | 98.0 | 148 | 392 |
| 5 | 2.8 | 2.3 | 2.2 | 2.7 | | | 97.8 | 97.3 | 70 | 85 |
| 10 | 6.5 | 5.5 | 3.5 | 4.5 | | | 96.5 | 95.5 | 30 | 35 |
| 15 | 9.5 | 8.5 | 4.7 | 6.5 | 0.40 | | 94.9 | 93.5 | 20 | 22 |
| 20 | 12.3 | 11.3 | 6.5 | 8.3 | 0.60 | 0.2 | 92.9 | 91.5 | 15 | 16 |
| 25 | 15.0 | 13.5 | 8.0 | 10.5 | 1.0 | 0.5 | 91.0 | 89.0 | 12 | 13 |
| 30 | 18.4 | 15.9 | 9.0 | 12.5 | 1.3 | 0.8 | 89.7 | 86.7 | 9.8 | 11 |
| 35 | 21.3 | 18.1 | 10.5 | 14.5 | 1.6 | 1.2 | 87.9 | 84.3 | 8.3 | 9.3 |
| 40 | 23.9 | 19.3 | 12.5 | 17.5 | 1.8 | 1.6 | 85.7 | 80.9 | 7.2 | 8.4 |
| 50 | 28.7 | 22.4 | 16.5 | 23.0 | 2.4 | 2.3 | 81.1 | 74.7 | 5.7 | 6.7 |
| 60 | 31.0 | 24.1 | 21.0 | 29.5 | 4.0 | 3.2 | 75.0 | 67.3 | 4.8 | 5.6 |
| 70 | 31.3 | 23.5 | 25.5 | 38.5 | 6.6 | 4.0 | 67.9 | 57.5 | 4.3 | 4.9 |
| 80 | 30.2 | | 31.0 | | 9.4 | | 59.6 | | 3.9 | |
| 90 | 22.5 | | 41.5 | | 13.0 | | 45.5 | | 4.0 | |
| 100 | 15.5 | | 50.5 | | 17.0 | | 32.5 | | 4.2 | |
| 110 | 15.2 | | 52.0 | | 21.4 | | 26.6 | | 3.5 | |

[a] Potato starch, 1% or linear substrate 0.25%; 0.01 *M* phosphate; 0.02 *M* chloride; *p*H 7.2; 40°.[10] [b] Glucose or maltose, by selective fermentation with washed bakers yeast; dextrins by difference.[6,7] [c] Please see Table III, footnote *c*.

the unfractionated starch and the linear substrate at different rates, but also that, for the same time intervals with the same concentration of amylase, the relative concentrations of the products formed from the two substrates differ.

A comparison of the products formed from the two substrates when equivalent numbers of glucosidic linkages had been ruptured is given in Table IV.

Examination of the data summarized in Tables III and IV shows that maltose was present in measurable concentrations from the very early stages of the hydrolysis. It was present in considerably larger concentrations in the hydrolyzates from the linear substrates than in those from potato starch whether the comparisons are made at the same time intervals with equal concentrations of amylase (after the first five minutes, Table III) or at equivalent stages in the hydrolyses of the two substrates (Table IV).

Glucose, also, was liberated by maltase-free pancreatic amylase from potato starch and from the linear components of corn starch although this sugar did not appear in the very early stages of the hydrolyses of these substrates. The data given in Table IV show that even after 15% of the glucosidic linkages of the substrates had been broken, only about 1% of glucose was present. Comparisons at the same time intervals with equal concentrations of amylase (Table III) and also at equivalent stages in the hydrolyses of the two substrates (Table IV) show that glucose appeared somewhat earlier and at equivalent hydrolysis was present in slightly larger concentrations in the hydrolyzates of potato starch than in those of the linear substrate. These differences in the concentrations of maltose and of glucose obtained from the two substrates suggest that the presence of 1,6-$\alpha$-D-glucosidic linkages in the branched chain components of starch interferes with the formation of maltose and favors the production of glucose by pancreatic amylase. This suggestion has received confirmation in subsequent studies with waxy maize starch, a branched chain substrate.[11]

The data given in Table IV also show that pancreatic amylase causes the rapid breakdown of both substrates to reducing dextrins of low average molecular weights and of relatively high reducing values. When the total reducing values of the hydrolyzates were equivalent to 50% theoretical maltose, reducing dextrins accounted for 57 and 45% of the total reducing value and for 81 and 75% by weight of the total products present in the hydrolyzates from the unfractionated starch and from the linear substrate, respectively. These findings are in accord with the observations of many investigators that pancreatic amylase causes a rapid decrease in the viscosities of its substrates and the rapid disappearance of products which give color with iodine. In the present studies, a clear red color with iodine was obtained when the reducing values of the reaction mixtures were equivalent to approximately 25% theoretical maltose. The achromic stage was reached at approximately 55% theoretical maltose.

Further study of the reducing dextrins (Tables III and IV) is of interest. During the early stages of the hydrolyses, the average molecular weights of the reducing dextrins liberated from the linear substrate were relatively high as compared to the average molecular weights of the dextrins from unfractionated potato starch. These findings again suggest that the branched chain components of starch offer more points of attack for pancreatic amylase than do the linear components. However, reducing dextrins were present in consistently lower concentrations in the hydrolyzates from the linear substrate than in those from the unfractionated starch. Therefore, the dextrins from the linear substrate appear to be hydrolyzed more readily than those from the branched chain components of starch.

Taken all together, the data lead to the conclusion that pancreatic amylase causes the random hydrolysis of both the branched and the linear components of starch.

Comparisons of the data obtained with unfractionated potato starch and with Lintner soluble potato starch, showed that a preliminary acid treatment of potato starch influences appreciably the course of the hydrolysis of starch by pancreatic amylase. As would be expected, the average molecular weights of the reducing dextrins were lower in the earlier stages of the hydrolysis of the acid treated, partially degraded starch. In the later stages of the hydrolyses, more maltose and smaller concentrations of residual dextrins of the same or of slightly higher average molecular weights were present in the hydrolyzates of Lintner soluble potato starch than in those of untreated potato starch.

## Summary and Conclusions

A study has been made of the action of purified maltase-free pancreatic amylase upon unfractionated potato starch, Lintner soluble potato starch and upon a linear fraction from corn starch.

No marked differences were observed in the rates of the hydrolysis of unfractionated potato starch, or of Lintner soluble potato starch when comparisons were based upon the total reducing values of the hydrolyzates obtained with the same concentrations of amylase reacting under comparable conditions.

On the other hand, marked differences were observed in the rates of hydrolysis of unfractionated potato starch and of the linear substrate.

The evidence indicates that there are more points for attack by pancreatic amylase in the branched chain components than in the linear components of starch but that the reducing dextrins formed from the branched chain components are hydrolyzed less readily by pancreatic amylase

(11) F. M. Mindell, A. L. Agnew and M. L. Caldwell, THIS JOURNAL, in press.

than are the reducing dextrins formed from the linear components. Marked differences were also found in the relative concentrations of the products formed by pancreatic amylase from unfractionated potato starch and from the linear substrate. These differences were observed whether the comparisons were made for the same time intervals with the same concentrations of amylase or at equivalent stages in the hydrolysis of the two substrates.

Maltose was present in measurable concentrations from the very early stages of the hydrolysis of unfractionated potato starch and of the linear substrate. However, this sugar was present in considerably higher concentrations in the hydrolyzates from the linear substrate than in those from potato starch whether comparisons are made at the same time intervals with equal concentrations of amylase or at equivalent stages in the hydrolysis of the two substrates.

Glucose was liberated by maltase-free pancreatic amylase from unfractionated potato starch and from the linear substrate although this sugar did not appear in the very early stages of the hydrolyses of these substrates. Comparisons made at the same time intervals with equal concentrations of amylase and also at equivalent stages in the hydrolyses of the two substrates show that glucose was liberated somewhat earlier and at equivalent hydrolysis was present in slightly larger concentrations in the hydrolyzates of potato starch than in those of the linear substrate.

A study of the results as a whole indicates that purified pancreatic amylase causes the random hydrolysis of both the straight and the branched chain components of starch.

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(12) Original manuscript received May 7, 1947.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

# Pantothenic Acid Studies. VI. A Biologically Active Conjugate of Pantothenic Acid[1]

BY TSOO E. KING, I. GORDON FELS AND VERNON H. CHELDELIN

In a previous paper from this Laboratory[2] glutamic acid was reported to enhance the growth promoting property of pantothenic acid in certain strains of yeast. A related observation was made by Woolley,[3] who found that glutamic acid was very active in reversing the inhibitory effect of ketone analogs of pantothenic acid in organisms which require the preformed vitamin in the medium. Although the mechanism of these actions is at present obscure, it appeared possible that glutamic acid might conjugate with pantothenic acid or β-alanine (and possibly with pantoic acid in the proper linkage) to produce a substance which is more active for the growth of microörganisms. Since numerous possibilities exist for combinations of pantothenic acid, glutamic acid and β-alanine, their direct preparation was deferred in favor of biosynthesis of active materials by resting cells.

Glutamic acid was incubated in buffered saline with β-alanine or with pantothenic acid in the presence of resting yeast cells (*S. cerevisiae* L.M. strain, A.T.C.C. No. 9371). The resulting mixture showed extremely great activity, occasionally over a thousand times that of the β-alanine or pantothenic acid present, as measured in a pantothenic acid-free medium using L.M. yeast. The incubated product from β-alanine was always more active than that from pantothenic acid. However, the results were not consistent; in six of eighteen experiments no increase in activity was obtained, and the trend among the later experiments was toward increases of twofold or less. It was not possible to tell whether this was due to inconsistencies in synthesis of active material or to variable requirements by the assay organisms. It was therefore decided to seek another assay organism for the active principle, as well as new sources from which it might be isolated.

## Stimulation of Growth in *S. cerevisiae* 2190

Strain 2190 (National Collection of Cultures, London) was observed previously[4] to grow very feebly in a pantothenic acid containing medium which was satisfactory for the growth of sixteen other yeasts. The addition of glutamic acid improved the growth considerably, although further enhancement was obtained with yeast extract. The effects are summarized in Table I. The glutamic acid effect recalls the similar observation in strains L.M. and 2504.[2] However, strain 2190 was not stimulated by the mixture resulting from incubation with resting L.M. yeast cells. The extra stimulatory effect of yeast extract upon 2190 was also manifested by acid-hydrolyzed casein, as well as by amino acid mixtures containing no additional glutamic acid.

(1) This investigation was supported by research grants from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service, the Nutrition Foundation, Inc., and Swift and Company. Published with the Approval of the Monographs Publications Committee, Oregon State College, Research Paper No. 131, School of Science, Department of Chemistry. Presented before the Division of Biological Chemistry, American Chemical Society, 114th meeting, Portland, Oregon, September, 1948. A preliminary report was given at the sixth meeting of the Oregon Academy of Science, Salem, Oregon, February, 1948. For the previous paper in this series, see T. E. King, R. L. Stearman and V. H. Cheldelin, THIS JOURNAL, **70**, 3969 (1948).

(2) T. E. King and V. H. Cheldelin, *Arch. Biochem.*, **16**, 231 (1948).

(3) D. W. Woolley, *J. Biol. Chem.*, **163**, 481 (1946).

(4) H. P. Sarett and V. H. Cheldelin, *J. Bact.*, **49**, 31 (1945).

TABLE I

THE INFLUENCE OF GLUTAMIC ACID (GA), YEAST EXTRACT (YE) AND CASEIN HYDROLYSATE (CH)[a] UPON THE GROWTH OF *S. cerevisiae* 2190

| Added PA[b] | Optical[c] density | 0.5 γ PA Added GA, mg. | 0.5 γ PA Optical density | 5 mg. YE Added PA, γ | 5 mg. YE Optical density | 5 mg. YE + 2 mg. GA Added PA, γ | 5 mg. YE + 2 mg. GA Optical density | 5 mg. CH Added PA, γ | 5 mg. CH Optical density |
|---|---|---|---|---|---|---|---|---|---|
| 0.0 | 0.000 | 0.5 | 0.210 | 0.1 | 0.320 | 0.1 | 0.320 | 0.00 | 0.000 |
| .1 | .100 | 1.0 | .240 | .5 | .320 | .5 | .320 | .01 | .020 |
| .5 | .090 | 2.0 | .250 | | | | | 0.50 | .580 |
| 1.0 | .080 | | | | | | | 1.00 | .580 |
| 2.0 | .100 | | | | | | | | |

[a] Vitamin-free casein was hydrolyzed with 20% hydrochloric acid and the hydrochloric acid was removed by repeated distillation *in vacuo*. [b] Weight of calcium pantothenate (PA). [c] Growth shown by turbidity in terms of optical density (= 2 − log per cent. transmission).

## The Response of Acetobacter suboxydans to Extracts of Natural Materials

Nachmansohn and Berman[5] have obtained active preparations of the coenzyme for acetylation of choline from heart tissue. In view of the fact that Lipmann and co-workers[6,7] showed this coenzyme (coenzyme A) to contain pantothenic acid, and in view of the failure of yeast 2190 to respond to the resting cell preparation, additional experiments were carried out with liver, yeast and heart extracts. The response of a given test organism to these extracts was measured in terms of pantothenic acid. The apparent pantothenic acid contents so obtained were checked by means of other assays using *L. arabinosus*, which utilized the intact vitamin, and by L.M. yeast, which, after hydrolysis of the preparations with 6 *N* hydrochloric acid for one hour, indicated the total β-alanine content. *A. suboxydans* was regarded as a preferred organism for study because of its relatively great sensitivity to pantoic acid[8] and the fact that *A. suboxydans* assays of certain tissues[8] frequently gave higher values than those obtained with *L. arabinosus*.

It was reported in a preliminary note[9] that when fresh liver or heart muscle was heated and brought to *p*H 4.5–5.0 to remove most of the protein, the filtrates from these preparations possessed considerably higher apparent pantothenic acid contents when assayed by *A. suboxydans* than when *L. arabinosus* or G.M. yeast was used. The activity of these extracts was far higher than could be accounted for by the pantothenic acid present, as measured by *L. arabinosus* after digestion with takadiastase and papain.[10] That the active material in these extracts contained pantothenic acid was strongly suggested by the fact that no compound is known to be able to substitute for the vitamin or the pantoic acid moiety in media in which it is lacking, and also by the observation that the β-alanine content increased upon hydrolysis. After six hours hydrolysis, the β-alanine values accounted for roughly half of the activity exhibited in *A. suboxydans*, and it was felt that the active principle was therefore about twice as effective as the free vitamin for this organism. The activity was thought to be due to a conjugated form of pantothenic acid which for convenience will be abbreviated PAC in the present paper.

When pantothenic acid (or pantoic acid[8]) was the limiting factor for growth of *A. suboxydans*, growth curves were sigmoidal in shape. The cultures containing adequate amounts of the vitamin grew rather slowly, requiring sixty to seventy hours to reach optical density values of 0.5 or greater. By contrast, the curves obtained with the conjugate were nearly straight and the rate of growth was much more rapid than in those containing pantothenic acid. As may be seen in Fig. 1, flasks containing pantothenic acid showed very little growth after twenty-four hours of incubation, whereas those containing the conjugate had already exhibited perceptible turbidity.

## Comparison of the Pantothenic Acid Conjugate with Coenzyme A. Acetylation Studies

**Sulfanilamide.**—Lipmann and co-workers[6] reported that coenzyme A possessed the ability to acetylate sulfanilamide in the presence of adenosine triphosphate (ATP) and an apoenzyme from pigeon liver. The question whether PAC is identical with coenzyme A can be answered by comparing the acetylating power of the

TABLE II

THE ACETYLATION OF SULFANILAMIDE BY COENZYME A AND THE PRESENT PANTOTHENIC ACID CONJUGATE (PAC)

| | Optical density |
|---|---|
| Sulfanilamide, 20γ | 0.039 |
| 50γ | .070 |
| 100γ | .110 |
| Lipmann's coenzyme A (1.1 mg.) + 100γ sulfanilamide | .082 |
| Duplicate | .081 |
| PAC (15 mg.) + 100γ sulfanilamide | .110 |
| Duplicate | .110 |

(5) D. Nachmansohn and M. Berman, *J. Biol. Chem.*, **165**, 55 (1946).

(6) F. Lipmann, N. D. Kaplan, G. D. Novelli, L. C. Tuttle and B. M. Guirard, *J. Biol. Chem.*, **167**, 869 (1947).

(7) F. Lipmann and N. O. Kaplan, *ibid.*, **162**, 743 (1946).

(8) H. P. Sarett and V. H. Cheldelin, *J. Biol. Chem.*, **159**, 311 (1945).

(9) T. E. King, L. M. Locher and V. H. Cheldelin, *Arch. Biochem.*, **17**, 483 (1948).

(10) E. H. Hoag, H. P. Sarett and V. H. Cheldelin, *Ind. Eng. Chem., Anal. Ed.*, **17**, 60 (1945).

two preparations. The results in Table II show that the present conjugate is not active in the acetylation of sulfanilamide. The sample of Lipmann's preparation used contained about 11γ of pantothenic acid, while 15 mg. of PAC contained about 10 γ of pantothenic acid activity for *A. suboxydans*.

**Choline.**—Since Lipmann and Kaplan have shown[7] that coenzyme A is also active in the acetylation of choline (and is therefore presumably identical with Nachmansohn and Berman's coenzyme[5]), the PAC preparation was also examined for ability to acetylate choline under the conditions described by Nachmansohn and co-workers.[5,11] The results are summarized in Table III, where the samples of PAC used contained approximately 58 γ, 21 γ and 15 γ of pantothenic acid activity, respectively. From this table, it is apparent that PAC possessed no activity in the acetylation of choline. The slight response in sample No. 300 was probably not significant.

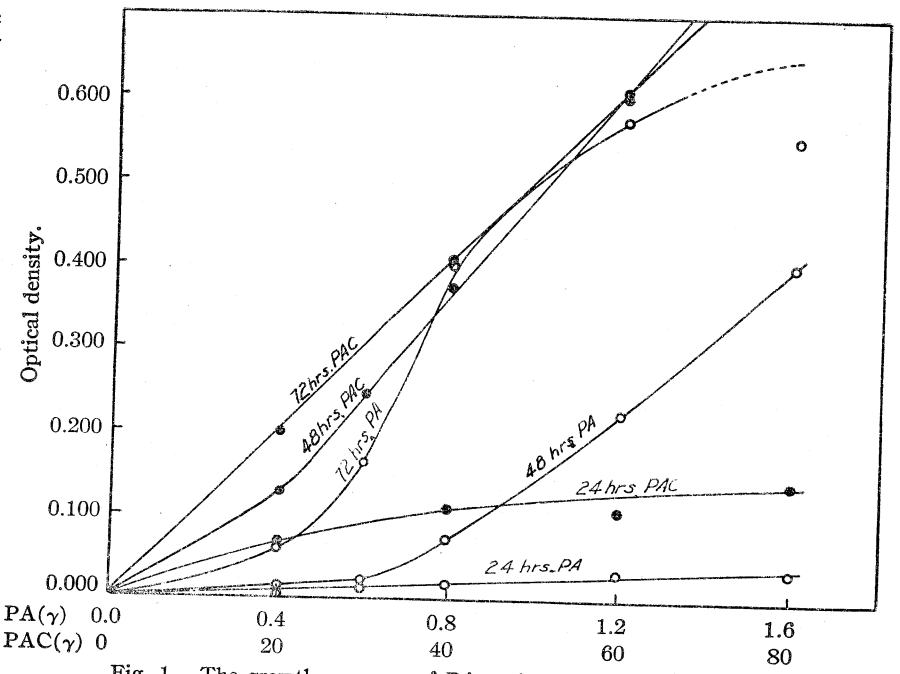



Fig. 1.—The growth response of PA and PAC in *A. suboxydans*.

TABLE III

THE ACETYLATION OF CHOLINE BY COENZYME A AND PAC

| Material added | Height of contraction curve, mm. | |
|---|---|---|
| Acetylcholine (6.5γ) | 50 | |
| Acetylcholine (3γ) | | 40 |
| Control without ATP | 3 | |
| Apoenzyme from rat brain without dialysis | 11 | 18 |
| Coenzyme A (3 mg.) | 11 | |
| PAC, no. 300 (30 mg.) | 6 | 4 |
| PAC, no. 700 (30 mg.) | 0 | 0 |
| PAC, no. 701 (30 mg.) | 0 | 0 |

## The Behavior of Alkali toward the Pantothenic Acid Conjugate

Neal and Strong[12] reported the existence of an alkali-stable form of pantothenic acid which remained in pork liver after alkaline hydrolysis and which could be utilized with greater efficiency by lactic acid bacteria after takadiastase and papain digestion. Since preliminary experiments had indicated that PAC was somewhat more resistant to alkali than the free vitamin, the possible similarity of PAC and the alkali-stable factor was tested. This was accomplished in two ways: by determining the *A. suboxydans* activity of liver autoclaved with alkali, and by noting the extent of degradation of PAC concentrates by alkali and their possible conversion into alkali-stable residues.

The results in Table IV indicate that the conjugate is different from the alkali-stable factor, since heating of sample 701 with alkali destroyed virtually all of the activity for *A. suboxydans*. On the other hand, a small residue of activity remained both in sample 701 and in fresh pork liver. This could be due either to the presence of the alkali-stable form in these preparations or to its formation from PAC during hydrolysis. That this conversion actually takes place is indicated by the increased activity of sample 701 for *L. arabinosus* after treatment with alkali (*cf.* samples 3 and 4, 6 and 7 of Table IV). The Neal–Strong factor (or something biologically indistinguishable from it) may thus be considered as one of the degradation products of PAC.

## Comparison of the Conjugate with Blood Pantothenic Acid

Wright[13] noted that pantothenic acid existed in bound form in blood. The vitamin appeared to be combined to protein, since it could be precipitated by tungstic acid and could be released from combination by takadiastase digestion or by autoclaving for short periods. In contrast, PAC is not precipitated by tungstic acid, and is not destroyed by heat or enzymes under the above conditions.

(11) D. Nachmansohn and A. L. Machado, *J. Neurophysiol.*, **6**, 397 (1943).

(12) A. L. Neal and F. M. Strong, THIS JOURNAL, **65**, 1659 (1943)

(13) L. D. Wright, *J. Biol. Chem.*, **141**, 261 (1943).

TABLE IV

THE BEHAVIOR OF ALKALI TOWARD THE PANTOTHENIC ACID CONJUGATE

| Sample no. | Sample | Weight | Total volume of sample Ml. | Subst. | Time of standing at room temp., hr. | Time of autoclaving (15#), hr. | Millimoles of NaCl added[a] | Pantothenic acid activity, γ/g. *L. arabinosus* Hot water extract[b] | *L. arabinosus* Enzyme digest[c] | *A. suboxydans* Hot water extract |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Pork liver | 100 g. | 600 | $H_2O$ | 0 | 2 | 600 | 33 | 33–40 | 30–60 |
| 2 | Pork liver | 100 g. | 600 | 0.1 *N* NaOH | 0 | 2 | 0 | 0.5 | 6.7–7.8 | 5.2 |
| 3 | PAC No. 701 | 200 mg. | 20 | $H_2O$ | 0 | 2 | 10 | 0.7 | 3 | 500 |
| 4 | PAC No. 701 | 200 mg. | 20 | 0.5 *N* NaOH | 0 | 2 | 0 | 1.0 | 10 | 12 |
| 5 | PAC No. 701 | 250 mg. | 5 | $H_2O$ | 48 | 0 | 0[d] | | 10 | 500 |
| 6 | PAC No. 701 | 250 mg. | 5 | 0.5 *N* NaOH | 48 | 0 | 0 | | 10 | 400 |
| 7 | PAC No. 701 | 250 mg. | 5 | 0.5 *N* NaOH | 48 | 1.5 | 0 | | 80 | 0 |

[a] Since *A. suboxydans* is influenced by moderate concentrations of sodium chloride, a sufficient amount was added to equal that present after alkali hydrolysis and neutralization. [b] Samples treated under stated conditions, filtered; filtrates assayed for PA with *L. arabinosus* 17–5(10). [c] Samples treated under stated conditions, then digested with takadiastase and papain, filtered and assayed for PA (10). [d] The amount of NaCl present in samples (6) and (7) would not influence the growth of *A. suboxydans*.

## Properties of the Conjugate

Certain important properties of the conjugate have been observed in connection with concentration studies. Although the molecule appears to be fairly large as indicated by its failure to dialyze through cellophane into running distilled water over a sixty-hour period, it is not precipitated at all by the Folin–Wu tungstic acid reagent. The latter behavior suggests that it may be a polypeptide containing several acidic groups. The previous statement[9] that the conjugate appears to contain glutamic acid is in line with these observations. In addition, a preparation of intestinal phosphodiesterase was found to liberate pantothenic acid from the conjugate. This indicates the presence of phosphoric acid linkages in the conjugate.

The conjugate is only slightly precipitated by barium hydroxide under the conditions employed by Nachmansohn and Berman.[5] This is in contrast to their results with the coenzyme for choline acetylation. The precipitation with barium hydroxide has been used in spite of the large losses in activity, however, since it is a very effective agent for removing the impurities associated with the conjugate. Concentrations of over ten-fold in *A. suboxydans* activity are regularly obtained by this means.

Charcoal (Norite A), which can be used for the adsorption of free pantothenic acid or the diphosphate,[14] also adsorbs the conjugate. Adsorption is nearly complete when 10% by weight of charcoal is employed. On the other hand, attempts at elution have so far been unsuccessful. Lloyd's reagent is effective (60–80% adsorbed when 200% by weight is used), and elution with dilute ammonia is nearly quantitative. Combination of this treatment with tungstic acid precipitation regularly results in concentrations in activity of over twenty fold. Lloyd's reagent removes much extraneous coloring matter, so that the eluates possess a light yellow color. The ion exchange resins are also fairly effective in both acid and alkaline solutions (equal weights adsorb 50–80%), but weaker adsorbents such as corn starch and barium sulfate are of little value.

(14) D. W. Woolley, *J. Biol. Chem.*, **134**, 461 (1940).

## Experimental Methods

The organisms used for testing β-alanine, pantothenic acid and PAC were *Saccharomyces cerevisiae*, strains L.M. and G.M., *Lactobacillus arabinosus* 17-5 and *Acetobacter suboxydans*, A.T.C.C. No. 621, respectively. All tests were performed using previously published methods.[2,8,10] "Free" pantothenic acid was determined by direct assay with *L. arabinosus*. Enzyme digestions were carried out with takadiastase and papain.[15]

The acetylation of sulfanilamide was performed according to Lipmann.[16]

Coenzyme A or PAC in proper concentrations were placed into the chambers of Warburg flasks, together with a salt mixture, sodium acetate, ATP, sulfanilamide and dialyzed pigeon liver. After shaking ninety minutes the residual sulfanilamide concentrations were determined by the method of Bratton and Marshall[17] in an electrophotometer.

The acetylation of choline in the presence of ATP was performed in a Warburg apparatus under an atmosphere of nitrogen with the same technique as used by Nachmansohn and co-workers.[5,11] The method for determining acetylcholine followed essentially Stephenson and Rowatt's modification[18] of Chang's method.[19] The standard acetylcholine solution was prepared immediately before use. A solution of eserine was likewise prepared in buffered frog Ringer's solution. The rectus abdominis muscle (frog) was excised and placed in a glass chamber of 30-ml. capacity with buffered Ringer's solution and aerated with a steady stream of oxygen bubbles for about one hour. The Ringer's solution was then drained off and replaced by eserinized buffered Ringer's solution and aerated for another hour. The muscle was then used for testing acetylcholine activity.

### Concentration Studies

Fresh pork heart was freed as much as possible from blood and connective tissue, passed several times through a fine meat grinder, and diluted with about twice its volume of water. Live steam was introduced and the mixture

(15) V. H. Cheldelin, M. A. Eppright, E. E. Snell and B. M. Guirard, Univ. Texas Publ. No. 4237, 15 (1942).

(16) F. Lipmann, *J. Biol. Chem.*, **160**, 173 (1945).

(17) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(18) M. Stephenson and E. Rowatt, *J. Gen. Microbiol.*, **1**, 279 (1947).

(19) H. C. Chang and J. H. Gaddum, *J. Physiol.*, **79**, 255 (1933).

was boiled for a few minutes. After cooling, the residue was removed by filtration, washed with water and discarded. The filtrate was brought to *p*H 4.0–4.5 with acetic acid, and after standing several hours at 5° was filtered again. The resulting filtrate was then precipitated either with 20–30 volumes of acetone, or with barium hydroxide until precipitation was complete and a slight excess of the alkali remained. The solid from the acetone precipitation was usually of a very dark color and contained a large percentage of protein. It was hygroscopic but would not redissolve completely in water. Since the volume of acetone required was so great, barium precipitation was usually employed.

The barium precipitate was separated by centrifugation and washed several times with water (*p*H 9.5–10.0) and finally with a small amount of distilled water. It was then decomposed with excess 0.5 *M* sodium sulfate. The filtrate after removal of barium sulfate was usually golden yellow in color, with *p*H approximately 10. This preparation, after precipitation with acetone, filtration and drying of the precipitate *in vacuo*, contained one to five $\gamma$ of pantothenic acid activity per mg. of organic solids.

By combining the above treatments with tungstic acid precipitation, adsorption with Lloyd reagent, and dialysis, concentrates containing up to 5% pantothenic acid activity have been obtained, based upon the total solid matter present. Further studies are in progress to accomplish the isolation of the pure conjugate.

**Acknowledgment.**—The authors wish to acknowledge with thanks, gifts of coenzyme A and alkaline phosphodiesterase from Drs. G. D. Novelli and F. Lippman, to Ruth S. Langdon and Eleanor C. Parsons for technical assistance, and to Dr. Rosalind Wulzen for helpful suggestions and the use of laboratory facilities for the testing of acetylcholine activity.

## Summary

A conjugate of pantothenic acid (abbr. PAC) has been obtained in partially purified form from pork heart. It appears to be roughly twice as active for the growth of *A. suboxydans* as is the free vitamin. Growth of this organism is also more rapid with the conjugate than with pantothenic acid. The present conjugate is different from coenzyme A, the alkali-stable form of pantothenic acid or the protein conjugate found in blood.

From the behavior toward tungstic acid and dialysis, PAC appears to be an acidic molecule of molecular size considerably greater than pantothenic acid. Studies are in progress to accomplish the isolation of the pure material.

CORVALLIS, OREGON RECEIVED JULY 6, 1948

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[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Streptomycin. IX.[1] The Stepwise Degradation of Mannosidostreptomycin

BY HOMER E. STAVELY[2] AND JOSEF FRIED

Streptomycin concentrates have been shown to contain in addition to streptomycin a second antibiotic substance which has been termed streptomycin B or mannosidostreptomycin.[1] The degradation of this substance to derivatives of streptidine, streptobiosamine and D-mannose has been the subject of a preliminary communication.[3] The present paper gives a detailed account of those findings and, moreover, presents experimental data showing that in mannosidostreptomycin D-mannose is attached glycosidically to the streptobiosamine moiety through one of the three free hydroxyl groups of N-methyl-L-glucosamine.

Mannosidostreptomycin was isolated in the pure state as the crystalline reineckate which was converted to an amorphous hydrochloride.[1] Analyses of these two salts indicated that this antibiotic is a triacidic base of the composition $C_{27}H_{49}O_{17}N_7$. The difference in composition, $C_6H_{10}O_5$, between this substance and streptomycin appeared to be due to one hexose unit attached to the latter with the loss of one molecule of water. This assumption was substantiated[4] by the following degradation reactions.

When a solution of mannosidostreptomycin in 1.3 *N* methanolic hydrogen chloride was allowed to stand at room temperature for two days and the residue from the methanol solution, after careful neutralization with silver carbonate, was acetylated, an amorphous material was obtained, which upon chromatography on alumina afforded the two anomers of methyl tetraacetyl-D-mannopyranoside, as well as methyl tetraacetyl streptobiosaminide dimethyl acetal[5] and octaacetyl streptidine,[6] the latter two substances identical with the products obtained by similar degradation of streptomycin.

Confirmatory evidence as to the presence of D-mannose, streptobiosamine and streptidine in

(1) Paper VIII of this series: J. Fried and E. Titus, THIS JOURNAL, **70**, 3615 (1948).

(2) Present address: Commercial Solvents Corporation, Terre Haute, Indiana.

(3) J. Fried and H. E. Stavely, THIS JOURNAL, **69**, 1549 (1947).

(4) The experimental evidence adduced in this paper does not permit any conclusions as to the position of attachment of the streptobiosamine moiety to streptidine in mannosidostreptomycin. It is most likely, however, that this linkage involves the 4-hydroxyl group of streptidine as has been shown to be the case in streptomycin by Kuehl, Peck, Hoffhine, Peel and Folkers, *ibid.*, **69**, 1234 (1947).

(5) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn and K. Folkers, *ibid.*, **68**, 2557 (1946).

(6) R. L. Peck, R. P. Graber, A. Walti, E. W. Peel, C. E. Hoffhine, Jr., and K. Folkers, *ibid.*, **68**, 29 (1946).

mannosidostreptomycin was adduced by mercaptolysis. In using the anhydrous conditions described by Kuehl, Flynn, Brink and Folkers[7] for the mercaptolysis of streptomycin incomplete reaction was often observed. However, when aqueous hydrochloric acid[8] was substituted for the gaseous hydrogen chloride reaction was complete after fifteen hours of shaking at room temperature. Chromatography of the crude acetylated product yielded octaacetyl streptidine, ethyl tetraacetyl-β-thiostreptobiosaminide diethyl mercaptal[8] and the α- and β-forms of ethyl tetraacetyl-1-thio-D-mannopyranoside.[9]

Following the identification of the cleavage products obtained from mannosidostreptomycin our efforts were directed toward ascertaining the site of the linkage joining D-mannose to the remaining portion of the molecule. On the assumption that the linkage between streptobiosamine and streptidine is identical for the two streptomycins, D-mannose could be attached glycosidally through one of the three free hydroxyl groups of the N-methyl-L-glucosamine moiety, through the 2-,5- or 6-hydroxyl groups of streptidine or, least probably, through the tertiary hydroxyl group of streptose. Moreover, the possibility of a linkage involving one of the nitrogenous groups could not be disregarded. Evidence that the D-mannose moiety is attached to N-methyl-L-glucosamine was adduced by partial cleavage to a product in which the linkage between these two moieties had remained intact. Initial trials to effect such an incomplete degradation by methanolysis of dihydromannosidostreptomycin[1] using a low enough concentration of hydrogen chloride to leave approximately half the starting material unreacted led to complete cleavage of the remaining portion into α- and β-methyl D-mannopyranosides, methyl-α-dihydrostreptobiosaminide[10] and streptidine, all isolated as the crystalline acetyl derivatives. Suitable experimental conditions were finally arrived at on the basis of the following observations. When a solution of mannosidostreptomycin or its dihydro-derivative in 1 *N* sulfuric acid was allowed to stand at 45° for twenty hours streptidine sulfate monohydrate separated in almost quantitative yield, but no mannose was detectable among the reaction products upon addition of phenylhydrazine to the neutralized hydrolysate. On the other hand, a quantitative yield of mannose phenylhydrazone was obtained when the hydrolysis was conducted at 100° for one hour. These findings indicated that D-mannose is attached to the streptobiosamine moiety and not to streptidine. Removal of the sulfate and excess chloride ions from the solution obtained by hydrolysis of dihydromannosidostreptomycin at 45°, followed by lyophilization, afforded a crude amorphous material which was acetylated immediately and purified by chromatography. The resulting product, although amorphous, gave analytical figures in accord with those calculated for the nonaacetate of a trisaccharide, which has been designated dihydromannosidostreptobiosamine on the basis of its cleavage by methanolysis into the anomeric methyl D-mannopyranosides and methyl dihydrostreptobiosaminide, and on the basis of further evidence discussed below. A differential acetyl determination on this nonaacetate indicated that eight of the acetyl groups were attached to oxygen and the remaining one to nitrogen, ruling out the possibility that D-mannose is linked to streptobiosamine via the N-methylamino group.

The acetolysis procedure of Hann and Hudson[11] when applied to methyl pentaacetyl dihydrostreptobiosaminide resulted in the quantitative cleavage of this disaccharide into its component sugars,[12] only one of which (pentaacetyl N-methyl-L-glucosamine) was extractable from the neutralized reaction mixture by chloroform. Whereas the residue remaining after evaporation of this chloroform solution invariably crystallized, the analogous fraction obtained by acetolysis of the nonaacetate of dihydromannosidostreptobiosamine remained amorphgus even after chromatooraphic purification on alumina. Indications from analytical figures that this product represents the octaacetate of a disaccharide composed of D-mannose and N-methyl-β-L-glucosamine were confirmed by methanolysis and reacetylation, which readily afforded the two anomeric methyl tetraacetyl-D-mannopyranosides as well as methyl tetraacetyl-N-methyl-β-L-glucosaminide. The latter was identified by comparison with the product obtained by methanolysis and reacetylation of pentaacetyl N-methyl-α-L-glucosamine. On the basis of this cleavage reaction and of the above described degradation of dihydromannosidostreptobiosamine to derivatives of D-mannose and dihydrostreptobiosamine the amorphous acetolysis product is formulated as the octaacetate of a D-mannoside of N-methyl-L-glucosamine.

Information concerning the anomeric character of the glycosidic linkage between the two sugars can be derived from available data by the application of Hudson's rules of isorotation.[13] On the assumption that the linkage between streptobiosamine and streptidine is of the α-type, as has been shown for streptomycin,[14] the molecular rotation of mannosidostreptomycin can be expressed as $[M]_B = [M]_A + A_{St.} + B_{Man.}$, where $[M]_B$ and $[M]_A$ are the molecular rotations of mannosidostreptomycin and streptomycin, respectively, $A_{St.}$

(7) F. A. Kuehl, Jr., E. H. Flynn, N. G. Brink and K. Folkers, *ibid.*, **68**, 2096 (1946).

(8) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, THIS JOURNAL, **68**, 2120 (1946).

(9) J. Fried and D. E. Walz, *ibid.*, **71**, 140 (1949).

(10) J. Fried and O. Wintersteiner, *ibid.*, **69**, 79 (1947).

(11) R. M. Hann and C. S. Hudson, *ibid.*, **56**, 2465 (1934).

(12) H. E. Stavely, O. Wintersteiner, J. Fried, H. L. White and M. Moore, *ibid.*, **69**, 2742 (1947).

(13) C. S. Hudson, THIS JOURNAL, **31**, 66 (1909).

(14) R. U. Lemieux, C. W. DeWalt and M. L. Wolfrom, *ibid.*, **69**, 1838 (1947).

the contribution of carbon atom one of D-mannose to the molecular rotation of mannosidostreptomycin, and $B_{Man.}$ the contribution of the basal chain of the mannose moiety as calculated from the molecular rotations of $\alpha$- and $\beta$-D-mannose ($A + B = +5380$, $-A + B = -2940$). $A_{St.}$, the quantity characteristic of the glycosidic linkage in question then becomes $A_{St.} = [M]_B - [M]_A - B_{Man.}$ or, after substitution of the experimental values, $A_{St.} = (871)(-47) - (691)(-86) - 1220 = +17180$. The positive numerical value for $A_{St.}$ and the fact that the mannose moiety in mannosidostreptomycin has the D-configuration indicate that the glycosidic linkage is of the $\alpha$-D type. The absolute value of 17180 is in reasonable agreement with the value for $A_{OMe}$ (14230) calculated from the molecular rotations of the two anomeric methyl D-mannopyranosides.

Experimental data establishing the exact site of the glycosidic linkage between D-mannose and the remaining portion of the molecule will be presented in a subsequent publication.

## Experimental[15]

**Methanolysis of Mannosidostreptomycin.**—Mannosidostreptomycin trihydrochloride[3](1.1 g.) was dissolved in 30 ml. of 1.3 *N* methanolic hydrogen chloride. After two days the spectrophotometric maltol assay[1] showed a decline from the original $\Delta E$ value of 126 to less than 3. An excess of silver carbonate was added to the flask and the mixture was stirred for four hours. After standing overnight the mixture was filtered and excess silver ion removed from the solution by means of hydrogen sulfide. After filtration through charcoal the filtrate was evaporated *in vacuo* and the residue (710 mg.) was acetylated in pyridine (5 ml.)-acetic anhydride (5 ml.) for twenty-four hours. After removal of the solvents *in vacuo* the residue was dissolved in chloroform, the solution washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and water, and the chloroform extract dried over sodium sulfate. The residue from the chloroform solution was dried and extracted several times with dry ether, most of the streptidine octaacetate remaining undissolved. It was crystallized from ethanol, m. p. 255–257° (dec.).

*Anal.* Calcd. for $C_8H_{10}N_6O_4(COCH_3)_8$: N, 14.04. Found: N, 13.68.

The dried ether residue (874 mg.) was dissolved in benzene (25 ml.) and chromatographed on an acetic acid-washed alumina[16] column, 1.5 × 20 cm. The chromatogram was developed with 100 ml. of benzene. The first 25 ml. of eluate yielded 270 mg. of residue which crystallized from an ether solution on evaporation. It was recrystallized twice from ether–pentane, $[\alpha]^{24}D$ +49° (*c*, 1.1 in chloroform). The m. p. was 65–66°, not depressed on admixture of an authentic sample of methyl tetraacetyl-$\alpha$-D-mannopyranoside.

*Anal.* Calcd. for $C_7H_{10}O_6(CH_3CO)_4$: C, 49.72; H, 6.12; $CH_3O$, 8.56; acetyl, 47.5. Found: C, 50.01; H, 6.08; $CH_3O$, 8.98; acetyl, 47.7.

The succeeding 25 ml. of benzene contained 30 mg. of a substance which likewise crystallized from ether but which melted unsharply from 130 to 150° and was probably a mixture of the $\alpha$- and $\beta$-anomers of methyl tetraacetyl-D-mannopyranoside. Further elution with 50 ml. of benzene yielded only 22 mg., likewise crystalline from ether, melting from 100 to 110°.

The column was then eluted with a mixture of 70 ml. of benzene and 30 ml. of ether and the eluate collected in 20-ml. portions. The residues all crystallized from ether and melted unsharply between 100 and 125°. Elution with 50 ml. of ether then yielded 131 mg. of crystalline material which melted at 124–125° after two recrystallizations from ether–hexane; $[\alpha]^{25}D$ −122° (*c*, 0.56 in chloroform). There was no melting point depression on admixture of an authentic specimen of methyl tetraacetyl-$\alpha$-streptobiosaminide dimethyl acetal.

*Anal.* Calcd. for $C_{13}H_{18}NO_7(OCH_3)_3(COCH_3)_4$: C, 50.97; H, 6.95; N, 2.48; $CH_3O$, 16.5; O-acetyl, 22.9. Found: C, 51.01; H, 6.74; N, 2.60; $CH_3O$, 16.9; O-acetyl,[17] 23.2.

The material which had been eluted with 30% ether in benzene was combined with the residue from the methyl tetraacetyl-$\alpha$-streptobiosaminide dimethyl acetal mother liquor, dissolved in 15 ml. of benzene and rechromatographed on a column of alumina, 0.8 × 15 cm. Nothing could be eluted with benzene. Elution with 100 ml. of 30% ether in benzene afforded 62 mg. of a substance which attained a constant m. p. of 117–119° after several recrystallizations from ether–hexane. The specific rotation was −102°.

*Anal.* Found: C, 51.58; H, 6.98.

This product was probably a mixture of the $\alpha$- and $\beta$-anomers of methyl tetraacetyl streptobiosaminide dimethyl acetal.

Elution of the column with ether yielded a further quantity (87 mg.) of methyl tetraacetyl-$\alpha$-streptobiosaminide dimethyl acetal, m. p. 123–125°, $[\alpha]D$ −121°.

**Mercaptolysis of Mannosidostreptomycin.**—Mannosidostreptomycin (2.38 g.) was added to 10 ml. of ethyl mercaptan and 4.5 ml. of concentrated hydrochloric acid and the mixture was shaken vigorously for a period of eighteen hours at room temperature. The reagents were distilled off *in vacuo* at a bath temperature not exceeding 30° and the last traces of water were removed by twice distilling absolute alcohol off the residue. The latter was acetylated by shaking for sixteen hours with 25 ml. of pyridine and an equal volume of acetic anhydride. The dark red solution was concentrated to a sirup and the latter partitioned between ice-water and chloroform. The chloroform layer was washed with dilute hydrochloric acid, sodium bicarbonate and finally with water. After drying over sodium sulfate the chloroform extract was evaporated to dryness *in vacuo* and the residue taken up in 10 ml. of absolute alcohol. On standing in the refrigerator overnight the alcoholic solution deposited crystals, which were filtered off and washed with cold ethanol. The filtrate and washings were evaporated to dryness *in vacuo* and chromatographed as described below.

The crystals, which appeared to be a mixture, were extracted with warm ether. This treatment left undissolved a fraction which was difficultly soluble in most organic solvents. Recrystallization from a large volume of alcohol produced small needles which melted at 255–257°, and were identified as octaacetylstreptidine.

The combined ether extracts were evaporated to dryness and the crystalline residue was recrystallized three times from absolute alcohol. Prismatic needles, 110 mg., melting at 160–161°, were obtained. The melting point was raised to 161–162° by chromatography of a benzene solution of this material on alumina, followed by an additional recrystallization from alcohol, $[\alpha]^{25}D$ −67° (*c*, 0.51 in chloroform). The substance showed no depression in melting point when mixed with an authentic sample of ethyl tetraacetyl-1-thio-$\beta$-D-mannopyranoside.[9]

*Anal.* Calcd. for $C_8H_{12}O_5S(CH_3CO)_4$: C, 48.98; H, 6.17; S, 8.16; $CH_3CO$, 43.84. Found: C, 49.22; H, 5.91; S, 8.33; $CH_3CO$, 43.4.

(15) The melting points reported in this paper were taken in capillary tubes and have been corrected for stem exposure.

(16) The alumina used for all chromatograms reported in this paper was purchased from the Harshaw Chemical Company, Cleveland, Ohio. It was washed with dilute acetic acid and then washed repeatedly with distilled water until the *p*H of a water suspension of the alumina had risen to 6.0. It was then filtered and dried at 150° for thirty-six to forty-eight hours.

(17) J. F. Alicino, *Anal. Chem.*, **20**, 590 (1948).

The residue from the above alcoholic filtrate and washings was dissolved in 15 ml. of benzene and after the addition of an equal volume of hexane was chromatographed on a column containing 30 g. of alumina. A mixture of equal volumes of benzene and hexane eluted a crystalline fraction (100 mg.) which after several recrystallizations from hexane containing a small amount of ether melted at 107–108°, $[\alpha]^{24}D$ +94° (*c*, 1.06 in chloroform). These data are in accord[18] with the constants for ethyl tetraacetyl-1-thio-α-D-mannoside.[9] No melting point depression was observed on admixture of an authentic sample of the latter.

*Anal.* Calcd. for $C_8H_{12}O_5S(CH_3CO)_4$: C, 48.98; H, 6.17; S, 8.16; $CH_3CO$, 43.84; mol. wt., 392.4. Found: C, 48.91; H, 6.04; S, 8.17; $CH_3CO$, 44.2; mol. wt. (Rast), 378.

Subsequent elution of the alumina column with 850 ml. of benzene yielded a second crystalline substance (530 mg.), which after recrystallization from ether–hexane melted at 111–112°, $[\alpha]^{25}D$ −31° (*c*, 0.95 in chloroform). There was no depression in melting point when this substance was mixed with an authentic sample of ethyl tetraacetyl-β-thiostreptobiosaminide diethyl mercaptal. The latter has been reported[8] to have m. p. 111–111.5° and $[\alpha]^{28}D$ −29° (*c*, 3.0 in chloroform).

*Anal.* Calcd. for $C_{27}H_{45}NO_{11}S_3$: C, 49.44; H, 6.92; N, 2.14; S, 14.66. Found: C, 49.45; H, 7.01; N, 2.52; S, 14.81.

**Methanolysis of Dihydromannosidostreptomycin.**—A solution of 800 mg. of vacuum-dried dihydromannosidostreptomycin in 16 ml. of 0.8 *N* methanolic hydrogen chloride was allowed to stand at room temperature for forty hours. Upon addition of 32 ml. of anhydrous ether to this solution a copious precipitate formed, which was filtered, washed with ether and dried *in vacuo*. The dried powder weighed 610 mg. and had $[\alpha]^{25}D$ −46° (*c*, 1.51 in methanol). The ether–methanol filtrate was concentrated *in vacuo* to a thin sirup and precipitated with a large excess of ether. After two hours of standing in the refrigerator, the oily deposit was separated from the supernatant by decantation and dried *in vacuo*. A white powder (169 mg.) was obtained which had $[\alpha]^{26}D$ −77° (*c*, 1.05 in methanol). All but 11 mg. of this material was acetylated with 4 ml. of pyridine and 3 ml. of acetic anhydride and the resulting acetylation product chromatographed in benzene solution (10 ml.) on 7 g. of alumina. Benzene eluted an oil which crystallized readily when its ether solution was allowed to evaporate at room temperature. The material on recrystallization from absolute alcohol yielded prismatic needles which melted at 159.5–160.5° and had $[\alpha]^{24}D$ −50° (*c*, 0.68 in chloroform). The melting point of this substance was not depressed on admixture of an authentic sample of methyl tetraacetyl-β-D-mannopyranoside. The latter has been reported[19] to have m. p. 161° and $[\alpha]^{25}D$ −50.4° (*c*, 1.4 in chloroform).

*Anal.* Calcd. for $C_7H_{10}O_6(CH_3CO)_4$: C, 49.72; H, 6.12; $OCH_3$, 8.56; $CH_3CO$, 47.5. Found: C, 49.61; H, 6.08; $OCH_3$, 8.35; $CH_3CO$, 48.3.

Subsequent elution of the column with a mixture of equal volumes of benzene and ether gave fractions which crystallized spontaneously upon evaporation of the solvents *in vacuo*. Recrystallization from absolute alcohol yielded a product (m. p. 192–193°; $[\alpha]^{24}D$ −119° (*c*, 0.48 in chloroform)) which proved to be identical with an authentic sample of methyl pentaacetyl-α-dihydrostreptobiosaminide prepared from dihydrostreptomycin.

*Anal.* Calcd. for $C_{14}H_{22}NO_9(CH_3CO)_5$: C, 51.14; H, 6.62; O-acetyl, 30.6. Found: C, 51.10; H, 6.64; O-acetyl, 30.4.

(18) The specific rotation of ethyl tetraacetyl-1-thio-α-D-mannoside prepared directly from D-mannose is +104°. The difference between this value and the one obtained for the substance prepared from mannosidostreptomycin is probably due to the presence of a small amount of the β-anomer in the latter.

(19) T. L. Harris, E. L. Hirst and C. E. Wood, *J. Chem. Soc.*, 2108 (1932).

The vacuum-dried ether precipitate (610 mg.) described above was acetylated with 5 ml. of acetic anhydride and 10 ml. of pyridine. The resulting acetylation product was dissolved in 5 ml. of absolute alcohol and allowed to stand in the refrigerator overnight. A crystalline precipitate formed, which consisted for the most part of octaacetylstreptidine. It was separated off by centrifugation and extracted several times with small portions of dry ether. The combined alcohol–ether filtrates were evaporated to dryness and the residue chromatographed in benzene solution on alumina. The two crystalline fractions obtained from the column proved to be identical with those described above.

**Aqueous Acid Hydrolysis of Mannosidostreptomycin.**—A solution of 1.08 g. of crude mannosidostreptomycin hydrochloride in 20 ml. of 1 *N* sulfuric acid was heated to 45° for twenty-four hours. After standing in the refrigerator for one day streptidine sulfate (0.45 g., 92% of the theoretical amount) was removed by filtration and the sulfate ion was removed from the filtrate by the addition of excess barium carbonate. To the supernate 0.4 g. of phenylhydrazine hydrochloride and 0.6 g. of sodium acetate were added. After standing for four hours the slight precipitate which had formed was centrifuged, washed and dried. It weighed only 26 mg. and could not be crystallized. Increasing the time of hydrolysis to sixty-five hours did not change the result. A quantitative yield of D-mannose phenylhydrazone was obtained, when the reaction was conducted at 100° for one hour.[20]

**Nonaacetyl-dihydromannosidostreptobiosamine.**—A solution of 8.1 g. of dihydromannosidostreptomycin trihydrochloride in 160 ml. of 1 *N* sulfuric acid was kept at 45° for twenty hours. After standing in the refrigerator for two days 3.28 g. (96% of the theoretical amount) of streptidine sulfate was removed by filtration. A sample was analyzed after drying at 100° for two hours.

*Anal.* Calcd. for $C_8H_{18}O_4N_6 \cdot H_2SO_4 \cdot H_2O$: C, 25.40; H, 5.86; N, 22.20; S, 8.46. Found: C, 25.42; H, 5.73; N, 22.14; S, 8.33.

The filtrate was neutralized with barium hydroxide, the barium sulfate removed by filtration, and silver carbonate was added with shaking until the *p*H attained a value of 6 to 6.5. The supernatant liquid was immediately lyophylized and the resulting amorphous solid acetylated with pyridine (50 ml.)–acetic anhydride (30 ml.) for two days at room temperature. The solvents were then removed under reduced pressure and the residue taken up in chloroform, which was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and water, and dried over sodium sulfate. The dried residue from the chloroform solution was dissolved in benzene and chromatographed on an acetic acid-washed alumina column, 3 × 20 cm. Material eluted with benzene (200 ml.) weighed 0.83 g. and had a specific rotation of −93°. It was discarded. Subsequent elutions with benzene–ether mixtures, ether and ethyl acetate yielded fractions which all had specific rotations of −45° ± 7°, and these were combined. Since this material could not be induced to crystallize it was lyophylized from benzene solution to an amorphous powder, $[\alpha]^{25}D$ −48° (*c*, 1.05 in chloroform), which was dried at 60° *in vacuo*.

*Anal.* Calcd. for $C_{19}H_{26}O_{14}N(COCH_3)_9$: C, 50.51; H, 6.04; N, 1.59; O-acetyl, 39.2; total acetyl, 44.0. Found: C, 50.58; H, 6.15; N, 1.91; O-acetyl, 37.9; total acetyl, 44.7.

**Methanolysis of Nonaacetyl-dihydromannosidostreptobiosamine.**—The acetylated trisaccharide (320 mg.) was dissolved in 10 ml. of 1.5 *N* methanolic hydrogen chloride. After standing for two days the acid was removed by shaking with excess silver carbonate followed by centrifugation. The supernatant liquid was evaporated to dryness *in*

(20) This experiment was carried out by Mr. J. Kowald, and provides the basis for an analytical procedure for the determination of mannosidostreptomycin, a detailed account of which will be published shortly by Dr. E. T. Stiller and Mr. J. Kowald of the Division of Chemical Development.

*vacuo* and the residue acetylated overnight in pyridine (5.0 ml.)-acetic anhydride (3.0 ml.). The dried acetylation product (307 mg.) worked up as in the acetylations described above was extracted with benzene, leaving undissolved 46 mg. of crystals, which after recrystallization from acetone–pentane had a m. p. of 191–193°, not depressed on admixture of authentic methyl pentaacetyl-α-dihydrostreptobiosaminide.

The benzene solution was chromatographed on an acetic acid-washed alumina column, 1 × 18 cm. Elution with 75 ml. of benzene yielded 57 mg. of methyl tetraacetyl-α-D-mannopyranoside, m. p. 63–65°. Further elution with 50 ml. of 30% ether in benzene afforded first 26 mg. of a crystalline material which melted over a wide range, 60 to 140°, and then 26 mg. of methyl tetraacetyl-β-D-mannopyranoside which melted at 153–155° after recrystallization from ether–pentane. The m. p. of a mixture with an authentic sample of m. p. 160° was 153–157°. A further quantity of methyl pentaacetyl dihydrostreptobiosaminide, 85 mg., m. p. 188–191°, was obtained by elution with 50 ml. of ether.

**Acetolysis of Nonaacetyl-dihydromannosidostreptobiosamine.**—In a preliminary experiment 90 mg. of the acetylated trisaccharide was dissolved in a mixture of 7.0 ml. of acetic anhydride, 3.0 ml. of acetic acid and 0.1 ml. of concentrated sulfuric acid. The initial rotation, $[\alpha]^{25}D$ −48°, dropped to −19° in five hours and remained constant at −10° after sixteen hours. The solution was then poured into a beaker containing crushed ice and solid sodium bicarbonate and shaken and stirred vigorously until the acids were neutralized. Extraction with chloroform yielded 75 mg. of a residue which was taken up in benzene and chromatographed on an alumina column, 1 × 15 cm. Elution with 40% ether in benzene afforded pentaacetyl-N-methyl-L-glucosamine (11 mg., m. p. 156°), but the bulk of the material (51 mg.) could be eluted only with ether. Since it could not be induced to crystallize, it was lyophilized from benzene solution and dried at 60° *in vacuo*, $[\alpha]^{25}D$ −31° (*c*, 0.6 in methanol).

*Anal.* Calcd. for $C_{13}H_{17}O_{10}N(COCH_3)_3$: N, 2.03; O-acetyl, 43.6; total acetyl, 49.8. Found: N, 1.92; O-acetyl, 40.8; total acetyl, 51.6.

Subsequent acetolyses on a larger scale always gave as the principal product an amorphous material having $[\alpha]D$ −32 ± 2°. The small amounts of pentaacetyl-N-methyl-L-glucosamine were probably derived from the estimated 5–10% streptomycin present in the mannosidostreptomycin used for degradation.

**Methanolysis of Octaacetyl-D-mannosido-N-methyl-L-glucosamine.**—A solution of 360 mg. of the acetylated disaccharide in 20 ml. of 1.1 *N* methanolic hydrogen chloride was allowed to stand at room temperature for forty-eight hours, and the mixture of products was isolated and acetylated as described above for the methanolysis of mannosidostreptomycin.

The acetylation product was dissolved in 20 ml. of benzene and chromatographed on a column of alumina, 1 × 18 cm. Elution with benzene (100 ml.) gave 52 mg. of crude methyl tetraacetyl-α-D-mannopyranoside, which melted at 64–66° after recrystallization from ether–pentane. Further elution with 40% ether in benzene yielded successively 30 mg. of methyl tetraacetyl-β-D-mannopyranoside, m. p. 157–159°, and 93 mg. of a crystalline substance which melted at 106–108° after several recrystallizations from ether–pentane, $[\alpha]^{25}D$ −4.0° (*c*, 0.5 in ethanol).

*Anal.* Calcd. for $C_7H_{10}O_4N(COCH_3)_4(OCH_3)$: C, 51.19; H, 6.71; N, 3.73; $CH_3O$, 8.27; O-acetyl, 34.4. Found: C, 51.28; H, 6.71; N, 3.58; $CH_3O$, 8.06; O-acetyl, 35.7.

There was no depression in m. p. on admixture of methyl tetraacetyl-N-methyl-β-L-glucosaminide, m. p. 105–108°, which had been prepared by methanolysis and reacetylation of pentaacetyl-N-methyl-α-L-glucosamine.

**Methyl Tetraacetyl-N-methyl-β-L-glucosaminide.**—Pentaacetyl-N-methyl-α-L-glucosamine (140 mg.) was dissolved in 10 ml. of 1.1 *N* methanolic hydrogen chloride. After two days standing the solution was stirred with excess silver carbonate for thirty minutes, then filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was acetylated overnight in acetic anhydride (2 ml.)-pyridine (2 ml.). The crude acetylation product was crystallized several times from ether–pentane, m. p. 103–105°, $[\alpha]^{25}D$ −4.2° (*c*, 0.5 in ethanol).

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## Summary

Mannosidostreptomycin has been cleaved by methanolic hydrogen chloride to streptidine, methyl α-streptobiosaminide dimethyl acetal, and the α- and β-forms of methyl D-mannopyranoside, and by ethyl mercaptan–hydrochloric acid to the corresponding ethyl thio-derivatives. The cleavage products were isolated as the crystalline acetates.

Dihydromannosidostreptomycin has been degraded by methanolic hydrogen chloride to the α- and β-anomers of methyl D-mannopyranoside and methyl dihydrostreptobiosaminide, all isolated as the crystalline acetates.

Hydrolysis of dihydromannosidostreptomycin with 1 *N* sulfuric acid at 45° yielded streptidine sulfate and a trisaccharide, dihydromannosidostreptobiosamine, isolated as the amorphous nonaacetate. This product was cleaved by methanolic hydrogen chloride to methyl β-D-mannopyranoside and methyl α-dihydrostreptobiosaminide, both isolated as the crystalline acetates.

Acetolysis of nonaacetyl dihydromannosidostreptobiosamine gave a disaccharide acetate, octaacetyl mannosido-N-methyl-L-glucosamine, which was cleaved by methanolic hydrogen chloride to methyl β-D-mannopyranoside and methyl N-methyl-β-L-glucosaminide, both isolated as the crystalline tetraacetates.

The conclusion is drawn from these data that mannosidostreptomycin is a D-mannosido-N-methyl-α-L-glucosaminido-L-streptoside of streptidine. The linkage between the D-mannose and the N-methyl-L-glucosamine moieties appears to be α.

NEW BRUNSWICK, NEW JERSEY

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[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Ethyl Thioglycosides of D-Mannose and D-Galactose and a New Synthesis of Styracitol

BY JOSEF FRIED AND DORIS E. WALZ

In the course of recent work on the structure of mannosidostreptomycin[1,2] two isomeric ethyl thiohexosides were obtained which were not identical with any of those described in the literature. The present work, originally undertaken for the purpose of identifying these two substances, has afforded a method for the preparation of ethyl thio-D-mannopyranosides and D-galactosides, as well as a new synthesis for styracitol (1,5-anhydromannitol).

The alkyl thioglycosides, in contrast to the well-explored sugar mercaptals, have met with but occasional interest and their study has been confined to derivatives of glucose and fructose. Schneider and Sepp[3] were the first to synthesize an ethyl thioglucoside, later shown to be the $\alpha$-furanoside,[4,5] by partial cleavage of glucose diethyl mercaptal with mercuric chloride. This substance has been found[6] to undergo an unusual sequence of reactions in the presence of 0.01 *N* hydrochloric acid. Under these conditions approximately one half of the material was converted into the $\beta$-furanoside and eventually into glucose and ethyl mercaptan, while the other half escaped the hydrolyzing effect of the acid by rearranging into the acid resistant pyranoid form. The ring shift resulted in the formation of ethyl $\alpha$-thioglucopyranoside which was isolated and characterized as the tetraacetate. Ethyl $\alpha$-thioglucopyranoside has also been prepared by the prolonged action of 22% hydrochloric acid on both glucose diethyl mercaptal and on an equimolecular mixture of glucose and ethyl mercaptan.[7,8] The fourth isomer, ethyl $\beta$-thioglucopyranoside, was prepared by Schneider and co-workers[9] according to the original Fischer method,[10] reaction of the potassium mercaptide with acetobromoglucose, and by the action of ethyl iodide on thioglucose.[11]

The formation of the two ethyl thiomannosides by mercaptolysis of mannosidostreptomycin[1,2] in the presence of concentrated hydrochloric acid suggested that simple glycosides might be mercaptolyzed in an analogous fashion. This was indeed found to be the case. Both $\alpha$- and $\beta$-methyl D-mannopyranoside on treatment with ethyl mercaptan and concentrated hydrochloric acid for eighteen hours at room temperature yielded after acetylation ethyl tetraacetyl-1-thio-$\beta$-D-mannopyranoside, $[\alpha]^{25}D$ $-67°$ and m. p. 161–162°. Methyl $\beta$-mannopyranoside yielded in addition a small amount of the $\alpha$-anomer ($[\alpha]^{25}D$ $+104°$; m. p. 107–108°). Better results from a preparative point of view were obtained when the above conditions were applied to the free sugar. Thus, when D-mannose was shaken with ethyl mercaptan and concentrated hydrochloric acid for eighteen hours at room temperature, and the resulting mixture after neutralization with sodium carbonate was evaporated to dryness *in vacuo*, the residue upon acetylation afforded a 32% yield of ethyl tetraacetyl-1-thio-$\beta$-D-mannopyranoside. Chromatography of the mother liquor yielded in addition a small amount of the $\alpha$-anomer. Catalytic deacetylation with barium methylate afforded the free $\alpha$- and $\beta$-ethyl thio-D-mannosides of which only the latter was obtained in crystalline form. Its properties are listed in Table I.

It is well known that the action of ethyl mercaptan and hydrochloric acid on D-mannose for a period of five minutes produces the diethyl mercaptal in 63% yield.[12] The absence of this substance from the products of the eighteen-hour reaction, as shown by careful chromatography of the mother liquor, after removal of the crystalline ethyl tetraacetyl-1-thio-$\beta$-D-mannopyranoside, indicated that the mercaptal is likely to be an intermediate in the formation of the thioglycosides.

The stability of the two ethyl thiomannosides toward strong acid suggested that they possess pyranoid ring structures. More definite proof, however, was sought by utilizing the demercaptalation reaction of Wolfrom and his collaborators,[13] using mercuric chloride and cadmium carbonate in methanol, in the hope of replacing the mercapto group of the more abundantly available $\beta$-anomer by methoxyl. In spite of the use of a large excess of mercuric chloride and a reaction time of twenty-four hours, the starting material was recovered unchanged. Conclusive evidence for the pyranose structure of ethyl 1-thio-$\beta$-D-mannoside was adduced by reductive desulfurization of the latter with Raney nickel, which afforded the 1,5-anhydrohexitol styracitol[14] in good yield. The 1,5-oxide structure of styracitol has been securely established by Zervas,[15] who succeeded in synthesizing this substance by catalytic reduction of tetra-

(1) J. Fried and H. E. Stavely, THIS JOURNAL, **69**, 1549 (1947).
(2) H. E. Stavely and J. Fried, *ibid.*, **71**, 135 (1949).
(3) W. Schneider and J. Sepp, *Ber.*, **49**, 2054 (1916).
(4) J. W. Green and E. Pacsu, THIS JOURNAL, **59**, 1205, 2569 (1937).
(5) M. L. Wolfrom, S. W. Waisbrot, D. I. Weisblat and A. Thompson, *ibid.*, **66**, 2063 (1944).
(6) E. Pacsu and E. J. Wilson, Jr., *ibid.*, **61**, 1450 (1939).
(7) P. Brigl, K. Gronemeier and A. Schulz, *Ber.*, **72**, 1052 (1939).
(8) E. Pacsu and E. J. Wilson, Jr., THIS JOURNAL, **61**, 1930 (1939).
(9) W. Schneider, J. Sepp and O. Stiehler, *Ber.*, **51**, 220 (1918).
(10) E. Fischer and K. Delbrück, *ibid.*, **42**, 1476 (1909).
(11) W. Schneider, R. Gille and K. Eisfeld, *ibid.*, **61**, 1244 (1928).
(12) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **74**, 695 (1927).
(13) M. L. Wolfrom, Leo J. Tanghe, R. W. George and S. W. Waisbrot, THIS JOURNAL, **60**, 132 (1938).
(14) Y. Asahina, *Arch. Pharm.*, **245**, 325 (1907); **247**, 157 (1909).
(15) L. Zervas, *Ber.*, **63**, 1689 (1930).

TABLE I

| Substance | M. p., °C. | $[\alpha]_D$ in $H_2O$[d] | $[M]_D$ | 2A | 2B |
|---|---|---|---|---|---|
| Ethyl thio-α-D-mannopyranoside | Amorphous | | | | |
| Ethyl thio-β-D-mannopyranoside | 118–119 | − 83° | −18600 | | |
| Ethyl thio-α-D-galactopyranoside | 153.5–154 | +320° | 71500 | | |
| Ethyl thio-β-D-galactopyranoside | 121.5–122.5 | − 23.5° | − 5300 | 76800 | 66200 |
| Ethyl thio-α-D-glucopyranoside | 117[a] | +269°[c] | 60200 | | |
| Ethyl thio-β-D-glucopyranoside | 99–100[b] | − 55.1°[c] | −12300 | 72500 | 47900 |
| Tetraacetates of | | $[\alpha]_D$ in $CHCl_3$[d] | | | |
| Ethyl thio-α-D-mannopyranoside | 107–108 | +104° | 40800 | | |
| Ethyl thio-β-D-mannopyranoside | 161–162 | − 67° | −26300 | 67000 | 14500 |
| Ethyl thio-α-D-galactopyranoside | 108–109 | +218° | 85400 | | |
| Ethyl thio-β-D-galactopyranoside | 74–75 | − 8.0° | − 3100 | 88500 | 82300 |
| Ethyl thio-α-D-glucopyranoside | 96–97.5[a] | +194°[c] | 76000 | | |
| Ethyl thio-β-D-glucopyranoside | 78–79[b] | − 25.6°[c] | −10030 | 86030 | 65970 |

[a] P. Brigl, K. Gronemeier and A. Schulz, *Ber.*, **72**, 1052 (1939). [b] W. Schneider, J. Sepp and O. Stiehler, *ibid.*, 51, 220 (1918). [c] E. Pacsu and E. J. Wilson, Jr., THIS JOURNAL, **61**, 1450 (1939). [d] The specific rotations were determined at temperatures ranging from 24 to 27°.

acetyl-2-hydroxyglucal, followed by deacetylation.

The structure of styracitol has been the subject of considerable controversy. Evidence has been presented by several groups of workers supporting either the 1,5-anhydromannitol[16,17] or the 1,5-anhydrosorbitol[18,19] structure. The present synthesis leaves little doubt that the mannitol structure, which is overwhelmingly favored by previous evidence, is the correct one.

In applying the conditions for the preparation of the ethyl thio-D-mannosides to D-galactose we obtained, after acetylation and chromatographic purification, two crystalline ethyl tetraacetyl-1-thio-D-galactosides. Their properties as well as those of the crystalline ethyl thiogalactosides obtained after deacetylation are listed in Table I. In the last two columns of this table are also given the 2A and 2B values calculated from the molecular rotations on the basis of Hudson's rules of isorotation.[20] For the sake of comparison, the values for the two anomeric ethyl thio-D-glucopyranosides and their tetraacetates have also been included. The agreement between the 2A values calculated from the molecular rotations of the two thiogalactosides (76800) and their tetraacetates (88500) and those for the thioglucopyranosides (72500) and their tetraacetates (86030) appears to be close enough to warrant the conclusion that the two ethyl thiogalactosides are anomeric and possess pyranoid structures. The 2A value for the tetraacetyl-thio-D-mannosides (67000) shows the deviation characteristic of all mannose derivatives.[21]

An attempt to prepare the ethyl thioglycosides of L-arabinose in an analogous manner yielded only arabinose diethyl mercaptal. This result demonstrates the influence of stereo configuration on the reactivity of the sugar mercaptals rendering difficult any prediction as to the general applicability of the above procedure.

(16) L. Zervas and I. Papadimitriou, *Ber.*, **73**, 174 (1940).

(17) R. C. Hockett and M. Conley, THIS JOURNAL, **66**, 464 (1944).

(18) Y. Asahina and H. Takimoto, *Ber.*, **64**, 1803 (1931).

(19) W. Freudenberg and J. T. Sheehan, THIS JOURNAL, **62**, 559 (1940).

(20) C. S. Hudson, *ibid.*, **31**, 66 (1909).

(21) E. Pacsu, *ibid.*, **61**, 2669 (1939).

## Experimental[22]

**α- and β-Ethyl Tetraacetyl-1-thio-D-mannopyranosides.**—D-Mannose (5.0 g.) was added to ice-cold concentrated hydrochloric acid (20 ml.) and ethyl mercaptan (20 ml.), and the mixture was shaken for sixteen hours at room temperature. At the end of this period the excess ethyl mercaptan and part of the hydrochloric acid were removed *in vacuo* at a bath temperature not exceeding 30°. The residual acid solution (10 ml.) was diluted with water (10 ml.) and alcohol (10 ml.) and alkalinized by the addition of solid sodium carbonate to a *p*H of 8. During the addition of the sodium carbonate it was necessary to add water and alcohol in order to prevent the mixture from solidifying. The solvents were then removed *in vacuo* and the resulting residue dried by distilling absolute alcohol (60 ml.) from it. The dried residue was then acetylated by shaking overnight with pyridine (40 ml.)–acetic anhydride (40 ml.), and the acetylation mixture was concentrated *in vacuo* to a sirup. The latter was partitioned between ice-water and chloroform and the chloroform layer was washed with dilute acid, sodium bicarbonate and water. The dried chloroform solution upon removal of the solvent *in vacuo* yielded a brown sirup (10.7 g.) which crystallized on standing at room temperature. Crystallization was complete after two days at 4° after which time the crystalline mass was digested with a small amount of cold absolute alcohol and filtered by suction. The crystals, after washing with cold alcohol (3.24 g.), melted at 157–158°. Recrystallization from absolute alcohol raised the melting point to 161–162°; $[\alpha]^{24}D$ −67° (*c*, 0.67 in chloroform).

*Anal.* Calcd. for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.17; S, 8.16; O-acetyl, 43.84. Found: C, 49.19; H, 5.98; S, 8.41; O-acetyl, 44.7.

The sirupy mother liquor from which the bulk of the ethyl tetraacetyl-1-thio-β-D-mannopyranoside had been removed by filtration was concentrated *in vacuo* and the alcohol-free oily residue (7.44 g.) was dissolved in a mixture of benzene (75 ml.) and hexane (185 ml.) for chromatography on alumina (100 g.). A mixture of 2 parts of benzene and 5 parts of hexane eluted at first (720 ml.) oily material, which was followed by a series of crystalline fractions. A total of 1270 ml. of the above solvent mixture eluted approximately 150 mg. of crystals which after several recrystallizations from ether–hexane melted at 107–108°; $[\alpha]^{25}D$ +104° (*c*, 0.88 in chloroform).

(22) The melting points reported in this paper were taken in capillary tubes and have been corrected for stem exposure.

*Anal.* Calcd. for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.17; S, 8.16. Found: C, 49.07; H, 5.98; S, 8.43.

**Mercaptolysis of Methyl α-D-Mannopyranoside.**—Methyl α-D-mannopyranoside (400 mg.) was shaken with concentrated hydrochloric acid (2 ml.) and ethyl mercaptan (5 ml.) for eighteen hours at room temperature. The mixture was cooled to 0°, neutralized with concentrated ammonia and evaporated to dryness *in vacuo*. The thoroughly dried residue was acetylated with pyridine (10 ml.)–acetic anhydride (10 ml.), and the acetylation mixture was worked up as in the preceding experiment. Chromatography on alumina (25 g.) from benzene (10 ml.)-hexane (15 ml.), yielded crystals (40 mg.), eluted by equal volumes of benzene and ether, which melted at 159.5–161° and were identified as ethyl tetraacetyl 1-thio-β-D-mannoside.

**Mercaptolysis of Methyl β-D-Mannopyranoside.**—Methyl β-D-mannopyranoside (190 mg.) was mercaptolyzed as described for the α-anomer. Acetylation of the crude product yielded a semicrystalline residue which when taken up in cold absolute alcohol (1.5 ml.) yielded crystalline ethyl tetraacetyl-1-thio-β-D-mannopyranoside. The alcoholic mother liquor was freed from solvent *in vacuo*, dissolved in benzene (4 ml.) and hexane (4 ml.) and chromatographed on acetic acid washed alumina (7 g.). A mixture of benzene (140 ml.) and hexane (140 ml.) eluted material which crystallized readily on seeding with ethyl tetraacetyl-1-thio-α-D-mannoside. After two recrystallizations the melting point remained constant at 107–108°, and showed no depression on admixture of ethyl tetraacetyl-1-thio-α-D-mannoside

**Ethyl 1-Thio-β-D-mannopyranoside.**—Ethyl tetraacetyl-1-thio-β-D-mannopyranoside (500 mg.) was suspended in dry methanol (75 ml.) and a 0.9 *N* solution of barium methylate (1 ml.) was added. The mixture was allowed to stand at room temperature for sixteen hours with occasional shaking during the first hour. Carbon dioxide was then passed through the solution for ten minutes and the methanol was removed *in vacuo*. The residue was taken up in water, the precipitate of barium carbonate centrifuged off and the solution evaporated to dryness *in vacuo*. Upon addition of a few drops of absolute alcohol the residue crystallized rapidly. Recrystallization from absolute alcohol yielded clusters of prismatic needles (145 mg.), which melted at 118–119°; $[\alpha]^{25}D$ −83° (*c*, 0.6 in water).

*Anal.* Calcd. for $C_8H_{16}O_5S$: C, 42.85; H, 7.19; S, 14.27. Found: C, 42.71; H, 6.98; S, 14.37.

**Reductive Desulfurization of Ethyl Tetraacetyl-1-thio-β-D-mannopyranoside to Styracitol.**—A solution of ethyl tetraacetyl-1-thio-β-D-mannopyranoside (300 mg.) in absolute alcohol (20 ml.) was refluxed with Raney nickel[23] (4 ml.) for four hours. The mixture was diluted with alcohol (20 ml.) and the Raney nickel removed by centrifugation and subsequent gravity filtration of the turbid supernate. The nickel was washed with fresh portions of hot alcohol and the combined filtrates were evaporated to dryness *in vacuo*. The sirupy residue was deacetylated in methanol (45 ml.) with 0.9 *N* barium methylate (0.6 ml.) at 4° for sixteen hours. After removal of the barium as described in the preceding experiment, the residue was dissolved in a small amount of absolute alcohol and was seeded with authentic styracitol.[24] On cooling, crystals (70 mg.) were obtained, which after two recrystallizations from methanol melted at 155–156° and had $[\alpha]^{27}D$ −48° (*c*, 1.1 in water). There was no depression in melting point on admixture of the above authentic sample of styracitol of m. p. 155–156° and $[\alpha]^{26}D$ −50° (*c*, 1.0 in water).

*Anal.* Calcd. for $C_6H_{10}O_5$: C, 43.94; H, 7.37. Found: C, 44.01; H, 7.44.

An additional amount of crystals (30 mg.) was obtained on concentration of the ethanolic mother liquor. The total yield of crude crystalline product was 100 mg. or 80%.

**Attempted Replacement of the Ethylmercapto Group in Ethyl Tetraacetyl-1-thio-β-D-mannopyranoside by Methoxyl.**—To a solution of ethyl tetraacetyl-1-thio-β-D-mannopyranoside (200 mg., 0.51 millimole) in absolute methanol (4 ml.) was added mercuric chloride (775 mg., 2.85 millimoles) and cadmium carbonate (575 mg.). The mixture was refluxed for eighteen hours, taken up in chloroform (20 ml.), filtered, and extracted with water to remove the mercuric chloride. The chloroform solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The crystalline residue proved to be unchanged starting material.

**α- and β-Ethyl Tetraacetyl-1-thio-D-galactopyranosides.**—D-Galactose (5.0 g.) was treated with concentrated hydrochloric acid (20 ml.) and ethyl mercaptan (20 ml.) exactly as described above for D-mannose. Upon acetylation with pyridine (40 ml.)–acetic anhydride (40 ml.) a brown sirup (7.7 g.) was obtained, which crystallized only to a small extent on long standing. A portion of the sirup (6.67 g.) was therefore chromatographed on alumina (100 g.) from a benzene (67 ml.)–hexane (167 ml.) solution. Elution of the column with benzene–hexane (2:5) yielded at first a considerable amount of oily material. After 600 ml. of the eluant had passed through the column the succeeding 900 ml. of effluent, collected in 13 fractions of 70 ml., yielded on evaporation crystals melting at 107–108°. Since no depression in melting point was observed when the first and the thirteenth fraction were mixed, all the fractions were combined and recrystallized from ether–hexane. The resulting material (287 mg.) melted at 108–109° and had $[\alpha]^{26}D$ +218° (*c*, 1.18 in chloroform).

*Anal.* Calcd. for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.17; S, 8.16; acetyl, 43.84. Found: C, 49.02; H, 6.10; S, 8.40; acetyl, 43.0.

Subsequent elution of the column with the same solvent mixture gave two fractions (240 ml. each) from which a small amount of the above crystalline material (m. p. 103–104°) was obtained on seeding. Continued elution with 1900 ml. of benzene–hexane yielded upon evaporation of the solvents a second crystalline substance, which after several recrystallizations from ether–hexane melted at 74–75° (114 mg.); $[\alpha]^{26}D$ −8.0 (*c*, 2.1 in chloroform).

*Anal.* Calcd. for $C_{16}H_{24}O_9S$: C, 48.98; H, 6.17; S, 8.16; acetyl, 43.84. Found: C, 48.91; H, 6.23; S, 8.53; acetyl, 44.1.

Elution with benzene (320 ml.) afforded a small amount of crystals (5.2 mg.), which melted at 141.5–142°. The substance contained no sulfur and was probably pentaacetyl-β-D-galactopyranose, which has been reported[25] to melt at 142°.

**Ethyl 1-Thio-α-D-galactopyranoside.**—Ethyl tetraacetyl-1-thio-α-D-galactopyranoside (130 mg.) was deacetylated in dry methanol solution (21 ml.) with 0.9 *N* barium methylate (0.28 ml.) as described above for ethyl thio-β-D-mannopyranoside. The residue, from which the barium had been removed, crystallized upon addition of absolute alcohol. On recrystallization from this solvent fine needles (49 mg.) were obtained which melted at 153.5–154° and had $[\alpha]^{27}D$ +320° (*c*, 0.55 in water).

*Anal.* Calcd. for $C_8H_{16}O_5S$: C, 42.85; H, 7.19; S, 14.27. Found: C, 42.81; H, 6.94; S, 14.55.

**Ethyl 1-Thio-β-D-galactopyranoside.**—Ethyl tetraacetyl-1-thio-β-D-galactopyranoside (60 mg.) was deacetylated as described in the preceding experiment. Since the barium-free residue could not be induced to crystallize it was dissolved in ethanol (0.5 ml.)–benzene (1.5 ml.) and chromatographed on alumina (1 g.). A mixture of alcohol (1 part) and benzene (3 parts) eluted at first (26 ml.) amorphous material, which was discarded. All subsequent fractions obtained with this solvent mixture (165 ml.) and with equal volumes of benzene and alcohol (300 ml.) crystallized on rubbing with ethyl acetate. The

(23) Similar yields were obtained with both freshly prepared and six-months-old Raney nickel.

(24) The authors wish to thank Dr. John T. Sheehan for kindly supplying them with a sample of pure styracitol isolated from *Styrax obassia*.

(25) E. Erwig and W. Koenig, *Ber.*, **22**, 2207 (1889).

combined fractions were recrystallized from a minimum of alcohol and ethyl acetate and yielded 13 mg. of long thin needles which melted at 121.5–122.5° and had $[\alpha]^{26}D$ −23.5° (*c*, 0.89 in water).

*Anal.* Calcd. for $C_8H_{16}O_5S$: C, 42.85; H, 7.19; S, 14.27. Found: C, 42.58; H, 6.77; S, 13.50.

**Reaction of L-Arabinose with Ethyl Mercaptan.**—L-Arabinose (2 g.) was treated with ethyl mercaptan (8 ml.) and hydrochloric acid (8 ml.) as described for methyl α-D-mannopyranoside. The dried neutralized residue was acetylated with pyridine (20 ml.)–acetic anhydride (20 ml.), the crude acetylation product dissolved in absolute alcohol (3 ml.), and the solution was allowed to stand in the refrigerator overnight. The resulting crystals (2.35 g.) were filtered and washed with cold alcohol. After two recrystallizations from 95% alcohol the crystals melted at 79–80° $[\alpha]^{27}D$ −27.0° (*c*, 1.6 in chloroform). These data are in accord with those given for tetraacetyl-L-arabinose diethyl mercaptal by Wolfrom and Newlin.[26]

*Anal.* Calcd. for $C_{17}H_{28}O_8S_2$: C, 48.11; H, 6.65; S, 15.08. Found: C, 48.27; H, 6.65; S, 15.27.

**Acknowledgment.**—The authors wish to thank Dr. Oskar Wintersteiner for helpful discussions during the course of this work and Mr. Joseph F. Alicino, Miss Anne C. Crickenberger and Miss Ruth Karitzky for the microanalytical determinations.

(26) M. L. Wolfrom and M. R. Newlin, THIS JOURNAL, **52**, 3619 (1930).

## Summary

α- and β-ethyl tetraacetyl-1-thio-D-mannopyranosides have been prepared by the prolonged action of ethyl mercaptan and hydrochloric acid on both D-mannose and methyl β-D-mannopyranoside. Methyl α-D-mannopyranoside yielded only the β-anomer. Ethyl 1-thio-β-D-mannopyranoside has been obtained in crystalline form.

Styracitol has been prepared from ethyl tetraacetyl-1-thio-β-D-mannopyranoside by desulfurization with Raney nickel.

α- and β-ethyl 1-thio-D-galactopyranosides and their tetraacetates have been prepared in crystalline form.

The action of ethyl mercaptan and hydrochloric acid on L-arabinose for eighteen hours led only to the diethyl mercaptal.

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[CONTRIBUTION NO. 1135 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

# The Reaction of Simple Antigens with Purified Antibody[1]

BY ARTHUR B. PARDEE[2] AND LINUS PAULING

Many biological reactions, including the interaction of antibodies and antigens, the effect of enzymes on their substrates, and the self-reproducing behavior of genes, are characterized by a high degree of specificity. The great problem of the nature of the forces responsible for this biological specificity is being attacked vigorously in many ways at the present time. During the past six years we have carried out a series of investigations[1] on the reactions of antisera with simple substances, extending and refining the work of Landsteiner.[3] The results obtained provide strong support for the concept that biological specificity is due to a detailed complementariness in surface configuration of the molecules involved (antigen and antibody) and that the forces which contribute to specific attraction of two molecules—van der Waals electronic forces, hydrogen bond forces, etc.—are in general short-range forces, effective over distances of a few Ångström units. The conclusion has been reached that the surface approximation of antibody and the haptenic groups of antigens is to within about 1 Å.

Much of our work has consisted of studies of the precipitation of an antiserum by a simple polyhaptenic substance. The observation that certain simple substances containing two or more haptenic groups would form precipitates with the homologous antiserum was made by Landsteiner and van der Scheer.[4] It was suggested by Landsteiner that the forces between dye molecules which favor the formation of colloidal solutions, that is, of polymerized aggregates, are responsible for the ready precipitability of these substances, many of which are dyes. We, however, have presented evidence that the presence of two or more haptenic groups in each molecule, making the formation of a framework possible, is responsible for their precipitability.

The suggestion that it is polymerization of these simple precipitating antigens that gives them their precipitating power has been revived by Boyd and Behnke,[5] who reported that they had found one of the simple antigens used by us to be highly (11-fold) polymerized in saline solution, and who stated that accordingly the results of our earlier investigations might not justify the

(1) The Serological Properties of Simple Substances. XIV. For number XIII of this series see D. Pressman, J. H. Bryden, and L. Pauling, THIS JOURNAL, **70**, 1352 (1948).

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(3) See K. Landsteiner, "The Specificity of Serological Reactions," Harvard University Press, Cambridge, Massachusetts, 1945.

(4) K. Landsteiner and J. van der Scheer, *Proc. Soc. Exptl. Biol. Med.*, **29**, 747 (1932); *J. Exptl. Med.*, **56**, 399 (1932); **57**, 633 (1933); **67**, 79 (1938).

(5) W. C. Boyd and J. Behnke, *Science*, **100**, 13 (1944). In this preliminary note about their work these authors wrote that details would be published elsewhere; their detailed paper has not yet appeared.

interpretation that we had given them. This criticism has been repeated by Kabat.[6]

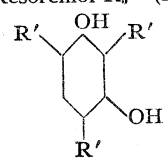
In the present paper we report the results of experiments on the interaction of simple precipitating antigens with purified antibody solutions. It has been found that the behavior of the simple antigens with purified antibody solutions is somewhat different from that with antiserum, the difference apparently being due to a rather strong non-specific combination of the dye molecules with the constituents of serum not present in purified antibody, presumably mainly albumin.[7,8] The effect of this combination seems to be to reduce the concentration of the free dye molecules to such an extent that in serum solution they react mainly in the monomeric form.

## Experimental

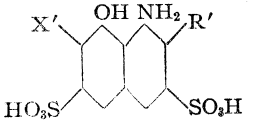
**Synthetic Antigens.**—The compounds used as synthetic antigens and their preparation have been described in previous papers except resorcinol-R$_3'$, which was prepared by Mr. A. L. Grossberg, by the method used for chloroglucinol-R$_3'$ (XI) with use of a different phenolic nucleus.[9,10]

R represents the *p*-azobenzenearsonic acid group, R′ the *p*-(*p*-azobenzeneazo)-benzenearsonic group, and X′ the *p*-(*p*-azobenzeneazo)-benzoic acid group.

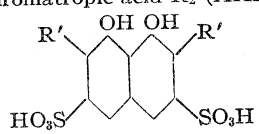
Resorcinol-R$_3'$ (R$_3'$)




H-acid-R′X′ (R′X′)




Chromatropic acid-R$_2'$ (XXX)




**Antibodies and Other Substances.**—The anti-R serum was obtained from rabbits by the method previously described.[9]

Specifically purified anti-R antibody (referred to in this paper as purified antibody) was prepared by Prof. D. H. Campbell.[11] Various preparations using resorcinol-R$_3'$ as precipitant were pooled and used for the succeeding experiments.

The pneumococcus type I antibody used in some of the experiments was a commercial preparation, Lederle Refined and Concentrated Rabbit Globulin. The purified polysaccharide was prepared by Dr. J. E. Cushing, Jr.

The rabbit serum albumin was prepared by Dr. George A. Feigen, by a single salt precipitation.

**Salt and Buffer.**—All experiments were done in 0.9% sodium chloride solution, without buffer present unless otherwise noted. When a buffer is referred to as *x*F it is meant that the sum of all forms of the buffering material is *x* formula weights per liter.

**Precipitation Reaction; General Methods.**—Antigen and antibody at approximately the final *p*H were mixed and allowed to stand for one hour at room temperature and then for two to five days at 5°. (It was found that resorcinol-R$_3'$ gave the same amount of precipitate in two hours as in three days, and that the maximum turbidity under the conditions used was reached in ten minutes at room temperature.) After having been washed,[9] the precipitates were analyzed for antigen by adding 2.5 ml. of 1 *N* sodium hydroxide, making up to 5.5 ml. in a centrifuge tube, and reading the light absorption on a Beckman spectrophotometer at an appropriate wave length and slit width. Compound resorcinol-R$_3'$ was read at 500 mμ and 0.03 mm. slit width, and antigens XXX and R′X′ at 600 mμ and 0.04 mm. slit width. The first two compounds showed no tendency to fade over a period of several days in alkali or over several months in approximately neutral solution, but R′X′ faded about 20% in a day in alkali. The compounds reacted slowly with the soft glass bottles. The error in the colorimetric procedure is estimated at ±3% or less for samples containing more than $4 \times 10^{-9}$ moles of antigen, and is somewhat greater for smaller samples.

The same sample was then analyzed for protein by the modified Folin–Ciocalteu method.[12] A correction was made for the color of the antigen. To test the method ten triplicate analyses were run on purified antibody samples by both the modified Folin–Ciocalteu and the Nessler method by two analysts. The first method gave values which averaged 1.035 ± 0.035 times the second.

In some of the experiments with purified antibody the supernatant liquids were decanted from the centrifuged precipitates, both parts were analyzed, and the precipitates were corrected for the small amount of antigen and protein in the remaining supernatant liquid. In some of the later experiments only the precipitates were analyzed and the correction was calculated from the amount of reactants added.

The molecular weight of the antibody was taken as 160,000 for calculations.

## Results

Precipitates were analyzed both with and without washing, as described in the previous section. The amounts of precipitate and the mole ratios in the precipitate for the two procedures are compared in Table I and also in Table II. It can be seen that for the antigen used (XXX) the amount of precipitate washed away is 30 to 45% of the original amount; the ratio of antigen to antibody in the precipitate remains about the same, however. Only 10 to 15% of the precipitate with antigen resorcinol-R$_3'$ (at *p*H 6.9) was lost on washing.

It was found that the amount of precipitate obtained with antigen XXX and purified antibody at *p*H 7.6 and 8.1 was only slightly dependent on the volume of the reaction mixture, the amount of precipitate varying over about a 20% range for any given amounts of antigen and antibody on three-fold dilution with buffer solution. The mole ratio in the precipitate was essentially independent of the volume of the mixture. In contrast, a three-fold increase in the volume of a system containing antiserum and a simple poly-

(6) E. A. Kabat, "Annual Review of Biochemistry," Annual Reviews, Inc., Stanford University, California, 1946, p. 528.

(7) B. D. Davis, *Am. Scientist*, **34**, 611 (1946).

(8) I. Klotz, THIS JOURNAL, **68**, 2299 (1946); **69**, 1609 (1947).

(9) L. Pauling, D. Pressman, D. H. Campbell, C. Ikeda, and M. Ikawa, *ibid.*, **64**, 2994 (1942).

(10) L. Pauling, D. Pressman, and D. H. Campbell, *ibid.*, **66**, 330 (1944).

(11) D. H. Campbell, R. H. Blaker, and A. B. Pardee, *ibid.*, **0**, (2496 1948).

(12) D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **15**, 357 (1943).

TABLE I

PRECIPITATION OF PURIFIED ANTIBODY BY ANTIGEN XXX

Varying amounts of antigen XXX in 2 ml. of saline were added to 2 ml. of saline containing $4.2 \times 10^{-9}$ mole of antibody. Final *p*H 8.1, no buffer. Values are averages of triplicate analyses

| Antigen added, moles $\times 10^9$ | Precipitated antibody, moles $\times 10^9$ [a] | | Mole ratio antigen / antibody in ppt.[a] | |
|---|---|---|---|---|
| 264 | 0.45 | 0.81 | 9.2 | 11.6 |
| 132 | .53 | .91 | 5.9 | 8.2 |
| 66 | .62 | 1.03 | 4.9 | 5.5 |
| 33 | .97 | 1.53 | 2.6 | 3.4 |
| 16 | 1.28 | 1.84 | 2.0 | 2.7 |
| 8 | 1.51 | 2.40 | 1.9 | 1.8 |
| 4 | 1.44 | 2.06 | 1.5 | 1.6 |
| 2 | 1.00 | 1.46 | 1.2 | 1.3 |
| 1 | 0.59 | 1.03 | (1.0) | (0.9) |

[a] The first column is for experiments in which the precipitate was washed in the conventional way; the second is for experiments in which the supernate was decanted from the precipitate and both were analyzed as described in the text.

TABLE II

PRECIPITATION OF PURIFIED ANTIBODY BY ANTIGEN XXX

Varying amounts of purified antibody in 2 ml. of saline were added to $4.1 \times 10^{-9}$ mole of antigen XXX in 2 ml. of saline. Final *p*H 8.1, no buffer. Analyses in triplicate

| Antibody added, moles $\times 10^9$ | Precipitated antibody, moles $\times 10^9$ [a] | | Mole ratio antigen / antibody in ppt.[a] | |
|---|---|---|---|---|
| 16.9 | 2.0 | 2.5 | 1.1 | 1.1 |
| 12.5 | 2.0 | 2.8 | 1.4 | 1.1 |
| 8.5 | 2.1 | 2.8 | 1.4 | 1.2 |
| 4.2 | 1.4 | 2.1 | 1.5 | 1.6 |
| 2.1 | 0.7 | 1.2 | 1.8 | 1.9 |
| 1.0 | .2 | 0.4 | (1.8) | (2.7) |

[a] See note of Table I.

haptenic antigen[13] caused the amount of precipitate to decrease by 50%.

A number of experiments other than those reported in Table II were carried out in which varying amounts of purified antibody were added to a constant amount of antigen in a constant volume of solution. A 5 to 10% decrease in precipitated protein was noted at the largest amounts of antibody in every experiment. This effect of inhibition of precipitation by antibody excess is similar to but not nearly so marked as the effect in serum,[10] in which a four-fold increase in amount of antiserum above the optimum was found to decrease the amount of precipitate to a third of the maximum value.

Many precipitation experiments in which constant amounts of purified antibody were added to various amounts of antigen were carried out. The detailed results were in all cases similar to those reported in Table I, and their important features are summarized in Table III. Some experiments with added serum are also reported at the end of Table III for comparison. The first two columns give the antigen used and the *p*H of the system. A stands for antigen and B stands for antibody. Columns 3 to 5 have to do with conditions at the optimum, *i. e.*, the conditions which give the maximum amount of precipitate. Column 3 gives the per cent. of total antibody precipitated. The values in this column depend on the antigen, and, for resorcinol-R$'_3$, decrease with increasing *p*H. In the presence of serum an optimum is obtained at about *p*H 9.0.[14] The presence of serum greatly reduces the amount of precipitable antibody, especially in the case of antigen R'X', which gives no precipitate in serum.

TABLE III

SUMMARY OF PRECIPITATION EXPERIMENTS WITH PURIFIED ANTIBODY

| Antigen | *p*H | Per cent. of antibody pptd. at optimum | Mole ratio A/B in system at optimum | Mole ratio A/B in precipitate at optimum | A/B in precipitate at A = 0 |
|---|---|---|---|---|---|
| XXX | 8.1 | 73 | 1.8 | 1.3 | 0.9 |
| XXX | 8.1 | 58 | 1.5 | 1.8 | 1.1 |
| Resorcinol-R$'_3$ | 6.6 | 82 | 18 | 19 | 2.5 |
| Resorcinol-R' | 6.9 | 84 | 7.0 | 10 | 5.0 |
| Resorcinol-R$'_3$ | 7.6[a] | 76 | 5.1 | 5.0 | 1.1 |
| Resorcinol-R$'_3$ | 7.9 | 68 | 5.7 | 4.5 | 2.0 |
| Resorcinol-R$'_3$ | 8.7[b] | 63 | 6.0 | 7.0 | 1.5 |
| R'X' | 7.9[b] | 50 | 12 | 4.6 | 2.8 |
| XXX (in serum) | 8.1[b] | 19 | 7 | .. | ... |
| Resorcinol-R$'_3$ (in serum) | 8.5 | 36 | 5.1 | 2.2 | 2.0 |
| R'X' (in serum) | 8.3 | 0 | .. | .. | ... |

[a] This experiment was started at *p*H 9.9; when no precipitate appeared, the mixtures were acidified to *p*H 7.6. [b] 0.01 F Veronal buffer present. Mr. Leonard Lerman found no non-specific precipitation between resorcinol-R'$_3$ and normal rabbit γ-globulin under conditions similar to the above.

Column 4 gives the number of moles of antigen required per mole of antibody to form the maximum amount of precipitate. The antigen resorcinol-R$'_3$, which is more highly associated than the others,[15] requires a higher ratio, and the ratio is greater at lower *p*H. Antigen R'X' has a strikingly different ratio than the structurally similar compound XXX. The presence of serum has little effect on this ratio for resorcinol-R$'_3$ but a large effect for XXX.

The fifth column gives the mole ratio of antigen to antibody in the precipitate at the optimum. The values are similar to those in column 4 in the absence of serum, and decrease with increasing *p*H. The antigen R'X' is an exception, requiring a much higher ratio in the system than in the precipitate. Experiments in serum also show a lower antigen–antibody ratio in the precipitate than in the system, probably because much of the antigen is non-specifically combined with serum proteins.

(13) L. Pauling, D. Pressman, D. H. Campbell, and C. Ikeda, THIS JOURNAL, 64, 3003 (1942).

(14) D. Pressman, unpublished work.

(15) See the following paper, THIS JOURNAL, 71, 148 (1949).

The sixth column gives the mole ratio of antigen to antibody in the precipitate extrapolated to zero antigen–antibody ratio. This value can be obtained from either an experiment with variable antigen and constant antibody or an experiment with constant antigen and variable antibody. The values for the two types of experiment are the same within experimental error for antigen resorcinol-$R_3'$ and for XXX but are 4.0 and 2.8 for R'X'. The ratio is of interest because one would expect non-specific reactions of antigen with proteins, and also association, to be least important when there is a large excess of antibody in the system. Ideally the ratio should be unity according to the framework theory.[16] This is the value found for antigen XXX and approached by resorcinol-$R_3'$ as the *p*H is increased. In the experiment which was started at *p*H 9.9 and finished at *p*H 7.6 it appeared as if the antigen combined as a small aggregate at the higher *p*H and remained unassociated as the *p*H was decreased. Earlier experiments by Pressman[14] showed that if resorcinol-$R_3'$ were aged for even one hour at *p*H values below 9 before addition to antibody, the amount of precipitate was appreciably decreased below the optimum amount obtained with antigen kept above *p*H 9. R'X' has a higher limiting ratio than the structurally similar antigen XXX, indicating that R'X' is associated in the precipitate even at antigen–antibody ratios less than unity. If the values in the fifth and sixth columns of Table III agree, the non-specific effect in the purified antibody experiments is probably small. Experiments in serum all led to fairly low ratios.[10]

The shapes of the plots of amount of precipitate *vs.* amount of antigen added were generally similar. One quarter to one sixth of the optimum amount of antigen was required to give half the maximum amount of precipitate with purified antibody, and slightly more was required with antiserum. Generally about eight times the optimum amount of antigen was required to reduce the amount of precipitate to a half by antigen-excess inhibition. An exception was R'X', which required more than a fifteen-fold excess.

**The Effect of Addition of Serum or Serum Albumin.**—Normal rabbit serum was added to the purified antibody and precipitation tests were made, with the results reported in Table III. The effect of the serum was to reduce the amount of precipitate with antigens resorcinol-$R_3'$ and XXX, and to prevent precipitation with antigen R'X'. Serum albumin had the same effect as normal rabbit serum: it completely inhibited precipitation with R'X', and reduced the amount of precipitate obtained with antigen XXX. The tests in serum albumin were made at *p*H 6.2.

(16) L. Pauling, THIS JOURNAL, **62**, 2643 (1940); L. Pauling, D. Pressman, and C. Ikeda, *ibid.*, **64**, 3010 (1942).

**A Study of Non-specific Adsorption.**—To see how much antigen was held non-specifically to the precipitates in the purified antibody experiments, precipitations were carried out between purified pneumococcus polysaccharide type I and a commercial globulin preparation from rabbit serum, containing about 10% antibody precipitable by the polysaccharide. In the first four tubes of the series reported in Table IV the compound resorcinol-$R_3'$ was present at the time of precipitation of approximately optimal amounts of the reactants. In tubes 5 to 8 the precipitation was completed and then the supernatant liquid was replaced by solutions of resorcinol-$R_3'$. The results given in the table show that there is a very strong non-specific affinity of the precipitate for the simple antigen. That the antigen is not merely trapped in the precipitate is shown by the fact that the second four experiments gave ratios very similar to the first four. Although there is ten times as much protein in the solution as in the precipitate, the precipitate can hold 80% of the antigen. That the increase in precipitate with increasing amounts of antigen is a non-specific effect is shown by the ninth and tenth tubes of the table, in which no polysaccharide was present. Experiments with compound XXX and the pneumococcus polysaccharide system showed that the protein in the precipitate is more effective for non-specific combination than is the protein in solution for this compound also, and that the effect is not due to a difference in the type of protein, because in some experiments only a fraction of the antibody was precipitated and there was still preferential

TABLE IV

NON-SPECIFIC ADSORPTION OF COMPOUND RESORCINOL-$R_3'$

To $10^{-4}$ g. pneumococcus polysaccharide type I in 1 ml. saline there was added 1 ml. of saline containing 4.5 mg. of commercial anti-polysaccharide type I. The precipitation was done in the presence of 1 ml. of saline containing compound resorcinol-$R_3'$ in tubes 1–4, and the supernate of the precipitate was replaced by 3 ml. of saline containing compound resorcinol-$R_3'$ in tubes 5–8. Tubes 9 and 10 were controls, containing no polysaccharide. Final *p*H 8.0, no buffer, duplicate analyses

| | Resorcinol-$R_3'$ added moles × $10^9$ | Precipitated protein moles × $10^9$ | Mole ratio $\frac{R_3'}{\text{protein in precipitate}}$ | % of total resorcinol-$R_3'$ in precipitate |
|---|---|---|---|---|
| 1 | 400 | 3.7 | 12.0 | 11 |
| 2 | 85 | 3.3 | 8.8 | 34 |
| 3 | 22 | 2.9 | 4.8 | 63 |
| 4 | 7 | 2.6 | 1.9 | 71 |
| 5 | 400 | 2.4 | 7.1 | 4 |
| 6 | 85 | 2.6 | 9.5 | 29 |
| 7 | 22 | 2.8 | 5.7 | 72 |
| 8 | 7 | 2.6 | 2.1 | 78 |
| 9 | 85 | 0.3 | 30 | 11 |
| 10 | 22 | .2 | 14 | 14 |

A Referee suggests that it would be preferable to carry out this experiment with antibody prepared by more gentle methods because the Lederle product may have an altered affinity for haptens due to its method of preparation.

combination with the precipitate. Compound XXX was not bound as strongly as was resorcinol-$R'_3$. R'X' was bound to about the same extent as XXX.

These observations can perhaps best be explained by considering the precipitate to have a few locations where a dye-polymer molecule can attach itself very firmly, perhaps by combining with several protein molecules. Such sites would be absent in the protein in solution. Since only a few polymer molecules could go into these locations, the fraction of dye combined with the precipitate would be large when there was little dye in the system, and would become smaller when the dye was increased and the stronger locations were filled. Then the protein in the solution would compete successfully with the smaller amount of precipitate.

**Hapten Inhibition.**—Varying amounts of the strong hapten *p*-(*p*-hydroxybenzeneazo)-benzenearsonic acid were added to an optimal mixture of purified antibody and antigen XXX at *p*H 7.6 before precipitation had begun. This hapten, in 20-fold excess over the added antigen, was able to inhibit the precipitation almost completely, and gave a heterogeneity index[17] of $\sigma = 1.5$. A 50-fold excess of the weaker hapten benzenearsonic acid had almost no effect on the amount of precipitate obtained with purified antibody and resorcinol-$R'_3$. These results on hapten inhibition with purified antibody are closely similar to those obtained with antiserum.

## Discussion of Results

In our earlier work on the molecular ratio of antigen to antibody in the precipitate formed by dye antigens with hapten-homologous antiserum, values of about 1.2 for this ratio were found. These values indicate a valence of approximately 2 (2.4) for antibody if the dyes are assumed to be bivalent. The equality of the values found for trihaptenic and tetrahaptenic dyes with those for dihaptenic dyes was explained as resulting from steric hindrance of the large antibody molecules, which prevents more than two of the haptenic groups of the small dye molecules from being effective. A constant antigen-antibody ratio was obtained (to within about ±20%) even when the amount of dye added to a constant amount of antiserum was varied over a wide range, from antigen excess to antigen deficiency, and when the *p*H was varied from 7.6 to 9.2. Essentially the same results were obtained for seven dyes. The new results, obtained with different dyes and with purified antibody, are much different. A strong dependence of the ratio on the amount of antigen is observed, and the ratios are much higher than those found before, except in the antibody-excess region. The results found in the present investigation are of the nature to be expected in case that the dyes form aggregates that are taken up by the precipitate through non-specific adsorption. The amount of non-specific adsorption of resorcinol-$R'_3$ shown in Table IV is enough to account for the high values of the molecular ratio of dye and antibody reported in Tables I, II and III.

The limiting values of the molecular ratio extrapolated to zero dye concentration are approximately 1.0 for antigen XXX and somewhat larger for resorcinol-$R'_3$.

We believe that the difference between the results obtained with purified antibody and those obtained earlier with antiserum is due to the non-specific combination of the dye molecules with serum albumin or other constituents of serum not present in the purified antiserum,[7,8] and that in the presence of serum this effect causes the concentration of uncombined dye molecules to be so small as to keep the amount of aggregation down to a low value. It seems likely that the high values for the amount of dye in the precipitates formed with purified antibody are due largely to the inclusion of the aggregates in the precipitate through non-specific adsorption, and possibly also to some extent to their incorporation in the framework as effective precipitating antigens.

The results obtained with the antigen R'X' indicate that dimers or larger aggregates of this molecule are able to form a precipitate with anti-R serum, the precipitation being inhibited by the presence of serum. In our earlier investigation[10] we observed that a small amount of precipitate was formed by R'X' with some pools of anti-R serum; it is likely that these precipitates were due, not to cross-reaction, but to the presence of aggregates, these pools of antiserum perhaps containing smaller amounts of the complexing material than are usually present.

The conclusion that may be reached from the experimental results obtained is that the earlier work, carried out with serum, is presumably reliable, despite the tendency of the dyes to aggregate, because this tendency was counteracted by the presence of complexing materials in the serum. Moreover, the limiting molecular ratio found by extrapolation to antibody excess of the results obtained in the present investigation, with purified antibody, supports the molecular ratio of about 1 given by the earlier work. It would, however, be desirable, in order to carry conviction, for additional experiments to be made, with use of non-aggregating polyhaptenic precipitating antigens.

In the earlier studies it was found that non-aggregating polyhaptenic compounds (amides, rather than azo dyes) form precipitates with antisera, whereas the monohaptenic substances do not; however, analyses of the precipitates were not made because of the difficulties of determining the amount of the colorless precipitating antigens.

It may be pointed out that the quantitative hapten inhibition experiments reported in earlier

(17) L. Pauling, D. Pressman, and A. L. Grossberg, THIS JOURNAL, 66, 784 (1944).

papers of this series are not made unreliable by the phenomenon of aggregation of the precipitating antigen, for two reasons: first, the experiments were carried out in the presence of serum, which presumably inhibited the aggregation of the antigens; and second, the experiments all involve the comparison of the concentration of hapten required for a standard amount of inhibition (50%) with the concentration of a standard hapten producing the same effect, and this concentration ratio of the haptens, which do not themselves form aggregates, would be expected to be the same whether the test substance (the precipitating antigen) was aggregated or not.

The investigation reported in this paper was carried out with the aid of a grant from The Rockefeller Foundation. We wish to thank Professors Dan H. Campbell and Verner Schomaker, and Drs. David Pressman, Frank Lanni, J. E. Cushing, Jr., George Feigen and Stanley Swingle for advice in connection with the work and for providing some of the materials used. Mr. Dan Rice carried out many of the protein analyses.

## Summary

Experiments have been carried out on the precipitation under various conditions of specifically purified anti-azobenzenearsonic acid antibodies by three azo dyes, serving as precipitating antigens. The non-specific combination of the dyes with pneumococcus polysaccharide: antipolysaccharide precipitates has also been investigated.

In solution these dyes exist as monomeric molecules and as aggregates. The molecular ratio of dye to antibody in the precipitate was found in general to be much larger than in earlier experiments involving antiserum, and to depend greatly upon conditions of the precipitation, whereas the earlier ratio (approximately 1.2) was essentially independent of these conditions. The dye is also carried down in non-specific serological precipitates (pneumococcus polysaccharide:antipolysaccharide antibody), apparently through non-specific adsorption or entrapment in the precipitate. The large molecular ratio in the precipitate formed with the homologous antibody is probably due mainly to the non-specific adsorption of dye aggregates. It is suggested that the results obtained with antiserum, which seem not to be affected by aggregation of the dye molecules, are to be explained as resulting from the combination of the dye molecules with constituents of serum, mainly albumin, which are not present in the purified antibody, this combination keeping the concentration of free antibody low, and preventing the formation of appreciable amounts of the aggregates.

PASADENA, CALIFORNIA RECEIVED JUNE 7, 1948

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1136]

# The Degree of Association of Some Simple Antigens

BY ARTHUR B. PARDEE AND STANLEY M. SWINGLE

In the preceding paper, which considers the effect of serum on the precipitin reaction between certain simple polyhaptenic precipitating antigens and antibodies, it was assumed that the antigens could be associated into aggregates. This paper presents measurements on some simple antigens which, because of their size and color, may be expected to be associated to a measurable extent.

In their treatment of the precipitin reaction between antisera and simple polyhaptenic substances (hereafter called simple antigens), Pauling and coworkers were aware of the possibility that their simple antigens might be associated, but did not consider association important and neglected it. This was done because some of the simple antigens used by them were colorless[1] and hence almost certainly not associated and because a simple substance containing one haptenic group against one antiserum and another against another antiserum did not precipitate against either antiserum separately, as it should if it were polymerized, but did precipitate with the mixed antisera.[2]

Landsteiner[3] was the first to suggest that the precipitating power of simple antigens might be connected with their association. He observed that some of the simple antigens have structures similar to those of associating dyes.[4,5] Many dyes are associated in solution; the forces involved have been explained on the basis of the color-producing resonance in the conjugated structure.

Boyd and Behnke[6] published a note stating that one large and highly colored simple antigen was polymerized 11-fold in a saline solution.

(1) L. Pauling, D. Pressman, D. H. Campbell, C. Ikeda, and M. Ikawa, THIS JOURNAL, **64**, 2994 (1942).

(2) L. Pauling, D. Pressman, and D. H. Campbell, *ibid.*, **66**, 330 (1944).

(3) K. Landsteiner, "The Specificity of Serological Reactions," Charles C. Thomas, Baltimore, Md., 1936, p. 120.

(4) C. Robinson, *Trans. Faraday Soc.*, **31**, 245 (1935).

(5) E. Rabinowitsch and L. F. Epstein, THIS JOURNAL, **63**, 69 (1941).

(6) W. C. Boyd and J. Behnke, *Science*, **100**, 13 (1944).

## Experimental Methods

**Simple Antigens.**—All the synthetic antigens used in the present work, and their preparation, have been described in references[1,2,7,8]; the symbols used in those papers will be used here. R is *p*-azobenzenearsonic acid. R′ is *p*-(*p*-azobenzene)-azobenzenearsonic acid, and X′ is *p*-(*p*-azobenzene)-azobenzoic acid.

Chromotropic acid is 1,8-dihydroxynaphthalene-3,6-disulfonic acid and H-acid is 1-amino-8-napthol-3,6-disulfonic acid. The polyhaptenic substances used are VI, resorcinol-$R_3$; XI, phloroglucinol-$R'_3$; XII, 4,4′-bis-(azo-2,4-dihydroxy)-3,5-di-R′-biphenyl; XXXV, chromotropic acid-$X'_2$; XXX, chromotropic acid-$R'_2$; and R′-X′, chromotropic acid-R′X′. Other antigens are referred to by name.

**Free Diffusion.**—Aqueous solutions of the antigens in 0.9% sodium chloride buffered at *p*H 8.0 to 8.5 with 0.1 *M* veronal (unless otherwise noted) were studied at 1.3° in a Lamm-type[9] diffusion cell made of bakelite (some of the antigens precipitate with traces of metal ions). A light-absorption method similar to that of Tiselius and Gross[10] was used, except that a reference cell with five solutions of concentration 1/8, 1/6, 1/4, 1/2 and 3/4, the initial concentration was photographed simultaneously with the diffusion cell so that the positions of the corresponding concentrations in the diffusing column could be determined by a direct comparison of the photographic densities, corrected for a slight non-uniformity of illumination. Photographs were taken periodically until the diffusion was interrupted. The diffusion coefficient was calculated at each concentration by the formula $D = \{\Delta X\}^2 f(c_0/c)/t$, in which $\Delta X$ is the distance between the given concentration $c$ and the 1/2 concentration after time $t$, and $f(c_0/c)$ is a function whose value may be obtained from tables.[11] Values of $\{\Delta X\}^2/t$ were obtained from the slopes of plots of $\{\Delta X\}^2$ *vs.* $t$. These plots generally gave a straight line for each concentration. The position of the 1/2 concentration generally moved toward the high concentration end of the cell, indicating that $D$ decreases with increasing concentration.[12,13] A numerical average of the value of $D$ obtained at each concentration is reported in Table I.

**Porous Diaphragm Diffusion.**—For the measurements of diffusion through a porous diaphragm,[14] five cells of the usual simple design with Jena G3 or G4 disks were used with a volume of 25 ml. on each side of the disk. The cells were used interchangeably after an intercomparison with the antigen H acid-azo-benzene gave an average deviation of 4% for 27 measurements, with no significant differences among the five cells. The antigens were dissolved in a solution containing 0.9% NaCl + 0.1 *M* veronal buffer at *p*H 8.0 and were allowed to diffuse for two weeks, during which time samples were periodically withdrawn for analysis. Convective stirring was brought about by making the salt concentration in the bottom layer slightly lower than that in the top layer. Analyses were colorimetric and accurate to about 2%. Values of the diffusion coefficient reported in Table I are for determinations using any one of the cells and the equation

$$D = \frac{K}{t} \log \left( \frac{c_1 + c_2}{c_2 - c_1} \right)$$

in which $c_1$ is the final concentration in the dilute solution, $c_2$ is the final concentration in the more concentrated solution, and $K$ is the cell constant obtained by calibration with 0.15 *M* KCl ($D = 9.6 \times 10^{-6}$ cm.²/sec. at 1.3°).

TABLE I

DEGREE OF ASSOCIATION FROM DIFFUSION DATA

| | Concn.[a] × 10⁵ | Method[e] | $D$, cm.²/sec. × 10⁶ | $n^i$ |
|---|---|---|---|---|
| H-Acid-azo-benzene | 10 | *f* | 2.13 | 1.3 |
| | 10 | *f* | 2.36 | 1.0 |
| | 19 | *d* | 1.83 ± 0.07 | 2.0 |
| H-Acid-azo-benzoic acid | 80 | *d* | 2.08 ± 0.05 | 1.3 |
| XXX | 5 | *f* | 0.77 | 10 |
| | 5 | *f* | 0.82 | 7 |
| | 50 | *d* | 1.14 ± 0.06 | 3 |
| XXXV | 6.5[b] | *f* | 1.07 | 4 |
| | 6.5[c] | *f* | 1.20 | 3 |
| | 6.5[b] | *d* | 1.25 ± 0.02 | 2 |
| | 6.5[c] | *d* | 0.97 ± 0.03 | 6 |
| | 11[g] | *d* | 1.44 ± 0.15 | 0.8 |
| R′X′ | 15 | *d* | 0.95 ± 0.08 | 6 |
| | 15 | *d*[h] | 2.23 ± 0.16 | 7 |
| | 10[g] | *d*[h] | 3.00 ± 0.20 | 0.8 |
| XII | 9.5 | *f* | 0.22 | 300[j] |
| | 9.5 | *f* | 0.20 | 400[j] |
| | 9.5 | *d* | Adsorbed by disk | |
| XI | 16 | *d* | Adsorbed by disk | |
| Phenol-phthalein | Satd. acid solution | *d* | 2.5 ± 0.60 | 1 |
| VI | 45 | *d* | 1.12 ± 0.05 | 4 |

[a] Concentrations are moles per liter in 0.9% saline + 0.1 *M* veronal buffer at *p*H 8.0 unless otherwise noted. [b] *p*H 10.0. [c] *p*H 7.5. [e] Diffusion by *f* free diffusion, or *d* porous diaphragm, all at 1.3° except as noted. [g] In ethanol. [h] At 35°. [i] The degree of association calculated from the Stokes–Einstein equation with an estimated shape correction. [j] Not corrected for shape.

**Osmotic Pressure.**—The osmotic pressures reported in Table II for two of the larger antigens were obtained with a simple osmometer consisting of a 15-ml. Cellophane sack tied to a 1-mm. capillary. The reported capillary rise is the value given by extrapolation to infinite time of a plot of rise *vs.* $1/t$. The other antigens leaked through the cellophane too rapidly for successful measurements, and less permeable membranes were too slow to equilibrate.

**Partition Coefficient.**—H-acid-azobenzene was found to have a measurable partition coefficient between water and *n*-butanol, the results of which indicate that this substance is associated to the same extent in both solvents, and is hence probably monomeric. On a plot of concentration in water *vs.* concentration in *n*-butanol, the experimental points fit the least squares line through the origin with an average deviation of ±4%, which is much better agreement than would be possible with even 25% dimerization in one solvent.

## Discussion

It is probable that the degree of association is dependent on the concentration, and that the values of diffusion coefficient reported here, being calculated in a simple manner, represent the coefficient at some intermediate concentration in the cell. The experimental data are not sufficiently complete or accurate to permit us to use a more refined treatment.[12,13] Values of $D$ from diffusion measurements at 1/8, 1/6 and 1/4 $c_0$ showed no consistent trend with concentration, but $D$ from 3/4 $c_0$ was generally 60 to 80% of the other three values.

(7) D. Pressman, J. T. Maynard, A. L. Grossberg, and L. Pauling, THIS JOURNAL, **65**, 728 (1943).

(8) D. Pressman, S. M. Swingle, A. L. Grossberg, and L. Pauling, *ibid.*, **66**, 1731 (1944).

(9) O. Lamm, Dissertation, Upsala, 1937; A. Polson, *Kolloid. Z.*, **87**, 149 (1939).

(10) A. Tiselius and D. Gross, *Kolloid. Z.*, **66**, 11 (1934).

(11) R. Furth, *Kolloid. Z.*, **41**, 300 (1927).

(12) C. O. Beckman and J. L. Rosenberg, *Ann. N. Y. Acad. Sci.*, **46**, 329 (1945).

(13) E. M. Bevilacqua, E. B. Bevilacqua, M. M. Bender and J. W. Williams, *ibid.*, **46**, 309 (1945).

(14) A. R. Gordon, *ibid.*, **46**, 285 (1945).

An assumption of spherical shape is made in calculating a particle radius $r$ from the Stokes–Einstein equation,[15] $D = RT/6\pi Nr\eta$ in which $\eta$ is the viscosity of the solvent. Actually the particles, particularly the monomeric ones, must be quite elongated. Somewhat better particle volumes were calculated by multiplying the diffusion coefficient by a correction factor[16] to account for the higher frictional resistance. This correction is based on the assumption that the particles resemble ellipsoids of revolution of dimensions estimated from their known structure and the assumption that they polymerize side by side. Using for the partial specific volume the value 0.64 ml./g. as measured for compound XXX, in agreement with Robinson[4] for a different dye, values of the degree of association $n$ were calculated, as reported in Table I. The corrected values of $n$ are smaller than uncorrected values by factors varying from 1 to 0.4. The error in $n$ is seen to be more than three times the error in $D$, which may be large in itself, so that tests of the validity of the results are desirable. Several are available.

TABLE II

THE DEGREE OF ASSOCIATION FROM OSMOTIC PRESSURE DATA

| | Concn. × $10^5$ | Temp., °C. | Capillary rise, cm. | $n$ |
|---|---|---|---|---|
| XXX | 7 | 37.5 | 1.0 | 2 |
| | 7 | 37.5 | 1.2 | 2 |
| XII | 9.5 | 37.5 | 0.55 | 4 |
| | 9.5 | 37.5 | 0.7 | 5 |
| XI | 16 | 25 | Adsorbed by osmometer | |

For H-acid-azobenzene the values $n = 1$ and 1.3 from free diffusion and $n = 2$ from 27 porous diaphragm measurements may be compared with the partition experiments which showed this substance probably monomeric. Diffusion gave $n = 1$ for phenolphthalein, which is presumably monomeric in the colorless form, in which it lacks the resonating electrons necessary for association. Similarly, compounds XXXV and R′X′ in ethanol solution are probably monomeric, in agreement with the diffusion results, $n = 0.8$.

The osmotic pressure data are in poor agreement with the diffusion data, but nevertheless indicate some degree of association. Attempts to gain useful information by studying the changes in absorption spectrum with concentration showed that for compounds VI, VII, XI, XXX and XXXV there is no change, as is in general true for azo dyes,[17] except that in the presence of borate ions the spectra of XXX and XXXV change somewhat, an observation which has not been explained.

The measurement of Boyd and Behnke[6] ($n = 11$ for compound XI) seems reasonable. This compound was adsorbed by both the porous disk and the osmosis membrane, so that we were unable to obtain data for it.

This investigation was carried out with the aid of a grant from the Rockefeller Foundation. We wish to thank Dr. David Pressman for furnishing the synthetic antigens.

## Summary

We have carried out measurements on the association of a number of polyhaptenic simple substances. Some of these colored simple antigens are probably associated several-fold in saline solution. Diffusion measurements seem to give an approximate measure of the degree of association, at least for those compounds which are not too highly associated.

(15) W. Sutherland, *Phil. Mag.*, [6] **9**, 781 (1905).

(16) T. Svedberg and K. O. Pederson, "The Ultracentrifuge," Clarenden Press, Oxford, 1940, p. 41.

(17) S. E. Sheppard and A. L. Geddes, THIS JOURNAL, **66**, 1995 (1944).

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# The Structure and Chemistry of Actidione, an Antibiotic from Streptomyces Griseus[1]

BY EDMUND C. KORNFELD, REUBEN G. JONES AND THOMAS V. PARKE

Recently Ford and Leach[2a,b] of the Upjohn Research Laboratories reported the isolation from *Streptomyces griseus* of a new antibiotic substance which they named "Actidione."[3] This interesting material is highly active against most yeasts but is relatively inactive against other microörganisms. Subsequently, Leighty and Fortune of these Laboratories also isolated Actidione from Streptomycin residues, and we undertook a study designed to elucidate the chemical structure of the new antibiotic. A preliminary communication[4] regarding this work has been published, in which structure I was proposed. It is the purpose of the present paper to give the evidence upon which this formulation is based.

The empirical formula of Actidione as originally determined in these laboratories and also ascertained by the Upjohn workers[2a] is $C_{15}H_{23}NO_4$. Nitrogen analyses by either the Dumas or Kjeldahl methods gave concordant results. It was

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Washington, D. C., meeting, 1948.

(2) (a) Ford and Leach, THIS JOURNAL, **70**, 1223 (1948). (b) Leach, Ford and Whiffen, *ibid.*, **69**, 474 (1947).

(3) The compound was given this name because it was originally believed to be a *di*ketone. However, the present work has shown the compound to be a *mono*ketone.

(4) Kornfeld and Jones, *Science*, **108**, 437 (1948).

then found that all of the nitrogen in Actidione was liberated as ammonia by simply boiling the compound with sodium hydroxide solution. This fact suggested the presence of an amide or imide grouping in Actidione. A determination of terminal methyl groups indicated that the molecule contained *two* such linkages.

Evidence for functional groups in Actidione was next sought, and it was found that the compound was easily converted to a *p*-nitrobenzoate and an acetate ($C_{17}H_{25}NO_5$).[2] Actidione also gave a qualitative test for primary or secondary alcoholic hydroxyl by the method of Fearon and Mitchell.[5] This test gives negative results with *tertiary* alcohols. The compound formed a monoxime[2] and a semicarbazone.[2] When subjected to catalytic reduction only *one* mole of hydrogen was absorbed, to yield dihydroactidione (II). The latter product was shown to be a *diol* by conversion to a diacetate ($C_{19}H_{29}NO_6$). However, it was not attacked by periodic acid, and, therefore, dihydroactidione was considered not to be a 1,2-diol. Actidione acetate, mentioned above, also underwent catalytic reduction to yield a dihydro derivative ($C_{17}H_{27}NO_5$). The dihydro compounds showed only end absorption in the ultraviolet, thus indicating that during the hydrogenation a carbonyl was reduced to a hydroxyl group.

Confirmation of the functional groups was found in further physical studies. The ultraviolet spectrum of Actidione (Fig. 1) showed a single maximum at 287 m$\mu$ ($\epsilon$ = 36.7), which is characteristic of a simple ketone group. The infrared spectrum (Fig. 3) contained bands at wave lengths which may be assigned to carbonyl (5.90 $\mu$) hydroxyl (2.80 $\mu$), C-methyl (7.28 $\mu$), >NH (3.00 $\mu$), aliphatic C–H (3.42 $\mu$) and others. A semiquantitative

(5) Fearon and Mitchell, *Analyst*, **57**, 372 (1932).

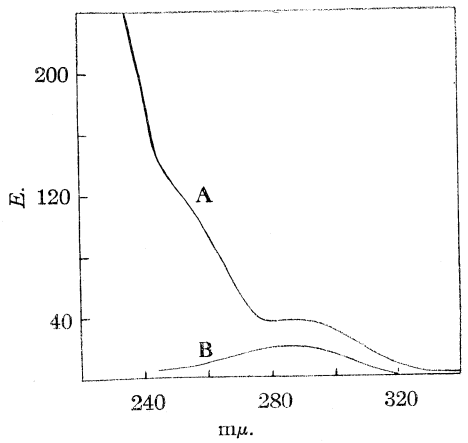



Fig. 1.—Ultraviolet absorption spectra of Actidione (A) and $C_8H_{14}O$ ketone (B) from Actidione.

study of this spectrum in comparison with that of other compounds indicated that Actidione contained *three* carbonyl groups. Rapid electrometric titration in water showed no titratable group from *p*H 2 to *p*H 10. Beginning at about *p*H 10, however, a weakly acidic group was titrated with a mid-point or $pK'_\alpha$ of 11.2. Discussion of this titration data is presented later. Thus, in summary, it was indicated that Actidione had two terminal methyl groups, one hydroxyl group (primary or secondary), one ketone group and an amide or imide linkage.

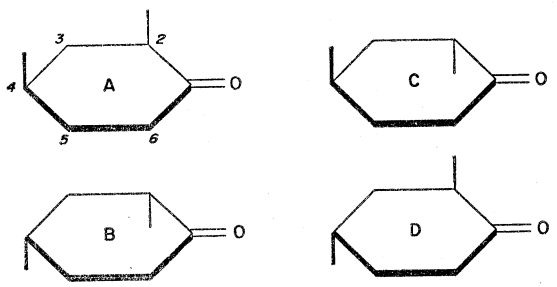
Degradative studies were next undertaken to determine whether identifiable fragments of the molecule could be isolated. Ford, Leach and Whiffen[2] had already discovered that Actidione was extremely labile under basic conditions. We observed that exposure of the molecule to even one-hundredth normal alkali at room temperature resulted in rapid inactivation and cleavage to form, among other things, a fragrant, volatile liquid. This liquid was isolated with facility either by ether extraction of the alkaline degradation mixture or by steam distillation. It was found to be dextrorotatory and to have the empirical formula $C_8H_{14}O$ (III). The ultraviolet absorption spectrum (Fig. 1) had a single maximum at 284 mμ ($\epsilon$ = 20.2) characteristic of a carbonyl group. The presence of a carbonyl group was confirmed by the preparation of an oxime, semicarbazone, 2,4-dinitrophenylhydrazone, *p*-nitrophenylhydrazone and a bisulfite addition product. Upon catalytic reduction the compound absorbed *one* mole of hydrogen. Tests for an aldehyde group were negative, so the fragrant liquid was considered to be a *cyclic ketone*. A literature search revealed that there were at least three known cyclic ketones of the formula $C_8H_{14}O$ with physical properties hardly distinguishable from the natural degradation product (see Table I). Consequently, these three isomeric ketones were synthesized for comparison. The melting points of the semicarbazones were of little help in the identification be-

TABLE I[a]

| Ketone | B. p., °C. | $n_D$ | M. p., °C., of semicarbazone |
|---|---|---|---|
| $C_8H_{14}O$ from Actidione | 175–176 | 1.4435 | 212–214 |
| Isopropylcyclopentanone[15] | 173–174 | 1.4395 | 201–202 |
| 2,4-Dimethylcyclohexanone[17] | 175–176 | 1.4430 | 200–202 |
| 2,5-Dimethylcyclohexanone[19] | 174–176 | 1.4406 | 155–157 |

[a] Experimental values as determined in this Laboratory.

cause the natural product was optically active while the synthetic ketones were racemic. However, a comparison of the infrared spectra of the four compounds (Fig. 2) showed in a very convincing manner that the natural ketone was an optical isomer of 2,4-dimethylcyclohexanone (III). It may be noted that the spectra of the natural and synthetic 2,4-dimethylcyclohexanones are identical in every way, while marked differences are found in the spectra of the isomeric ketones. Additional confirmation of the identity of the natural degradation product was obtained by resolution of the synthetic *dl*-2,4-dimethylcyclohexanone. This was accomplished by fractional crystallization of the *l*-menthydrazones obtained from the *dl*-ketone. The least soluble *l*-menthydrazone was found to be identical with the *l*-menthydrazone of the natural dextrorotatory ketone. This identity was established by melting point, mixed melting point, optical rotation, and finally by comparison of the X-ray diffraction patterns (see Experimental). Of the four possible optical isomers of 2,4-dimethylcyclohexanone (A to D), A and B would have identical




infrared spectra as would also C and D.[6] The spectra of the *cis*- and *trans*-forms, however, would differ. Obviously, the natural and synthetic ketones must *both* be either all *cis* or all *trans* depending on which is the more stable, or each may consist of the same equilibrium proportion of *cis* and *trans* forms.

With the identification of the $C_8$ ketone from Actidione there remained yet seven carbon atoms to be accounted for. At this point certain evidence on hand suggested that Actidione might be a glutarimide derivative. In the first place, the infrared spectrum of Actidione, mentioned above, indicated the presence of *three* carbonyl groups. One had been identified as a simple ketonic linkage, so there remained *two* carbonyl groups which *could*

(6) Thompson and Sutherland, *Trans. Faraday Soc.*, **41**, 197 (1945).

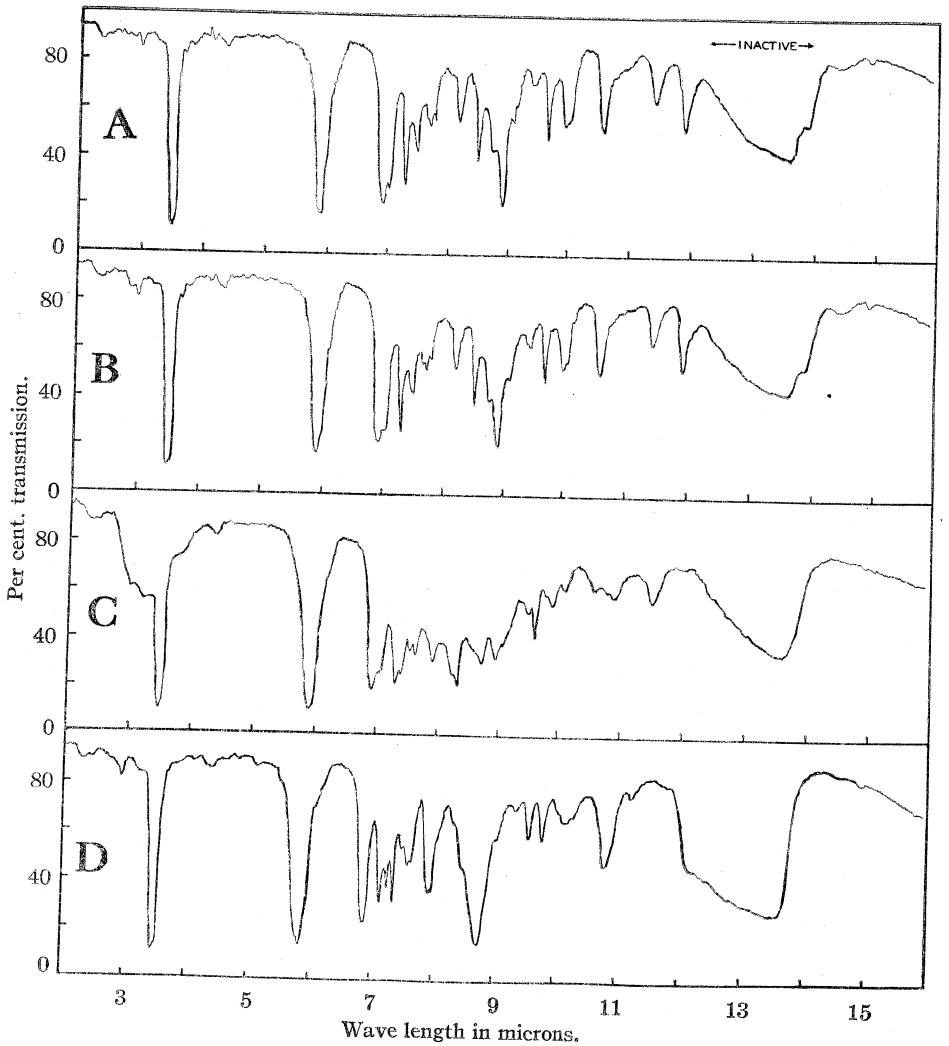



Fig. 2.—Infrared absorption spectra of $C_8H_{14}O$ from Actidione (A), 2,4-dimethylcyclohexanone (B), 2,5-dimethylcyclohexanone (C) and $\alpha$-isopropylcyclopentanone (D). Concentration, 20% in carbon tetrachloride; cell length, 0.132 mm. Inactive region is due to solvent absorption.

be accounted for by a cyclic imide structure. Furthermore, the weakly acidic character of Actidione ($pK'_\alpha$ 11.2) as revealed in the electrometric titration was consistent with a cyclic imide formulation. To confirm this point an electrometric titration of glutarimide was carried out, and it was found that the acidic >NH group had a $pK'_\alpha$ of 11.2, identical with that of Actidione. Succinimide, on the other hand, was found to have a $pK'_\alpha$ of 9.35. Having thus obtained evidence for the presence of a glutarimide ring system in Actidione it was of interest to determine the point of attachment of that ring to the other part of the Actidione molecule. Two model compounds, $\alpha$-ethylglutarimide and $\beta$-ethylglutarimide, were synthesized, and their infrared spectra were compared with that of Actidione (Fig. 3). Both Actidione and $\beta$-ethylglutarimide had bands at 8.75 $\mu$, while this band was completely missing in the spectrum of the $\alpha$-ethyl isomer. This was tentatively accepted as evidence that Actidione was a $\beta$-substituted glutarimide.

Substantial *chemical* evidence for a $\beta$-substituted glutarimide structure was sought next. Proof of the presence of a cyclic imide grouping was furnished when dihydroactidione (II) was allowed to react with diazomethane to form an N-methyl derivative (IV). This is a characteristic reaction of glutarimide.[7] That the methyl group was attached to nitrogen was demonstrated by alkaline degradation of the N-methyldihydroactidione to yield methylamine. When Actidione was degraded in alkaline solution and the ammonia and 2,4-dimethylcyclohexanone so formed were removed, the residue yielded a seven-carbon acidic fragment, presumably propionaldehyde-2,2-diacetic acid. This product was not obtained in pure condition but on oxidation it afforded

(7) Irrera, *Gazz. chim. ital.*, **65**, 464 (1935). Compare also Labruto, *ibid.*, **63**, 266 (1933).

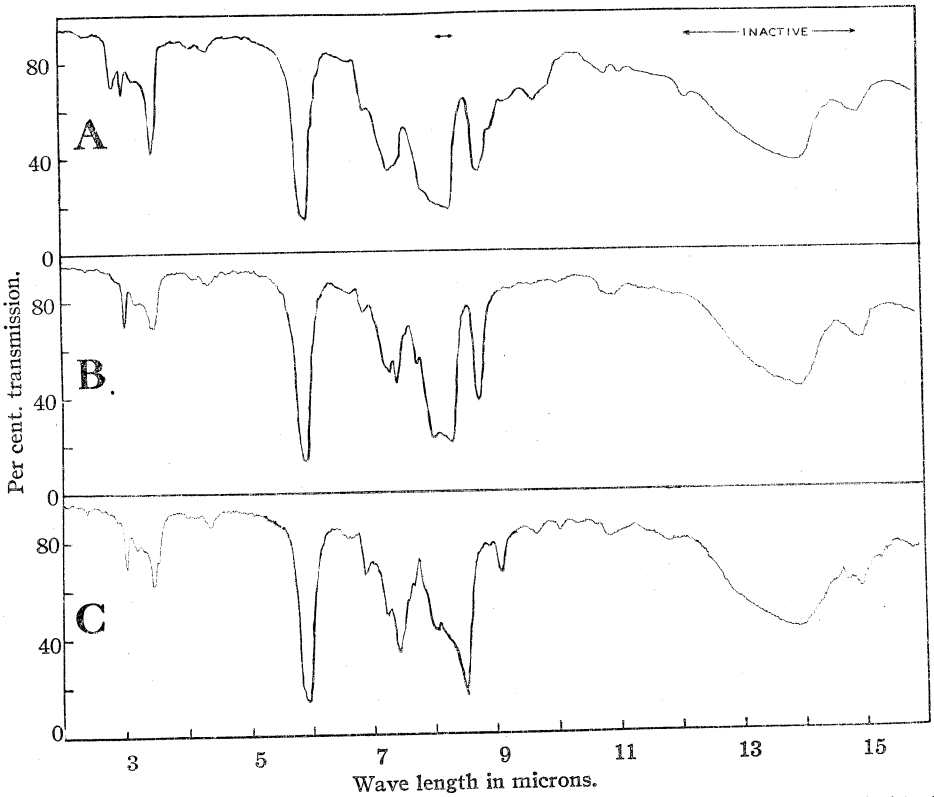



Fig. 3.—Infrared absorption spectra of Actidione (A), β-ethylglutarimide (B) and α-ethylglutarimide (C). Concentrations, 6.3%, 2.8% and 3.3%, respectively, in chloroform; cell length 0.132 mm. Inactive regions are due to solvent absorption.

methanetriacetic acid (V), which was identified by a mixed melting point determination with an authentic sample, and by conversion to the tri-*p*-bromophenacyl ester. In another experiment Actidione was first oxidized by means of chromic acid to the diketone, dehydroactidione (VI), which was characterized as a *1,3* diketone by its ultraviolet absorption spectrum ($\lambda_{max.}$ 292 mμ; ε, 9910)[8] and by conversion to a copper complex. Dehydroactidione was then degraded in alkaline solution to form 2,4-dimethylcyclohexanone, ammonia, and methanetriacetic acid (V). This hydrolysis of the 1,3-diketone took place almost exclusively by fission of the carbon–carbon bond *exo*cyclic to the cyclohexanone ring.

On the basis of the evidence presented up to this point then, structure I may be proposed for Actidione. The hydrolytic cleavage of the antibiotic may be looked upon as a reverse aldol reaction accompanied by opening of the glutarimide ring. Additional confirmation in support of structure I was obtained by a number of further transformations and reactions.

As was mentioned above the propionaldehyde-2,2-diacetic acid formed on alkaline degradation of Actidione was not obtained analytically pure. A derivative of this aldehyde–diacid was obtained, however, when Actidione was allowed to react with benzylamine. Benzylamine caused an opening of the glutarimide ring accompanied by a reverse aldol fission of the molecule. This was followed by condensation of the resulting aldehyde with benzylamine. The end-product of this series of reactions was the derivative VII.

Thus far it had not been established whether the point of attachment of the seven-carbon section of the Actidione molecule was at the 2 or 6 position on the 2,4-dimethylcyclohexanone ring (III). Evidence proving linkage through the 6 position was obtained by dehydration of Actidione in the presence of phosphorus pentoxide to form anhydroactidione (VIII). This product, which had a typical α,β unsaturated ketone absorption spectra in the ultraviolet ($\lambda_{max.}$, 241 mμ; ε, 8250)[9] could not result if attachment had been at position 2. Catalytic reduction of anhydroactidione gave tetrahydroanhydroactidione (IX).

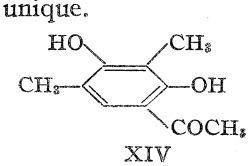
Several interesting transformations in the dihydroactidione (II) series were also carried out. Dihydroactidione was found to be stable to hydrolytic carbon–carbon cleavage because of the absence of the aldol configuration. Alkaline hydrolysis of this compound merely opened the glutarimide ring with elimination of ammonia.

(8) 2-Acetylcyclohexanone has $\lambda_{max.}$ = 290 mμ (ε = 8750).

(9) Woodward's rule (THIS JOURNAL, 64, 76 (1942)) predicts $\lambda_{max.}$ = 240 mμ.

On acidification of the hydrolysis mixture an acidic product, dihydroactidione acid, was isolated, which on the basis of its properties and reactions was formulated as the lactone acid (X). This acid formed a monomethyl ester (XI) on treatment with diazomethane, and the ester was converted by means of alcoholic ammonia to the diamide (XII). This diamide was also produced directly by the reaction of dihydroactidione (II) with ammonia, and it was reconverted by alkaline hydrolysis to dihydroactidione acid (X). When dihydroactidione acid (X) was treated with ammonia, the lactone ring was again opened to give the ammonium salt of a monoamide-acid which was isolated as the silver salt (XIII). Reaction of the lactone-acid (X) with two equivalents of alkali and two moles of *p*-bromophenacyl bromide gave a *di-p*-bromophenacyl ester. All of these transformations are adequately interpreted on the basis of the formulations presented.

Finally, it was of interest to discover if natural products similar to Actidione had been previously isolated. The literature reveals a mould metabolic product which has a skeletal arrangement resembling that of a portion of Actidione. Clavatol, a product isolated from *Aspergillus clavatus* by Hassall and Todd,[10] has the structure XIV. The glutarimide ring in Actidione, however, seems to be unique.




XIV

**Acknowledgments.**—The authors express their appreciation to Drs. W. W. Davis and R. B. Woodward for helpful discussions. Dr. Woodward was the first to suggest the possibility of a cyclic imide formula. We also thank Mr. R. A. Kern for some of the ultraviolet work, Mr. G. Vaughan for the X-ray diffraction data and Mr. W. L. Brown and Mr. H. L. Hunter for the microanalyses. We are especially indebted to Drs. J. H. Ford and B. E. Leach of the Upjohn Laboratories for their continued interest and for generously supplying part of the Actidione used in this work.

## Experimental[11]

**Purification of Actidione (I).**—Actidione was purified for analysis by repeated recrystallization from water containing a little methanol, from which it separated slowly, m. p. 119.5–121°, $[\alpha]^{29}D$ −3.38° (*c* = 9.47 in ethanol).

*Anal.* Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.37; H, 8.55; N, 5.08. Nitrogen by Kjeldahl method, found: 5.11. Nitrogen by Kjeldahl method omitting acid digestion, found: 4.84. C-methyl determination,[12] found: 1.32. (Synthetic 2,4-dimethylcyclohexanone gave a value of 1.28).

**Isolation of Ammonia from Alkaline Degradation of Actidione.**—Actidione (5 g.) was dissolved in 100 ml. by 12 *N* sodium hydroxide solution. The solution was refluxed for one-half hour, and the evolved gas was absorbed in 25 ml. of ice-water. To this aqueous solution was added 1 g. of phenyl isothiocyanate, and the mixture was shaken well. Long prismatic crystals of phenylthiourea had separated from the solution after standing overnight, m. p. 157–158°. A mixed melting point with an authentic sample of phenylthiourea was also 157–158°.

**Actidione-*p*-nitrobenzoate.**—Actidione (1 g.) was dissolved in 3 ml. of dry pyridine, and 0.66 g. of *p*-nitrobenzoyl chloride was added. The mixture became warm and partly solidified. It was heated on a steam-bath until all solids were dissolved and was then cooled. Ice-water was added, and the aqueous phase was decanted. The residue was rubbed with a little ethanol, and the product was filtered, washed with ethanol, and dried; yield, 0.75 g. A sample was purified for analysis by recrystallization from aqueous dioxane, m. p. 215–220° (dec.).

*Anal.* Calcd. for $C_{22}H_{26}N_2O_7$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.13; H, 6.24; N, 6.53.

**Actidione Acetate.**—This was prepared by a method similar to that of Ford and Leach[2a]; m. p. after recrystallization from dilute ethanol, 150–152°.

*Anal.* Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.56; H, 7.67; N, 4.50; C-methyl, 2.17.

**Reduction of Actidione Acetate.**—A small sample of the acetate was reduced catalytically in glacial acetic acid using platinum oxide as catalyst. Absorption of hydrogen ceased after 1.03 moles had been taken up. The catalyst was filtered, and the solvent was distilled *in vacuo*. The residue was recrystallized several times from dilute ethanol. Dihydroactidionemonoacetate was obtained as shiny needles, m. p. 169–171°.

*Anal.* Calcd. for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.37; N, 4.31. Found: C, 63.10; H, 8.32; N, 4.26.

**Actidione Semicarbazone.**—This derivative was prepared by essentially the same method used by Ford and Leach.[2a] It was obtained as a hydrate, m. p. 187–188°.

*Anal.* Calcd. for $C_{16}H_{26}N_4O_4.H_2O$: C, 53.92; H, 7.92; N, 15.72. Found: C, 54.01; H, 7.89; N, 15.65, 15.75.

**Dihydroactidione (II).**—Actidione (3 g.) was reduced at atmospheric pressure in 40 ml. of glacial acetic acid using 1 g. of platinum oxide catalyst. Reduction was complete after 1.05 moles of hydrogen had been absorbed (two to three hours). The solution was filtered, and the acetic acid was removed *in vacuo*. The residue was recrystallized from water containing a little acetone; m. p. 137–139° after thorough drying *in vacuo*.

*Anal.* Calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.50; H, 8.88; N, 5.29.

Dihydroactidione was recovered unchanged after being exposed at room temperature to aqueous periodic acid for twenty-four hours.

**Dihydroactidione Diacetate.**—Dihydroactidione (II) (1.1 g.) was dissolved in a mixture of 20 ml. of acetic anhydride and 10 ml. of dry pyridine, and the solution was allowed to stand overnight. The solvents were then evaporated *in vacuo*, and the residue was stirred with dilute ethanol. The product which soon crystallized was purified by recrystallization from dilute methanol, m. p. 72–75°.

*Anal.* Calcd. for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.01; H, 7.90; N, 3.78; C-methyl, 3.44.

***d*-2,4-Dimethylcyclohexanone (III) by Alkaline Degradation of Actidione.**—Actidione (10 g.) was dissolved in 200 ml. of 20% sodium hydroxide solution, and about one-half of the solution was distilled. The distillate was saturated with sodium chloride and extracted with ether. The extracts were dried over sodium sulfate, and the ether

(10) Hassall and Todd, *J. Chem. Soc.*, 611 (1947).

(11) All melting points were taken on a Fisher-Johns melting point block and are corrected.

(12) Ginger, *J. Biol. Chem.*, **156**, 453 (1944).

was removed. The residue was distilled, b. p. 175–176°, yield, 3.0–3.5 g., $[\alpha]^{29}D$ +11.52° ($c$ = 5.417 in ethanol), $n^{25}D$ 1.4435.

*Anal.* Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.45; H, 11.08.

The 2,4-dinitrophenylhydrazone of *d*-2,4-dimethylcyclohexanone was obtained in the usual manner and was recrystallized from dilute dioxane, m. p. 169–172°.

*Anal.* Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.64; H, 5.75; N, 18.76.

The *p*-nitrophenylhydrazone was prepared in ethanol using acetic acid as catalyst. The derivative separated as golden, matty needles from dilute ethanol, m. p. 152–153°.

*Anal.* Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.33; H, 7.10; N, 15.82.

The oxime, prepared as usual, was sublimed for analysis, m. p. 48–51°.

*Anal.* Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.71; H, 10.94; N, 10.32.

The semicarbazone was prepared and purified by recrystallization from dilute ethanol, m. p. 212–214°.

*Anal.* Calcd. for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.93. Found: C, 59.37; H, 9.47; N, 23.07.

The *l*-menthydrazone of *d*-2,4-dimethylcyclohexanone was prepared by the method of Woodward, Kohman and Harris[13] and was recrystallized from ethanol, m. p. 164–165°, $[\alpha]^{29}D$ −58.7° ($c$ = 1.524 in ethanol).

*Anal.* Calcd. for $C_{19}H_{34}N_2O_2$: N, 8.69. Found: N, 8.91.

**Resolution of Synthetic *dl*-2,4-Dimethylcyclohexanone.**—A solution of 10 g. of the pure ketone (see below), 17 g. of *l*-menthydrazide, 4 g. of sodium acetate, and 2 ml. of glacial acetic acid in 200 ml. of ethanol was refluxed for forty minutes. The solution was seeded with *d*-2,4-dimethylcyclohexanone-*l*-menthydrazone and was cooled overnight. The first crop of crystals weighed 5.2 g., m. p. 135–143°. After four recrystallizations from ethanol the melting point was 164–165° and showed no depression when mixed with the *d*-2,4-dimethylcyclohexanone-*l*-menthydrazone obtained above from the natural 2,4-dimethylcyclohexanone; $[\alpha]^{29}D$ −56.8° ($c$ = 1.54 in ethanol).

*Anal.* Calcd. for $C_{19}H_{34}N_2O_2$: N, 8.69. Found: N, 8.69.

**X-Ray Diffraction Identification of the Natural and Synthetic *d*-2,4-Dimethylcyclohexanone-1-menthydrazones.**—X-Ray powder patterns of the natural and synthetic *d*-2,4-dimethylcyclohexanone-*l*-menthydrazones were taken on a North American Philips Unit with a circular camera. The patterns obtained were identical. Calculated D values of identical lines on the two patterns were duplicated to an average error of ±0.01 Å. unit with a maximum deviation of 0.05 Å. unit. Relative intensities of the corresponding lines on the two patterns were identical.

**N-Methyldihydroactidione (IV).**—An ether solution of diazomethane was prepared from 5 g. of nitrosomethylurea, dried over potassium hydroxide, and filtered into a solution of 2.8 g. of dihydroactidione (II) in 40 ml. of methanol. The mixture was allowed to stand overnight and was then evaporated *in vacuo* to yield a colorless oil. Acetone and water were added, and after scratching the oil crystallized. The product was purified for analysis by recrystallization from aqueous acetone, m. p. 129–132°.

*Anal.* Calcd. for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.09; H, 8.91; N, 4.68.

**Alkaline Degradation of N-Methyldihydroactidione (IV).**—The N-methyl derivative (0.35 g.) was boiled in 2 ml. of water containing 0.5 g. of potassium hydroxide, and 1 ml. of distillate was collected under 1 ml. of ice-water. The aqueous solution containing the distillate was mixed with 0.1 g. of phenyl isothiocyanate, warmed to 40°, and shaken until the product crystallized. The N-methyl-N′-phenylthiourea was filtered, washed and dried, m. p. 119–121°. A mixed melting point with an authentic sample was also 119–121°.

The residue from the distillation was acidified with hydrochloric acid, and the product which separated was recrystallized from dilute ethanol. It was shown to be dihydroactidione acid (X) (see below) by melting point and mixed melting point determinations.

**Degradation of Actidione to Methanetriacetic Acid (V).**—Actidione (10 g.) was dissolved in a solution of 20 g. of sodium hydroxide in 100 ml. of water. The mixture was distilled until 150 ml. of distillate was collected, the original volume being kept constant by periodic addition of water. The residue was cooled and neutralized with 13.5 ml. of concentrated sulfuric acid. The solution was then cooled in an ice-bath while 3.74 g. of powdered potassium permanganate was added. The mixture was shaken until the permanganate color was discharged, after which it was warmed for a few minutes on a steam-bath, made just alkaline with sodium hydroxide and filtered to remove manganese dioxide. The filtrate was saturated with sodium sulfate, acidified with sulfuric acid and exhaustively extracted with ether. Evaporation of the ether left 4.8 g. of crude, sirupy methanetriacetic acid (V). The acid was dissolved in water and was added to an aqueous solution of excess lead acetate. The insoluble lead salt was filtered and washed with water. It was resuspended in water, and the mixture was saturated with hydrogen sulfide. Lead sulfide was removed by filtration, and the filtrate was concentrated *in vacuo* to a crude sirupy residue. Neutral equivalent, calcd. for methanetriacetic acid 63.4; found, 74.9. Part of the sirupy acid on long standing in ether solution crystallized to give methanetriacetic acid, m. p. 112–116°; a mixed m. p. with a sample of the synthetic acid was 114–117°. Another part of the crude acid (0.57 g.) was dissolved in 10 ml. of water and was neutralized with 0.636 g. of sodium bicarbonate. Ethanol (65 ml.) containing 2.12 g. of *p*-bromophenacyl bromide was added, and the mixture was refluxed for three and one-half hours. Most of the ethanol was removed by distillation *in vacuo*, and water was added. The gummy derivative which separated was taken up in dilute acetone. The product crystallized and was recrystallized twice from aqueous acetone, m. p. 110–112°. A mixed melting point with an authentic sample of methanetriacetic acid-tri-*p*-bromophenacyl-ester (m. p. 115–116°) was 112–115°.

**Benzylamine Reaction Product (VII) from Actidione.**—Three grams of actidione was warmed on a steam-bath for two hours with 7.5 ml. of benzylamine. The odor of 2,4-dimethylcyclohexanone was evident. The mixture was cooled, and the product was filtered and washed with chloroform; yield, 0.7 g. The derivative was recrystallized several times from methanol for analysis, m. p. 180–182°.

*Anal.* Calcd. for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.35; H, 6.75; N, 12.09.

**Oxidation of Actidione; Dehydroactidione (VI).**—Pure actidione (3 g.) was dissolved in 75 ml. of glacial acetic acid, and to this solution was added dropwise, during a period of ten minutes, a solution of 0.80 g. of 98% chromium trioxide in 10 ml. of water. The reaction mixture was allowed to stand at room temperature for two hours after which it was warmed for a few minutes on a steam-bath. The solvents were then removed completely *in vacuo*. Water was added to the residue, and the product was extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from dilute ethanol, m. p. 177–180°; yield, 0.8 g.

*Anal.* Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.20; H, 7.39; N, 4.87.

On catalytic reduction of a small sample of dehydroactidione in glacial acetic acid using platinum oxide as

(13) Woodward, Kohman and Harris, THIS JOURNAL, **63**, 120 (1941).

catalyst 2.3 moles of hydrogen were absorbed. Separation of the resulting mixture of racemates of dihydroactidione in analytically pure condition has not been accomplished as yet.

**Copper Complex from Dehydroactidione.**—The diketone (VI) was dissolved in hot dilute ethanol, and the solution was filtered into an excess of aqueous copper acetate. The olive-green complex soon crystallized and was filtered and washed with water, ethanol and ether, m. p. 228–230° (dec.).

*Anal.* Calcd. for $C_{30}H_{40}N_2O_8Cu$: Cu, 10.25. Found: Cu, 10.20.

Under similar conditions no copper salts were formed with actidione, dihydroactidione or glutarimide.

**Alkaline Degradation of Dehydroactidione (VI).**—The diketone (VI) (2.3 g.) was dissolved in a solution of 4.6 g. of sodium hydroxide in 23 ml. of water. The solution was boiled, and 45 ml. of distillate was collected, while the volume of the hydrolysis mixture was kept constant by frequent addition of water. The distillate was mixed with 100 ml. of ethanol containing 1.6 g. of 2,4-dinitrophenylhydrazine. This solution was heated to boiling, and 2 ml. of concentrated hydrochloric acid was added. The mixture was boiled for a few minutes, cooled, and the derivative was filtered and washed with methanol. A 68% yield (1.7 g.) of 2,4-dimethylcyclohexanone-2,4-dinitrophenylhydrazone was thus obtained. The residue in the distillation flask was cooled and acidified with 5 ml. of concentrated sulfuric acid. The resulting solution was exaustively extracted with ether and the extract concentrated *in vacuo*. The crude sirup so obtained could not be induced to crystallize, so it was dissolved in 25 ml. of water containing 1 g. of Girard reagent P[14] and 1 ml. of acetic acid. The solution was refluxed for one-half hour, saturated with sodium sulfate, and again extracted continuously with ether overnight. Evaporation of the extract left 1.5 g. of sirup. On cooling an ether–nitromethane solution of the sirup overnight crystalline methanetriacetic acid (V) was obtained, m. p. 117–119°; mixed melting point with synthetic methanetriacetic acid, 119–121°.

*Anal.* Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.30. Found: C, 44.50; H, 5.35.

Part of the crude acid above (0.8 g.) was neutralized with 11.15 ml. of 1 *N* sodium hydroxide solution and mixed with 100 ml. of ethanol and 3.1 g. of *p*-bromophenacyl bromide. The solution was refluxed for three hours, after which it was concentrated *in vacuo* to about half the original volume, and water was added. The gum which separated was washed with sodium bicarbonate solution, water and methanol. It was then taken up in acetone and methanol and cooled slowly. The crystalline product which separated was recrystallized from acetone–methanol, m. p. 115–116°. The mixed melting point with authentic methanetriacetic acid–tri-*p*-bromophenacyl ester was also 115–116°.

*Anal.* Calcd. for $C_{31}H_{25}Br_3O_9$: C, 47.65; H, 3.23; Br, 30.69. Found: C, 47.36; H, 3.09; Br, 30.32.

**Dehydration of Actidione; Anhydroactidione (VIII).**—Pure actidione (3 g.) dissolved in 100 ml. of dry benzene was mixed with 6 g. of phosphorus pentoxide. The mixture was heated slowly (15 min.) to boiling with frequent shaking and was then allowed to cool. The benzene solution was filtered, and the solvent was removed *in vacuo*. The residual colorless sirup was crystallized from benzene–petroleum ether; yield, 1.0 g. It was recrystallized for analysis from benzene–ether, m. p. 134–135°.

*Anal.* Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.53; H, 8.44; N, 5.48.

This product on warming in alkaline solution gave the volatile ketone, *d*-2,4-dimethylcyclohexanone (III).

**Reduction of Anhydroactidione (VIII).**—A small sample of anhydroactidione (VIII) on catalytic reduction in acetic acid using platinum oxide as catalyst absorbed 2.16 moles of hydrogen in one hour. The solvent was distilled *in vacuo*, and the crude tetrahydroanhydroactidione (IX) was purified by recrystallization from benzene–petroleum ether, m. p. 125–127°.

*Anal.* Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.57; H, 9.94.

**Alkaline Degradation of Dihydroactidione; Dihydroactidione Acid (X).**—Dihydroactidione (II) (1 g.) was dissolved in 10 ml. of 20% sodium hydroxide, and the solution was heated to boiling for five minutes. The reaction mixture was cooled, and 4.5 ml. of concentrated hydrochloric acid was added. The product which separated was filtered, washed with water and recrystallized from dilute ethanol; m. p. 180–183°, yield 85%.

*Anal.* Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51; neut. equiv., 284.3. Found: C, 63.70; H, 8.71; neut. equiv., 284.0.

In an oxidation experiment using two-thirds mole (two equivalents) of potassium permanganate to one of dihydroactidione acid in dilute acetic acid, only unchanged starting material was isolated. This indicated the absence of a free secondary alcoholic group.

**Di-*p*-bromophenacyl Ester of Dihydroactidione Acid.**—One gram of the acid (X) was dissolved in 7.04 ml. of 1 *N* sodium hydroxide (two equivalents) and 60 ml. of ethanol, and 1.953 g. (two moles) of *p*-bromophenacyl bromide were added. The solution was refluxed for three hours and was then concentrated *in vacuo*. Water was added to the gelatinous product, and the solid was filtered, washed with water and methanol and dried; yield, 2.4 g. No suitable solvent for purification was found. The ester gelled out under all conditions tried, so the sample was dissolved in ethanol and precipitated with water, m. p. 130–135°.

*Anal.* Calcd. for $C_{31}H_{36}Br_2O_8$: C, 53.46; H, 5.21; Br, 22.95. Found: C, 53.39; H, 5.46; Br, 22.23.

**Methyl Ester of Dihydroactidione Acid (XI).**—Diazomethane was prepared in 20 ml. of ether from 2 g. of nitrosomethylurea. The solution was dried over potassium hydroxide and filtered onto 1.5 g. of dihydroactidione acid (X) in a few ml. of methanol. After standing for ten minutes the solution was filtered and concentrated *in vacuo*. The methyl ester which separated was crystallized from methanol–ether, m. p. 139–141°.

*Anal.* Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.40; H, 8.46.

**Diamide (XII) from the Methyl Ester of Dihydroactidione Acid.**—The filtrate from the preparation of the crystalline methyl ester above was treated with 30 ml. of methanol saturated with ammonia and allowed to stand overnight. The solvents were then distilled *in vacuo*, and the crude diamide was recrystallized from dioxane–methanol. The product melted at about 100° with loss of solvent of crystallization, resolidified and remelted at 165–168°. Analysis showed that the compound contained one molecule of dioxane of crystallization.

*Anal.* Calcd. for $C_{15}H_{28}N_2O_4 \cdot C_4H_8O_2$: C, 58.75; H, 9.34; N, 7.21; loss at 120°, 22.68. Found: C, 57.57; H, 8.89; N, 7.08; loss at 120°, 22.36.

The sample was then dried at 120° *in vacuo* and reanalyzed, m. p. 167–171°.

*Anal.* Calcd. for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.39; N, 9.32. Found: C, 60.26; H, 8.99; N, 8.53.

**Diamide (XII) from Dihydroactidione.**—The dihydro compound (II) (2 g.) was dissolved in 30 ml. of methanol, and 30 ml. of liquid ammonia was added. The mixture was allowed to stand overnight after which the solvent was distilled *in vacuo*, and the residue was recrystallized twice from water. The colorless needles melted at about 100° with loss of water of hydration, resolidified and remelted at 174–177°.

*Anal.* (Dried at 25°.) Calcd. for $C_{15}H_{28}N_2O_4 \cdot 0.5H_2O$: C, 58.23; H, 9.45; N, 9.06. Found: C, 58.86; H, 10.18; N, 8.68.

(14) Girard, *Helv. Chim. Acta*, **19**, 1095 (1936).

A sample was then dried at 120° *in vacuo* and reanalyzed, m. p. 176–178°.

*Anal.* Calcd. for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.39. Found: C, 59.64; H, 8.84.

A mixed melting point with the slightly less pure diamide (m. p. 167–171°) prepared from the methyl ester of dihydroactidione acid was 170–174°.

**Dihydroactidione Acid (X) from the Diamide (XII).**—The above diamide (0.15 g.) was boiled in a solution containing 0.25 g. of sodium hydroxide in 3 ml. of water until no more ammonia was evolved (five minutes). The mixture was cooled and acidified with hydrochloric acid. The product was filtered, washed and recrystallized from dilute ethanol, m. p. 179–183°. A mixed m. p. with dihydroactidione acid (X) was 180–183°.

**Silver Salt of the Amide Acid (XIII) Obtained from Dihydroactidione Acid.**—The dihydroacid (X) (1 g.) was mixed with 30 ml. of methanol and 50 ml. of liquid ammonia and allowed to stand for several days. The solvents were evaporated *in vacuo* leaving the amorphous ammonium salt of the amide acid, which was not obtained in crystalline condition. A portion was dissolved in water, filtered and the silver salt (XIII) precipitated with aqueous silver nitrate solution. The salt was collected on a filter and washed with water, m. p. 171–174°.

*Anal.* Calcd. for $C_{15}H_{26}AgNO_5$: N, 3.43; Ag, 26.43. Found: N, 3.17; Ag, 26.33.

**2-Isopropylcyclopentanone.**—This ketone was prepared by a modification of the method of Cornubert and Borrel.[15] Acetone was condensed with cyclopentanone to give isopropylidenecyclopentanone, b. p. 94–97° (32 mm.); yield, 20%. Catalytic hydrogenation of the unsaturated ketone to isopropylcyclopentanone was effected smoothly in the presence of 5% palladium–charcoal catalyst in glacial acetic acid. The product had a b. p. 172–174°; yield, 88%. It was purified by conversion in the usual fashion to the semicarbazone (m. p. 201–202°). Regeneration of the ketone was brought about by hydrolysis in 20% sulfuric acid. The pure ketone boiled at 173–173.5°, $n^{29}D$ 1.4395.

*Anal.* Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.82; H, 11.56.

***dl*-2,4-Dimethylcyclohexanone.**—1-Hydroxy-2,4-dimethylbenzene (145 g.) was hydrogenated in 100 ml. of glacial acetic acid in a 500-ml. steel bomb at 4000 pounds pressure at room temperature using 5 g. of platinum oxide catalyst.[16] The reduction was complete in one hour. The catalyst was filtered and the acetic acid was neutralized with aqueous sodium hydroxide solution. The 2,4-dimethylcyclohexanol was extracted with ether, and the extracts were dried over sodium sulfate. The ether was removed and the product distilled, b. p. 175–179°; yield, 60%.

The alcohol (183 g.) was then added to a solution of 135 ml. of concentrated sulfuric acid in 1500 ml. of water. The resulting mixture was warmed to 45°, and with vigorous stirring 291 g. of powdered potassium dichromate was added portionwise during a period of eleven to twelve minutes while the temperature was maintained at 42–48° by external cooling in ice water. The reaction mixture was stirred for one-half hour longer, after which the product was extracted with ether. The extracts were washed thoroughly with 5% sodium hydroxide and water and were dried over calcium chloride and distilled, b. p. 175–178°; yield, 79%. The ketone was purified in the usual manner by conversion to the semicarbazone, m. p. 198–200°. The pure 2,4-dimethylcyclohexanone had a b. p. 175–176°, $n^{25}D$ 1.4430. Sabatier[17] gives b. p. 176.5°.

*Anal.* Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.00; H, 11.37.

(15) Cornubert and Borrel, *Bull. soc. chim. France*, [4] **47**, 958 (1930).

(16) Baker and Schuetz, THIS JOURNAL, **69**, 1250 (1947), have developed this method of high pressure room temperature hydrogenation using platinum oxide.

(17) Sabatier, *Compt. rend.*, **142**, 554 (1901).

Determination of C-methyl gave a value of 1.28. A sample of the ketone was exposed to the known[18] racemizing action of 90% sulfuric acid, but it was recovered unchanged. The portion so treated gave a semicarbazone identical with the untreated material. Therefore, if any preferential *cis* hydrogenation occurred in the reduction step above, racemization must have taken place during the chromic acid oxidation to give an equilibrium mixture of racemates.

**2,5-Dimethylcyclohexanone.**—This isomeric ketone was prepared from 1-hydroxy-2,5-dimethylbenzene in a manner similar to that described above for 2,4-dimethylcyclohexanone except that the reduction was carried out in ethanol at 150–165° using Raney nickel catalyst. After purification through the semicarbazone (m. p. 155–157°) the 2,5-dimethylcyclohexanone was obtained as a colorless liquid, b. p. 175–176°, $n^{29}D$ 1.4406. Sabatier[19] gives b. p. 174–177°.

*Anal.* Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.07; H, 11.19.

**Methanetriacetic Acid and Derivatives.**—This acid (m. p. 119–121°) was prepared by the procedure of Kohler and Reid[20] using glutaconic ester prepared by the method of Lochte and Pickard.[21] The tri-*p*-bromophenacyl ester was made using the general directions of Shriner and Fuson.[22] It was recrystallized from dilute acetone, m. p. 115–116°.

*Anal.* Calcd. for $C_{31}H_{25}Br_3O_9$: C, 47.65; H, 3.23; Br, 30.69. Found: C, 47.36; H, 3.11; Br, 30.76.

The benzylisothiouronium salt was prepared by the method of Shriner and Fuson.[22] Dilute ethanol was the solvent used in the purification of this derivative, m. p. 139–140°.

*Anal.* Calcd. for $C_{31}H_{40}N_6O_6S_3$: N, 12.20; S, 13.96. Found: N, 11.38; S, 14.23.

**Glutarimide.**—Glutaric anhydride (20 g.) was heated to 130–140°, and ammonia gas was bubbled in rapidly for one-half hour. The mixture was then heated slowly to 250° (twenty-five minutes), and the imide was distilled at 275–280°. It was purified by recrystallization from acetone, m. p. 163–165°. Wolffenstein gives m. p. 154.5°.[23]

**α-Ethylglutarimide.**—α-Ethylglutaric acid was prepared by the following modification of the method of Auwers.[24] One mole of sodium was dissolved in 400 ml. of absolute ethanol, and one mole of ethyl diethylmalonate was added. To the hot solution was then added with stirring one mole of ethyl β-bromopropionate at such a rate as to maintain a gentle reflux (ten minutes). Stirring was continued twenty minutes longer, after which the sodium bromide was removed by filtration and the ethanol distilled *in vacuo*. Water and a little chloroform were added to the residue, and the organic layer was separated and fractionated *in vacuo*. A 61% yield of diethyl α-ethyl-α-carbethoxyglutarate was obtained, b. p. 177–182° at 13 mm. The ester was refluxed with a mixture of 600 ml. of concentrated hydrochloric acid and 500 ml. of water for seventeen hours. The solvents were removed completely *in vacuo*, and the residual α-ethylglutaric acid was refluxed with 450 g. of acetyl chloride for two hours. Excess reagent was distilled *in vacuo*, and the α-ethylglutaric anhydride was fractionated, b. p. 163–165° at 13 mm.; yield, 51% based on ethyl diethylmalonate.

The anhydride was converted to the cyclic imide by the procedure given above for glutarimide. It had a b. p. 265–280°; yield, 85%. Purification was effected by recrystallization from acetone–ether, m. p. 107–108°.

(18) Beckmann, *Ann.*, **250**, 334 (1889).

(19) Sabatier, *Compt. rend.*, **142**, 555 (1901).

(20) Kohler and Reid, THIS JOURNAL, **47**, 2808 (1925).

(21) Lochte and Pickard, *ibid.*, **68**, 721 (1946).

(22) "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y.

(23) Wolffenstein, *Ber.*, **25**, 2777 (1892).

(24) Auwers, *Ann.*, **292**, 144, 213 (1896).

*Anal.* Calcd. for $C_7H_{11}NO_2$: N, 9.92. Found: N, 10.02.

**β-Ethylglutarimide.**—This imide was prepared in a manner similar to that for the α-isomer starting with β-ethylglutaric acid, which was made by the procedure of Jeffery and Vogel.[25] It had a m. p. 88–89°. Sircar[26] gives m. p. 87°.

**Absorption Spectra.**—The ultraviolet spectra were determined in 95% ethanol solution using a Beckman Model DU spectrophotometer. The infrared spectra were obtained on a Baird recording infrared spectrophotometer. Pertinent data are included with the spectrograms.

(25) Jeffery and Vogel, *J. Chem. Soc.*, 446 (1939).
(26) Sircar, *ibid.*, 600 (1927).

## Summary

1. Actidione, a new antibiotic isolated from *Streptomyces griseus*, has been shown to have the structure I.

2. A number of reactions and transformations of Actidione have been carried out.

INDIANAPOLIS, INDIANA RECEIVED JULY 10, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

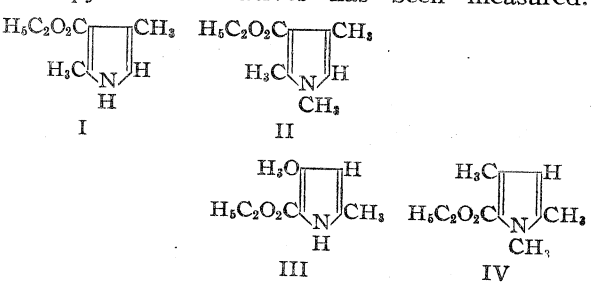
# Kinetics of Pyrrole Substitutions. The Iodination Reaction[1]

BY KENNETH W. DOAK[2] AND ALSOPH H. CORWIN

Wibaut[3] first showed that the presence of a methyl group in the benzene ring greatly increases its reactivity toward nitration. Ingold and Shaw[4] conclude that the rate of nitration by nitric acid in acetic anhydride is increased about 40–55-fold in each ortho and para position, while the reactivity in a meta position is increased threefold. McDuffie and Dougherty[5] have observed that toluene is acetylated about thirteen times as rapidly as benzene. The explanation for this increased reactivity is given in the general electronic theory of organic reactions, developed to a large extent by Lapworth, Robinson and Ingold,[6] which assumes that the attacking reagent seeks a pair of electrons from the aromatic nucleus. The methyl group facilitates the donation of an electron pair, by favoring polarization of the type $CH_3-\overset{+}{\langle\rangle}-$ and thus lowering the energy of the activated intermediate.[7]

Kinetic investigations of substitution reactions are entirely lacking in pyrrole chemistry. A fundamental difference between the benzene and pyrrole systems exists, since the major resonance in benzene is between two normal valence forms while the resonance in pyrrole[8] is mainly ionic, involving five principal structures.[6b] The ionic structures should have fairly low energy, since no octets are broken and no double bonds are lost. The large contribution of these structures to the normal state of the molecule makes the nitrogen positive, with the result that the N—H group is weakly acidic[9] instead of basic, as would be expected for a secondary amine. Activated structures involving them probably have much lower energy than the activated structures in benzene; this accounts for the well-known fact that pyrrole is more reactive than benzene to electron-seeking reagents. For example, when pyrrole is treated with bromine, chlorine or iodine, in dilute solution, the mono-alpha derivative is formed first. If excess halogen is used, the tetrahalogenated pyrrole is formed[10a] more readily than monohalogenated benzenes.

In order to obtain kinetic data upon the substitution of pyrroles, the velocity of iodination of four pyrrole derivatives has been measured.



I II III IV

In the presence of potassium iodide in a buffered solution, the iodinations proceed almost to completion with velocities which can be measured accurately. Pyrroles which have substituents in all α- and β-positions except one were chosen in order to eliminate competing reactions. The N-methylated compounds were studied in order to determine whether or not the N-methyl group has an effect similar to that of a methyl group in the benzene nucleus. A comparison of pyrroles II and IV, in which steric effects should be quite

(1) Studies in the Pyrrole Series. XXII. Paper XXI, Corwin and Straughn, THIS JOURNAL, **70**, 2968 (1948). This work represents a portion of a doctoral dissertation by Kenneth W. Doak, The Johns Hopkins University, Baltimore, Md.

(2) The William R. Warner and Co., Inc., Fellow, The Johns Hopkins University. Present address: United States Rubber Company, Passaic, New Jersey.

(3) Wibaut, *Rec. trav. chim.*, **34**, 241 (1915).

(4) Ingold and Shaw, *J. Chem. Soc.*, 2918 (1927); 1959 (1931); 905, 918 (1938).

(5) McDuffie and Dougherty, THIS JOURNAL, **64**, 297 (1942).

(6) Ingold, (a) *Rec. trav. chim.*, **48**, 797 (1929); (b) *J. Chem. Soc.*, 1120 (1933); (c) *Chem. Rev.*, **15**, 225 (1934); (d) Robinson, "Outline of Electronic Theory of Organic Reactions," Inst. of Chem. of Gr. Br. and Ireland, London (1932).

(7) Wheland, THIS JOURNAL, **64**, 900 (1942).

(8) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 137.

(9) Bamberger, *Ber.*, **26**, 1946 (1893); McEwen, THIS JOURNAL, **58**, 1124 (1936); Ingold and Goss, *J. Chem. Soc.*, 1268 (1938).

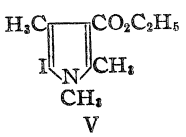
(10) Fischer, "Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, (a) p. 75, 83, 101; (b) p. 102.

similar, should give an estimate of the relative reactivities of an $\alpha$- and $\beta$-position. These relative rates may be altered somewhat by the fact that the substituent methyl and carbethoxy groups are not quite equivalent in both pyrroles, due to the fact that one ring member is nitrogen. In each pyrrole, however, there are two methyl groups alpha to the reactive center, and a methyl and a carbethoxy group beta to it.

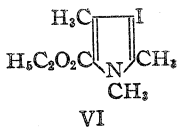
The reverse reaction, the reduction of an $\alpha$- or $\beta$-iodopyrrole to an $\alpha$- or $\beta$-free pyrrole, will occur



in a solution of hydriodic acid. Two experiments were carried out in order to obtain the approximate relative velocities of reduction of two iodopyrroles, V and VI.



V



VI

## Experimental

**Method for Measurement of Velocities of Iodination.**—These velocity measurements were carried out in aqueous dioxane (28% dioxane by weight) buffered by monosodium phosphate and disodium phosphate (0.035 *M* each) to a *p*H of 6.8–6.9. This was necessary to remove the hydriodic acid formed and drive the reaction to completion. The temperature was 26.5 ± 0.1°. Solutions of the pyrroles (0.020–0.035 *M*) were made up by dissolving them in dioxane freshly distilled from sodium amalgam. The reactions were started by adding to 40 cc. of pyrrole solution 100 cc. of aqueous iodine solution (0.0075–0.0120 *M*) containing 0.049 *M* phosphates and a large concentration of potassium iodide (0.560–1.200 *M*). The ionic strength was kept constant by the addition of sodium chloride. At intervals throughout the course of a reaction, 10.00-ml. samples of the reaction mixture were pipetted into 5.00 ml. excess standard sodium arsenite to destroy the iodine. This solution was buffered to a *p*H of 7.0 or slightly greater by addition of 1 ml. of monosodium phosphate (0.25 *M*) and 3 ml. of disodium phosphate (0.25 *M*), 2 g. of potassium iodide was added, and the excess arsenite ion was titrated with standard iodine solution.

If the *p*H is too low, some iodine is used during the back titration to iodinate the pyrroles, particularly the $\alpha$-free pyrroles. If the *p*H is too high, the titration of arsenite ion is inaccurate, as shown by Washburn.[11]

Second order velocity constants were determined by the equation

$$k_{obs.} = \frac{2.303}{(a - b)t} \log \frac{b(a - x)}{a(b - x)} \qquad (1)$$

in which $a$ and $b$ are the initial concentrations of pyrrole and titratable iodine, and $x$ is the concentration of iodopyrrole. Log $(a - x)/(b - x)$ was plotted against time, and $k_{obs.}$ was determined by the slope of the straight line, after converting the time to seconds.

$$k_{obs.} = 2.303/(a - b) \text{ (Slope)} \qquad (2)$$

Tables I and II give the data for two typical experiments. The apparent drift in velocity constant calculated from the data in Table I is due to the initial heating of mixing. This is shown by Fig. 1. Figures 1 and 2 are plots of log $(a - x)/(b - x)$ against time and show the straight lines required for a second order equation. Table IV summarizes the data for the iodination of the four pyrroles. Second order velocity constants were determined for different concentrations of iodide ion.

TABLE I

Reaction of Pyrrole I: $[I^-] = 0.805$, $[I_3^-]_0 = a = 0.00672$, $[Py]_0 = b = 0.00551$

| Time, min. | $10^5x$ |
|---|---|
| 0 | 0 |
| 19.5 | 114 |
| 20.7 | 117 |
| 43.7 | 198 |
| 44.7 | 198 |
| 65.3 | 250 |
| 66.3 | 253 |
| 100.2 | 312 |
| 101.3 | 312 |
| 146.0 | 366 |
| 147.0 | 369 |

$k_{obs.}$ = 0.0280 liters per mole sec. (by graphical solution)

TABLE II

Reaction of Pyrrole III: $[I^-] = 0.857$, $[I_3^-]_0 = a = 0.00921$, $[Py]_0 = b = .00580$

| Time, min. | $10^5x$ |
|---|---|
| 0 | 0 |
| 232 | 59 |
| 233 | 58 |
| 283 | 74 |
| 555 | 137 |
| 556 | 137 |
| 1062 | 224 |
| 1063 | 223 |
| 1614 | 289 |
| 1615 | 290 |

$k_{obs.}$ = 0.00096 liter per mole sec. (graphical solution)

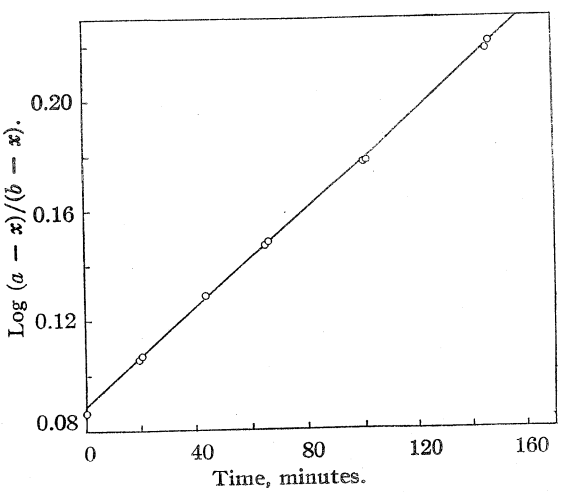



Fig. 1.—Iodination of Pyrrole I; data from Table I.

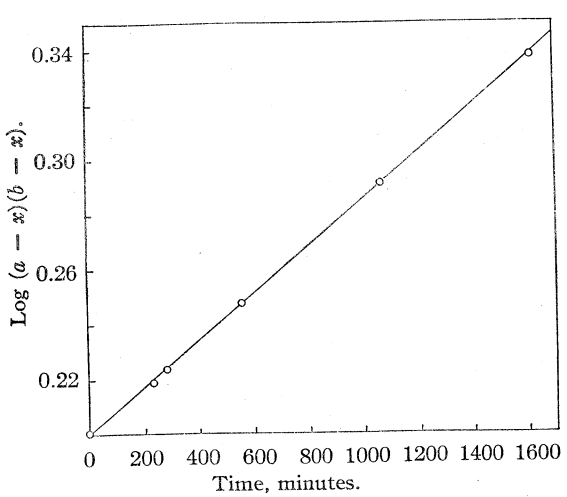



Fig. 2.—Iodination of Pyrrole III; data from Table II.

(11) Washburn, THIS JOURNAL, **30**, 31 (1908).

**Rates of Reduction of Iodopyrroles with Hydriodic Acid.**—A solution of the iodopyrrole to be examined (0.200 g. in 20.0 cc. of purified dioxane) was added to 10.0 cc. of water containing 1.5 g. of potassium iodide. The reaction was started by the addition of 1.00 cc. of 2.0 *N* hydrochloric acid. At intervals, 5.00-cc. samples were pipetted into 10 cc. of water saturated with potassium iodide and containing 1 g. of sodium acetate. The reaction is made extremely slow by the excess sodium acetate, while the iodination is checked by the large excess of iodide ion. If the iodine is titrated immediately by sodium thiosulfate, consistent results can be obtained. The data for two experiments are given in Table III.

TABLE III

REDUCTION OF PYRROLES

$[I^-] = a = 0.0645$, $[Py]_0 = b = 0.0210$, $[H\ Solv^+]_0 = c = 0.292$

| Pyrrole | Time, min. | $I_2^- = x$ |
|---|---|---|
| V | 0 | 0 |
| | 4 | 0.0036 |
| | 174 | .0192 |
| | 666 | .0211 |
| | | $k = 0.0140$ (l.²/mole² sec.) |
| VI | 0 | 0 |
| | 11 | 0.0003 |
| | 183 | .0042 |
| | 661 | .0101 |
| | 1573 | .0153 |
| | | $k = 6.87 \times 10^{-4}$ (l.²/mole² sec.) |

The reduction of pyrrole VI, for which more points are available, follows a third order rate equation closely and the plot extrapolates to zero time. The reduction of pyrrole V is assumed to obey the same law. Because of the speed of this reaction, there was a marked heating effect on mixing and the plot extrapolates to −212 seconds.

**Synthesis of α- and β-Free Pyrroles.**—These pyrroles were synthesized by the method of Corwin and Quattlebaum.[12] They were recrystallized from methanol at Dry Ice temperature and were dried under vacuum. Dioxane solutions were prepared, which were kept frozen until they were used.

**Synthesis of 2-Iodo-3,5-dimethyl-4-carbethoxypyrrole, and 3-Iodo-2,4-dimethyl-5-carbethoxypyrrole.**—These compounds were prepared by the method of Fischer.[10b]

**Synthesis of 2-Iodo-1,3,5-trimethyl-4-carbethoxypyrrole.**—Two grams of 1,3,5-trimethyl-4-carbethoxypyrrole was dissolved in 25 cc. of methanol, and water was added until precipitation began. The theoretical amount of iodine was dissolved in a minimum of alcohol and added over a period of several minutes to the pyrrole solution. Several grams of sodium bicarbonate was added. After twenty minutes, water was added to complete the precipitation of the iodopyrrole. The iodopyrrole was decolorized with bone black and recrystallized twice from methanol at Dry Ice temperature; yield, 78%, m. p. 103.0–103.5°.

*Anal.* Calcd. for $C_{10}H_{14}O_2NI$: C, 39.11; H, 4.59. Found: C, 39.28; H, 4.22.

**Synthesis of 3-Iodo-1,2,4-trimethyl-5-carbethoxypyrrole.**—This iodopyrrole was synthesized from 1,2,4-trimethyl-5-carbethoxypyrrole in a manner similar to that described above for its isomer; yield, 75%, m. p. 87°.

*Anal.* Calcd. for $C_{10}H_{14}O_2NI$: C, 39.11; H, 4.59. Found: C, 39.36; H, 4.53.

**Reduction of Iodopyrroles by Hydriodic Acid.**—The following experiment is typical of the reduction of an α-iodopyrrole to the corresponding α-free pyrrole. 2-Iodo-1,3,5-trimethyl-4-carbethoxypyrrole (1.8 g.), potassium iodide (1.0 g.), glacial acetic acid (5.0 cc.) and sodium bisulfite (1.5 g.) were added to 75 cc. methanol (80%) in an erlenmeyer flask, the flask was stoppered, and the mixture was allowed to stand overnight. The solution was evaporated under vacuum until the pyrrole began to precipitate. Water was added to complete the precipitation. The product was recrystallized from methanol at Dry Ice temperature; yield, 75%, m. p. 59–60°, mixed m. p. with 1,3,5-trimethyl-4-carbethoxypyrrole, 59–60°.

The β-iodopyrroles were less reactive and required hydrochloric acid instead of acetic acid. The sodium bisulfite is necessary to destroy free iodine as fast as it is formed and drive the reaction to completion. That the bisulfite ion (or sulfur dioxide) is not the reducing agent was demonstrated in an experiment in which the potassium iodide was omitted.

(12) Corwin and Quattlebaum, THIS JOURNAL, **58**, 1081 (1936).

## Discussion

**The Mechanism of Iodination of Pyrroles.**—The fact that the velocity of iodination of pyrroles is greatly dependent upon the concentration of iodide ion leads to the following considerations which best explain the observed results. Iodide ion and free iodine are in equilibrium with triiodide ion.

$$K = (I_2)(I^-)/(I_3^-) \qquad (3)$$

This equilibrium constant in water can be calculated from the data of Jones and Kaplan.[13] For the temperature 26.5° we have used the value, $K = 0.00145$. This should be close to the correct value in dioxane–water because of the equivalence of charge in numerator and denominator. If the concentration of iodide ion is large compared with that of titratable iodine, then the liberation of iodide ion during the iodination reaction will change the concentration of iodide ion by a negligible amount, and it may be considered to be a constant. If the iodination is an electrophilic one, then triiodide ion will be repelled by negative centers in the pyrrole ring, and will not react, or will react at a specific rate much lower than that for the reaction with free iodine, the concentration of which is determined by the above equilibrium.

The appropriate kinetic equation is[14]:

$$\frac{dx}{dt} = \frac{k_2K}{K + (I^-)}(a - x)(n - x) \qquad (4)$$

If we substitute

$$k_{obs.} = k_2K/(K + I^-) \qquad (5)$$

this becomes the ordinary second order equation, which integrates to eqn. 1.

If $K$ is considered to be small compared to $(I^-)$ then

$$k_{obs.} = \frac{k_2K}{(I^-)} \text{ or } k_{obs.}(I^-) = k_2K = \text{constant} \qquad (6)$$

Equation 6 thus requires that the experimentally observed velocity constant multiplied by the iodide ion concentration be a constant for each pyrrole. Table IV shows that the relationship holds fairly well. There is, however, a drift

(13) Jones and Kaplan, *ibid.*, **50**, 1845 (1928).

(14) Soper and Smith, *J. Chem. Soc.*, 2757 (1927); Bartlett and Tarbell, THIS JOURNAL, **58**, 446 (1936).

upwards as the concentration of iodide ion becomes small.

TABLE IV

IODINATION OF PYRROLES

| Pyrrole | $I_2$ added | $(I^-)$ | $[Py]_0$ | $k_{obs.}$ | $(I^-)x$ $k_{obs.}$ | $k_2$[a] |
|---|---|---|---|---|---|---|
| I | 0.00672 | 0.805 | 0.00551 | 0.0280 | 0.0225 | 15.5 |
| | .00827 | .696 | .00777 | .0326 | .0227 | 15.6 |
| | .00827 | .696 | .00563 | .0328 | .0228 | 15.7 |
| | .00850 | .497 | .00638 | .0467 | .0232 | 16.0 |
| II | .00651 | .805 | .00853 | .0296 | .0238 | 16.4 |
| | .00580 | .600 | .00990 | .0412 | .0246 | 17.0 |
| | .00679 | .518 | .00948 | .0485 | .0251 | 17.3 |
| III | .00921 | .857 | .00580 | .00096 | .00083 | 0.57 |
| | .00662 | .676 | .00513 | .00135 | .00091 | 0.63 |
| | .00578 | .600 | .00513 | .00150 | .00090 | 0.61 |
| | .00568 | .400 | .00580 | .00280 | .00112 | (0.77) |
| IV | .00788 | .600 | .00622 | .00167 | .00100 | 0.69 |
| | .00853 | .497 | .00622 | .00201 | .00100 | 0.69 |
| | .00568 | .400 | .00550 | .00300 | .00120 | (0.83) |

[a] Liters per mole sec.

This drift may be caused by some reaction of hypoiodous acid with the pyrrole. Li[15] showed that in the iodination of tyrosine by iodine solutions containing a low concentration of iodide ion (less than 0.10 molar) the observed second order constant obeys the following relationship

$$k_{obs.} = \frac{A}{(I^-)^2} + \frac{B}{(I^-)}$$

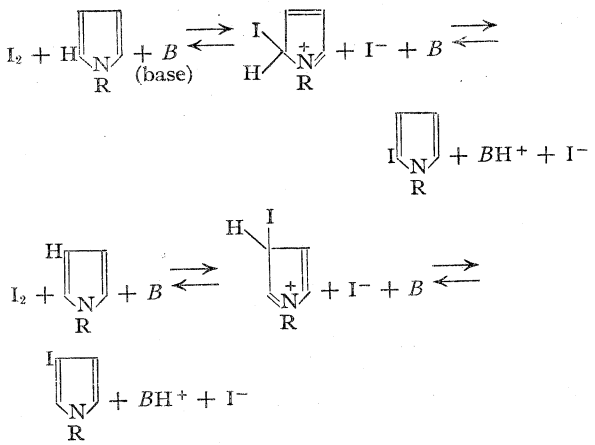
The first term is due to the reaction of hypoiodous acid, the second due to reaction by free iodine. At very low concentrations of iodide ion, the first term is very important. At higher concentrations of iodide ion, the second term increases in importance, and will eventually become much larger than the first term. Then, $k_{obs.} = B/I^-$, which is eqn. 4, in which $B = k_2K$. In the experiments reported here, the concentrations of iodide ion were much higher than in the experiments of Li (0.40–0.86 $M$, compared with 0.03–0.10 $M$), so that eqn. 4 is obeyed fairly well. Free iodine thus is shown to be the principal iodinating agent under the conditions of these experiments.

**Details of Mechanism.**—Sidgwick, Taylor and Baker[16] have expressed the belief that the great reactivity of pyrroles in both an $\alpha$ and a $\beta$-position may be due to their ability to assume pyrrolenine structures.



This view has been opposed by Brunings and Corwin.[17] The similar kinetics of iodination of both N-methyl and N—H pyrroles is consistent with that expected for typical electrophilic reactions. It is impossible for the N-methyl pyrroles to assume a pyrrolenine structure without the migration of a methyl group. Since they can be iodinated without a change in the carbon skeleton by a reaction which is reversible, it is extremely unlikely that a pyrrolenine intermediate is involved.

The facts of the forward and reverse reactions presented below are consistent with a mechanism involving an ionic intermediate, in which the first step is rate-determining:



**Relationship Between Structure and Reactivity. (a) The Effect of N-Methyl.**—The specific velocity constants for the iodination of the four pyrroles were estimated by the use of eqn. 6. The value of $K = 0.00145$ was used, although it may be somewhat in error. However, this does not affect the relative velocity constants. The averages of these constants (from Table IV, neglecting those for the experiments with the lowest concentration of iodide ion) are recorded in Table V.

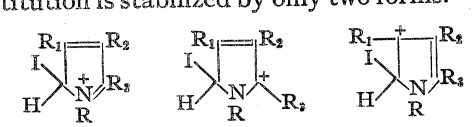
TABLE V

RELATIVE RATES OF IODINATION OF PYRROLES

| | Pyrrole | $k$ (l. per mole sec.) | Ratios | |
|---|---|---|---|---|
| I | N–H, $\alpha$–H | 15.7 | I/III | 26.2 |
| II | N–$CH_3$, $\alpha$–H | 16.9 | II/I | 1.08 |
| III | N–H, $\beta$–H | 0.60 | IV/III | 1.15 |
| IV | N–$CH_3$, $\beta$–H | 0.69 | II/IV | 24.5 |

The results in Table V show that in both cases N-methylation has slightly increased the reactivity, although the differences are small. The N-methyl group thus increases the reactivity of pyrroles to a much smaller extent than a methyl group increases the reactivity of the benzene ring.

**(b) The Effect of Position.**—Table V shows that the $\alpha$-free pyrroles are much more reactive than the $\beta$-free pyrroles. The ionic intermediate mechanism is consistent with this relationship, since the intermediate in $\alpha$-substitution is stabilized by three resonance forms while that in $\beta$-substitution is stabilized by only two forms.



$\alpha$-Substitution Intermediate

(15) Li, *ibid.*, **64**, 1147 (1942).

(16) Sidgwick, Taylor and Baker, "The Organic Chemistry of Nitrogen," Oxford, 1937, pp. 482–490.

(17) Brunings and Corwin, THIS JOURNAL, **64**, 594 (1942).



β-Substitution Intermediate

**Iodopyrroles as "Positive Halogen" Compounds.**—The results in Table III on the reaction of two iodopyrroles with hydriodic acid are shown graphically in Fig. 3. The α-iodopyrrole is shown to be twenty times as reactive as the β-iodopyrrole. A difference of 24.5-fold was observed for the iodination of the corresponding unsubstituted pyrroles II and IV in Table V. This suggests a mechanism in which a proton attacks an electron pair, forming the same ionic intermediate present in the iodination, which then reacts with an iodide ion to form free iodine. The factors which determine the reactivity toward iodine also determine the reactivity toward a proton in the reverse reaction.

The iodopyrroles thus belong to class of "positive halogen" compounds, discussed by Bartlett and Tarbell and Altschul and Bartlett.[18] In compounds of this type, a halogen atom may be transferred as a positive group from one compound to another in a manner similar to that in which a proton is transferred. The iodine atom simultaneously loses an electron pair and shares another pair in both the forward and the reverse reaction, and probably does not exist as a positive atom.

**The Iodination Equilibrium.**—The estimation of the forward and reverse velocity constants permits an approximation to the magnitude of the equilibrium constant of the iodination reaction to be made. The constant

$$K = \frac{[RI][HSolv^+][I^-]}{[RH][Solv][I_2]}$$

is approximately 24 for the α iodination and 21 for the β, assuming the solvent to be 48.2 molar. The ratio of equilibrium constants is thus about 1.1 while the corresponding ratio of rate constants is 24.5. This is clearly a case in which rate constants and equilibrium constants are not parallel. A possible explanation is that the attacking reagents in both directions are sufficiently similar that a structural change which affects the rate of reaction of the unsubstituted pyrrole affects that of the iodopyrrole almost equally.

(18) Bartlett and Tarbell, THIS JOURNAL, **58**, 466 (1936); Altschul and Bartlett, *J. Org. Chem.*, **5**, 622 (1941).

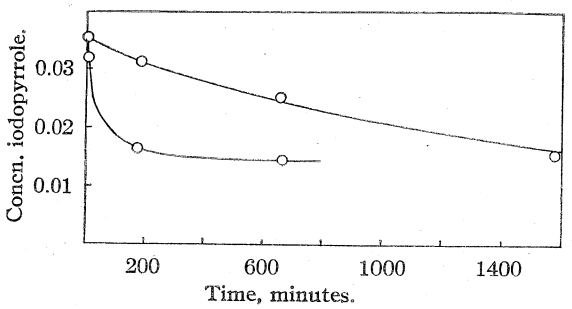



Fig. 3.—Reduction of iodopyrrole; data from Table III; upper curve, Pyrrole VI; lower curve, Pyrrole V.

One of us, K.W.D., wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

## Summary

1. The kinetics of iodination of four similar pyrrole derivatives have been studied.
2. The rates of these reactions are dependent upon the concentration of the pyrrole derivative and of the free iodine in the solution.
3. The kinetics indicate that still another species, perhaps hypoiodous acid, is active in iodination.
4. The α-position is found to be about 25 times as reactive as the β position in the pyrrole ring.
5. N-Methyl groups increase the reactivity of the pyrrole ring by 8–15%.
6. This effect is much smaller than the effect of methyl on the reactivity of benzene.
7. Iodopyrroles can be reduced to pyrroles with hydriodic acid.
8. The α position is approximately twenty times as reactive to hydrogen iodide reduction as the β position.
9. Rough values for the equilibrium constant of the iodination reaction have been obtained in two cases.
10. This equilibrium constant is little affected by a structural change in the pyrrole.
11. The significance of these findings with respect to the mechanism of the iodination reaction is discussed.

BALTIMORE 18, MD. RECEIVED JULY 19, 1948

[CONTRIBUTION NO. 673 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# Furan and Tetrahydrofuran Derivatives. IX. On *epi*-Oxybiotin and the Four Racemic 3,4-Diamino-2-tetrahydrofuran Valeric Acids[1]

BY KLAUS HOFMANN[2]

In recent communications[3,4] the first total synthesis of *dl*-oxybiotin has been described. The key to this synthesis was the catalytic hydrogenation of 3,4-dicarbethoxyamino-2-furanpentanol (II) to a *cis*-3,4-dicarbethoxyamino-2-tetrahydrofuranpentanol. Hydrogenation of a tri-substitution product of furan such as II creates three asymmetric carbon atoms in the molecule, and four racemic tetrahydrofurans, V, VI, VII, and VIII, may be expected. Two of these, V and VI, have a *trans*, and the others, VII and VIII, a *cis*-configuration of the carbethoxyamino groups. The isomers in each pair differ in the spatial configuration of the side chain R′. They may be designated as the *trans*, *cis* V, the *trans*, *trans* VI, the *cis*, *cis* VII and the *cis*, *trans* VIII isomers, respectively. All of the theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids, XV, XVI, XVII and XVIII, have been prepared. Their synthesis and some of their properties will be described in this communication. In the last analysis, this work represents a study of the catalytic hydrogenation of 3,4-dicarbethoxy-2-furanpentanol (I) and of 3,4-dicarbethoxyamino-2-furanpentanol (II).

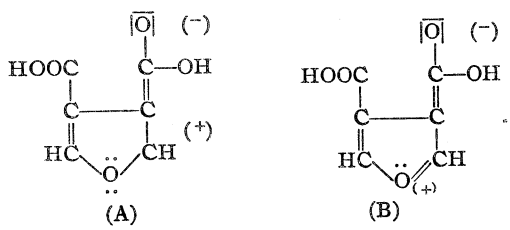
Attempts to reduce compound I or the corresponding free dicarboxylic acid in glacial acetic acid over a platinum oxide catalyst were unsuccessful. This observation is in agreement with the work of Archer and Pratt,[5] who also were unable to effect reduction of methyl-3,4-dicarboxy-2-furan acetate under similar conditions. Substitution of the furan nucleus with carboxyl groups endows this otherwise labile ring system with an unusual stability which reflects itself in resistance toward catalytic hydrogenation and stability toward strong mineral acids.[5,6]

These observations may be explained by the resonance concept. In addition to the obvious structures which contribute to the resonance hybrid of furan, additional structures such as A and B may be written for the furan dicarboxylic acids. They are the result of a conjugation between the unsaturation of the ring and the carboxyl groups. The electron-attracting carboxyl groups tend to remove electrons from the ring, thus lowering its affinity for electrophilic reagents and increasing its stability. The fact that resonance tends to bring the carboxyl groups into planarity with the ring may explain the finding that furan-3,4-dicarboxylic acids do not undergo intramolecular anhydride formation.[7,8] The failure of (I) to undergo hydrogenation under the above-mentioned conditions led us to investigate other reduction procedures. It was observed that the compound was smoothly reduced when subjected to high-pressure hydrogenation over a Raney nickel catalyst. A mixture of reduction products was obtained which on treatment with hydrazine hydrate yielded two crystalline isomeric hydrazides $C_{11}H_{22}O_4N_4$ of m. p. 208–210° and m. p. 177–180°.

Based on experimental evidence which will be presented later, we have assigned the *trans*, *cis*-structure III to the higher, and the *trans*, *trans*-configuration IV to the lower melting isomer.

Degradation of these hydrazides by the Curtius procedure with ethanol as the solvent for the decomposition of the corresponding azides yielded two isomeric urethans, V and VI, which on oxidation with chromic acid gave the corresponding 3,4-dicarbethoxyamino-2-tetrahydrofuran valeric acids XI and XII. These compounds were hydrolyzed with aqueous barium hydroxide and the resulting 3,4-diamino-2-tetrahydrofuran valeric acids, XV and XVI, were isolated as the crystalline sulfates and characterized as the dibenzoates and the dibenzoylmethyl esters. Treatment of these diaminocarboxylic acids with phosgene under a variety of experimental conditions did not result in the formation of the corresponding hexahydro-2-oxo-1-furo-(3,4)-imidazoles. Both compounds, therefore, must have a *trans* configuration of the amino groups.

Hydrolysis of the hydrazide (III) with aqueous barium hydroxide at 120° resulted in the formation of an acid. This material was esterified and the dimethyl ester reacted with hydrazine hydrate. Instead of the original hydrazide (III), the isomeric hydrazide (IV) was thus obtained. This was further substantiated by transformation of the isomerized hydrazide into the urethan (VI). The hydrazide (III) was then hydrolyzed with 2 *N* hydrochloric acid, and the hydrazide re-




(1) A preliminary report on some of the experiments herein described has appeared in THIS JOURNAL, **66**, 157 (1944).

(2) We wish to express our thanks to Ciba Pharmaceutical Products, Inc., and to the Buhl Foundation for their generous support.

(3) Hofmann, THIS JOURNAL, **67**, 694 (1945).

(4) Hofmann, *ibid.*, **67**, 1459 (1945).

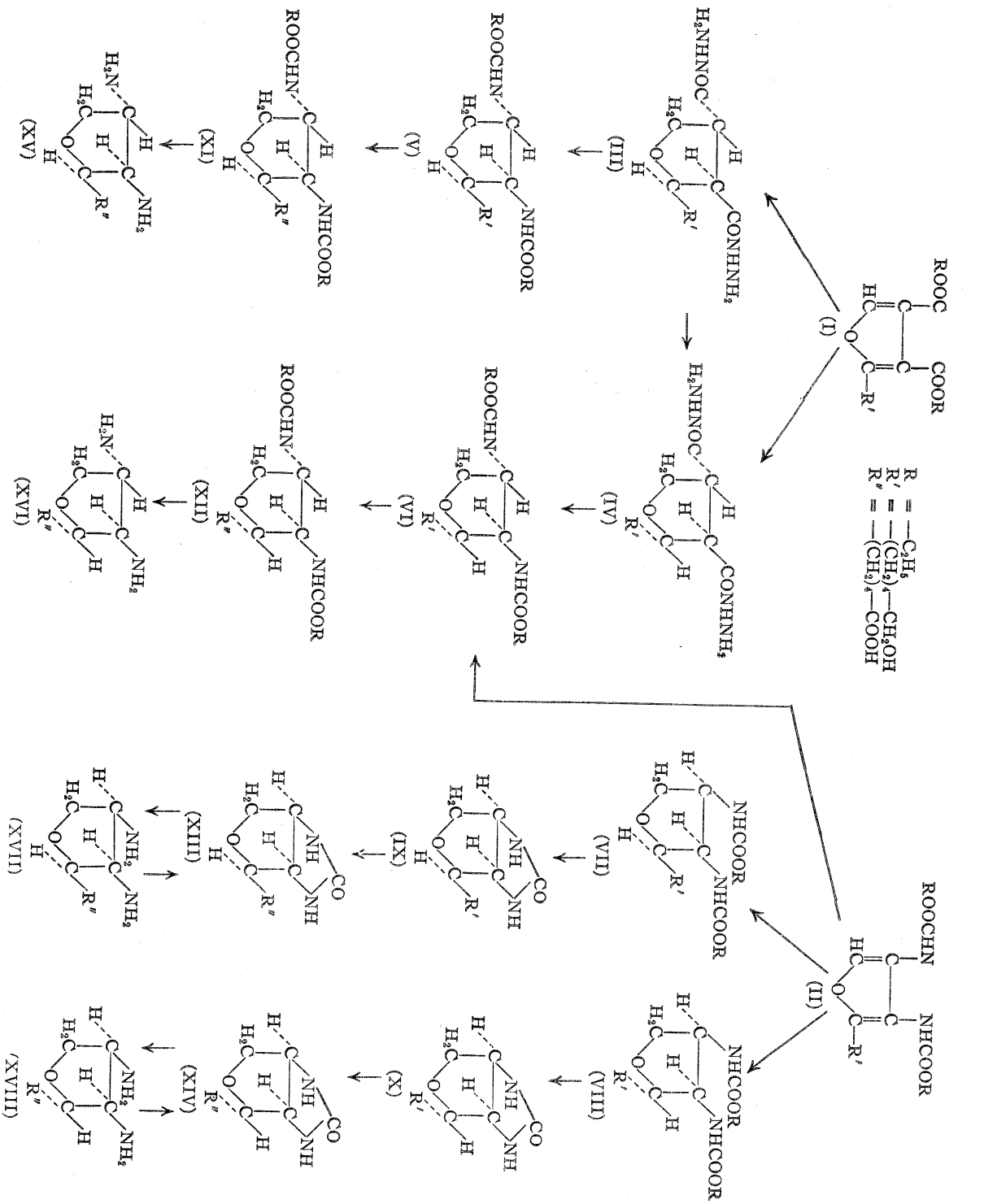
(5) Archer and Pratt, *ibid.*, **66**, 1656 (1944).

(6) Reichstein, *Helv. Chim. Acta*, **16**, 276 (1933).

(7) Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(8) Hofmann, THIS JOURNAL, **67**, 421 (1945).

generated from the resulting dicarboxylic acid. No rearrangement occurred under these conditions since III was obtained. Therefore, the barium hydroxide treatment must have racemized the molecule. In pairs of stereoisomers it is usually the *cis*-oid compound which has the higher energy content and the lower stability, and it seems logical to assume that the hydrazide (III) has the *trans, cis*- and the hydrazide (IV) the *trans, trans*-configuration. The rearrangement which occurs during the barium hydroxide treatment must involve positions 3 and 4, since the asymmet-



ric center at position 2 is stereochemically stable. These observations, in conjunction with the established *trans*-configuration of the substituents in positions 3 and 4 for both isomers, provide strong evidence for the correctness of the assigned stereo structures. The finding that two different diaminocarboxylic acids, XV and XVI, resulted from the degradation of the hydrazides, III and IV, indicated that no rearrangement had occurred during these transformations. Consequently, the configuration of the diaminocarboxylic acids also is established.

The 3,4-dicarbethoxyaminofurans are less "aromatic" than the 3,4-dicarboxyfurans, and undergo hydrogenation at room temperature and atmospheric pressure in the presence of a palladium-on-barium sulfate catalyst. Thus far, this has been demonstrated for 3,4-dicarbethoxyamino-2-furanpropanol,[9] -butanol,[10] and -pentanol.[3,4]

A careful study of the hydrogenation products of (II) revealed the presence of three isomeric 3,4-dicarbethoxyamino-2-tetrahydrofuranpentanols, VI, VII and VIII. During the development of the oxybiotin synthesis[3,4] these hydrogenation products were treated with barium hydroxide and no attempts were made to isolate the different isomeric urethans. It has now been possible to isolate the *trans*-isomer (VI) from this mixture. Its identity with the urethan obtained from the hydrazide (IV) was definitely established by degradation through the 3,4-dicarbethoxyamino-2-tetrahydrofuran valeric acid (XII) to the diaminocarboxylic acid (XVI). Therefore, hydrogenation of II under conditions which favor a *cis*-addition of hydrogen gave a mixture of hydrogenation products containing approximately 24% of the *trans,trans*-isomer (VI). Although the *cis*-3,4-dicarbethoxyaminotetrahydrofurans, VII and VIII, have not been isolated, their presence among the hydrogenation products was conclusively demonstrated by their transformation into cyclic urea derivatives. This has already been demonstrated[3,4] for the isomer which on treatment with barium hydroxide yielded a hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo-(3,4)-imidazole of melting point 153–154°. Because the spatial position of the side chain has not yet been established, this compound may have structure IX or X. It could be expected that the mother liquors from the above pentanol might contain its epimer with the opposite configuration of the side chain. These fractions have now been subjected to a chromatographic fractionation and it was possible to isolate a hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo-(3,4)-imidazole of melting point 104–106° which for reasons presented below must be the epimer of the derivative of m. p. 153–154° (structure IX or X). Oxidation of this material, followed by esterification, gave *epi*-oxybiotin methyl ester. *epi*-Oxybiotin was obtained upon hydrolysis of the ester, and on drastic hydrolysis was transformed into a *cis*-3,4-diamino-2-tetrahydrofuran valeric acid, XVII or XVIII. This substance also was characterized as its dibenzoate and its dibenzoyl methyl ester. Treatment of the above diaminocarboxylic acid with phosgene resulted in the regeneration of *dl-epi*-oxybiotin. This series of reactions establishes the constitution of *epi*-oxybiotin as XIII or XIV beyond any question.[11]

The experiments herein described have led to the isolation of three out of the four theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids. The fourth isomer, namely, the one which stereochemically corresponds to oxybiotin has already been described.[4] This compound has now been transformed into its dibenzoate and the dibenzoylmethyl ester. It is of considerable interest to compare the reactions of these substances with those of the corresponding 3,4-diamino-2-tetrahydrothiophenevaleric acids which became known as a result of synthetic studies on biotin. In contrast to our tetrahydrofurans where only the isomers with a *cis*-configuration of the amino groups are capable of ring formation, the *trans*-3,4-diaminotetrahydrothiophenevaleric acids form bicyclic urea derivatives on treatment with phosgene.[12] This suggests fundamental differences between the two ring systems. One would conclude from this preliminary evidence that stereochemically the tetrahydrothiophene ring resembles the cyclohexane ring in contrast to the tetrahydrofuran ring which behaves more like cyclopentane. The suggested stereochemical differences between these two ring systems will be further investigated. Work is also in progress to establish the spatial arrangement of the side chain in oxybiotin and *epi*-oxybiotin.

## Experimental[13,14,15]

**Hydrogenation of 3,4-Dicarbethoxy-2-furanpentanol (I).**—3,4-Dicarbethoxy-2-furanpentanol[16] (20 g.) was dissolved in 120 cc. of grain alcohol and hydrogenated for three hours at an initial pressure of 1800 lb./sq. in. and a temperature of 180° over a Raney nickel catalyst prepared from 10 g. of the alloy. The catalyst was removed by filtration through Filter-Cel, the alcohol removed *in vacuo*, and the resulting oil dissolved in ether. The ethereal solution was washed with 2 *N* sodium carbonate and water and dried over sodium sulfate; the ether was removed on the steam-bath. The residue on distillation yielded 15.7 g. (78%) of hydrogenated esters which boiled at 175–180° at 0.02 mm.

(9) Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, 69, 191 (1947).

(10) Hofmann, Bridgwater and Axelrod, *ibid.*, 69, 1550 (1947).

(11) When tested with *L. arabinosus*, *dl-epi*-oxybiotin was found to possess 0.1% of the growth-promoting activity of *d*-biotin. It seems very likely that this activity is due to contamination with *dl*-oxybiotin.

(12) Harris, Mozingo, Wolf, Wilson and Folkers, THIS JOURNAL, 67, 2102 (1945).

(13) The microanalyses were performed in our microanalytical laboratories by Mr. George L. Stragand.

(14) All melting points were determined with short stem Anschütz thermometers and are not corrected.

(15) The tetrahydrofuran derivatives described in this paper are *dl*-forms.

(16) Hofmann, THIS JOURNAL, 67, 421 (1945).

*Anal.* Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.66; $OC_2H_5$, 29.8. Found: C, 59.64; H, 8.42; $OC_2H_5$, 26.7.

**3,4-Dicarboxy-2-tetrahydrofurandihydrazide of m. p. 208–210° (III).**—A mixture of 15 g. of the above hydrogenated esters and 15 g. of hydrazine hydrate was refluxed for two hours and then placed in a refrigerator for twelve hours. The resulting crystals were collected, washed with absolute ethanol, and dried over concentrated sulfuric acid *in vacuo*. Recrystallization from dilute ethanol gave 3.2 g. of needles (24%) which melted at 208–210°.

*Anal.* Calcd. for $C_{11}H_{22}O_4N_4$: C, 48.16; H, 8.08; N, 20.41. Found: C, 48.15; H, 7.85; N, 20.18.

**3,4-Dicarboxy-2-tetrahydrofurandihydrazide of m. p. 177–180° (IV).**—The combined mother liquors from the preparation of III were concentrated *in vacuo* to a thick sirup which was kept over concentrated sulfuric acid for several days. The material was then dissolved in a small amount of absolute ethanol and the solution placed in a refrigerator for two days. The resulting crystals were collected, washed with a small amount of ice-cold ethanol, and purified by several recrystallizations from the same solvent; 1.5 g. (11%) of crystals melting at 177–180° was obtained.

*Anal.* Calcd. for $C_{11}H_{22}O_4N_4$: C, 48.16; H, 8.08; N, 20.41. Found: C, 48.01; H, 7.95; N, 20.27.

**Transformation of the Hydrazide (III) into the Isomer (IV).**—A solution of 6 g. of III, 15 g. of barium hydroxide octahydrate, and 80 cc. of water was heated to 120° for five hours in a sealed tube. A slow stream of carbon dioxide was passed into the hot solution and the resulting barium carbonate removed by filtration through Filter-Cel. The filtrate was concentrated to a small volume *in vacuo*, acidified to congo red with concentrated hydrochloric acid, and extracted with five 20-cc. portions of ethyl acetate. The combined ethyl acetate extracts were washed with a small amount of water, dried over sodium sulfate, and concentrated to dryness *in vacuo*. The resulting oily acid, 4.48 g. (83%), was esterified with diazomethane, and the methyl ester distilled *in vacuo*. Treatment of 656 mg. of this ester with 600 mg. of hydrazine hydrate gave 312 mg. (48%) of IV melting at 177–179°. Degradation of this hydrazide by the method given below yielded the urethan (VI) of melting point 128–130°.

**Hydrolysis of (III) with Hydrochloric Acid.**—A solution of 1.37 g. of III in 15 cc. of 2 *N* hydrochloric acid was refluxed overnight, and then evaporated to dryness *in vacuo*. The resulting acid was isolated and esterified as described above, and the methyl ester transformed into the hydrazide; 490 mg. of the ester gave 260 mg. (53%) of III melting at 207–209°. Degradation of this hydrazide by the method given below yielded the urethan (V) of melting point 108–110°.

**3,4-Dicarbethoxyamino-2-tetrahydrofuranpentanol of m. p. 108–110° (V).**—A solution of 1.1 g. of (III) in 10 cc. of 2 *N* hydrochloric acid was cooled in an ice-bath, and 6 cc. of a 10% solution of sodium nitrite was slowly added with vigorous stirring. Stirring was continued for an additional ten minutes and the resulting oily azide extracted with ice-cold ether. The ethereal solution was washed with ice-cold 2 *N* sodium carbonate and water, dried over sodium sulfate and filtered. Absolute alcohol (40 cc.) was then added and the solution slowly heated until the ether had evaporated. The resulting alcoholic solution was refluxed for one hour, and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate; 523 mg. (40%) of V, melting at 108–110° was obtained.

*Anal.* Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.92; H, 8.09; N, 8.57.

**3,4-Dicarbethoxyamino-2-tetrahydrofuran-pentanol of m. p. 128–130° (VI). a. From the Hydrazide (IV).**—The hydrazide (IV) (3.2 g.) was transformed into the corresponding urethan (VI) as described above. Crystallization from ethyl acetate gave 1.3 g. (34%) of needles melting at 128–130°.

*Anal.* Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.84; H, 8.19; N, 8.64.

**b. From 3,4-Dicarbethoxyamino-2-furanpentanol (II).**—The hydrogenation products obtained from 61.2 g. of (II) as previously described[4] were seeded with a small amount of the above urethan and kept at room temperature overnight. The resulting crystals were collected, washed with ice-cold ethyl acetate, and recrystallized from the same solvent; 15 g. (24%) of needles was obtained which melted at 130–131°. No depression of the melting point was observed when this sample was mixed with a sample of the urethan prepared according to a above.

*Anal.* Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.99; H, 8.20; N, 8.62.

**3,4-Dicarbethoxyamino-2-tetrahydrofuran Valeric Acid of m. p. 121–122° (XI).**—To a solution of the urethan (V) (3.2 g.) in 50 cc. of glacial acetic acid, 100 cc. of a 2% solution of chromium trioxide in glacial acetic acid was slowly added. The mixture was kept at room temperature for twelve hours; methanol (1 cc.) was then added and the solution heated on the steam-bath for thirty minutes. The solvents were removed *in vacuo*, the green residue dissolved in ethyl acetate, and the ethyl acetate solution washed with water. The acidic oxidation products were extracted from the ethyl acetate solution with 2 *N* sodium carbonate, and the acids liberated by acidification and re-extraction with ethyl acetate. The extracts containing the acidic material were dried over sodium sulfate, the ethyl acetate removed *in vacuo* and the crystalline residue purified by recrystallization from ethyl acetate at −20°; 1.3 g. (40%) of crystals was obtained which melted at 121–122°.

*Anal.* Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 52.10; H, 7.34; N, 8.60.

**3,4-Dicarbethoxyamino-2-tetrahydrofuran Valeric Acid of m. p. 158–160° (XII).**—Compound (VI) (664 mg.) was oxidized as described above and the resulting crystals purified by crystallization from ethyl acetate; 280 mg. (40%) of needles melting at 158–160° was obtained.

*Anal.* Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 52.05; H, 7.14; N, 8.21.

Oxidation by the same procedure of one gram of the urethan (VI) obtained from the hydrogenation of (II) yielded 600 mg. (58%) of needles, melting at 160–161.5°, which did not depress the melting point of the above material.

*Anal.* Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 51.85; H, 7.32; N, 8.25.

***epi*-Hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo(3,4)-imidazole (IX or X).**—The combined mother liquors from several preparations of the hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo(3,4)imidazole of m. p. 153–154°[4] were concentrated to dryness *in vacuo*. The oily residue (15 g.) was dissolved in 500 cc. of acetone and the solution poured on a column prepared from 300 g. of aluminum oxide (Fisher adsorption alumina). The column was then eluted with 250-cc. portions of each of the following solvent mixtures which removed the amounts of material indicated in parentheses: acetone (3.1 g. of oil); acetone 90, methanol 10 (0.7 g. of oil); acetone 80, methanol 20 (1.7 g. of oil); acetone 70, methanol 30 (3.7 g. of crystals); acetone 60, methanol 40 (3 g. of crystals); acetone 50, methanol 50 (0.7 g. of oil). The fractions containing crystalline material were combined and recrystallized several times from 95% ethanol at −20°; 1.5 g. of the *epi*-pentanol was thus obtained which melted at 104–106°.

*Anal.* Calcd. for $C_{10}H_{18}O_3N_2$: C, 56.07; H, 8.47; N, 13.07. Found: C, 56.12; H, 8.30; N, 13.31.

***epi*-Oxybiotin Methyl Ester.**—To a solution of the above *epi*-pentanol (760 mg.) in 35 cc. of 0.1 *N* sodium hydroxide, 25 cc. of a 5% solution of potassium permanganate was added slowly and the mixture kept at room temperature for twelve hours. The manganese dioxide was removed by filtration through Filter-Cel. The filter cake

of manganese dioxide was washed repeatedly with hot water and the combined filtrate and washings were acidified to congo red with concentrated hydrochloric acid, and concentrated to dryness *in vacuo*.

The dry residue was extracted with two 25-cc. portions of methanol and an ethereal solution of diazomethane was added to the combined extracts until the yellow color remained. The mixture was kept for ten minutes and was then evaporated to dryness and the residue extracted with ethyl acetate. The combined ethyl acetate extracts were filtered and evaporated to dryness *in vacuo*, leaving a semicrystalline residue. This material was dissolved in 20 cc. of acetone and the solution chromatographed on 10 g. of Fisher alumina. The column was eluted with several 10-cc. portions of a mixture containing 90% acetone and 10% methanol. All of the eluates containing crystalline material were combined and the substance recrystallized from ethyl acetate; 190 mg. (22%) of needles was obtained which melted at 104–106°.

*Anal.* Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.45; N, 11.55. Found: C, 54.67; H, 7.35; N, 11.64.

**epi-Oxybiotin (XIII or XIV). a. From the Methyl Ester.**—A mixture of the above methyl ester (190 mg.), $Ba(OH)_2 \cdot 8H_2O$ (0.5 g.), and water (5 cc.) was heated to 100° for two hours in a sealed tube. Most of the barium was then precipitated with carbon dioxide and the resulting solution acidified to congo red with 2 *N* sulfuric acid. The barium sulfate was removed by filtration and the filtrate concentrated to a small volume *in vacuo*. The resulting *epi*-oxybiotin was collected and recrystallized from hot water; 150 mg. (83%) of prismatic crystals was obtained which melted at 185–186°.

*Anal.* Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.91; H, 7.04; N, 12.23.

**b. From the Corresponding Diaminocarboxylic Acid and Phosgene.**—A solution of 50 mg. of the diaminocarboxylic acid prepared from *epi*-oxybiotin as described below, in 1 cc. of 10% sodium bicarbonate, was treated with phosgene in the usual manner.[4] The resulting *epi*-oxybiotin (25 mg.) (66%) melted at 183–184°. No depression of the melting point was observed when this material was mixed with a sample of *epi*-oxybiotin prepared according to a above.

***trans*-3,4-Diamino-2-tetrahydrofuran Valeric Acid (XV).**—A solution of 1.32 g. of (XI), 8 g. of $Ba(OH)_2 \cdot 8H_2O$ and 40 cc. of water was heated to 110° for three hours in a sealed tube. The crystalline sulfate of (XV) (870 mg.) (75%) was isolated in the usual manner.

**Dibenzoate of XV.**—A sample of the sulfate was benzoylated with benzoyl chloride and 5 *N* potassium hydroxide, and the dibenzoate recrystallized from dilute methanol. The substance melted at 215–217°.

*Anal.* Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.15; H, 6.23; N, 6.96.

**Dibenzoyl Methyl Ester of XV.**—A sample of the dibenzoate was esterified with diazomethane and the resulting ester recrystallized from a mixture of methanol and ether. The substance melted at 183–185°.

*Anal.* Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.87; H, 6.38; N, 6.62.

***trans*-3,4-Diamino-2-tetrahydrofuran Valeric Acid (XVI).**—Compound XII (720 mg.) was hydrolyzed with barium hydroxide as described above; 465 mg. (74%) of the sulfate of (XVI) was obtained.

**Dibenzoate of XVI.**—A sample of the sulfate was benzoylated and the dibenzoate recrystallized from dilute methanol. The substance melted at 194–195°.

*Anal.* Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.57; H, 6.52; N, 6.76.

**Dibenzoyl Methyl Ester of (XVI).**—This derivative was prepared from the dibenzoate with diazomethane and was recrystallized from a mixture of ethanol and ether. The substance melted at 171–173°.

*Anal.* Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.96; H, 6.31; N, 6.68.

***cis*-3,4-Diamino-2-tetrahydrofuranvaleric Acid from Oxybiotin.**—A sample of oxybiotin was hydrolyzed with barium hydroxide and the sulfate of the diamino carboxylic acid isolated as previously described.[4]

**Dibenzoate.**—A sample of the sulfate was benzoylated. The dibenzoate after recrystallization from a mixture of methanol and ethyl acetate melted at 230–231°.

*Anal.* Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.17; H, 6.36; N, 6.83.

**Dibenzoyl Methyl Ester.**—This derivative was prepared from the dibenzoate with diazomethane. After recrystallization from methanol the material melted at 148–150°.

*Anal.* Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.86; H, 6.35; N, 6.54.

***cis*-3,4-Diamino-2-tetrahydrofuranvaleric Acid from *epi*-Oxybiotin.**—A sample of *epi*-oxybiotin (100 mg.) was hydrolyzed with 1.5 g. of $Ba(OH)_2 \cdot 8H_2O$ in 7.5 cc. of water as described.[4] The resulting sulfate of the diaminocarboxylic acid (70 mg., 53%) melted at 233–234° with decomposition.

**Dibenzoate.**—This derivative was prepared in the usual manner and after recrystallization from dilute methanol melted at 188–189°.

*Anal.* Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.52; H, 6.56; N, 6.67.

**Dibenzoyl Methyl Ester.**—This derivative, prepared from the dibenzoate with diazomethane, after recrystallization from methanol, melted at 162–165°.

*Anal.* Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.49; H, 6.46; N, 6.98.

**Acknowledgments.**—The author wishes to express his thanks to Florence Baker and Anna Bridgwater for their valuable assistance.

## Summary

The four theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids have been prepared and characterized. Only the two isomers with a *cis*-configuration of the amino groups were found to form bicyclic urea derivatives on treatment with phosgene. Definite stereo structures have been assigned to the two *trans*-isomers. *epi*-Oxybiotin has been prepared and its structure partially established. Differences between the 3,4-diamino-2-tetrahydrothiophenevaleric acids and the corresponding tetrahydrofurans have been discussed.

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

# Aromatization Studies. VIII. Catalytic Dehydrogenation of Di- and Trialkylcyclohexenones to Phenols

BY E. C. HORNING, M. G. HORNING AND G. N. WALKER[1]

An investigation[2] of the catalytic (palladium–carbon) dehydrogenation of 3-methyl-5-aryl-2-cyclohexen-1-ones indicated that aromatization of the alicyclic system to a phenolic system could be accomplished in good yield (*ca.* 70–85%) in a variety of boiling solvents. In contrast to most previous observations, it was found that the dehydrogenation process occurred rapidly under ordinary conditions of boiling, with the major part of the reaction taking place within the first fifteen minutes.

In order to study the effect of substituent groups on dehydrogenations leading to phenols, an investigation has now been carried out with several di- and trialkyl-2-cyclohexen-1-ones. 3-Methyl-5-alkyl-2-cyclohexene-1-ones, in which the alkyl group was methyl, ethyl, *n*-propyl, isopropyl and *n*-hexyl, were treated with a 5% palladium–carbon catalyst in a boiling solvent (usually trimethylbenzene) under the same general conditions employed previously.[2] The effects of variations in time and solvents on the yield of phenol are given in Table I. The effect of variations in the 5-alkyl group on the yield, for a two-hour reaction period at 168°, is shown in Table II. The 3-methyl-2,5-dialkyl-2-cyclohexen-1-ones listed in Table III were also aromatized, under the same conditions, to the corresponding phenols whose properties are in Table IV. The observed yields were generally in the range 40–50% (Tables I, II and IV) for a two-hour reaction period. This range is considerably below that found for 3-methyl-5-arylcyclohexenones, and the explanation is evidently to be found in a greater tendency of alkylcyclohexenones to undergo disproportionation. In the case of 3,5-dimethyl-2-cyclohexen-1-one, the expected 3,5-dimethylcyclohexanone was isolated as the semicarbazone (in about 25% of the total, or 50% of the expected yield) from the reaction mixture. The yields of phenols obtained here are not high, but the method described provides a convenient and useful means for obtaining alkyl phenols which are not available through ordinary aromatic reaction methods.

The 3-methyl-5-alkyl-2-cyclohexen-1-ones were obtained through the Knoevenagel condensation.[3] The fact that 3-methyl-5-alkyl-4-carbethoxy-2-cyclohexen-1-ones may be alkylated in the 2-position is well established, but when the reaction is carried out in ethanol with sodium ethoxide, the predominant reaction is loss of the 4-carbethoxy group by alcoholysis. Sodamide alkylation affords a better means of obtaining alkylated esters,[4] although the low degree of reactivity and the tendency of the sodium salts to form gums may make it difficult to carry out this reaction. After careful fractionation of the alkylated esters, the 4-carbethoxy group was removed by alkaline hydrolysis and decarboxylation. The resulting cyclohexenones are listed in Table III.

TABLE I

DEHYDROGENATION OF 3,5-DIMETHYL-2-CYCLOHEXEN-1-ONE

| Solvent | B. p., °C. | Time, hr. | Yield of phenol, % |
|---|---|---|---|
| Trimethylbenzene | 168 | 0.5 | 37 |
| Trimethylbenzene | 168 | 2 | 38 |
| Trimethylbenzene | 168 | 4 | 39 |
| Trimethylbenzene | 168 | 6 | 44 |
| Cymene | 177 | 2 | 50 |
| Triethylbenzene | 214 | 2 | 46 |
| Phenyl ether | 252 | 2 | 48 |

TABLE II

DEHYDROGENATION TO 3-METHYL-5-ALKYLPHENOLS

| 5-Alkyl | Yield, % | M. p. or b. p., °C. |
|---|---|---|
| Methyl | 38 | 62–63° |
| Ethyl | 42 | 52–54°[a] |
| *n*-Propyl[b,c] | 49 | 152–154° (40 mm.) |
| Isopropyl | 49 | 49–51°[d] |
| *n*-Hexyl[e,f] | 54 | 190–192° (35 mm.) |

[a] Reported m. p. 55° (Kruber and Schmitt, *Ber.*, 64, 2270 (1931)). [b] *Anal.* Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.27. [c] Phenylurethan, m. p. 90–91° from cyclohexane–hexane. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.83; H, 7.28. [d] Reported m. p. 48–49° and 54° (Horning, THIS JOURNAL, 67, 142 (1945); Knoevenagel, *Ber.*, 27, 2347 (1894)). [e] *Anal.* Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 81.33; H, 10.49. [f] Aryloxyacetic acid, m. p. 76–77.5° from cyclohexane–hexane. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.99; H, 8.70.

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## Experimental

All melting points are corrected.

**Palladium Catalyst.**—A 5% palladium–carbon catalyst was prepared according to Hartung's method.[5]

**Solvents.**—All solvents were distilled before use. The trimethylbenzene solvent was the technical grade (mixed isomers) of the Eastman Kodak Co., b. p. 168–172°. This solvent was found to give particularly clean products.

**Dehydrogenation.**—The general procedure is illustrated by the following example. To 5.00 g. of 3,5-dimethyl-2-cyclohexen-1-one in 15 ml. of trimethylbenzene was added 1.50 g. of 5% palladium–carbon catalyst. The mixture was maintained under vigorous reflux for

(1) Research Corporation Research Assistant.

(2) Horning and Horning, THIS JOURNAL, **69**, 1359 (1947).

(3) Horning, Denekas and Field, *J. Org. Chem.*, **9**, 547 (1944).

(4) Hogg, THIS JOURNAL, **70**, 161 (1948).

(5) "Organic Syntheses," **26**, 77 (1946).

TABLE III

3-METHYL-2,5-DIALKYL-2-CYCLOHEXEN-1-ONES

| 2-Alkyl | 5-Alkyl | Yield, % | B. p., °C. | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| Ethyl | Methyl | 52 | 97–106 (11 mm.) | 78.89 | 10.59 | 78.87 | 10.43 |
| Ethyl | Isopropyl | 40 | 257–268 (atm.) | 79.94 | 11.18 | 78.82[a] | 10.60[a] |
| *n*-Butyl | Methyl | 61 | 134–141 (18 mm.) | 79.94 | 11.18 | 79.76 | 11.27 |

[a] Not improved on further fractionation.

2,4-DINITROPHENYLHYDRAZONES OF 3-METHYL-2,5-DIALKYL-2-CYCLOHEXEN-1-ONES

| 2-Alkyl | 5-Alkyl | M. p., °C. | Color | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| Ethyl | Methyl | 215–217 | Red | 57.81 | 6.06 | 57.75 | 5.98 |
| Ethyl | Isopropyl | 116.5–118.5 | Red | 59.98 | 6.71 | 60.00 | 6.53 |
| *n*-Butyl | Methyl | 121.5–123.5 | Red | 59.98 | 6.71 | 59.66 | 6.60 |

TABLE IV

DEHYDROGENATION TO 3-METHYL-2,5-DIALKYLPHENOLS

| 2-Alkyl | 5-Alkyl | Yield, % | M. p. or b. p., °C. | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| Ethyl | Methyl | 45 | 78–80[a] | 79.96 | 9.39 | 79.95 | 9.31 |
| Ethyl | Isopropyl | 35 | 150–153 (26 mm.) | 80.85 | 10.17 | 80.90 | 10.33 |
| *n*-Butyl | Methyl | 41 | 64–65.5[b] 152–155 (20 mm.) | 80.85 | 10.17 | 80.91 | 10.33 |

[a] Recrystallized from hexane. [b] Recrystallized from pentane.

DERIVATIVES OF 3-METHYL-2,5-DIALKYLPHENOLS

| 2-Alkyl | 5-Alkyl | Derivative | M. p., °C. | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| Ethyl | Methyl | 4,6-Dibromo | 51–53.5[a] | 38.99 | 3.93 | 38.86 | 3.81 |
| Ethyl | Isopropyl | Phenylurethan | 131.5–133.5[b] | 76.73 | 7.79 | 76.60 | 7.90 |
| *n*-Butyl | Methyl | 4,6-Dibromo | 72.5–74[a] | 42.89 | 4.80 | 43.04 | 4.86 |

[a] Recrystallized from pentane. [b] Recrystallized from cyclohexane.

two hours. After cooling to about 50°, the catalyst was removed by filtration, and washed with four 5-ml. portions of hot ethyl acetate. The solution was extracted with three 40-ml. portions of 10% sodium hydroxide solution. The combined alkaline extracts were washed with 40 ml. of pentane, and diluted with 100 ml. of water. Five milliliters of concentrated hydrochloric acid was added; the solution was chilled in an ice-bath and acidified with dilute hydrochloric acid. The phenol crystallized immediately. After chilling for several hours, the product was removed by filtration, washed well with water and air-dried. The yield was 1.89 g. (38%) of slightly discolored flakes, m. p. 62–63°.

Further extraction of the organic solution with Claisen solution and acidification of the alkaline extract did not yield additional 3,5-dimethylphenol.

The effect of variations in temperature of the boiling solvent and reaction time on the yield is shown in Table I. The yields given are for crude, dry product; all melting points were in the range 62–64°.

This general procedure, using trimethylbenzene as a solvent, with a two hour reaction time, was applied to 3-methyl-5-alkyl-2-cyclohexen-1-ones to provide the results shown in Table II. The dehydrogenation of the 3-methyl-2,5-dialkyl-2-cyclohexen-1-ones listed in Table III gave the corresponding phenols in the yield indicated in Table IV. In the case of trialkylphenols, the isolation procedure was modified in the following way. After removal of the catalyst, the organic solution was extracted with 5% sodium hydroxide solution; this alkaline wash was discarded. (In preliminary experiments, there were indications that small amounts of unchanged 4-carbethoxycyclohexenones were occasionally present in the alkylated products, and this in turn would perhaps result in small amounts of 3,5-dialkylphenols along with the desired 2,3,5-trialkylphenols. In later experiments, the alkylated esters and ketones were fractionated carefully, but at the same time this step was retained. 3,5-Dialkylphenols may be extracted from organic solvents with aqueous alkali, while 2,3,5-trialkylphenols require Claisen alkali for extraction.) The phenolic product was then extracted with Claisen solution, and the extract was washed with pentane. The alkaline solution was diluted and acidified with hydrochloric acid, with cooling. Liquid phenols were isolated by extraction with ether, and the crude products were distilled under reduced pressure through a small Vigreux column.

**Disproportionation to 3,5-Dimethylcyclohexanone.**—The dehydrogenation of 5.00 g. of 3,5-dimethyl-2-cyclohexen-1-one was carried out under the usual conditions in 15 ml. of phenyl ether. After extraction of the phenolic fraction with 10% sodium hydroxide solution, the organic solution was steam distilled to provide a distillate which included ethyl acetate, a ketonic fraction, and traces of phenyl ether. The organic layer was separated, and the aqueous layer extracted with 30 ml. of ether. The combined organic solutions were dried with magnesium sulfate, and the ether was evaporated by warming. The residue was added to 15 ml. of ethanol containing 2.7 g. of semicarbazide hydrochloride, and 5.0 ml. of pyridine. After a reflux period of four hours, 30 ml. of ethanol was added, and approximately 30 ml. of solvents (ethanol-ethyl acetate) was removed by distillation. The residue was poured into 100 ml. of ice-water, and the colorless crystalline product was removed by filtration, washed well with water, and air dried. The dry product was triturated with pentane to remove traces of phenyl ether; the residue was 1.58 g. of colorless material, m. p. 192–194° (dec.). A mixed m. p. with a sample of 3,5-dimethylcyclohexanone semicarbazone, prepared separately, was not depressed.

In a separate experiment, it was found that the semicarbazone of 3,5-dimethylcyclohexanone could be obtained in 88% yield, using the alcohol–pyridine method

with the quantities indicated above, with 2.50 g. of ketone. This indicated that the isolation methods used in the experiment described accounted for approximately 25% of the starting material as 3,5-dimethylcyclohexanone, and about 50% as 3,5-dimethylphenol.

**3,5-Dimethylcyclohexanone.**—3,5-Dimethyl-2-cyclohexen-1-one was hydrogenated in a low-pressure apparatus, using a 5% palladium–carbon catalyst without added solvent. The boiling point of the product was 62–66° (9 mm.). The semicarbazone, prepared by the alcohol–pyridine method, was a colorless solid, m. p. 194–195° (dec.) after crystallization from methanol (crude m. p. 194–196° (dec.)).

This ketone was described by Knoevenagel[6] as a mixture of *cis* and *trans* forms, giving a semicarbazone melting at 190–196°. The configuration of the methyl groups of the product obtained here is not known, but the materials obtained by catalytic reduction and by disproportionation were evidently identical.

**3-Methyl-2,5-dialkyl-2-cyclohexen-1-ones.**—These ketones were prepared through the sodamide alkylation of 3-methyl-5-alkyl-4-carbethoxy-2-cyclohexen-1-ones[3] with the appropriate alkyl iodide, as illustrated by the following example.

A. Alkylation: Sodamide was prepared in the usual way from 12.0 g. (0.52 mole) of sodium and about 500 ml. of liquid ammonia, using ferric nitrate nonohydrate as a catalyst. There was added 98.6 g. (0.50 mole) of 3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one over ten minutes; a yellow amorphous salt formed immediately. About 350 ml. of dry ether was added, and the ammonia was allowed to evaporate. The precipitated salt became increasingly viscous, but stirring was continued as much as possible. A total of 125 g. (0.8 mole) of ethyl iodide was added in small portions as the mixture was brought to reflux temperature, and finally 100 ml. of dry ether and 100 ml. of dry toluene was added. The mixture was heated under reflux with stirring in a nitrogen atmosphere for nine hours. After addition of water, the organic solution was separated, washed with 5% aqueous acetic acid and water, and dried over magnesium sulfate. The ether and toluene were removed by distillation at atmospheric pressure, and the residue was fractionated through a 12-inch Vigreux column. The yield was 78.7 g. (70%) of **2-ethyl-3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one** as a light yellow oil, b. p. 128–135° (4 mm.).

*Anal.* Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.80; H, 9.09.

The red-orange **2,4-dinitrophenylhydrazone** melted at 107.5–109°.

*Anal.* Calcd. for $C_{19}H_{24}O_6N_4$: C, 56.43; H, 5.98. Found: C, 56.53; H, 5.89.

Alkylation of the same ketoester with *n*-butyl iodide (with a thirty-six-hour reflux period) gave a 43% yield of **2-*n*-butyl-3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one**, b. p. 150–151° (4–5 mm.).

*Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.77.

An alkylation of 3-methyl-5-isopropyl-4-carbethoxy-2-cyclohexen-1-one with ethyl iodide gave a 61% yield of 2-ethyl-3-methyl-5-isopropyl-4-carbethoxy-2-cyclohexen-1-one, b. p. 137–150° (4 mm.). The boiling range indicated that this material was not homogeneous, and it was hydrolyzed directly to the desired ketone without additional fractionation.

These two alkylated esters gave 2,4-dinitrophenylhydrazones which could be obtained only as red, noncrystalline gums. In the course of alkylation it is necessary for the double bond to shift to the 3,4-position, and this unusual behavior of the dinitrophenylhydrazones may indicate that the esters are mixtures of 2,3- and 3,4-double bond isomers.

B. Hydrolysis and decarboxylation: A solution of 71.2 g. (0.32 mole) of 2-ethyl-3,5-dimethyl-4-carbethoxy-2-cyclohexen-1-one, 40 g. (1.0 mole) of sodium hydroxide, 160 ml. of water and 75 ml. of ethanol (95%) was heated under reflux for three and one-half hours. The warm solution was acidified by the slow addition of 150 ml. of 1:1 sulfuric acid; a vigorous evolution of carbon dioxide resulted. The acidified mixture was boiled under reflux one and one-half hours, cooled and extracted with ether. The ether solution was washed well with 5% sodium hydroxide solution, with 2% aqueous acetic acid, with water, and dried over magnesium sulfate. The ether was removed, and the residue distilled under reduced pressure through a 12-inch Vigreux column to yield 25.1 g. (52%) of 2-ethyl-3,5-dimethyl-2-cyclohexen-1-one.

The yields, boiling points and derivatives of these trialkylcyclohexenones are liste in Table III.

## Summary

A series of di- and trialkylcyclohexenones have been dehydrogenated with a palladium–carbon catalyst to the corresponding di- and trialkylphenols. The yields were usually 40–50%; in the case of arylcyclohexenones the yield is usually 70–85%, and the lowered yield observed here is apparently due to a greater tendency for the alkylcyclohexenones to undergo disproportionation.

The procedures described here provide a route to certain types of alkyl-substituted phenols which are not available by ordinary aromatic substitution methods.

PHILADELPHIA 4, PENNSYLVANIA RECEIVED JULY 14, 1948

(6) Knoevenagel, *Ann.*, **297**, 183 (1897).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

# The Synthesis of Some Cyclopropane Hydrocarbons from Methyl Cyclopropyl Ketone[1]

BY ROSS VAN VOLKENBURGH, K. W. GREENLEE, J. M. DERFER AND C. E. BOORD

This paper describes the synthesis of three cyclopropane hydrocarbons from methyl cyclopropyl ketone obtained from a commercial source.[2]

Ethylcyclopropane was prepared by a Wolff–Kishner reduction of the ketone at atmospheric pressure, the method used being a modification of that of Herr, Whitmore and Schiessler[3] who first described a practical procedure for carrying out this reaction without the use of pressure equipment. These workers decomposed the hydrazone of methyl cyclopropyl ketone with sodium methylate in triethylene glycol by heating the mixture to a maximum temperature of 200°; the yield of ethylcyclopropane was about 60%. In the present work the reaction was carried out in diethylene glycol and the cheaper and more easily handled sodium hydroxide was used in place of sodium methylate; the yield of purified ethylcyclopropane was 72%, and the physical properties obtained were an improvement over the best previously reported (Table II).

Isopropenylcyclopropane was produced by dehydration of dimethylcyclopropylcarbinol, this product being obtained from the reaction of methyl cyclopropyl ketone and the Grignard reagent from methyl chloride. Four methods of dehydration were investigated: catalytically over (A) activated alumina, (B) oxalic acid, (C) sulfuric acid, and chemically (D) by the Tschugaeff xanthate method. Table I summarizes the products and yields (from the carbinol) obtained by fractional distillation (25 plates) of the organic material resulting by each method; headings, tailings and residues (largely polymerization products) are not shown in the table because of the inherent difficulty of calculating yields on these mixtures.

TABLE I

| | Method A | B | C | D |
|---|---|---|---|---|
| Isopropenylcyclopropane, % | 12 | 57 | 80 | 24 |
| Methylpentadiene, % | 20 | .. | .. | .. |
| 2,2-Dimethyltetrahydrofuran, % | 10 | 15 | .. | .. |

It will be noted that of the first three methods, the one employing the strongest acid (sulfuric) gave the highest yield of isopropenylcyclopropane. The formation of this hydrocarbon is best explained by a Whitmore-type[4] mechanism involving a carbonium ion, this ion (cyclopropyldimethylcarbonium) apparently being most easily stabilized without rearrangement by expulsion of a proton from one of the methyl groups, rather than by ring rupture or expansion. It is noteworthy that the tertiary hydrogen atom on the cyclopropane ring is not expelled to produce isopropylidenecyclopropane. An explanation of this behavior is possible if it is recalled that the cyclopropane group sometimes appears to have many of the attributes of a double bond and the structure of isopropenylcyclopropane may thus be considered as somewhat analogous to that of isoprene. This would account for the failure in the present case of hydrogen to be expelled according to Saytzeff's rule (since its nature would be somewhat vinylic) and for the consequent expulsion of a hydrogen atom from a methyl group normally low in reactivity, to form the pseudoconjugate isopropenylcyclopropane, stabilized to some extent by resonance. Further, the strain of a double bond attached to a three membered ring may also be a factor. Since more than one mechanism is apparently involved in methods (A) and (B), it appears that as the acid strength of the catalyst is increased, the reaction proceeds through the carbonium ion to a greater extent. Inasmuch as nothing except isopropenylcyclopropane was found when method C was used, the dehydration over sulfuric acid must have proceeded almost exclusively through the carbonium ion mechanism.

The structure of isopropenylcyclopropane was proved by an ozonolysis experiment (on a sample prepared by method C) from which methyl cyclopropyl ketone was isolated and identified through its semicarbazone; a mixed melting point with the corresponding derivative of an authentic sample of the ketone showed no depression. The physical properties of a sample of isopropenylcyclopropane of 99.4 mole per cent. purity are given in Table II. In order to verify the identity of the isopropenylcyclopropane prepared by the other three methods, a series of mixed melting points were determined with a portion of the hydrocarbon whose structure had been proved by ozonolysis; no significant depression occurred with any of the samples.

The preparation of isopropylcyclopropane by the hydrogenation of isopropenylcyclopropane under mild conditions was investigated. In the

(1) This paper forms part of a thesis which will be submitted by Ross Van Volkenburgh to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The investigation was sponsored by the American Petroleum Institute (Research Project 45) in coöperation with The Ohio State University Research Foundation.

(2) U. S. Industrial Chemicals, Inc., 60 E. 42nd Street, New York, N. Y.

(3) Herr, Whitmore and Schiessler, THIS JOURNAL, **67**, 2061 (1945).

(4) Whitmore, *ibid.*, **54**, 3274 (1932).

TABLE II

| | B. p., °C. (760 mm.) | F. p., °C. | $d^{20}_4$ | $n^{20}D$ | Estimated purity[a] |
|---|---|---|---|---|---|
| Ethylcyclopropane (this work) | 35.94 | −149.41 | 0.6839 | 1.3786 | 99% |
| Ethylcyclopropane (Whitmore)[3] | 36.0 | ..... | .... | 1.3784 | .. |
| Isopropenylcyclopropane (this work) | 70.41 | −102.36 | .7514 | 1.4254 | 99.4 |
| Isopropenylcyclopropane (Van Keersbilck[7]) | 69.5 to 70.0/751 | ..... | .74999 | 1.42524 | .. |
| Isopropylcyclopropane (this work) | 58.7 | −118.3 | .6889 | 1.3833 | 85 |
| 2-Methylpentane[8] | 60.27 | −153.68 | .6532 | 1.3715 | .. |
| 2,3-Dimethylbutane[8] | 57.99 | −128.41 | .6616 | 1.3750 | .. |

[a] These values were calculated from cryoscopic data. For isopropenylcyclopropane the $\Delta t$/mole per cent. impurity was determined as 0.25°, and by use of this datum and analysis of the freezing curve the "100% pure" freezing point for this hydrocarbon was calculated to be −102.20°. Likewise for isopropylcyclopropane the $\Delta t$/mole per cent. impurity was 0.20° and the "100% pure" freezing point was −115.24°.

three trials, the best sample of isopropylcyclopropane[5] obtained (see Table II) was only 85 mole per cent. pure as calculated from cryoscopic data. The chief impurity appeared to be 2-methylpentane formed by rupture of the cyclopropane ring at the bond adjacent to the side chain; 2,3-dimethylbutane (the other possible product formed by ring rupture) was not detected.

While the completely preferential hydrogenation of a double bond in the presence of a cyclopropane ring would seem feasible in consideration of the severity of conditions required for rupturing the cyclopropane ring,[6] the present case appears to be an exception. This may be explained if, as before, isopropenylcyclopropane is considered to be pseudoconjugated. It may then be proposed that some addition of hydrogen proceeded "1,4-," as in the case of a truly conjugated diene, leading to rupture of a ring C–C bond adjacent to the side chain, with the intermediate formation of 2-methyl-2-pentene and finally 2-methylpentane.

When a sample of about 80% pure isopropylcyclopropane was hydrogenated under conditions vigorous enough to cause hydrogenolysis, 2,3-dimethylbutane was the major component of the resulting mixture.[5] 2-Methylpentane (the impurity in the isopropylcyclopropane hydrogenated) was detected as only a minor component, and an unidentified paraffin was also present in very small amount. No unchanged isopropylcyclopropane was found. This study seems to indicate that in the hydrogenation of isopropenylcyclopropane under mild conditions, the 2-methylpentane impurity was not formed by hydrogenolysis of the newly formed isopropylcyclopropane, but by some mechanism such as that proposed above.

Striking evidence for conjugation is found in the boiling point of isopropenylcyclopropane which is 11.7° higher than that of isopropylcyclopropane. This suggests that isopropenylcyclopropane is comparable to 2,3-dimethyl-1,3-butadiene which, due to conjugation, boils about 13.3° higher than 2,3-dimethyl-1-butene; the latter, by contrast, actually boils 2.4° lower than the saturated analog, 2,3-dimethylbutane. Similarly, the refractive index of isopropenylcyclopropane shows an exaltation of 0.0267 (at 20°) which approaches the exaltation of 0.0332 exhibited by 2,3-dimethyl-1,3-butadiene.

## Experimental

**Methyl Cyclopropyl Ketone.**—The commercial product[2] was distilled at about 25-plate efficiency, 78% of the charge being obtained as good product with the following physical properties: b. p. 111.2° (760 mm.), f. p. −68.3°, $d^{20}_4$ 0.8991, $n^{20}D$ 1.4250.

**Ethylcyclopropane.**—The apparatus and general procedure described by Whitmore and his co-workers[3] were used with the following exceptions: The hydrazone from 74 g. (0.879 mole) of methyl cyclopropyl ketone was prepared using 122 g. (2.06 moles) of hydrazine hydrate,[9] 200 ml. of diethylene glycol, and 5 ml. of acetic acid. The hydrazone was cooled and dropped slowly into a solution of 60 g. (1.5 moles) of sodium hydroxide in 200 ml. of diethylene glycol at a temperature of 180–200°. The hydrocarbon collected weighed 47.0 g. (76% yield from the ketone) and had a refractive index of 1.3786 at 20°. Distillation of this material at about 15-plate efficiency gave 44.2 g. of constant index material ($n^{20}D$ 1.3786), a 72% yield. The physical properties of ethylcyclopropane (Table II) were determined on a center cut from the redistillation of the constant index fractions. The product did not absorb bromine from a carbon tetrachloride solution in the cold.

**Dimethylcyclopropylcarbinol.**—Methyl chloride was added as a gas below the liquid surface to 267 g. (11.0 moles) of magnesium turnings in 4 liters of ether in a 5-gallon copper-lined reactor provided with a steel stirrer. Addition was continued until all of the magnesium turnings were used up, after which the mixture was refluxed about an hour before the slow addition of 841 g. (10.0 moles) of methyl cyclopropyl ketone in 2 liters of dry ether was begun. When the last of the ketone had been added and reflux had been maintained for a period of two days, the reaction mixture was hydrolyzed with 1 liter of saturated ammonium chloride solution. (A large excess of ammonium chloride is undesirable as it apparently converts significant quantities of the newly formed carbinol to a chloride which appears as "tailings" when the product is distilled.) The mixture was then washed, stripped of ether, and distilled at about 20-plate efficiency to obtain 679 g. (68% yield from ketone) of good dimethylcyclopropylcarbinol, 146 g. (15% yield) of material

(5) This sample was examined spectroscopically (infrared) by F. P. Hochgesang of the Socony-Vacuum Laboratories, Paulsboro, N. J.

(6) Shortridge, Craig, Greenlee, Derfer and Boord, THIS JOURNAL, **70**, 946 (1948).

(7) Van Keersbilck, *Bull. soc. chim. Belg.*, **38**, 205 (1929).

(8) "Selected Values of Properties of Hydrocarbons," N. B. S. Circular C461, Rossini, *et al.*, U. S. Gov. Printing Office, Washington, D. C., p. 38.

(9) Purchased from the Edwal Laboratories.

worth redistillation and 50 g. of a high boiling residue. In a subsequent run of 5-mole proportions over twice as much of the high boiling material was obtained and had the following physical properties: b.p. *ca.* 73° (50 mm.), $n^{20}D$ 1.443 to 1.495; this material contained chloride (or chlorides), the probable genesis of which has been explained. The physical properties determined for the carbinol follow, the values in brackets are those of Bruylants[10] given for comparison: b.p. 123.4° (760 mm.) (123.4 to 123.6° (752 mm.)), $d^{20}_4$ 0.8842 (0.88063), $n^{20}D$ 1.4337 (1.43257), f. p. −43.0°.

**Isopropenylcyclopropane.**—Dimethylcyclopropylcarbinol was dehydrated in four different ways:

**A. Over Activated Alumina.**—A 2.4 (i.d.) × 120.0 cm. pyrex tube was placed in a vertical furnace and packed with 4–8 mesh, Grade F-1, Alorco alumina which was activated by heating to 300° and passing air through the tube overnight. The tube and its contents were cooled to 250° and the carbinol (154 g., 1.54 moles) was passed through at a rate of one drop per three seconds at this temperature. The conversion based on the water collected was 49%, and the yield of organic material was 95 g. This was distilled at about 30-plate efficiency with the results shown in Table I. No evidence was found for the presence of unchanged carbinol, and a subsequent run at 300° showed that the yield of isopropenylcyclopropane was decreased at the higher temperature, more of the other products being formed.

**B. Over Oxalic Acid.**—The carbinol (197 g., 1.97 moles) was dehydrated by boiling it with 10% its weight of oxalic acid and distilling off the low boiling products as they formed. After washing and drying, the product weighed 145 g. and was distilled at about 30-plate efficiency. The analysis of this distillation is shown in Table I.

**C. Over Sulfuric Acid.**—Twelve drops of concentrated sulfuric acid were added to 152 g. (1.52 moles) of the carbinol in a half-liter flask attached to a glass packed distilling column. The mixture was heated to a gentle boil, and the hydrocarbon was distilled through the column and collected as the carbinol was dehydrated. The crude product, washed and dried, weighed 104 g. and was distilled at about 20-plate efficiency (see Table I).

**D. By the Tschugaeff Xanthate Method.**[11]—Two liters of reagent grade "xylene" were dried by percolation through a column of silica gel and placed in a 5-liter flask equipped with a stirrer, dropping funnel and reflux condenser. Sixty-nine grams (1.76 moles) of metallic potassium, scraped free of oxide, were added, and the flask was heated until the potassium melted. The addition of 176 g. (1.76 moles) of dimethylcyclopropylcarbinol was begun dropwise and continued until complete (one and one-half hours). Carbon disulfide (151 g., 1.98 moles) was added slowly to the cooled mixture, after which 286 g. (2.02 moles) of methyl iodide was added over a period of one and one-half hours. After standing overnight, the mixture was refluxed at 65° for about ten hours and then was allowed to cool and stand for several days at room temperature. The solid potassium iodide was removed by filtration and the organic material adhering to it was leached with xylene. The bulked xylene solution of the xanthate was placed in a flask attached to a column packed with glass helices, and the xanthate was decomposed by heating at 130–135° for about eight hours, the hydrocarbon being distilled from the mixture as it formed. The distillate was washed with 25% sodium hydroxide, steam distilled, and fractionated at about 20-plate efficiency to obtain 80 g. of material (b.p. 53–80°) which smelled strongly of organic sulfur compounds. This product was washed again with 25% sodium hydroxide, then with water, and was dried over anhydrous sodium sulfate before being treated with sodium in liquid ammonia. The treated material still had a strong odor so it was shaken with saturated mercuric chloride solution and water, and, after steam distillation, was washed with dilute hydrochloric acid and dried over sodium sulfate. By distillation of this product at about 30-plate efficiency nothing except isopropenylcyclopropane was detected, but the yield was low (Table I).

**Proof of Structure of Isopropenylcyclopropane by Ozonolysis.**—A portion (11.79 g.) of the isopropenylcyclopropane obtained from the sulfuric acid dehydration of dimethylcyclopropylcarbinol was ozonized by the procedure and in the apparatus described by Henne and Perilstein,[12] acetic acid being used as the solvent. The solution of the ozonide was poured into 25 ml. of water, 5 g. of zinc dust was added, and, after standing overnight, the mixture was heated on a steam-bath for one-half hour. After decantation from the zinc, the organic material was distilled at about 20-plate efficiency, that portion boiling under 100° being collected. This water–ketone fraction was treated with 10 g. of semicarbazide hydrochloride, 15 g. of sodium acetate, and sufficient water to make a total volume of 100 ml. The mixture was heated on a steam-bath for a few minutes, and, on cooling, 6.3 g. (32% yield) of the crude semicarbazone crystallized. After 4 recrystallizations from absolute alcohol 3.2 g. (16% yield) of the semicarbazone remained and had a melting point of 121.4 to 122.5°. The semicarbazone prepared from an authentic sample of methyl cyclopropyl ketone in the same manner melted at 121.7 to 122.4°, and a mixed melting point showed no depression.

**Isopropylcyclopropane.**—A sample (56 g., 0.68 mole) of isopropenylcyclopropane was hydrogenated in a glass liner over Raney nickel at 40° and a pressure of 900 p.s.i. Fractionation of the hydrogenate indicated that the reduction was only about 40% complete, and that some 2-methylpentane (ring fission product) was present. A "best" fraction from this distillation had the following properties: b. p. 58.2 to 58.6° (uncor.), $n^{20}D$ 1.3850 to 1.3851.

A second hydrogenation was carried out as before using 70 g. (0.86 mole) of isopropenylcyclopropane (known purity 98.7 mole per cent.); the maximum temperature reached was 97°, and the maximum pressure 800 p.s.i. The product, separated from the nickel catalyst, was washed with 10% permanganate solution several times, but after steam distillation it still showed unsaturation. Instead of further permanganate treatment, the material was distilled at 20-plate efficiency. The main portion boiled at 58.5 to 58.8°, but the refractive index after rising to a maximum of 1.3842 for the second fraction dropped off gradually to 1.3774 toward the end of the distillation. It was evident that far more 2-methylpentane was present than that contained in the sample hydrogenated. The amount of impurity present in the hydrogenate, assuming the impurity to be 2-methylpentane, was calculated to be 12 to 13 g., or about 17 mole per cent. of the charge.

In a third attempt, 80 g. of isopropenylcyclopropane were hydrogenated over Raney nickel catalyst, at 35–40° and 1100 p.s.i., with 90% of the theoretical amount of hydrogen absorbed. The hydrocarbon recovered by washing the crude hydrogenate with water, steam distilling, and drying over anhydrous sodium sulfate was 82% of theory; it was distilled at about 30-plate efficiency. The first 6% of the distillate boiled from 57.9 to 58.6° and may have contained a little 2,3-dimethylbutane, but the refractive index, 1.3834 at 20°, was only slightly lower than the maximum which followed immediately on the curve. The next 45% boiled from 58.6 to 58.8° while the refractive index slowly dropped from 1.3836 to 1.3829; the physical properties listed in Table II were determined on this portion. Distillation was continued until a temperature of 59.0° was reached; meanwhile the refractive index dropped to 1.3811, presumably due to 2-methylpentane which would be expected to appear in the tailings. By a study of infrared absorption spectra,[5] 2-methylpentane was identified as an impurity in the portion of the distillate used in determining physical properties; 2,3-dimethylbutane was not detected and was judged to comprise less than 6% of the sample, if present at all.

(10) Bruylants, *Bull. soc. chim. Belg.*, **36**, 153 (1927).

(11) Tschugaeff, *Ber.*, **32** 3332 (1899).

(12) Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

**Hydrogenolysis of Isopropylcyclopropane.**—A sample of isopropylcyclopropane (b. p. 58.5 to 58.8°, $n^{20}D$ 1.3823–1.3841) was hydrogenated over 10% its weight of nickel-on-kieselguhr catalyst. Absorption of hydrogen began at 150° and 1250 p. s. i. When absorption had ceased, the temperature was raised to 200°, whereupon further absorption occurred (from 1220 p. s. i.). Further increase in temperature did not cause additional reaction. The hydrogenate was washed with water and dried over anhydrous sodium sulfate; this material (b. p. 53–61° (760 mm.), $n^{20}D$ 1.3740) was sent for infrared analysis.

**Acknowledgment.**—Sincere appreciation is expressed to Dr. F. P. Hochgesang for his determination and interpretation of the infrared absorption spectra of some of the hydrocarbon samples described herein.

## Summary

Ethylcyclopropane, isopropenylcyclopropane and isopropylcyclopropane have been synthesized from methyl cyclopropyl ketone. Evidence for the behavior of isopropenylcyclopropane as a pseudoconjugated system has been presented.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY AND THE AMERICAN PETROLEUM INSTITUTE RESEARCH PROJECT 45]

# A New Synthesis of Monoalkylcyclobutanes: Reduction of Neopentyl Type Tribromides[1]

BY JOHN M. DERFER, KENNETH W. GREENLEE AND CECIL E. BOORD

## Introduction

Hydrocarbons of the cyclopropane or cyclobutane series have been produced by the dehalogenation (or dehydrohalogenation) of mono-, di- and tetrahalo derivatives of neopentane.

Whitmore[2,3,4] and his co-workers have shown that the reaction of neopentyl chloride with an equivalent amount of metallic sodium gives a 25% yield of 1,1-dimethylcyclopropane; the overall yield of this hydrocarbon is increased to 51% when a four-fold excess of the chloride is employed. When propyl sodium is used instead of metallic sodium, the cyclopropane hydrocarbon is formed in 75% yield.

The debromation of *sym*-dibromoneopentane by either the Gustavson[5a] or the Hass–McBee[6] method gives good yields of 1,1-dimethylcyclopropane.[3,5b,7]

The products from the reduction of pentaerythrityl tetrabromide by the Gustavson method have been identified by Whitmore and Williams[8] as 2-methyl-1-butene and methylenecyclobutane in the ratio of about 1:11, respectively; Murray and Stevenson,[9] using Raman spectra, found traces of spiropentane also to be present. Slabey[10] found that when sodium iodide and sodium carbonate are added to the reaction mixture, the hydrocarbon product (obtained in 79–89% yield) consists of spiropentane (25%), methylenecyclobutane (56%), 2-methyl-1-butene (15%) and traces of 1,1-dimethylcyclopropane. When the Hass–McBee procedure is employed in the reduction of pentaerythrityl tetrabromide, a 38% yield of hydrocarbon material is obtained; this consists of 47–60% of spiropentane and smaller amounts of methylenecyclobutane and 2-methyl-1-butene.[10,11]

There is no indication in the literature that any investigation has ever been made concerning the debromination (or dehydrobromination) of tribromides containing the neopentyl structure, or even that such halides have ever been prepared. The present work not only closes this gap, but also appears to furnish a general and practical method for the preparation of monoalkylcyclobutanes with the possible exception of methylcyclobutane.

The general scheme employed in this work has been to prepare neopentyl type tribromides from the corresponding trihydric alcohols and to treat them with zinc by the Hass–McBee[6] procedure. Alkylidenecyclobutanes are formed in about 50% yield and can be hydrogenated to the corresponding alkylcyclobutanes. The method has been applied to three tribromides: 1,1,1-tris-(bromomethyl)-propane, 1,1,1-tris-(bromomethyl)-2-methylpropane and 1,1,1-tris-(bromomethyl)-ethane.

## Discussion

**Reduction of 1,1,1-tris-(Bromomethyl)-propane.**—The reaction of this tribromide with zinc by the Hass–McBee procedure[6] produced a mixture of hydrocarbons in yields of 90–93% of theory. Fractionation of this material at about

(1) The material in this paper was abstracted from the dissertation submitted by John M. Derfer to the Graduate School of the Ohio State University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in 1946. Parts of this work were presented before the Organic Division at the 109th and 111th meetings of the American Chemical Society; see also THIS JOURNAL, **67**, 1863 (1945).

(2) Whitmore, Popkin and Pfister, *ibid.*, **61**, 1616 (1939).

(3) Whitmore, Popkin, Bernstein and Wilkens, *ibid.*, **63**, 124 (1941).

(4) Whitmore and Zook, *ibid.*, **64**, 1783 (1942).

(5) (a) Gustavson, *J. prakt. Chem.*, **36**, 300 (1887); (b) Gustavson and Popper, *ibid.*, **58**, 458 (1898).

(6) Hass, McBee, Hinds and Glusenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936).

(7) Shortridge, Craig, Greenlee, Derfer and Boord, THIS JOURNAL, **70**, 946 (1948).

(8) See footnote to article by Bauer and Beach, *ibid.*, **64**, 1142 (1942).

(9) Murray and Stevenson, *ibid.*, **66**, 314 (1944).

(10) Slabey, *ibid.*, **68**, 1335 (1946).

(11) Murray and Stevenson, *ibid.*, **66**, 812 (1944).

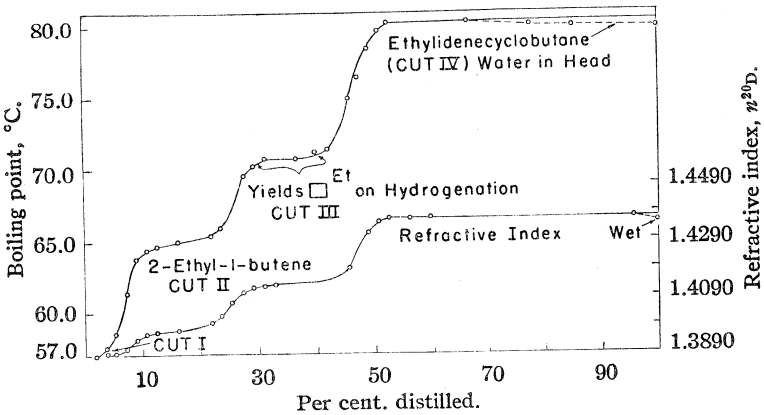



Fig. 1.—Curves describing the distillation of the crude product from the reduction of 1,1,1-tris-(bromomethyl)-propane.

40-plate efficiency[12] (Fig. 1) separated it into four cuts boiling at approximately 56, 64, 70 and 80°; these fractions constituted 3 (estm.) 12, 18, and 54% of the crude hydrocarbon mixture by weight, respectively and will be designated as Cut I, Cut II, Cut III and Cut IV.

The highest boiling and preponderant fraction (Cut IV) was shown to be a very pure individual compound by its time–temperature freezing curve and it was identified as ethylidenecyclobutane (not previously reported) by an ozonolysis experiment[13] from which both acetaldehyde and cyclobutanone were isolated and identified. Hydrogenation of ethylidenecyclobutane over Raney nickel at low pressures and temperatures gave ethylcyclobutane exclusively and quantitatively; the physical properties for this material were an improvement over those reported by Wibaut[14] for ethylcyclobutane prepared by another method.

Refractionation of Cut III at about 40-plate efficiency and determination of densities, refractive indices and standard boiling points on about every third fraction showed that this material was a mixture, and that it could not be separated by fractionation (Fig. 2) on the best column available (40-plates). The mixture gave ethylcyclobutane exclusively on hydrogenation, thus limiting the possible constituents to five substances: the two ethylcyclobutenes, ethylidenecyclobutane, vinylcyclobutane and ethylcyclobutane, itself. Oxidation of Cut III with chromic anhydride and glacial acetic acid failed to attack about 30% of it; the unoxidized material was identified as ethylcyclobutane on the basis of its physical properties and a mixed freezing point determination with an authentic sample of this hydrocarbon. By oxidation of Cut III with aqueous sodium dichromate–sulfuric acid solution, a small amount of material was isolated with physical properties in good agreement with those of cyclobutane carboxylic acid; esterification of this material with ethyl alcohol produced a substance which had approximately the same boiling point as the ethyl ester of cyclobutane carboxylic acid, and a carbon–hydrogen analysis gave values in fair agreement with the values calculated for this ester. Identification of this acid in the oxidation products indicated that a second component (about 70% of Cut III) was vinylcyclobutane; no evidence for the presence of either of the ethylcyclobutenes was found. The infrared absorption spectrogram of Cut III (Fig. 3) shows the characteristic absorption of an alpha olefin at 6.1 microns; vinylcyclobutane is the only olefin which would both exhibit this characteristic and hydrogenate to ethylcyclobutane.

Since both Cut III and Cut IV can be hydrogenated quantitatively to ethylcyclobutane, the over-all yield of ethylcyclobutane which can be produced by this reaction is about 65% of theory, based on the tribromide.

Cut II was identified as 2-ethyl-1-butene on the basis of its physical properties and by a mixed freezing point determination with an authentic sample of 2-ethyl-1-butene.

Cut I was shown conclusively to be 1-methyl-1-ethylcyclopropane (hitherto unreported) by subjecting it to hydrogenation at high pressures and temperatures and identifying the 2,2-dimethylbutane (neohexane) produced in this manner. (This type of hydrogenation is known to rupture the cyclopropane ring by splitting the bond opposite to the gem-substituted carbon atom.[7])

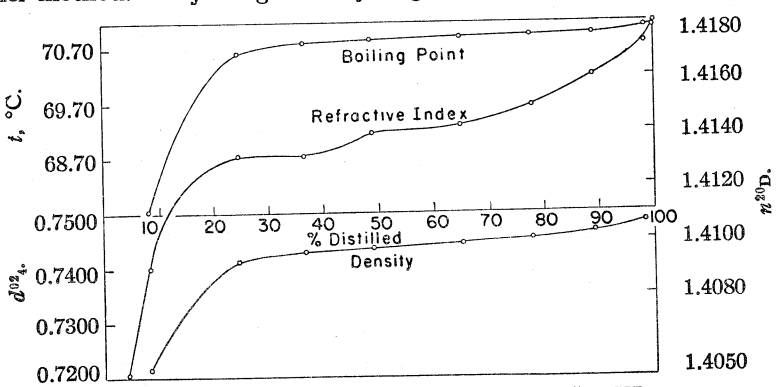



Fig. 2.—Curves describing the redistillation of Cut III.

Reduction of 1,1,1-tris-(bromomethyl)-propane by zinc in 45–80% *aqueous ethanol* produced chiefly an ether, tentatively identified as ethyl 1-ethylcyclopropylcarbinyl ether. No apparent reaction

(12) All plate ratings given in this paper represent estimates of column efficiency under actual operating conditions.

(13) Arnold, Master's Thesis, The Ohio State University, 1945.

(14) Wibaut, *Rec. trav. chim.*, 329 (1939).

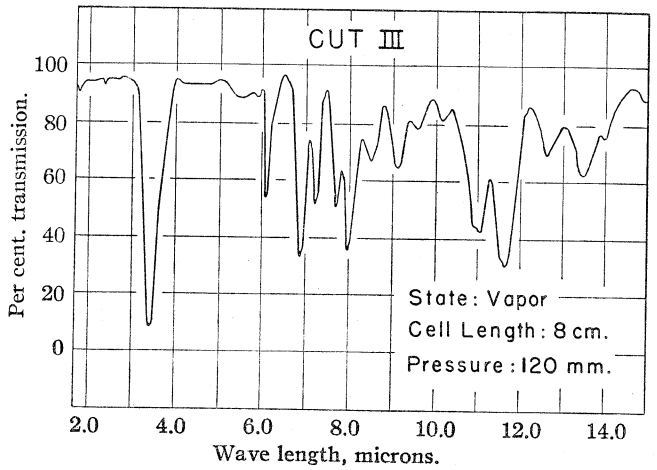



Fig. 3.—Infrared absorption spectrogram of Cut III.

took place between zinc and the tribromide in *anhydrous dioxane;* when a small amount of water was added to the mixture, reaction occurred, but no single product could be isolated.

**Reduction of 1,1,1-tris-(Bromomethyl)-2-methylpropane.**—The reaction of this tribromide with zinc by the Hass–McBee procedure produced a 97% yield of crude hydrocarbon material. Fractionation of this material at about 40-plate efficiency (Fig. 4) separated it into a forerun containing no constant refractive index or constant boiling fractions and a higher boiling cut (about 50% of the charge) which distilled at an essentially constant temperature (107°) and had a constant refractive index (1.4459).

The 107° material was shown to be a very pure individual compound by its time-temperature freezing curve, and was identified as isopropylidenecyclobutane (not previously reported) by an ozonolysis experiment from which both acetone and cyclobutanone were isolated and identified. Hydrogenation of isopropylidenecyclobutane over Raney nickel at low pressures and temperatures gave isopropylcyclobutane exclusively; physical properties determined on this material were an improvement over those reported for it by Kasansky.[15] The forerun was hydrogenated to saturation over Raney nickel at low pressures and temperatures; about 57% of the theoretical amount of hydrogen was absorbed, indicating that about this percentage of the forerun consisted of olefinic hydrocarbons. Fractionation of the hydrogenated material at about 40-plate efficiency separated it into two cuts boiling 81.7–83.2° and 88.8–92.1°. The lower boiling material was shown to be 1-methyl-1-isopropylcyclopropane (hitherto unreported) by a comparison of the infrared absorption spectrograms of its high pressure hydrogenation product (Fig. 5-A) with that of the expected product, 2,2,3-trimethylbutane (Fig. 5-B); these spectrograms are, for practical purposes, identical. The higher boiling material was found to be a mixture of 2,3-dimethylpentane and isopropylcyclobutane by a comparison of physical data (Table I), including infrared absorption spectrograms (Fig. 5-C-D-E). All characteristic bands of these two substances are present in the spectrogram of the mixture. By analogy with the corresponding study of the reaction producing ethylidenecyclobutane as the chief product, isopropylcyclobutane was undoubtedly a component of the unhydrogenated forerun; the 2,3-dimethylpentane identified in the hydrogenated material came from olefins with the same carbon skeleton, chief among which, by further analogy, was undoubtedly 3-methyl-2-ethyl-1-butene. Some isopropenylcyclobutane may also have been present, but the presence of one or both of the isopropylcyclobutenes seems improbable.

TABLE I

| | 2,3-Dimethylpentane | Isopropylcyclobutane | This material |
|---|---|---|---|
| B. p., °C. (760 mm.) | 89.8 | 92.70 | 88.8–92.1 |
| $d^{20}_4$ | 0.6951 | 0.7376 | 0.7213 |
| $n^{20}D$ | 1.3920 | 1.4080 | 1.4013–1.4087 |

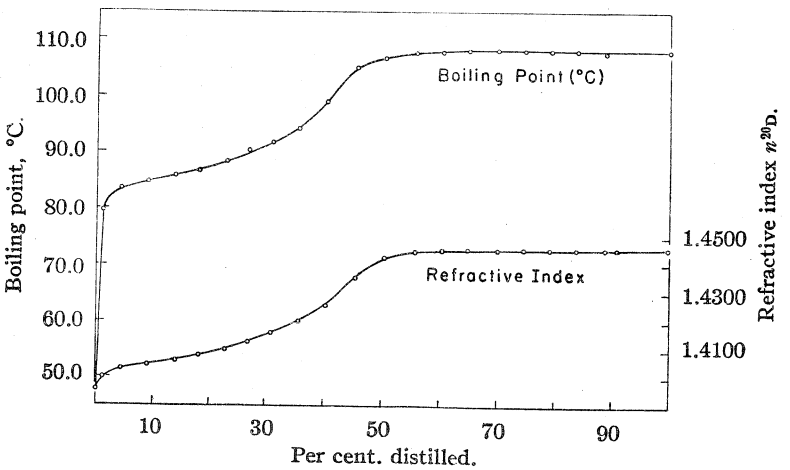



Fig. 4.—Curves describing the distillation of the crude product from the reduction of 1,1,1-tris-(bromomethyl)-2-methylpropane.

**Reduction of 1,1,1-tris-(Bromomethyl)-ethane.**—This tribromide was treated with zinc by the Hass–McBee procedure in the usual manner. The highest yield of hydrocarbon material obtained was 65%. Fractionation of this material at about 40-plate efficiency (Fig. 6) separated it into three cuts boiling at approximately 20, 31 and 37–43°; these fractions were

(15) Kasansky, *Ber.*, **69**, 950 (1936).

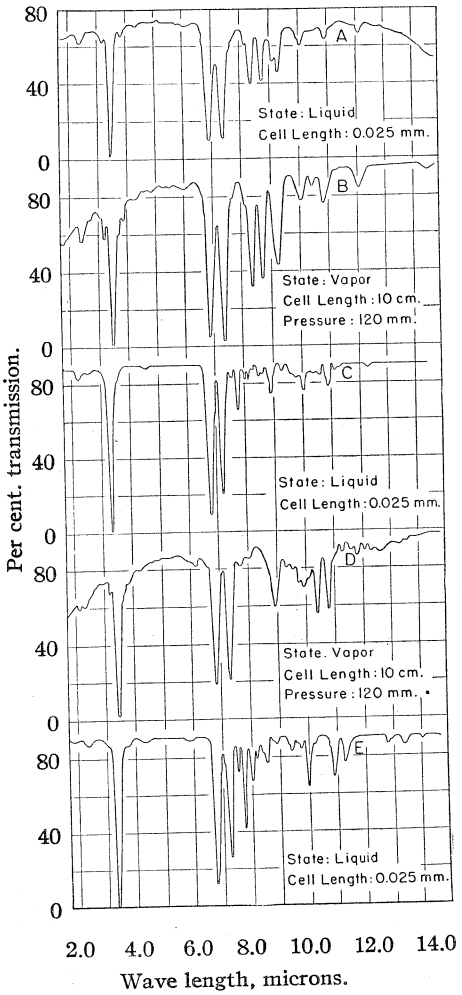



Fig. 5.—Infrared absorption spectrograms of: A, product formed by the hydrogenation of 1-methyl-1-isopropylcyclopropane; B, authentic sample of 2,2,3-trimethylbutane; C, 90° cut in the distillation of the hydrogenated forerun from the isopropylidenecyclobutane synthesis; D, authentic sample of 2,3-dimethylpentane; E, isopropylcyclobutane.

about 15, 38 and 47% of the crude hydrocarbon mixture by weight, respectively.

The 37–43° cut (expected to be relatively pure methylenecyclobutane) was a mixture ($n^{20}$D 1.3970–1.4203) which could not be separated into its components by redistillation at about 25-plate efficiency. About 78% of the theoretical amount of hydrogen was absorbed when this mixture was hydrogenated to saturation at low pressures and temperatures. Fractionation of the hydrogenate at about 20-plate efficiency produced no constant refractive index material (b. p. 34.6–36.6°, $n^{20}$D 1.3800–1.3880). An infrared absorption spectrogram of a cut soon after the obvious headings showed the material to be largely methylcyclobutane; no positive evidence as to the identity of the impurity could be obtained from the spectrogram. None of the fractions crystallized at liquid air temperature, but rather formed a viscous sirup. It is believed that methylcyclobutane of good purity could be obtained if the reaction were carried out on a large enough scale to permit the use of high-efficiency columns and other techniques not used in this work because of the small quantities of material involved. The original unhydrogenated material probably consisted of methylenecyclobutane (b. p. 42.2°, $n^{20}$D 1.4208), methylcyclobutane (b. p. 36.6°, $n^{20}$D 1.3875), and an unidentified impurity.

The 31 and 20° cuts were identified as 2-methyl-1-butene and 1,1-dimethylcyclopropane, respectively, as anticipated.

From the reaction residue were isolated two high-boiling by-products tentatively identified as 1-methylcyclopropylcarbinol and di-(1-methylcyclopropylmethyl) ether. Their formation was attributed to the reaction of 1-methyl-1-(bromomethyl)-cyclopropane with water produced by the interaction of protons with carbonate ions, carbonic acid thus being formed; evolution of carbon dioxide was noted during the reaction.

## Reaction Mechanisms

Logical mechanisms have been proposed for the formation of all products from these reactions. These mechanisms will be demonstrated for the reaction which produced ethylidenecyclobutane as the chief product, since this reaction has been described the most completely.

The products identified from this reaction were ethylidenecyclobutane (I), vinylcyclobutane (II), 1-methyl-1-ethylcyclopropane (III), ethylcyclobutane (IV), and 2-ethyl-1-butene (V). It will be noted that the products from this reaction fall into two categories on the basis of their carbon–hydrogen ratios; I and II contain both a cycle and a double bond, whereas the other products contain *either* a cycle *or* a double bond. This suggests that two different mechanisms are involved simultaneously.

We believe that the first reaction to occur is the closing of a cyclopropane ring, as shown in Equation 1. Isolation of ethyl 1-ethylcyclopropylcarbinyl ether from the reaction of this tribromide with zinc in ethanol supports this belief. The intermediate monobromide (1-ethyl-1-bromomethylcyclopropane) could not be isolated when the tribromide was reacted with a limited amount of zinc (in various solvents); this is as would be expected, since the monobromide is somewhat allylic in nature due to the cyclopropane ring embracing the beta and gamma carbon atoms. Additional zinc would be expected to react with this "allylic type" bromide in preference to reaction with a new molecule of tribromide when both were present in the reaction mixture.

The formation of I and II is best explained by a Whitmore-type[16] mechanism. Zinc bromide acts

(16) Whitmore, THIS JOURNAL, 54, 3274 (1932).

as the acid (electron seeking) reagent in much the same manner as it catalyzes the conversion of an alcohol to an alkyl halide in the presence of a hydrogen halide. The carbonium ion produced by Equation 2 undergoes rearrangement with ring expansion to form a new carbonium ion which stabilizes itself by expulsion of a proton to form I (Equation 3). In the formation of II, the same rearranged carbonium ion is formed, but migration of the alpha hydrogen atom with its bonding electrons (to the adjacent ring carbon atom) precedes the expulsion of a proton, as shown in Equation 4. It is possible that I rearranges to II in the presence of zinc bromide, but this seems less likely.

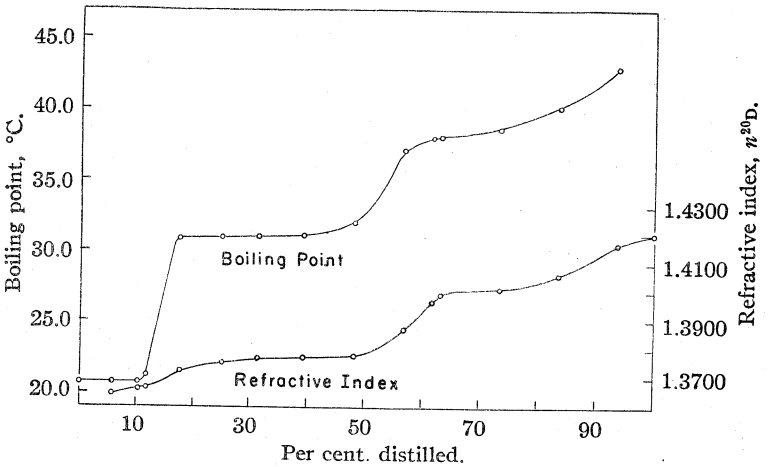



Fig. 6.—Curves describing the distillation of the crude product from the reduction of 1,1,1-tris-(bromomethyl)-ethane.

The formation of the other three products must involve an organozinc intermediate which can abstract an active hydrogen, probably by reaction with the enol form of the solvent, acetamide.

III is then formed without rearrangement, according to Equation 5 (HQ is acetamide or other molecule containing an active hydrogen).

IV results through a Whitmore-type rearrangement of the intermediate monobromide (as in the case of I), followed by the formation of an organozinc bromide which then reacts with an active hydrogen (Equation 6). It is not surprising that a bromide ion should combine with the rearranged carbonium ion as shown, since the concentration of bromide ions in the reaction mixture must be high, and since recombination with an original negative ion is one possibility suggested by Whitmore for rearrangements involving carbonium ions.

V is probably formed according to Equation 7. The initial electron shift is similar to that in Equation 3, except that the methylene group does not accompany the electron pair, but becomes positively charged. A methyl group is then formed by way of the organozinc intermediate, as shown. The similarity of this rearrangement to an allylic rearrangement will be noticed; other cases in which the cyclopropane ring appears to have some of the functions of a double bond have been noted.[17]

## Experimental

### Production of Trihydric Alcohols

**1,1,1-tris-(Hydroxymethyl)-propane.**—This triol was purchased from the Heyden Chemical Corporation, Garfield, New Jersey.

**1,1,1-tris-(Hydroxymethyl)-2-methylpropane.**

The procedure was developed by considerably modifying that of Von Marle and Tollens.[18] In a flask suitably equipped, were placed 172 g. (2 moles) of isovaleric aldehyde (Eastman Kodak Co.)and 650 g. (8 moles) of formalin (Merck, C.P.); stirring was started, and the slow addition of solid calcium hydroxide (1 mole) was begun from a side flask, the rate of addition being such that the temperature within the reaction flask remained at 55–65°. The reaction mixture was then heated (with stirring) for twelve hours at 32°, twenty-four hours at 50–60°, and six hours at 85°. The mixture was then filtered by suction, while hot, and evaporated to a volume of 600 ml. This residue was treated with about three times its volume of boiling 95% ethanol, and the solid calcium formate remaining was separated by filtration. The filtrate was stripped of alcohol and distilled at reduced pressure; 156 g. (53% yield, based on isovaleric aldehyde) of the desired triol boiling at 170–175° (6 mm.) was obtained. In subsequent runs, the reaction mixture was subjected to continuous ether extraction, and the triol concentrate obtained (after ether stripping) was treated, as such, with phosphorus tribromide, thus avoiding some decomposition during distillation.

The purified triol is hygroscopic, but a sample of the distilled triol, recrystallized five times from ether and dried for two days *in vacuo*, melted sharply at 82.0–82.1°.

*Anal.* Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 56.74; H, 10.69.

**1,1,1-tris-(Hydroxymethyl)-ethane.**—This triol was prepared from propionaldehyde and formalin by the procedure of Brubaker and Jacobson[19] except that the solid sodium formate was removed by filtration of the acetone solution of the triol which was then purified by crystallization (yield from the aldehyde was 51%). After two recrystallizations from acetone solution this compound melted at 198.0–198.2°.

*Anal.* Calcd. for $C_5H_{12}O_3$: C, 49.98; H, 10.06. Found: C, 50.03; H, 10.21.

### Production of Tribromides

**1,1,1-tris-(Bromomethyl)-propane.**—This compound was prepared from the corresponding triol and phosphorus tribromide by the same procedure as that described by Schurink[20] for the preparation of pentaerythrityl tetrabromide, except that the heating period was at 140°. The orange-red impurity (13% by weight) was removed by filtration from the hot alcohol solution of the tribromide which was then purified by crystallization (59% yield from triol). After two recrystallizations from alcohol solution, the tribromide melted at 94.3°. Separation of the colored impurity was found unnecessary for the present purpose.

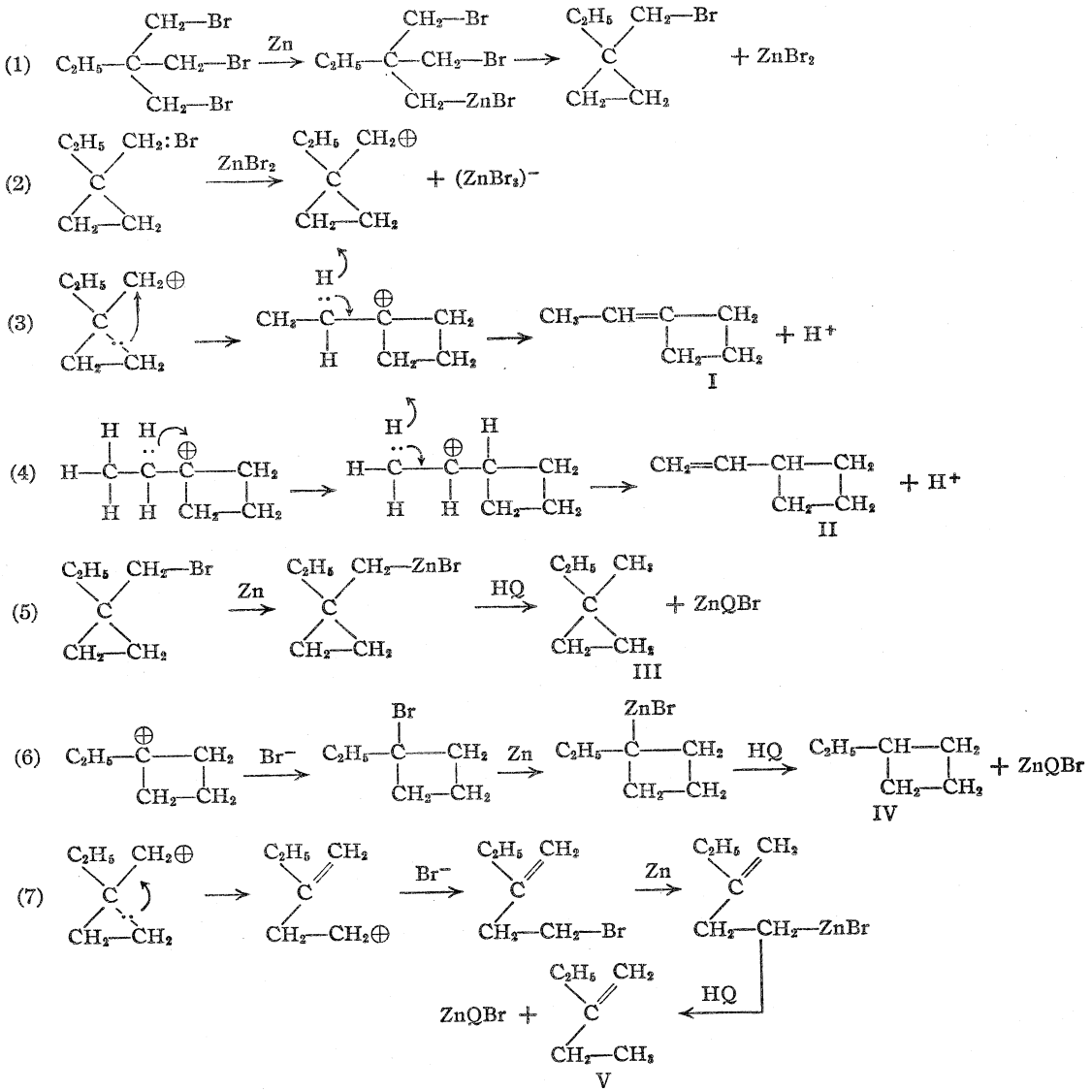
(17) Van Volkenburgh, Greenlee, Derfer and Boord, THIS JOURNAL, **70**, 172 (1948).

(18) Von Marle and Tollens, *Ber.*, **36**, 1342 (1903).

(19) Brubaker and Jacobson, U. S. Patent 2,292,926.

(20) "Organic Syntheses," Coll. Vol. II, Editor A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 476.

EQUATIONS DEMONSTRATING REACTION MECHANISMS




*Anal.* Calcd. for $C_6H_{11}Br_3$: C, 22.35; H, 3.42. Found: C, 22.38; H, 3.49.

**1,1,1-tris-(Bromomethyl)-2-methylpropane.**—This tribromide was prepared from the corresponding triol in the same way as the one above, except that the temperature was 145–150° during the heating period. This compound was a liquid and (after washing) was separated from the usual red impurity by suction filtration; after drying it was purified by vacuum distillation (yield 48%, based on triol). Physical properties were determined on a center fraction: f. p. +1.8°; b. p. 106° (3 mm.); $n^{20}D$ 1.5568; $d^{20}_4$ 1.9122.

*Anal.* Calcd. for $C_7H_{13}Br_3$: C, 24.99; H, 3.89. Found: C, 25.36; H, 3.93.

**1,1,1-tris-(Bromomethyl)-ethane.**—This tribromide (also a liquid) was prepared from the corresponding triol by the same procedure used in preparing 1,1,1-tris-(bromomethyl)-2-methylpropane; it was purified by vacuum distillation (68% yield, based on triol). Physical properties determined were: f. p. +9.2°; b. p. 108° (6 mm.); $n^{20}D$ 1.5593; $d^{20}_4$ 2.0917.

*Anal.* Calcd. for $C_5H_9Br_3$: Br, 77.67: Found: Br, 77.5.

**Production and Identification of Hydrocarbons**

**FROM 1,1,1-TRIS-(BROMOMETHYL)-PROPANE.**—In a flask, suitably equipped and surrounded by an oil-bath, were placed 1062 g. (18 moles) of acetamide (Merck C.P.), 636 g. (6 moles) of sodium carbonate, 27.0 g. (0.18 mole) of sodium iodide, and 392 g. (6 gram atoms) of powdered zinc. The mixture was heated to 110°, and stirring was started as soon as the contents of the flask had softened sufficiently. Crude red tribromide (1431 g., corresponding to 3.17 moles of pure tribromide) was added in small chunks through a side flask. As the hydrocarbon formed, it distilled from the reaction mixture through a 1 × 25 cm. Vigreux column into a series of two traps surrounded by a Dry Ice–acetone-bath. The yield was 244 g. or 93%, based on pure tribromide and the empirical formula $C_6H_{10}$; no significant difference in yield was noted when pure tribromide was used. The crude product was dried by passage through a column of silica gel and was fractionated at about 40-plate efficiency.

**Ethylidenecyclobutane (Cut IV, Fig. 1).**—The details of the ozonolysis of this substance are found elsewhere.[13] Acetaldehyde was identified through its 2,4-dinitrophenylhydrazone, m. p. 156–162° after five recrystallizations.

An authentic sample of this derivative also melted at 156–162°, and the mixed melting point was identical; a mixed melting point with the corresponding derivative of formaldehyde showed a 20° depression. A second ozonolysis product boiling at 100° was identified as cyclobutanone (b. p. 99°) and gave a 2,4-dinitrophenylhydrazone which melted (after two recrystallizations) at 140–142°; this derivative was not further purified, since it already melted higher than the literature value, which has since been shown to be erroneous (see under **Isopropylidenecyclobutane**). Physical properties: b. p. 80.26° (760 mm.), f. p. −105.37°; $d^{20}_4$ 0.7678; $n^{20}D$ 1.4370; $dt/dp$ 0.0505°/mm.

*Anal.* Calcd. for $C_8H_{10}$: C, 87.22; H, 12.27. Found: C, 87.25; H, 12.61.

**Ethylcyclobutane.**—This compound was produced by hydrogenation of ethylidenecyclobutane (1.0 mole) over Raney nickel (5 g.) at temperatures up to 90° on a Burgess–Parr low pressure hydrogenator (pressures up to 50 p. s. i.); the theoretical amount of hydrogen was absorbed. The hydrogenated material was distilled at about 25-plate efficiency to give ethylcyclobutane exclusively; physical properties determined on a center cut were (the values in brackets are those of Wibaut[14]): b. p. 70.64° (760 mm.) (70.7); f. p. −142.85°.[21] (−143.2); $d^{20}_4$ 0.7280 (0.7279); $n^{20}D$ 1.4020 (1.4021).

**Vinylcyclobutane–Ethylcyclobutane (Cut III, Fig. 1).**—Part of Cut III (335 g.) was hydrogenated to saturation over 15 g. of Raney nickel suspended in 20 cc. of ethylcyclohexane; an Aminco high pressure hydrogenation outfit was used, and the temperature was not allowed to exceed 100° (pressure, *ca.* 1000 p. s. i.). Fractionation of this material at about 40-plate efficiency produced (except for a very small amount of "heads") only ethylcyclobutane; physical properties of a center cut were: b. p. 70.64° (760 mm.); f. p. −143.16°; $d^{20}_4$ 0.7278, $n^{20}D$ 1.4021. This material was mixed with about 1/3 its weight of authentic ethylcyclobutane (f. p., −143.11°) and the mixed freezing point determined as −143.17° (no depression).

A portion of Cut III (20 g.) was subjected to oxidation by chromic anhydride in glacial acetic acid, according to the procedure of Chavanne and Becker.[22] About 30% (6.9 g.) of the hydrocarbon material remained unoxidized. Isolated by steam distillation, washed with 5% sodium bicarbonate and water, and dried over a chip of metallic sodium, this product (b. p. 71.8° (760 mm.), $n^{20}D$ 1.4058) exhibited a slight residual unsaturation to bromine. Therefore, the material (7 cc.) was treated exhaustively with permanganate, distilled, and dried over a chip of sodium ($n^{20}D$ 1.4021, the same as ethylcyclobutane). This sample (5 cc.) was mixed with 40 cc. of authentic ethylcyclobutane (f. p. −143.16°); the freezing point of the mixture was −143.17° (no depression). Distillation of the ether extract of the acidified (sulfuric acid) reaction residue produced acetic acid, largely; however, about 7 cc. of material thought to be cyclobutanecarboxylic acid was isolated: b. p. 190–192° (uncor.); $n^{20}D$ 1.4405; $n^{25}D$ 1.4394 (cyclobutanecarboxylic acid b. p. 195°; $n^{25}D$ 1.4403).[23]

Another oxidation of Cut III (90 g.) was carried out according to the procedure of Whitmore, *et al.*[24] Distillation of the lighter-than-water layer (50 g.) at about 10-plate efficiency gave 36.1 g. of ethylcyclobutane, 3.9 g. of intermediates, and 7.4 g. of cyclobutanecarboxylic acid which was then esterified in the usual manner.

*Anal.* Calcd. for ethyl ester ($C_7H_{12}O_2$): C, 65.7; H, 9.5. Found: C, 67.0; H, 10.4. (The material analyzed was distilled directly from the esterification mixture and was insufficient for further purification, hence the noticeable discrepancy between the C–H analysis and theory).

(21) This corresponds to a purity of 99.6 mole % as calculated from cryoscopic data.

(22) Chavanne and Becker, *Bull. soc. chim. Belg.*, **36**, 594 (1927).

(23) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1943.

(24) Whitmore, Homeyer and Trent, U. S. Patent 2,004,066 (1935).

TABLE II

| | This material | Cyclobutanecarboxylic acid: Perkin[25] | Cyclobutanecarboxylic acid: Other sources |
|---|---|---|---|
| B. p. | 190–192 (749 mm.) | 191 (720 mm.) | 189–191[26] |
| $n^{25}D$ | 1.4411 | ..... | 1.4403[23] |
| B. p. of Et ester | 152–154 (749 mm.) | 151 (720 mm.) | 159–162[27] |
| $n^{20}D$ of Et ester | 1.425 | ..... | ..... |

**2-Ethyl-1-butene (Cut II, Fig. 1).**—Cut II was redistilled at about 35-plate efficiency; physical properties determined on a center fraction were (values in parentheses are those listed by Rossini, *et al.*[28]): b. p. 64.69° (760 mm.) (64.95); f. p. −132.02° (−131.92); $d^{20}_4$ 0.6899 (0.6894); $n^{20}D$ 1.3969 (1.3969).

This material was mixed with an equal volume of authentic 2-ethyl-1-butene (f. p., −132.11°), and the mixed freezing point determined as −132.04° (no depression).

**1-Methyl-1-ethylcyclopropane (Cut I, Fig. 1).**—This material was treated exhaustively with permanganate, steam distilled, and refractionated at about 35-plate efficiency. Physical properties were determined on a center cut: b. p. 56.79° (760 mm.), f. p. −130.23°, $n^{20}D$ 1.3888, $d^{20}_4$ 0.7015.

Cut I was then hydrogenated at high temperature (250°) and pressure (2600 p. s. i.). Neohexane was the exclusive product; its physical properties were (values in brackets from Footnote 28 for comparison): b. p. 49.65° (760 mm.) (49.74); $n^{20}D$ 1.3688 (1.3688); $d^{20}_4$ 0.6491 (0.6491).

1,1,1-tris-(Bromomethyl)-propane also reacted with zinc in ethanol by the Gustavson[5a] procedure. The reaction mixture was distilled (1-plate) at atmospheric pressure, and the distillate (clear homogeneous liquid) boiling up to 90° was collected. Dilution of the distillate with about four times its volume of water caused it to separate into two layers. The organic layer (40% yield, based on tribromide and the empirical formula ($C_8H_{16}O$) was treated with sodium in liquid ammonia to remove any residual halide and was fractionated at about 35-plate efficiency. This material was probably ethyl 1-ethylcyclopropylcarbinyl ether (a new compound). Physical properties determined on a center cut were: b. p. 135° (760 mm.) $d^{20}_4$ 0.8352; $n^{20}D$ 1.4209. Mol. refraction: Calcd. for ethyl 1-ethylcyclopropylcarbinyl ether: 39.28; observed: 38.92. *Anal.* Calcd. for $C_8H_{16}O$: C, 74.95; H, 12.58. Found: C, 74.94; H, 12.66.

The infrared absorption spectrogram of this compound appeared to substantiate both the ether linkage (evidenced by a band at about 9 $\mu$) and the cyclopropane ring.[29] The material peroxidized extensively on standing.

**FROM 1,1,1-TRIS-(BROMOMETHYL)-2-METHYLPROPANE.**—This tribromide was treated with zinc in molten acetamide in the same manner as was 1,1,1-tris-(bromomethyl)-propane, the only difference being that a slightly higher reaction temperature (135–140°) was maintained; the yield of crude hydrocarbon material was 97% of theory, based on tribromide and the empirical formula $C_7H_{12}$. The crude hydrocarbon mixture was dried over metallic sodium and fractionated at about 40-plate efficiency (Fig. 4).

**Isopropylidenecyclobutane.**—A part of the 107° cut (Fig. 4) was ozonized and the ozonide decomposed by low pressure hydrogenation according to the procedure of Henne and Perilstein.[30] Acetone was identified by the

(25) Perkin, *J. Chem. Soc.*, **51**, 12 (1887).

(26) Perkin, *ibid.*, **61**, 40 (1892).

(27) Freund and Gudeman, *Ber.*, **21**, 2696 (1888).

(28) Rossini, *et al.*, "Selected Values of Properties of Hydrocarbons," U. S. Government Printing Office, 1947.

(29) A study of the infrared absorption spectra of a considerable number of cyclopropane and cyclobutane hydrocarbons has been carried out in this Laboratory and a paper on this subject is in preparation.

(30) Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

melting points of its 2,4-dinitrophenylhydrazone (125.7–125.8°) and semicarbazone (187.0–187.3°); mixed melting point determinations with authentic samples of these derivatives showed no depression. Cyclobutanone ($n^{16}D$ 1.4221, literature[23] $n^{16}D$ 1.4220) was identified through its semicarbazone (m. p. 202.6–203.0°, lit. 204°); the 2,4-dinitrophenylhydrazone of this material melted 146.3–146.7°; the literature gives a value of 132.3° for this derivative and must be considered in error.

Physical properties were determined on a center cut from the 40-plate refractionation of the 107° material: b. p. 107.26° (760 mm.); f. p. −58.33°, $d^{20}_4$ 0.7823, $n^{20}D$ 1.4459.

**Isopropylcyclobutane.**—Hydrogenation of isopropylidenecyclobutane over Raney nickel at 50–60 p. s. i. and 80–100° gave isopropylcyclobutane exclusively; the hydrogenation proceeded less readily than in the case of ethylidenecyclobutane. Physical properties were determined on a center cut from a 40-plate fractionation of the hydrogenated material (values in brackets are those of Kasansky[15]): b. p. 92.70° (760 mm.) (90.5–91.5 (750)); f. p. −106.43°; $d^{20}_4$ 0.7376 (0.7464 at 14.5°); $n^{20}D$ 1.4080 (1.4096 at 19°).

*Anal.* Calcd. for $C_7H_{14}$: C, 85.62; H, 14.38. Found: C, 85.44; H, 14.46.

**Purification and Identification of Forerun.**—The material boiling at 79.5–98.1° (Fig. 4) was refractionated at about 40-plate efficiency; no further separation was effected. All fractions were recombined and hydrogenated to saturation in the same way as was isopropylidenecyclobutane. The hydrogenated material was fractionated at about 40-plate efficiency.

The 82° cut (1-methyl-1-isopropylcyclopropane) made up about 15% of the distillate and had the following physical properties: b. p. 82.1° (760 mm.), $d^{20}_4$ 0.7227, $n^{20}D$ 1.3998; there was insufficient material for a freezing point determination. This material was hydrogenated under the same conditions as was 1-methyl-1-ethylcyclopropane.

The 88.8–92.1° cut had the following physical properties: $d^{20}_4$ 0.7213; $n^{20}D$ 1.4013–1.4087.

**FROM 1,1,1-TRIS-(BROMOMETHYL)-ETHANE.**—The reaction of this tribromide with zinc in molten acetamide was carried out in exactly the same manner as in the case of 1,1,1-tris-(bromomethyl)-propane. The major portion of the tribromide used was purified only to the extent of filtering out the solid red impurity; further purification seemed unnecessary, since a batch of crude, assayed by fractionation, was found to be about 97% pure. In three runs the yields of hydrocarbon material obtained ranged from 45–65%. The crude hydrocarbon mixture (214 g.) was dried and distilled at about 40-plate effiiciency (Fig. 6).

**Methylcyclobutane.**—Hydrogenation of the later fractions (66 g., b. p. 38.6–43.0°, $n^{20}D$ 1.4014–1.4203) from the redistillation of the 37–43° cut was carried out over Raney nickel at 50 p. s. i. and 55°.

**2-Methyl-1-butene.**—The 31° cut (Fig. 6) was refluxed over metallic sodium and redistilled at about 40-plate efficiency. Physical properties determined on a center fraction were (the values in parentheses are those listed by Rossini, *et al.*[28]): b p. 30.9° (760 mm.) (31.10); f. p. −138.06° (−137.58); $d^{20}_4$ 0.6508 (0.6504); $n^{20}D$ 1.3778 (1.3778).

**1,1-Dimethylcyclopropane.**—The best fraction from the 20° cut (Fig. 6) (b. p. 20.67° (760 mm.); $n^{20}D$ 1.3662) was essentially saturated; 3-methyl-1-butene (b. p. 20.06° (760 mm.) $n^{15}D$ 1.3675)[28] is the only other hydrocarbon having physical properties in this range, and it is unsaturated. Shortridge, *et al.*,[7] give the following properties for 1,1-dimethylcyclopropane: b. p. 20.63° (760 mm.); $n^{20}D$ 1.3668.

**High Boiling By-products.**—Steam distillation of the reaction residues produced a lighter than water layer; distillation at 25-plate efficiency separated the material into two fractions boiling at about120 and 174° in the ratio of 2:1.

**1-Methylcyclopropylcarbinol.**—Physical properties of the 120° cut were: b. p. 120–121° (760 mm.); f. p. (approx.) −15°, $d^{20}_4$ 0.9033, $n^{20}D$ 1.4333. Mol. ref.: Calcd. for 1-methylcyclopropylcarbinol, 25.3; obs., 24.8.

This substance reacted slowly with metallic sodium; its 3,5-dinitrobenzoate melted sharply at 133.3–133.4° after five crystallizations from a water–ethanol mixture.

*Anal.* Calcd. for $C_5H_{10}O$: C, 69.7; H, 11.7. Found: C, 69.4; H, 11.7.

**Di-(1-methylcyclopropylmethyl) Ether.**—The 174° material was refluxed two days over metallic sodium and redistilled at about 5-plate efficiency. Its physical properties were: b. p. 174° (760 mm.), $d^{20}_4$ 0.8892, $n^{20}D$ 1.4501. Mol. ref.: Calcd. for di-(1-methylcyclopropylmethyl) ether, 47.0; obs., 46.6.

*Anal.* Calcd. for $C_{10}H_{18}O$: C, 78.0; H, 11.7. Found: C, 78.05; H, 11.76.

Infrared absorption spectrograms of the two compounds above seem to substantiate the identities tentatively assigned to them.

**Acknowledgment.**—The authors are indebted to E. E. Pickett for aid in interpreting the infrared spectra, and to R. G. Kelso and W. L. Perilstein for technical assistance and advice. Sincere appreciation is expressed to M. S. Newman for his counsel concerning reaction mechanisms.

## Summary

Three neopentyl-type tribromides have been prepared for the first time, and their reactions with zinc in molten acetamide have been carefully studied. The hydrocarbon mixtures obtained were separated by distillation insofar as possible and the components were identified, four of them being new compounds. This reduction has been shown to constitute a general and practical method for synthesizing monoalkylidene and monalkyl cyclobutanes.

Reaction mechanisms, based on well recognized theories, have been proposed to account for all of the products identified.

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[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES]

# Studies of the Fischer–Tropsch Synthesis. V. Activities and Surface Areas of Reduced and Carburized Cobalt Catalysts[1]

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## Introduction

Although the Fischer–Tropsch synthesis has been studied for more than twenty years, Craxford[3,4,5] was the first to attempt to relate activity and product distribution to the nature of the catalyst surface and the adsorbed layer of hydrocarbons upon it. Recently Hofer,[6,7] Weller,[8,9] Anderson[1,10–12] and Storch[13] have presented kinetic studies, X-ray diffraction data and surface area and pore volume studies of cobalt catalysts, and Pichler[14] has prepared a critical summary of the data of German research pertaining to the Fischer–Tropsch synthesis in which many of these factors are considered. The present paper relates surface area and surface accessibility to activity and product distribution. The data reported previously on the effect of bulk carbide on the activity of cobalt catalysts[9] have been extended to include the surface areas, activities and distribution of products in the synthesis with catalysts carburized with carbon monoxide under conditions which form carbide ($Co_2C$), "free" carbon or both.

## Experimental

The catalysts studied in this paper were Co:$ThO_2$:MgO:kieselguhr (100:6:12:200) catalysts characterized as number 89 and Co:$ThO_2$:kieselguhr (100:18:100) catalyst number 108 B. Descriptions have been published of the preparation and testing of these catalysts[10,11,13] as well as their surface areas,[1,11] mercury and helium densities[1,11] and activities at 185°.[12] In all tests described in this paper approximately two volumes of hydrogen to one volume of carbon monoxide synthesis gas was used. Surface areas were determined from adsorption isotherms of nitrogen at −195° by the simple equation of Brunauer, Emmett and Teller.[15] The method of determination of the volume of chemisorbed carbon monoxide at −195° has been described previously.[1]

Surface areas and mercury and helium densities were determined on a catalyst removed from a converter during the twelfth week of operation. The catalyst was dropped from the converter in an atmosphere of synthesis gas and at synthesis temperature into a tube through which pure argon was flowing. This tube was joined to the bottom of the converter by a rubber sleeve in which there was a small hole to allow the argon and synthesis gas to escape. When the catalyst had cooled to room temperature, it was transferred in a stream of carbon dioxide to suitable adsorption and density tubes. In this method of transfer, there was no possibility of exposure of the catalyst to air.

In the carburization studies reduced catalysts were treated with pure carbon monoxide prepared by dehydration of formic acid in the presence of phosphoric acid.[16] For surface area determinations, the catalyst was carburized in a glass adsorption tube[17] in a small automatically controlled electric furnace. For tests of carburized catalysts in the synthesis, the samples were treated with carbon monoxide in the converter. Before carburization, the catalyst that had been used in the synthesis was treated with hydrogen at 208° to remove most of the adsorbed hydrocarbons.

In many instances in this paper the results from cobalt–thoria–kieselguhr and cobalt–thoria–magnesia–kieselguhr catalysts have been compared as though the catalysts were the same. This is permissible since it has been found that the distribution of products, dependencies of rate upon temperature and pressure and the behavior of catalysts during and after carburization were very similar for these two types of catalysts.

### Surface Areas and Pore Volumes of Catalysts Used in the Synthesis

Pelleted catalyst 89FF (Co–$ThO_2$–MgO–kieselguhr) was removed from the converter during the twelfth week of operation at atmospheric pressure and transferred to suitable adsorption and density tubes in a manner that precluded exposure to air. The catalyst had been operated at an average temperature of 183° for eleven weekly periods of five days each with a two-hour reactivation in hydrogen at 195° followed by a forty-four-hour period in which a very slow stream of hydrogen was passed over the catalyst at about 150° between operating periods. Although the activity decreased somewhat during each period, the average activity of each period was the same for all eleven weeks. When removed from the converter, the catalyst had been operated for four days in the twelfth week. Since as indicated in Table I about 90% of the hydrocarbons on the catalyst should be removed by hydrogenation at 195°, most of the hydrocarbon on the catalyst was formed in the four days of operation prior to its transfer. Data of adsorption and mercury and helium densities are given in Tables I and II.

After use in the synthesis, the area of the catalyst was 4.36 square meters per gram compared with 80.0 square meters per gram after the initial reduction. The hydrogen reactivation at 200° for two hours decreased the weight of the sample by 23.5% and increased the surface area to 70.5 square meters per gram. Further reduction at 200° for twenty hours produced only a slight loss in weight and a small increase in area. Reduction at 400° under conditions of the original reduction f the catalyst caused only a slight loss in weight and increased the area to nearly that

(1) Part IV of this series Anderson, Hall and Hofer, THIS JOURNAL, **70**, 2465 (1948).

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(3) Craxford and Rideal, *J. Chem. Soc.*, 1604 (1939).

(4) Craxford, *Trans. Faraday Soc.*, **42**, 580 (1946).

(5) Craxford, *Fuel in Sci. and Practice*, **26**, 119 (1947).

(6) Hofer and Peebles, THIS JOURNAL, **69**, 2497 (1947).

(7) Hofer and Peebles, *ibid.*, to be published.

(8) Weller, *ibid.*, **69**, 2432 (1947).

(9) Weller, Hofer and Anderson, *ibid.*, **70**, 799 (1948).

(10) Anderson, Krieg, Seligman and O'Neill, *Ind. Eng. Chem.*, **39**, 1548 (1947).

(11) Anderson, Hall, Hewlett and Seligman, THIS JOURNAL, **69**, 3114 (1947).

(12) Anderson, Krieg, Seligman and Tarn, *Ind. Eng. Chem.*, in press.

(13) Storch, *et al.*, Bureau of Mines Technical Paper 709, "Synthetic Liquid Fuel Process. Hydrogenation of Carbon Monoxide," Part I, 1948.

(14) Pichler, "Synthesis of Hydrocarbons from Carbon Monoxide and Hydrogen," Bureau of Mines, Special Report, 1947.

(15) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

(16) Thompson, *Ind. Eng. Chem.*, , 389 (1929).

(17) Anderson, *Ind. Eng. Chem., Anal. Ed.*, **18**, 156 (1946).

TABLE I

ADSORPTION DATA FOR REDUCED AND USED COBALT CATALYST 89FF[a]

All adsorption data per gram of unreduced catalyst

| Treatment | Cumulative weight loss, %[b] | Surface area, sq. m./g. | $V_m$,[c] cc./g. | $V_{CO}$,[d] cc./g. | $V_{CO}/V_m$ |
|---|---|---|---|---|---|
| a. Reduced 2 hr. of $H_2$ at 400°, SVH = 6000[e] | .. | 80.8 | 18.45 | 3.2 | 0.173 |
| b. Used (a) plus 12 weeks of synthesis | 0.0 | 4.36 | 1.00 | 0.13 | .130 |
| c. (b) plus 2 hr. of $H_2$ at 200°, SVH = 200 | 23.5 | 70.5 | 16.1 | 2.7 | .168 |
| d. (c) plus 20 hr. of $H_2$ at 200°, SVH = 200 | 23.7 | 74.2 | 16.9 | 3.2 | .189 |
| e. (d) plus 2 hr. of $H_2$ at 400°, SVH = 6000 | 25.3 | 79.1 | 18.1 | 3.8 | .210 |

[a] Cobalt:thoria:magnesia:kieselguhr = 100:6:12:200 [b] Weight based on weight of used catalyst as removed from converter. [c] Volume of nitrogen corresponding to a physically adsorbed monolayer. [d] Volume of carbon monoxide chemisorbed at −195°. [e] Space velocity per hour, volumes of gas (S.T.P.) per volume of catalyst per hour.

TABLE II

DENSITY AND PORE VOLUME DATA ON REDUCED AND USED COBALT CATALYST 89FF[a]

| Treatment | Cumulative weight[b] loss, % | $d_{He}$ g./cc. | $d_{Hg}$, g./cc. | Pore volume, cc./g. |
|---|---|---|---|---|
| a. Reduced 2 hr. at $H_2$ at 400° SVH[c] = 6000 | .. | 3.031 | 1.138 | 0.549[d] |
| b. Used (a) plus 12 weeks of synthesis | 0.0 | 1.891 | 1.471 | 0.151[e] (0.201)[d] |
| c. (b) plus 2 hr. of $H_2$ at 200°, SVH = 200 | 23.8 | 2.881 | ... | ..... |
| d. (c) plus 2 hrs. of $H_2$ at 400°, SVH = 6000 | 25.5 | 3.007 | 1.112 | 0.566[d] |

[a] Cobalt:thoria:magnesia:kieselguhr = 100:6:12:200. [b] Weight was based on weight of used catalyst as removed from converter. [c] Space velocity per hour, volumes of gas (S.T.P.) per volume of catalyst per hour. [d] Pore volume in cc. per gram of reduced catalyst. [e] Pore volume in cc. per gram of catalyst as removed from converter.

of the original reduced catalyst. The ratio of volume of chemisorbed carbon monoxide to $V_m$[18] for nitrogen varied from 0.13 to 0.21, the ratio increasing with increasing surface area of the sample. It is interesting to note that even on the catalyst removed from the converter some cobalt was accessible to chemisorb carbon monoxide.

The helium density of the used catalyst was 1.891 and after reduction at 400°, 3.007, which is nearly equal to that of the original reduced catalyst. The mercury density of the used catalyst decreased on reduction at 400° from 1.471 to 1.112, while the pore volume (volume of pores with openings smaller than 5 microns in diameter[1,19]) increased from 0.201 to 0.566 cc. per gram of unreduced catalyst. Thus, the surface area, densities and pore volume of the used catalyst after reduction at 400° were very nearly identical to those of the original reduced catalyst.

The volumes of mercury displaced by the used catalyst before and after reduction per unit weight of cobalt were identical, indicating that the adsorbed hydrocarbons were located within the pellet in the space not penetrated by mercury and not on the external surface of the catalyst. At 30°, 65% of the pore volume of the used catalyst was filled with hydrocarbons. The hydrocarbons removed by hydrogenation had a density of 0.90 as calculated from change in weight and change in volume of helium displaced. This density compares well with the densities of soft and hard paraffins from atmospheric pressure synthesis, 0.90 and 0.93, respectively, as reported by Pichler.[14]

The data in Tables I and II establish definitely that the catalyst in its normal condition of operation at atmospheric pressure is heavily covered with hydrocarbons. In pressure operation, the catalyst is believed to be completely filled with hydrocarbon product at all times.[5] Experiments given in Table III indicate that the activities[20] of pelleted cobalt catalysts at one atmosphere are equal or slightly greater than at 7.8 atmospheres operating pressure. Pelleted catalysts produced greater percentages of methane and light hydrocarbons at 7.8 atmospheres than at one atmosphere, but granular catalysts produced nearly the same products under both conditions.

At atmospheric pressure, it was found that the percentage of methane and light hydrocarbons increased with increasing mercury density of the catalyst.[12] It was also found that granular and pelleted forms of the same catalyst had the same activity per gram of catalyst.[12] At 7.8 atmospheres a pelleted catalyst of higher density and greater pellet size had a lower activity and formed greater amounts of light hydrocarbons than a less dense and smaller size pelleted catalyst as shown in Table IV. Thus the larger pellets in test X-58 at a 4° higher temperature than in X-45 produced less oil than the smaller pellets, even though a greater weight of catalyst was used in X-58.

In Table V, data are presented for a test of a pelleted catalyst operated alternately at 1 and 7.8 atmospheres. After six weekly periods of operation at atmospheric pressure, the catalyst was operated at 7.8 atmospheres. No change in activity was observed. After a hydrogen reactivation, operation at one atmosphere required a 5° higher temperature to produce the same degree of conversion. After hydrogen reactivation, it was possible to operate at 7.8 atmospheres at 3° lower than in the previous period (h). In week j, operation at one atmosphere without a hydrogen reactivation required a temperature 10° higher than in the week i. Subsequent operation at 7.8 atmospheres after hydrogen reactivation was possible at the same temperature as in week j. Operation at one atmosphere in week 1 without reactivation required a 21° higher temperature than in week f.

Thus, operation at 7.8 atmospheres decreased the activity at atmospheric pressure. When hydrogen reactivation was omitted, the decrease in activity at atmospheric pressure operation after a period at 7.8 atmospheres was greater. In addition to changes in activity, alternation of operation at 1 and 7.8 atmospheres increased the percentage of methane and light hydrocarbons in the products compared with previous periods of operation at 1 and 7.8 atmospheres, respectively.

## Surface Areas and Activities of Carburized Cobalt Catalysts

Studies were made of the surface areas and activities (at atmospheric pressure) of pelleted Co–$ThO_2$–kieselguhr catalyst 108B after carburization at 208, 235 and 275°. Hofer[6,7] has shown that carburization at 208° formed chiefly cobalt carbide, $Co_2C$; at 235° cobalt carbide and "free" carbon were formed; and at 275° chiefly "free" carbon. After the surface area determination or activity test, the catalyst was hydrogenated under varying conditions, and the area or activity again determined. The data of surface area and activity studies are presented in Tables VI and VII.

The surface area data (Table VI) show that the surface area of the reduced catalyst (Period 1-R) does not decrease appreciably on carburization at 208° (1-C) and on subsequent reduction at 208° (2-R); however, the volume of chemisorbed carbon monoxide decreased on carburization

(18) $V_m$ is the volume of physically adsorbed gas, cc. (S. T. P.), required to form a monolayer on the surface.

(19) Pores not penetrated by mercury at atmospheric pressure. See Ritter and Drake, *Ind Eng. Chem., Anal. Ed.*, **17**, 782 (1945).

(20) In Tables III, IV and V, the space velocity of synthesis gas was constant with the temperature varied to maintain a 70% contraction. Thus the lower temperature of operation corresponds to the greater activity.

TABLE III

EFFECT OF OPERATING PRESSURE ON COBALT CATALYSTS

Tests at a space velocity per hour of 100

| Test | Operating periods | Pressure, atm. | Average temp.,[a] °C. | Apparent[b] contraction, % | Products, % | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | $CH_4$ | $C_3 + C_4$ | $C_1 - C_4$ | Liquids and solids |
| Pelleted[c] $Co-ThO_2$-kieselguhr catalyst 108B | | | | | | | | |
| X-29 | b-g | 1 | 185 (186) | 70.9 | 12.1 | 10.0 | 24.5 | 75.5 |
| X-29 | i-p | 7.8 | 189 (186) | 71.3 | 19.0 | 10.9 | 33.5 | 66.5 |
| X-31 | b-j | 7.8 | 187 | 71.8 | 18.6 | 10.5 | 32.0 | 68.0 |
| Granular[d] $Co-ThO_2-MgO$-kieselguhr catalyst 89K | | | | | | | | |
| X-17 | b-k | 1 | 186 (187) | 74.4 | 13.1 | 10.2 | 25.6 | 74.4 |
| X-17 | v-z | 7.8 | 188 (188) | 72.0 | 14.0 | 8.6 | 23.2 | 76.8 |
| Pelleted[e] $Co-ThO_2-MgO$-kieselguhr catalyst 89J | | | | | | | | |
| X-21 | c-l | 1 | 186 (186) | 72.0 | 15.6 | 8.1 | 24.9 | 76.1 |
| X-21 | o-u | 7.8 | 191 (188) | 69.5 | 18.2 | 10.4 | 28.3 | 71.7 |

[a] The temperatures in parentheses are for the last two weeks of operation at one atmosphere and the first two weeks of operation at 7.8 atmospheres. [b] Apparent contraction computed by $100\ (1 - V_E/V_I)$ where $V_E$ is the flow of exit gas and $V_I$ the flow of synthesis gas. [c] Cylindrical pellets, 3.2 mm. in diameter by 3.2 mm. in length. [d] Broken filter cake. [e] Cylindrical pellets, 3.2 mm. in diameter by 1.6 mm. in length.

TABLE IV

EFFECT OF SIZE AND DENSITY OF PELLETS ON $Co-ThO_2$-KIESELGUHR CATALYST 108B AT 7.8 ATMOSPHERES

Tests at space velocity per hour of 100. Methods of reduction and induction were the same.

| Test | Catalyst charge, g. | Length, mm. | Diameter, mm. | Mercury density,[a] g./cc. | Av. temp., °C. | Apparent contraction,[b] % | Products, % | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $CH_4$ | $C_3 + C_4$ | $C_1 - C_4$ | Liquids and solids |
| X-45 | 36.8 | 3.17 | 3.2 | 1.13 | 187 | 71.6 | 19.9 | 11.6 | 34.9 | 65.1 |
| X-58 | 44.9 | 6.35 | 3.2 | 1.51 | 191 | 71.4 | 25.8 | 13.4 | 43.4 | 56.6 |

[a] Densities determined with mercury at atmospheric pressure. [b] See note *b* of Table III.

TABLE V

ALTERNATE OPERATION AT 1 AND 7.8 ATMOSPHERES OF PELLETED $Co-ThO_2$-KIESELGUHR CATALYST 108B

Operating periods five to six days, space velocity = 100 per hour

| Operating periods[b] | Pressure, atm. | Av. temp., °C. | Apparent contraction,[a] % | Products, % | | | |
|---|---|---|---|---|---|---|---|
| | | | | $CH_4$ | $C_2 + C_4$ | $C_1 - C_4$ | Liquids and solids |
| e | 1 | 187 | 72.1 | 14.9 | 10.8 | 31.9 | 68.0 |
| f | 1 | 186 | 70.1 | 15.4 | 16.5 | 34.0 | 66.0 |
| g | 7.8 | 186 | 67.2 | 21.0 | 13.0 | 34.9 | 65.1 |
| h | 1 | 191 | 70.3 | 19.2 | 10.0 | 36.4 | 63.6 |
| i | 7.8 | 188 | 69.9 | 24.6 | 13.4 | 42.5 | 57.5 |
| j | 1 | 198 | 69.1 | .. | .. | .. | .. |
| k | 7.8 | 198 | 71.3 | 41.4 | 10.3 | 53.6 | 46.4 |
| l | 1 | 207 | 68.7 | 24.6[c] | .. | .. | .. |

[a] See note *b* of Table III. [b] A two-hour hydrogen activation at 10° higher than the previous operating temperature preceded operating periods. [c] Approximate.

and increased on reduction to only about 50% of the chemisorption found on the freshly reduced catalyst.

Carburization at 235° (2-C) deposited carbon equivalent to 130% of carbide, and about the equivalent of carbon in $Co_2C$ was removable by reduction at 208° (3-R). In these steps, the surface area did not change greatly, but the chemisorbed carbon monoxide was less than for the carburization 1-C and reduction 2-R. The residual carbon may be termed "free carbon" as contrasted to the readily hydrogenated carbide carbon.[6,7] Carburization at 275° (3-C) increased the carbon content to the equivalent of 418% $Co_2C$ and increased the surface area and carbon monoxide chemisorption sizably. Reduction 4-R decreased the carbon content only slightly, and subsequent carburization at 208° (4-C) increased carbon by only the equivalent of 25% of $Co_2C$. Thus, after carburization at 275° the cobalt no longer contained sizable amounts of carbide, and carburization at 208° did not increase the carbide content appreciably. The surface area was increased to 50.6 square meters per gram in the carburization at 275° (3-C); the increase in area was probably that of the "free" carbon deposited in the catalyst. Hydrogenation (4-R) and carburization (4-C) at 208° did not significantly change the surface area. The volume of chemisorbed carbon monoxide after carburization at 275° was nearly equal to that after reduction 2-R.

Rereduction 5-R at 360° which was similar to 1-R removed carbon about equivalent to $Co_2C$, but did not increase the surface area or carbon monoxide chemisorption significantly over that of the catalyst after 3-C. Carburization 5-C at 208° increased the carbon content only by the equivalent of 30% $Co_2C$, indicating that carbide formation was still inhibited. In reduction 6-R at 360°, the carbon was slowly removed until after 296 hours only the equivalent of 7.9% $Co_2C$ remained. During the rereduction, the area decreased to only slightly greater than that of the original reduced catalyst, and the volume of chemisorbed carbon monoxide increased to two-thirds of that of the original reduced catalyst. The catalyst was still poisoned with respect to formation of carbide as indicated by carburization 6-C at 208°.

A similar carburization and reduction cycle was made on $Co-ThO_2-MgO$-kieselguhr catalyst 89K. The results were very similar to the data in Table VI. After several carburization and reduction cycles at 200°, catalyst 89K was carburized at 275° until 16 times the equivalent of the carbon in $Co_2C$ was deposited. In addition to an increase in total surface area from 62.0 sq. m. per gram for the original reduced catalyst to 149.4 sq. m. per gram the volume of chemisorbed carbon monoxide increased from 3.1 cc. (S.T.P.) per gram to 3.6 cc. (S.T.P.) per gram. (The adsorption data are given per gram of unreduced catalyst.) This indicates an increase in area of the cobalt possibly due to splitting of the metal lattice by carbon.

TABLE VI

EFFECT OF CARBURIZATION AND HYDROGENATION ON THE SURFACE AREA OF COBALT CATALYST 108B

| No. | Treatment SVH[a] | Gas | Temp., °C. | Hours | Weight change on treatment, mg./g. | Carbon, %, based on $Co_2C$ | Surface area, sq. m./g. | $V_m$,[b] cc./g. | $V_{CO}$,[c] cc./g. | $V_{CO}/V_m$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Original catalyst | | | ..... | ... | 71.6 | 16.3 | 0.0 | ... |
| 1-R | 3000 | $H_2$ | 360 | 2.0 | −230.0 | 0.0 | 32.6 | 7.44 | 3.00 | 0.403 |
| 1-C | 100 | CO | 208 | 15.5 | + 34.4 | 112.0 | 31.5 | 7.18 | 0.94 | .131 |
| 2-R | 100 | $H_2$ | 208 | 16.0 | − 34.7 | 6.1 | 30.1 | 6.88 | 1.44 | .209 |
| 2-C | 100 | CO | 235 | 12.5 | + 32.9 | 114.5 | ... | ... | .. | ... |
| | | | | 59.5 | + 5.1 | 130.1 | 32.0 | 7.32 | 0.78 | .107 |
| 3-R | 100 | $H_2$ | 208[d] | 12.5 | − 33.4 | 30.5 | 31.2 | 7.12 | .. | ... |
| | | | | 30.7 | − 0.4 | 29.3 | 31.3 | 7.14 | 0.85 | .119 |
| 3-C | 100 | CO | 275 | 16.0 | +127.4 | 418.2 | 50.6 | 11.54 | 1.30 | .113 |
| 4-R | 100 | $H_2$ | 208 | 18.0 | − 7.1 | 398.0 | 50.0 | 11.40 | 1.29 | .113 |
| 4-C | 100 | CO | 208 | 16.0 | + 8.1 | 423.5 | 50.8 | 11.59 | 1.05 | .091 |
| 5-R | 3000 | $H_2$ | 360 | 2.0 | − 35.3 | 319.0 | 51.4 | 11.74 | 1.30 | .111 |
| 5-C | 100 | CO | 208 | 17.3 | + 10.6 | 354.8 | 52.2 | 11.92 | .. | ... |
| 6-R | 3000 | $H_2$ | 360 | 22.0 | − 45.1 | 216.5 | .. | ... | .. | ... |
| | | | | 64.0 | − 19.8 | 156.1 | 46.8 | 10.7 | 1.48 | .138 |
| | | | | 157.3 | − 20.4 | 93.8 | .. | ... | .. | ... |
| | | | | 296.3[e] | − 28.1 | 7.8 | 35.2 | 8.03 | 1.99 | .248 |
| 6-C | 100 | CO | 208 | 18.0 | + 18.0 | 72.3 | .. | ... | .. | ... |

[a] Space velocity per hour (volumes of gas (S. T. P.) per volume catalyst per hour). [b] Volume of nitrogen necessary to form a monolayer. [c] Volume of chemisorbed carbon monoxide at −195°. [d] Temperature controller failed and temperature rose to 250° for a short period. [e] Temperature controller failed and temperature rose to 450° in part of this period.

TABLE VII

EFFECT OF CARBURIZATION AND HYDROGENATION ON ACTIVITY AND PRODUCT DISTRIBUTION OF COBALT CATALYST 108B

Space velocity of synthesis gas per hour was 100.

| Period | Pretreatment Gas | SVH | Temp., °C. | Hours | Hours | Av. temp., °C. | Synthesis gas reacted, % | Products g. cu. m. of synthesis gas reacted— $CH_4$ | $C_3+C_4$ | $C_1-C_4$ | Liquids and solids |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | $H_2$ | 3000 | 360 | 2 | 73 | 173 | 66.6 | 21.8 | 27.2 | 55.9 | 105.7 |
| b | CO | 100 | 208 | 16 | 126 | 195 | 47.4 | 41.8 | 37.8 | 90.1 | 64.4 |
| c | $H_2$ | 100 | 208 | 16 | 149 | 190 | 63.8 | 27.7 | 38.7 | 72.6 | 106.9 |
| d | CO | 100 | 208 | 16 | 149 | 191 | 32.7 | 41.6 | 33.0 | 82.3 | ... |
| e | $H_2$ | 100 | 208 | 16 | 127 | 190 | 51.7 | 34.8 | .. | ... | 81.8 |
| f | CO | 100 | 208 | 16 | 176 | 193 | 22.9 | 84.3 | .. | ... | ... |
| g | $H_2$ | 100 | 208 | 16 | 126 | 190 | 42.3 | ... | .. | ... | ... |
| h | CO | 100 | 208 | 16 | 125 | 191 | 17.5 | 122.9 | 53.7 | 189.1 | 46.9 |
| i | CO | 100 | 274 | 15 | 149 | 191 | 18.9 | 106.3 | 18.5 | 132.3 | 10.6 |
| j | $H_2$ | 100 | 208 | 16 | 119 | 191 | 56.3 | 73.5 | 34.5 | 108.2 | 15.8 |
| k | $H_2$ | 100 | 200 | 2 | 165 | 189 | 48.9 | 83.2 | 47.2 | 137.4 | 18.4 |
| l | $H_2$ | 3000 | 360 | 2 | 166 | 190 | 64.5 | 36.7 | 45.9 | 98.6 | 76.1 |

In Table VII are presented activity and product distribution data for another sample of catalyst 108B, tested at atmospheric pressure with two volumes of hydrogen to one volume of carbon monoxide gas. Reduction and carburization steps were arranged to be somewhat similar to those of Table VI. Before each carburization step, the catalyst was stripped of adsorbed hydrocarbons by hydrogenation for two hours at 208° to insure that the surface was accessible during the carburization. In these tests (weeks c–l) the temperature and flow of synthesis gas were held constant, and the activity was expressed as the fraction of the gas consumed, *i. e.*, the real contraction. Products are given as grams per cubic meter of synthesis gas consumed.

After carburization b at 208° the activity decreased and yields of methane and $C_1$–$C_4$ hydrocarbons were increased. Although hydrogenation at 208° (c) increased the activity and shifted the product distribution as compared with period b, the products contained a higher percentage of light hydrocarbons, and the activity was considerably lower than in operating period a. In the following carburization and reduction cycles (d to h), the hydrogenated catalyst was more active and had a more favorable product distribution than the corresponding carburized one, but the activity of the catalyst in the hydrogenated or carburized state decreased steadily, and greater fractions of methane and light hydrocarbons were formed. Thus, carbide formation has a marked effect on both activity and product distribution. Repeated cycles of carburization and reduction at 208° caused a gradual decrease in activity and a shift toward formation of lighter hydrocarbons that was super-imposed on the effect of carbide on activity and product distribution. After carburization at 275° in period i, the activity and methane formation were not significantly different from that of period h. Reduction at 208° in period j increased the activity sizably, but the product distribution was strongly shifted toward light hydrocarbons compared with period a. Reduction 1 at 400° increased the activity to that of period c, but distribution of products was less favorable than in the period c. Thus "free" carbon does not decrease the activity very much but has a marked effect on the product distribution.

## Discussion

The Fischer–Tropsch synthesis is a slow catalytic process compared with simple reaction such as the catalytic hydrogenation of ethylene, and in no case did the synthesis proceed to equilibrium. Although the catalyst was heavily covered with wax, the rate of synthesis does not appear dependent upon diffusion: First, the temperature coefficient was considerably higher than that expected for diffusional processes,[8,10] and second, the pressure coefficient was about zero. Thus, the rate must be dependent upon the rate of some surface process that is not pressure dependent, and the linear dependency of activity on surface area should be expected.

The study of the catalyst used in the synthesis at atmospheric pressure (Tables I and II) indicated the amount of the hydrocarbon on the catalyst. Hydrogen treatment at 200° for two hours removed 90% of the adsorbed wax. Further hydrogenation at this temperature caused only a very small loss in weight. However, reduction at 400° restored the catalyst to the same condition as after the initial reduction. The surface area and pore volume were unchanged after the eleven weeks of operation. This agrees with the fact that the activity remained constant during the operation of this catalyst and the observation that the X-ray diffraction patterns of the catalyst did not change during the synthesis.[9] The results indicate that little if any "free" carbon was deposited during the synthesis. The stability of the catalyst to sintering was not entirely unexpected since the temperature of the synthesis was more than 200° lower than the reduction temperature.

Thus, the surface of catalysts operated at atmospheric pressure was heavily covered with wax, and the pores of those operated at elevated pressures were probably almost entirely filled.[5] Although catalysts operated at elevated pressure produce a greater fraction of higher molecular weight hydrocarbons, it is probable that the average molecular weight of the product in the catalyst operated at elevated pressures is lower than that in catalysts used at atmospheric pressure. At elevated pressures hydrocarbons of lower molecular weight than at atmospheric pressure should condense in the catalyst bed and should flow over the catalyst as liquid. The liquid should continuously remove higher molecular weight hydrocarbons.[14] Catalysts operated entirely at elevated pressures or at elevated pressures after several weeks of operation at atmospheric pressure had the same activity as in atmospheric pressure operation. However, activities at atmospheric pressure after operation at the higher pressure were considerably less, this effect being more pronounced when the catalyst was not hydrogen treated between periods of operation. Alternate atmospheric and pressure operation decreased the activity compared with previous periods of atmospheric and pressure operation, respectively.

In operation at atmospheric pressure, the activity remains nearly constant for two or three weeks of continuous operation followed by a rapid decrease in activity. This loss in activity may be related to the time at which the pores of the catalyst are quite completely filled with adsorbed hydrocarbon; and reactivation involves removal of this hydrocarbon by hydrogenation or solvent extraction.[5,21] The pores of the catalyst operated at elevated pressures are assumed to be quite completely filled with hydrocarbons at all times, and the activity remains constant for periods of three or more months without any reactivation. Thus, in atmospheric pressure operation it appears that pores entirely filled with hydrocarbons are considerably less accessible than only partially filled pores, but in pressure operation, the rate of diffusion of reactants is sufficient to maintain constant activity even with completely filled pores.

Parallel to the decrease in activity (Table V), the product distribution was shifted toward the formation of larger fractions of methane and other light hydrocarbons. From these and other data (Tables III and IV and refs. 10 and 12), the following generalization may be made: Decrease of the accessibility of the surface either by deposition of excessive quantities of wax by operation at elevated pressure or by decreasing the average pore diameter by pelleting causes an increase in the fraction of methane and other light hydrocarbons and in some cases a decrease in activity. In pressure operation the greater proportion of light hydrocarbons may be due to the greater rate of diffusion of hydrogen compared with that of carbon monoxide through the hydrocarbon film covering the surface as postulated by Craxford,[5] so that the gas reaching the catalyst surface is richer in hydrogen than the synthesis gas.

The conversion of the cobalt in a catalyst to carbide did not appreciably change the total surface area (1-R and 1-C of Table VI); hence, the lower activity of the carbided catalyst (b of Table VI) must be related to the presence of the carbide. The volume of chemisorbed carbon monoxide at −195° on the carbided catalyst was only one-third of that chemisorbed on the original reduced catalyst. On reduction (2-R of Table VI) the volume of chemisorbed carbon monoxide was less than half that of the original reduced sample. This may be due to poisoning by the small amount of residual carbon. Repeated carbiding and reduction at 208° decreased the activity in the corresponding reduced and carbided states compared with the original reduced and carbided states.

Accompanying the decrease in activity of carbided catalysts, the fraction of light hydrocarbons in the products increased. "Free" carbon deposited from carbon monoxide at 235° and higher temperatures had a smaller effect on activity, but the product distribution was more strongly shifted

(21) Hall and Smith, *J. Soc. Chem. Ind.*, **65**, 128 (1946).

toward light hydrocarbons than in the presence of cobalt carbide.

It was found that "free" carbon or processes accompanying its formation inhibited carbide formation from carbon monoxide at 208°, some inhibition being observed even after the "free" carbon had been decreased to 2 mg./g. of catalyst by reduction at 360° (6-R of Table VI). The data indicate that the catalytic activity was not decreased by the "free" carbon even though the extent of carbide formation was decreased. This appears to be evidence against cobalt carbide as an intermediate in the synthesis.

At least part of the greater yield of methane and light hydrocarbons from the carbided catalyst may be formed by reduction of the carbide with hydrogen of the synthesis gas, and accompanying this process the activity of the carbided catalyst increased for the first several days.[9] The higher yields of light hydrocarbons with catalysts containing "free" carbon cannot be explained in this manner since "free" carbon does not hydrogenate at synthesis temperatures. It is possible that the presence of carbon atoms decreases the extent of polymerization at the surface by breaking the continuity of cobalt atoms in the cobalt crystallites. Although deposition of large amounts of "free" carbon slightly increased the area of the cobalt surface indicating some splitting of the cobalt lattice by carbon, this increase was small compared with the increase in the total area. Thus it appears that most of the "free" carbon was deposited at the surface and not within the crystallites of cobalt.

The results presented in this paper are in general agreement with those of Craxford.[3,4,5] The present paper and a previous one[9] show that the presence of bulk phase carbide decreased the catalytic activity and that bulk phase carbide was not formed in the synthesis. Thus, carbide if present at all in the catalyst in the synthesis must reside near the surface. In a recent paper[5] Craxford has postulated a surface carbide as an intermediate in the synthesis, because in his catalysts the cobalt atoms must be distributed into layers less than two atoms thick to account for the observed surface area. For purposes of reaction mechanisms the distinction between surface carbide and chemisorbed carbon monoxide is difficult.

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## Summary

1. The surface of a catalyst used in the synthesis was found to be heavily covered with hydrocarbon. Hydrogenation at 200° removed 90% of these adsorbed hydrocarbons, and reduction with hydrogen at 400° restored the catalyst to the same condition as after the initial reduction. There was no evidence of sintering of the catalyst or of carbon deposition.

2. Activity data for operation at 1 and 7.8 atmospheres are related to the adsorbed hydrocarbon film.

3. Decrease in the accessibility of the surface of these catalysts either by deposition of excessive quantities of wax or by reduction of average pore diameter by pelleting caused an increase in the fraction of methane and other light hydrocarbons and in some cases a decrease in activity.

4. The presence of bulk phase carbide in these catalysts caused a marked decrease in activity, but "free" carbon did not affect the activity very much. The presence of carbon in both forms shifted the product distribution toward light hydrocarbons. The surface area did not change appreciably when the cobalt in the catalysts was converted to cobalt carbide. Carburization at 275°, under conditions which form predominantly "free" carbon, increased the area sizably.

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[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

# The Modifications of the Carbide, $Fe_2C$; Their Properties and Identification

BY L. J. E. HOFER,[1] E. M. COHN,[1] AND W. C. PEEBLES[2]

In addition to the well-known carbides of iron, cementite and martensite, and the less-well-known iron acetylide, carbides of the formula $Fe_2C$ have been reported. Recent X-ray diffraction studies by Halle and Herbst[3] indicate the existence of a carbide in which the iron atoms are arranged in hexagonal structure. X-Ray diffraction studies also were made by Hägg[4] and later by Jack[5] on a more complex iron carbide whose structure has not yet been worked out. Pichler and Merkel[6] have recently made thermomagnetic studies of iron carbides, and they conclude that there are two ferromagnetic iron carbides with the formula $Fe_2C$ and with Curie points at 265° and 380°, respectively. Unfortunately, no X-ray diffraction experiments were made by Pichler and Merkel; and similarly Hägg, Jack, and Halle and Herbst made no thermomagnetic measurements. It is therefore impossible to interpret the thermomagnetic studies in terms of the X-ray diffraction studies and *vice versa*.

The chief purpose of this paper is to determine the relationship between the $Fe_2C$ carbides which were reported in thermomagnetic studies and those reported in X-ray diffraction studies. In addition, the results obtained with iron catalysts in this paper have made possible a general unification of data presented in the literature.

## Experimental

**Thermomagnetic Analysis.**—This method of analysis is based on the observation that every ferromagnetic phase loses its ferromagnetism at a temperature characteristic of the phase, known as the Curie point. The method has been described by many authors (see, for example, Lange and Mathieu[7]).

The magnetic balance used has been previously described.[8,9] The balance suspension assembly is shown in Fig. 1. A strong torsion wire (about 0.1° twist per gram-centimeter torque) was used. The sample holders used for the iron synthetic ammonia catalyst consisted of 6 mm. i. d. graded vitreous silica to Pyrex seals which were closed at the silica end and provided with a standard taper joint at the Pyrex end. (This sample holder is particularly useful for determining Curie points at high temperatures but was not essential to the experiments here described.) The sample holders used for the copper-promoted, precipitated iron catalysts were 7-mm. o. d. Pyrex tubes, closed at one end and also provided with a standard taper at the other. The samples were held in position at the bottom of the sample holders by means of Pyrex glass wool plugs. A coin-silver cap (i. d. 8.8 mm., o. d. 13.9 mm., length 38.4 mm., bottom thickness 2.5 mm.), provided with a groove on the inside for a thermocouple and its porcelain protective tube, was slipped over the end of the sample holders. This cap assured a uniform temperature distribution throughout the sample and also the identity of the temperature of the thermocouple with that of the sample. The junction of the thermocouple was placed as near the sample as possible. Two non-ferromagnetic thermocouples were used, platinum–platinum + 10% rhodium, or Chromel–constantan. To insure unrestricted motion of the suspension assembly, the ends of the thermocouple dipped into two mercury pools from which two wires, identical with those of the thermocouple, led to an ice-bath cold junction. The furnace consisted of an Alundum thimble about 0.9 cm. long and 1.5 cm. i. d., wound non-inductively with asbestos-covered 24-gage Nichrome wire, and insulated on the outside with a layer of asbestos paper. It was supported between the poles of the magnet by a brass holder and was adjusted so that it made no contact with the suspension assembly.

Normally, a thermomagnetic analysis is made by heating the unknown sample sufficiently slowly in the magnetic balance so that the magnetic moment can be measured at suitable intervals. The magnet is operated at a field strength of 2160 gauss. When a predetermined temperature has been reached, the heating is stopped, and the sample is allowed to cool slowly so that the magnetic moment can again be measured at suitable intervals. The whole process takes about one to two hours. Due to the excellent thermal characteristics of this system, the curves obtained on heating and cooling can be very nearly superimposed in every case where the sample has undergone no change during heating.

The thermocouples were calibrated in the following boiling baths, using proper pressure corrections: water, naphthalene, benzophenone and sulfur.

**X-Ray Diffraction Analysis.**—The X-ray diffraction studies were carried out with a simple Debye–Scherrer powder camera of 71.62 mm. inside diameter. Radiation, as obtained from a sealed-off iron target X-ray tube equipped with beryllium windows and manganese dioxide filters, was used. The tube was operated at 40 p.k.v. and 7.0 milliamperes. The samples were preserved under petroleum ether. They were ground to a fine paste while still wet with petroleum ether, mixed with collodion, and partly extruded from a short section of 19-gauge, 0.7-mm. i. d. stainless steel tubing. This procedure was effective in preventing oxidation of the samples, which otherwise were quite pyrophoric. The diameters of the diffracted rings on the films from which the $d/n$ values were obtained were determined by measuring to the outside of the ring and subtracting the sample diameter (0.7 mm.).

**Preparation of Carbide in Synthetic Ammonia Catalyst.**—The synthetic ammonia catalyst used was a commercial preparation obtained from the Hercules Powder Company. Its chemical analysis is as follows: Iron as $Fe_3O_4$, 92.6%; magnesium as MgO, 4.2%; silicon as $SiO_2$, 0.7%; and chromium as $Cr_2O_3$, 0.4%. This catalyst has been tried in the Fischer–Tropsch testing units previously described,[10] and yields of 70 g. of solid and liquid hydrocarbons were obtained per cubic meter of synthesis gas (one part carbon monoxide and one part hydrogen) per single pass over 50 cc. of catalyst at 255°.

The reduction and carburization of the catalyst were

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(3) Group Leader Conference Ludwigshafen, T.O.M. Reel 26, Bag 2463. Report Dr. Wenzel, T.O.M. Reel 134, Item II/10.

(4) G. Hägg, *Z. Krist.*, **89**, 92 (1934).

(5) K. H. Jack, *Nature*, **158**, 60 (1946).

(6) H. Pichler and H. Merkel, Ph.D. thesis describing work carried on at the Kaiser Wilhelm Institut für Kohlenforschung. A translation of this document will be published in a Bureau of Mines Technical Paper.

(7) H. Lange and K. Mathieu, *Mitt. Kaiser-Wilhelm Inst. Eisenforsch. Düsseldorf*, **20**, 239 (1938).

(8) L. J. E. Hofer, W. C. Peebles and W. E. Dieter, THIS JOURNAL, **68**, 1953 (1946).

(9) R. Buehl and J. Wulf, *Rev. Sci. Instruments*, **9**, 224 (1938).

(10) R. B. Anderson, A. Krieg, B. Seligman and W. E. O'Neill, *Ind. Eng. Chem.*, **39**, 1548 (1947).

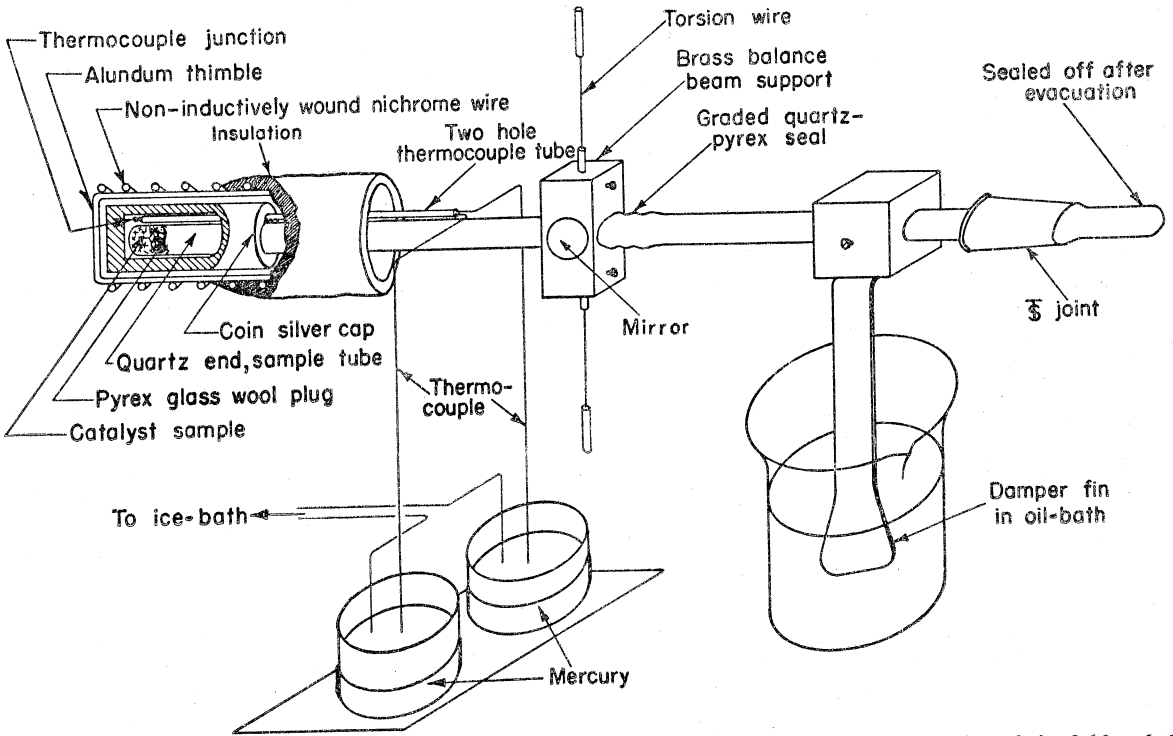



Fig. 1.—Schematic diagram of suspension assembly with quartz-Pyrex sample tube. The direction of the field and the field gradient is perpendicular to the plane of the paper.

carried out in an apparatus similar to that previously described.[11] Samples of about 5 g. each were weighed into four reaction vessels, which were placed side by side in the aluminum block furnace. A stream of electrolytic hydrogen (flowing at 0.75 liter per hour and purified by passage over palladized asbestos at 360°, soda lime, Ascarite and anhydrous magnesium perchlorate) was admitted to the reaction vessels. The temperature was maintained at 450°. During this time the reaction vessels were periodically disconnected and weighed. After eighty-two hours, the change in weight was less than 0.05 mg. per hour per sample.

At this point carburization was started. The carbon monoxide used in the carburization was made from formic acid and orthophosphoric acid at 150–200°. It was purified over sodium hydroxide, copper at red heat, soda lime and anhydrous magnesium perchlorate. The carburization was carried out at 240° for 539 hours. During this time the reaction vessels were periodically disconnected and weighed. (The samples were heated and cooled in an atmosphere of nitrogen to prevent carbonyl formation.) The weight increase observed is due almost entirely to the deposition of carbon rather than of oxygen. This was demonstrated by the fact that the products of hydrogenation of similar carburized catalysts are not absorbed in anhydrous magnesium perchlorate. The results of the carburization are summarized in Fig. 2. The final, average carbon:iron ratio (for 3 tubes) was 0.1164 (theoretical for $Fe_2C$ is 0.1076).

The reaction vessel was opened in a carbon dioxide atmosphere to prevent oxidation.

**Preparation of Carbide in Iron–Copper–Potassium Oxide (100:10:0.32) Catalyst.**—This catalyst is analogous to those used at the Kaiser Wilhelm Institut für Kohlenforschung.

Ferric nitrate nonahydrate (41.35 lb.) and copper nitrate trihydrate (2.17 lb.) were dissolved in 22.5 gallons of distilled water. A sodium carbonate solution (18.10 lb. in 20 gallons of distilled water) was made. Sixteen gallons of this solution were added to the nitrate solution at room temperature. The mixture was then heated to 70°, and the remaining carbonate solution (at room temperature) was added to form the precipitate. The mixture was then heated rapidly to boiling and held there for several minutes, after which it was filtered in a filter press and washed with 400 gallons of hot distilled water until the filtrate was free of nitrate ion. The filter cake was then dropped from the press and mixed into a smooth paste with a solution of 13 g. of potassium carbonate dissolved in 2 liters of distilled water. The catalyst was then dried at 105–110° for forty-eight hours.

The activity of this catalyst, when tried in the Fischer-Tropsch testing units, gave yields of 103 g. of liquid and solid hydrocarbons per cubic meter of synthesis gas (one part carbon monoxide and one part hydrogen) per pass over 50 cc. of catalyst at 236°.

The reduction and carburization were carried out with the same apparatus and using a procedure similar to that described above for the iron-synthetic ammonia catalyst. After reduction with hydrogen for 327 hours at 220°, the 7-g. samples did not vary more than 0.05 mg. per hour. The carburization (as shown in Fig. 2) was carried out at 188° for 211 hours when the carbon:iron ratio (average for 3 reaction tubes) had reached 0.1072. In a similar experiment a catalyst carburized at 205° for 239 hours to a carbon:iron ratio of 0.1068 lost all but 18% of the carbon as methane when heated with hydrogen at 250°. Thus the carbon in this catalyst was held largely as carbidic carbon.

The reaction vessel was opened in an atmosphere of carbon dioxide to prevent oxidation. The samples for the magnetic balance were transferred to sample holders in a carbon dioxide atmosphere, connected to a high-vacuum system, evacuated for two hours, and then sealed off.

## Results

**Carburized Iron Synthetic Ammonia Catalyst.**—The X-ray diffraction powder pattern of this

(11) L. J. E. Hofer and W. C. Peebles, THIS JOURNAL, 69, 893 (1947).

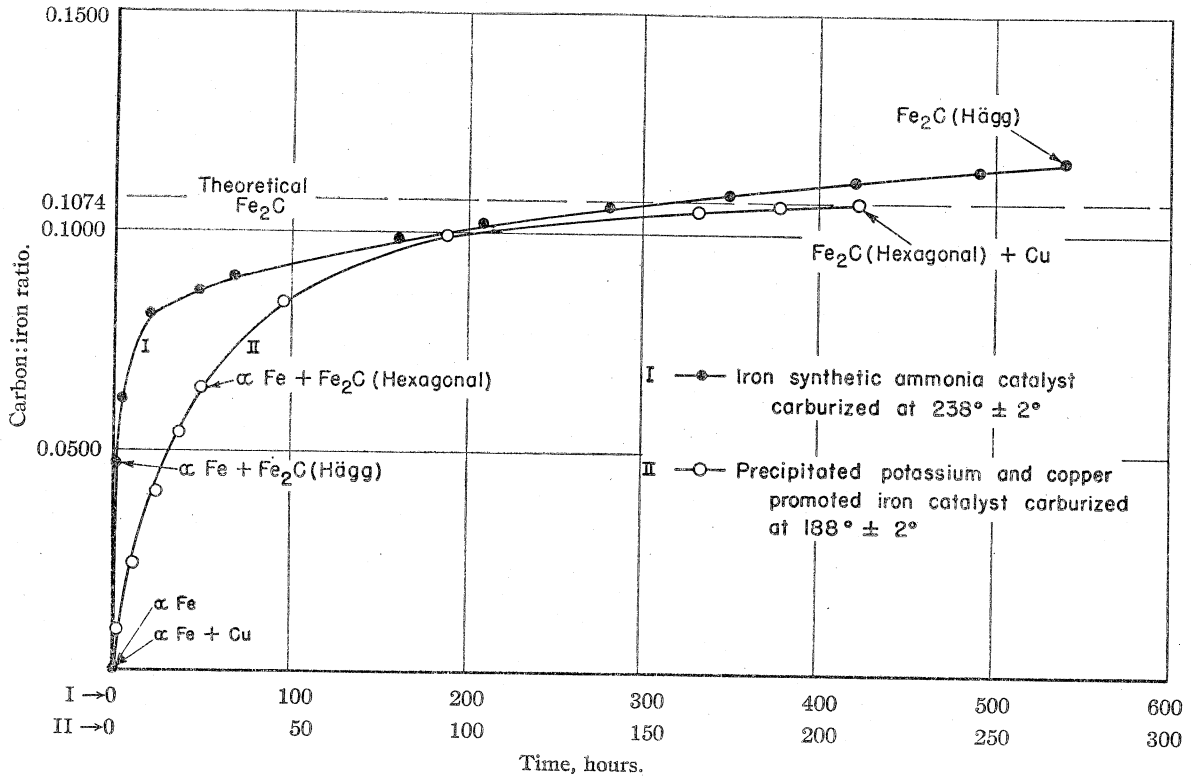



Fig. 2.—Carburization of two types of iron Fischer–Tropsch catalysts.

product was that of the Hägg[4] carbide. The $d/n$ values obtained are compared with those reported by Hägg in Table I, column 2. The diffraction pattern was diffuse, and some of the weaker lines reported by Hägg are missing; nevertheless, the match is good. Comparison of the pattern of Hägg carbide with that of cementite (column 1) reveals some similarities, but both patterns have enough characteristic lines to make identification positive.

TABLE I

COMPARATIVE X-RAY DIFFRACTION DATA FOR CEMENTITE, HÄGG CARBIDE AND THE HEXAGONAL CARBIDE

| (1) Cementite data | | | | | (2) Hägg carbide data | | | | (3) Hexagonal iron carbide data | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Westgren (calcd.) $d/n$ | | $hkl$ | Sample 7-68 $I$ | $d/n$ | Hägg $I$ | $d/n$ | Sample 7-255 $I$ | $d/n$ | $hkl$ | Sample 8-20 $I$ | $d/n$ |
| | | | | | w− | 2.64 | vw | 2.62 | | | |
| | | | | | w | 2.49 | w | 2.48 | | | |
| 1800 | 2.38 | 112 | | | w+ | 2.41 | w | 2.39 | | | |
| 1900 | 2.37 | 021 | M | 2.37 | | | | | 100 | w | 2.38 |
| 1600 | 2.26 | 200 | w | 2.25 | M | 2.27 | M | 2.26 | | | |
| | | | | | vw | 2.24 | | | | | |
| 1400 | 2.18 | 120 | w | 2.18 | M | 2.20 | M | 2.18 | | | |
| | | | | | w | 2.18 | | | | | |
| | | | | | | | | | 200 | M | 2.16 |
| 3800 | 2.10 | 121 | w | 2.10 | w+ | 2.10 | | | | | |
| 3800 | 2.06 | 210 | M | 2.06 | S | 2.07 | vS | 2.06 | 101 | vS | 2.08 |
| 3500 | 2.02 | 022 | | | S | 2.04 | vS | 2.03 | | | |
| 6300 | 2.01 | 103 | vS | 2.01 | w | 2.01 | | | | | |
| | | | | | w | 2.00 | | | | | |
| 3700 | 1.97 | 211 | M | 1.97 | w | 1.97 | $w_{(br)}$ | 1.98 | | | |
| | | | | | w+ | 1.91 | M | 1.91 | | | |
| 3400 | 1.87 | 113 | M | 1.87 | | | | | | | |
| 4200 | 1.85 | 122 | M | 1.85 | | | | | | | |
| | | | | | M | 1.81 | S | 1.80 | | | |
| | | | | | w | 1.76 | vw | 1.76 | | | |
| | | | | | $w_{(br)}$ | 1.72 | vw | 1.72 | | | |

TABLE I (*Continued*)

| (1) Westgren (calcd.) | | Cementite data Sample 7-68 | | | (2) Hägg carbide data Hägg | | Sample 7-255 | | (3) Hexagonal iron carbide data Sample 8-20 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *I* | *d/n* | *hk* | *I* | *d/n* | *I* | *d/n* | *I* | *d/n* | *hkl* | *I* | *d/n* |
| 430 | 1.68 | 004 | | | | | | | | | |
| 1100 | 1.68 | 023 | w | 1.68 | w(br) | 1.68 | vw | 1.67 | | | |
| | | | | | vw(br) | 1.625 | | | | | |
| | | | | | vw | 1.623 | vw | 1.62 | | | |
| | | | | | | | | | 102 | M | 1.60 |
| 1600 | 1.58 | 130 | w | 1.58 | M | 1.57 | S | 1.57 | | | |
| 950 | 1.51 | 222 | | | | | | | | | |
| 240 | 1.51 | 114 | w | 1.51 | w | 1.51 | vw | 1.50 | | | |
| | | | | | w | 1.47 | | | | | |
| | | | | | w | 1.41 | | | | | |
| 510 | 1.401 | 024 | vw | 1.403 | | | | | | | |
| | | | | | w | 1.38 | vw | 1.37 | 110 | M | 1.37 |
| | | | | | w | 1.33 | vw | 1.34 | | | |
| 6200 | 1.324 | 312 | M | 1.322 | w | 1.32 | vw | 1.32 | | | |
| | | | | | w(br) | 1.27 | w | 1.27 | | | |
| | | | | | w | 1.25 | w | 1.25 | 103 | M | 1.24 |
| 3200 | 1.219 | 140 | M | 1.222 | | | | | | | |
| 400 | 1.211 | 313 | M | 1.214 | | | | | | | |
| | | | | | S | 1.21 | M | 1.21 | | | |
| | | | | | w | 1.20 | | | | | |
| 580 | 1.200 | 141 | | | | | | | | | |
| 280 | 1.190 | 224 | M | 1.189 | w(br) | 1.19 | w | 1.17 | | | |
| 4800 | 1.157 | 233 | S | 1.159 | w(br) | 1.16 | w | 1.16 | 112 | M | 1.16 |
| 190 | 1.152 | 134 | | | | | | | 201 | | |
| 540 | 1.148 | 125 | | | | | | | | | |
| 170 | 1.146 | 142 | M | 1.149 | M | 1.15 | w | 1.14 | | | |
| 750 | 1.127 | 400 | | | | | | | | | |
| 3500 | 1.126 | 215 | | | | | | | | | |
| 4600 | 1.122 | 330 | | | | | | | | | |
| 2300 | 1.121 | 006 | S | 1.124 | S | 1.12 | M | 1.13 | | | |
| 4800 | 1.102 | 043 | S | 1.104 | w(br) | 1.10 | w(br) | 1.11 | | | |
| 2000 | 1.094 | 314 | vw | 1.096 | | | | | | | |
| | | | | | w(br) | 1.08 | w(br) | 1.09 | | | |
| 1800 | 1.085 | 411 | vw | 1.087 | | | | | | | |
| 2000 | 1.050 | 225 | | | | | | | | | |
| 1100 | 1.045 | 412 | w | 1.052 | | | | | | | |
| 1400 | 1.017 | 421 | vw | 1.002 | | | | | | | |
| 1500 | 1.003 | 206 | w | 0.992 | | | | | | | |
| 6800 | 0.991 | 243 | M(br) | 0.986 | | | | | | | |

vS = very Strong, S = Strong, M = Medium, w = weak, vw = very weak, + = slightly more intense, − = slightly less intense, br = broad.

The thermomagnetic curve for this product is given in Fig. 3, curve I. The temperature was not raised above 300° so as not to decompose the sample. The values obtained during the first heating (circles) correspond very closely to those obtained during the first cooling (X's), showing that the sample remained unchanged. Furthermore, a second heating and cooling (not shown) gave the same results. As an additional check on the thermal stability of the sample at temperatures up to 300°, another sample (with which a thermomagnetic curve similar to Fig. 3, curve I, had been obtained) was removed for X-ray diffraction analysis and found to consist of Hägg carbide. Thus the average Curie point at 247° is undoubtedly characteristic of the Hägg carbide. The uncertainty in this value as determined by thermomagnetic curves on different samples of this and similar products is ±3°. It will be noted that the magnetic moment at 300° is not zero. This is probably due either to some residual iron which was not converted to carbide, or to some magnetite formed during the carburization. The observed magnetic moment above the Curie point of the Hägg carbide can be accounted for by not more than 2% metallic iron or 6% magnetite.

The above-described sample was then heated at 580° for two hours and the thermomagnetic curve shown in Fig. 3, curve II, was obtained. This curve has a Curie point at 208°, considerably lower than that of curve I. After curve II was obtained, the sample was removed for X-ray diffraction analysis which proved that the sample contained cementite. The diffraction pattern was very sharp, and in Table I, column 1, the measured *d/n* values for the sample are compared with the

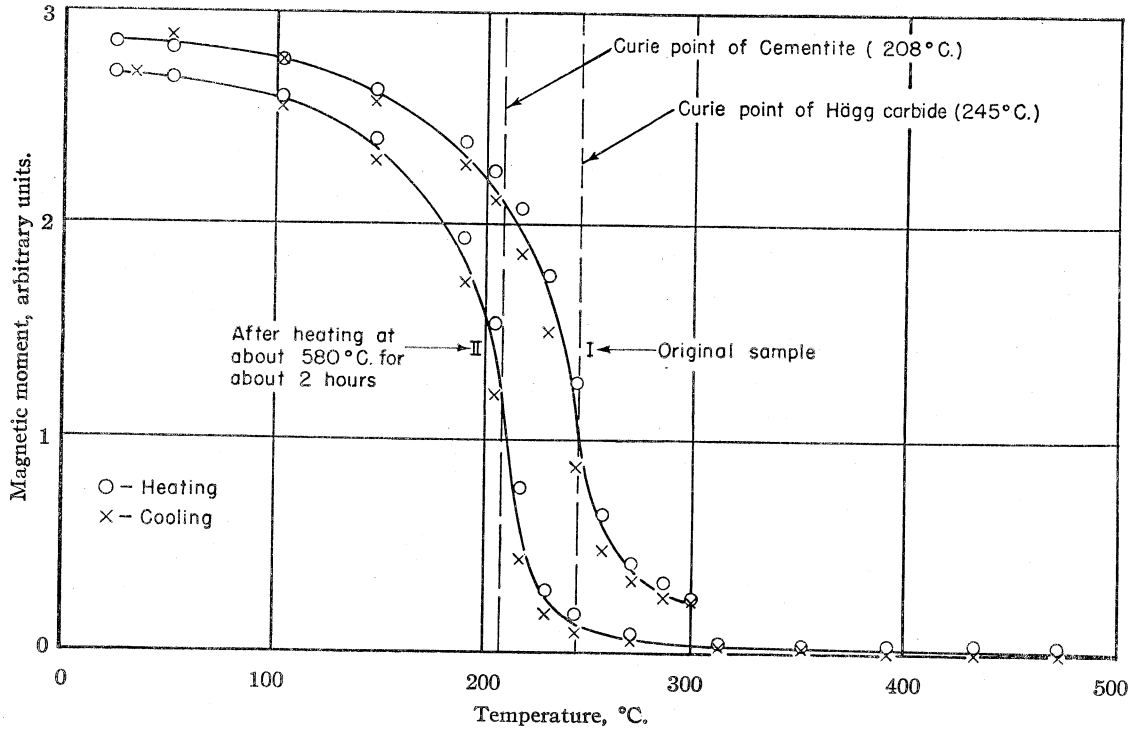



Fig. 3.—Thermomagnetic curves showing: I, presence of Hägg carbide in iron synthetic ammonia catalyst; II, same catalyst decomposed into cementite.

reported values for cementite as determined by Westgren.[12] (Only that part of Westgren's data is shown for which his calculated intensities are greater than 500 of his arbitrary units.) The agreement is very good. The Curie point, 208°, also checks the Curie points given for cementite in the literature, which range from 205° to 220°. (This wide range is due in part to experimental difficulties and in part to a certain arbitrariness in the definition of the term "Curie point." In the present paper, it has been defined as the point of inflection in the thermomagnetic curve.) Thus the Hägg carbide, with its characteristic diffraction pattern and its 247° Curie point, reacts at a sufficiently high temperature to form cementite with a different diffraction pattern and a different Curie point, according to the reaction

$$3Fe_2C \longrightarrow 2Fe_3C + C$$

Hägg Carbide Cementite Free Carbon

As can be seen from the curves in Fig. 3, the magnetic moment due to the Hägg carbide is roughly the same as that of an equivalent amount of cementite, since both curves were made on the same sample and with the balance at the same adjustment. Furthermore, the equivalent amounts of cementite and Hägg carbide are nearly equal in weight. As a result, the specific magnetizations of cementite and Hägg carbide must be about the same, or about 139 c. g. s. units per gram, according to Lange and Mathieu.[1]

(12) A. Westgren, *Jernkontorets Ann.*, **114**, 457 (1932).

**Carburized Iron–Copper–Potassium Oxide (100:10:0.32) Catalyst.**—The X-ray diffraction pattern contained faint lines due to the 200, 220, 311 and 222 reflections of face-centered copper metal. In addition, the relatively strong lines presented in Table I, column 3, were present. (One of the lines of the hexagonal iron carbide as observed in the diffraction pattern, the 2.08 Å., 101 line of the hexagonal carbide, coincides with the 111 line of copper. However, since this line is by far the strongest line of the pattern and since the copper lines are relatively weak due to the low percentage of copper, the high intensity of this line must be due to the hexagonal carbide.) No other lines were observed in the pattern.

Thermomagnetic analysis gave the curves shown in Fig. 4. During the first heating two Curie points were found, one at 247° and one at 380°, indicating the presence of two different ferromagnetic phases. As has been demonstrated, the first Curie point can be identified with the Hägg carbide. The occurrence of this phase is somewhat surprising because no lines from the X-ray diffraction pattern of the Hägg carbide could be detected. The other phase with the Curie point at 380° is unstable and decomposes below 435°, for upon cooling from 435° the curve (X's) does not coincide with the first heating curve (circles) but instead is the curve of a typical Hägg carbide. Similar experiments with other samples of this same preparation show that the 380° Curie point carbide decomposes appreciably in the range

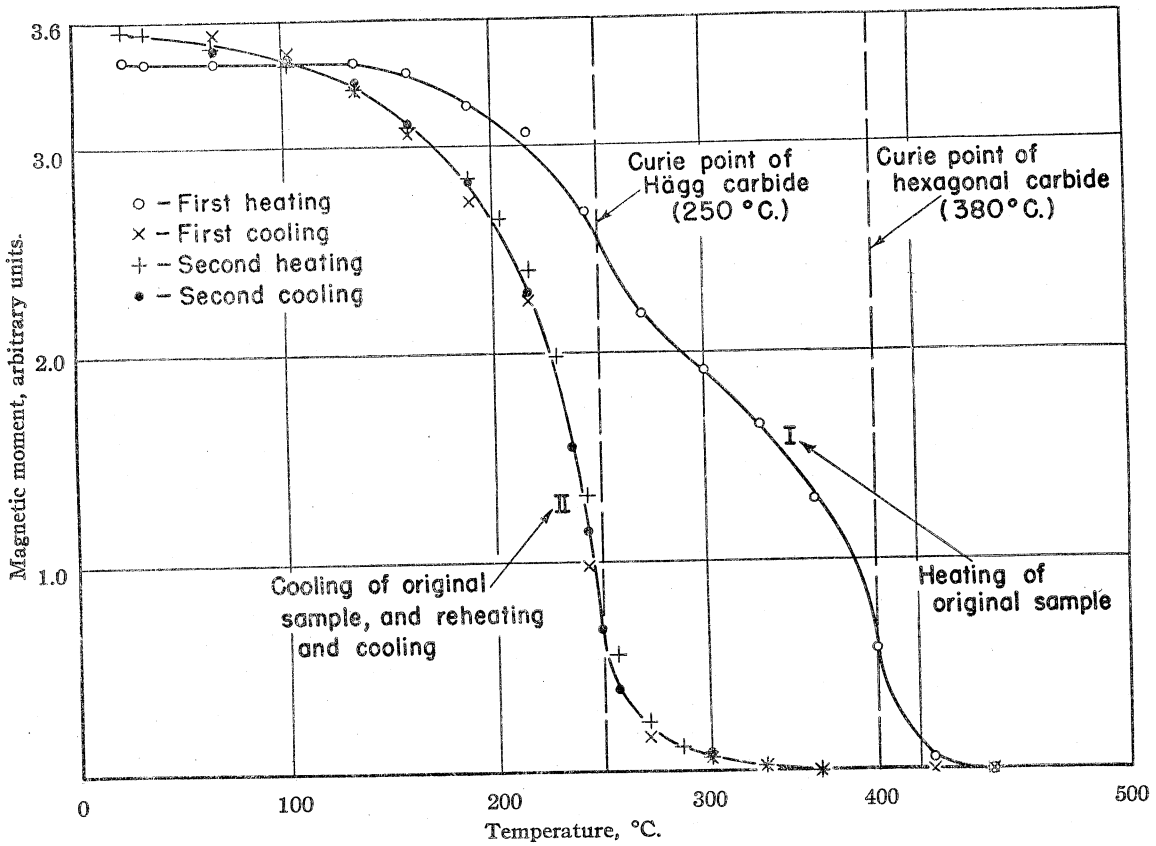



Fig. 4.—Thermomagnetic curves showing the presence of the Hägg and hexagonal iron carbides in copper-promoted Fischer–Tropsch catalyst, and the reversibility of the Hägg carbide curve.

300–380°. If the thermomagnetic measurements are made sufficiently rapidly, the point of inflection of the curve is invariant at 380° showing that it is a real transition temperature. The magnetic moment at 435° is very nearly zero, showing that no measurable amount of metallic iron or magnetite was present at that point. A second heating curve (crosses) and a second cooling curve( heavy dots) again coincided with the curve for Hägg carbide, showing the stability of the carbide under the conditions. This sample, when removed from the magnetic balance for X-ray diffraction analysis, was found to contain only Hägg carbide and copper. From these experiments one must conclude that the unstable carbide (Curie point 380°) is none other than the hexagonal close-packed iron carbide.

Since the formula of the Hägg carbide is nearly $Fe_2C$, as determined by both Hägg[4] and Jack,[5] and since the gross formula of this preparation is also $Fe_2C$, the formula of the hexagonal carbide must be $Fe_2C$. This formula can also be based on the similarity of structure between the hexagonal carbide and $Fe_2N$, which had been studied by Hägg.[13]

The over-all magnetic moment of the original sample is nearly the same as that of the Hägg carbide formed from it. Since the formulas of the two carbides are the same, one must conclude that the specific magnetization of the two carbides is the same, namely, about 140 c. g. s. units. Since the specific magnetization of both the Hägg carbide and the hexagonal carbide is known and since both carbides have the same formula, one can estimate the fraction of each carbide present from the shape of the thermomagnetic curve (Fig. 4, curve I). Calculated in this way, the Hägg carbide in the carburized catalyst is 10–30% of the total carbide.

Using the method previously described[14] and using the lattice parameter of face-centered cubic copper as 3.608kX, the lattice parameters of the hexagonal carbide were determined as $a_0$ = 2.749kX, $c_0$ = 4.340kX, and $a_0/c_0$ = 1.579.

In other experiments, the thermal stability of Hägg carbide was shown to be about the same in this catalyst as in the iron synthetic ammonia catalyst.

## Discussion

The 247° Curie point carbide or Hägg carbide is readily identified as the 265° Curie point carbide of Pichler and Merkel, since it was produced under similar conditions and behaved similarly. The

(13) G. Hägg, *Z. physik. Chem.*, **B8**, 455 (1930).

(14) L. J. E. Hofer and W. C. Peebles, THIS JOURNAL, **69**, 2497 (1947).

Curie points are sufficiently close together to support this identification. This carbide can also be identified with the so-called "cubic ferric sesquioxide saturated with potassium oxide" of Lefebvre and LeClerc.[15] This phase develops in iron Fischer–Tropsch catalysts during synthesis in the same way as the 265° Curie point carbide of Pichler and Merkel. Claims are made by both Lefebvre and LeClerc and by Pichler and Merkel that the phase improves the characteristics of the catalyst. Lefebvre and LeClerc place the Curie point at 250°, which is very close to that found in the present paper. On the other hand, Lefebvre and LeClerc present no positive evidence, such as X-ray diffraction data, that the phase with the 250° Curie point is really the cubic ferric sesquioxide ($\gamma$ $Fe_2O_3$) saturated with potassium oxide, which has been described in the literature. This *bona fide* cubic ferric sesquioxide saturated with potassium oxide does not have a Curie point at 250° but does have one at 630°.[16] From fragmentary data[17] it appears that the Hägg carbide (Curie point found about 250°) was also formed in Rheinpreussen (Moers, Ruhr Valley) catalysts during synthesis, although the distinctly different carbide was not recognized as such but was termed "unstable cementite."

The 380° Curie point carbide or hexagonal carbide is evidently the same as Pichler and Merkel's 380° Curie point carbide. Pichler and Merkel emphasized the importance of copper in promoting the formation of this carbide.

This carbide may possibly be identified with the carbides of Tutiya,[18] Hofmann and Groll,[19] and Brill and Mark.[20] For purposes of comparison the X-ray diffraction data of all three groups of investigators are compared with those for the hexagonal iron carbide in Table II. With the exception of a few extra lines contained in the data of Tutiya, and Hofmann and Groll, the data of these authors agree very well with those for the hexagonal carbide. The data of Brill and Mark, however, bear little resemblance to those for the hexagonal carbide.

The hexagonal carbide forms the carbon-rich extreme of the series of hexagonal close-packed $\epsilon$-phase carbonitrides studied by Jack.[3]

**Acknowledgment.**—The authors wish to thank Dr. H. H. Storch for his assistance and interest in this project, and Dr. H. P. Klug of Mellon Institute for helpful discussions. In addition they wish to thank Dr. R. B. Anderson and the personnel of the Catalyst Testing Unit for the activity data, H. Hewlett and K. Stein for the preparation of one of the catalysts, and W. E. Dieter for the ultimate chemical analysis.

TABLE II

COMPARATIVE *d/n* VALUES OF THE HEXAGONAL CLOSE-PACKED CARBIDE WITH THOSE OF THE CARBIDES OF TUTIYA, HOFMANN AND GROLL, AND BRILL AND MARK

vS = very Strong, S = Strong, M = Medium, w = weak, vw = very weak.

| Hexagonal Close-Packed Carbide *d/n* | *I* | Tutiya *d/n* | Hofmann and Groll *d/n* | *I* | Brill and Mark *d/n* |
|---|---|---|---|---|---|
| 2.38 | w | 2.32 | 2.263 | M | 2.28 |
| 2.16 | M | 2.20 | 2.172 | M | ... |
| 2.08 | vS | 2.065 | 2.050 | S | 2.12 |
| | | 1.815 | 1.802 | w | 1.826 |
| | | 1.706 | ... | | 1.716 |
| | | ... | 1.543 | M | ... |
| | | ... | 1.465 | w | 1.491 |
| 1.37 | M | 1.377 | 1.372 | w | 1.367 |
| 1.24 | M | 1.251 | 1.244 | vw | ... |
| | | 1.212 | 1.212 | M | 1.206 |
| 1.16 | M | 1.165 | 1.167 | M | 1.148 |

## Summary

1. The existence of two carbides of iron with formula $Fe_2C$ and having Curie points at 247° and 380° has been confirmed. (Pichler and Merkel reported the Curie points at 265° and 380°, respectively.)

2. A hexagonal close-packed carbide of iron has been prepared; this carbide has properties similar to those of the carbide described by Halle and Herbst.

3. The identity of the 380° Curie point carbide of Pichler and Merkel with the hexagonal carbide has been established.

4. The identity of the 247° (265° according to Pichler and Merkel) Curie point carbide with the Hägg carbide has been established.

5. The carbides reported by Hofmann and Groll and by Tutiya seem to be the hexagonal carbide.

6. The hexagonal carbide decomposes above about 300° to Hägg carbide which in turn decomposes at about 550° in one hour to cementite and free carbon.

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(15) H. Lefebvre and G. LeClerc, *Compt. rend.*, **203**, 1378 (1936); H. Lefebvre and G. LeClerc, *Congres. chim. ind. Compt. rend.*, 98th Congr. Nancy, France, Sept.–Oct., 1938, 725; G. LeClerc, *Compt. rend.*, **207**, 1099 (1938).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

# Polarography of Selenium and Tellurium. II. The +4 States

BY JAMES J. LINGANE AND L. W. NIEDRACH[1]

The polarographic behavior of the −2 states of selenium and tellurium has been discussed in a preceding paper.[2] The present paper is concerned with the polarography of the +4 states of these elements.

The only previous study is that of Schwaer and Suchy,[3] who observed three waves for selenium (IV) and tellurium(IV) in 1 *N* hydrochloric acid which they attributed to reduction to the +2, elemental, and −2 oxidation states. In very dilute solutions the first and second waves merged into one, which Schwaer and Suchy concluded was due to reduction to the elemental states. We observed an additional wave to those reported by Schwaer and Suchy in acid medium, and have been unable to confirm their hypothesis that one of the waves results from reduction to the +2 state.

With ammoniacal buffers Schwaer and Suchy observed a single well-developed wave with both selenium(IV) and tellurium(IV), which they concluded was due to reduction to the elemental state in both cases. Our experiments confirm this conclusion only in the case of tellurium, and we have found that the reduction of selenium(IV) proceeds completely to the −2 state in ammoniacal media.

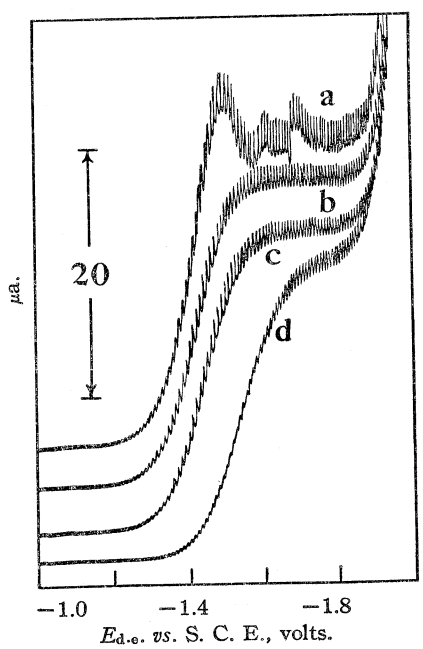



Fig. 1.—Polarograms of 1.5 millimolar selenium(IV) in 1 *M* ammonium chloride–ammonia at *p*H 8.0 with (a) 0, (b) 0.001, (c) 0.003 and (d) 0.01% gelatin.

Schwaer and Suchy found that tellurium(IV) is reduced from an approximately neutral tartrate solution, and they recommended this medium for the simultaneous determination of copper, bismuth and tellurium. They also observed that tellurium(IV) produces a wave in strongly alkaline solution, but selenium(IV) does not. The reduction product in alkaline medium was not identified.

In this investigation the polarographic characteristics of selenium(IV) and tellurium(IV) have been studied over a wide range of conditions, and the reduction states have been established conclusively by the coulometric analysis technique[4] based on controlled potential electrolysis with a large mercury cathode.

## Results and Discussion

The preparation of the pure selenium dioxide and tellurium dioxide used, and the technique of the coulometric and polarographic measurements, have been described in previous papers.[2,5]

**Selenium.**—The polarograms in Fig. 1 demonstrate the influence of gelatin on the selenium(IV) wave in ammoniacal medium. Decreasing the ammonium chloride concentration from 1 to 0.1 *M* at constant *p*H causes a slight negative shift of the half-wave potential, and the wave remains well developed when 0.001 to 0.003% gelatin is present. The *p*H of the solution may vary from 8.0 to 9.5, but at greater *p*H the wave shifts to a more negative potential and merges with the final current rise, and when the *p*H of the ammoniacal supporting electrolyte is smaller than about 8 additional ill-developed waves appear. The most satisfactory supporting electrolyte is 1 *M* ammonium chloride containing not more than 0.003% gelatin and ammonia to adjust the *p*H to 8.0 to 9.5. Under these conditions the diffusion current is directly proportional to the concentration of selenium(IV) as shown by the data in Table I. The half-wave potential is independent of the selenium(IV) concentration at a constant *p*H, but shifts to more negative values with increasing *p*H.

The reduction state in ammoniacal medium (1 *M* ammonium chloride and ammonia to *p*H 8.0) was established by electrolyzing a 1.59 millimolar solution of selenium(IV) with a large mercury cathode whose potential was maintained at −1.65 v. *vs.* S. C. E. by an automatic

(1) Allied Chemical and Dye Corporation Fellow, 1947–1948.

(2) J. J. Lingane and L. W. Niedrach, THIS JOURNAL, **70**, 4115 (1948).

(3) L. Schwaer and K. Suchy, *Coll. Czechoslov. Chem. Commun.*, **7**, 25 (1935).

(4) J. J. Lingane, THIS JOURNAL, **67**, 1916 (1945); *Anal. Chim. Acta*, in press (1948).

(5) J. J. Lingane and L. W. Niedrach, *ibid.*, **70**, 1997 (1948).

TABLE I

+4 SELENIUM IN AMMONIACAL BUFFERS (0.003% GELATIN) AT 25°

$m^{2/3}t^{1/6}$ = 1.450 mg.$^{2/3}$ sec.$^{-1/2}$

| Buffer | pH | Se(IV) millimolar | $E_{1/2}$ volts vs. S. C. E. | $i_d$ microamp. | $i_d/Cm^{2/3}t^{1/6}$ |
|---|---|---|---|---|---|
| 1 *M* $NH_4Cl$ | 6.9 | 1.00 | −1.39 | 16.2 | 11.2 |
| | 8.4 | 0.199 | −1.46 | 3.28 | 11.4 |
| | | .500 | −1.46 | 8.07 | 11.13 |
| | | .73 | −1.45 | 11.6 | 11.0 |
| | | .73 | −1.44 | 11.7 | 11.1 |
| | | 1.000 | −1.46 | 16.10 | 11.10 |
| | | 2.000 | −1.44 | 31.63 | 10.92 |
| | 9.4 | 0.199 | −1.53 | 3.20 | 11.1 |
| | | 0.500 | −1.53 | 7.95 | 10.97 |
| | | 1.000 | −1.53 | 16.04 | 11.06 |
| | | 2.000 | −1.52 | 31.74 | 10.96 |
| 0.1 *M* $NH_4Cl$ | 6.8 | 0.990 | −1.50 | 17.18 | 11.96 |
| | 8.2 | 1.000 | −1.56 | 17.18 | 11.86 |
| | 9.2 | 0.92 | −1.64 | 15.39 | 11.1 |
| | 10.0 | 0.81 | −1.73 | 13.0 | 11.0 |
| 1 *M* $NH_4$-Tartrate | 7.9 | 2.04 | −1.40 | 28.4 | 9.8 |
| | 9.4 | 2.04 | −1.53 | 29.4 | 10.2 |
| 0.1 *M* $NH_4$-Tartrate | 9.4 | 2.04 | −1.59 | 29.6 | 10.2 |

potentiostat.[6] The quantity of electricity passed was determined by a hydrogen–oxygen coulometer, and was found to correspond to 6 electrons per mole of selenium(IV). Thus at *p*H 8.0 the reduction proceeds to the −2 state, according to

$$HSeO_3^- + 6H^+ + 6e^- = HSe^- + 3H_2O \quad (1)$$

The change in current with time during the controlled potential coulometric electrolysis is shown in Fig. 2. Soon after the start the solution showed a light pink coloration which gradually deepened to a bright red as the current decreased to the minimum. The current then increased rapidly and the color of the solution changed to orange. After passing through the maximum the current decreased continuously while the color became less intense and finally the solution became colorless. Although no solid phase was observed, the red color was undoubtedly due to colloidal selenium. Since in a controlled potential reduction the current at any instant is directly proportional to the momentary concentration of the electroreducible substance, the minimum and maximum in Fig. 2 are readily understandable. The −2 selenium formed in the primary electrode reaction 1 reacted with the remaining +4 compound and precipitated the element, $HSO_3^- + 2HSe^- + 3H^+ = 3Se + 3H_2O$. When all the +4 compound had been reduced in this manner, the current went through the minimum. The slow reduction of the element then produced −2 selenium which dissolved the element as polyselenide, $xSe + Se^{--} = Se_x^{--}$. The current increased until all the element had dissolved, and then decreased finally as the polyselenide was reduced.

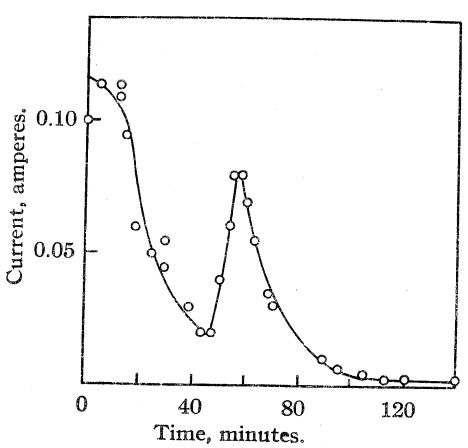



Fig. 2.—Current–time curve during coulometric reduction of 1.59 millimolar selenium(IV) in 1 *M* ammonium chloride–ammonia at *p*H 8.0 with potential of large mercury cathode at −1.65 v. *vs.* S. C. E.

(6) J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **17**, 332 (1945).

Polarograms recorded at various stages of the electrolysis confirmed the absence of −2 selenium when the +4 compound was present. A polarogram obtained with the final clear and colorless solution, agreed with those for −2 selenium.[2]

The effect of *p*H from 0 to 14 is illustrated by

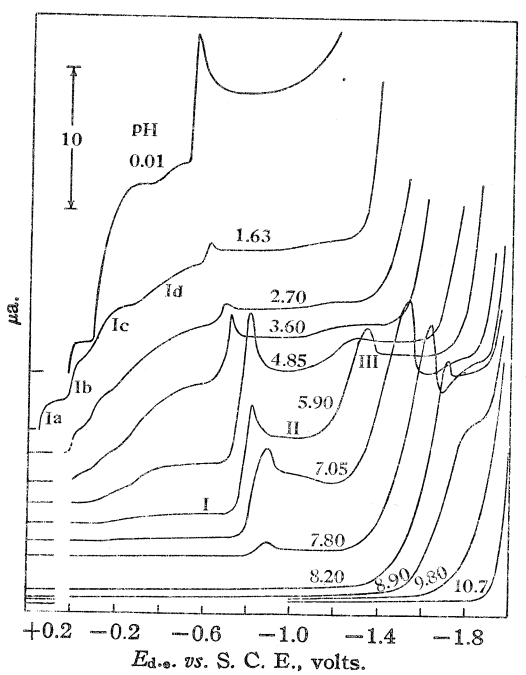



Fig. 3.—Tracings of polarograms of 1 millimolar +4 selenium at the various *p*H values indicated for each curve. The galvanometer zero for each curve is indicated by the short lines on the left ordinate. At low *p*H, hydrochloric acid and citrate buffers were used, at intermediate *p*H, phosphate buffers, and borate and carbonate buffers were used for the alkaline region. No gelatin or other maximum suppressor was present.

the tracings of automatically recorded polarograms in Fig. 3. The solutions used were 1 millimolar in +4 selenium and contained no maximum suppressor. No specific effects of the buffer constituents were found upon comparing polarograms obtained in the ranges where the buffers overlapped.

The presence of three major waves is illustrated by the polarograms at *p*H 4.85 and 5.90 in Fig. 3. The first of these is resolved into several additional waves in the lower *p*H range.

Moderate amounts of gelatin eliminated the maxima from all waves; however, at the higher *p*H as little as 0.001% suppressed the wave III quite markedly, while in hydrochloric acid (*p*H 0.01) wave II is sensitive to gelatin.

In 1 *N* hydrochloric acid the three waves mentioned by Schwaer and Suchy were found, and the effects of the selenium(IV) concentration on their form was confirmed. A fourth wave at the very start of the polarogram in 1 *N* hydrochloric is also observable, which indicates that the reduction potential of selenium(IV) is more positive than the dissolution potential of mercury in 1 *N* hydrochloric acid.

The effects of selenium(IV) concentration at *p*H 1.63 are illustrated in Fig. 4. Several additional steps develop as the concentration of selenium(IV) is increased. At higher values of *p*H the additional steps do not appear and the general form does not change with the selenium (IV) concentration.

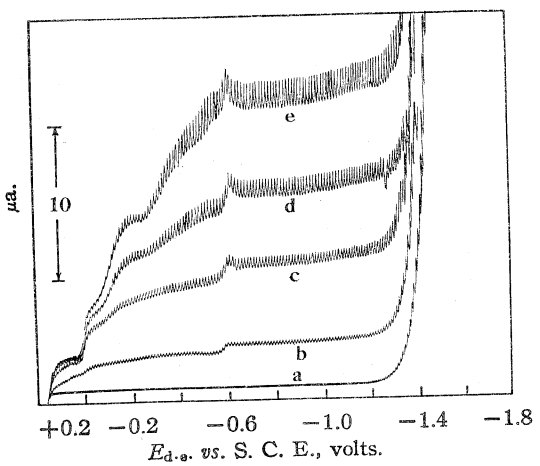



Fig. 4.—Polarograms of (a) 0, (b) 0.199, (c) 0.61, (d) 1.00 and (e) 1.50 millimolar selenium(IV) in 0.5 *M* citric acid at *p*H 1.63.

Figure 5 shows polarograms of selenium(IV) in unbuffered potassium chloride and ammonium chloride. In potassium chloride at *p*H 3.3 reduction begins but normal development of the waves is prevented by the increasing *p*H at the electrode surface as hydrogen ion is consumed. In neutral potassium chloride (curve b) the production of hydroxide ion at the surface of the mercury drops completely inhibits the reduction until the potential exceeds about −1.6 v. In the unbuffered ammonium chloride solutions (curves c and d) nearly normal waves are obtained because the hydrogen ion required for the reduction is furnished by ammonium ion, and the resultant production of ammonia buffers the solution at the electrode surface and prevents the *p*H from increasing.

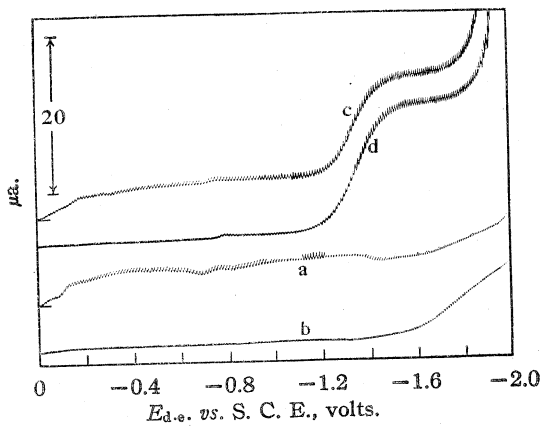



Fig. 5.—Polarograms of 1 millimolar selenium(IV) in (a) 1 *M* potassium chloride at *p*H 3.3, (b) 1 *M* potassium chloride at *p*H 7.2, (c) 1 *M* ammonium chloride at *p*H 3.2 and (d) 1 *M* ammonium chloride at *p*H 6.2. All solutions contained 0.003% gelatin.

The absence of anodic waves under all conditions shows that oxidation of +4 selenium to the +6 state does not occur at the dropping electrode. Furthermore, in agreement with Schwaer and Suchy, we found no reduction waves for either +6 selenium or +6 tellurium at any *p*H.

The complexity of the cathodic waves in Fig. 3 is due in part to stepwise reduction and it also suggests the reduction at different potentials of the different species formed by the dissociation of selenous acid. It is well known that the different ionization species of certain weak acids can produce separate reduction waves when the establishment of dissociation equilibrium is slow compared to the drop time.[7,8,9] Brdicka and his collaborators[10,11] have recently developed quantitative relations by means of which the several wave heights observed in such cases can be correlated with the rate constants involved in the establishment of the dissociation equilibria.

The upper graph in Fig. 6 shows the *total* diffusion current constant $i_d/(Cm^{2/3}t^{1/6})$ as a function of *p*H, and the solid curves in the lower graph show the observed *relative* heights of waves I, II and III as a function of *p*H. The dotted curves in the lower graph of Fig. 6 show the

(7) N. H. Furman and C. E. Bricker, THIS JOURNAL, **64**, 660 (1942).

(8) P. Herasymenko, *Z. Elektrochem.*, **34**, 129 (1928).

(9) L. Meites, Ph.D. Thesis, Harvard University, 1947.

(10) R. Brdicka and K. Weisner, *Coll. Czech. Chem. Commun.*, **12**, 138 (1947).

(11) J. Koutecky and R. Brdicka, *ibid.*, **12**, 337 (1947).

relative proportions of the three species $H_2SO_3$, $HSeO_3^-$, and $SeO_3^=$ as a function of *p*H, and they were computed using the values $2.4 \times 10^{-3}$ and $4.8 \times 10^{-9}$ for the dissociation constants of selenous acid.[12]

There is seen to be approximate agreement of the shapes of the curves for the relative heights of the three waves and the relative equilibrium concentrations of the $H_2SeO_3$, $HSeO_3^-$, and $SeO_3^=$, which might be regarded as evidence that the three main waves result from reduction of the three different species. However, there are two facts which indicate that this is not a satisfactory interpretation. In the first place the change of the total diffusion current constant with *p*H shown by the upper curve in Fig. 6 is much too large to be attributed to different diffusion coefficients of the three species, and it points to a different reduction product, involving fewer electrons, at intermediate *p*H values. Since the coulometric analyses conclusively prove that reduction proceeds all the way to −2 selenium ($n = 6$) at *p*H 8.0 and above, and since the total diffusion current constant at small *p*H values is of the same order of magnitude as at high *p*H, the reduction at low *p*H must also involve 6 electrons. The diffusion current constants at intermediate *p*H are very nearly two-thirds of the extreme values, indicating a 4-electron reduction at *p*H values between about 3 and 7. Secondly, the cathodic half-wave potentials of wave II are the same (within 0.03 v.) at all *p*H values as the half-wave potentials of the *anodic* wave of −2 selenium discussed in a previous paper.[2] This anodic wave was shown[2] to result from the reaction

$$Hg + H_2Se = HgSe + 2H^+ + 2e \qquad (2)$$

at small *p*H values, and to the analogous reactions involving $HSe^-$ and $Se^=$ at intermediate and high *p*H, and the observed anodic half-wave potentials agreed very well with values computed from the standard potential of reaction 2 and the ionization constants of hydroselenic acid over the entire *p*H range. Wave II is thus the cathodic reflection of the anodic wave of −2 selenium.

It is evident, therefore, that wave I cannot be due to a net reduction to −2 selenium because at potentials more positive than wave II the −2 selenium depolarizes the dropping electrode anodically according to reaction 2. We believe that the *primary* electrode reaction at potentials more positive than wave II (*i. e.*, on wave I) is a 6-electron reduction producing −2 selenium according to

$$H_2SeO_3 + 6e + 6H^+ = H_2Se + 3H_2O \qquad (3)$$

and this is followed by the 2-electron anodic reaction 2. The *net* result is a 4-electron reduction in which mercuric selenide is the final product

$$H_2SeO_3 + 4e^- + 4H^+ + Hg = HgSe + 3H_2O \qquad (4)$$

(12) D. M. Yost and H. Russell, "Systematic Inorganic Chemistry," Prentice-Hall Inc., New York, N. Y., 1944.

This interpretation of wave I was confirmed by coulometric reduction of a 1 millimolar solution of selenium(IV) in a citrate buffer of *p*H 1.6. The potential of the large mercury cathode was maintained constant at −0.45 v. *vs.* S. C. E., a value corresponding to the top of wave I at this *p*H (see Fig. 3), and the coulometer reading corresponded to a 4-electron reduction. The reduction product was a black solid which qualitative tests showed to be a mercury compound (*i. e.*, mercuric selenide).

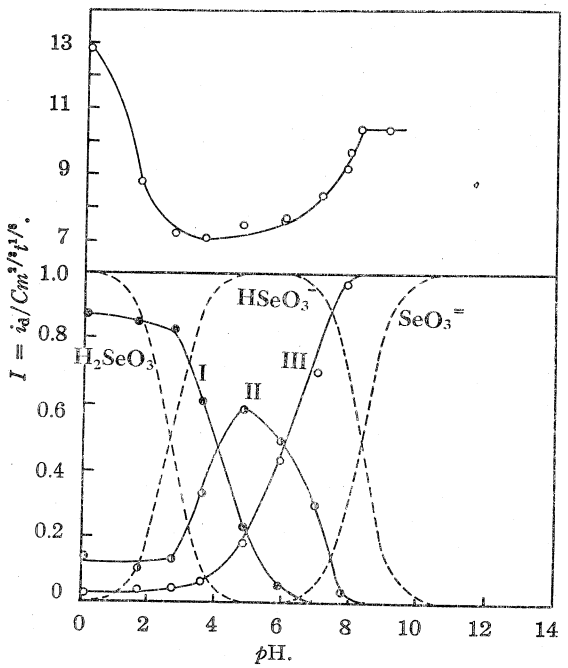



Fig. 6.—The upper curve shows the variation of the *total* diffusion current constant of 1 millimolar selenium(IV) with *p*H. The solid curves in the lower graph are the *relative* observed heights of the main waves I, II and III, and the dashed curves show the relative equilibrium concentrations of $H_2SeO_3$ (left), $HSeO_3^-$ (middle) and $SeO_3^=$ (right), calculated from the dissociation constants of selenous acid.

The fact that at potentials more negative than the half-wave potential of wave II the anodic reaction 2 is excluded, and yet at intermediate *p*H values the *total* diffusion current constant corresponds to only a 4-electron reduction, is, we believe, due to the formation of elemental selenium. The −2 selenium produced by the primary reaction 3 diffuses away from the electrode surface and reacts in the diffusion layer with the incoming hydrogen selenite ion to precipitate elemental selenium

$$HSeO_3^- + 2H_2Se + H^+ = 3Se + 3H_2O \qquad (5)$$

Since it is known from the coulometric electrolyses that elemental selenium is only slowly reduced (see Fig. 2), and since it is formed in the diffusion layer at some distance from the electrode surface,

the *net* reaction at intermediate *p*H is the 4-electron reduction

$$HSeO_3^- + 4e^- + 5H^+ = Se + 3H_2O \qquad (6)$$

At a *p*H of 8 or above, and at low *p*H values, reaction 5 (or the analogous reactions involving $H_2SeO_3$, $SeO_3^=$, $HSe^-$ and $Se^=$) proceeds so slowly that no appreciable formation of elemental selenium occurs during the drop life, and the final product is −2 selenium.

No evidence has been obtained at any *p*H for the reduction to +2 selenium postulated by Schwaer and Suchy.

At *p*H values below 8 the diffusion current quotients $i_d/C$ of the separate waves, as well as that of the total wave, were found to vary significantly with the concentration of +4 selenium. For example at *p*H = 5.0 the value of $i_d/(C\,m^{2/3}t^{1/6})$ for the total wave decreased from 10.5 and 8.5 when the concentration of selenium(IV) was increased from 0.2 to 2 millimolar. Hence supporting electrolytes of *p*H smaller than about 8 are not suitable for practical analytical purposes.

**Copper and Selenium.**—Since copper and selenium frequently occur together their simultaneous polarographic determination in ammoniacal medium was investigated. As shown in Fig. 7, polarograms of ammoniacal mixtures of +2 copper and +4 selenium display the familiar double wave which results from the stepwise reduction of the tetramminocupric ion, followed by the well-developed selenium wave.

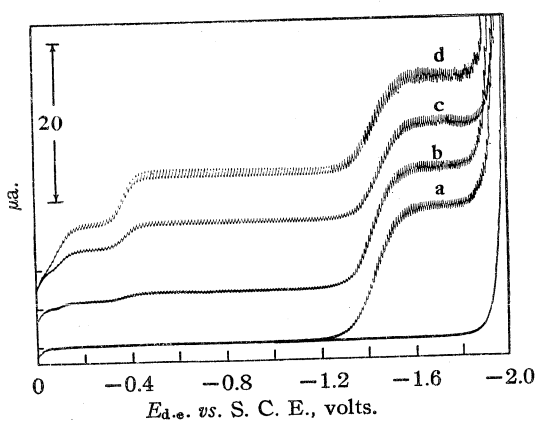



Fig. 7.—Polarograms of 1 millimolar selenium(IV) in 1 *M* ammonium chloride-ammonia at *p*H 8.4 with (a) 0, (b) 0.302, (c) 1.00 and (d) 2.00 millimolar copper(II). Gelatin (0.003%) was used as maximum suppressor. The galvanometer zero for each curve is indicated by the short marks on the left-hand ordinate.

Although the waves of both elements are well developed their analytical application is complicated by the fact that the height of the selenium wave decreases markedly with increasing concentration of copper. With 1.00 and 2.00 millimolar copper the height of the selenium wave in Fig. 7 is only 72 and 75% of its value in the absence of copper. This interesting effect is not due to a decreased diffusion current of the selenium, but rather to a smaller contribution of copper to the total diffusion current at potentials at which selenium(IV) is reduced. The −2 selenium formed at the electrode surface reacts with the incoming tetramminocupric ion in the diffusion layer, precipitating cupric selenide

$$Cu(NH_3)_4^{++} + Se^= = CuSe + 4NH_3 \qquad (7)$$

and the contribution of copper to the total diffusion current is correspondingly diminished. Since 6 electrons are involved in the formation of each selenide ion, but the reduction of the copper complex requires only 2 electrons, it is evident that if the diffusion coefficients of copper(II) and selenium(IV) were the same, then increasing the concentration of copper should decrease the apparent height of the selenium wave only until the molar concentrations of copper and selenium are equal. At this point the apparent height of the selenium wave alone should be two-thirds of its original value. The observed selenium wave height (72%) is slightly larger than two-thirds its original value because the diffusion coefficient of the tetramminocupric ion is somewhat larger than that of selenium(IV), and also because the precipitation of cupric selenide is not quite complete. With still larger concentrations of copper the apparent height of the selenium wave should remain constant, and this is the observed result. In other words, the *total* diffusion current at the potential of the selenium wave (−1.6 to −1.8 v.) remains practically constant until the quantity $CD^{1/2}$ for copper exceeds that for the tellurium, and then increases in direct proportion to the increased copper concentration.

Correction for this effect is complicated by the fact that the precipitation of cupric selenide is not quite complete, and hence in practical work the correction will have to be determined empirically. This same effect will doubtless also be observed with other metals that form insoluble selenides.

**Tellurium.**—The low solubility of tellurium dioxide in neutral and acid solutions limits the choice of supporting electrolytes for experiments at *p*H less than 7. It was found that the solubility in acid medium is greatly increased by the presence of citrate or tartrate, apparently because of the formation of telluryl citrate complexes, and in citrate media it is possible to work with concentrations of tellurium(IV) up to about 5 millimolar. Tellurium dioxide is freely soluble in ammoniacal and alkaline media.

Figure 8 shows tracings of polarograms of 1 millimolar tellurium(IV) in 0.5 *M* citrate buffers of *p*H between 0.4 and 6.88. Maximum suppressors such as methyl red, thymol blue, α-naphthol and thiourea are without effect, and even gelatin up to 0.01% does not eliminate the very large maximum.

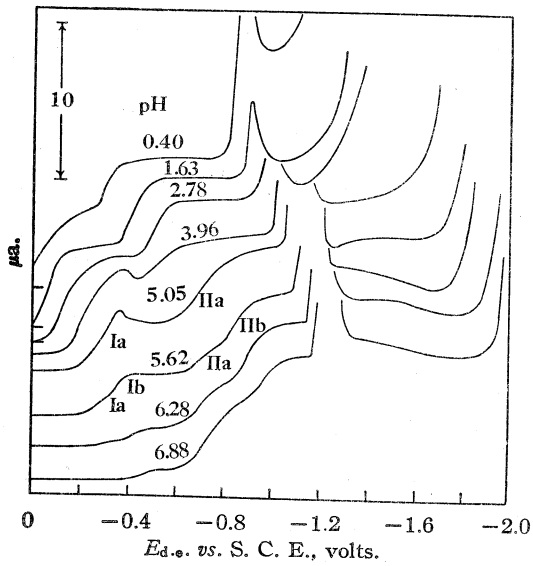



Fig. 8.—Polarograms of 1 millimolar +4 tellurium in 0.5 *M* citrate buffers at the *p*H values indicated for each curve. No maximum suppressor was present.

There are two main waves preceding the large maximum, and these are best developed at *p*H values between 0.4 and 3. The approximate equality of the heights of these two waves with 1 millimolar tellurium(IV) up to about *p*H 5 is purely fortuitous, and does not correspond to stepwise reduction, nor to the intermediate production of +2 tellurium. For example, with a citrate buffer of *p*H 1.63 only a single wave preceding the maximum is observed when the concentration of tellurium(IV) is smaller than about 0.4 millimolar. With increasing tellurium(IV) concentration the second wave at −0.4 v. develops, but the first wave retains a virtually constant height. With 3 millimolar tellurium(IV) the second wave height becomes nearly four times the height of the first wave. At *p*H 1.63, the *total* diffusion current measured at −0.6 to −0.8 v. was strictly proportional to the concentration of tellurium(IV) between 0.1 and 3 millimolar, with $i_d/(C\ m^{2/3}t^{1/6})$ equal to 5.72 ± 0.07. The diffusion current constant increases from 4.8 at at *p*H of 0.4 to a maximal value of 5.75 at about *p*H 2, and then gradually decreases to 4.8 as the *p*H is increased to 7.

The virtual constancy of the first wave height with increasing concentration of tellurium(IV) suggests the formation of a film of reduction product (elemental tellurium) on the electrode surface which inhibits further reduction until the potential exceeds about −0.4 v.

Coulometric analysis at −0.65 v. showed that the total double wave at *p*H 1.63 results from a 4-electron reduction to elemental tellurium

$$H_2TeO_3 + 4e^- + 4H^+ = Te + 3H_2O \qquad (8)$$

Since the change in the total diffusion current constant is not very great between *p*H 0.4 and 7, it is evident that the total wave over this *p*H range is due to reduction to the element.

At *p*H values between 5.5 and 7.0 additional poorly defined waves are observable before the maximum. These may be due in part to reduction to the +2 state, but film formation and reduction of the different ionization species of tellurous acid are probably more important factors.

In ammoniacal medium only one very well developed wave appears as shown in Fig. 9. In two coulometric reductions with the potential of the large mercury cathode at −0.90 v. *vs.* S.C.E. the coulometer reading corresponded to 4.07 and 3.95 electrons per mole of tellurium (IV) reduced, proving that the wave results from reduction to the element.

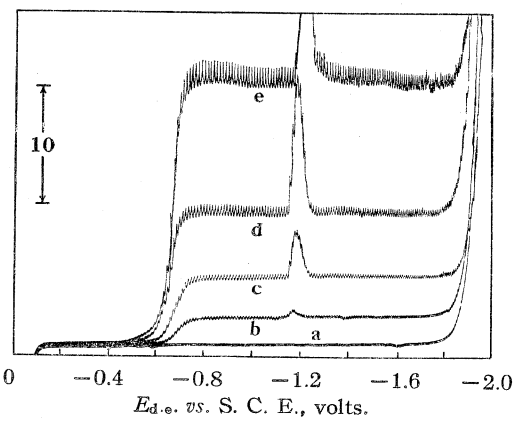



Fig. 9.—Polarograms of (a) 0, (b) 0.202, (c) 0.500, (d) 1.00 and (e) 2.00 millimolar tellurium(IV) in 1 *M* ammonium chloride–ammonia at *p*H 9.4 in the presence of 0.003% gelatin.

The polarographic characteristics in ammoniacal buffers are summarized in Table II. All the solutions contained 0.003% gelatin. The values of $i_d/(Cm^{2/3}t^{1/6})$ in the last column display a

TABLE II

+4 TELLURIUM IN AMMONIACAL BUFFERS AT 25°

| Buffer | *p*H | *C*, millimolar | $E_{1/2}$ *vs.* S.C.E. | $i_d$, microamp. | $\frac{i_d}{Cm^{2/3}t^{1/6}}$ |
|---|---|---|---|---|---|
| 1 *M* $NH_4Cl$ | 8.4 | 0.202 | | 2.37 | 7.75 |
| | | 0.500 | −0.64 | 5.83 | 7.72 |
| | | 1.000 | − .63 | 11.40 | 7.54 |
| | | 2.000 | − .62 | 22.48 | 7.43 |
| | 9.4 | 0.202 | − .69 | 2.43 | 7.95 |
| | | 0.500 | − .67 | 6.04 | 7.99 |
| | | 1.000 | − .66 | 11.74 | 7.76 |
| | | 2.000 | − .66 | 22.44 | 7.75 |
| 1 *M* $NH_4$ Tartrate | 9.3 | 0.083 | − .72 | 0.85 | 6.7 |
| | | 1.67 | − .68 | 15.4 | 6.1 |
| | 10.0 | 0.083 | − .80 | 0.80 | 6.3 |
| | | 1.67 | − .77 | 15.8 | 6.3 |
| 0.1 *M* $NH_4$ Tartrate | 9.0 | 0.083 | − .76 | 0.98 | 7.8 |
| | | 1.67 | − .76 | 18.9 | 7.5 |
| | 10.0 | 0.083 | − .83 | 0.92 | 7.3 |
| | | 1.67 | − .79 | 18.1 | 7.2 |

small but significant decrease with increasing concentration of tellurium(IV) at any given *p*H, the trend being less pronounced the higher the *p*H. Thus the diffusion current is not strictly proportional to $C$ over a wide range of concentrations, but the discrepancy is small.

Single well developed waves were also obtained in borate and carbonate buffers between *p*H 7.8 and 11.1. The half-wave potentials at a given *p*H are somewhat more negative in borate and carbonate buffers than in ammoniacal medium. For example, at *p*H 9.4 the half-wave potentials in 0.5 *M* carbonate and borate buffers were −0.87 v. and −0.88 v., respectively, compared to −0.68 v. in 1 *M* ammonium chloride–ammonia at the same *p*H. The half-wave potential of the alkaline wave shifts markedly to more negative values with increasing *p*H; in 0.5 *M* borate buffers of *p*H 7.8, 8.8, 10.5 and 11.1 the values were *seriatim* −0.74, −0.84, −0.96 and −1.18 v. *vs.* S.C.E.

In 0.1 and 1 *M* sodium hydroxide in the presence of gelatin, a very well developed single wave is obtained as shown in Fig. 10. Without gelatin a small prewave precedes the main wave, but this is completely eliminated with 0.01% gelatin. The half-wave potentials in 0.1 and 1 *M* sodium hydroxide in the presence of 0.003% gelatin are −1.22 v. and −1.19 v., respectively. It is interesting to note that these values are very close to the standard potential (−1.21 v. with 1 millimolar tellurium) of the couple $Te + 2e = Te^{=}$ (see ref. 2). This indicates that the reduction proceeds all the way to −2 tellurium and that the $Te \rightarrow Te^{=}$ stage is the potential determining step.

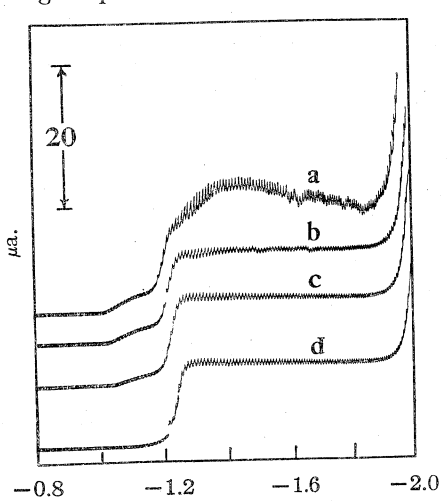



Fig. 10.—Polarograms of 0.837 millimolar tellurium(IV) in 1 *M* sodium hydroxide with (a) 0, (b) 0.001, (c) 0.003 and (d) 0.01% gelatin.

That reduction in sodium hydroxide medium proceeds to −2 tellurium, according to

$$TeO_3^{=} + 3H_2O + 6e^{-} = Te^{=} + 6OH^{-} \qquad (9)$$

was verified by the coulometric technique. A 1.37 millimolar solution of tellurium(IV) in 1 *M* sodium hydroxide was reduced with the potential of the large mercury cathode at −1-60 v. *vs.* S.C.E. The coulometer reading after the current decreased to zero corresponded to 5.97 electrons per mole of tellurium(IV) reduced. The current decreased from an initial value of 135 milliamp. to less than 1 milliamp., showing that reduction at this potential proceeds with 100% current efficiency. The current–time curve during this reduction had the same shape as that for the reduction of selenium(IV) shown in Fig. 2. During the first stage of the electrolysis elemental tellurium precipitated, then dissolved to form deep violet polytelluride ion, and the latter was finally completely reduced to colorless telluride ion.

The data in Table III show that $i_d/(C\,m^{2/3}t^{1/6})$ for tellurium(IV) in 1 *M* sodium hydroxide shows a significant variation with concentration. The trend is smaller with 0.003% gelatin than with either 0.001 or 0.01%. In the former case $i_d$ is a linear function of $C$ to ±1% over the concentration range 0.2 to about 2.8 millimolar.

TABLE III

DIFFUSION CURRENT CONSTANT OF +4 TELLURIUM IN 1 *M* SODIUM HYDROXIDE AT 25°

| $C$, millimolar | $i$, microamp. | $i_d/Cm^{2/3}t^{1/6}$ | $C$, millimolar | $i$, microamp. | $i_d/Cm^{2/3}t^{1/6}$ |
|---|---|---|---|---|---|
| 0.001% gelatin | | | 0.334 | 4.70 | 9.75 |
| 0.0837 | 1.17 | 9.7 | .500 | 7.03 | 9.75 |
| .1674 | 2.37 | 9.8 | .834 | 11.67 | 9.70 |
| .3344 | 4.92 | 10.18 | 1.169 | 16.62 | 9.85 |
| .502 | 7.46 | 10.32 | 1.668 | 23.34 | 9.70 |
| .837 | 11.66 | 9.65 | 2.167 | 30.48 | 9.75 |
| 1.172 | 16.78 | 9.92 | 2.835 | 39.37 | 9.62 |
| 1.674 | 23.72 | 9.82 | 3.335 | 44.08 | 9.16 |
| 2.175 | 30.24 | 9.64 | 0.010% gelatin | | |
| 2.845 | 36.13 | 8.81 | 0.0839 | 0.86 | 7.1 |
| 3.344 | 40.32 | 8.35 | .1672 | 2.14 | 8.9 |
| 0.003% gelatin | | | .335 | 4.32 | 8.92 |
| 0.0834 | 1.12 | 9.3 | .839 | 11.62 | 9.60 |
| .1668 | 2.32 | 9.6 | 1.677 | 23.65 | 9.77 |
| | | | 3.34 | 46.31 | 9.60 |

Since +4 selenium does not produce a wave in 1 *M* sodium hydroxide this is a most suitable supporting electrolyte for the determination of tellurium in the presence of selenium, especially when selenium predominates. As Schwaer and Suchy[3] pointed out, an ammoniacal supporting electrolyte is useful for the simultaneous determination of both elements, the wave of tellurium preceding that of selenium by about 0.8 v.

A most striking feature of the polarograms of +4 tellurium is the very large maximum which appears in the diffusion current plateau at all *p*H values in all the supporting electrolytes, except sodium hydroxide. This maximum is unusual in that it occurs after the diffusion current plateau has been reached, or in the middle of the plateau in ammoniacal media and in borate and

carbonate buffers, rather than as an extension of the rising part of the wave as in the case of ordinary maxima. The maximum is also exceptionally indifferent to the usual maximum suppressors. Significantly the potential at which the maximum develops coincides at all *p*H values with the half-wave potential of the *anodic* wave of the reaction $Te^{=} = Te + 2e^{-}$ discussed in a preceding paper.[2] It is also significant that the only medium in which the maximum is absent is 1 *M* sodium hydroxide, which is probably related to the fact that the cathodic tellurium(IV) wave occurs at almost exactly the same potential as the anodic $Te^{=}$ wave in this medium.[2] The occurrence of the maximum is thus intimately related to the $Te^{=}$–Te couple.

Apparently the rising part of the maximum reflects the beginning of reduction of the tellurium(IV) to the −2 state, but when this starts the normal diffusion layer at the surface of the mercury drops, is disrupted, and a vigorous stirring action ensues which causes the current to rise to a very large value. Observations under the microscope revealed the formation of a brown turbidity (elemental tellurium) as a succession of bands which expanded radially from the drop. At potentials before the maximum, as well as after it, the deposited tellurium formed an adherent coating on the drop and no streaming or turbidity near the drop was observed. The band pattern suggests a rhythmically recurrent process during the drop life. A likely mechanism is that the $Te^{=}$ which forms partially dissolves the adherent tellurium deposit, forming polytelluride ion in the diffusion layer and freeing part of the electrode surface. Part of the relatively large concentration of polytelluride ion formed near the electrode surface is rapidly reduced to $Te^{=}$, causing a large surge of current, and part of it diffuses outward from the electrode and reacts with tellurium(IV) to precipitate elemental tellurium and produce the observed bands. The combination of these processes and the resultant density gradients disturbs the diffusion layer and produces stirring which accelerates the transfer of tellurium(IV) to the electrode surface. The reduction of the enhanced concentration of tellurium(IV) to elemental tellurium proceeds at a faster rate than its reduction to $Te^{=}$, and than the reaction between the elemental tellurium and $Te^{=}$, so that the adherent tellurium coating tends to reform, the current surge decreases, and the diffusion layer begins to reestablish itself until the formation of polytelluride again catches up with the decreased rate of reduction of tellurium(IV). The cycle then repeats. The fact that at a slightly more negative potential these processes abruptly cease, so that the current falls to the original value corresponding to only a 4-electron reduction, remains to be explained.

**Tellurium in Presence of Other Metals.**—Metals which produce polarographic waves preceding that of tellurium(IV) and which form insoluble tellurides exert a pronounced suppressing effect on the apparent height of the tellurium wave in strongly alkaline medium. This effect, which is analogous to the suppressive action of copper on the selenium wave, is illustrated by the polarograms in Fig. 11 of mixtures of lead and tellurium in 1 *M* sodium hydroxide. The first wave at −0.76 v. is the normal wave due to reduction of the hydrogen plumbite ion, and the second is that for the reduction of tellurium(IV) to telluride ion.

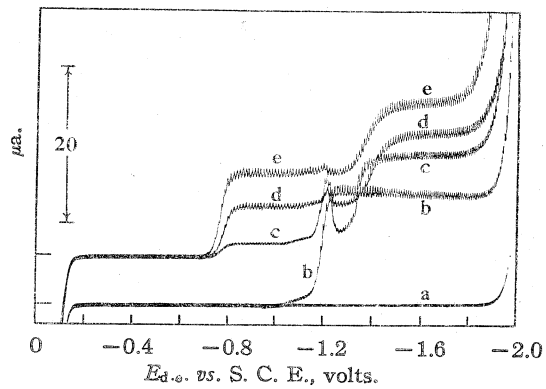



Fig. 11.—Polarograms of 1 millimolar tellurium(IV) in 1 *M* sodium hydroxide containing 0.003% gelatin with (a) 0, (b) 0.30, (c) 1.20 and (e) 2.00 millimolar lead ion added.

Amounts of lead up to the point where the product $CD^{1/2}$ for the plumbite ion becomes equal to this product for the tellurium(IV) produce no increase in the *total* diffusion current between −1.5 and −1.8 v., but the apparent height of the tellurium wave decreases. With larger amounts of lead the height of the tellurium wave remains constant and the *total* diffusion current increases in direct proportion to the excess lead added. These phenomena are due to the fact that the telluride ion produced at the electrode surface reacts in the diffusion layer with the incoming hydrogen plumbite ion to precipitate lead telluride

$$Te^{=} + HPbO_2^{-} + H_2O = PbTe + 3OH^{-} \quad (10)$$

Hence the hydrogen plumbite ion cannot contribute to the total diffusion current until its flux at the electrode (proportional to $CD^{1/2}$) exceeds the flux of +4 tellurium. Because the reduction of tellurium(IV) requires 6 electrons, and that of the plumbite ion only 2 electrons, it is to be expected that the apparent height of the tellurium wave will decrease only to $^2/_3$ of its original value, and this is precisely what we observed. With 1 millimolar tellurium the apparent height of the tellurium wave was 81, 69, 68 and 66% of its original value when the respective concentrations of lead were 0.30, 0.70, 1.20 and 2.00 millimolar. The same effect was produced by copper and mixtures of copper and lead.

From Fig. 11 it is seen that addition of lead

also shifts the half-wave potential of tellurium from its normal value of −1.20 v. to nearly −1.4 v. With relatively small amounts of lead a maximum appears at the normal half-wave potential of the tellurium, but this fades out as the relative concentration of lead is increased. This shift of the half-wave potential of the tellurium is probably connected with the production of hydroxyl ion both by reaction 10 and by the reduction of hydrogen plumbite ion, $HPbO_2^- + H_2O + 2e^- = Pb + 3OH^-$, which results in a much larger concentration of hydroxyl ion at the electrode surface than in the body of the solution.

## Summary

The polarographic characteristics of the +4 oxidation states of selenium and tellurium have been investigated over a wide range of *p*H and other conditions, and systematic data have been obtained for half-wave potentials and diffusion current constants. The reduction states of the various waves observed have been established conclusively by the coulometric analysis technique based on controlled potential electrolysis with a large mercury cathode.

In strongly acid medium and in buffered solutions above *p*H 8 the reduction of selenium(IV) proceeds all the way to the −2 state, but in buffered solutions of *p*H between 3 and 7 reduction stops at the elemental state.

In buffered solutions of *p*H between 0.4 and about 11 reduction of tellurium(IV) proceeds only to the element, but the wave observed in sodium hydroxide solutions does result from complete reduction to the −2 state.

The multiplicity of waves observed with both elements at low and intermediate *p*H values results from a combination of several factors, including reductions of the several ionization species of selenous and tellurous acids and the production of films of the elements on the surface of the dropping electrode. In the case of selenium one of the waves is a cathodic reflection of the anodic wave of selenide ion. No evidence of reduction to the +2 state has been obtained with either element.

The +6 states of selenium and tellurium are not reduced at the dropping electrode under any of the conditions investigated.

CAMBRIDGE 38, MASS. RECEIVED AUGUST 13, 1948

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

# The Electrolytic Oxidation of Arsenic(III) in Acid Solution[1]

BY WILLIAM MARSHALL MACNEVIN AND GEORGE LLOYD MARTIN[2,3]

This paper reports a study of the electrolytic oxidation of trivalent arsenic in acid solution. The purpose of the investigation was to determine whether conditions could be defined which would produce 100% efficient electrolytic conversion of trivalent to pentavalent arsenic.

Previous investigations of the electrolytic oxidation of As(III)[4,5,6,7,8] have dealt with the industrial preparation of arsenates. Alkaline media have been used almost entirely. One reason for this is that oxidation in excess of the current consumption occurs in alkaline solution if air is in contact with the cathode. Apparent current efficiencies of 150% have been obtained.[9,10] Metal impurities also increase the efficiency in alkaline solution in contact with air.[11]

Aleksyeev[4] reports that oxidation occurs in acid solution with lead dioxide anodes. Aleksyeev also states that a platinum electrode may be used for the oxidation in alkaline solution. The data are, however, insufficient to indicate the maximum efficiency obtainable and the absence of side reactions, or that a platinum electrode can be used in acid solution.

In the work described in the present paper, the effects of *p*H, current density and contact with air on the current efficiency have been determined. As will be seen, the current efficiency is low in the *p*H range 3–11, but quickly increases to 100% in strongly acid solutions.

## Experimental

**Current Measurement.**—The electrolyses were conducted with d. c. current held constant within 1%. The current was measured by balancing the drop in potential across a standard resistance with a potentiometer using a recording galvanometer as a null point indicator. Corrections for the small fluctuations of the current were calculated from the galvanometer record. The time intervals were measured with a stop watch.

**The Electrolysis Cell.**—The cell for electrolysis was assembled using two 400 ml. beakers sealed together with a 20 mm. tube which had two sintered glass disks sealed into it at the ends. Thus the cell was divided into cathode,

(1) From a thesis submitted by George Lloyd Martin to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the degree Doctor of Philosophy.

(2) Monsanto Fellow, The Ohio State University, 1946–1947.

(3) Present address: Mallinckrodt Chemical Works, St. Louis, Missouri.

(4) D. Aleksyeev, *J. Russ. Phys.-Chem. Soc.*, **41**, 1155 (1909).

(5) S. J. Lloyd and A. M. Kennedy, *Trans. Am. Inst. Chem. Engrs.*, **16**, 29 (1924).

(6) S. J. Lloyd and A. M. Kennedy, *Chem. & Met. Eng.*, **32**, 624 (1925).

(7) O. A. Essin, *Z. Elektrochem.*, **35**, 234 (1929).

(8) O. W. Brown, J. E. Hatfield and J. M. Church, *Trans. Electrochem. Soc.*, **70**, 323 (1936).

(9) G. W. Heise, *Trans. Electrochem. Soc.*, **75**, 147 (1932).

(10) M. Janes, *ibid.*, **77**, 411 (1940)

(11) L. Lowenstein, U. S. Patent 2,375,933, May 15, 1945.

anode and bridge compartments. The bridge, in addition, had two 7 mm. tubes with stopcocks sealed into it. This provided a means of filling the bridge and of keeping it either under slight pressure during a run to prevent diffusion of the solutions from the electrode chambers, or under greater pressure when the anode chamber was being emptied. The bridge was kept filled with saturated potassium sulfate solution throughout the work. The cathode chamber was filled with potassium sulfate solution. A platinum cathode was used. The solution in the anode chamber was stirred steadily to reduce polarization effects. The temperature of the cell during electrolysis was not controlled. A thermometer was kept in the solution and the temperature was noted for each run.

**Electrodes.**—All oxidations were conducted with sand blasted platinum gauze electrodes of the type supplied for the Sargent–Slomin Electroanalyzer. The large electrode by geometric measurement had an apparent surface of 0.65 sq. dm. The small electrode had an apparent surface of 0.342 sq. dm. Due to the fact that the surfaces were sand blasted, the effective areas of both electrodes were probably larger than these values.

**Buffer Solutions and *p*H Adjustments.**—Standard buffer solutions were added to the arsenite solution to give the desired *p*H value. In most cases, the change of *p*H during electrolysis was 0.2–0.4 of a *p*H unit. This includes the change due to dilution as well as that due to electrolytic reaction.

All *p*H measurements were made with a Beckman Industrial Model M *p*H meter. The meter was calibrated regularly using standard buffer solutions. For measurement of *p*H values greater than 9.5, a Beckman High *p*H electrode was used.

**The Determination of Arsenic(III).**—The arsenic(III) was determined by titration with 0.1 *N* ceric sulfate using osmium tetroxide as catalyst and ferroin indicator according to the procedure developed by Gleu.[12] All solutions were made 1 *N* in sulfuric acid before titration. The buffers were shown to have no effect on the titration. The ceric sulfate solution was standardized against Primary Standard Arsenic Trioxide by the same procedure.

**The Determination of Arsenic(V).**—An adaptation of the method for arsenate given by Kolthoff and Furman[13] was used. This method uses the reduction of arsenate by iodide in acid solution followed by the determination of the iodine formed by thiosulfate titration. Kolthoff and Furman recommended a volume of 30 ml. of 4 *N* acid and 1 g. potassium iodide for 0.1 g. of arsenic pentoxide. The solution must be freed from air with bicarbonate.

The volume limitation could not be conveniently met in the solutions removed from the electrolytic cells. Thus it was necessary to establish the proper conditions for the determination of arsenate in these solutions. The volume used was 100 ml., and it was found that satisfactory results could be obtained by making the solution 6 *N* in sulfuric acid, using 2 g. of sodium carbonate for removing air, adding 6 g. of potassium iodide, and allowing it to stand at least thirty minutes before titrating with thiosulfate. The end-point was determined by adding carbon tetrachloride when the iodine was nearly gone and titrating until the organic layer was colorless.

**The Method of Calculating the Current Efficiency.**—On all the runs except those in which arsenic(V) was also determined, the current efficiency was based upon the difference between the amounts of arsenic(III) present before and after electrolysis. Stock solutions containing 0.020–0.025 g. arsenic trioxide/ml. were made up and the concentration determined by titration with standard ceric sulfate. Aliquots of these solutions were used for the electrolyses and the amount of arsenic trioxide present at the end was determined by ceric sulfate titration. The difference between the amount of arsenic trioxide present and the amount recovered was divided by the theoretical amount of arsenic trioxide oxidized as calculated from the number of coulombs passed. The arsenic (III) stock solutions were made up by dissolving the required amount of Primary Standard Arsenic Trioxide in dilute potassium hydroxide solution and making slightly acid with sulfuric acid. A small amount of reddish-brown precipitate appeared after the solution stood for some time and was filtered off before use. Reagent grade chemicals and distilled water were used throughout.

**Air Oxidation of Arsenic(III) Solutions.**—Runs to determine the effect of air oxidation were made by placing an electrode in a beaker containing an arsenic(III) solution prepared in exactly the same manner as the electrolysis solutions, and stirring the solution at the same rate and for the same length of time as the cell solutions. These solutions were then titrated to determine the change due to air oxidation.

Runs were also made under nitrogen in the electrolysis cell. A brass cap was constructed with sleeves for stirrer, electrode and gas inlet. The solution was outgassed with tank nitrogen for at least two hours before being placed in the cell, and the cell was swept for twenty minutes before electrolysis started.

## Results and Discussion

**The Effect of *p*H on the Current Efficiency.**—The results of a series of runs in which the *p*H of the arsenic(III) solution was varied are given in Table I.

TABLE I

THE EFFECT OF CHANGING *p*H ON THE CURRENT EFFICIENCY

(0.5 g. $As_2O_3$ in 200 ml., apparent current density 0.123 amp. per. sq. dm., 50% oxidized, sand-blasted platinum electrode)

| Temperature, °C. | *p*H | Current efficiency, % |
|---|---|---|
| 23 | (6 *N* $H_2SO_4$) | 100.08 |
| 24 | (1.25 *N* $H_2SO_4$) | 99.80 |
| 21 | (1.25 *N* $H_2SO_4$) | 100.20 |
| 24 | 1.8 | 100.07 |
| 24 | 3.4 | 94.83 |
| 23 | 5.4 | 54.06 |
| 21 | 5.4 | 51.52 |
| 22 | 5.5 | 66.80 |
| 24 | 6.6 | 48.13 |
| 21 | 6.6 | 22.43 |
| 24 | 8.3 | 58.65 |
| 21 | 9.3 | 30.50 |
| 23 | 9.4 | 32.50 |
| 25 | 11.0 | 99.20 |
| 25 | (1 *N* NaOH) | 109.20 |
| 21 | (1 *N* NaOH) | 118.00 |

Examination of the data in Table I shows that the oxidation proceeds smoothly with 100% current efficiency in strongly acid solution. The efficiency decreases through the neutral range, reaches a minimum, and then increases and becomes greater than 100% in strongly alkaline solution.

The exact position of the minimum cannot be located from these data, since it was found that the reaction is quite sensitive to temperature changes through this range. For this reason, no attempt has been made to correlate the location of the minimum with a possible reaction mechanism.

From the equation for the reaction $HAsO_2 + 2H_2O = H_3AsO_4 + 2H^+ + 2e^-$, one would

(12) L. Gleu, *Z. anal. Chem.*, **95**, 305 (1933).

(13) I. M. Kolthoff and N. H. Furman, "Volumetric Analysis," Volume II, John Wiley and Sons, Inc., New York, N. Y., 1929, p. 350.

expect the oxidation to go more smoothly in alkaline solution. Brown, Hatfield and Church[8] state that an alkaline bicarbonate solution just acid to phenolphthalein (probably *p*H 7–8) is the best for carbon and platinum anodes, but cite no data comparing results in solutions of different *p*H.

The existence of the minimum in the current efficiency values indicates that the reaction probably proceeds by different mechanisms in acid and alkaline solutions. The high current efficiencies in acid solution have not been previously observed and indicate the possibility of preparing alkali free arsenic(V) solutions.

Electrolyses in acid solution in the presence and absence of air showed no detectable difference in the amount of oxidation produced. Catalytic oxidation by air which occurs up to one-third of the total oxidation in alkaline solution therefore does not occur in acid solution. The electrolytic oxidation is free from appreciable side reactions.

**The Effect of Other Variables on the Oxidation Process.**—The results of a study of the effect of changing the current density on the current efficiency are given in Table II.

TABLE II

THE EFFECT OF CHANGING CURRENT DENSITY ON THE CURRENT EFFICIENCY

Temperature 24° and sand-blasted platinum electrode, 1.25 *N* $H_2SO_4$

| $As_2O_3$ per 200 ml., g. | Apparent current density, Amp./sq. dm. | Current efficiency, % |
|---|---|---|
| 0.5 | 0.123 | 100.2 |
| .5 | .185 | 100.3 |
| .5 | .230 | 99.2 |
| 1.0 | .230 | 100.4 |
| 0.5 | .269 | 99.6 |
| 0.5 | .307 | 99.1 |
| 1.0 | .307 | 98.8 |

It is seen that the current efficiency begins to decrease as the current density increases above about 0.2 amp./sq. dm. From the figures obtained, the best value of the current density to use for quantitative electrolysis is the lowest one given, 0.123 amp./sq. dm. Use of this value gives a considerable margin of safety before side reactions, usually the evolution of oxygen, begin.

Taking 0.123 amp./sq. dm. as the optimum current density, the effect of changing the per cent. oxidation was investigated. The results are given in Table III.

TABLE III

THE EFFECT OF CHANGING THE PER CENT. OXIDATION ON THE CURRENT EFFICIENCY

0.5 g. $As_2O_3$ in 200 ml. 1.23 *N* $H_2SO_4$ current density 0.123 amp./sq. dm., sand blasted platinum electrode

| Temperature, °C. | Oxidation, % | Current efficiency |
|---|---|---|
| 24 | 51.0 | 99.80 |
| 21 | 50.4 | 100.20 |
| 26 | 74.9 | 99.75 |
| 30 | 85.2 | 99.82 |
| 30 | 95.5 | 99.65 |
| 30 | 98.0 | 98.36 |

These results show that the current efficiency remains high even when 90% of the arsenic(III) has been oxidized.

On seven runs the arsenic(V) produced was determined as well as the arsenic(III) consumed. The average difference was less than 0.3%, which is within the limits of error of the determinations. This agreement indicates the absence of intermediate oxidation stages.

## Summary

1. The electrolytic oxidation of arsenic(III) at a platinum electrode has been shown to proceed at 100% current efficiency in strongly acidic solutions.

2. Air oxidation of arsenic(III) does not occur during electrolysis in acid solution.

3. The oxidation of arsenic(III) to arsenic(V) gives no indication of the presence of intermediate oxidation states.

RECEIVED SEPTEMBER 27, 1948

[CONTRIBUTION FROM CALGON, INC.]

# The Sodium Metaphosphate System. Two New Crystalline Phases of Sodium Metaphosphate Produced by Thermal Means[1]

BY ROBERT W. LIDDELL

The present contribution is primarily a study of two new forms of crystalline sodium metaphosphate obtained by a controlled crystallization from the melt. Previous investigators, with the exception of Huber and Klumpner,[2] have confined their work almost entirely to studying the more stable crystalline materials produced by molecular dehydration of monosodium orthophosphate or disodium pyrophosphate at various temperatures, ignoring the possibility of any intermediate forms.

In the study by Partridge, Hicks and Smith,[3] the following diagram showing the relationship between the various forms of sodium metaphosphate was presented.

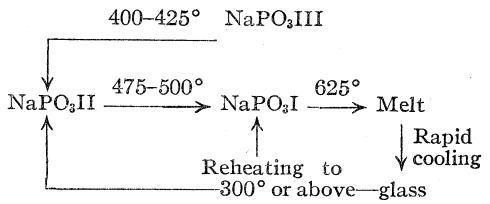



Fig. 1.—The sodium metaphosphate system according to Partridge, Hicks and Smith.

Since then the high-temperature fibrous sodium Kurrol salt has again been prepared and recharacterized by Huber and Klumpner,[2] and their results have been verified in this laboratory. Also a $NaPO_3$ (III) has been reported which has different X-ray spacings[4] than given by the above authors. The author has prepared two additional crystalline forms of sodium metaphosphate which in aqueous solutions exhibit the same properties as those of $NaPO_3$ (I), commonly referred to as trimetaphosphate. On crystallization from aqueous solution, each of these forms yields the hexahydrate of trimetaphosphate, $(NaPO_3)_3.6H_2O$, at 20°, or the monohydrate $(NaPO_3)_3.H_2O$, at approximately 40°, with mixtures of these two forms and perhaps others at intermediate temperatures.

## Experimental

**First New Form.**—Sufficient reagent grade monosodium orthophosphate monohydrate in a platinum dish was melted in an electric muffle furnace to produce a clear melt at 750–800° about 3 mm. deep. The dish was then transferred quickly into another furnace at 500° and the furnace set on automatic control at 525°. After about ten minutes, crystallization to characteristic brilliant plates took place. After a few more minutes incipient recrystallization into the ordinary $NaPO_3$ (I) was observed. When this was noted, the dish was removed from the furnace and cooled quickly by placing it on a heavy steel plate.

TABLE I

| First new phase | | Second new phase | | $NaPO_3$I | |
|---|---|---|---|---|---|
| I[a] | *d* in Å. | I[a] | *d* in Å. | I[a] | *d* in Å. |
| 4 | 7.5 | 4 | 8.6 | 9 | 6.8 |
| 4 | 6.7 | 4 | 6.2 | 8 | 5.1 |
| 10 | 5.7 | 10 | 5.2 | 3 | 3.98 |
| 6 | 5.1 | 4 | 4.29 | 8 | 3.87 |
| 6 | 5.0 | 4 | 3.97 | 10 | 3.41 |
| 4 | 4.77 | 4 | 3.35 | 5 | 3.34 |
| 2 | 4.38 | 3 | 3.32 | 1 | 3.11 |
| 2 | 4.29 | 4 | 3.22 | 7 | 3.05 |
| 1 | 4.06 | 8 | 3.08 | 2 | 2.85 |
| 2 | 3.83 | 7 | 3.03 | 6 | 2.78 |
| 7 | 3.45 | 6 | 2.91 | 3 | 2.73 |
| 4 | 3.37 | 8 | 2.86 | 1 | 2.66 |
| 3 | 3.30 | 3 | 2.70 | 2 | 2.60 |
| 10 | 3.25 | 3 | 2.64 | 6 | 2.54 |
| 1 | 3.14 | 6 | 2.59 | 2 | 2.47 |
| 8 | 3.07 | 4 | 2.53 | 3 | 2.41 |
| 8 | 3.02 | 4 | 2.41 | 1 | 2.27 |
| 8 | 2.98 | 3 | 2.29 | 1 | 2.21 |
| 2 | 2.80 | 4 | 2.25 | 3 | 2.18 |
| 3 | 2.75 | 2 | 2.18 | 3 | 2.14 |
| 3 | 2.62 | 2 | 2.16 | 4 | 2.03 |
| 4 | 2.51 | 2 | 2.09 | 3 | 1.988 |
| 4 | 2.47 | 5 | 2.04 | 2 | 1.956 |
| 1 | 2.38 | 3 | 1.97 | 1 | 1.931 |
| 4 | 2.23 | 5 | 1.94 | 3 | 1.913 |
| 4 | 2.17 | 2 | 1.87 | 4 | 1.874 |
| 2 | 2.15 | 2 | 1.83 | 3 | 1.851 |
| 2 | 1.95 | 6 | 1.81 | 1 | 1.807 |
| 4 | 1.90 | 6 | 1.78 | 1 | 1.765 |
| 6 | 1.88 | 5 | 1.674 | 1 | 1.725 |
| 3 | 1.78 | 4 | 1.651 | 2 | 1.699 |
| 3 | 1.75 | 3 | 1.600 | 3 | 1.674 |
| 3 | 1.71 | 3 | 1.533 | 1 | 1.632 |
| 3 | 1.695 | 4 | 1.452 | 2 | 1.613 |
| 3 | 1.620 | 3 | 1.430 | 1 | 1.585 |
| 3 | 1.607 | 3 | 1.387 | 3 | 1.556 |
| 2 | 1.477 | 2 | 1.360 | 2 | 1.513 |
| 4 | 1.451 | 4 | 1.335 | 2 | 1.504 |
| | | 3 | 1.285 | 2 | 1.465 |
| | | 3 | 1.262 | 2 | 1.452 |
| | | | | 5 | 1.430 |
| | | | | 1 | 1.411 |
| | | | | 1 | 1.390 |
| | | | | 2 | 1.379 |
| | | | | 1 | 1.365 |
| | | | | 2 | 1.344 |
| | | | | 1 | 1.332 |
| | | | | 2 | 1.323 |
| | | | | 2 | 1.313 |

[a] Relative intensities are estimated on a scale of 10, the higher figures denoting the stronger lines.

(1) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society, Chicago, Ill., April, 1948.

(2) Huber and Klumpner, *Z. anorg. allgem. Chem.*, **251**, 213 (1943).

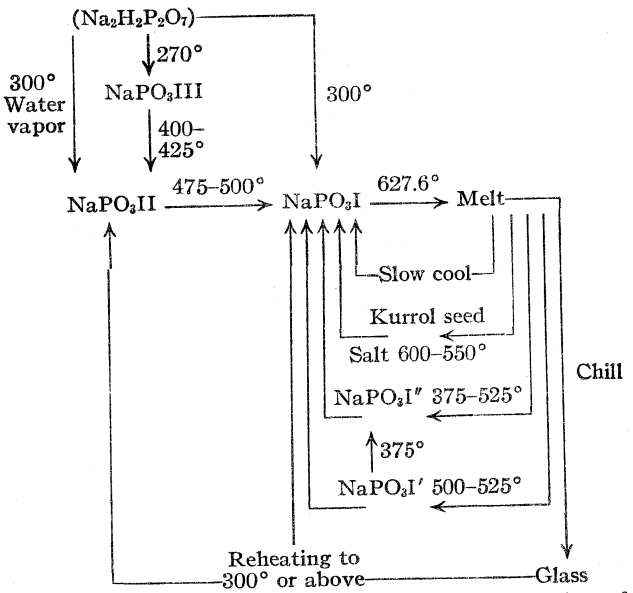
(3) Partridge, Hicks and Smith, THIS JOURNAL, **63**, 454 (1941).

(4) A. S. T. M. Card Index of X-Ray Diffraction Data, First Supplementary Set, II-1725 (1945).

It was necessary to keep the melt shallow in order to prevent excessive temperature lag with resultant inversion into $NaPO_3$ (I). The products consisted mainly of a crystalline material having maximum and minimum refractive indices of 1.500 and 1.495, together with a small amount of $NaPO_3$ (I) at the surface with indices of 1.480 and 1.474 and a little residual glass. Table I shows the X-ray spacings determined by the Debye–Scherrer powder method with a General Electric Model XRD Type I unit using a camera of 143.2 mm. diameter and copper K$\alpha$ radiation filtered through a nickel foil.

This same new crystal form was also produced from an $NaPO_3$ melt dried by heating for two hours at 1000°, which had a water content of 0.03% as determined by mixing with three parts by weight of freshly ignited anhydrous tetrasodium pyrophosphate and igniting at 1000° to constant weight. By the use of a commercial glass with an $Na_2O:P_2O_5$ ratio of 1.15, the inversion to ordinary $NaPO_3$ (I) could be inhibited for a longer time although in this case $Na_5P_3O_{10}$ (II) was formed as an impurity.

**Second New Form.**—The second new crystal form was obtained by placing a clear sodium metaphosphate melt at about 650° in a furnace controlled at 375°. Secondary crystallization to trimetaphosphate was not as rapid as with the first form, perhaps due to the lower temperature, but a small amount of glass in parts of the material was frequently obtained. This second new form was also produced, with $Na_5P_3O_{10}$ (II) as an impurity, from a commercial glass with an $Na_2O:P_2O_5$ ratio of 1.15 by the same controlled crystallization from the melt, or by annealing at 375° for three hours the mixture of the first new form and $Na_5P_3O_{10}$ (II), prepared as described previously. The maximum and minimum refractive indices of this second new crystal form were found to be 1.520 and 1.475. The X-ray spacings are listed in Table I. Occasionally refractive indices of 1.501 and 1.515 were obtained, but this was thought due merely to a different orientation of the crystals and not to another crystal form, since the X-ray patterns were always identical.




The sodium metaphosphate system according to the data of the present study.

There was considerable overlapping in the temperature range of formation of these two forms. The first form has been produced at temperatures of from 375° to 525°; its proportion to the second form varied with the temperature. At temperatures much above 525° it was either not produced or was too transient to be retained readily; in the lower temperature ranges it may also have been formed during the cooling process and not after the material in the platinum dish had reached the recorded temperature. The second form has been found at temperatures as high as 525°, accompanying the first form, and at temperatures as low as 350°, along with considerable residual glass, but the conditions for producing the maximum amount of the relatively pure materials are given above. More than a dozen preparations of each form were made by the preferred method and practically all of these were of the composition described.

In aqueous solution the chemical properties of both of these new crystal forms were similar to those of ordinary $NaPO_3$ (I). They did not repress calcium ion against soap, and when free from glass gave no precipitate with dilute silver nitrate or barium chloride solution. The solubility in the water was approximately that of the trimetaphosphate. These facts together with the formation of hydrates identical with those of $NaPO_3$ (I) indicate that both the first and the second new form are merely different crystal forms of $NaPO_3$ (I), which may therefore be called $NaPO_3$ (I′) and $NaPO_3$ (I″), respectively.

**Sodium Kurrol Salt.**—On treating a sodium metaphosphate melt at 600–550° with seed crystals as described by Huber and Klumpner,[2] long fibrous crystals of Kurrol salt having essentially the properties given by these authors were obtained. The author was unable to obtain seed crystals from an acid melt in the 650–550° range given by Huber and Klumpner and a temperature slightly below 500° gave the best results. Several attempts to prepare the Kurrol salt from a sodium metaphosphate melt without seeding were unsuccessful.

## Discussion

In the present state of confusion in the nomenclature of inorganic chemistry and mineralogy and the still obscure relationships among all of the possible forms of metaphosphate, it seems unwise to attempt to change the accepted nomenclature of the known members of this series. Therefore, for this reason, the general scheme of nomenclature of Partridge, Hicks and Smith[3] will be used so far as possible, particularly since this system has been followed by Morey and Ingerson,[5] and Quimby.[6]

It has been found impossible to duplicate the $NaPO_3$ III of Partridge, Hicks and Smith,[3] and further study of their X-ray films and data by R. K. Scott of our Laboratories has led to the conclusion that their material was a mixture of $NaPO_3$ (I) and $NaPO_3$ (II). It should, therefore, be noted that the $NaPO_3$ (III) in the second diagram is not the $NaPO_3$ (III) of Partridge, Hicks and Smith.[3] The $NaPO_3$ (III) having the X-ray spacings given in the reference[4] was prepared by heating monosodium orthophosphate monohydrate to a temperature of 270 ± 5° for sixteen hours and then washing out the residual soluble material. Heating for the same period at 225 ± 5° and 245 ± 5° gave a product which was completely soluble in water. On heating, the insoluble $NaPO_3$ (III) was transformed wholly into the insoluble $NaPO_3$ (II) at a temperature of 425° and into $NaPO_3$ (I) at temperatures of 500° and above.

It is interesting to note that under apparently identical conditions of heating, varying amounts of $NaPO_3$ (I) and $NaPO_3$ (II) have been obtained from both monosodium orthophosphate and

(5) Morey and Ingerson, *Am. J. Sci.*, **242**, 1 (1944).

(6) Quimby, *Chem. Revs.*, **40**, 141 (1947).

disodium pyrophosphate. Thus Tammann,[7] and Karbe and Jander[8] reported that the results obtained at approximately 300° were inconsistent, but could offer no explanation. Boulle[9] found that when this heating was carried out in a stream of water vapor, his form B ($NaPO_3$ (II) was produced in a pure state. Such a condition may also be approximated by rapidly heating the monohydrate of monosodium orthophosphate in a fairly thick layer to 300°. The author has found that when the reverse is true, namely, when the vapor pressure of water was low, as when anhydrous disodium pyrophosphate was sprinkled in a very thin layer in a platinum dish and introduced into a furnace at 330°, $NaPO_3$ (III) was the principal product. Intermediate conditions, as for example slow heating to 300° using a moderately thick layer of material gave $NaPO_3$ (I) as the major product.

Quite a number of chemical compounds exhibit different polymorphic forms which, however, have the same chemical properties; the metaphosphate system appears to be unique in the fact that it comprises a number of crystalline phases, some of which in aqueous solution exhibit different chemical properties, while others behave identically when dissolved.

The diagram presents the current state of information concerning the sodium metaphosphate system.

**Acknowledgments.**—The author wishes to express his appreciation to Miss Catherine Hester who made most of the microscopical examinations and to Mrs. Jeanne Pfister and Mr. R. K. Scott who carried out the X-ray analysis.

## Summary

1. Two new crystalline sodium metaphosphates have been produced which in aqueous solution behave like $NaPO_3$ I.

2. The sodium metaphosphate diagram of Partridge, Hicks and Smith has been revised to show more recent developments including those of the present study.

PITTSBURGH, PA. RECEIVED JUNE 12, 1948

(7) Tammann, *J. prakt. Chem.*, **45**, 463 (1892).
(8) Karbe and Jander, *Kolloid-Beihefte*, **54**, 9 (1944).
(9) Boulle, *Compt. rend.*, **206**, 915 (1938).

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[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

# Cuprammonium–Glycoside Complexes. I. Conductometric Measurements

BY RICHARD E. REEVES AND JULIUS R. JUNG, JR.

In the continued investigation of cuprammonium–glycoside complexes, a means other than one dependent upon optical activity was required for the recognition of these complexes. Such a method was necessary for the study of complex formation between cuprammonium and inactive glycols, as well as for those substances which, though optically active, form complexes without exhibiting large rotatory changes.

Our earlier work,[2,3] dealing exclusively with the optical method of measurements, had shown that highly active complexes form between cuprammonium and properly oriented glycol groups. It was found that such complex formation was associated with a decrease in conductivity in the cuprammonium solution; hence it was decided to follow this phenomenon by the conductometric method of measurement.

By this method many degrees of affinity for cuprammonium could be detected in the various substances tested. It was possible to distinguish the D- and L-forms of 2,3-butanediol from the *meso* variety. Various methyl α-hexopyranosides could be sharply distinguished from each other, and a difference was encountered between the complex-forming tendency of a number of α- and β-glycoside pairs. Furthermore, it was shown that the substance D-glucosan<1,5>β<1,6> (levoglucosan) does react with cuprammonium, although on the basis of optical rotation measurements it was previously reported not to react.[4]

## Experimental Part

The physical properties of all the substances employed in this investigation were in excellent agreement with the properties listed in the literature.

A stock solution containing between 5 and 8 g. of copper per liter was prepared by passing a current of air through a concentrated A. C. S. standard ammonium hydroxide solution in the presence of copper turnings. The ammonia and turnings were contained in a tall glass cylinder which was cooled in an ice-bath during the reaction. This stock solution may be preserved in the refrigerator without added stabilizer for a long time. After analysis for copper and ammonia, portions of the stock solution were diluted to contain 0.01 mole of copper (0.635 g.), 3 moles of ammonia, and 10 ml. of ethanol per liter. This standard solution, "cupra A," was employed in most of the conductivity experiments; whenever a different solution was used a notation will be made regarding its composition.

To permit the use of small amounts of glycosides very dilute cuprammonium solutions were required. The specific conductance of various ammonium hydroxide solutions with and without 0.01 molar copper are shown in Fig. 1. Inspection of this figure shows that conductance is least sensitive to ammonia concentration in the region

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.
(2) R. E. Reeves, *Sci.*, **99**, 148 (1944).
(3) R. E. Reeves, *J. Biol. Chem.*, **154**, 49 (1944).
(4) K. Hess, W. Weltzien and E. Messmer, *Ann.*, **435**, 1–144 (1924).

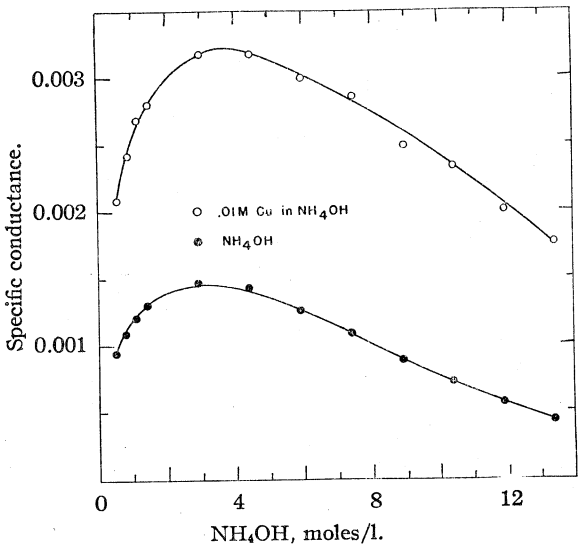



Fig. 1.—The specific conductance of ammonia solutions with and without copper.

of 3 molar ammonia (the region of maximum conductance) hence this concentration was chosen. The reason for the incorporation of ethanol is illustrated by the ethanol curve of Fig. 2. By its incorporation a "hydroxyl effect" is considerably levelled off, and only true complex-forming substances show a pronounced change in conductance.

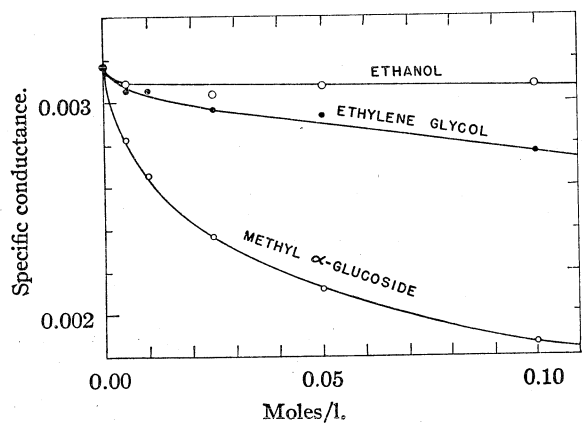



Fig. 2.—The change in specific conductance upon adding various substances to a solution containing 0.01 mole of copper and 3 moles of ammonia per liter.

Substances which ionize in solution, or esters which may decompose into ionizable substances, cannot be used in the conductometric method without obscuring the effect of the conductance change due to complex formation.

Conductivity measurements were made with a commercial 1000-cycle conductivity bridge using a dip-type cell capable of operating with 14 ml. of solution. The readings were made in terms of resistance (ohms, Ω), and specific conductance ($L$) was calculated by the formula $L = c/\Omega$. The cell constant, $c$, determined with 0.1 $M$ potassium chloride, was found to be 0.116. The temperature at the time of measurement was controlled by immersion of the tube containing the liquid in a water thermostat held at 25 ± 0.2°. Except while measurements were in progress the tubes were stoppered to prevent loss of ammonia and the attendant cooling of the cuprammonium solution. The small amounts of materia were added directly to the cupra and concentrations were calculated upon the original volume of solution.

## Results

**Aliphatic Glycols.**—In Fig. 3 are shown the resistance *versus* glycol concentration relationships for the three forms of 2,3-butanediol dissolved in the standard cuprammonium solution. The D- and L-forms are, of course, indistinguishable from each other, by this method, but they show a marked difference from the *meso* variety, the latter giving a smaller change in resistance. The behavior of ethylene glycol (not shown in the figure) was almost identical with that of the *meso* form of the butanediol. A type of behavior believed to be different is illustrated in Fig. 3 by trimethylene glycol. This substance has two hydroxyl groups separated by a methylene group and the data are regarded as indicating no significant change in conductivity. From this it is deduced that trimethylene glycol belongs in the group of substances which fail to form a copper complex.

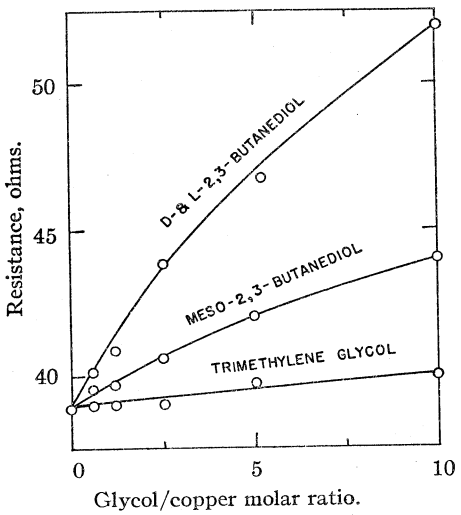



Fig. 3.—The resistance *versus* concentration relationships of various aliphatic glycols in cupra A.

**Glycopyranosides.**—In Fig. 4 are shown the resistance *versus* glycoside concentration relationships for a number of methyl α-hexosides. That these glycosides are much more actively complex-forming substances than the aliphatic glycols is indicated by the lower concentrations required to produce similar conductivity changes. The glycosides exhibited affinities for cuprammonium increasing in the order glucoside, galactoside, altroside, mannoside and guloside. In Fig. 5 comparison is made between a number of α- and β-pyranoside pairs. It will be noted, in each of these instances, that the curve for the β-glycoside lies above that of the corresponding α-glycoside.

**D-Glucosan <1,5>β<1,6>.**—The behavior of this substance in cuprammonium solution was first examined by Hess, Weltzien and Messmer,[4] who concluded that there was no reaction

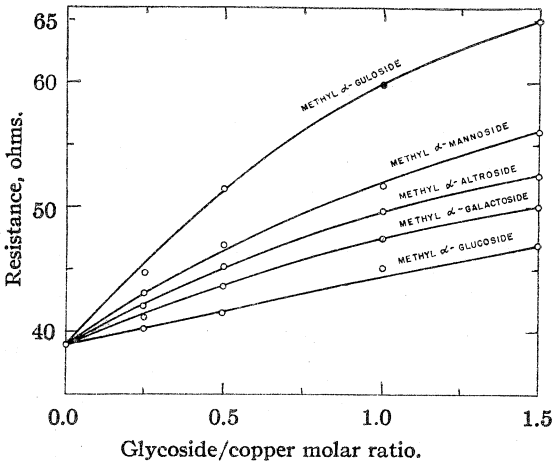



Fig. 4.—The resistance *versus* concentration relationships of various methyl α-D-hexopyranosides in cupra A.

between it and cuprammonium, since the optical rotation in this solvent was practically the same as in a copper-free solution. Their finding in regard to lack of rotatory shift was later confirmed,[3] but the conclusion that no complex formation occurred was shown to be incorrect by the data given in Fig. 6. The effect on conductivity of levoglucosan is at least equivalent to that of methyl α-glucoside, a substance known to be complex-forming because of its optical behavior, as well as because of the conductivity effect noted above.

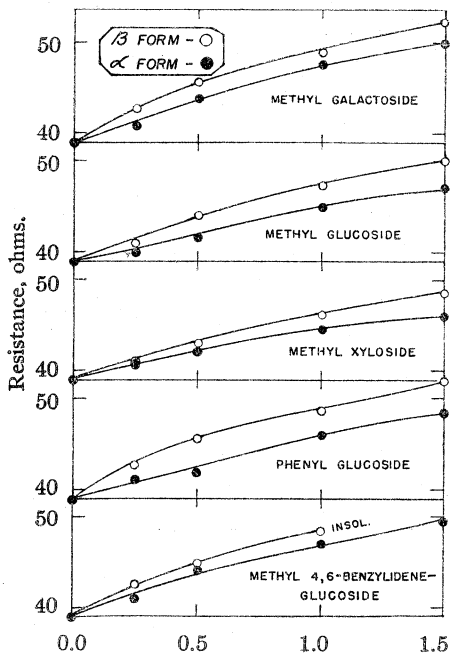



Fig. 5.—Comparison of resistance–concentration relationships of various α- and β-D-glycopyranoside pairs in cupra A.

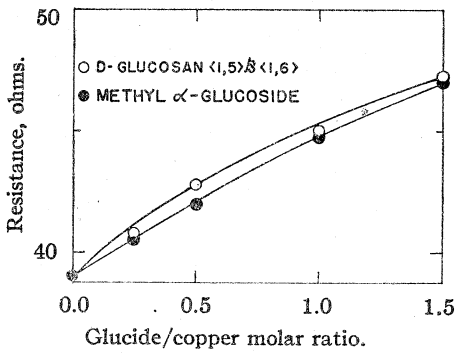



Fig. 6.—Comparison of the effect on resistance of D-glucosan<1,5>β<1,6>(levoglucosan) and methyl α-D-glucoside in cupra A.

Our studies to date indicate that complex formation is always accompanied by a marked decrease in the conductance of a dilute cuprammonium solution unless the effect is obscured by decomposition or ionization of the substance being examined. Complex formation may or may not be associated with a large shift in optical rotation. The conditions which determine the rotatory behavior will be considered more fully in subsequent communications.

**Acknowledgment.**—We are indebted to Dr. R. D. Coghill, Professor C. S. Hudson and Dr. H. S. Isbell for supplying some of the substances employed in this investigation.

## Summary

A conductometric method is described that is capable of measuring the relative affinities of various substances for cuprammonium. Differences in affinity were observed for the optically active and *meso* forms of 2,3-butanediol. Differences were noted in the behavior of various methyl α-hexosides, and between various α- and β-pyranoside pairs. The substance D-glucosan<1,5>β<1,6> was shown to react with cuprammonium solution.

NEW ORLEANS, LA. RECEIVED JULY 6, 1948

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

# Cuprammonium–Glycoside Complexes. II.[2] The Angle Between Hydroxyl Groups on Adjacent Carbon Atoms

BY RICHARD E. REEVES

During the examination of a large number of cuprammonium–glycoside complexes some relationships were observed which appeared to cast light on the subject of the shape (conformation) of glycoside molecules in solution. However, before the problem of conformation could be attacked it was necessary to secure a better understanding of the meaning of complex formation. In the present communication a theory applicable to complex formation is proposed and selected examples involving hydroxyl groups on adjacent carbon atoms are cited in its support. In forthcoming reports the theory will be tested by examining its application to a large number of carbohydrate derivatives.

Let it be assumed that there is a particular distance between hydroxyl groups most favorable for complex formation with cuprammonium, and a range of distances over which complex formation may occur more or less readily depending on the variation from the optimum distance. Thus, affinity for cuprammonium would be inversely related to the deviation of rigidly fixed hydroxyl groups from a particular position, or, for hydroxyl groups not rigidly fixed, to the energy required to move the groups to a complex-forming position.

In dealing with adjacent hydroxyl groups located on pyranose and furanose rings the relative position of the groups is determined by the configuration of the carbon atoms and shape of the rings. Regarding the latter the following first approximations have been assumed: (1) the shape of a pyranoside ring in solution may be represented, adequately for the present purpose, by a regular skew hexagon having the tetrahedral angle between sides, arranged in one of the eight Sachse strainless ring conformations; (2) the furanoside ring may be adequately represented by a flat structure having coplanar, or essentially coplanar, ring carbon atoms. In such ideal structures the angle between any pair of adjacent carbon–oxygen bonds projected onto a plane perpendicular to the carbon–carbon axis must be one of the following angles[3] for pyranoside boat forms, 0°, ±60°, ±120°, 180°; for pyranoside chair forms, ±60°, 180°; for furanosides, 0°, ±120°. Note that the projection of the tetrahedral angle in this manner yields a projected angle of exactly 120°. The sign of the projected angle is defined with the aid of three dimensional molecular models in the following manner. Sighting along a line through the centers of the two hydroxyl-bearing carbon atoms, the reference plane is defined as that passing through the centers of these two atoms and the center of the hydroxyl oxygen atom nearer the observer. The divergent plane passes through the centers of the same two carbon atoms and the center of the far oxygen atom. When the divergent plane makes a clockwise angle with the reference plane the angle will be designated negative; when the angle is counterclockwise, positive.

## What Angle Is Capable of Complex Formation?

Having assumed that optimum conditions for complex formation occur when two hydroxyl groups are located at a particular distance from each other, it is apparent that for hydroxyl groups on adjacent carbon atoms this distance is a direct function of the projected angle between the carbon valences on which the hydroxyl groups are bound. There are cyclic substances in which this angle is fixed, for a particular conformation, more or less rigidly, by the spatial requirements of the whole molecule. A selected group of these substances will now be examined to see if there appears to be an optimum angle for complex formation.

**Cellulose** is the classical example of a complex-forming substance. In cellulose, the hydroxyl groups at positions 2 and 3 of each glucose unit react with cuprammonium to form a soluble complex.[4] Crystalline cellulose is composed of β-D-glucopyranoside units oriented in the particular chair form conformation in which the pyranoside oxygen and 6-carbon atom project on the same side of the plane of the 1,2,4,5-carbon atoms.[5,6,7] Cellulose is a very insoluble substance, and were it not for complex formation there is no reason to believe it would dissolve in cuprammonium. Furthermore, after regeneration from cuprammonium, cellulose exhibits the same unit cell length[8] and hence probably the same ring con-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) R. E. Reeves and J. R. Jung, Jr., THIS JOURNAL, **70**, 209 (1948).

(3) Admittedly in the actual molecules these angles are subject to small variations. In a rigorous determination of ring conformation exact knowledge of interatomic distances and valence angles would be required, and in studies dealing with the crystalline state these quantities would necessarily be emphasized. However, when the problem is one of conformation in solution, where shapes are undoubtedly more elastic than in the crystalline state, and where interchange of conformations is a possibility, it has not been attempted to interpret the results in terms of the exact angles and distances found for the crystalline state.

(4) R. E. Reeves, *Science*, **99**, 148 (1944).

(5) W. T. Astbury and M. M. Davies, *Nature*, **154**, 84 (1944).

(6) E. G. Cox, *ibid.*, **154**, 84 (1944).

(7) F. T. Peirce, *ibid.*, **154**, 398 (1944); *Shirley Inst. Memoirs*, **20**, 81–97 (1946). Peirce's contention that the X-ray data better fit a slightly modified chair conformation need not concern us here for the proposal retains the recognizable conformation.

(8) W. A. Sisson in "High Polymers," Vol. V, Emil Ott, Ed., Interscience Publishers, Inc., New York, N. Y., 1943, p. 212.

formation as native cellulose. Since cuprammonium undoubtedly reacts with cellulose as it exists in the crystalline state, it may be concluded that the angle between the hydroxyl groups on positions 2 and 3 of the glucose units of cellulose is capable of complex formation. Inspection of a D-glucopyranoside model oriented in the cellulose conformation discloses this angle to be $-60°$.

***cis*-2,3-Dihydroxytetrahydrofuran** (erythritol anhydride) contains hydroxyl groups which according to assumption 2 must be situated at the true *cis* (0° projected angle) angle with respect to each other. That the groups are actually in the *cis* position has been confirmed by behavior of this substance toward cleavage by lead tetraacetate.[9] This substance, being optically inactive, can only show complex formation by the conductometric method, however, by this technique the evidence for complex formation was unmistakable.

A substance which must possess the true *cis* (0°) relationship for a pair of adjacent hydroxyl groups on a pyranoside ring is **methyl 2,6-anhydro-α-D-altroside** recently described by Rosenfeld, Richtmyer and Hudson (THIS JOURNAL, **70,** 2201 (1948)). The molecular model of this substance shows only one possible ring conformation, a boat form in which the hydroxyl groups at positions 3 and 4 are in the true *cis* position. A sample of this material was kindly furnished the writer by Dr. Richtmyer. The glycol group could be titrated directly with lead tetraacetate. An 0.01 molar concentration increased the specific resistance of cupra A from 324 to 564 ohm, cm. Its specific rotations (25°, 436 mμ) were +84° (*c*, 1.01, water) and +350° (*c*, 0.66, cupra B) corresponding to a rotational shift of +467°. The behavior with lead tetraacetate confirms the true *cis* relationship of the glycol and the behavior with cuprammonium indicates a strongly complex-forming group with an intermediate rotational shift.

**Non-Complex-Forming Substances.**—There are a number of substances which, though possessing hydroxyl groups on adjacent carbon atoms, fail to form cuprammonium complexes under the usual conditions. Among these is the newly discovered glucose anhydride, D-glucosan $<1,4>\beta<1,6>$. Examination of a molecular model representing this substance discloses that the groups are very rigidly held at the $-120°$ angle. Dimler, Davis and Hilbert[10] have commented on the resistance of this substance against oxidation by the glycol cleavage reagents, and have attributed this property to the widely spaced *trans* orientation of the hydroxyl pair. It seems probable that its failure to form a cuprammonium complex is also due to this condition.

A second non-complex-forming substance was 2,5-anhydrosorbitol. The *trans* (+120°) orientation for the hydroxyl groups has been confirmed by the low rate of reaction of this substance with the glycol cleavage reagents.[11]

The two preceding substances illustrate non-complex-formation in *trans* spaced hydroxyl groups located on a furan ring. A pyranoside derivative, methyl 4,6-benzylidene-α-D-altroside, also failed to form a complex, and consideration of molecular models of this substance shows that the benzylidene ring limits the possibilities to three of the eight conformations, one chair and two boat forms. Since the theoretical arguments of Gorin, Kauzmann and Walter[12] and Scattergood and Pacsu[13] tend to exclude the two boat forms, it is most probable that methyl 4,6-benzylidene-α-D-altroside exists in the chair form in which the angle between hydroxyl groups would be 180°.

These examples have included substances having hydroxyl pairs oriented at 0°, 60°, 120°, and (probably) 180°, and of the four angles only the 60° and 0° angles have shown a marked reaction with cuprammonium. Considered in relation to the theory, it may be said either that the latter two angles are sufficiently close to the optimum angle to allow complex formation to occur, or that the substances which possessed these angles had sufficient elasticity to allow the hydroxyl groups to move to a position capable of complex formation; while neither of these possibilities apply to the non-complex-forming substances.

## Experimental Results and Discussion

Conductivity measurements were made by the method described in the preceding communication.[2] The constant for the cell employed at the start of this work was 0.116. As the cell showed small changes with use all readings were recalculated to this value. Optical rotations were measured with the mercury blue line (436 mμ) or the sodium D line, as indicated. The cuprammonium solution used for optical rotations contained 15 g. of copper, 240 g. of ammonia and 1 g. of glycerol per liter. This solution is designated cupra B.

The results of conductivity measurements on the non-complex-forming substances in cuprammonium solution (cupra A)[2] are shown in Fig. 1, curve B. Observed resistances are plotted against molar glucide concentrations. Included for comparison is the curve representing methyl 4,6-benzylidene-α-D-glucoside, a typical complex-former. The results with this substance also show that the presence of a benzylidene ring does not inhibit complex formation provided the hydroxyl pair is properly oriented. In Table I are listed the specific rotations in water and

(9) R. E. Reeves, *Anal. Chem.*, in press.

(10) R. J. Dimler, H. A. Davis and G. E. Hilbert, THIS JOURNAL, **68,** 1377–1380 (1946).

(11) R. C. Hockett, M. Zief and R. M. Goepp, Jr., *ibid.*, **68,** 935–937 (1946).

(12) E. Gorin, W. Kauzmann and J. Walter, *J. Chem. Phys*, **7,** 327 (1939).

(13) A. Scattergood and E. Pacsu, THIS JOURNAL, **62,** 903–910 (1940).

TABLE I

OPTICAL BEHAVIOR OF VARIOUS SUBSTANCES IN WATER AND CUPRAMMONIUM HYDROXIDE SOLUTION

| | $[\alpha]^{25}_{436}$ Water | $[\alpha]^{25}_{436}$ Cupra B | Rotational shift[a] |
|---|---|---|---|
| D-Glucosan <1,4>β<1,6> | + 78° | + 69° | − 15° |
| 2,5-Anhydrosorbitol | + 48° | − 32° | − 132° |
| Methyl 4,6-benzylidene-α-D glucoside[b] | +159° | −608° | −2163° |
| Methyl 4,6-benzylidene-α-D altroside | +204° | +188° | − 45° |

[a] [Sp. rot. (cupra B) − sp. rot. (water)] × Mol. wt./100. [b] Reference 4.

cuprammonium, and the rotational shifts ([α] cupra B [α] water) × Mol. wt./100 for the substances considered in Fig. 1.

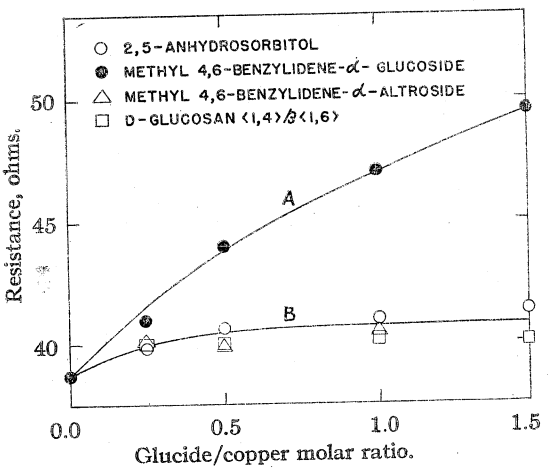



Fig. 1.—Resistance *vs.* concentration relationships for a complex-forming substance (curve A) and three non-complex-forming substances (curve B) in cupra A.

It is apparent that the non-complex-formers produced neither a marked change in conductance nor a pronounced shift in rotation (Table I) comparable with that caused by the complex-forming methyl 4,6-benzylidene-α-D-glucoside.

The complex-forming action of erythritol anhydride as measured conductometrically is shown in Fig. 2. For comparison the curve previously reported[2] for an active complex-forming substance, methyl α-D-gulopyranoside is reproduced in this figure.

The D-glucosan <1,4>β<1,6>, m. p. 110–11°, gave the following optical rotations: $[\alpha]^{25}_{436}$ +78° (*c*, 0.94 water), and +69° (*c*, 0.81 cupra B).

The sirupy 2,5-anhydrosorbitol was prepared by debenzoylation of the crystalline 1,6-dibenzoate[11] in methanol solution with barium methylate. It was purified by distillation at 0.002 mm. pressure at a bath temperature of 170°. The colorless

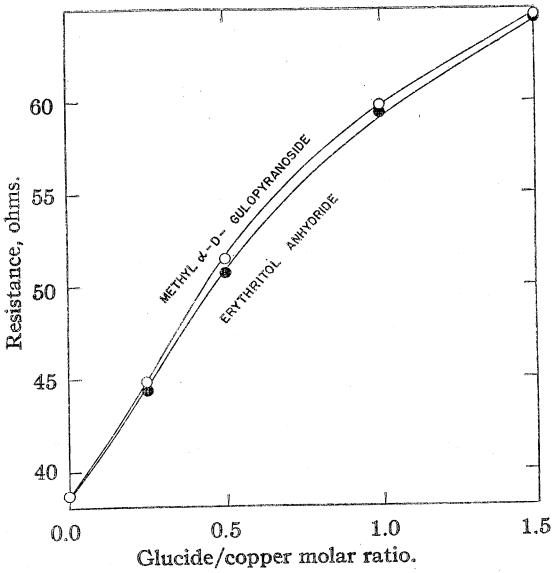



Fig. 2.—Resistance *versus* concentration relationships for erythritol anhydride and methyl α-D-glucoside in cupra A.

distillate gave the correct carbon–hydrogen analyses. Its optical rotations were [α] $D^{25}$ + 21° (*c*, 0.95 water); $[\alpha]^{25}_{436}$ + 48° (*c*, 0.95 water); −32° (*c*, 0.43 cupra B).

Methyl 4,6-benzylidene-α-D-altroside, m. p. 171–172°, was prepared from methyl benzylidene-α-D-glucoside by the method of Richtmyer and Hudson.[14] The optical rotations of the benzylidenealtroside were [α]$^{25}$D + 106° (*c*, 1 water), $[\alpha]^{25}_{436}$ + 204° (*c*, 1 water) and + 188° (*c*, 1.16 cupra B).

The writer wishes to thank Dr. R. J. Dimler of the Northern Regional Research Laboratory and Dr. Morris Zief of the Sugar Research Foundation, who kindly supplied some of the substances used in this investigation, and Mr. J. R. Jung, Jr., who made the conductometric measurements.

## Summary

The position is taken that complex formation between cuprammonium and two hydroxyl groups occurs most readily when the hydroxyl groups are located at a particular distance apart. Examination of a number of substances having hydroxyl groups on adjacent carbon atoms held more or less rigidly at a number of angles (hence distances) has shown complex formation to occur readily at the true *cis*-position (0° angle) and the 60° angle, but not at the 120° or the 180° angle.

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(14) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727–1731 (1941).

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

# Cuprammonium–Glycoside Complexes. III. The Conformation of the D-Glucopyranoside Ring in Solution

BY RICHARD E. REEVES

In the preceding article of this series[2] a theory has been presented which defines some necessary conditions for complex formation between cuprammonium and two hydroxyl groups. According to this speculation the two complex-forming hydroxyl groups must be located at or near a particular optimum distance from each other. Distances capable of complex formation occur when hydroxyl groups on adjacent carbon atoms are oriented at the true *cis*-position (0° projected angle) or the ±60° projected angle positions. When the properties of numerous D-glucopyranoside derivatives were considered in the light of these findings it became possible to draw certain conclusions in regard to the ring conformation of glucopyranoside molecules in solution.

In an earlier communication[3] it was concluded on the basis of optical rotation measurements that glucopyranoside derivatives can form complexes at the 2–3 and 3–4 positions but the possibility of complex formation between other hydroxyl pairs was not rigorously excluded. Since that time it has been recognized that cuprammonium complexes can form without appreciable shift in optical rotation, hence the question of possible sites for complex formation has been reinvestigated by a conductometric technique. These results, given in the last column of Table II, indicate that only the above mentioned hydroxyl pairs are capable of complex formation, as far as the substituted ordinary D-glucopyranosides are concerned.

Proceeding on the assumption that the pyranoside ring can be adequately represented by a regular skew hexagon with tetrahedral angles between sides, oriented in one of the eight Sachse strainless ring conformations, it is possible by inspection of molecular models to evaluate, approximately, the angle between any pair of adjacent hydroxyl groups. These angles between the hydroxyl groups of positions 2–3 and 3–4 of D-glucopyranosides have been estimated and are shown in Table I. The conformations are those illustrated in Fig. 1 and the angles are those projected onto a plane perpendicular to the carbon–carbon bond as defined in the preceding article.[2] It is apparent by inspection of models that the hydroxyl pair at the 2–3 position can assume the complex-forming −60° angle, but not the 0° or the + 60° angles, while the hydroxyl pair at position 3–4 can form the + 60° angle but not the 0° or −60° angles. This situation is probably responsible for the strikingly different optical behavior of the first two groups of substances listed in Table II. Group I contains D-glucopyranosides substituted to allow complex formation only at position 2–3 while the second group is substituted to allow reaction only at posi-

TABLE I

THE ANGLE BETWEEN ADJACENT HYDROXYL GROUPS OF THE D-GLUCOPYRANOSE RING

| Conformation | 2–3 hydroxyls | 3–4 hydroxyls |
|---|---|---|
| C1 | − 60° | + 60° |
| 1C | 180° | 180° |
| B1 | −120° | + 60° |
| 1B | −120° | 180° |
| B2 | − 60° | +120° |
| 2B | 180° | +120° |
| B3 | 180° | 180° |
| 3B | − 60° | + 60° |

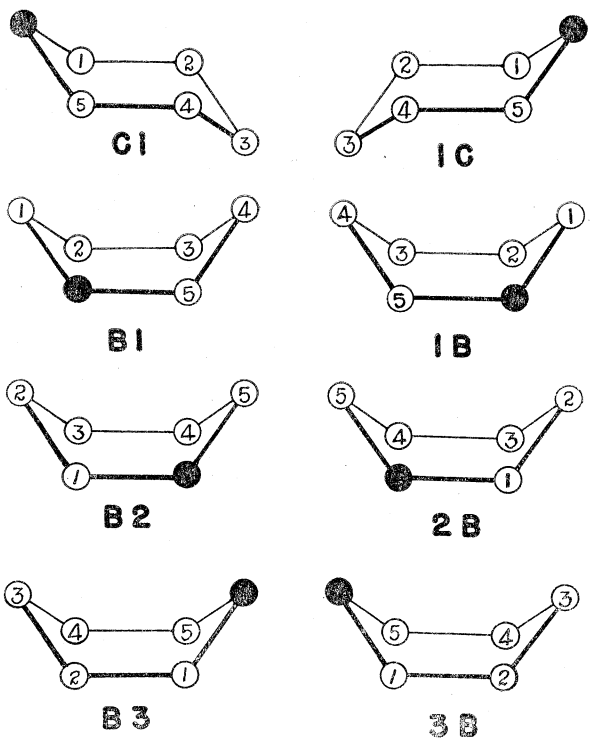



Fig. 1.—The eight pyranose strainless ring conformations and the corresponding symbols. By convention the heavy lines represent the sides of the three-dimensional figure nearer the observer. The dark circles represent ring oxygen atoms, and the numbered circles carbon atoms 1 to 5.

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) R. E. Reeves, Part II, THIS JOURNAL, 70, 212 (1948).

(3) R. E. Reeves, *J. Biol. Chem.*, 154, 49–55 (1944).

tion 3–4. It is apparent that strongly levorotatory complexes form at position 2–3 (−60° angle), while complexes of similar dextrorotation form at position 3–4 (+ 60° angle, Table II, Group II).

TABLE II

THE BEHAVIOR OF VARIOUS SUBSTANCES IN CUPRAMMONIUM SOLUTION

| D-Glucopyranoside | Rotational shift[a] deg. | Increase in sp. res.[b] ohm., cm. | Proof of position of complex |
|---|---|---|---|
| (Group I, complex at 2–3 position) | | | |
| Methyl 4-methyl-β- | −2020[c] | .. | ..... |
| Methyl 4,6-dimethyl-β- | −1990 | 52 | Levo at 2–3 |
| Methyl 4,6-ethylidene-β- | −1970[d] | 73 | Levo at 2–3 |
| Methyl 4,6-benzylidene-α- | −2160[d] | 69 | Levo at 2–3 |
| Methyl 4,6-benzylidene-β- | −2230 | 82 | Levo at 2–3 |
| (Group II, complex at 3–4 position) | | | |
| Methyl 2-methyl-β- | +2190[e] | 67 | ..... |
| Methyl 2,6-dimethyl-α- | +2110[e] | .. | Dextro at 3–4 |
| (Group III, compensating complexes) | | | |
| Methyl 6-methyl-β- | + 435[c] | 70 | ..... |
| Methyl α- | + 244[d] | 50 | ..... |
| Methyl β- | + 250[d] | 67 | ..... |
| Phenyl α- | + 292 | 61 | ..... |
| Phenyl β- | − 74 | 85 | ..... |
| (Group IV, regarded as non-complex forming) | | | |
| Methyl 3-methyl-β- | − 83[c] | 16 | No complex at 2–4, 2–6, or 4–6 |
| Phenyl 3-methyl-β- | + 32 | 2 | |
| Methyl 2,3-dimethyl-α- | + 20 | 10 | No complex at 4–6 |
| Methyl 2,3-dimethyl-β- | − 9 | 14 | No complex at 4–6 |
| Methyl 2,4-dimethyl-α- | − 74[d] | 7 | No complex at 3–6 |
| Secondary alcohols | | | |
| Isopropyl alcohol | .... | 18 | ..... |
| Butanol-2 | .... | 20 | ..... |

[a] Rotational shift equals ($[\alpha]_{436}$ Cupra B − $[\alpha]_{436}$ water) × mol. wt./100. For composition of Cupra B see Experimental part. [b] Increase in specific resistance of 0.01 molar glucoside or *s*-alcohol in Cupra A. For composition of Cupra A see Experimental part. [c] See footnote 3. [d] R. E. Reeves, *Science*, 99, 148–9 (1944). [e] R. E. Reeves, THIS JOURNAL, 70, 259–60 (1948). The rotational shift previously given did not include the mol. wt./100 factor.

The third group of substances listed in Table II have hydroxyl groups at positions 2, 3 and 4, unsubstituted (*i. e.*, with both the 2–3 and 3–4 glycol groups free). Complex formation in these substances produces a much smaller shift in optical rotation than it does in those compounds which can react at only one site. The affinities for cuprammonium of the substances in groups I–III (Table II) have been found to be approximately equal by the conductometric technique. Examples illustrating this similar affinity of the three complex-forming groups are given in Fig. 2. Since there is no reason to suspect a marked difference in the amount of cuprammonium complex formed by the three classes of substances under similar conditions, the reason for the relatively low shift in rotation for the third class may lie in simultaneous formation of dextro- and levorotatory complexes (compensating complexes). Table I shows that only the C1 and 3B conformations would allow the formation of compensating complexes in the glucopyranoside series.

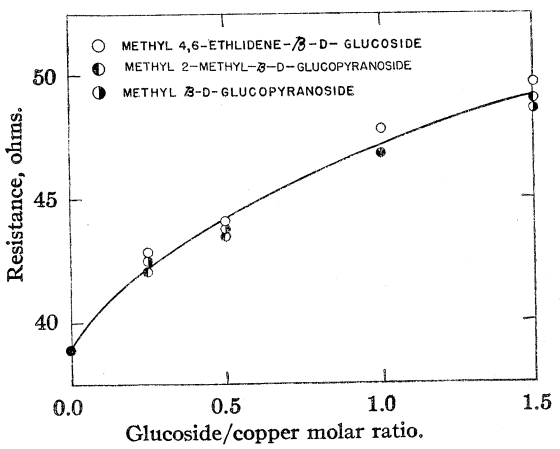



Fig. 2.—Resistance *versus* concentration relationships for some glucopyranosides in cupra A.

The group IV substances of Table II include simple alcohols and glucopyranoside derivatives regarded as non-complex forming because of their low rotatory shifts and the small changes in specific resistances. That these values are not zero is believed to be due to the formation of alcoholates between the basic cuprammonium and the secondary alcohol groups. Although they may be a particular form of bivalent alcoholate, complexes show a more pronounced increase in resistance and the effect increases more rapidly with increasing concentration than is the case in the reaction between cuprammonium and non-complex forming alcohols.

All the glucosides substituted to restrict complex formation to the 2–3 position showed marked evidence of reaction with cuprammonium. This behavior would be compatible with ring conformations C1, B2 and 3B. However, three of the sustances, the 4,6-ethylidene and 4,6-benzylidene compounds, could not exist in either the B2 or 3B conformations for steric reasons because of the spatial requirements of the second ring; hence, for these three substances a definite assignment of ring conformation can be made—they must exist in the C1 conformation.

Both of the glucosides substituted to allow complex formation only at the 3–4 position showed marked evidence of complex formation, behavior compatible with ring conformations C1, B1 or 3B.

It is noteworthy that a single conformation, C1, is compatible with the properties of all the complex forming D-glucopyranoside derivatives here examined. Furthermore this is the form which has been assigned to the D-glucopyranoside units of cellulose[4] and sucrose[5] which have been examined by physical methods in the crystalline state. Cox[6] has listed some reasons for believing

(4) W. T. Astbury and M. M. Davies, *Nature*, 154, 84 (1944).
(5) C. A. Beevers and W. Cochran, *ibid.*, 157, 872 (1946).
(6) E. G. Cox, T. H. Goodwin and A. I. Wagstaff, *J. Chem. Soc.* 1495–1504, (1935).

TABLE III

SPECIFIC ROTATION OF SOME D-GLUCOPYRANOSIDES IN WATER AND IN CUPRA B

| D-Glucopyranoside | M. p., °C. | $[\alpha]^{25}D$ in $H_2O$ $c$ | deg. | $[\alpha]^{25}_{436}$ in $H_2O$ $c$ | deg. | $[\alpha]^{25}_{436}$ in Cupra B[a] $c$ | deg. |
|---|---|---|---|---|---|---|---|
| Methyl 4,6-dimethyl-β- | 67–68[b] | 0.92 | − 17 | 0.92 | − 33 | 0.47 | −920 |
| Methyl 4,6-benzylidene-β- | 202 | 0.3 | − 71 | 0.3 | −146 | 0.95 | −938 |
| Phenyl α-[c] | 171–173 | 1.0 | +175 | 1.0 | +353 | 0.95 | +467 |
| Phenyl β- | 174–175 | 1.1 | − 65 | 1.1 | −135 | 1.0 | −164 |
| Phenyl 3-methyl-β- | 144–145 | 0.8 | − 64 | 0.6 | −124 | 0.8 | −112 |
| Methyl 2,3-dimethyl-α- | 84–85 | 0.7 | +154[d] | 0.69 | +290 | 0.69 | +299 |
| Methyl 2,3-dimethyl-β- | 52–53 | 0.97 | − 34 | 0.72 | − 62 | 0.56 | − 66 |

[a] A standard cuprammonium solution containing 15 g. copper, 240 g. ammonia and 1 g. glycerol per liter. [b] Bell and Synge give m. p. 50–52°. See ref. 9. [c] The rotations determined with the monohydrate were recalculated to the anhydrous basis. [d] In acetone.

that glycoside molecules do not readily change from one conformation to another in solution, or even in the change of state, crystalline⇄solution. While it does not seem that the arguments so far advanced against possible interchange of conformation can apply with equal validity to all glucosides and all permutations of conformation changes, nevertheless the data in the glucopyranoside series are consistent with a single conformation persisting in the crystalline state and, at ordinary temperatures, in solution.

## Experimental

Resistance measurements were made by the procedure previously described.[7] The readings were plotted against molar concentration of glucoside and the values at 0.01 molar concentration were taken from the smooth curve through the experimental points. The resistances were divided by the cell constant (0.116) to give specific resistance at 25°. The cuprammonium solution used for conductivity measurements, cupra A, contained 0.01 mole copper, 3 moles ammonia and 10 ml. ethanol per liter. It had a specific resistance of 336 ohm, cm. at 25°.

Melting points were measured between crossed polaroids in a Fisher–Johns melting point apparatus drilled to allow the passage of a 1 mm. beam of light.

Optical rotations were measured in a Gaertner polarimeter with the mercury blue line (436 mμ) or the sodium D line, as indicated. The cuprammonium solution used for optical measurements, cupra B, contained 15 g. copper, 240 ± 5 g. ammonia and 1 g. glycerol per liter. Copper to glucoside ratios of approximately 7:1 were employed to ensure essentially complete reaction between cuprammonium and the complex forming glucosides. The blue line specific rotations not previously recorded are given in Table III together with melting points and D line rotations which identify the substances and establish the purity of the preparations employed.

**Methyl 2,3-di-N-phenylcarbamyl-4,6-dimethyl-β-D-glucoside** was prepared from four grams of the methyl 2,3-di-N-phenylcarbamyl-β-glucoside[8] by methylation with methyl iodide and silver oxide in the presence of anhydrous calcium sulfate and dry acetone. After several recrystallizations from alcohol the product melted at 222–225°, $[\alpha]^{25}D$ −12° (*c* 2.5, acetone). It was dried at 78° in vacuum over phosphoric anhydride for analysis.

*Anal.* Calcd. for $C_{23}H_{28}O_8N_2$ (460.47): C, 59.99; H, 6.13. Found: C, 59.98; H, 6.16.

**Methyl 4,6-dimethyl-β-glucoside** was prepared by hydrolyzing 377 mg. of the above substance with barium hydroxide for four hours in boiling dilute ethanol. Carbon dioxide was passed through the solution which was then filtered and evaporated to dryness *in vacuo*. The residue was taken up in warm acetone which left 171 mg. residue on evaporation of the solvent. This material was distilled at 0.2 mm. pressure at 100° and the distillate crystallized on the condenser. At first the product melted at 52–55°, but on standing a higher melting form, m. p. 65–67°, appeared, and on recrystallization from a mixture of ether and petroleum ether the substance melted sharply at 67–68°. The high melting form was not hygroscopic. Its optical rotation in chloroform was $[\alpha]^{25}D$ −27° (*c* 0.92). Bell and Synge[9] give m. p. 50–52°, $[\alpha]D$ −28.8° (chloroform) for this substance.

**Acknowledgments.**—The writer is indebted to Lawrence E. Brown for micro carbon–hydrogen analyses and J. R. Jung, Jr., for conductometric measurements.

## Summary

Consideration of the properties of seventeen D-glucopyranoside derivatives has led to the conclusion that, in this series, complex formation between cuprammonium and two hydroxyl groups occurs only with the glycol on the second and third or third and fourth carbon atoms.

Consideration of the behavior of twelve complex-forming glucosides in the light of a previously presented theory reduces from eight to not more than three the number of conformations which need be considered to represent the shape of the pyranoside ring of each glucoside in solution; for three of the substances only one ring conformation appears to be possible. It is noted that a single ring conformation, the *trans* "chair form" in which the ring oxygen and 6-carbon atom project on the same side of the plane of the 1,2,4,5-carbon atoms, is sufficient to explain the behavior of all the complex forming glucosides in solution.

Methyl 2,3-di-N-phenylcarbamyl-4,6-dimethyl-β-D-glucoside has been prepared and a higher-melting form of methyl 4,6-dimethyl-β-D-glucoside has been described.

A symbol has been assigned to each of the eight pyranose strainless ring conformations.

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(7) R. E. Reeves and J. R. Jung, Jr., I, THIS JOURNAL, **70**, 209 (1948).

(8) W. M. Hearon, G. D. Hiatt and C. R. Fordyce, *ibid.* **66**, 995 (1944).

(9) D. J. Bell and R. L. M. Synge, *J. Chem. Soc.*, 1711 (1937).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY UNIVERSITY OF PITTSBURGH]

# Electric Moments and Structure of Substituted Thiophenes. I. Certain Halogenated Derivatives[1]

BY RAM KESWANI AND HENRY FREISER

Interest in the structure of thiophene and in the influence of substituents upon that structure has prompted the initiation of a program for the determination of the dipole moments of substituted thiophenes. Aside from thiophene[2] itself and 2-nitrothiophene,[3] no measurements of dipole moments of members of this interesting heterocyclic family have been reported. The measurement of thiophene and 2-nitrothiophene have been repeated here for purposes of comparison. The work reported here on certain of the halogenated thiophenes represents the first phase of the program.

## Experimental

**Purification of Materials.**—Jones and Laughlin reagent-grade benzene was distilled in a three-foot glass helices-packed fractionating column and a central portion boiling within 0.03° was collected. It was found to have a density of 0.868231 g./ml. and a refractive index ($n_D$) of 1.49475, both measured at 30°.

Socony-Vacuum 99 mole per cent. thiophene was shaken with hydrochloric acid, washed, dried, and carefully distilled in the three-foot column. Fractions boiling at 82.5° at 747.1 mm. within a range of 0.02° were collected for use; $d^{30}_4$ 1.04760, $n^{30}D$ 1.5214.

The 2-chlorothiophene, 2-bromothiophene and 2,5-dichlorothiophene, which were obtained from the Michigan Chemical Corporation, were dried and fractionated prior to use. The boiling points obtained were 126.28–126.30° at 736.7 mm., 150.6–150.7° at 734.7 mm., and 160.0–160.1° at 734.0 mm. respectively, while the corresponding densities and refractive indices ($n_D$) measured at 30.0° were 1.27316 g./ml. and 1.5432, 1.69288 g./ml. and 1.5815, and 1.42901 g./ml. and 1.5575, respectively.

2-Nitrothiophene was prepared by the method of Babasinian[4] under the direction of Dr. M. F. Dull. It was recrystallized twice from petroleum ether without any change in freezing point which was found from melting curves to be 42.6°. This value differs from that reported by Steinkopf,[5] but is in good agreement with that obtained by Von Seemann and Lucas.[6]

2-Iodothiophene and tetrabromothiophene were also prepared under the direction of Dr. M. F. Dull from directions given by Steinkopf.[5] The 2-iodothiophene was purified by fractional crystallization followed by vacuum distillation; b. p. at 13 mm. 65.0°, $d^{30}_4$ 2.04926 g./ml.

The tetrabromothiophene was recrystallized until no further change in its melting point, 117°, was observed.

**Measurements and Calculations.**—The dielectric constants were measured at a frequency of 250 kilocycles with a heterodyne beat apparatus consisting of a Clough–Brengle Beat Frequency Audio Oscillator Model 179A whose variable frequency oscillator circuit was modified by the replacement of some of the original capacitance by a General Radio Precision Condenser 722 F and a dielectric cell in parallel. The measurement procedure has been reported elsewhere.[7] The cell, similar in design to that previously reported,[7] was constructed of stainless steel and Teflon. The densities of the liquids and solutions were measured in flask-type pycnometers of 20 ml. and 100 ml. capacities, respectively, in a manner similar to that previously reported,[8] with an estimated accuracy better than one part in 100,000. The dielectric constants, $\epsilon$, and the densities, $d$, of benzene solutions containing mole fraction, $f_2$, of the substance indicated are given in Table I.

TABLE I

DIELECTRIC CONSTANTS, DENSITIES OF BENZENE SOLUTIONS MOLAR REFRACTIONS, POLARIZATIONS AT 30° AND DIPOLE MOMENTS

| $f_2$ | $\epsilon$ | $d$ | $P_2$ | $MR_D$ | $P_\infty$ | $\mu \times 10^{18}$ |
|---|---|---|---|---|---|---|
| Thiophene | | | | 24.36 | 30.1 | 0.53 |
| 0.00000 | 2.2627 | 0.868231 | ... | | | |
| .04560 | 2.2816 | .875494 | 29.9 | | | |
| .04954 | 2.2810 | .876139 | 29.2 | | | |
| .05022 | 2.2838 | .876247 | 30.0 | | | |
| .06531 | 2.2911 | .878696 | 30.2 | | | |
| 2-Nitrothiophene | | | | 31.55 | 393 | 4.23 |
| 0.002974 | 2.3364 | 0.869920 | 388.4 | | | |
| .005919 | 2.4105 | .871588 | 385.2 | | | |
| .006646 | 2.4277 | .871999 | 381.7 | | | |
| .007522 | 2.4486 | .872497 | 378.4 | | | |
| 2-Chlorothiophene | | | | 29.37 | 81.0 | 1.60 |
| 0.01249 | 2.3040 | 0.873441 | 82.9 | | | |
| .01946 | 2.3260 | .876350 | 78.3 | | | |
| .02526 | 2.3439 | .878770 | 77.7 | | | |
| .03707 | 2.3822 | .883776 | 76.3 | | | |
| 2-Bromothiophene | | | | 32.10 | 70.0 | 1.37 |
| 0.01130 | 2.2952 | 0.878260 | 70.9 | | | |
| .01687 | 2.3104 | .883164 | 70.0 | | | |
| .03075 | 2.3504 | .895450 | 70.0 | | | |
| .03427 | 2.3607 | .898573 | 70.0 | | | |
| 2-Iodothiophene | | | | 37.2 | 63.1 | 1.14 |
| 0.01462 | 2.2954 | 0.888006 | 63.1 | | | |
| .02131 | 2.3101 | .897053 | 62.8 | | | |
| .02564 | 2.3207 | .902917 | 63.3 | | | |
| 2,5-Dichlorothiophene | | | | 34.50 | 59.7 | 1.12 |
| 0.008979 | 2.2806 | 0.874630 | 60.0 | | | |
| .01403 | 2.2895 | .877633 | 59.9 | | | |
| .02539 | 2.3106 | .885248 | 59.4 | | | |
| .03244 | 2.3225 | .889088 | 59.5 | | | |
| Tetrabromothiophene | | | | 55.5 | 66.5 | 0.73 |
| 0.004296 | 2.2693 | 0.881420 | 64.8 | | | |
| .006934 | 2.2742 | .889442 | 67.2 | | | |
| .01187 | 2.2837 | .904428 | 67.6 | | | |

(1) This work is abstracted from a portion of the thesis to be submitted by Ram Keswani to the University of Pittsburgh in partial fulfillment of the requirements for the Master of Science degree.

(2) H. de V. Robles, *Rec. trav. chim.*, **58**, 111 (1939).

(3) P. F. Oesper, G. L. Lewis, and C. P. Smyth, THIS JOURNAL, **64**, 1130 (1942).

(4) V. S. Babasinian, *ibid.*, **50**, 2749 (1928).

(5) W. Steinkopf, "Die Chemie des Thiophenes," Theodor Steinkopf, Dresden, 1941.

(6) C. Von Seemann and C. C. Lucas, *Can. J. Research*, **19B**, 292 (1941).

(7) A. J. Weith, M. E. Hobbs, and P. M. Gross, THIS JOURNAL, **70**, 805 (1948).

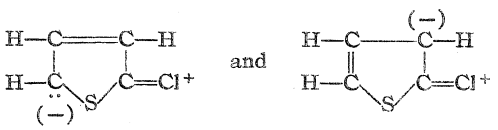
(8) H. Freiser and W. L. Glowacki, *ibid.*, **70**, 2575 (1948).

along with the molar polarization, $P_2$, in the fourth column. This table also lists in the fifth column the values of $MR_D$, the molar refraction for the sodium D line, obtained directly for thiophene, 2-chloro-, 2-bromo and 2,5-dichlorothiophene, from the solutions of 2-nitrothiophene and for the remaining substances the values were calculated from that of thiophene and the following atomic refraction values: hydrogen 1.1, iodine 13.9, and bromine 8.8[7].

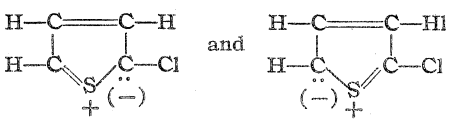
The sixth column gives the polarization, $P_\infty$, obtained by extrapolation to $f_2 = 0$ of the values of $P_2$ in Table I, and the seventh column gives the dipole moments calculated in the usual manner. When the $P_2$ values showed no trend with concentration, the average value was taken as $P_\infty$. The precision of the electric moment determination is about 1%.

## Discussion of Results

The values of the moments of thiophene and 2-nitrothiophene are in good agreement with those previously reported.[2,3] In order to evaluate structural influences in the 2-halothiophenes the observed moment values were compared to those calculated on the basis of vector addition. The calculations were made in the following manner: The angles taken for the bonds in the thiophene nucleus were those obtained by Schomaker and Pauling[9] by electron diffraction studies on the thiophene itself. The halogen–carbon bond moment was assumed to act in the line bisecting the bond angle of the corresponding ring carbon atom while the sulfur bond moment, taken to be 0.53, was assumed to act in the line bisecting the CSC angle. Because the chemical properties of the halothiophenes resemble those of the corresponding halobenzenes, the values of the carbon–halogen bond moments were taken to be those in monohalogenbenzenes ($\mu_{C-Cl} = 1.58$, $\mu_{C-Br} = 1.48$, and $\mu_{C-I} = 1.25$). The values thus calculated for 2-halothiophenes are 1.76, 1.67, and 1.45 for 2-chloro, 2-bromo- and 2-iodothiophene, respectively. The over-all agreement between these calculated values and those experimentally determined is fair and confirms the belief that the carbon–halogen bonds in the thiophene series are very similar to those in the benzene series, making structures such as




as well as




of significance in the description of the ground state of 2-chlorothiophene.

The calculated values of the moments of the 2-halothiophenes while in general agreement with the observed values are somewhat higher than the latter, being about 0.16 $D$ higher for 2-chlorothiophene and twice that, about 0.31, in the case of the corresponding bromo- and iodine derivatives. These deviations may well be compared with similar deviations observed in ortho disubstituted benzene derivatives which are attributed to mutual inductive effects, since the 2-substituted thiophenes are structurally similar to the ortho disubstituted benzenes with the sulfur considered as one of the substituents. Mutual inductance of the two groups will cause a decrease in the moments of these compounds from the calculated values. It is possible that the smaller deviations encountered in the case of the chlorothiophene might be related to the greater importance of structures involving a double bond between carbon and halogen in the case of chlorine over that of the bromine or iodine. These structures as pictured above would tend to make the sulfur more negative in chlorothiophene than in thiophene itself.

The moment of 2,5-dichlorothiophene calculated in the manner mentioned above was found to be in exact agreement with the experimentally observed result. It must be observed, however, that because of the geometrical relationships in this compounds, the two C–Cl bonds meeting at an angle of 158°, the net moment is not at all sensitive to changes in the C–Cl bond moment. Also because of the importance of structures similar to that shown above for 2-chlorothiophene in which C–Cl has double bond character, the negative deviation expected in the 2,5-dichlorothiophene because of mutual inductive interaction is possibly counter-balanced by the resulting increase in negative character of the sulfur.

The value calculated for the moment of tetrabromothiophene in the manner explained above is 1.37 $D$ acting in the direction opposite to the thiophene moment. The large difference between this and the observed value of 0.73 $D$ may be accounted for on the basis of the mutual inductive effects of the four bromine atoms which are all close together. A similar negative deviation is encountered in the case of 1,2,3-trichlorobenzene whose observed moment, 2.31 $D$,[10] is 0.85 unit lower than that calculated by vector addition. Likewise, the observed moment of 1,2,3,4-tetrachlorobenzene, 1.90 $D$,[11] is 0.84 unit lower than that calculated by vector addition and 0.36 unit lower than the observed value of *o*-dichlorobenzene[12] with which, according to calculations based on vector addition, the value of tetrachlorobenzene should coincide. These cases lend weight to the above argument.

## Summary

1. Dielectric constants and densities at 30° are reported for benzene solutions of thiophene, 2-

(9) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

(10) J. A. A. Ketelaar, *Rec. trav. chim.*, **59**, 757 (1940).

(11) C. P. Smyth and G. L. Lewis, THIS JOURNAL, **62**, 721 (1940).

(12) E. Fischer and F. Rogowski, *Physik. Z.*, **40**, 331 (1939).

nitrothiophene, 2-chlorothiophene, 2-bromothiophene, 2-iodothiophene, 2,5-dichlorothiophene and tetrabromothiophene.

2. The dipole moments for these compounds, calculated by use of the Debye equation, have been found to be 0.53, 4.23, 1.60, 1.37, 1.14, 1.12 and 0.73, respectively.

3. The dipole moment values show the general resemblance of the structures of these substituted thiophenes to those of the corresponding benzene derivatives. Deviations between observed moment values and those calculated on the basis of vector additivity have been attributed largely to dipole-polarizability interactions. The possibility of decreased participation of the sulfur electrons in the thiophene ring resonance for the chloro-derivatives is also considered.

RECEIVED AUGUST 16, 1948

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# Viscosity–Molecular Weight Relations for Various Synthetic Rubbers[1]

BY ROBERT L. SCOTT,[2] WALTER C. CARTER AND MICHAEL MAGAT[3]

## Introduction

Houwink[4] and Flory[5] have shown that the relation between the intrinsic viscosity of a high-polymer solution and the molecular weight of the polymer is of the form

$$[\eta] = KM^a \qquad (1)$$

where in the case of polyvinyl acetate compounds[4] and polymethacrylate[4] $a \sim 0.6$ and in the case of polyisobutylene[5] $a = 0.64$. More recently the authors[6] have shown that for natural rubber, the relation is

$$[\eta] = 5.02 \times 10^{-4} M^{0.667} \qquad (2)$$

In this paper, we are reporting viscosity–molecular weight relations for four more polymers: a butadiene–styrene copolymer (Buna S), sodium polymerized polybutadiene, a butadiene–acrylonitrile copolymer (Buna N), and neoprene. As will be shown, these measurements confirm the hypothesis that for these essentially linear polymers $a$ is very close, if not equal to, two-thirds.

## Experimental

**Materials.**—The rubber samples used in these experiments were kindly supplied by the Firestone Tire and Rubber Company of Akron, Ohio. The Buna S (GR-S) was of three kinds: one of low degree of conversion (100% soluble), one of medium degree of conversion (53.5% soluble) and one of high degree of conversion (32% soluble). The polybutadiene was polymerized with sodium according to methods similar to those used in the preparation of Russian SK.[7]

The toluene used was the commercial solvent dried with calcium chloride.

**Fractionation.**—Unlike natural rubber, the synthetic rubbers are not subject to rapid oxidative degradation in solution, so some of the precautions reported in the previous paper[6] are unnecessary. The rubbers were dissolved in toluene and fractionally precipitated[8] by methanol; in some cases fractions were refractionated into subfractions. Anti-oxidant ("Agerite," aldol - $\alpha$ - naphthylamine), although possibly unnecessary for these synthetics, was added to all solutions.

In certain polymers, a portion of the soluble fraction consists of "microgel," a material which is not easily removed by slow extraction with good solvents in the absence of agitation, but is more or less easily dissolved by energetic shaking, leaving only the insoluble cross-linked "macrogel." A second portion of the 100% soluble polymer was fractionated as follows: After extraction of the acetone-soluble fraction (9.0%) the rubber was dried under vacuum and then extracted with toluene in an atmosphere of carbon dioxide. Agitation of the mixture was avoided in order to minimize dispersion of the "microgel." At intervals of several days the supernatant liquid was carefully pipetted out and additional toluene added with as little disturbance to the swollen "microgel" at the bottom as possible. After much of the "sol" had been extracted in this way, fresh toluene was added and the mixture shaken. One or two shakes sufficed to bring the "microgel" into solution indicating that, for this sample at least, the bonds between the molecules of "microgel" are extremely weak. The resulting solution was completely stable, no material settling out after even a month's standing.[9] The "sol" and "microgel" portions were separately fractionated. A sample of the "macrogel" was degraded and solubilized by oxidation at high temperatures and subsequently fractionated.

**Measurements.**—The molecular weights of the fractions were calculated from osmotic pressures measured in a Flory-type osmometer, while solution viscosities were determined in an Ostwald viscosimeter. The details of these procedures were reported in the previous paper.[6]

For Buna N, the viscosity relation for various solvents was determined in the following manner: After measurements of the osmotic pressure and the viscosity in toluene, a sample of each fraction was dried in vacuum at room temperature and redissolved successively in acetone, chloroform and benzene[10] and its intrinsic viscosity in each of these solvents determined.

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(1) This research was carried out during 1943 on a grant from the Reconstruction Finance Corporation, Office of Rubber Reserve, for fundamental research on the physical properties of synthetic rubbers.

(2) Present address: Department of Chemistry, University of California, Los Angeles 24, California.

(3) Present address: Laboratoire de Chimie Physique de la Sorbonne, 11 rue Pierre Curie, Paris, France.

(4) R. Houwink, *J. prakt. Chem.*, **157**, 15 (1940–1941).

(5) P. J. Flory, THIS JOURNAL, **65**, 372 (1943).

(6) W. C. Carter, R. L. Scott and M. Magat, *ibid.*, **68**, 1480 (1946).

(7) For details of the preparation of SK see A. Talalay and M. Magat, "Synthetic Rubber from Alcohol," Interscience Publishers, New York, N. Y., 1945.

(8) In the fractionations of GR-S, the inhibitor, anti-oxidant and the lowest molecular weights were extracted with acetone before the remainder of the soluble material was extracted with toluene.

(9) No significance should be attached to the relative amounts of "sol," (23%) and "microgel" in view of the crude method of separation; the "microgel" portion undoubtedly contains some "sol."

(10) No significant oxidative degradation was observed in Buna N fractions, unlike natural rubber where the breakdown is rapid, or Buna S where the breakdown is slow but appreciable.

## Results

The viscosity–molecular weight measurements on the five series of fractions of GR-S (Buna S, 75% butadiene, 25% styrene) are shown in Fig. 1.

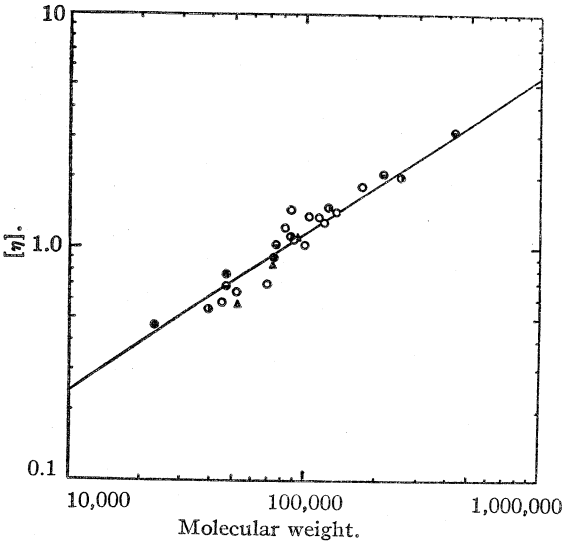



Fig. 1.—Viscosity of GR-S (Buna S) in toluene: ○, GR-S medium conversion-sol; ●, GR-S medium conversion-degraded macrogel; ◑, GR-S, low conversion-"sol"; ◒, GR-S low conversion, "microgel"; △, GR-S high conversion.

The same log–log straight line relation seems to hold approximately for all types of GR-S independent of the degree of conversion or the nature of the material: "sol," "microgel," or degraded "macrogel." Analytically the intrinsic viscosity of GR-S in toluene at 25° may be expressed as

$$[\eta] \text{ (toluene)} = 5.25 \times 10^{-4} M^{2/3} \qquad (3)$$

This relation is accurate to at least 10% for molecular weights between 25,000 and 500,000 and probably is valid for much higher molecular weights. Lower molecular weights could not be measured with our osmometer because of the permeability of the membrane.

The relations found for the other three polymers are shown in Table I and Figs. 2 and 3.

TABLE I

| Polymer | Solvent | $K \times 10^4$ | $a$ |
|---|---|---|---|
| Buna N | Toluene | 4.9 | 0.64 |
| | Acetone | 5.0 | .64 |
| | Chloroform | 5.4 | .68 |
| | Benzene | 1.3 | .55 |
| Neoprene | Toluene | 5.0 | .615 |
| Sodium polymerized polybutadiene | Toluene | 11.0 | .62 |

The reader may judge the accuracy of the determination of the exponent $a$ from the experimental data in Figs. 1–3. For GR-S $a$ is probably 0.67 ± 0.05. For the other polymers the accuracy is considerably better.

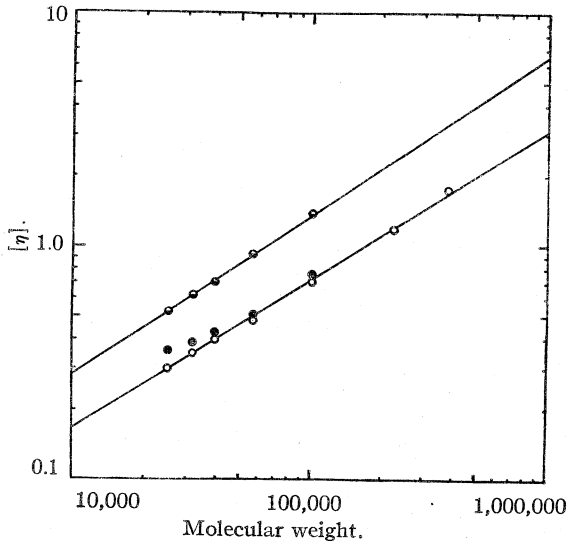



Fig. 2.—Viscosity of Buna N solutions: ○, toluene; ●, benzene; ◒, chloroform.

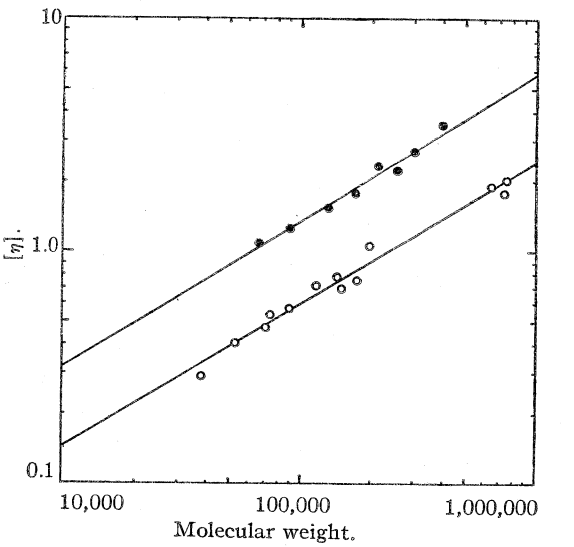



Fig. 3.—Viscosity of sodium polymerized polybutadiene (●) and neoprene (○) in toluene.

The data for Buna N in different solvents are further shown in Table II.

TABLE II

INTRINSIC VISCOSITY OF BUNA N SOLUTIONS

| Fraction | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Mol. wt. × 1000 | 25.0 | 31.8 | 39.5 | 57.0 | 101 | 224 | 380 |
| Toluene | 0.30 | 0.35 | 0.40 | 0.48 | 0.71 | 1.16 | 1.76 |
| Acetone | .317 | .38 | .405 | .475 | 0.715 | | |
| Chloroform | .52 | .62 | .70 | .93 | 1.38 | | |
| Benzene | .36 | .39 | .43 | .51 | 0.76 | | |

No systematic work was done on polyisobutylene since this polymer has been studied exhaustively by Flory.[5] However, at the beginning of our work Dr. Flory kindly sent us three fractions of known molecular weight to check the

accuracy of our osmometer. As seen in Table III the agreement between the data of the two laboratories is quite satisfactory.

TABLE III

POLYISOBUTYLENE FRACTIONS

| No. | Osmotic molecular weight: Flory | Osmotic molecular weight: Scott and Magat | Intrinsic viscosity: In toluene (Scott and Magat) | Intrinsic viscosity: In diisobutylene (Flory) |
|---|---|---|---|---|
| 1 | 206,000 | 223,000 | 0.635 | 0.90 |
| 2 | 515,000 | 495,000 | 1.25 | 1.64 |
| 3 | 1,200,000 | 1,340,000 | 2.06 | 2.82 |

We have used these data to determine in a very rough way the dependence of the viscosity in toluene on the molecular weight. Figure 4 shows this relation (in broken line since based on but three points it is only very approximate) and the well-established relation for the viscosity in diisobutylene.[5] These relations expressed analytically are

$$[\eta] \text{ (toluene)} = 2.6 \times 10^{-4} M^{0.64} \quad (4)$$

$$[\eta] \text{ (diisobutylene)} = 3.60 \times 10^{-4} M^{0.64} \quad (5)$$

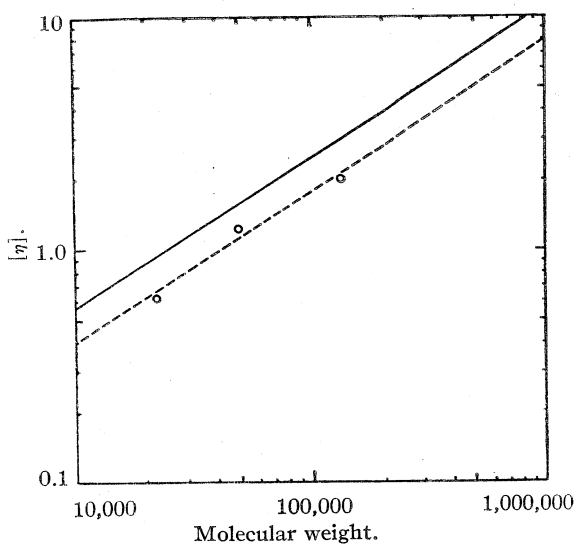



Fig. 4.—Viscosity of polyisobutylene: —, in diisobutylene (Flory); --O--, in toluene (this paper).

## Discussion

At about the same time as our research was carried out, Ewart and co-workers at the United States Rubber Company Laboratories measured solutions of fractionated GR-S in a glass osmometer using cellophane membranes.[11] While most, if not all, of their measurements were made upon benzene solutions, they fit our relation for toluene solutions remarkably well. Figure 5 shows the results of two different series of data by Ewart and French[12] and Tingey, Ewart and Hulse[13]; the line is our relation for toluene taken from Fig. 1. It should be emphasized that the U. S. Rubber measurements were made in an entirely different osmometer using a different kind of membrane, so that the possibility of systematic error is almost certainly excluded.

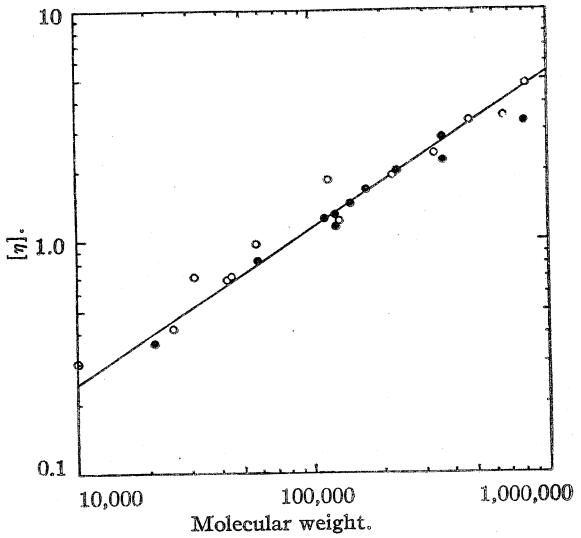



Fig. 5.—Viscosity of Buna S (GR-S) in benzene (U. S. Rubber Company measurements): O, Ewart and French; ●, Tingey, Ewart and Hulse.

In the previous paper on natural rubber,[6] the authors have discussed in some detail the various theories which attempt to explain the viscosity of high polymer solutions. Since those comments seem to be equally valid for these data, they need not be repeated here, but one additional point is worth consideration. The intrinsic viscosity should be a function of the chain length rather than the actual molecular weight.[14] Since the chain length is proportional to the molecular weight, the viscosity should be proportional to some inverse power of $w$, the weight per chain atom. That this seems to be true can be seen from Table IV.

TABLE IV

| Polymers | $w$ | $K \times 10^4$ |
|---|---|---|
| Polybutadiene | 13.5–27[15] | 6.34 |
| GR-S | 18–20 | 5.25 |
| Hevea | 18 | 5.02 |
| Buna NM | 15–26[15] | 3.35 |
| Neoprene GN | 22 | 2.73 |
| Polyisobutylene | 28 | 2.01 |

($w$ = molar weight per chain carbon atom)

The value of the empirical constant $K$ is given for a variety of rubbers (in toluene solutions); to secure uniformity, they are all recalculated for $a = 2/3$. We see that as $w$ increases, there is a systematic decrease in $K$, corresponding to lower solution viscosities for equal molecular

(11) D. M. French and R. H. Ewart, *Anal. Chem.*, **19**, 165 (1947).

(12) R. H. Ewart and D. M. French, private communication. Most but not all of these data were reported in reference 9.

(13) H. C. Tingey, R. H. Ewart and G. E. Hulse, private communication.

(14) Hence the expression of concentration in "base moles" in some treatments of the so-called Staudinger "law."

(15) Depending on the extent of 1,2 and 1,4 additions. Russian SK is said to be 75% 1,2 additions.

weights. This shift of the intrinsic viscosity–molecular weight curves is summarized graphically in Fig. 6. The theoretical expressions of Huggins[16] and of Hulburt, Harmon, Tobolsky and Eyring[17] represent the viscosity as proportional to inverse powers of the weight per chain atom so in this respect at least they are approximately valid.

It is interesting to note that of the various theories only that of Haller[18] predicts accurately the dependence of the viscosity on the two-thirds power of the molecular weight.[19]

**Acknowledgments.**—The authors wish to thank Dr. Paul J. Flory and the Esso Laboratories for furnishing the three fractions of polyisobutylene; the Firestone Tire and Rubber Company, in particular Dr. J. H. Dillon, for furnishing the rubber samples; Professor Arthur V. Tobolsky for several helpful discussions; and Professor Hugh S. Taylor for his generous interest and valuable advice.

(16) M. L. Huggins, *J. Phys. Chem.*, **42**, 910 (1938); **43**, 439 (1939); *J. Appl. Phys.*, **10**, 700 (1939).

(17) H. M. Hulburt, R. A. Harmon, A. V. Tobolsky and H. Eyring, *Ann. N. Y. Acad. Sci.*, **44**, 371 (1943).

(18) W. Haller, *Kolloid Z.*, **56**, 257 (1931).

(19) Since this paper was first submitted to the Editor of The Journal, two new theories of viscosity have appeared, one by P. Debye and A. M. Bueche (*J. Chem. Phys.*, **16**, 573, 1948) and one by J. G. Kirkwood and J. Riseman (*ibid.*, **16**, 565, 1948). On preliminary inspection, it seems that our data are entirely consistent with these new theories, but rather than further delay publication of these results, we postpone a detailed discussion to a subsequent paper.

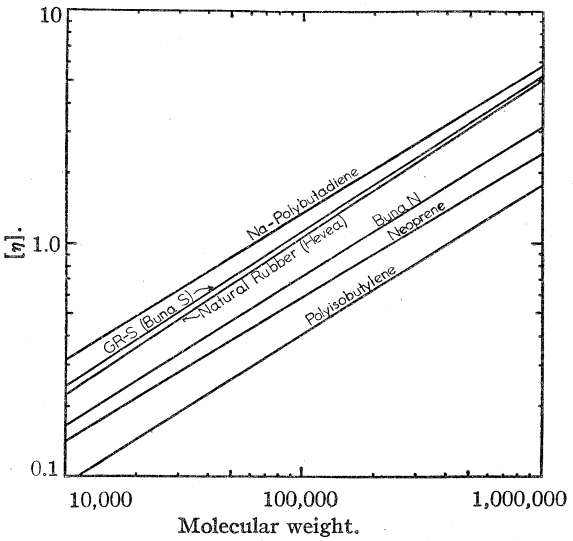



Fig. 6.—Viscosity–molecular weight relations for toluene solutions of various polymers.

## Summary

Measurements on six different high polymers have shown that the intrinsic viscosity of the solutions depends on approximately the two-thirds power of the molecular weight. Dependence of the viscosity on the weight per chain atom of the polymer is indicated.

LOS ANGELES 24, CALIFORNIA RECEIVED APRIL 20, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

# The Kinetics of Semicarbazone Formation with Para Substituted Acetophenones[1]

BY ROBERT P. CROSS AND PAUL FUGASSI

The kinetics of the reactions of *d*-carvone with semicarbazide and other carbonyl reagents have been investigated previously by Stempel and Schaffel[2] and Mariella[3] using a polarimetric method. It is the purpose of this investigation to examine the kinetics of semicarbazone formation with para substituted acetophenones by a competitive method in which *d*-carvone and acetophenone react simultaneously with semicarbazide, present in sufficiently low concentration that the carbonyl reagent distributes itself between the two ketones. The extent of reaction of the *d*-carvone is determined polarimetrically.

(1) Abstracted from the thesis submitted by Robert P. Cross on August 12, 1947, to the Committee on Graduate Degrees, Carnegie Institute of Technology, in partial fulfillment of the requirements for the degree of Doctor of Science. Presented before the Division of Physical and Inorganic Chemistry at the 113th meeting of the American Chemical Society at Chicago, April, 1948.

(2) Stempel and Schaffel, THIS JOURNAL, **66**, 1158 (1944).

(3) Mariella, Thesis, Carnegie Institute of Technology, October 4, 1945.

## Experimental Technique

**Preparation of Compounds.**—*d*-Carvone was obtained from Magnus, Mabee and Reynard. It was purified by preparing the solid hydrosulfide.[4,5] After several recrystallizations of the hydrogen sulfide compound, *d*-carvone was recovered by treating the compound with concentrated sodium hydroxide solution and steam distilling the mixture. Following extraction of the carvone with ether, the extract was vacuum distilled several times and a fraction collected boiling at 78° at 3 mm. The physical constants of our sample agreed with those found by Stempel and Schaffel.[2] Semicarbazide hydrochloride (an Eastman Kodak Co. product) was recrystallized from hydrochloric acid solution. Acetophenone was purified by the method of Flexser, Hammett and Dingwall.[6] The sample of acetophenone used boiled at 193° at 743 mm. *p*-methoxyacetophenone and *p*-chloroacetophenone were prepared by the method of Adams and Noller.[7] The

(4) Wallach, *Ann.*, **305**, 224 (1889).

(5) Hooper, Macbeth and Price, *J. Chem. Soc.*, 1147 (1934).

(6) Flexser, Hammett and Dingwall, THIS JOURNAL, **57**, 2103 (1935).

(7) Adams and Noller, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 109–111.

former compound melted at 38° and the latter boiled at 85° at 5 mm. *p*-Methyl and *p*-bromo acetophenone were Eastman chemicals. The *p*-bromoacetophenone was recrystallized several times from hot ethanol to give a sample with a melting point of 50.5°. *p*-Methylacetophenone was distilled several times at reduced pressure. The fraction used boiled at 94° at 10 mm.

**Physical Measurements.**—Rotations were measured with a Hilger M-8 polarimeter using the mercury green line at 5461 Å. Readings could be made to 0.01°. The polarimeter tube, 5 decimeters long, was provided with a water jacket, insulated with magnesia–asbestos, through which thermostatted water was pumped. Beckmann thermometers were placed at the inlet and outlet water connections and the thermostat adjusted so that the mean temperature of the polarimeter tube was 30, 40 or 50°.

Two general types of experiments were made. In the first type of experiment *d*-carvone reacted with semicarbazide, while in the other type *d*-carvone and an acetophenone reacted with semicarbazide. For the experiments with carvone alone the reactants were brought to the temperature of the experiment and mixed in a volumetric flask kept at the temperature of the experiment. Sufficient solvent (83% ethanol in water) was then added so that the starting concentrations of semicarbazide, semicarbazide hydrochloride and *d*-carvone were all equal to 0.015 mole/liter. After thorough mixing, the solution was transferred to the polarimeter tube and the rotations measured at definite time intervals taking zero time as the instant when the reactants were mixed. In the second type of experiment the reactants were mixed in a volumetric flask kept at the temperature of the experiment and sufficient 83% ethanol added so that the starting concentrations of carvone, substituted acetophenone, semicarbazide, and semicarbazide hydrochloride were all equal to 0.015 mole/liter. After mixing the solution was allowed to remain in the thermostat for a period of approximately twenty, ten or five hours depending on whether the temperature of the experiment was 30, 40 or 50°, respectively. These periods of time correspond to the time interval necessary for 99% of the reaction to take place when carvone alone is reacted with semicarbazide.

## Calculation of Velocity Constants

In the experiments with *d*-carvone a first order plot of $-\log(1-f)$ against time fits the experimental data for values of $f$ (fraction decomposed) up to 0.5. For the experiments at 30°, $f$ values of about 0.5 were the highest that could be obtained in reasonable reaction times. At 50°, however, $f$ values up to 0.93 were obtained. For the higher temperature experiments the experimental points corresponding to $f$ values greater than 0.5 were above the straight line first order plot. The experimental points at these higher values of $f$ diverged more and more from the first order line as $f$ increased in value. The direction of the drift indicates that in the later stages the reaction is approaching zero order. However, in view of the fact that we are dealing with a complex system and a reversible reaction in which the points obtained at low $f$ values should be stressed to minimize the effect of the reverse reaction, it does not seem desirable to stress fitting of the experimental points at high $f$ values. Consequently, the experimental data for the experiments with *d*-carvone alone were calculated on the basis of the first order equation, $kt = -2.3\log(1-f)$.

In the experiments where two ketones reacted simultaneously with semicarbazide, it appears possible to ignore the reverse reactions. Experimentally it is known that the semicarbazones of either carvone or acetophenone do not react appreciably, in the time intervals used here, with acetophenone or carvone, respectively. The equilibrium constant for the formation of carvone semicarbazone is known to be large. The equilibrium constant for the formation of acetophenone semicarbazone is also believed to be large. A value for the latter equilibrium constant is not cited because in the periods of time (weeks) necessary for equilibrium the solutions darken even if protective nitrogen atmospheres are employed. The darkening of the solution interferes somewhat with the measurement of the rotation and might be indicative of slow side reaction which would influence the equilibrium but would have little or no influence on the kinetics because of their slowness. In the kinetics measurements reported here all solutions were colorless at the end of the time intervals used. Until the origin of the darkening of the solutions is discovered it does not seem desirable to list numerical values for the equilibrium constant. With regard to substituted acetophenones it is fairly certain that the substitution of groups on acetophenone will change the numerical values of the equilibrium constant for semicarbazone formation but will not change its order of magnitude.

Accordingly we assume following Grazzi[8] that each ketone follows a rate equation of the form

$$dx_i/dt = k_i(a_i - x_i)f(x_i)$$

where $a_i$ is the starting concentration of the ketone, $x_i$ the concentration of ketone which has reacted at time $t$, and $f(x_i)$ a function of the concentrations of all the other reactants involved. Under the experimental conditions employed it is assumed that $f(x_i)$ has the same value for all ketones so that we may write

$$\frac{dx_1}{k_1(a_1 - x_1)} = \frac{dx_2}{k_2(a_2 - x_2)}$$

where the subscripts 1 and 2 refer to *d*-carvone and the other ketone, respectively. Integration of this equation together with the use of the boundary condition that at zero time the concentrations of *d*-carvone, other ketone, semicarbazide and semicarbazide hydrochloride are all equal gives the equation

$$k_2 = k_1\frac{\log f'}{\log(1-f')}$$

where $f'$ is the fraction of *d*-carvone which has reacted at the given time interval with the other ketone present, relative to the amount of reaction undergone by *d*-carvone at infinite time when the other ketone is absent.

## Experimental Data

For the experiments with *d*-carvone alone the following average values of $k$ representing the

(8) Grazzi, *Gazz. chim. ital.*, **38**, 32 (1908); **40**, 140 (1910).

mean of three determinations at each temperature were obtained: 30°, $3.74 \times 10^{-3}$ min.$^{-1}$; 40°, $7.68 \times 10^{-3}$ min.$^{-1}$; and 50°, $1.6 \times 10^{-3}$ min.$^{-1}$.

With experiments using two ketones a minimum of five experiments were made at each temperature for each ketone. The average values of the velocity constants were plotted on a typical Arrhenius plot and the constants in the Arrhenius equation, $\log k = A - \frac{E_A}{2.3RT}$, were evaluated. $E_A$ is the energy of activation. The values of the constants are collected in Table I.

TABLE I

ARRHENIUS EQUATION CONSTANTS

| Ketone | $A$, min.$^{-1}$ | $E_A$, cal. |
|---|---|---|
| *p*-Methoxyacetophenone | −0.57 | 4,000 |
| *p*-Methylacetophenone | 1.38 | 6,540 |
| Acetophenone | 2.33 | 7,800 |
| *p*-Chloroacetophenone | 4.44 | 10,330 |
| *p*-Bromoacetophenone | 5.00 | 11,040 |

## Discussion

Reference to Table I indicates that the activation energy of semicarbazone formation varies with the nature of the substituting group in the para position and that in order of decreasing activation energy the substituting groups would fall in the sequence Br > Cl > H > $CH_3$ > $CH_3O$. It is obvious that the above sequence is the same one that would be obtained if the substituting groups were arranged in the order of their ability to withdraw electrons from the ring. As semicarbazone formation only involves the carbonyl group, it is apparent that the charge density on the carbon atom is the determining factor and that the influence of the substituting group is due to its effect upon the charge density of the carbonyl carbon. A number of reactions are influenced by substitution in this manner and to these Hammett has applied the equation, $\log k - \log k^0 = \rho\sigma$. In this equation $k$ is the rate constant for the substituted compound, $k^0$ is the rate constant for the unsubstituted compound, $\sigma$ is a constant depending upon the nature of the substituting group, and $\rho$ is a constant characteristic of the reaction. If the values of $\sigma$ evaluated by Hammett are used, a plot of log $k$ *versus* $\sigma$ gives a straight line of slope $\rho$. The slope and value of $\rho$ for the semicarbazone formation turns out to be 0.91. Another method of illustrating the effect of the substituting groups is to plot log $K_{(\text{dissociation})}$ which is proportional to the free energy of dissociation of the corresponding substituted benzoic acid, against the energy of activation of the corresponding substituted ketone. Such a plot is illustrated in Fig. 1. Reference to Fig. 1 shows that the carbonyl carbon having the highest charge density as exemplified by the highest positive free energy of dissociation of the corresponding substituted benzoic acid also has the lowest activation energy. This behavior suggests that the rate-determining step in the semicarbazone reaction is a reaction involving the transfer of a proton to the reaction complex. However, the suggested mechanism for semicarbazone formation is quite complicated as will be seen by reference to Stempel and Schaffel.[2] Since for such a mechanism the experimental velocity constant is the product of the velocity constant of the rate determining step and a number of equilibrium constants, the activation energy obtained from the experimental velocity constant is a composite term in the sense that it includes heats of reactions for the various equilibrium reactions. Consequently the effect of a substituting group might be due in part to changes in heats of reactions caused by such groups.

**Acknowledgment.**—The authors wish to thank Dr. A. A. Orning, Dr. Gerson S. Schaffel and Dr. Guido H. Stempel for their comments and suggestions.

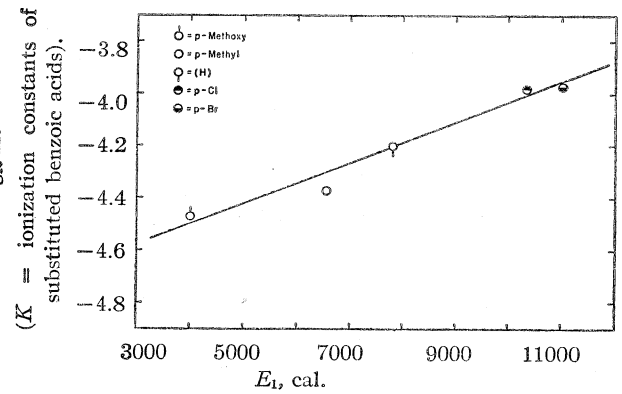



Fig. 1.—Energy of activation for semicarbazone formation of acetophenone series.

## Summary

1. The rate of semicarbazone formation of acetophenone and substituted acetophenones has been determined by a competitive method using *d*-carvone as the competing ketone.

2. The effect of para substitution upon the experimental activation energy of the semicarbazone reaction with acetophenone is given by the sequence, Br > Cl > H > $CH_3$ > $CH_3O$, with *p*-bromoacetophenone showing the highest activation energy.

3. It is suggested that the rate determining step is a reaction involving transfer of a proton to the reaction complex.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

# The Mechanism of the Thermal Decomposition of Alkyl Nitrites in the Liquid Phase: the Pyrolysis of Optically Active 2-Octyl Nitrite

BY NATHAN KORNBLUM AND EUGENE P. OLIVETO[1,2]

The thermal decomposition of methyl, ethyl, *n*-propyl, isopropyl and *n*-butyl nitrites in the vapor phase at 170–240° has been investigated by Steacie and his co-workers.[3] They concluded that the major over-all reaction is the same in each case, *viz.*

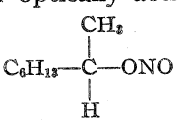
$$2RCH_2ONO \longrightarrow RCHO + RCH_2OH + 2NO \quad (1)$$

The vapor phase reaction has also been studied by F. O. Rice and Rodowskas,[4] who proposed the mechanism[5]

$$RCH_2ONO \longrightarrow RCH_2O\cdot + NO$$
$$RCH_2O\cdot + RCH_2ONO \longrightarrow RCH_2OH + R\dot{C}HONO$$
$$R\dot{C}HONO \longrightarrow RCHO + NO$$

$$2RCH_2ONO \longrightarrow RCH_2OH + RCHO + 2NO$$

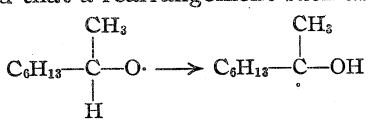
The present investigation represents a test of Rice's hypothesis. According to the proposed mechanism pyrolysis of optically active 2-octyl nitrite



should give 2-octanol, 2-octanone and nitric oxide, and the 2-octanol should be optically active.

Upon treating *d*-2-octanol, $[\alpha]^{25}D$ +9.30°, with nitrosyl chloride in pyridine *d*-2-octyl nitrite, $[\alpha]^{25}D$ +6.44°, was obtained. This, when heated at 100° for eight days, underwent complete decomposition and the 2-octanol produced (80% yield) had $[\alpha]^{25}D$ +9.23°. Thus, in complete conformity with Rice's mechanism, no racemization had taken place.

If Rice's mechanism is accepted, then it follows that the secondary alkoxyl radical is optically stable and that a rearrangement such as



does not take place with facility, if at all, in the liquid phase at 100°. Clearly, more precise information concerning the optical stability of alkoxyl radicals will be of value not only because of its bearing on the mechanism of the thermal decomposition of alkyl nitrites, but also because of its own rather considerable intrinsic interest.

The present study was also concerned with the possibility that the pyrolysis of alkyl nitrites might not follow the same course in the liquid and vapor phases. Since all previous work on the thermal decomposition of alkyl nitrites had been conducted in the gas phase, at temperatures distinctly greater than 100°, it was of interest to establish whether or not the products of the liquid phase decomposition correspond to those previously obtained in the vapor phase.

In addition to *d*-2-octanol, the liquid phase thermal decomposition of *d*-2-octyl nitrite at 100° gave a number of other products. As one would anticipate from equation (1), 2-octanone was the other principal organic product. Just as with *d*-2-octanol, it was also formed in 80% yield so that these two, between them, account for four-fifths of the organic material. Nitric oxide, however, was produced in only 37% of the amount to be expected from equation (1). This led to a careful study of the other components of the reaction mixture whereupon eight additional compounds were found (Table I).

TABLE I

PRODUCTS FROM THE THERMAL DECOMPOSITION OF 1.02 MOLES OF *d*-2-OCTYL NITRITE

| Product | Amount, millimoles | Nitrogen, gram-atoms |
|---|---|---|
| *d*-2-Octanol | 380 | |
| 2-Octanone | 380 | |
| Nitric oxide | 380 | 0.38 |
| Nitrogen | 280 | .56 |
| Nitrous oxide | 24 | .05 |
| Acetic acid | 22.6 | |
| Heptanoic acid | 12.6 | |
| 2-Octyl acetate | 3 | |
| 2-Octyl heptanoate | 3 | |
| Capronitrile | 20 | .02 |
| Tarry residue | (11.2 g.) | .02 |
| Carbon dioxide[a] | | |
| | Total | 1.03 |

[a] This required a separate experiment since ordinarily the system was swept out with carbon dioxide.

Nitric oxide has recently been found to react with 2-octanone at 100°, in the dark, with the production of acetic acid, heptanoic acid and capronitrile, the nitric oxide being reduced to

(1) E. I. du Pont de Nemours and Co. Fellow, 1946–1947.

(2) Present address: Schering Corporation, Bloomfield, New Jersey.

(3) Steacie, "Atomic and Free Radical Reactions," Reinhold Publishing Corp., New York, N. Y., 1946, pp. 141–143.

(4) F. O. Rice and Rodowskas, THIS JOURNAL, **57**, 350 (1935).

(5) Rice and Rodowskas (ref. 4) studied the ethyl nitrite decomposition at 425°. They concluded that at pressures greater than about one third of an atmosphere, reaction (1) preponderates. However, at pressures of approximately 1 mm. they found that methyl radicals are formed in abundance and suggested that the predominant reaction is

$$CH_3CH_2ONO \longrightarrow CH_3CH_2\text{—}O\cdot + NO$$
$$CH_3CH_2\text{—}O\cdot \longrightarrow HCHO + CH_3\cdot$$
$$CH_3\cdot + CH_3CH_2ONO \longrightarrow CH_4 + CH_3\dot{C}H\text{—}ONO$$
$$CH_3\dot{C}HONO \longrightarrow CH_3CHO + NO$$

$$2CH_3CH_2ONO \longrightarrow HCHO + CH_4 + CH_3CHO + 2NO$$

nitrogen and nitrous oxide.[6] It appears probable, therefore, that the various minor products obtained upon heating 2-octyl nitrite at 100° arise from a set of secondary reactions, namely, cleavage of 2-octanone by nitric oxide and esterification of 2-octanol by the acids formed. The large amount of elementary nitrogen produced is especially noteworthy.

## Experimental[7,8]

*d*-2-Octanol.—Racemic 2-octanol was resolved according to Ingersoll.[9] The *d*-2-octanol obtained had $n^{20}D$ 1.4262; lit. value,[10] $n^{20}D$ 1.4264, $[\alpha]^{25}D$ + 9.30° ($c$ = 5, ethanol); lit. value,[9] $[\alpha]^{17}D$ + 9.8°.

*d*-2-Octyl Nitrite.—*d*-2-Octyl nitrite was prepared in 80% yield by the action of nitrosyl chloride on *d*-2-octanol; $n^{20}D$ 1.4080; $[\alpha]^{25}D$ + 6.44 ($c$ = 5, ethanol); lit. value,[11] $n^{20}D$ 1.4082.

**Thermal Decomposition of *d*-2-Octyl Nitrite.**—One hundred and sixty-two grams (1.02 moles) of *d*-2-octyl nitrite was decomposed by heating at 100 ± 2° for eight days in a three-neck flask fitted with a condenser, thermometer and a gas inlet tube. Prior to the reaction the system was swept out overnight with a stream of carbon dioxide which had previously passed through 96% sulfuric acid, Drierite and cotton. During the reaction a slow stream of carbon dioxide was maintained. The exit gases, upon leaving the condenser, were passed through two ice-traps, two wash bottles containing mixed acid (9 parts 96% sulfuric acid: 1 part 65% nitric acid) and finally collected over 50% aqueous potassium hydroxide. To eliminate photochemical effects, the reaction flask and condenser were painted black, and the reaction was carried out in a dark-room.[12] At the end of eight days there was no nitrite left, as evidenced by a negative Griess–Ilosvay test.[13] The liquid in the reaction flask now weighed 124 g. and was dark-brown in color. There was less than 0.1 ml. of liquid in the ice-traps. The organic liquid (124 g.) was extracted with three 50-ml. portions of water, giving a water extract (fractions $A_1$, $A_2$, $A_3$) and an organic residue (fraction B).

**Acetic Acid.**—Fraction $A_1$ required 14.9 meq. of sodium hydroxide for neutralization; fraction $A_2$ required 7.0 meq., and fraction $A_3$ 0.7 meq.

Fraction $A_1$ (which did not decolorize alkaline permanganate) was concentrated under reduced pressure at room temperature to *ca.* 25 ml. (fraction $A_4$). When the first 50-ml. portion of the distillate was rectified through an 18″ concentric tube column rated at 65 plates, no liquid boiling lower than 100° was obtained. (The column easily and cleanly separated a prepared solution of 3% acetonitrile in water into its components.) Thus, little or no acetonitrile was present.

A portion of fraction $A_4$ was converted to the S-benzyl thiuronium salt in 50% yield; m.p. 138–139°. This did not depress the m.p. of authentic S-benzyl thiuronium acetate[6]; m.p. 139–140°. *Anal.* Calcd. for $C_{10}H_{14}N_2O_2S$: N, 12.4. Found: N, 12.2. Another portion of fraction $A_4$ was converted to the *p*-phenylphenacyl ester in 65% yield. This melted at 107–108° and did not depress the m.p. of authentic *p*-phenylphenacyl ester of acetic acid; m. p. 108–109°. *Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6. Found: C, 75.8; H, 5.4.

**Heptanoic Acid.**—Fraction B was extracted with three 35-ml. portions of 30% sodium carbonate solution, giving an aqueous alkaline extract (fraction C) and an organic residue (fraction D). Fraction C was acidified with 85% phosphoric acid and steam distilled. The distillate, which required 12.6 meq. of sodium hydroxide for neutralization, was then concentrated under reduced pressure at room temperature to a volume of *ca.* 15 ml. A portion was converted to the S-benzyl thiuronium salt in 70% yield; m.p. 147–148°; it did not depress the m.p. of an authentic sample[6] of S-benzyl thiuronium heptanoate, m.p. 148–149°. *Anal.* Calcd. for $C_{15}H_{24}N_2O_2S$: N, 9.4. Found: N, 9.6.

A *p*-phenylphenacyl ester was also prepared in 80% yield, m.p. 60–61°; this did not depress the m.p. of an authentic sample of the *p*-phenylphenacyl ester of heptanoic acid, m.p. 61–62°. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.8; H, 7.5. Found: C, 77.7; H, 7.5.

**Fraction D.**—Extraction of fraction D with 0.1 *N* alkali did not remove any more acids. About 500 ml. of water was added and the mixture was distilled under reduced pressure at 30–35°. The non-distillable residue was extracted with petroleum ether, dried over Drierite, and the solvent was removed by ordinary distillation; there was left 11.2 g. of a black, viscous liquid. *Anal.* Found: C, 71.0; H, 12.0; N, 2.9.

The organic distillate (fraction $D_1$) was mechanically separated from the water layer and treated with Drierite. The dry, yellow liquid weighed 106 g., had $n^{20}D$ 1.4193, and analyzed 45% 2-octanone[14] and 44% 2-octanol.[15]

One hundred grams of the yellow liquid ($n^{20}D$ 1.4193) was rectified under reduced pressure. Twenty-two fractions were obtained and these, with the exception of fraction 3 (3.1 g.), were further studied.

**Identification of Capronitrile.**—Fractions 1 and 2, b.p. 63–68° at 27 mm. pressure, $n^{20}D$ 1.4100 to 1.4113, were combined (total 3.1 g.). Only these two fractions contained nitrogen. An unsuccessful attempt was made to isolate the nitrogen-containing component by rectification through a 65-plate column. A 0.5-ml. portion of the distillate, now about 20% richer in the nitrogen-containing component, was hydrolyzed to the amide.[16] The amide (50 mg.) had m.p. 98–99° (lit. m.p. 101°)[17] and did not depress the m.p. of authentic caproamide, m.p. 99–100°. *Anal.* Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.3; N, 12.1. Found: C, 62.4, 62.5; H, 11.3, 11.5; N, 12.1.

Another 0.5-ml. portion of the distillate was converted to the anilide[18] (150 mg.), m.p. 94–95° (lit. m.p. 96°),[17] which did not depress the m.p. of authentic caproanilide, m.p. 94–95°. *Anal.* Calcd. for $C_{12}H_{17}NO$: N, 7.4. Found: N, 7.5, 7.6.

**Isolation of 2-Octanone.**—Fractions 4–10; b.p. 69–70° (27 mm.); $n^{20}D$ 1.4148 to 1.4150; were combined (total, 39.6 g.) and an 8.4-g. sample was rectified through the 65 plate column. There was obtained 7.5 g. of analytically pure 2-octanone, b.p. 75–76° (20 mm.), $n^{20}D$ 1.4159; lit. value[19] $n^{20}D$ 1.41518. *Anal.* Calcd. for $C_8H_{16}O$: C, 74.9; H, 12.6. Found: C, 74.9; H, 12.5.

**Isolation of 2-Octyl Acetate.**—Fractions 11–16, b.p. 70° (27 mm.) to 68° (15 mm.); $n^{20}D$ 1.4150 to 1.4235; gave a positive hydroxamic acid test for esters[20] and were

(6) Oliveto, Ph.D. Thesis, Purdue University, June, 1948.

(7) Analyses by Miss L. Roth and Mr. H. Galbraith of this department.

(8) All melting points uncorrected.

(9) Ingersoll, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, p. 400.

(10) Kornblum, Lichtin, Patton and Iffland, THIS JOURNAL, **69**, 307 (1947).

(11) Kornblum and Oliveto, *ibid.*, **69**, 465 (1947).

(12) The photochemical decomposition of alkyl nitrites is well established; *cf.* ref. 2 p. 143; Coe and Doumani, THIS JOURNAL, **70**, 1516 (1948); Horswell and Silverman, *Ind. Eng. Chem., Anal. Ed.*, **13**, 555 (1941).

(13) Bose, *Analyst*, **56**, 504 (1931).

(14) The procedure of Iddles [*Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939)] was adapted to 2-octanone (*cf.* ref. 6). The accuracy is 3–5%. The 2,4-dinitrophenylhydrazone produced had m. p. 66–67° (lit. m. p[6]. 66–67°) and did not depress the m. p. of authentic 2-octanone-2,4-dinitrophenylhydrazone. *Anal.* Calcd. for $C_{14}H_{21}N_4O_4$: N, 18.2. Found: N, 18.4.

(15) Determined by the acetic anhydride method (Shriner, "Quantitative Analysis of Organic Compounds," Edward Bros., Ann Arbor, Mich., 1940, p. 39). An accuracy of 5% was obtained.

(16) McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 146.

(17) McElvain, *ibid.*, p. 186.

(18) McElvain, *ibid.*, p. 184.

(19) Ceuterick, *Bull. soc. chim. Belg.*, **45**, 545 (1936).

(20) Davidson, *J. Chem. Ed.*, **17**, 81 (1940).

combined (total = 3.9 g.). Upon rectification through the 65-plate column there was obtained 0.6 g. of a colorless liquid, b.p. 81° (18 mm.), $n^{20}D$ 1.4180. *Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.8; H, 11.7; sapon. equiv., 172. Found: C, 69.9; H, 11.9; sapon. equiv., 166. An S-benzylthiuronium salt was prepared from the neutral solution; m.p. 138–139° (40% yield). It did not depress the m.p. of an authentic sample of S-benzyl thiuronium acetate, m.p. 139–140°.

**Isolation of *d*-2-Octanol.**—Fractions 17–22, b.p. 68° (15 mm.), were combined (total = 40.1 g.); $n^{20}D$ 1.4249, lit. value,[10] $n^{20}D$ 1.4264; $[\alpha]^{25}D$ + 9.23° (*c* = 5, ethanol). A 5-g. portion, esterified with phthalic anhydride in the presence of pyridine,[10] gave a 95% yield of *d*-2-octyl hydrogen phthalate, m.p. 71–73°. This, after one recrystallization from petroleum ether (b.p. 60–70°), melted at 73–74° (lit. m.p.[9] 75°) and did not depress the m.p. of authentic *d*-2-octyl hydrogen phthalate, m.p. 74–75°. The purified ester had $[\alpha]^{25}D$ + 47.5° (*c* = 5, ethanol). (The *d*-2-octyl hydrogen phthalate obtained during the resolution of 2-octanol had $[\alpha]^{25}D$ + 47.7°). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.0; H, 8.0. Found: C, 69.1; H, 8.2. The ester was hydrolyzed[9] to *d*-2-octanol; $n^{20}D$ 1.4262 (lit.[10] 1.4264), $[\alpha]^{25}D$ + 9.27° (*c* = 5, ethanol). The *d*-2-octanol used to prepare the *d*-2-octyl nitrite had $[\alpha]^{25}D$ + 9.30°.

**Isolation of 2-Octyl Heptanoate.**—A yellow 4-g. residue remained from the rectification of 100 g. of yellow liquid ($n^{20}D$ 1.4193). This had $n^{20}D$ 1.4285 and gave a test for esters.[20] It was rectified through the 65-plate column. There was obtained 0.7 g. of a colorless liquid; b.p. 112° at 10 mm., $n^{20}D$ 1.4320. *Anal.* Calcd. for $C_{15}H_{30}O_2$: C, 74.3; H, 12.4; sapon. equiv., 242. Found: C, 74.4; H, 12.2; sapon. equiv., 240. An S-benzylthiuronium salt was prepared from the neutral solution; m.p. 147–148° (65% yield). It did not depress the m.p. of authentic S-benzylthiuronium heptanoate, m.p. 148–149°.

**Nitric Oxide.**—The two wash-bottles containing 96% sulfuric acid + 65% nitric acid had absorbed 11.4 g. of nitric oxide (titration with standard permanganate).[21]

**Nitrous Oxide and Nitrogen.**[22]—The gases collected over potassium hydroxide totaled 6750 ml. (S.T.P.). Upon analysis in a conventional Orsat apparatus, 8% of the gas was found to be nitrous oxide (determined by slow combustion with hydrogen) and the remaining 92% was inert (nitrogen). Carbon dioxide, carbon monoxide, olefins, saturated hydrocarbons, oxygen, nitric oxide and nitrogen dioxide were all absent.

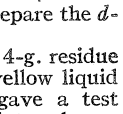
**Demonstration of the Formation of Carbon Dioxide in the Thermal Decomposition of *dl*-2-Octyl Nitrite.**—Ten grams of *dl*-2-octyl nitrite was decomposed at 100 ± 2° over a period of eight days in a slow stream of dry oxygen-free nitrogen. The exit gases were passed through 96% sulfuric acid, glass wool and finally through two U-tubes containing Ascarite; the Ascarite tubes gained 177 mg. (4.0 meq. of carbon dioxide). The Ascarite which reacted did not give a test for cyanide.[23] The liquid remaining in the flask weighed 7.3 g., and contained 0.9 meq. of acetic acid and 0.7 meq. of heptanoic acid.

(21) Milligan, *J. Phys. Chem.*, **28**, 544 (1924).

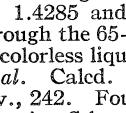
(22) We are indebted to Professor P. J. Elving of this department for his kind assistance in connection with the gas analyses.

## Summary

The thermal decomposition of *d*-2-octyl nitrite in the liquid phase at 100° gives *optically pure* *d*-2-octanol in excellent yield. In addition to confirming F. O. Rice's mechanism for the pyrolysis of alkyl nitrites, this indicates that alkoxyl radicals of the type



do not rearrange to



in the liquid phase at 100°.

The other major organic product is 2-octanone. Small amounts of acetic acid, heptanoic acid, 2-octyl acetate, 2-octyl heptanoate and capronitrile are also produced. These probably arise from the cleavage of 2-octanone by nitric oxide followed by esterification of 2-octanol by the acids formed.

The gaseous products of the reaction are nitrogen, nitric oxide, nitrous oxide and carbon dioxide.

(23) Lander and Walden, *Analyst*, **36**, 266 (1911).

LAFAYETTE, INDIANA RECEIVED AUGUST 10, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

# The Optical Crystallographic Properties of Some Sulfonamides and their Derivatives

BY RAYMOND N. CASTLE,[1] NORMAN F. WITT AND C. F. POE

The optical crystallographic properties of organic compounds are useful for purposes of identification. This is particularly true of compounds containing aromatic or heterocyclic ring systems where examples of strong dispersion of several types and strong double refraction are frequently observed. Thus the optical crystallographic properties of the sulfonamides and their derivatives should prove useful in their characterization.

Optical crystallographic studies of some of the therapeutically important sulfonamides have received the attention of several investigators. Except for sulfanilamide these data are more or less incomplete. The optical properties of sulfanilamide and of a series of Schiff bases have been determined by White.[2] Grove and Keenan[3] reported the optical properties of two forms of sulfathiazole. Prien and Frondel[4] reported the application of the optical properties of sulfanilamide, sulfathiazole and sulfapyridine, and their

(1) (a) From a portion of the dissertation submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy at the University of Colorado, August, 1944. (b) Present address: University of New Mexico, Albuquerque, New Mexico.

(2) White, unpublished thesis, University of Colorado, 1940.

(3) Grove and Keenan, THIS JOURNAL, **63**, 97 (1941).

(4) Prien and Frondel, *J. Urol.*, **46**, 784 (1941).

TABLE I

MELTING POINTS, FORMULAS AND ANALYSES

| Compound | M. p., °C.[a] | Formula | N content, % Calcd. | Found |
|---|---|---|---|---|
| Sulfacetimide | 184–184.5 | $C_8H_{10}N_2O_3S$ | 13.08 | 13.07 |
| Sulfadiazine | 251–252 dec. | $C_{10}H_{10}N_4O_2S$ | 22.40 | 22.33 |
| Sulfaguanidine monohydrate | 191–191.5 | $C_7H_{10}N_4O_2S \cdot H_2O$ | 24.13 | 24.09 |
| Sulfamerazine | 233.5–235 | $C_{11}H_{12}N_4O_2S$ | 21.20 | 21.19 |
| Sulfapyridine, Phase I[b] | 191.5–192 sl. dec. | $C_{11}H_{11}N_3O_2S$ | 16.86 | 16.75 |
| Sulfathiazole | 173–175 (201–201.5)[c] | $C_9H_9N_3O_2S_2$ | 16.46 | 16.62 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfacetimide | 231–232 dec. | $C_{16}H_{16}N_2O_5S$ | 8.04 | 7.93 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfadiazine | 226–227 dec.[d] | $C_{18}H_{16}N_4O_4S$ | 14.57 | 14.56 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfaguanidine | 226 | $C_{15}H_{16}N_4O_4S$ | 16.08 | 16.01 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfamerazine | 212 | $C_{19}H_{18}N_4O_4S$ | 14.06 | 14.12 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfapyridine | 204–205 | $C_{19}H_{17}N_3O_4S$ | 10.97 | 11.10 |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfathiazole | 199–200 | $C_{17}H_{15}N_3O_4S_2$ | 10.79 | 10.80 |
| $N^4$-(2-Hydroxybenzylidene) sulfacetimide | 212–214[e] | $C_{15}H_{14}N_2O_4S$ | 8.80 | 8.58 |
| $N^4$-(2-Hydroxybenzylidene) sulfadiazine | 244–245 dec. | $C_{17}H_{14}N_4O_3S$ | 15.81 | 15.82 |
| $N^4$-(2-Hydroxybenzylidene) sulfaguanidine | 225–226 | $C_{14}H_{14}N_4O_3S$ | 17.60 | 17.45 |
| $N^4$-(2-Hydroxybenzylidene) sulfamerazine | 225[f] | $C_{18}H_{16}N_4O_3S$ | 15.21 | 15.21 |
| $N^4$-(2-Hydroxybenzylidene) sulfapyridine | 241–242[g] | $C_{18}H_{15}N_3O_3S$ | 11.89 | 11.73 |
| $N^4$-(2-Hydroxybenzylidene) sulfathiazole | 215–217 dec. | $C_{16}H_{13}N_3O_3S_2$ | 11.69 | 11.60 |
| Sulfanilamide dilituarate | 270[h] | $C_{16}H_{11}N_5O_7S \cdot H_2O$ | 19.28 | 19.34 |
| Sulfacetimide dilituarate | 221–222 dec.[i] | $C_{12}H_{13}N_5O_8S \cdot 1.5H_2O$ | 16.90 | 16.76 |
| Sulfadiazine dilituarate | 210–211 dec. | $C_{14}H_{13}N_7O_7S \cdot 2H_2O$ | 21.34 | 21.34 |
| Sulfaguanidine dilituarate | 255[j] | $C_{11}H_{13}N_7O_7S$ | 25.32 | 25.48 |
| Sulfamerazine dilituarate | 230–232 dec. | $C_{15}H_{15}N_7O_7S \cdot H_2O$ | 21.53 | 21.52 |
| Sulfapyridine dilituarate | 219–220 dec.[i] | $C_{15}H_{14}N_6O_7S \cdot H_2O$ | 19.08 | 18.98 |
| Sulfathiazole dilituarate | 200 dec. | $C_{13}H_{12}N_6O_7S_2 \cdot 2H_2O$ | 18.12 | 18.01 |

[a] The melting points of the Schiff bases and the parent sulfonamides were taken in the usual capillary tubing immersed in a mechanically stirred bath. A 76 mm. immersion thermometer calibrated against a Bureau of Standards thermometer was used. The melting points of the dilituarates were determined on the bloc-maquenne apparatus and are of little value due to excessive decomposition. [b] For data on the other four phases of sulfapyridine see ref. 8. [c] Sulfathiazole is dimorphic. See ref. 3. [d] Softens at 223. [e] Softens at 208°. [f] The yellow solid turns brick red at 80–90°. [g] Softens at 237. [h] Becomes opaque at 150°. Chars rapidly at 270°. [i] Melts with evolution of gas. [j] Decomposes rapidly at 255° but does not actually melt.

acetyl derivatives to the identification of these compounds in urine. Williams and Maresh[5] presented the optical properties for five phases of sulfanilamide, for sulfaguanidine, and for their acetyl derivatives. The optical properties of sulfadiazine have been reported by Wilkerson.[6] The refractive indices of sulfanilamide, sulfapyridine and sodium sulfapyridine have been reported by Keenan.[7] More recently the optical crystallographic properties of five phases of sulfapyridine have been reported by the authors.[8]

The present communication reports the optical crystallographic properties of the following sulfanilamide derivatives: sulfacetimide ($N^1$-acetylsulfanilamide), sulfadiazine (2-sulfanilamidopyrimidine), sulfaguanidine (sulfanilamidoguanidine), sulfamerazine (2-sulfanilamidothiazole) and sulfapyridine (2-sulfanilamidopyridine). In addition, the optical crystallographic properties of two series of Schiff bases and of a series of dilituric acid salts of the above amines are reported. The Schiff bases were prepared from the above amines with salicylaldehyde and 2-hydroxy-3-methoxybenzaldehyde.

The melting points, formulas, and analyses are recorded in Table I, and the optical crystallographic data are recorded in Table II.

## Experimental

**Material.**—The sulfapyridine and sulfathiazole were obtained from Merck and Company, the sulfamerazine from Sharp and Dohme, and the sulfanilamide from the Mallinckrodt Chemical Works. The sulfaguanidine was supplied by E. R. Squibb and Sons, the sulfadiazine by the Calco Chemical Division of the American Cyanamid Company, and the sulfacetimide from the Schering Corporation.[9] The salicylaldehyde was Eastman Kodak Co. no. 225 purified from the bisulfite addition compound. The 2-hydroxy-3-methoxybenzaldehyde available only as the practical product was purified by the bisulfite addition compound and thrice recrystallized from aqueous ethyl alcohol. The dilituric acid was prepared and purified by the method described in "Organic Syntheses."[10]

(5) Williams and Maresh, Abstracts of Papers, 104th American Chemical Society Meeting, September, 1942, p. 2L. No quantitative optical data are presented in the abstract.

(6) Wilkerson, THIS JOURNAL, **64**, 2230 (1942).

(7) Keenan, *J. Assoc. Offic. Agr. Chemists*, **27**, 157 (1944).

(8) Castle and Witt, THIS JOURNAL, **68**, 64 (1946).

(9) To the three firms, E. R. Squibb and Sons, Calco Chemical Division of the American Cyanamid, and the Schering Corporation who supplied the samples of sulfaguanidine, sulfadiazine and sulfacetimide, respectively, the authors wish to express sincere appreciation.

(10) "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p. 440–441.

TABLE II

| Compound | Habit and color | Pleochroism | Crystal system |
|---|---|---|---|
| Sulfacetimide | Columnar[c] | | Orthorhombic |
| Sulfadiazine[e] | Lath shaped | | Monoclinic |
| Sulfaguanidine monohydrate | Lath shaped | | Monoclinic |
| Sulfamerazine | Tabular[g] | | Orthorhombic |
| Sulfapyridine, Phase I[i] | Tabular to equant | | Monoclinic |
| Sulfathiazole, Phase II[j] | Lath shaped | | Monoclinic |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfacetimide | Deep red, acicular | Strong red-yellow Z>Y>X | Orthorhombic |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfadiazine | Brick red, tabular | Strong yellow-colorless Z>Y>X | Monoclinic |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfaguanidine | Orange, tabular | Z>Y>X | Monoclinic |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfamerazine | Brick red, columnar | Slight Z>Y>X | Triclinic (?) |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfapyridine | Brick red, tabular | Yes[1] | Monoclinic |
| $N^4$-(2-Hydroxy-3-methoxybenzylidene) sulfathiazole | Brick red, lamellar | Strong Z>Y>X | Orthorhombic |
| $N^4$-(2-Hydroxybenzylidene) sulfacetimide | Orange, acicular | Z>Y>X | Monoclinic |
| $N^4$-(2-Hydroxybenzylidene) sulfadiazine | Yellow, boat-shaped | Slight Z>Y>X | Monoclinic |
| $N^4$-(2-Hydroxybenzylidene) sulfaguanidine | Yellow, lamellar | None | Orthorhombic |
| $N^4$-(2-Hydroxybenzylidene) sulfamerazine | Yellow, tabular | Yellow, colorless Z>Y>X | Monoclinic |
| $N^4$-(2-Hydroxybenzylidene) sulfapyridine | Yellow, lamellar | None | Monoclinic |
| $N^4$-(2-Hydroxybenzylidene) sulfathiazole | Yellow, tabular | Z>Y>X | Monoclinic |
| Sulfanilamide dilituarate | Pinkish, tabular | None | Monoclinic |
| Sulfacetimide dilituarate | Lamellar | ... | (?) |
| Sulfadiazine dilituarate | Yellow, elongated | None | Monoclinic |
| Sulfaguanidine dilituarate | Buff, equant | None | Triclinic |
| Sulfamerazine dilituarate | Yellow, columnar | None | Orthorhombic |
| Sulfapyridine dilituarate | Yellow, lamellar | None | Monoclinic |
| Sulfathiazole dilituarate | Yellow, columnar | None | Monoclinic |

The sulfonamides were used without further purification for the preparation of derivatives. For determination of their optical properties sulfacetamide and sulfaguanidine were recrystallized from hot water. Sulfadiazine, sulfamerazine and sulfapyridine were recrystallized from 95% ethyl alcohol.

**Preparation of the Schiff Bases.**—The Schiff bases were prepared by adding the aldehyde (0.01 mole) to a hot, nearly saturated absolute alcohol solution of the sulfonamide (0.01 mole). The solutions were refluxed for varying periods of time up to three hours. In many instances crystals of the Schiff bases separated immediately. The Schiff bases from sulfacetimide, sulfaguanidine and sulfathiazole separated within five minutes. Sulfapyridine required refluxing up to one hour and sulfamerazine and sulfadiazine from one to three hours. In most instances crystals were filtered from the hot mother liquor and washed with several portions of cold alcohol. Yields were sacrificed, but by this procedure the Schiff bases were usually directly pure. When recrystallization was necessary, absolute ethyl alcohol was the solvent of choice. All Schiff bases were dried *in vacuo* at 100°.

**Preparation of the Dilituates.**—The dilituric acid (0.01 mole) dissolved in hot water or aqueous ethyl alcohol was poured into a hot solution of the sulfonamide (0.01 mole) dissolved in hot water, or hot aqueous alcohol depending upon the solubility of the particular sulfonamide. The mixture was refluxed a few minutes. The dilituates crystallize well on standing. Recrystallization was from hot water or hot aqueous ethyl alcohol. The dilituates were air-dried at room temperature.

### Optical and Crystallographic Properties

**Apparatus and Technique.**—A Leitz petrographic microscope Model No. 30 CM was used in the present investigation. The light source was a fluorescent lamp equipped with a 15-watt G. E. Mazda Fluorescent tube, 3500° white.

The principal refractive indices $\alpha$, $\beta$ and $\gamma$ at 25 ± 1°, were determined by the immersion method, using interference figures as a guide in selecting correctly oriented crystals. The immersion liquids used were those described by Winchell[11a] and Larsen and Berman.[11b] The optical axial angle $2V$ was calculated from the refractive indices $\alpha$, $\beta$ and $\gamma$, using the more exact formula suggested by Larsen and Berman.[12]

## Summary

1. The optical crystallographic properties of sulfacetimide, sulfaguanidine, sulfathiazole, Phase II, sulfadiazine, sulfamerazine and sulfapyridine have been determined. Certain corrections and additions have been made to existing optical crystallographic data.

2. Two series of Schiff bases of the above sulfanilamide derivatives have been prepared and their melting points, analyses and optical crystallographic properties have been determined.

3. A series of dilituric acid salts of the above sulfanilamide derivatives have been prepared and their melting points, analyses and optical crystallographic properties have been determined.

4. The optical crystallographic properties of the sulfonamides and their derivatives are useful in their identification.

(11) (a) Winchell, "Elements of Optical Mineralogy," 5th ed., John Wiley and Sons, Inc., New York, N. Y., 1937, p. 81. (b) Larsen and Berman, "The Microscopic Determination of Nonopaque Minerals," 2nd ed., U. S. Department of the Interior, Geological Survey Bulletin No. 848, Washington, D. C., 1934, p. 42.

(12) Ref. 11b, p. 5.

TABLE II (*Continued*)

| Extinction | Elongation | $2V^a$ | Optic sign | Dispersion | Refractive indices[b] $\alpha$ | $\beta$ | $\gamma$ |
|---|---|---|---|---|---|---|---|
| Symmetrical | Parallel to $c$ | 21°[d] | + | None | 1.559 | 1.564 | 1.727 |
| $Y\|\|b$, $Z\wedge c = 35°$ | Parallel to $b$ (±) | 76° | + | Axial, $r>v$ | 1.596 | 1.675 | 1.830 |
| $Y\|\|b$, $Z\wedge c = 17°$ | Parallel to $b$ (±) | 86° ? | + | Axial, $r>v$ | 1.586 | 1.649[f] | 1.731 |
| Parallel | (±) | 58° | − | Very strong, rhombic, $r>v$[h] | 1.568 | 1.657 | 1.687 |
| $Y\|\|b$, $Z\wedge c = 39°$ | (±) | 88° | + | Very strong axial, $r>v$ | 1.670 | 1.736 | 1.813 |
| $Y\|\|b$, $X\wedge c = 23°$[k] | Parallel to $b$ (±) | 52° | − | Inclined, $r>v$ | 1.598 | 1.741 | 1.780 |
| Parallel | Parallel to $c$ (±) | Very large | + | Rhombic, $r>v$ | 1.507 | 1.682 | >1.86 |
| $Y\|\|c$, $Z\wedge a = 40°$ (?) | (±) | Large | + | Axial, $r>v$ | 1.563 | 1.695 | >1.86 |
| $Y\|\|b$, $Z\wedge c = 58°$ | (±) | Small | + | Slight axial, $r>v$ | 1.577 | 1.614 | >1.86 |
| Variable (?) | (−) | Large | + | Anomalous, $r>v$ | 1.548 | 1.669 | >1.86 |
| Maximum = 21°,[m] | (+) | Very large | − | None | 1.542 | 1.750 | >1.86 |
| Parallel | Parallel to $c$ | Very large | + | Rhombic $r>v$ | 1.632 | 1.734 | >1.86 |
| Maximum = 12°,[m] | (±) | Very large | + | Very great axial, $r>v$ | 1.491 | 1.689 | >1.86 |
| $Y\|\|b$, $Z\wedge c = 38°$[k] | Parallel to $b$ (±) | Large | + | Slight axial $r>v$ | 1.573 | 1.686 | >1.86 |
| Parallel | (±) | Large | + | None | 1.561 | 1.668 | >1.86 |
| $Y\|\|b$, max. = 22°[m] | (+) | Large | + | Slight axial $r>v$ | 1.553 | 1.679 | >1.86 |
| $Z\|\|b$, $X\wedge c = 43°$ | (±) | Large | + | Axial, $r>v$ | 1.619 | 1.750 | >1.86 |
| $Y\|\|b$, $Z\wedge c = 31°$ | Parallel to $b$ (±) | Large | + | Axial, $r>v$ | 1.601 | 1.735 | >1.86 |
| $X\|\|b$, max. = 40° (?) | (±) | 51° | − | Very strong crossed, $v>r$ | 1.561 | 1.724 | 1.769 |
| (?) | (?) | Large | − | Slight axial, $v>r$ | 1.399? | 1.659 | 1.754? |
| (?) | (?) | Variable[n] | − | Very strong crossed, $v>r$ | ? | 1.714 | ? |
| Variable oblique | (+) | 87° | + | Axial, $r>v$ | 1.572 | 1.688 | 1.854 |
| Parallel | Parallel to $c$ (−) | 40° | − | Rhombic, $v>r$ | 1.506 | 1.720 | 1.755 |
| $Y\|\|b$(?), $X\wedge c = 26°$ | (±) | 24° | − | Axial, $r>v$ | 1.542 | 1.785 | 1.799° |
| Maximum = 10° (?) | (−) | 63° | − | Strong axial, $v>r$ | 1.565 | 1.716 | 1.785 |

[a] Calcd. from $\alpha$, $\beta$ and $\gamma$. [b] The values of the refractive indices are accurate to ±0.002 unless otherwise noted. [c] The crystals show only the pyramid faces. [d] The calculated value appears to be too high since the isogyres scarcely separate on rotation. [e] Wilkerson[6] has published the following data: $\alpha = 1.680$, $\beta = 1.695$, $\gamma = 1.788$, $2V = 45$–$46°$, $Z\wedge c = 20°$?. [f] Dispersion of the $\beta$ index of refraction. [g] Equant from hot water, skeleton crystals from butanol-1, and tabular from ethanol. [h] The interference figure shows characteristic purple color fringes. [i] For the details of the optical properties of sulfapyridine, Phase I–V see ref. 8. [j] Grove and Keenan[3] reported the following: $\alpha = 1.605$, $\beta = 1.733$, $\gamma > 1.733$, and parallel extinction. [k] Common orientation shows parallel extinction. [l] The absorption formula was not readily determinable. [m] The relationship of the ellipsoidal axes to the crystallographic axes was not readily determinable, thus a maximum extinction angle is reported. [n] $2V$ varies from 15 to 60° (estimated). The value for $\beta$ is constant regardless of $2V$. $\gamma$ varies greatly depending upon $2V$. The reason for this variation in optic axis is not understood. [o] Accuracy probably not greater than ±0.008.

BOULDER, COLORADO RECEIVED APRIL 27, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# The Ultraviolet Absorption Spectra of Organic Sulfur Compounds. II. Compounds Containing the Sulfone Function[1]

BY EDWARD A. FEHNEL[2] AND MARVIN CARMACK

In a continuation of the work described in the preceding paper in this series,[3] we have determined the ultraviolet absorption spectra of a number of mono- and polysulfones, ketosulfones and carbalkoxysulfones in both neutral and alkaline solutions. As was anticipated on the basis of the limited spectroscopic data previously available for several simple aromatic sulfones,[4] no characteristic absorption bands attributable to the isolated sulfone function were observed in ethanol solutions in the near-ultraviolet region of the spectrum, and interaction between the sulfur-containing function and adjacent chromophores was found to be of a much lower order than in the corresponding sulfides. Strong conjugative effects were ap-

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society at the Washington meeting, August, 1948.

(2) American Chemical Society Postdoctoral Fellow, 1946–1948. Present address: Department of Chemistry, Swarthmore College, Swarthmore, Pa.

(3) Fehnel and Carmack, THIS JOURNAL, **71**, 84 (1949).

(4) (a) Chaix, *Bull. soc. chim.*, [4] **53**, 700 (1933); (b) Gibson, Graham and Reid, *J. Chem. Soc.*, **123**, 874 (1923); (c) Böhme and Wagner, *Ber.*, **75**, 606 (1942).

parent, however, in the spectra of the anions formed by the methylene disulfones, β-ketosulfones, and α-carbalkoxysulfones in alkaline solutions. These observations are of interest from the theoretical point of view because of their bearing on the question of the ability of the sulfonyl sulfur atom to accommodate more than eight electrons in its valence shell.

**Monosulfones.**—Solutions of the simple alkyl sulfones, such as ethyl sulfone, in ethanol and in ethanolic sodium ethoxide are completely transparent throughout the range of the Beckman quartz spectrophotometer (down to *ca.* 210 mμ). Ethanol solutions of the α,β-unsaturated sulfone, vinyl ethyl sulfone, however, begin to absorb strongly at about 240 mμ and appear to have a maximum in the neighborhood of 208–212 mμ[5] (Fig. 1). This represents a marked bathochromic displacement (*ca.* 15–20 mμ) of the absorption characteristic of the isolated vinyl group, as observed, for example, in the spectra of the simple alkenes, which exhibit maxima below 200 mμ.[6]

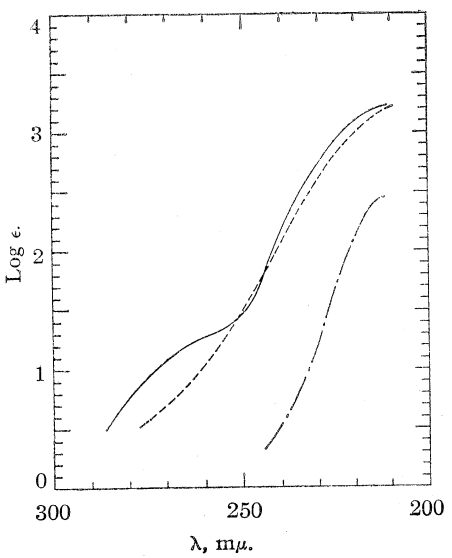
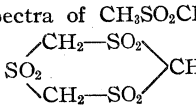



Fig. 1.—Absorption spectra of $CH_3SO_2CH_2SO_2CH_3$ in 0.01 *N* NaOEt, —;  in 0.01 *N* NaOEt, - - - -; $CH_2=CHSO_2C_2H_5$ in EtOH, –·–·–.

The aralkyl sulfones, benzyl ethyl sulfone (Fig. 2), benzyl sulfone (Fig. 3) and phenethyl sulfone (Fig. 3), give absorption curves which are essentially the same as those of the analogous benzenoid hydrocarbons.[7] When the sulfone function is attached directly to a benzene ring, as in phenyl sulfone (Fig. 3) and the phenyl alkyl sulfones (Fig. 2), bathochromic and hyperchromic displacements of the benzenoid absorption are observed which are very similar to the effects produced by the carboxyl group in benzoic acid. The absorp-

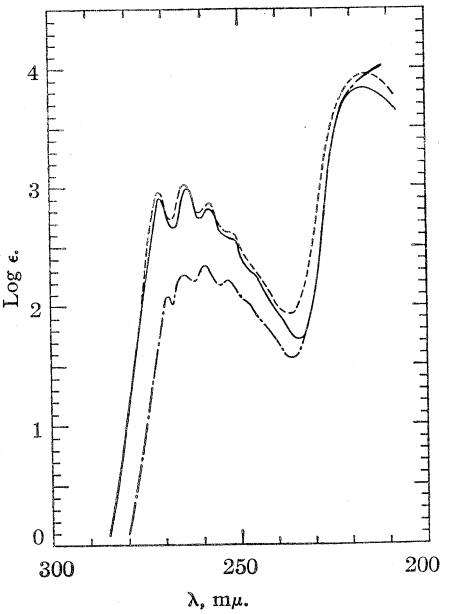



Fig. 2.—Absorption spectra of $C_6H_5SO_2CH_3$, —; $C_6H_5SO_2C(CH_3)_3$, - - - -; $C_6H_5CH_2SO_2C_2H_5$, –·–·–; (in EtOH).

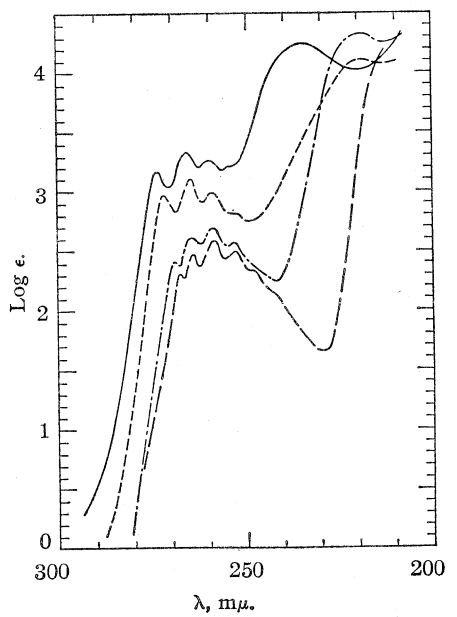



Fig. 3.—Absorption spectra of $(C_6H_5)_2SO_2$, —; $C_6H_5SO_2CH_2C_6H_5$, - - - -; $(C_6H_5CH_2)_2SO_2$, –·–·–; $(C_6H_5CH_2CH_2)_2SO_2$, — — —; (in EtOH).

(5) The uncertainties involved in making readings close to the lower limit of observation (below *ca.* 215 mμ with the ethanol used in the present work) do not permit an accurate description of this portion of the curve.

(6) Absorption spectra of most of the comparison compounds mentioned in this paper may be found in the "International Critical Tables," Vol. V, McGraw-Hill Book Co., New York, N. Y., 1929, p. 359 ff.

(7) Compare, for example, benzyl ethyl sulfone with the alkylbenzenes (*e. g.*, toluene) and the symmetrical aralkyl sulfones with the diphenylalkanes (*e. g.*, diphenylmethane).

tion spectra of these aromatic monosulfones remain unchanged in ethanolic sodium ethoxide.

**Polysulfones.**—Like the corresponding monosulfones, the simple aliphatic methylene disulfones, *e. g.*, bis-(methylsulfonyl)-methane, are transparent in ethanol solution throughout the range of the Beckman spectrophotometer, and aromatic methylene disulfones, *e. g.*, bis-(phenylsulfonyl)-methane (Fig. 4), exhibit spectra characteristic of the phenylsulfonyl portions of the molecule. On formation of the sulfone anions by solution of these compounds in ethanolic sodium ethoxide, the optical properties are greatly modified. Under these conditions bis-(methylsulfonyl)-methane and trimethylene trisulfone begin to absorb strongly in the near-ultraviolet region of the spectrum and appear to have an intense absorption band with a maximum somewhat below 210 mμ (Fig. 1).[8] In alkaline solutions of bis-(phenylsulfonyl)-methane the benzenoid fine structure is replaced by a single broad absorption band of much higher intensity (Fig. 4). When the central carbon atom of a methylene disulfone is completely alkylated so that no anion can be formed in alkaline solution, the spectra in neutral and alkaline media are identical (Table I).

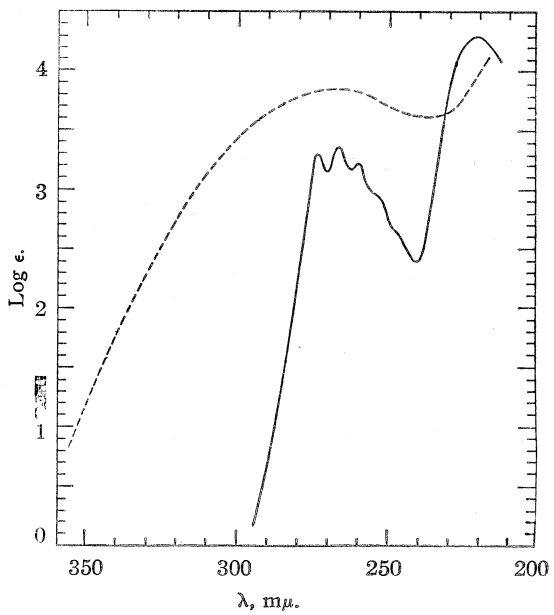



Fig. 4.—Absorption spectra of $C_6H_5SO_2CH_2SO_2C_6H_5$ in EtOH, —; in 0.01 *N* NaOEt, - - - -.

**Ketosulfones and Carbalkoxysulfones.**—As in the case of the methylene disulfones described above, the spectra of the β-ketosulfones, $RSO_2CH_2COR$, and α-carbalkoxysulfones, $RSO_2CH_2CO_2R$, are greatly modified in the presence of strong alkali. The effect is illustrated by the absorption curves for *n*-butylsulfonylacetone (Fig. 5), phenylsulfonylacetone (Fig. 6), and ethyl phenylsulfonylacetate (Fig. 7). In ethanol the spectra of these compounds are approximately summations of the spectra of the component chromophores, while in ethanolic sodium ethoxide marked changes in the form, intensity and location of the absorption bands are observed. The spectrum of α-phenylsulfonylisopropyl methyl

(8) *Cf.* ref. 4c.

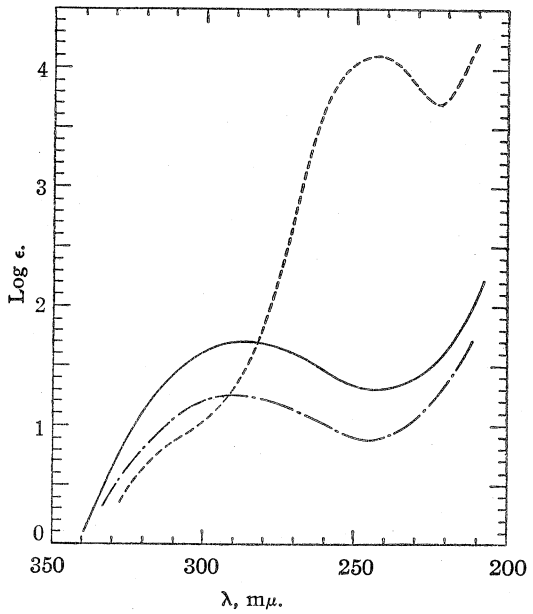
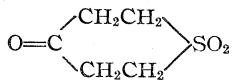



Fig. 5.—Absorption spectra of $n$-$C_4H_9SO_2CH_2COCH_3$ in EtOH, —; in 0.01 *N* NaOEt, - - - -; in EtOH, -·-·-.



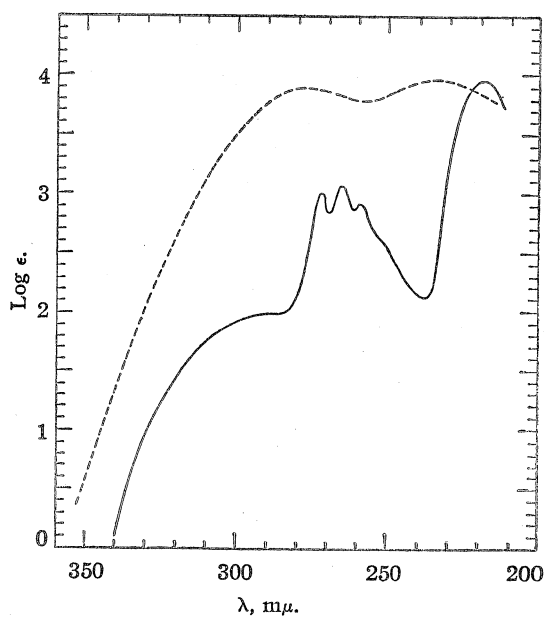




Fig. 6.—Absorption spectra of $C_6H_5SO_2CH_2COCH_3$ in EtOH, —; in 0.01 *N* NaOEt, - - - -.

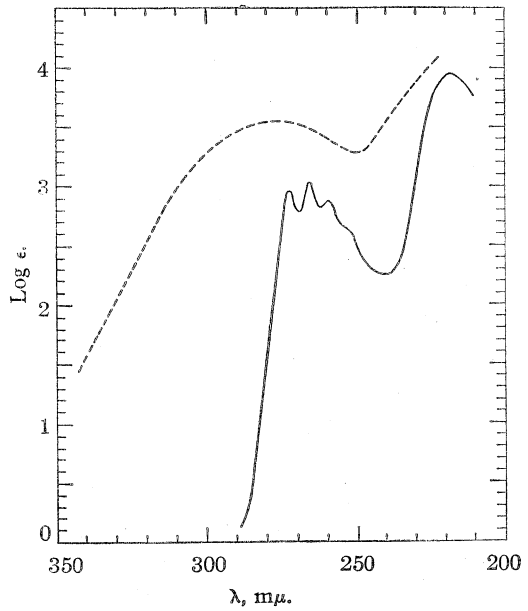
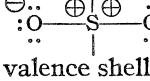



Fig. 7.—Absorption spectra of $C_6H_5SO_2CH_2CO_2C_2H_5$ in EtOH, —; in 0.01 *N* NaOEt, - - - -.

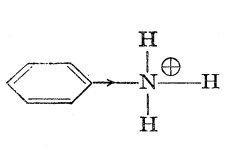
ketone (Table I), which is incapable of forming a stable anion in ethanolic alkali, shows no change in alkaline solution.

## Discussion

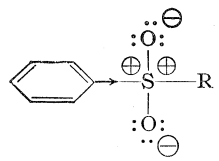
Although the question of the ability of the sulfur atom in the sulfone function to undergo an expansion of the valence shell has stimulated many interesting investigations, no general agreement seems to have been reached on the interpretation of the results.[9] A large body of chemical evidence[10] has accumulated which reveals an extensive similarity in the activating influence of the sulfonyl, carbonyl and nitro functions on adjacent methylene groups and olefinic bonds. These observations seem to favor the interpretation that the sulfonyl group, like the carbonyl and nitro groups, promotes an electromeric withdrawal of electrons from the adjacent carbon atoms. The application of such a resonance mechanism to the sulfones, however, requires that the sulfonyl sulfur atom be capable of accommodating, at least temporarily, more than eight electrons in its valence shell. Several investigators[11] have concluded on the basis of the chemical evidence that this is quite probably the case.

Others[9c,12] have preferred to attribute the activating influence of the sulfone function to the inductive effect produced by the net positive charge on the sulfur atom in the static system  ; the assumption of an expanded valence shell is rejected on the grounds that it violates the classical "octet rule" and that there is no evidence for sulfur–oxygen double bonds in the sulfone group. As G. N. Lewis has clearly pointed out, however, it is entirely possible that under certain conditions the sulfur atom (and other atoms beyond the first period of the periodic table) may exceed a covalence of four.[13] In support of this view, recent physical evidence based on X-ray[14] and electron-diffraction[15] studies, dipole moment measurements,[16] and thermochemical data[16] has indicated that the sulfur–oxygen link in sulfones possesses considerable double-bond character. In addition, evidence for the conjugative interaction of the sulfone function with an attached benzene ring has been obtained in studies of the dipole moments of aryl sulfones[17] and sulfonamides[18] and in a study of the ultraviolet absorption spectra of several benzenesulfonamides.[19]

An expansion of the sulfur valence shell also appears to provide the only satisfactory basis on which to account for the spectroscopic data obtained in the present investigation. Like the spectrum of the anilinium cation[20] (I), the spectrum of a phenyl alkyl sulfone would be expected to be very nearly identical with that of benzene, if the sulfonyl sulfur atom bears a fixed positive charge and exerts only a coulombic displacement effect on the electrons of the benzene ring (structure II).[19,21] The observed shift of the absorption



I



II

(9) See, for example, (a) Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 658–660, 740; (b) Connor, Gilman's "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 879–885; (c) Shriner, Adams and Marvel, *ibid.*, pp. 393–396; (d) Johnson, *ibid.*, p. 1839; (e) Gibson, *Chem. Revs.*, **14**, 431 (1934); (f) Price, "Mechanisms of Reactions at Carbon–Carbon Double Bonds," Interscience Publishers, New York, N. Y., 1946, pp. 7, 12, 32.

(10) This evidence is summarized in refs. 9a and 9b.

(11) (a) Kohler and Potter, THIS JOURNAL, **57**, 1316 (1935); (b) Connor, Fleming and Clayton, *ibid.*, **58**, 1386 (1936); (c) Rothstein, *J. Chem. Soc.*, 309 (1937). *Cf.* also ref. 9a, p. 740; ref. 9b, p. 885.

(12) (a) Shriner, Struck and Jorison, THIS JOURNAL, **52**, 2060 (1930); (b) Arndt and Martius, *Ann.*, **499**, 228 (1932); (c) Arndt and Eistert, *Ber.*, **74B**, 423 (1941); (d) Eistert, *Z. Elektrochem.*, **47**, 35 (1941).

(13) Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York, N. Y., 1923, pp. 97, 101–103. *Cf.* also Sidgwick, "The Electronic Theory of Valency," Oxford University Press, London, 1927, pp. 62–63, 152, 284; Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, p. 239 ff.

(14) Toussaint, *Bull. soc. chim. Belg.*, **54**, 319 (1945); *C. A.*, **41**, 2297 (1947).

(15) Lister and Sutton, *Trans. Faraday Soc.*, **35**, 495 (1939).

(16) Phillips, Hunter and Sutton, *J. Chem. Soc.*, 146 (1945).

(17) Leonard and Sutton, THIS JOURNAL, **70**, 1564 (1948).

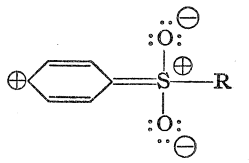
(18) Kumler and Halverstadt, *ibid.*, **63**, 2182 (1941).

(19) Kumler and Strait, *ibid.*, **65**, 2349 (1943).

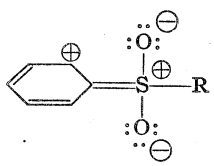
(20) Flexser, Hammett and Dingwall, *ibid.*, **57**, 2103 (1935); *cf.* also ref. 19.

(21) The usefulness of ultraviolet absorption spectra as a means of detecting mesomeric interactions between unsaturated groups has been discussed by Price, ref. 9f, pp. 9–12; *cf.* also Doub and Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).

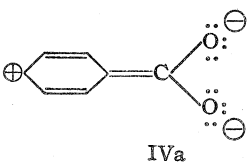
curves of the phenyl alkyl sulfones toward longer wave lengths and higher intensities, as compared with benzene, can be readily accounted for, however, if structures such as IIIa and IIIb may be considered to make significant contributions to the resonance in these molecules. The close resemblance between the spectra of the phenyl alkyl sulfones and the spectrum of the benzoate anion[19,22] is consistent with this interpretation, since the displacement of the benzenoid absorption by the substituent carboxylate function is attributed to resonance involving structures IVa and IVb.



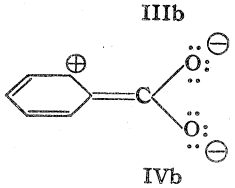
IIIa



IIIb



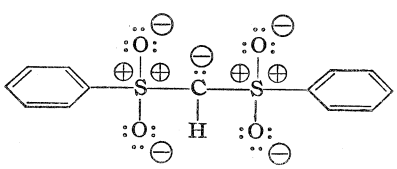
IVa



IVb

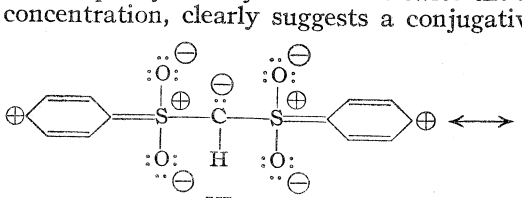
Similar considerations lead to the conclusion that the observed bathochromic displacement of the ethylenic absorption in vinyl ethyl sulfone must result from the conjugative interaction between the sulfone function and the attached vinyl group.

Resonance interactions between the sulfone functions in the methylene disulfone anions appear to provide the only satisfactory basis on which to account for the profound differences in the optical properties of neutral and alkaline solutions of these polysulfones. Thus, for example, a static charge distribution such as that represented in structure V should have little or no effect on the



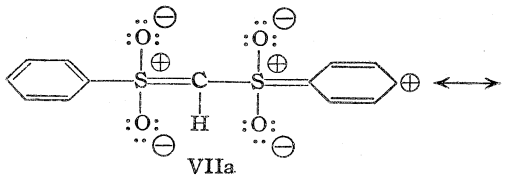
V

absorption by the benzenoid portions of the carbanion derived from bis-(phenylsulfonyl-methane). The fact that the anion exhibits greatly increased absorption at longer wave lengths, while the spectrum of the undissociated molecule is essentially that of phenyl methyl sulfone at twice the molar concentration, clearly suggests a conjugative re-

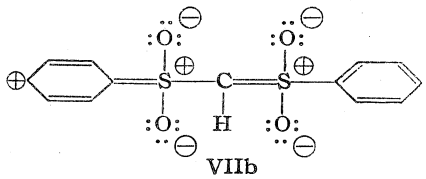


VI

(22) Doub and Vandenbelt, ref. 21.

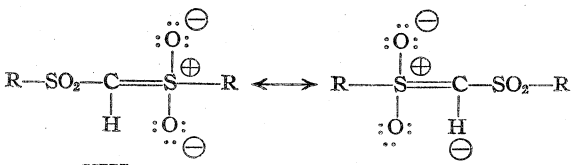


VIIa



VIIb

distribution of charge involving the unshared pair of electrons on the central carbon atom, as in structures VI, VIIa and VIIb. In the case of the bis-(alkylsulfonyl)-methane anions, similar considerations lead to structures VIIIa and VIIIb,



VIIIa VIIIb

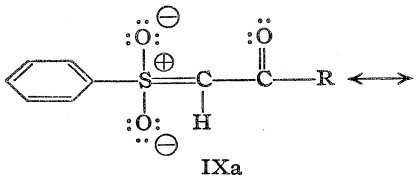
which are identical with those previously proposed by Rothstein[11c] to account for the chemical properties of these compounds.

The application of these concepts to the interpretation of the spectra of the analogous keto- and carbalkoxysulfones might, of course, be questioned on the ground that enolization in the —CH—C=O system could, by itself, give rise to the observed effects.[23] It seems reasonable to assume, however, that if the sulfonyl sulfur atom is capable of expanding its valence shell in the bis-sulfonylmethane anions, it is capable of doing so in the anions of the $\beta$-ketosulfones and $\alpha$-carbalkoxysulfones. Our observations on the spectra of these compounds are consistent with this interpretation. It does not seem possible, for example, to account for the intense absorption of the anions of phenylsulfonylacetone or ethyl phenylsulfonylacetate in terms of isolated enolic and benzenoid chromophores. Displacement of the benzenoid absorption toward longer wave lengths and higher intensities and loss of fine structure are features which are characteristic of benzene derivatives having unsaturated substituents conjugated with the aromatic nucleus.[24] The striking similarity of the absorption spectra of the $\beta$-keto- and $\alpha$-carbalkoxysulfone anions and the spectra of benzalacetone ($\lambda_{max.}$ 286, 220.5 m$\mu$; log $\epsilon$ 4.37, 4.08, resp.[24a]) and cinnamic acid ($\lambda_{max.}$ 282, 222 m$\mu$; log $\epsilon$ 4.30, 4.16, resp.[24b]) clearly suggests a conjugative interaction, *through the sulfone function*, of

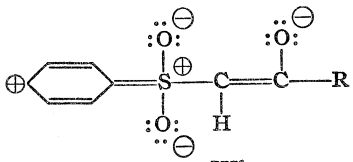
(23) Böhme and Wolff, *Chem. Ber.*, **80**, 193 (1947); *C. A.*, **42**, 864 (1948).

(24) (a) Wilds, Beck, Close, Djerassi, Johnson, Johnson and Shunk, THIS JOURNAL, **69**, 1985 (1947); (b) Campbell, Linden, Godshalk and Young, *ibid.*, **69**, 880 (1947).

the carbonyl group with the benzene ring, as in structures IXa and IXb

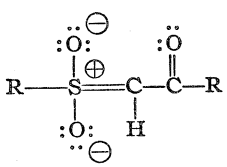


IXa



IXb

In the case of the aliphatic β-ketosulfone anions, significant contributions from structures such as X are indicated by the close resemblance between



X

the spectrum of the *n*-butylsulfonylacetone anion and the spectra of aliphatic compounds containing the grouping —C(OR)=C—C(=O)— (*e. g.*, γ-pyrone, $\lambda_{infl.}$ 278 mμ, log ε 1.73; $\lambda_{max.}$ 246 mμ, log ε 4.09[25]).

## Experimental[26]

The ultraviolet absorption measurements were made as described in the preceding paper in this series.[3] The wave lengths and logarithms of the molar extinction coefficients at the absorption maxima and at prominent points of inflection are listed in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SULFONES

| Compound | Source[a] | Solvent[b] | Maxima[c] λ (mμ) | Log ε |
|---|---|---|---|---|
| Ethyl sulfone | 1 | EtOH | Transparent[d] | |
| Ethyl sulfone | 1 | NaOEt | Transparent | |
| Vinyl ethyl sulfone | 2 | EtOH | ~210?[e] | 2.45 |
| bis-(Methylsulfonyl)-methane | 3 | EtOH | Transparent | |
| bis-(Methylsulfonyl)-methane | 3 | NaOEt | (256) | 1.33 |
| | | | <210 | >3.20 |
| 2,2-bis-(Methylsulfonyl)-propane | 4 | EtOH | Transparent | |
| 2,2-bis-(Methylsulfonyl)-propane | 4 | NaOEt | Transparent | |
| Trimethylene trisulfone | 5 | NaOEt | <210 | >3.20 |
| Phenyl methyl sulfone[f] | 6 | EtOH | 271 | 2.91 |
| | | | 264 | 2.99 |
| | | | 258 | 2.82 |
| | | | (253) | 2.58 |
| | | | 217 | 3.83 |
| Phenyl *t*-butyl sulfone | 7 | EtOH | 271 | 2.95 |
| | | | 265 | 3.02 |
| | | | 258 | 2.87 |
| | | | (253) | 2.62 |
| | | | 216 | 3.94 |
| Benzyl ethyl sulfone | 8 | EtOH | 269 | 2.08 |
| | | | 265 | 2.26 |
| | | | 259 | 2.34 |
| | | | 253 | 2.21 |
| Benzyl phenyl sulfone | 9 | EtOH | 272 | 2.97 |
| | | | 265 | 3.09 |
| | | | 259 | 2.98 |
| | | | (253) | 2.81 |
| | | | 219 | 4.10 |
| Benzyl phenyl sulfone | 9 | NaOEt | 272 | 2.96 |
| | | | 265 | 3.08 |
| | | | 259 | 2.97 |
| | | | (253) | 2.80 |
| | | | 219 | 4.10 |
| Benzyl sulfone[f] | 10 | EtOH | 269 | 2.41 |
| | | | 265 | 2.61 |
| | | | 259 | 2.68 |
| | | | 253 | 2.56 |
| | | | 219 | 4.32 |
| Phenethyl sulfone | 11 | EtOH | 268 | 2.29 |
| | | | 264 | 2.47 |
| | | | 259 | 2.58 |
| | | | 253 | 2.50 |
| | | | (249) | 2.34 |
| Phenyl sulfone[f,g] | 12 | EtOH | 274 | 3.16 |
| | | | 266 | 3.33 |
| | | | 260 | 3.25 |
| | | | (254) | 3.21 |
| | | | 235 | 4.24 |
| bis-(Phenylsulfonyl)-methane | 13 | EtOH | 274 | 3.28 |
| | | | 267 | 3.35 |
| | | | 260 | 3.20 |
| | | | (254) | 2.96 |
| | | | 221 | 4.29 |
| bis-(Phenylsulfonyl)-methane | 13 | NaOEt | ~267 | 3.85 |
| 2,2-bis-(Phenylsulfonyl)-propane | 14 | EtOH | 274 | 3.29 |
| | | | 267 | 3.38 |
| | | | 261 | 3.22 |
| | | | (255) | 3.00 |
| | | | 222 | 4.34 |
| 2,2-bis-(Phenylsulfonyl)-propane | 14 | NaOEt | 274 | 3.29 |
| | | | 267 | 3.37 |
| | | | 261 | 3.21 |
| | | | (255) | 3.00 |
| | | | 222 | 4.32 |
| *n*-Butylsulfonylacetone | 2 | EtOH | 287 | 1.71 |
| *n*-Butylsulfonylacetone | 2 | NaOEt | (306) | 0.93 |
| | | | 243 | 4.11 |

(25) Baer, Cavalieri and Carmack, unpublished work. An interesting study of the relation between absorption spectra and constitution of keto-enols has been made by Morton, Hassan and Calloway, *J. Chem. Soc.*, 883 (1934).

(26) Microanalyses were performed by Mrs. Sarah M. Woods.

TABLE I (*Continued*)

| Compound | Source[a] | Solvent[b] | Maxima[c] λ (mμ) | Log ε |
|---|---|---|---|---|
| Phenylsulfonylacetone | 15 | EtOH | 289 | 1.98 |
| | | | 272 | 3.00 |
| | | | 265 | 3.05 |
| | | | 259 | 2.90 |
| | | | 219 | 3.94 |
| Phenylsulfonylacetone | 15 | NaOEt | 278 | 3.88 |
| | | | 236 | 3.96 |
| α-Phenylsulfonylisopropyl methyl ketone | 2 | EtOH | 294 | 2.08 |
| | | | 273 | 3.00 |
| | | | 266 | 3.06 |
| | | | 260 | 2.90 |
| | | | 218 | 4.00 |
| α-Phenylsulfonylisopropyl methyl ketone | 2 | NaOEt | 294 | 2.10 |
| | | | 273 | 3.00 |
| | | | 266 | 3.05 |
| | | | 260 | 2.90 |
| | | | 218 | 4.01 |
| Tetrahydro-1,4-thiapyrone 1-dioxide | 16 | EtOH | 290 | 1.25 |
| Ethyl phenylsulfonylacetate | 17 | EtOH | 272 | 2.95 |
| | | | 266 | 3.02 |
| | | | 259 | 2.87 |
| | | | (254) | 2.65 |
| | | | 218 | 3.94 |
| Ethyl phenylsulfonylacetate | 17 | NaOEt | 275 | 3.55 |

[a] Source references: (1) Pummerer, *Ber.*, **43**, 1407 (1910); (2) see section on "Preparation of Compounds"; (3) Böhme and Marx, *Ber.*, **74B**, 1667 (1941); (4) Baumann, *ibid.*, **23**, 1875 (1890); (5) Camps, *ibid.*, **25**, 233 (1892); (6) oxidation of phenyl methyl sulfide with 30% hydrogen peroxide in acetic acid; (7) Ipatieff, Pines and Friedman, THIS JOURNAL, **60**, 2731 (1938); (8) Böhme, *Ber.*, **69B**, 1610 (1936); (9) Knoevenagel, *ibid.*, **21**, 1344 (1888); (10) Smythe, *J. Chem. Soc.*, **101**, 2079 (1912); (11) Bermejo and Herrera, *IX Congr. intern. quim. pura aplicada*, **4**, 238 (1934) [*C. A.*, **30**, 3418 (1936)]; (12) Hinsberg, *Ber.*, **43**, 289 (1910); (13) Kohler and Tishler, THIS JOURNAL, **57**, 217 (1935); (14) Fromm, *Ann.*, **253**, 135 (1889); (15) Otto and Otto, *J. prakt. Chem.*, [2] **36**, 401 (1887); (16) Fehnel and Carmack, THIS JOURNAL, **70**, 1813 (1948); (17) Michael and Comey, *Am. Chem. J.*, **5**, 116 (1883). [b] EtOH designates absolute ethanol; NaOEt designates 0.01 *N* sodium ethoxide prepared by dissolving sodium in absolute ethanol. [c] The wave lengths in parentheses refer to inflection points. [d] A 0.1 *M* solution in a 1-cm. cell gave transmission readings above 90% at all wave lengths down to limit of observation (*ca.* 208 mμ). [e] See footnote 5. [f] *Cf.* Gibson, Graham and Reid, ref. 4b. [g] *Cf.* Chaix, ref. 4a.

**Preparation of Compounds.**—Most of the previously known compounds were prepared by procedures described in the literature, and were purified by two or more recrystallizations[27] immediately before determination of the spectra. Source references are given in Table I.

**Vinyl ethyl sulfone**[28] was obtained by treating a solution of 52.8 g. (0.26 mole) of ethyl β-bromoethyl sulfone in 600 ml. of benzene with 55.5 g. (0.55 mole) of triethylamine and allowing the mixture to stand for thirty minutes. The precipitate of triethylamine hydrobromide was filtered off, the solvent and excess amine were removed on the steam-bath, and the residual oil was distilled under diminished pressure to yield 24.8 g. (79%) of almost colorless oil, b. p. 103–107° at 8 mm. Redistillation of this product offered a colorless oil, b. p. 105–106° at 8 mm.

*Anal.* Calcd. for $C_4H_8O_2S$: C, 39.94; H, 6.71. Found: C, 39.85; H, 6.63.

***n*-Butylsulfonylacetone** was prepared by refluxing a mixture of 13.9 g. (0.15 mole) of chloroacetone, 21.6 g. (0.15 mole) of sodium butanesulfinate, and 100 ml. of ethanol for one hour. At the end of this time, most of the solvent was removed by distillation and the residue was diluted with several times its volume of water. The layers were separated and the aqueous layer was extracted several times with ether. The combined oil layer and ether extracts were dried over anhydrous magnesium sulfate and distilled under diminished pressure to yield 16.5 g. (62%) of a yellow oil, b. p. 147–150° at 7 mm. Redistillation of this material gave the pure product as a viscous, colorless oil, b. p. 136–137° at 4 mm.

*Anal.* Calcd. for $C_7H_{14}O_3S$: C, 47.18; H, 7.92. Found: C, 47.32; H, 7.73.

**α-Phenylsulfonylisopropyl methyl ketone** was prepared in a similar manner by treating 16.5 g. (0.10 mole) of α-bromoisopropyl methyl ketone with 20.0 g. (0.10 mole) of sodium benzenesulfinate dihydrate in refluxing ethanol. The oily product slowly crystallized on standing; yield, 10.8 g. (48%) of colorless crystals, m. p. (cor.) 42–46°. Recrystallization from aqueous ethanol afforded colorless leaflets melting at 47–48° (cor.).

*Anal.* Calcd. for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24. Found: C, 58.24, 58.47; H, 6.13, 6.10.

## Summary

The ultraviolet absorption spectra of a number of mono- and polysulfones, ketosulfones and carbalkoxysulfones have been determined in both neutral and alkaline solutions. The preparation of vinyl ethyl sulfone and two new ketosulfones is described.

No characteristic absorption bands attributable to the isolated sulfone function are observed in ethanol solutions in the near-ultraviolet region of the spectrum, although the attachment of a sulfonyl group to benzene shifts and intensifies the benzenoid peaks in a manner similar to the carboxyl group in benzoic acid. Strong conjugative effects are observed in the anions formed by the methylene disulfones, β-ketosulfones and α-carbalkoxysulfones in alkaline solutions. When the central carbon atom in the latter compounds is completely alkylated so that no anion can be formed, the spectra in neutral and alkaline solutions are identical.

These effects are interpreted as evidence for the conjugative interaction of the sulfone function with attached aromatic nuclei in aryl sulfones and with the unshared pair of electrons on the central carbon atom in sulfone anions. Resonance forms involving pentacovalent sulfur are discussed.

PHILADELPHIA, PA. RECEIVED JULY 30, 1948

(27) Trimethylene trisulfone was purified by recrystallization of the potassium salt from aqueous potassium hydroxide, followed by reprecipitation with hydrochloric acid.

(28) *Cf.* Ramberg and Bäcklund, *Arkiv. Kemi. Mineral. Geol.*, **13A**, No. 27 (1940); *C. A.*, **34**, 4725 (1940).

[CONTRIBUTION OF THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Absorption Spectra of Heterocyclic Compounds. V. Some Substituted 4-Quinolones[1]

BY EDGAR A. STECK, GALEN W. EWING[1a] AND FREDERICK C. NACHOD

## Introduction

A discussion of the influence of the position of hydroxyl groups upon the absorption spectra of quinolinols and isoquinolinols has been presented in the first paper of this series.[2] The behavior of the 4-substituted compound, which was indicated to have the quinoline structure, was sufficiently interesting to warrant an extension of the study. A considerable number of 4-quinolone derivatives were available from other work in these Laboratories.[3-5] All compounds were prepared through use of the synthetic method of Conrad and Limpach,[6] with some recent improvements.[7]

## Discussion

A bifurcation in the 320–360 mμ region of the spectra of 4-quinolone and its 2- and 3-methyl homologs was observed when the studies were made in alcoholic solution.[2] This unique character of the 4-quinolones was much less noticeable or absent in the absorption spectra in acidic or basic media. It was of interest to examine the influence of substituents upon the pattern of 4-quinolone spectra. The 3-substituted types were employed not solely because of ready accessibility, but also because certain features in the molecule result in an amplification of fine structure in the spectra.

A comparison of the patterns exhibited by 4-quinolone and the 3-methyl derivative in alcoholic solution[2] shows a definite batho- and hypochromic shifting which is greater than when the alkyl group is in position 2. The bifurcation in the 320–360 mμ region is affected to a varying extent by the steric and electron-repelling effects of the alkyl rest. In the case of the parent compound and the 3-substituted one in alcohol, the second peak of the twin maxima is the greater, while the 2-methyl-4-quinolone spectrum shows a higher maximum around 320 mμ. While 4-quinolone shows a bifurcation in alcohol and *p*H 7 buffer, the spectra in acid and base fail to present this feature. This twinning is absent only with the spectrum in acid for 2-methyl-4-quinolone; however, the related 3-methyl compound exhibits it in alcohol, acid and base. The principal underlying causes of these effects, and also the shoulder around 280–300 mμ presumably resides in the influence of the substituents upon the tautomerism of the quinolinol–quinolone type. It should not be forgotten that the 2-methyl group may also complicate the pattern due to its lability and concomitant effects (Fig. 1). These are also to be observed in chemical behavior of the several types.

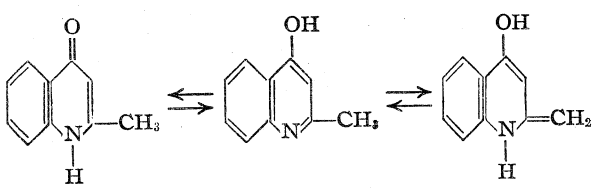



Fig. 1.

The introduction of substituents into the benzene moiety of quinolinone types and the concomitant alterations in spectral characteristics is closely akin in form to our earlier studies on aminoquinolines[8] and certain 4-aminoquinoline derivatives.[9] The comparison of the spectra of the 4-quinolone types was carried out using alcoholic solutions because the greatest amount of structural resolution was found in that solvent. The characteristic bifurcations in the short wave range (below 260 mμ) are approximately the same for the bz-methyl- and bz-chloro-3-methyl-4-quinolones (Figs. 2 and 3). The chloro-3-methyl types show a constant bathochromic shift of 6 mμ when compared with the corresponding dimethyl compounds. It should be noted that the resolution of spectral characteristics is more pronounced with the more electrophilic chloro group. This is not only true for the doublet peaks in the 320–360 mμ region, but also for the inflection which occurred around 280–300 mμ in the case of the parent 4-quinolone. While the inflection does become a true secondary maximum with the introduction of a 3-methyl group, substitution of the benzenoid ring results in marked alterations in form. The positions being considered *in toto*, we notice that the most profound change occurs when the methyl or the chloro group is introduced into position 7. The character of the alkyl substituent would be expected to result in less influence upon the tautomerism than the more electron-attracting halogen. This is indeed the case, as has been shown in Figs. 2 and 3. In all instances, the resolution of the dimethyl compounds is less marked than of the 3-methyl-bz-chloro compounds. There is not only a greater

(1) Presented before the 114th session of the American Chemical Society in Washington, D. C., on Aug. 30, 1948.

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(2) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).

(3) Steck, Hallock and Holland, *ibid.*, **68**, 129, 131, 380 (1946).

(4) Steck and Hallock, forthcoming publication.

(5) Surrey and Cutler, THIS JOURNAL, **68**, 2570 (1946).

(6) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Limpach, *ibid.*, **64**, 969 (1931).

(7) Steck, Hallock and Holland, THIS JOURNAL, **68**, 1241 (1946).

(8) Steck and Ewing, *ibid.*, **70**, 3397 (1948).

(9) Steck, Ewing and Nachod, *ibid.*, **70**, 3410 (1948).

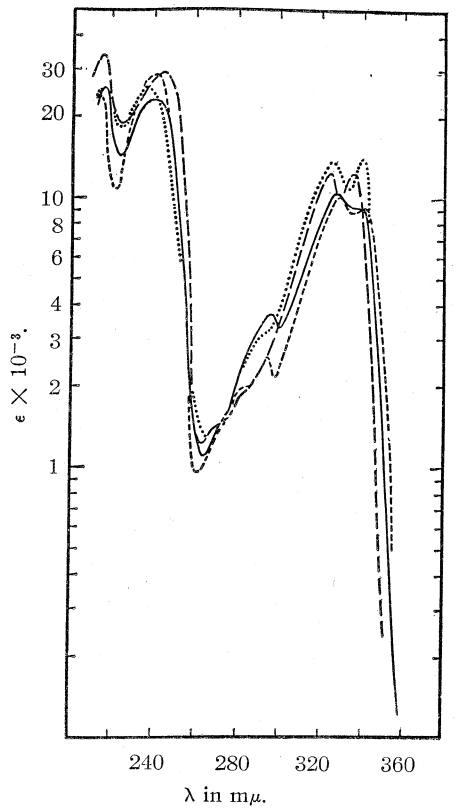



Fig. 2.—Absorption spectra of: —, 3,5-dimethyl-4-quinolone; – – – –, 3,6-dimethyl-4-quinolone; — —, 3,7-dimethyl-4-quinolone; . . . . . , 3,8-dimethyl-4-quinolone; in 95% ethanol.

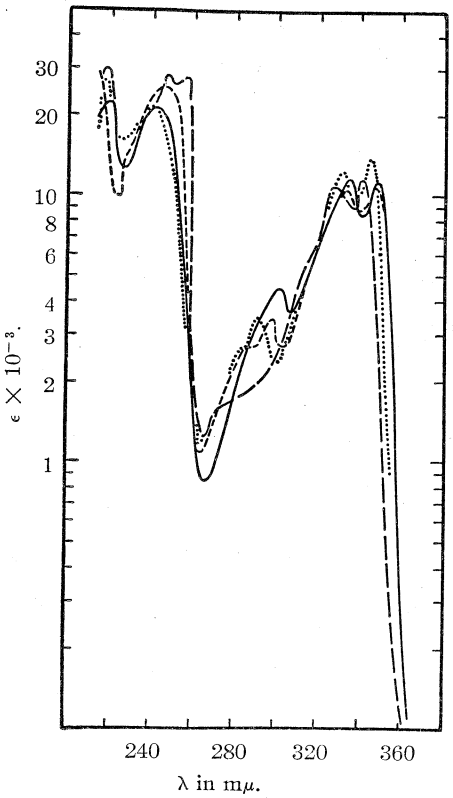



Fig. 3.—Absorption spectra of: —, 5-chloro-3-methyl-4-quinolone; – – – –, 6-chloro-3-methyl-4-quinolone; — —, 7-chloro-3-methyl-4-quinolone; . . . . . , 8-chloro-3-methyl-4-quinolone; in 95% ethanol.

retention of the secondary maximum in the 280–300 mμ region throughout, but also the 7-chloro-3-methyl-4-quinolone exhibits an additional feature of structure in the twinning of the peak in the 240–260 mμ region. The importance of the position of a nucleophilic grouping is apparently less marked than an electrophilic rest. The substituent in the benzene ring influences the state in a molecule through resonance effects, and also the dipoles which are associated with its location (Fig. 4). It is in position 7 of the 4-quinolones that the grouping might well prove to be of greater importance than in positions 5, 6 or 8. An analogous effect has been indicated for derivatives of 4-aminoquinoline.[9,10] The combination of these influences appear to be responsible factors in the poorly developed character in the 3,8-dimethyl-4-quinolone spectrum.

The extent of the influence of a halo substituent is brought into focus when a comparison is made of the spectra of 3-methyl, 3,5-dimethyl, and 3,5-dichloro-4-quinolones, all in alcoholic solution (Fig. 5). While the additional alkyl group in position 5 does cause a slight batho- and hyperchromic shifting, the 3,5-dimethyl compound shows a decrease in the second peak of the bifurcation in the 320–360 mμ region. This may well be due to steric effects. The 3,5-dichloro-4-quinolone exhibits the expected characteristics

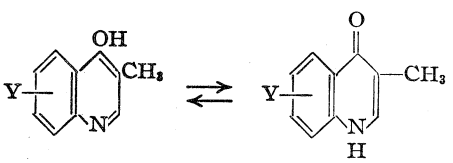



Fig. 4.

resulting from the electrophilic halogen substituents. The entire spectrum is bathochromically shifted, and, for the most part, also a displacement is noted. Of particular interest is the batho- and hyperchromic shifting of the secondary maxima in the 290 mμ region with increase in nucleophilic substitution.

In Fig. 6, the spectra of five bz-alkoxy-3-methyl-4-quinolones are compared. The differences in effect of the methoxy and ethoxy groupings are but slight, as is to be seen in the figure. The 7-ethoxy-3-methyl-4-quinolone is unique in the lack of a secondary maximum in the 260–320 mμ region. Actually there are two secondary maxima in the case of both the 6-methoxy and 6-ethoxy compounds, whereas the 8-methoxy shows an inflection and the 8-ethoxy-

(10) Irvin and Irvin, THIS JOURNAL, 69, 1091 (1947).

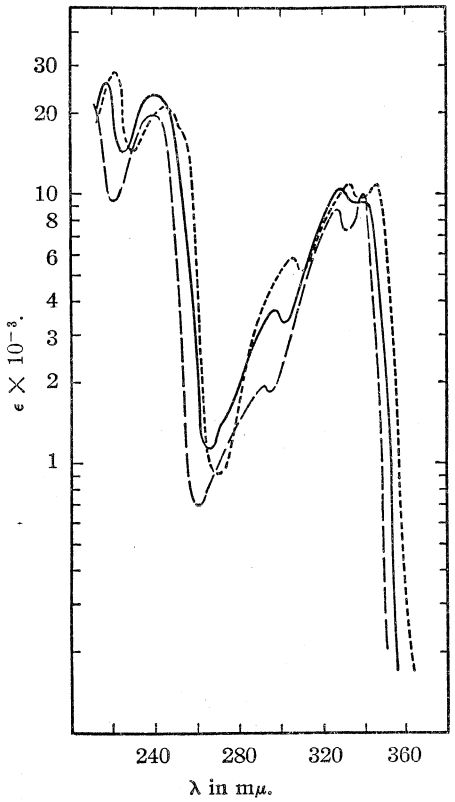



Fig. 5.—Absorption spectra of: — —, 3-methyl-4-quinolone; —, 3,5-dimethyl-4-quinolone; . . . . ., 3,5-dichloro-4-quinolone; in 95% ethanol.

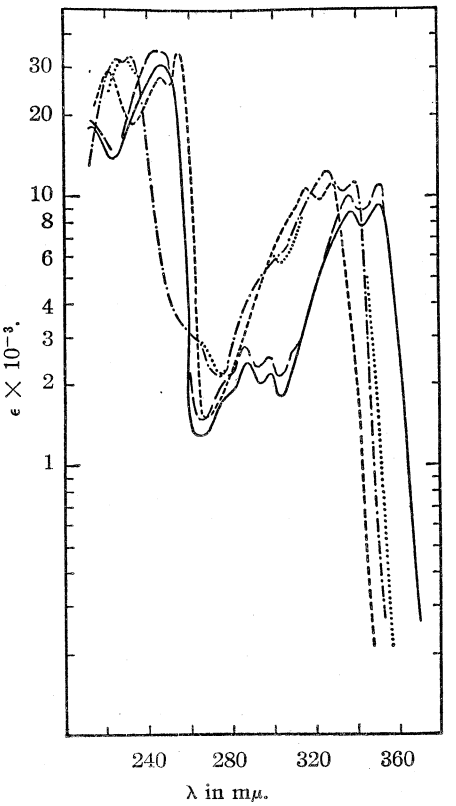



Fig. 6.—Absorption spectra of: —, 6-methoxy-3-methyl-4-quinolone; — —, 6-ethoxy-3-methyl-4-quinolone; – – –, 7-ethoxy-3-methyl-4-quinolone; —·—, 8-methoxy-3-methyl-4-quinolone; . . . . ., 8-ethoxy-3-methyl-4-quinolone; in 95% ethanol.

3-methyl-4-quinolone a slight singular inflection apart from the related methoxy analog. All of the alkoxy compounds show the characteristic bifurcations in the 300–360 mμ region. The 6- and 8-alkoxy-substituted 3-methyl-quinolones are bathochromically shifted with respect to the 7-ethoxy derivative. While there is little difference in the patterns presented by the methoxy and ethoxy compounds when the substituent is in position 8, the influence of the additional methylene group in the alkoxy substituent is made apparent when that rest is in position 6. The passage from 6-methoxy-3-methyl-4-quinolone to the 6-ethoxy analog results in a definite hyperchromic intensification of all maxima.

The evidence presented concerning the spectra of the disubstituted 4-quinolones indicates that the 7-position of the molecule is exceptional in its influences. This is in agreement with our earlier observations.[9]

## Experimental

**I. 4-Quinolones.**—The preparation of the requisite compounds has been described in detail in contributions relating to 4-substituted quinoline types.[3–5]

**II. Absorption Spectra.**—All spectra were determined with a Beckman Quartz Spectrophotometer, Model DU, Serial No. D-377. The method has been indicated in the first paper of this series.[2]

**Acknowledgments.**—The authors wish to express their appreciation to Mrs. E. R. Falkner and Mrs. M. Becker for technical assistance, and to Mrs. B. Beecher for her aid in tracing the curves required.

## Summary

The absorption spectra of fourteen disubstituted 4-quinolones have been determined and the effects of substitution discussed critically.

RENSSELAER, NEW YORK RECEIVED JULY 21, 1948

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH AND THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL OF CANADA[1]]

# Studies in Steroid Metabolism. VI. The Characterization of 11- and 12-Oxygenated Steroids by Infrared Spectrometry

BY R. NORMAN JONES, P. HUMPHRIES AND KONRAD DOBRINER

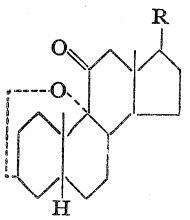
The use of infrared spectrometry for the detection and identification of steroid metabolites in human urine has been reported in a previous publication in this series.[2] It has also been demonstrated that the presence of certain functional groups in the steroid molecule can be recognized by infrared spectrometry,[3] and a distinction between ketosteroids in which the carbonyl group is at the 3, 17 or 20 positions can be made from a determination of the location of the carbon–oxygen stretching vibration in the region between 1660 and 1780 cm.$^{-1}$.

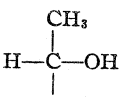
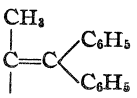
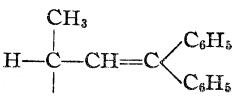
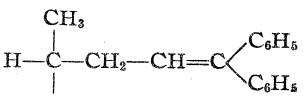
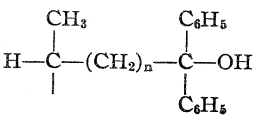
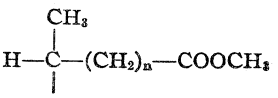
It seemed reasonable to anticipate that a carbonyl group at positions 11 and 12 might also absorb at characteristic frequencies and a systematic investigation of the infrared spectra of a number of steroids containing ketonic and hydroxyl groups at these positions has been carried out.

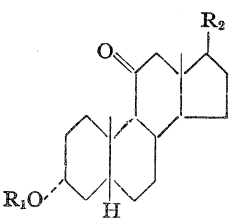
The recognition of steroids oxygenated at position 11 is of special importance in connection with steroid metabolism, since carbonyl or hydroxyl groups at this position are indicative of steroids originating in the cortex of the adrenal gland. Among the twenty-eight steroids isolated from the adrenal gland[4] fifteen contain a ketone or hydroxyl group at this position.

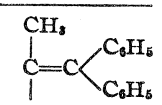
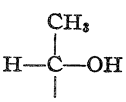
It has already been demonstrated[5,6] that metabolites of 11-oxygenated adrenocortical hormones are present in human urine. Androstanediol-3$\alpha$,-11$\beta$-one-17, etiocholanol-3$\alpha$-dione-11,17, and androstanol-3$\alpha$-dione-11,17 occur in the urine of both normal and diseased persons,[5,6,7] while etiocholanediol-3$\alpha$,11$\beta$-one-17, its transformation product $\Delta^{9,11}$-etiocholenol-3$\alpha$-one-17 and pregnanol-3$\alpha$-dione-11, 20 have been observed frequently in the urine of diseased persons and rarely in the urine of healthy individuals.[6]

In addition to these completely characterized compounds, a variety of additional steroids containing a hydroxyl or a carbonyl group at position 11 may be found in human urine, and some of



| | R |
|---|---|
| I |  |
| II |  |
| III |  |
| IV |  |
| V ($n$ = 1), VI ($n$ = 2) |  |
| VII ($n$ = 0), VIII ($n$ = 1), IX ($n$ = 2) |  |



| | $R_1$ | $R_2$ |
|---|---|---|
| X | —H |  |
| XI | —H |  |
| XII | —H | OH |
| XIII | —$COCH_3$ | O—$COCH_3$ |
| XIV | —H | $COOCH_3$ |

(1) Published as Contribution No. 1667 from the Laboratories of The National Research Council of Canada.

(2) Dobriner, Lieberman, Rhoads, Jones, Williams and Barnes, *J. Biol. Chem.*, **172**, 297 (1948).

(3) Jones, Williams, Whalen and Dobriner, THIS JOURNAL, **70**, 2024 (1948).

(4) T. Reichstein and C. W. Shoppee, "The Hormones of the Adrenal Cortex," Vitamins and Hormones, Vol. I, Academic Press, Inc., New York, N. Y., 1943, pp. 345-413.

(5) Mason, *J. Biol. Chem.*, **158**, 719 (1945).

(6) Lieberman, Fukushima and Dobriner, Federation of American Societies for Experimental Biology, Proceedings, Vol. VII, 168 (1948). See also Dobriner, Lieberman, Hariton, Sarett and Rhoads, *J. Biol. Chem.*, **169**, 221 (1947).

(7) Lieberman and Dobriner, *J. Biol. Chem.*, **166**, 773 (1946).

TABLE I

CARBON–OXYGEN STRETCHING VIBRATION OF 11-KETOSTEROIDS

| Compound | No. structure | Position of max. cm.$^{-1}$ ($CS_2$) | Source[a] |
|---|---|---|---|
| **A. 11-Monoketosteroids** | | | |
| 3α,9α-Epoxypregnanol-20-one-11 | I | 1713 | 12 |
| $\Delta^{20,22}$-3α,9α-Epoxy-22,22′-diphenylbisnorcholenone-11 | II | 1713 | 12 |
| $\Delta^{22}$-3α,9α-Epoxy-23,23′-diphenylnorcholenone-11 | III | 1713 | 12 |
| $\Delta^{23}$-3α,9α-Epoxy-24,24′-diphenylcholenone-11 | IV | 1713 | 12 |
| 3α,9α-Epoxy-23,23′-diphenylnorcholanol-23-one-11 | V | 1713 | 12 |
| 3α,9α-Epoxy-24,24′-diphenylcholanol-24-one-11 | VI | 1713 | 12 |
| $\Delta^{20,22}$-22,22′-Diphenylbisnorcholanol-3α-one-11 | X | 1713 | 12 |
| Pregnanediol-3α,20(*epi*)-one-11[b] | XI | 1710, 1742[d] | 9 |
| Etiocholanediol-3α,17α-one-11 | XII | 1716[c] | 9 |
| **B. 11-Ketosteroid Esters** | | | |
| 3α,9α-Epoxy-11-ketobisnorcholanic acid methyl ester | VII | 1742, 1713 | 12 |
| 3α,9α-Epoxy-11-ketonorcholanic acid methyl ester | VIII | 1742, 1713 | 12 |
| 3α,9α-Epoxy-11-ketocholanic acid methyl ester | IX | 1745, 1713 | 12 |
| Etiocholanediol-3α,17α-one-11-diacetate | XIII | 1742, 1713 | 9 |
| 3α-Hydroxy-11-ketoetiocholanic acid methyl ester | XIV | 1742, 1713 | 12 |
| 3α-Hydroxy-11-ketobisnorcholanic acid methyl ester | XV | 1742, 1710 | 12 |
| 3α-Hydroxy-11-ketonorcholanic acid methyl ester | XVI | 1742, 1710 | 12 |
| 3α-Acetoxy-11-ketonorcholanic acid methyl ester | XVII | 1739, 1710 | 12 |
| 3α-Hydroxy-11-ketocholanic acid methyl ester | XVIII | 1742, 1710 | 12 |
| 3α-Acetoxy-11-ketocholanic acid methyl ester | XIX | 1742, 1710 | 12 |
| Pregnanediol-3α-20-one-11-diacetate | XX | 1739, 1710 | 9 |
| Pregnanediol-3α-20(*epi*)-one-11-diacetate[b] | XXI | 1739, 1710 | 9 |
| **C. 3,11-, 11,20- and 3,11,20-Ketosteroids and Related Esters** | | | |
| Pregnanol-3α-dione-11,20 | XXII | 1713 | 8, 9, 12 |
| Pregnanol-3α-dione-11,20-acetate | XXIII | 1739, 1710 | 12 |
| Uranedione-3,11 | XXIV | 1713 | 5 |
| Pregnanetrione-3,11,20 | XXV | 1713 | 1, 12 |
| **D. 11,17-, 3,11,17-Ketosteroids and Related Esters** | | | |
| Androstanol-3α-dione-11,17 | ... | 1751, 1713 | 6 |
| Etiocholanol-3α-dione-11,17 | ... | 1754, 1716 | 9 |
| Androstanol-3α-dione-11,17-acetate | XXVI | 1745[e], 1713 | 6 |
| Etiocholanol-3α-dione-11,17-acetate | ... | 1748, 1739, 1713 | 9 |
| Androstanetrione-3,11,17 | ... | 1751, 1716[e] | 4 |
| Etiocholanetrione-3,11,17 | XXVII | 1751, 1716[e] | 4, 9 |
| $\Delta^4$-Androstenetrione-3,11,17 (adrenosterone) | XXVIII | 1751, 1719, 1674 | 2 |
| **E. 11,20-Diketo-21-acetoxysteroids** | | | |
| Pregnanediol-3α-21-dione-11,20-acetate-21 | XXIX | 1758, 1732, 1713 | 9 |
| Pregnanol-21-trione-3,11,20-acetate | XXX | 1758[f], 1732, 1713 | 9 |
| $\Delta^4$-Pregnenol-21-trione-3,11,20-acetate (11-dehydrocorticosterone acetate) | XXXI | 1758, 1732<br>1716, 1674 | 9 |

[a] (1) T. F. Gallagher, Sloan–Kettering Inst., New York, N. Y. (2) E. C. Kendall, Mayo Clinic, Rochester, Minn. (3) A. Lardon, University of Basel, Basel, Switzerland. (4) S. Lieberman, Sloan–Kettering Inst., New York, N. Y. (5) R. E. Marker, Pennsylvania State College, State College, Penna. (6) Compound prepared or isolated at Memorial Hospital, New York, N. Y. (7) V. Prelog, Eidg, Tech. Hochschule, Zurich, Switzerland. (8) T. Reichstein, University of Basel, Basel, Switzerland. (9) L. H. Sarett, Merck and Co., Rahway, N. J. (10) C. R. Scholz, Ciba Pharmaceutical Products, Inc., Summit, N. J. (11) E. Schwenk, The Schering Corp., Bloomfield, N. J. (12) R. Turner, Harvard University, Cambridge, Mass. (13) A. L. Wilds, University of Wisconsin, Madison, Wis. [b] In these compounds the configuration at position 20 is uncertain and the prefix "epi" is used arbitrarily for convenient reference. [c] Solvent tetrachlorethane. [d] Weak band attributed to an impurity. [e] Broad maximum. [f] Suspension of crystalline material in saturated solution in carbon disulfide.

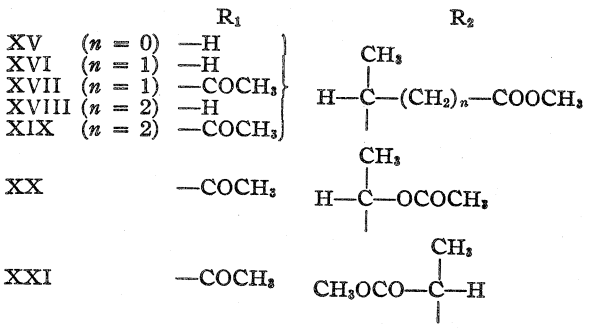
these may be included among compounds which have already been isolated, but which have not, as yet, been fully characterized.[8]

**11-Ketosteroids.**—The recognition of an absorption band associated with the 11-ketone group could be achieved unequivocally from measurements on 11-monocarbonyl compounds in which there could be no interference from carbonyl groups located elsewhere in the molecule. Unfortunately, the number of such compounds is limited, but through the kind coöperation of Dr. R. Turner and Dr. L. H. Sarett we have obtained

(8) Lieberman, Dobriner, Hill, Fieser and Rhoads, *J. Biol. Chem.*, **172**, 263 (1948).

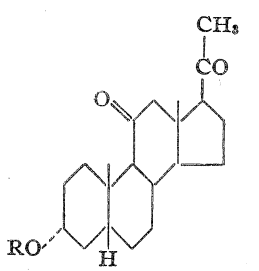
nine 11-ketosteroids which satisfy this criterion.

The infrared absorption spectra of carbon disulfide solutions of eight of these substances (I–VI, X–XI) exhibit one maximum only in the carbonyl region at 1710–1713 cm.$^{-1}$. The ninth compound (XII) gave a maximum at 1716 cm.$^{-1}$ in solution in tetrachlorethane (Table IA). Similar data are also listed in Table IB for twelve 11-ketosteroid esters (VII–IX, XIII–XXI), all of which possess two maxima in the carbonyl region at 1710–1713 and 1739–1742 cm.$^{-1}$, respectively.



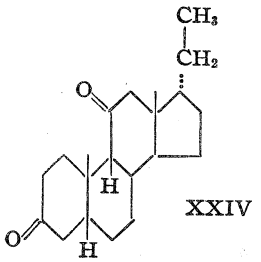

It has been shown previously[3] that both the 3- and 17-acyl esters of steroid alcohols as well as the methyl esters of cholanic acid derivatives possess a maximum at 1739–1742 cm.$^{-1}$. Consequently in these compounds it may be inferred that the absorption band at 1710–1713 cm.$^{-1}$ is associated with the carbonyl group at position 11, and that no interactions occur between the vibrations associated with the ketone group at this position and ester groups at positions 3, 17 or on the side chain.

**11,20-Diketones.**—In the non-conjugated 20-ketosteroids the carbonyl absorption maximum is at 1706–1710 cm.$^{-1}$ and because of the proximity of the 11-ketone and 20-ketone band maxima a simple spectrometric differentiation of these two important structures is uncertain (*vide* p. 246). Two compounds containing 11,20-diketone grouping have been examined. In XXII only a single band at 1713 cm.$^{-1}$ occurs, while XXIII has two bands at 1710 and 1739 cm.$^{-1}$, the latter due to the ester group at position 3.

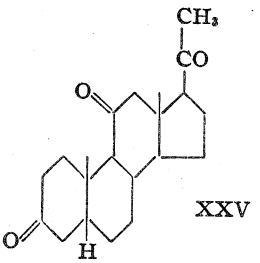



XXII (R = —H)
XXIII (R = —CO—CH3)

**3,11-Diketones.**—A similar situation arises in the identification of 11-ketosteroids which contain a second (unconjugated) ketone group at position 3, as the non-conjugated 3-ketone group absorbs at 1715–1719 cm.$^{-1}$ which is also very close to the frequency of the 11-ketone band. The only compound of this kind so far examined is uranedione-3,11 (XXIV) which gives a single maximum at 1713 cm.$^{-1}$. Measurements on compounds XXV and XXVII support the evidence from XXIV in indicating that no anomalous displacements of the band positions are associated with the 3,11-diketone structure.



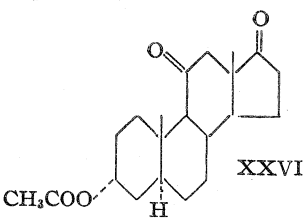

XXIV



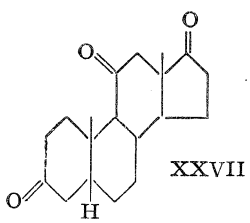

XXV

In 11-ketosteroids containing a conjugated ketone group at position 3, the band at 1674–1677 cm.$^{-1}$ characteristic of this conjugated group occurs at the expected position.

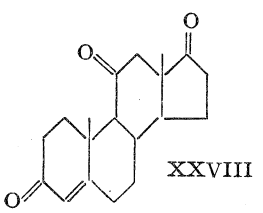
**11,17-Diketones.**—In 17-ketosteroids in which ring D is saturated, an absorption maximum occurs at 1742–1745 cm.$^{-1}$, but in 11,17-diketones this band is displaced to 1748–1754; the band normal to the 11-ketone at 1710–1716 cm.$^{-1}$ is present also.[9]




XXVI




XXVII




XXVIII

**Interaction Effects.**—These measurements indicate that interaction occurs between carbonyl groups at positions 11 and 17 which displace the bands from their normal positions. A similar interaction effect has been noted previously between a ketone group at position 20 and an acetoxy group at position 21 in the acetylated derivatives of steroids containing the ketol side chain.[3] Compounds XXIX–XXXI contain both the 11-ketone and the 20-keto-21-acetoxy groupings and are of particular interest as they are derivatives of adrenocortical steroid hormones. The bands at 1732 and at 1756–1758 cm.$^{-1}$,

(9) In compound XXVI which contains an acetate group at position 3 in addition to the 11,17-diketone group, the band maxima are at 1745 and 1713 cm.$^{-1}$. It is presumed that the former band is an unresolved doublet, due to the acetate band at 1739–1742 and a band at 1748–1754 cm.$^{-1}$. In the corresponding compound in the etiocholane stereochemical series this band is resolved (see Table ID).

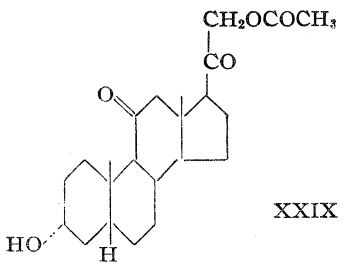
TABLE II

CARBON–OXYGEN STRETCHING VIBRATION OF 12-KETOSTEROIDS

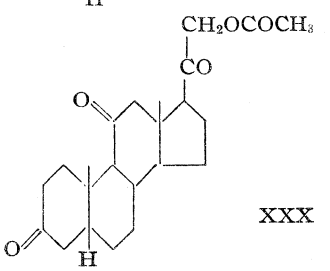
| Compound | Structure | Position of max. (cm.$^{-1}$) solvent $CS_2$ | Source[a] |
|---|---|---|---|
| Pregnanone-12 | ..... | 1710 | 8 |
| 3α-Acetoxy-12-ketocholanic acid methyl ester | XXXII | 1742, 1710 | 10, 12 |
| Δ$^4$-Pregnenol-21-trione-3,12,20-acetate | XXXIII | 1758, 1732, 1716, 1677 | 10 |
| 3α,7α-Dihydroxy-12-ketoetiocholanic acid methyl ester | XXXIV | 1739, 1723[b] | 8 |
| 3α-7α-Diacetoxy-12-ketoetiocholanic acid methyl ester | XXXV | 1742, 1723 | 8 |
| 3α-Succinoxy-7α-acetoxy-12-ketoetiocholanic acid methyl ester | XXXVI | 1742, 1723 | 8 |
| Δ$^{9,11}$-3α-Acetoxy-12-ketocholenic acid | ..... | 1742, 1713, 1684 | 10 |
| Δ$^{9,11}$-3α-Acetoxy-12-ketocholenic acid methyl ester | ..... | 1742, 1680 | 11 |
| 11,12-Diketonorcholanic acid methyl ester | ..... | 1742, 1726 | 3 |
| 3,11,12-Triketonorcholanic acid methyl ester | ..... | 1739[c], 1726 | 12 |
| 3,12-Diketocholanic acid methyl ester | ..... | 1742, 1716 | 12 |

[a] See footnote to Table I. [b] See footnote to Table I. [c] Inflection only.

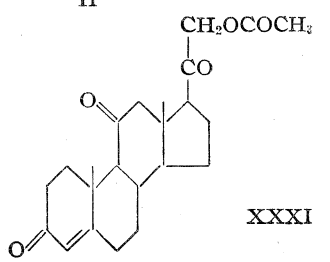
characteristic of the 20-keto-21-acetoxy group in addition to the 11-ketosteroid maximum at 1710–1713 cm.$^{-1}$ occur in all three compounds.[10]




XXIX




XXX

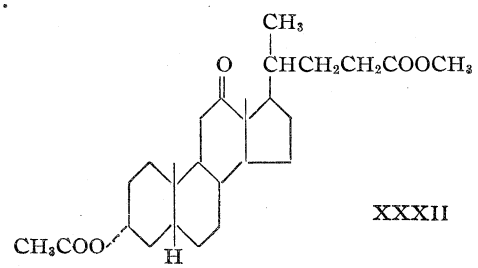



XXXI

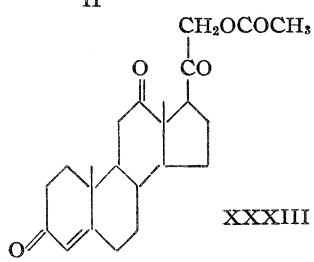
It may be concluded that a band at 1754–1760 cm.$^{-1}$ is suggestive of the presence of either the 11,17-diketone or the 20-keto-21-acetoxy grouping. The former structure also produces a second maximum at 1710–1716 cm.$^{-1}$ whereas in the latter case the second band is near 1730 cm.$^{-1}$. The distinction between these two groupings can be confirmed from measurements in the 1200–1250 cm.$^{-1}$ region since a strong band characteristic of the acetoxy group and lacking in the carbonyl group occurs near 1230 cm.$^{-1}$.

(10) In XXX the non-conjugated 3-ketone group no doubt contributes also to the maximum at 1713 cm.$^{-1}$.

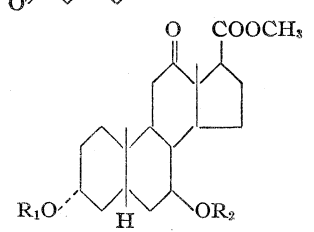
**12-Ketosteroids.**—Eleven compounds containing a carbonyl group at position 12 have been examined (see Table II). In pregnanone-12 and XXXII the band at 1710 cm.$^{-1}$ can be assigned to the unconjugated 12-ketone grouping. The spectrum of XXXIII, which contains the acetylated ketol side chain and the conjugated ketone group at position 3 exhibits the maxima characteristic of all four carbonyl groups (*cf.* Fig. 1). In compounds XXXIV–XXXVI which contain the 12-keto-17-carbomethoxy grouping, the 12-ketone band is displaced to 1723 cm.$^{-1}$ (*vide p.* 246).




XXXII




XXXIII




XXXIV ($R_1 = R_2 = H$)
XXXV ($R_1 = R_2 = —CO—CH_3$)
XXXVI ($R_1 = —CO—CH_2—CH_2—COOH$; $R_2 = —CO—CH_3$)

In the Δ$^9$–12 ketones the maximum is at 1680–1684 cm.$^{-1}$. This is significantly higher than the

frequency observed for $\Delta^4$-3-ketosteroids (1674–1677 cm.$^{-1}$) and for $\Delta^{16}$-20-ketosteroids (1666–1669 cm.$^{-1}$). The two 11,12-diketones listed in Table II possess a maximum at 1726 cm.$^{-1}$. The displacement of this band from 1706–1716 to 1726 cm.$^{-1}$ is indicative of interaction in the $\alpha$-diketone structure.

**Other Ketosteroids.**—As these investigations were initiated with the primary object of improving techniques for the identification of steroid hormones and hormone metabolites, attention has been chiefly directed to steroids containing functional groups at the positions which are of major importance in relation to the hormonal activity. Up to the present time only a few steroids containing carbonyl groups at other positions have been examined; the results, summarized in Table III, suggest that the non-conjugated 7-ketone group absorbs near 1719 cm.$^{-1}$, the non-conjugated 16-ketone near 1754 cm.$^{-1}$, the 3,6-diketosteroid group at 1723 cm.$^{-1}$ and the $\Delta^{3,5}$-diene-one-7 group at 1663 cm.$^{-1}$. One monoketosteroid of uncertain structure kindly supplied by Dr. Heard[11] and believed to contain a ketone group at position 15 had an absorption maximum at 1751 cm.$^{-1}$. The location of this band is in general agreement with the observation that a carbonyl group in a cyclopentanone ring system absorbs at a high frequency, and would seem to be consistent with the postulated structure of this compound.

**11-Hydroxy Compounds.**—The position of the hydrogen–oxygen stretching vibration of the hydroxyl group in a steroid molecule cannot be related to the position of substitution in the molecule in a manner similar to that for the carbon–oxygen bond of the carbonyl group.[3] Nevertheless, the presence of an absorption band near 3600 cm.$^{-1}$ in the spectrum of a solution of a steroid is associated with the presence of a hydroxyl group in the molecule.

TABLE III

CARBON–OXYGEN STRETCHING VIBRATION OF KETOSTEROIDS WITH CARBONYL GROUPS AT POSITIONS OTHER THAN 3, 11, 12, 17 AND 20

| Compound | Position of max. (cm.$^{-1}$) solvent $CS_2$ | Sources[a] |
|---|---|---|
| Sitostanedione-3,6 | 1723 | 5 |
| $\Delta^{22}$-Sitostenedione-3,6 | 1723 | 5 |
| 3$\alpha$,12$\alpha$-Diacetoxy-7-ketocholanic acid methyl ester | 1742<br>1719 | 1 |
| 3$\alpha$-Succinoxy-12$\alpha$-acetoxy-7-ketoetiocholanic acid methyl ester | 1742<br>1719 | 8 |
| 3$\alpha$-12$\alpha$-Dihydroxy-7-ketocholanic acid | 1719 | 1 |
| $\Delta^{3,5}$-Cholestadiene-one-7 | 1663 | 7 |
| $\Delta^{1,3,5:10,6,8}$-Estrapentaene-one-16 | 1754 | 13 |

[a] See footnote to Table I.

(11) Heard and McKay, *J. Biol. Chem.*, **131**, 371 (1939); **165**, 677 (1946).

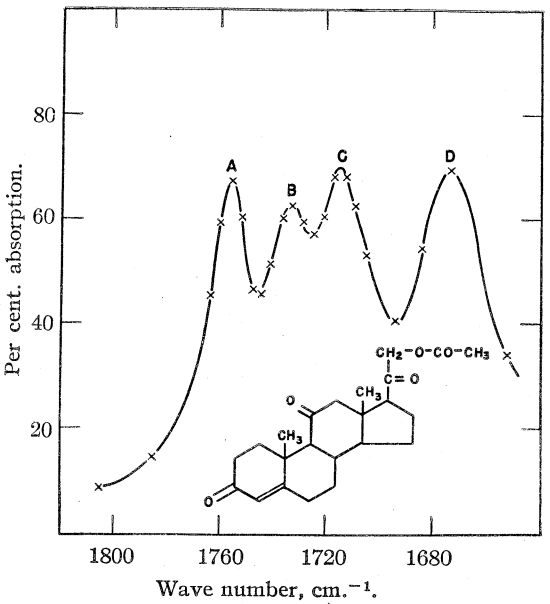



Fig. 1.—Infrared absorption spectrum of 11-dehydrocorticosterone acetate between 1640 and 1800 cm.$^{-1}$. Maxima A and B are associated with the acetylated ketol side chain, maximum C with the ketone group at position 11, and maximum D with the $\alpha\beta$-unsaturated ketone group at position 3 (solvent carbon disulfide).

No simple 11-monohydroxy steroids have been available for measurement, but several dihydroxy steroids in which one of the hydroxyl groups is at position 11 have been examined. In these spectra the normal hydroxyl absorption band near 3600 cm.$^{-1}$ is observed and no behavior specifically relatable to the 11 position is to be noted. In a compound such as androstanediol-3$\alpha$,11$\beta$-one-17-acetate-3, where the hydroxyl group at position 3 is esterified, the absorption band at 3616 cm.$^{-1}$ can be attributed to the 11-hydroxyl group.

## Discussion

The relationships which have been observed between the frequencies of the carbonyl band maxima, and the structure for all types of steroids are summarized in Table IV. In evaluating these data, it must be noted that they apply to solutions in carbon disulfide only. The significance which is to be attached to them is dependent on the number of compounds of each type examined, and this is indicated in the third column of the table.

The recognition of the 11-ketone group in a steroid by infrared spectrometry is only partially successful. Such identification is possible provided certain other ketone groupings are known to be absent, but non-conjugated ketone groups at other positions on the hexacyclic rings or in the side chain may absorb quite close to the same frequency. This is certainly true of 3-ketones and 20-ketones, and probably also of ketone groups at positions 6, 7 and 12. With the spec-

TABLE IV

SUMMARY OF POSITIONS OF CARBONYL BAND MAXIMA

Carbon disulfide solutions

| Carbonyl type | Position of max. (cm.$^{-1}$) | Compounds examined |
|---|---|---|
| Phenolic 3-acetate (naphthalenoid) | 1770 | 1 |
| Phenolic 3-acetate (benzenoid) | 1767–1764 | 4 |
| 21-Acetoxy-20-ketone | 1758–1756[a] | 4 |
| $\Delta^{14}$-17-Ketone | 1754 | 2 |
| 16-Ketone | 1754 | 1 |
| $\Delta^{3,5}$-Diene-ol-3-acetate | 1754 | 1 |
| 11,17-Diketone | 1754–1751[a] | 5 |
| 17-Ketone | 1745–1742 | 15 |
| Acyl esters of 3-, 11-, 12-, 17- and 20-hydroxysteroids | | |
| Alkyl esters of cholanic, norcholanic, bisnorcholanic acids and related unsaturated acids | 1742–1735 | 60 |
| 21-Acetoxy-20-ketone | 1732[a] | 7 |
| 11,12-Diketone | 1726 | 2 |
| Benzoates of steroid alcohols | 1724–1717 | 5 |
| 12-Keto-etiocholanic acid alkyl esters | 1723[b] | 3 |
| 3,6-Diketone | 1723 | 2 |
| 7-Ketone | 1719 | 3 |
| 3-Ketone | 1719–1717 | 14 |
| $\Delta^{15}$-17-Ketone | 1716 | 2 |
| 11,17-Diketone | 1716–1713[a] | 5 |
| 11-Ketone | 1716–1710 | 21 |
| 12-Ketone | 1710 | 2 |
| 20-Ketone | 1710–1706 | 19 |
| $\Delta^{9}$-12-Ketone | 1684–1680 | 2 |
| $\Delta^{4}$-3-Ketone | 1677–1674 | 17 |
| $\Delta^{16}$-20-Ketone | 1670–1666 | 5 |
| $\Delta^{4,6}$-Diene-3-ketone | 1669–1666 | 2 |
| $\Delta^{3,5}$-Diene-7-ketone | 1663 | 1 |

[a] These structures give rise to two maxima both of which are listed in the table. [b] Second maximum at 1739 cm.$^{-1}$.

trometers at present available and using a sodium chloride prism, an accuracy of ± 3 cm.$^{-1}$ in the determination of the maximum is about the best which can be achieved. If this could be increased to better than ± 1 cm.$^{-1}$ a distinction between 3-, 11- and 20-ketones could be made more certainly. In the case of 3-, 11- and 11,20-diketones an increase in the resolving power of the spectrometer might separate the bands. A careful analysis of the widths and absolute intensities of the absorption bands may also yield further information; such measurements are being made, and will be reported in a subsequent communication.

Certain dicarbonyl groupings, notably the 11,17-diketones and 11,12-diketones, appear to exhibit characteristic absorption. The band at 1726 cm.$^{-1}$ associated with the 11,12-diketone may be common to other $\alpha$-diketosteroids, none of which has yet been studied. The absorption specific to the 20-keto-21-acetoxy group is significant in connection with the identification of adrenocortical hormones and their metabolites, as also is the observation that the introduction of the 11-ketone group does not disturb the position of these bands. An example is provided by the spectrum of dehydrocorticosterone acetate (XXXI) in which all of the four carbonyl maxima can be related to distinct carbonyl groups as indicated in Fig. 1.

The interaction effects which occur when two or more carbonyl groups are present are of theoretical interest. Such effects have only been encountered when the two carbonyl groups are in the 1:2, 1:3 or 1:4 positions relative to one another. In the 12-keto-17-carbomethoxy compounds (XXXIV–XXXVI), where the carbonyl groups are 1:4, the 12-ketone maximum is displaced from 1706–1710 cm.$^{-1}$ to 1723 cm.$^{-1}$, but in XIV, which contains the 11-keto-17-carbomethoxy 1:5-grouping, there is a maximum at 1713 cm.$^{-1}$ the location normal to the 11-ketone. In a similar manner, the 1:4 diketone group of 11,17-diketones exhibits an interaction effect while the 1:5-diketone group of 11,20-diketones does not.

The most effective application of infrared spectrometry to the characterization of 11-oxygenated ketosteroids will result from a combination with chemical methods. Advantage might be taken of the inertness of the 11-ketone group to reaction with the common carbonyl reagents, whereby the carbonyl absorption bands of the more reactive 3, 12, 17 and 20 ketone groups could be removed, and the 11-ketone band observed in the spectrum of the derivative. The inertness of the 11-ketone group to reaction with the Girard reagent has already been utilized in this manner. The appearance of an intense band near 1713 cm.$^{-1}$ in the spectrum of a "non-ketonic" urinary steroid fraction led to the isolation and identification of pregnanediol-3$\alpha$,20-*epi*[b]-one-11.[12]

A similar method might be applied to characterize the unreactive 11$\beta$-hydroxyl group, which fails to acetylate under conditions which bring about acetylation of hydroxyl groups at 3, 12, 20, 21, and also at 17 in the androstane and etiocholane series. In the pregnane and allopregnane series the tertiary 17-hydroxyl group is also resistive to acetylation but can be made to react under mildly forcing conditions which still leave the 11$\beta$-hydroxyl group unattacked.[13]

The characterization of the readily acetylated 11$\alpha$-hydroxyl group will be more difficult, but this is of less consequence since it appears that in the naturally occurring steroid hormones and hormone metabolites the 11-hydroxyl group commonly occurs in the $\beta$ configuration.

## Experimental

The spectra were determined in carbon disulfide solution using a Perkin–Elmer model 12a spectrometer with sodium chloride prism and recording galvanometer. Full details of the

(12) Reported by Dr. S. Lieberman at the Laurentian Hormone Conference, St. Adele, Quebec, Sept., 1947.

(13) Long and Gallagher, *J. Biol. Chem.*, **162**, 511 (1946).

experimental techniques have been given in earlier publications.[2,3]

**Acknowledgments.**—The authors wish to acknowledge their indebtedness to the several investigators, listed individually in a footnote to Table I, whose collaboration in supplying many of the compounds made these studies possible. The technical assistance of Miss E. Packard of the Sloan–Kettering Institute is also gratefully acknowledged.

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## Summary

A comparative study has been made of the infrared absorption spectra between 1660 and 1780 cm.$^{-1}$ of ketosteroids containing a carbonyl group at positions 11 and 12.

A non-conjugated ketone group at position 11 gives rise to a maximum at 1710–1713 cm.$^{-1}$ in carbon disulfide solution. In 3,11- and 11,20-diketosteroids the maxima associated with the two carbonyl groups are too close to be separated, but there is no evidence of interaction effects causing displacements of the bands. In the 11,17-diketosteroids the band attributed to the 11-ketone group occurs at the normal position (1710–1713 cm.$^{-1}$) but the band attributed to the 17-ketone group is displaced from 1742–1745 to 1748–1754 cm.$^{-1}$.

Similar data are given also for 12-ketosteroids and the significance of these observations in the elucidation of steroid structure is discussed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

# The Dehydration of 22-Phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene

BY F. W. HEYL, M. E. HERR AND A. P. CENTOLELLA

The reaction of 3-acetoxy-bisnor-5-cholenaldehyde with phenylmagnesium bromide, yielding 22-phenyl-3,22-dihydroxy-bisnor-5-cholene (I) as well as the preparation of several analogous 22-phenyl-3-alkoxy-22-hydroxy-bisnor-5-cholenes from stigmasteryl ethers have been reported.[1,2] The problem of introducing a double bond into the C-20,22 position of the side chain involves the difficulties usually encountered in the dehydration of a secondary alcohol.

For the purpose of studying this dehydration reaction, it was decided to use 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene (III) which was prepared from stigmasteryl methyl ether as previously reported,[2] and also by refluxing the monotosylate (II) prepared from 22-phenyl-3,22-dihydroxy-bisnor-5-cholene (I), with methanol, whereby the same methoxy compound (III) is obtained and the position of this tosyl group is established.

The dehydration of this 3-methoxy-22-ol (III) was accomplished by using a variation of the method of Wuyts[3] in which the alcohol was refluxed in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid and a trace of phenol. The desired 22-phenyl-3-methoxy-bisnor-5,20-choladiene (IV) was obtained in good yields.

The 5,6 dibromo compound of the diene (IV) was ozonized directly to pregnene-3$\beta$-ol-20-one methyl ether (V) which was isolated as the semicarbazone in 62% yields. Acid hydrolysis of the semicarbazone resulted in a 92% yield of pregnenolone methyl ether (V). This compound was converted to pregnene-3$\beta$-ol-20-one acetate (VI), the immediate precursor of progesterone, according to the recently described method of Huffman and Lott.[4]

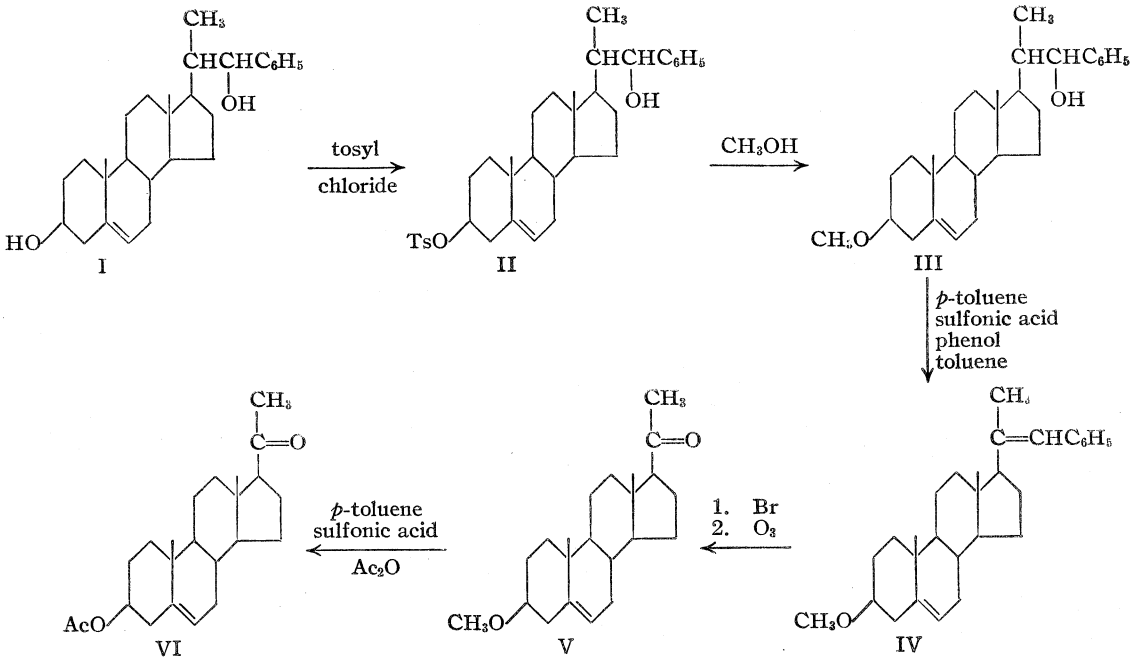
## Experimental[5]

**22-Phenyl-3,22-dihydroxy-bisnor-5-cholene-3-tosylate (II).** —To 3.14 g. of diol (I) dissolved in 25 ml. of dry pyridine was added 2.2 g. (1$^1/_2$ moles) of *p*-toluene-sulfonyl chloride. After standing twenty-four hours at 37° it was poured into ice and sodium bicarbonate (1 g.) and the tosyl ester extracted with benzene. The solution was dried over sodium sulfate and upon removing the benzene and remaining pyridine *in vacuo* there was obtained a quantitative yield of crystalline residue. Recrystallization from benzene–hexane gave 2.85 g. of silky needles, m. p. 157–159° (dec.). Working up the mother liquor gave a second crop of slightly lower melting tosyl ester.

*Anal.* Calcd. for $C_{35}H_{46}O_4S$: C, 74.69; H, 8.24; S, 5.7. Found: C, 74.82; H, 7.98; S, 5.7. $[\alpha]^{25}D$ −38.9 (79.1 mg. made up to 10 ml. in chloroform, $\alpha^{25}D$ −0.308, *l*, 1 dm.).

When the above esterification was carried out at room temperature most of the diol was recovered. When the

(1) Heyl, Centolella and Herr, THIS JOURNAL, **69**, 1957 (1947).
(2) Centolella, Heyl and Herr, *ibid.*, **70**, 2953 (1948).
(3) Wuyts, *Bull. soc. chim. Belg.*, **26**, 304 (1912).
(4) Huffman and Lott, *J. Biol. Chem.*, **172**, 793 (1948).
(5) Analyses and rotations by members of the Upjohn microanalytical group. Melting points are as read on Fisher–Johns melting point apparatus.




reaction was allowed to proceed twenty-four hours at 55–58° little of the desired tosyl ester could be obtained. Considerable material resulted which was insoluble in ether. When recrystallized from large volumes of acetone high melting fractions separated. One melting at 272–275° contained no sulfur and was not investigated further.

**22-Phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene (III).**—The above tosyl ester was refluxed for three hours with an amount of methanol sufficient to dissolve it and upon cooling an almost quantitative yield of crystals separated out. Recrystallized from methanol-chloroform, it melted at 205–206°, and, when mixed with the 3-methoxy-ol (III) previously reported,[2] there was no m. p. depression.

*Anal.* Calcd. for $C_{29}H_{42}O_2$: C, 82.43; H, 10.02. Found: C, 81.93; H, 9.9. $[\alpha]^{25}D$ −45.7 (0.09623 g. made up to 10 ml. with chloroform, $\alpha^{25}D$ −0.44, *l*, 1 dm.).

**22-Phenyl-3-methoxy-22-chloro-bisnor-5-cholene.**—0.42 g. of 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene was dissolved in 15 ml. of hot benzene and to this was added a slight excess of thionyl chloride and the mixture was refluxed for one hour. After removal of most of the solvent the chloro compound crystallized out. Recrystallized from hexane, it melted at 189–190°.

*Anal.* Calcd. for $C_{29}H_{41}OCl$: Cl, 8.04. Found: 8.20.

**22-Phenyl-3-methoxy-22-acetoxy-bisnor-5-cholene.**—250 mg. of 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene was dissolved in 20 ml. of dry pyridine and 5 ml. of acetic anhydride added. The mixture was refluxed one-half hour, cooled, and poured, with stirring, into a mixture of 15 ml. of concentrated hydrochloric acid and ice. This was extracted with ether, washed with saturated sodium bicarbonate solution and water, and dried over magnesium sulfate. Upon evaporating the solvent and recrystallizing the residue from chloroform–methanol the compound melted at 216–217°.

*Anal.* Calcd. for $C_{31}H_{44}O_3$: C, 80.12; H, 9.54. Found: C, 80.24; H, 9.59.

**22-Phenyl-3-methoxy-bisnor-5,20-choladiene (IV).**—500 mg. of 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene was dissolved in 200 ml. of toluene by heating and 20 mg. of phenol was added. The mixture was heated until the phenol was in solution and 50 mg. of *p*-toluene sulfonic acid monohydrate was added. The solution was refluxed eighteen hours, using a water trap. After cooling the solution was washed with five per cent sodium hydroxide and with water until neutral and the toluene was removed *in vacuo*. The crystalline residue was dissolved in 50 ml. of boiling benzene and, after cooling, the clear solution was passed over a column of 15 g. of activated alumina (Fisher adsorption), and the product eluted with benzene in 40 ml. fractions. The first four fractions in several runs weighed 305–370 mg. (60–75%) and were nicely crystalline. Recrystallized from methanol–chloroform the melting point was 166–169°.

*Anal.* Calcd. for $C_{29}H_{20}O$: C, 86.11; H, 9.97. Found: C, 86.45; H, 10.47.

**Pregnene-3β-ol-20-one Methyl Ether Semicarbazone.**—400 mg. of the diene (IV) was dissolved in 25 ml. of chloroform and, while cooling in an ice-bath, 0.158 g. of bromine in 5 ml. of chloroform was added dropwise with mechanical stirring. The ice cooled solution was ozonized for thirty minutes (*ca.* 7.2 mg. of ozone per minute). The solvent was removed *in vacuo* below 30° and the residue taken up in 20 ml. of glacial acetic acid and debrominated by careful addition of 0.5 g. of zinc dust. The product was extracted with ether, washed with 5% sodium hydroxide and then water till neutral. After drying the ether solution over sodium sulfate the solvent was removed to yield 0.34 g. of oily crystalline material having a strong odor of benzaldehyde. Upon refluxing this residue with 30 ml. of methanol, 3 ml. of water, 0.4 g. of semicarbazide hydrochloride and 0.4 g. of sodium acetate for one hour, the semicarbazone of V precipitated. After cooling, filtering and washing with water and a little methanol, 240 mg. of the semicarbazone was obtained, m. p. 224–228°. Recrystallized from methanol–chloroform it melted at 235–237°. A mixed m. p. with a sample of semicarbazone made from an authentic sample of pregnene-3β-ol-20-one methyl ether prepared according to the method of Butenandt and Gross[6] showed no depression.

*Anal.* Calcd. for $C_{23}H_{37}O_2N_3$: N, 10.84. Found: N, 10.76.

**Pregnene-3β-ol-20-one Methyl Ether (V).**—240 mg. of the semicarbazone was taken up in 50 ml. of methanol and 25 ml. of 5 *N* sulfuric acid was added. After refluxing one-half hour and diluting with 125 ml. of water the prod-

(6) Butenandt and Gross, *Ber.*, **70**, 1448 (1937).

uct was extracted with ether. The ether solution was washed with water till neutral and dried over sodium sulfate. Upon removing the ether 192 mg. of nicely crystalline product was recovered, m. p. 118–121°. When recrystallized from a small volume of dilute acetone it melted at 124–125° and did not depress the m. p. of an authentic sample of V.

*Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.37. Found: C, 79.68; H, 10.45.

**Pregnene-3β-ol-20-one Acetate (VI).**—80 mg. of pregnene-3β-ol-20-one methyl ether and 40 mg. of *p*-toluene sulfonic acid monohydrate was covered with 4 ml. of redistilled acetic anhydride and heated on a steam cone with stirring for one-half hour. The mixture was cooled and poured into ice-water with stirring, and allowed to stand two hours. The product was extracted with ether, washed with sodium bicarbonate solution and water and dried over sodium sulfate. Upon removing the solvent and recrystallizing the residue three times from dilute methanol the product melted at 143–144° and did not depress the melting point of an authentic sample of VI.

## Summary

1. The secondary carbinol, 22-phenyl-3-methoxy-22-hydroxy-bisnor-5-cholene (III), has been dehydrated in yields of 60–75% and the resulting diene (IV) has been degraded to give pregnene-3β-ol-20-one methyl ether (V).

2. The mono tosylate mentioned previously[1] has been shown to be 22-phenyl-3,22-dihydroxy-bisnor-5-cholene-3-tosylate (II).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF MEDICINE, NEW YORK UNIVERSITY]

# A Method for the Determination of Organic Compounds in the Form of Isotopic Derivatives.[1,2] I. Estimation of Amino Acids by the Carrier Technique

BY ALBERT S. KESTON, SIDNEY UDENFRIEND[3] AND R. KEITH CANNAN

In a preliminary communication[4] we have outlined a general method for the estimation of organic compounds in the form of isotopically labelled derivatives. The method is of particular value for the estimation of the components of mixtures of related compounds for which individual chemical methods of analysis are not available. We have applied it to the estimation of certain of the amino acids which are present in hydrolysates of proteins.

The mixture is treated with a reagent containing a stable or a radioactive isotope under such conditions that the components which are to be estimated are quantitatively converted into derivatives of the reagent. If any one of these derivatives can be separated quantitatively from the others, it can then be directly estimated[5] with the precision and sensitivity characteristic of isotopic measurements. In the analysis of mixtures of amino acids, however—and, indeed, of most biological materials—the quantitative separation of a single component is not always attainable. In this situation, the isotopic method may be applied with the aid of carrier or indicator techniques.[4,5]

In the carrier method, an overwhelming excess, $W$ moles, of the unlabelled derivative of the desired constituent is added to the mixture and is then separated and purified to constant molal isotope concentration, $Cc$. If $Cr$ be the molal isotope concentration of a pure isotopic derivative which has been prepared with the same sample of the reagent, then the amount of the isotopic derivative ($w$) which was present in the mixture is

$$w = Cc(w + W)/Cr$$

When relatively large amounts of the carrier are added, this equation reduces to

$$w = WCc/Cr$$

The carrier principle gives the method wide scope and flexibility. It makes it possible to carry out estimations of very minute amounts of the compound of interest and yet to operate with milligram quantities of material. It is, moreover unnecessary to seek a quantitative recovery of the compound in pure form. What is essential is the rigorous purification of the carrier from significant amounts of isotopic impurities. To accomplish this large losses of the product may be accepted. Finally, in the analysis of optically active compounds, the use of a large excess of a racemic carrier ensures the estimation of the total of both of the active forms. This is a significant advantage in the analysis of proteins in which indeterminate degrees of racemization may have occurred during hydrolysis. If, on the other hand, one wishes to estimate only one of the isomers the corresponding carrier may be used.

The validity and precision of the method which has been outlined depend primarily on, (a) the completeness of the reaction between the isotopic reagent and the compound which is to be estimated, (b) the rigorous purification from radioactive contaminants of the carrier after addition to and isolation from the reaction mixture and (c) the precision of the measurements of $Cc$ and $Cr$.

(1) Taken from a thesis submitted in December, 1947, by Sidney Udenfriend to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

(2) This work was done under a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

(3) Present address: Department of Biological Chemistry, Washington University School of Medicine, St. Louis, Mo.

(4) A. S. Keston, S. Udenfriend and R. K. Cannan, THIS JOURNAL, **68**, 1390 (1946).

(5) A. S. Keston, S. Udenfriend and M. Levy, *ibid.*, **69**, 3151 (1947).

In this communication, we describe in detail the application of the carrier technique to the estimation of glycine, alanine and proline in hydrolysates of proteins. The reagent which we have used is *p*-iodophenylsulfonyl chloride (pipsyl chloride) containing $I^{131}$. The evidence that the above analytical criteria are met in the estimation of these amino acids in mixtures will first be reviewed.

**The Reaction of Pipsyl Chloride with Amino Acids.**—In preliminary investigations[4] the amino acid was dissolved in a solution of carbonate and treated with a substantial excess of pipsyl chloride. The progress of the reaction was followed by the rate of disappearance of amino nitrogen as indicated by Folin's naphthoquinone reaction.[6] When all of the amino nitrogen had disappeared it was assumed that the sole product was the monosubstituted sulfonamide. In some later experiments, however, the presence of a small amount of a second radioactive product was observed. These products, which were obtained from alanine and isoleucine but not from glycine or proline, were well-defined crystalline substances, highly insoluble in water both as free acids and as potassium salts. They have not been rigorously identified but, since they have been found to contain two atoms of labelled iodine per atom of nitrogen, we may assume that they are the disubstituted sulfonamides (dipipsyl derivatives).

The attempt was made to drive the secondary reaction to completion with the object of using the dipipsyl derivatives as carriers. Good yields were obtained when a solution of aniline or of isoleucine in saturated potassium carbonate was shaken with a large excess of pipsyl chloride dissolved in acetone.[7] Under the best conditions, however, the secondary reaction attained only about 90% completion. The attempt to use the dipipsyl derivatives as carriers was, therefore, abandoned.

Re-investigation of the over-all reaction indicated that the second stage occurs to a significant extent only after substantial completion of the first. When a series of successive partial reactions is carried out with intermittent removal of the monopipsyl compound formed it has been possible, consistently, to recover 98–100% of the amino acid as the monopipsyl derivative. This manner of carrying out the reaction has been adopted as the standard analytical procedure. Mono- and dipipsyl carriers have been used to estimate the amounts of these two types of derivative which are formed under the standard conditions (Table I). In our experience, so little dipipsyl material is formed in a protein hydrolysate that the use only of a monopipsyl carrier gives results of sufficient accuracy. If desired, of course, a second estimation may be made using the dipipsyl carrier and correcting the monopipsyl estimation for any dipipsyl compound which may be found. Since proline and hydroxyproline are secondary amines, they cannot form dipipsyl compounds. Apparently glycine does not readily do so.

(6) O. Folin, *J. Biol. Chem.*, **51**, 377 (1922).

(7) The aqueous and acetone phases were immiscible in the presence of the high concentration of carbonate.

**The Purification of the Carriers.**—The radioactive impurities which may be expected to be present in a protein hydrolysate which has been treated with pipsyl chloride are the monopipsyl derivatives of the amino acids together with traces of the dipipsyl compounds of some of them, pipsyl amide arising from reaction with ammonia and *p*-iodophenyl sulfonic acid which is formed by the hydrolysis of the excess of pipsyl chloride. The pipsyl amino acids are readily extracted by ether from acid solutions and return to the aqueous phase when shaken with dilute ammonia. The iodophenyl sulfonic acid is not readily extracted by ether from dilute acid, whereas the pipsyl amide remains in the ether when shaken with ammonia. Thus the removal of the major radioactive contaminants from the pipsyl amino acids presents no great difficulty.

TABLE I

RECOVERY OF AMINO ACIDS AS THE MONOPIPSYL AND DIPIPSYL DERIVATIVES[a]

| Amino acid | Amount added, mg. | % recovered as monopipsyl | % recovered as dipipsyl | Total, % |
|---|---|---|---|---|
| Glycine | 1.000 | 100.2 | ...[b] | 100.2 |
| | 1.000 | 99.8 | ...[b] | 99.8 |
| D,L-Alanine | 1.000 | 98.7 | 1.3 | 100.0 |
| | 1.000 | 99.1 | 1.2 | 100.3 |
| D,L-Isoleucine | 2.000 | 98.0 | 1.5 | 99.5 |
| L-Proline | 3.232 | 98.6 | ...[c] | 98.6 |

[a] These recoveries are from analyses of the individual pure amino acids, using the standard procedure. [b] No dipipsyl derivative of glycine could be isolated for use as carrier. [c] Proline is a secondary amine and can form only the monosubstituted derivative.

A more difficult problem has been the separation of the carrier from traces of other pipsyl amino acids. We have found alternate repeated crystallization and treatment with charcoal to be effective though sometimes tedious. The free pipsyl amino acids are poorly soluble. Consequently, crystallization is readily carried out by acidification of an ammoniacal solution. The crystals may then be dissolved again in ammonia, treated with charcoal and recrystallized. This cycle must be repeated very many times before constant isotopic concentration is attained. The pipsyl derivatives of leucine and isoleucine, for example, are very difficult to separate from one another by crystallization. The purification of pipsylalanine in the presence of pipsylglycine or pipsylproline has also proved to be very tedious if crystallization alone is relied on.

The pipsyl amino acids, like the amino acids themselves (unpublished data), evidently have a strong tendency to co-precipitate. We have found that the phenomenon results in a distribution between the solid and the dissolved carrier as though the impurities were distributing between

two immiscible solvents. The distribution co-precipitation constant $k$ equals

$$\frac{\left(\frac{\text{Amount of impurity}}{\text{Amount of carrier}}\right)_{\text{Supernatant}}}{\left(\frac{\text{Amount of impurity}}{\text{Amount of carrier}}\right)_{\text{Crystals}}} = k$$

The absolute amount of the impurity has little effect on the magnitude of the distribution constant. Dilution of the isotopic impurity with its nonisotopic analog is thus of little value. The value of $k$ and the amount sacrificed determine the degree of purification in a crystallization. The various pipsyl amino acids have individual characteristic distribution coefficients in the presence of a particular carrier. The coefficients can be determined in simple experiments and are helpful in determining which particular pipsyl amino acid impurities will be difficult to remove from a given carrier.

When this type of distribution obtains, the efficiency of purification in relation to the amount of material lost increases as the number of crystallizations over which the loss is spread is increased. If the distribution coefficient is unfavorable, the asymptotic approach to isotopic purity is very slow. We accept a carrier as pure only when its isotope concentration has remained constant, within the error of measurement, through several recrystallizations and treatments with charcoal so conducted that there have been large losses of carrier.

The tedium of crystallization in some cases made it desirable to find other methods of purification. The work of Martin and Synge[8,9,10] on the distribution of the N-acetyl amino acids between solvent pairs was suggestive. Accordingly, we determined approximate distribution coefficients of the pipsyl amino acids between selected pairs of solvents. Representative results are given in Table II where the coefficient is expressed as the concentration in the organic phase divided by that in the aqueous phase.

The coefficients in Table II show wide characteristic differences. It is interesting to note from columns 4 and 5 that the relative coefficients of the pipsyl amino acids in a chloroform–water system closely parallel those of the acetyl amino acids. The range of distribution coefficients is so wide that some groups of pipsyl amino acids can be effectively separated from others by simple extraction. The leucine derivatives, for example, can be separated from those of the dicarboxylic acids by extracting an acid solution of the mixture with carbon tetrachloride.

Advantage may be taken of smaller differences in distribution by the use of an appropriate form of counter-current separation. For the separations with which this paper is concerned, we have found that a ten-plate discontinuous counter-current process of the type exploited by Craig[11] is adequate. The conduct of such a separation is described in a later section. From the crude fractions which are obtained, pure samples of the pipsyl derivatives of glycine, alanine and proline are readily obtained by crystallization. The adoption of this process of preliminary purification has made it possible to carry out several estimations on a single aliquot of a protein hydrolysate by adding several carriers to it prior to counter-current separation. Glycine, alanine and proline can be conveniently estimated in this way. We have also used the counter-current technique to ascertain the isotopic homogeneity of supposedly purified carriers.

The traces of dipipsyl derivatives which are formed in the reaction with pipsyl chloride tend to accumulate in the proline fraction of the counter-current process. They are difficult to remove by crystallization. The dipipsyl derivatives show a notable tendency to co-precipitate. We have been able to expedite the purification of pipsylproline by taking advantage of this characteristic. A small amount of sodium dipipsylalanine is added to an ammoniacal solution of the pipsylproline fraction and is then precipitated by addition of potassium chloride. This removes much of the radioactivity impurity in the fraction and facilitates final purification of the pipsylproline by crystallization.

TABLE II

DISTRIBUTION COEFFICIENTS OF SEVERAL PIPSYL AMINO ACIDS

Column I. Distribution coefficients of pipsyl derivatives between normal butanol and 0.2 *M* sodium hydroxide. Column II. Distribution coefficients of pipsyl derivatives between chloroform and 0.2 *M* hydrochloric acid. Column III. Distribution coefficients of pipsyl derivatives between carbon tetrachloride and 0.2 *M* HCl. Column IV. Relative partition coefficients of pipsyl derivatives between chloroform and 0.2 *M* HCl; pipsylglycine as unity. Column V. Relative partition coefficients of the N-acetyl derivatives between chloroform and water; acetylglycine as unity.

| Amino acid | I | II | III | IV | V[a] |
|---|---|---|---|---|---|
| Glycine | 0.14 | 0.67 | 0.006 | 1 | 1 |
| Alanine | 0.13 | 3.25 | 0.04 | 4.8 | 3.5 |
| α-Aminoisobutyric acid | 0.59 | 7.0 | 0.11 | 10.5 | ... |
| Valine | 0.60 | 20.0 | 0.40 | 30 | 20 |
| Leucine | 1.5 | 43 | 1.2 | 64 | 85 |
| Isoleucine | 1.7 | 50 | 1.4 | 75 | 100 |
| Serine | 0.06 | 0.04 | 0.00 | 0.06 | 0.6 |
| Threonine | .. | ... | 0.00 | ... | ... |
| Methionine | 0.37 | ... | 0.26 | ... | 27 |
| Proline | .. | 28 | ... | 40 | 40 |
| Aspartic acid | 0.01 | 0.04 | 0.00 | 0.06 | ... |
| Glutamic acid | 0.02 | 0.04 | 0.00 | 0.06 | 0.6 |

[a] R. L. M. Synge, *Biochem. J.*, **33**, 1913 (1–4) (1939).

**Measurements.**—Two measurements are made on an aliquot of the carrier at each stage of purification until constant specific activity is

(8) A. J. P. Martin and R. L. M. Synge, *Biochem. J.*, **35**, 91 (1941).
(9) A. J. P. Martin and R. L. M. Synge, *ibid.*, **35**, 1358 (1941).
(10) R. L. M. Synge, *ibid.*, **33**, 1913 (1–4) (1939).
(11) L. C. Craig, *J. Biol. Chem.*, **155**, 519 (1944).

TABLE III

PROPERTIES OF PIPSYL DERIVATIVES OF SEVERAL AMINO ACIDS

| Pipsyl amino acid | Melting point (cor., °C.) | Mol. extinct. coeff. at 250 mμ × $10^{-3}$ | Neutralization equivalent Found | Neutralization equivalent Theoretical |
|---|---|---|---|---|
| Glycine | 205–205.5 | 15.9 | 339.6 | 341.0 |
| DL-Alanine | 194.5 | 15.8 | 355.3 | 355.0 |
| D-Alanine | ... | 15.8 | 356.2 | 355.0 |
| Aminoisobutyric acid | 183.0 | .. | 372.0 | 369.1 |
| DL-Valine | 181.5 | .. | ... | ... |
| DL-Leucine | 125.5–126.5 | .. | ... | ... |
| DL-Isoleucine | 149.0 | 15.8 | 397.6 | 397.0 |
| DL-Serine | 209.5 (dec.) | 15.7 | ... | ... |
| DL-Methionine | 127.0 | .. | 416.7 | 416.0 |
| DL-Proline | ... | 16.5 | ... | ... |
| L-Proline | 126.0 | 16.5 | 384.0 | 382.0 |
| DL-Aspartic acid | 182.0–184.0 | .. | ... | ... |

attained. The first is a measurement of the amount of carrier which remains. This may be done conveniently on a very small sample by measuring the absorption at 250 mμ (Table III). The second is a measurement of radioactivity. We use a double-walled thin glass cylinder[12] which is slipped over a Geiger–Müller counter filled with tetramethyllead vapor[13] together with a Technical Associates model GS-4 scaling unit.

sis. This corrects for radioactive decay. The standard is purified by extraction into ether and re-extraction into dilute alkali followed by recrystallization. A solution of the purified material is prepared, standardized photometrically and used in all assays.

The spectrophotometric measurements may be made with an accuracy better than 0.5%. The measurement of radioactivity, when carried out as described, is capable of a high degree of accuracy. The probable error due to randomness of counting is equal to $1.67\sqrt{A + 2B}$, where $A$ is the number of counts of the sample and $B$ is the background count. We have routinely relied on observations involving 5,000–10,000 counts in a two-minute period. With a background count of 20 the error due to randomness is about 1%. Several two-minute counts have been averaged to reduce this error.

The procedure which is described in the section headed "Analytical Procedure" has been applied to the estimation of glycine, alanine and proline in a mixture of pure synthetic amino acids (Table IV) and to the acid hydrolysates of four crystalline proteins for which some comparative analytical data are available (Tables V–VIII). Control estimations have also been carried out on amino acid mixtures from which the particular amino acid to be estimated was omitted.

In the absence of the amino acid, it has in all

TABLE IV

RECOVERY OF ADDED AMOUNTS OF GLYCINE, ALANINE AND PROLINE FROM A MIXTURE[a] OF AMINO ACIDS

| Added γ | Glycine carrier remaining at various stages of purification % | Amino acid found at corresponding stages γ | Added γ | Alanine[b] carrier remaining at various stages of purification % | Amino acid found at corresponding stages γ | Added γ | Proline carrier remaining at various stages of purification % | Amino acid found at corresponding stages γ |
|---|---|---|---|---|---|---|---|---|
| 0.00 | 40.5 | 24.5 | 0.00 | 15.6 | 18.5 | 0.00 | 27.5 | 4.60 |
| | 30.0 | 12.0 | | 12.2 | 5.0 | | 20.6 | 0.48 |
| | 17.6 | 4.2 | | 10.0 | 3.0 | | 16.5 | 0.00 |
| | 11.1 | 1.2 | | 8.4 | 1.55 | | | |
| | 9.1 | 0.11 | | 7.5 | 0.67 | | | |
| | | | | 6.2 | 0.08 | | | |
| 50.0 | 17.9 | 50.5 | 99.5 | 24.1 | 97.5 | 80.8 | 42.0 | 81.1 |
| | 14.7 | 50.1 | | 18.4 | 96.4 | | 30.5 | 82.9 |
| | 11.3 | 50.6 | | 14.7 | 99.3 | | 19.5 | 80.6 |
| | Average | 50.4 | | Average | 97.7 | | Average | 81.5 |
| 50.0 | 18.5 | 51.0 | 99.5 | 23.9 | 102.1 | 80.8 | 42.0 | 81.1 |
| | 13.8 | 50.7 | | 19.8 | 102.1 | | 33.1 | 81.7 |
| | 9.9 | 50.4 | | 16.3 | 99.6 | | 23.1 | 80.9 |
| | Average | 50.7 | | Average | 101.3 | | Average | 81.2 |

[a] The amino acid mixture contained 150 μg of leucine and of lysine, 110 μg of glutamic acid, 100 μg of isoleucine and of phenylalanine, 99.5 μg of alanine, 80.8 μg of proline, 50 μg of threonine, of glycine and of valine and 25 μg each of methionine and aspartic acid. In all cases (except glycine) the synthetic racemic forms were used. In the control analyses the glycine, alanine and proline were omitted from the mixture. [b] The value for alanine is corrected for 1.3% dipipsylalanine.

With each set of determinations of the unknown counts are also made of a standard solution of an isotopic monopipsyl derivative prepared from the same radioactive reagent as is used in the analy-

cases been possible to purify the carrier to an isotopic concentration corresponding to a negligible content of the amino acid in the mixture analyzed. In the presence of the amino acid, very satisfactory recoveries have been recorded on mixtures of known composition.

(12) E. Chargaff, *J. Biol. Chem.*, **128**, 579 (1939).

(13) A. S. Keston, *Rev. Sci. Inst.*, **14**, 295 (1943).

TABLE V

ANALYSIS OF β-LACTOGLOBULIN, 15.6% NITROGEN[a]

| Amino acid | Amount of protein employed, mg. | Amount of carrier added, mg. | Carrier remaining, % | Grams of amino acid per 100 g. of protein | Values in the literature |
|---|---|---|---|---|---|
| Glycine | 1.319 | 200.0 | 11.5 | 1.62 | |
| | | | 8.2 | 1.56 | |
| | | | 5.6 | 1.57 | |
| | | | Average | 1.58 | |
| | 1.319 | 200.0 | 14.7 | 1.49 | 1.5[d] |
| | | | 11.7 | 1.57 | 1.4[a] |
| | | | 8.6 | 1.56 | |
| | | | Average | 1.54 | |
| Alanine | 1.319 | 300.0 | 13.5 | 7.14 | |
| | | | 7.9 | 7.09 | |
| | | | 6.5 | 7.11 | 6.64[e] |
| | | | Average | 7.11 | |
| | 2.638 | 300.0 | 22.0 | 6.87 | 6.2[a] |
| | | | 18.4 | 6.96 | |
| | | | 14.3 | 7.09 | 6.2[f] |
| | | | 9.9 | 7.08 | |
| | | | Average | 7.00 | |
| D-Alanine[b] | 2.000 | 200.0 | 7.4 | 0.1 | |
| Proline (total) | 2.638 | 200.0 | 49.4 | 4.74 | |
| | | | 41.8 | 4.80 | |
| | | | 31.8 | 4.82 | |
| | | | Average | 4.79 | |
| | 2.638 | 200.0 | 48.8 | 4.96 | 4.1[a] |
| | | | 41.1 | 4.80 | |
| | | | 35.6 | 4.90 | 5.4[f] |
| | | | Average | 4.89 | |
| L-Proline[c] | 2.638 | 200.0 | 16.1 | 4.86 | |
| | | | 10.4 | 4.94 | |
| | | | 6.7 | 4.83 | |
| | | | Average | 4.88 | |

[a] E. Brand, L. J. Saidel, W. H. Goldwater, B. Kassel and F. J. Ryan, THIS JOURNAL, **67**, 1524 (1945). [b] The pipsyl derivative of D-alanine was used as carrier in this determination. [c] The derivative of the natural form of proline was used as carrier in this case. [d] G. L. Foster, *J. Biol. Chem.*, **159**, 431 (1945). [e] A. C. Chibnall, *J. Intern. Soc. Leather Trades' Chemists*, **30**, 1 (1946). [f] G. R. Tristram, *Biochem. J.*, **40**, 721 (1946).

TABLE VI

ANALYSIS OF HUMAN HEMOGLOBIN, 16.9% NITROGEN[a]

| Amino acid | Amount of protein employed, mg. | Amount of carrier added, mg. | Carrier remaining, % | Grams of amino acid per 100 g. of protein | Values in the literature |
|---|---|---|---|---|---|
| Glycine | 2.056 | 160.0 | 7.6 | 4.52 | |
| | | | 5.7 | 4.44 | |
| | | | 4.0 | 4.42 | |
| | | | Average | 4.46 | |
| | 2.056 | 160.0 | 21.6 | 4.48 | |
| | | | 16.9 | 4.54 | |
| | | | 13.2 | 4.44 | |
| | | | Average | 4.49 | |
| Alanine (total) | 2.056 | 300.0 | 23.3 | 10.20 | |
| | | | 17.3 | 9.75 | |
| | | | 13.2 | 10.30 | |
| | | | Average | 10.08 | |
| | 2.056 | 300.0 | 25.2 | 9.85 | 9.9[b] |
| | | | 19.1 | 9.70 | |
| | | | 15.9 | 9.90 | |
| | | | Average | 9.82 | |
| Proline (total) | 2.056 | 160.0 | 57.8 | 5.06 | |
| | | | 49.1 | 4.88 | |
| | | | 37.1 | 4.93 | |
| | | | Average | 4.96 | |
| | 2.056 | 160.0 | 42.3 | 4.90 | |
| | | | 30.7 | 5.02 | |
| | | | 25.1 | 4.85 | |
| | | | Average | 4.92 | |
| Isoleucine | 2.000 | 200.0 | .. | <0.2 | 0.7[c] |
| | | | | | 0.30[d] |
| | 2.000 | 200.0 | .. | <0.5 | 0[e] |

[a] H. B. Vickery, *J. Biol. Chem.*, **144**, 719 (1942). [b] J. Roche and M. Mourgue, *Trav. membres soc. chim. biol.*, **23**, 1329 (1941). [c] A. A. Albanese and T. M. Barnes, *J. Biol. Chem.*, **157**, 613 (1945). [d] H. B. Devline and C. A. Zittle, *J. Biol. Chem.*, **156**, 393 (1944). [e] E. Brand and J. Grantham, THIS JOURNAL, **68**, 724 1946).

The four proteins were hydrolyzed in 6 *M* hydrochloric acid for about twenty hours in sealed tubes at 110–120°. The amount of protein was based on the weight of an air-dried sample and corrected for the moisture which was determined by drying to constant weight at 110°. The hydrolysates were partially neutralized and diluted to contain about 5–10 mg. protein per ml. For analysis, an aliquot was measured with a constriction micro pipet,[14] transferred to a Folin sugar tube, neutralized and analyzed by the procedure described below.

The alanine and proline carriers were prepared from the DL amino acids except in two cases noted in the tables. The isoleucine carrier used in the hemoglobin analysis was prepared from a sample of the synthetic product which was stated to be free from leucine (The Winthrop Chemical Co.). The analyses recorded in the tables for alanine include a correction of 1.3% for the amount of dipipsylalanine presumed to have been formed (Table I). No corrections have been applied to the glycine and proline results.

The samples of β-lactoglobulin[15] and of crystalline human hemoglobin[16] were prepared in this Laboratory. The crystalline preparations of aldolase and phosphoglyceric aldehyde dehydrogenase of rabbit skeletal muscle were supplied by Dr. S. F. Velick of Washington University, St. Louis.

In the analysis of β-lactoglobulin, the estima-

(14) M. Levy, *Compt. rend. Lab. Carlsberg*, **21**, No. 6, 101 (1936).

(15) A. H. Palmer, *J. Biol. Chem.*, **104**, 359 (1934).

(16) R. K. Cannan and J. Redish, "Blood Substitutes and Blood Transfusions," Charles C. Thomas, Publisher, 1942, p. 147.

TABLE VII

ANALYSIS OF ALDOLASE (RABBIT SKELETAL MUSCLE), 16.8% NITROGEN[a]

| Amino acid | Amount of protein employed, mg. | Amount of carrier added, mg. | Carrier remaining, % | Grams of amino acid per 100 g. of protein | Values in the literature |
|---|---|---|---|---|---|
| Glycine | 1.426 | 200.0 | 21.3 | 5.62 | |
| | | | 16.8 | 5.70 | |
| | | | 11.0 | 5.65 | |
| | | | Average | 5.66 | 6.12[a] |
| | 1.426 | 300.0 | 30.0 | 5.55 | |
| | | | 24.0 | 5.55 | |
| | | | 19.0 | 5.56 | |
| | | | Average | 5.55 | |
| Alanine | 1.426 | 301.2 | 16.8 | 8.79 | |
| | | | 10.9 | 8.68 | |
| | | | 6.7 | 8.70 | |
| | | | Average | 8.72 | 7.87[a] |
| | 1.426 | 301.2 | 26.2 | 8.43 | |
| | | | 20.7 | 8.43 | |
| | | | 14.5 | 8.48 | |
| | | | Average | 8.45 | |
| Proline | 1.426 | 160.0 | 20.5 | 5.90 | |
| | | | 13.3 | 5.85 | |
| | | | 9.6 | 5.92 | |
| | | | Average | 5.89 | |
| | 1.426 | 160.0 | 45.6 | 5.80 | |
| | | | 36.4 | 5.61 | |
| | | | 29.3 | 5.68 | |
| | | | Average | 5.69 | |

[a] S. F. Velick and F. Ronzoni, *J. Biol. Chem.*, **173**, 627 (1948).

TABLE VIII

ANALYSIS OF PHOSPHOGLYCERALDEHYDE DEHYDROGENASE (RABBIT SKELETAL MUSCLE), 16.4% NITROGEN[a]

| Amino acid | Amount of protein employed, mg. | Amount of carrier added, mg. | Carrier remaining, % | Grams of amino acid per 100 g. of protein | Values in the literature |
|---|---|---|---|---|---|
| Glycine | 1.925 | 200.0 | 22.3 | 5.90 | |
| | | | 18.0 | 5.94 | |
| | | | 13.2 | 6.08 | 6.15[a] |
| | | | Average | 5.97 | |
| | 1.925 | 200.0 | 19.7 | 6.13 | |
| | | | 16.0 | 6.10 | |
| | | | 9.0 | 6.10 | |
| | | | Average | 6.11 | |
| Alanine | 1.925 | 301.2 | 16.1 | 6.80 | |
| | | | 10.9 | 6.66 | |
| | | | 6.9 | 6.66 | |
| | | | Average | 6.71 | 5.92[a] |
| | 1.925 | 301.2 | 16.6 | 6.64 | |
| | | | 11.1 | 6.81 | |
| | | | 7.7 | 6.82 | |
| | | | Average | 6.76 | |
| Proline | 1.925 | 160.0 | 29.0 | 3.65 | |
| | | | 20.8 | 3.58 | |
| | | | 16.1 | 3.57 | |
| | | | Average | 3.60 | |
| | 1.925 | 160.0 | 31.6 | 3.78 | |
| | | | 24.8 | 3.82 | |
| | | | 20.8 | 3.81 | |
| | | | Average | 3.80 | |

[a] S. F. Velick and F. Ronzoni, *J. Biol. Chem.*, 173, 627 (1948). Attention is drawn to an error in the text of this paper (p. 637). The glycine content of the dehydrogenase given as 6.88 per cent. by the isotopic derivative method should be corrected to 6.04 and the value for microbiological assay given as 6.98 per cent. should be corrected to 6.15. The correct values are those in the tables in the same article.

tion of total proline and of L-proline are in excellent agreement. The D-alanine estimation is a maximum one because constant isotope concentration was not attained. It is evident, however, that no significant amount was present in the hydrolysate. The same comment applies to the isoleucine estimation of human hemoglobin. This protein contains a large amount of leucine which, at the present stage of development of the method, is not easily separated from isoleucine.

## Analytical Procedure

The procedure described below for the determination of glycine, alanine and proline in a single sample is given in detail to illustrate the use of more than one carrier.

To a Folin sugar tube, containing an amount of hydrolysate corresponding to 0.3–2 mg. protein, are added 15 mg. of sodium bicarbonate, 9 mg. of radioactive pipsyl chloride and water to a volume of 0.6 ml. The tube is placed in a boiling water-bath. When the pipsyl chloride has melted, the tube is agitated with an efficient vibrator for a few minutes. We have used an electrical massaging unit so attached to the ring stand holding the reaction tube as to produce high frequency-short amplitude vibrations sufficient to emulsify the pipsyl chloride and water.

After ten minutes the tube is cooled and acidified with 0.2 ml. of *M* hydrochloric acid. A glass bead and 2 ml. of ether are added and the pipsyl derivatives are extracted into the organic solvent. The ether is transferred by a rubber-bulb pipet to a vessel containing measured amounts (about 200 mg. each) of the appropriate carriers in ammoniacal solution. Three more extractions with ether are made and the extracts are transferred without loss to the carrier mixture. The contents of the sugar tube are reduced to dryness by heat and suction, 9 mg. of pipsyl chloride, 15 mg. of sodium bicarbonate and 0.6 ml. of water are added and the reaction is repeated as before. The mixture is acidified and extracted with ether and then is submitted to a third reaction with 12 mg. of pipsyl chloride.

The vessel containing the carriers and the combined ether extracts is warmed to remove the ether. Water and hydrochloric acid are added to make a final volume of 150 ml. of approximately 0.2 *M* hydrochloric acid and the solution is transferred to the first of ten numbered 500-ml. separating funnels. The succeeding funnels each contain 150 ml. of 0.2 *M* hydrochloric acid. To the first funnel is added 150 ml. of chloroform and the mixture is shaken to establish equilibrium. The chloroform layer is then passed on to the succeeding funnel. This procedure is continued until chloroform reaches the tenth funnel. The distribution of the components at this point may be calculated from their distribution coefficients with the aid

TABLE IX

THE CALCULATED DISTRIBUTIONS OF THE PIPSYL DERIVATIVES OF GLYCINE, ALANINE AND PROLINE BETWEEN CHLOROFORM AND DILUTE HYDROCHLORIC ACID, IN A TEN-PLATE COUNTER-CURRENT DISTRIBUTION

| Compound | Phase | Per cent. of compound in each separatory funnel (funnel number) 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Glycine | Aqueous | 0.60 | 3.7 | 9.7 | 14.9 | 15.0 | 10.0 | 4.5 | 2.2 | 0.22 | 0.01 |
| | Solvent | .40 | 2.4 | 6.4 | 9.9 | 9.9 | 6.7 | 3.0 | 0.86 | .14 | .01 |
| Alanine | Aqueous | .00 | 0.00 | 0.00 | 0.06 | 0.34 | 1.4 | 3.6 | 5.9 | 6.0 | 2.7 |
| | Solvent | .00 | .00 | .02 | .22 | 1.4 | 5.6 | 14.3 | 23.7 | 24.1 | 10.7 |
| Proline | Aqueous | .00 | .00 | .00 | .00 | 0.00 | 0.00 | 0.00 | 0.1 | 0.7 | 2.4 |
| | Solvent | .00 | .00 | .00 | .00 | .00 | .00 | .2 | 2.7 | 21.3 | 72.6 |

of the binomial expansion (Table IX). The experimental distributions have agreed well with those calculated.

By pooling the fractions as indicated below, one obtains pipsylglycine substantially free from the pipsyl derivatives of proline and alanine. The latter are combined in a single fraction from which pipsylproline may be removed by extraction with a mixture of chloroform and carbon tetrachloride.

**Glycine Carrier.**—The chloroform phase of funnels 2, 3 and 4 and the aqueous phase of funnels 3, 4 and 5 are combined and made alkaline (Table IX). The aqueous phase, which now contains the pipsylglycine is acidified and extracted with about 100 ml. of normal butanol. The butanol is washed with several volumes of water and then mixed with about 200 ml. of petroleum ether. The mixture is extracted twice with 10 ml. of 0.2 *M* NaOH and the alkaline extract is treated with charcoal and filtered into a centrifuge tube. Upon acidification with hydrochloric acid, pipsylglycine crystallizes out. The product is submitted to repeated alternate recrystallizations and charcoal treatments to constant specific activity.

**Alanine Carrier.**—The chloroform phase of funnel 8 and both phases of funnels 9 and 10 are combined, made alkaline and shaken. The aqueous layer is acidified with hydrochloric acid and extracted five times with a 60:40 mixture by volume of chloroform and carbon tetrachloride. The first three extracts are pooled for the proline estimation and the last two are discarded. The aqueous phase, which contains the pipsylalanine is extracted with butanol and further purified in the manner described for pipsylglycine.

**Proline Carrier.**—The three pipsylproline extracts referred to above are pooled and extracted twice with 10 ml. of 0.2 *M* NaOH. The alkaline solution is treated with dipipsylalanine and potassium chloride as described in an earlier section and is then further purified in the same way as the pipsylglycine.

**The Preparation of Non-Isotopic Pipsyl Chloride.**—This has been prepared in kilogram quantities for use in the preparation of carriers. *p*-Diazobenzene sulfonic acid is prepared[17] in quantities of about 100 g. at a time and treated with potassium iodide, while still wet, to yield *p*-iodophenyl sulfonic acid.[18]

The sodium salt of the latter is salted out with sodium chloride and dried. The acid chloride is prepared from this by addition of phosphorus pentachloride in phosphorus oxychloride. After reaction, the mixture is dissolved in benzene, washed with ice-water to remove phosphorus halides and dried over anhydrous sodium sulfate. Further purification by vacuum distillation below 150° is desirable. The acid chloride crystallizes on addition of excess of petroleum ether to the benzene solution in colorless crystals melting at 86° (literature, 86–87°).[19]

**The Synthesis of Isotopic Pipsyl Chloride.**—Quantities of a few hundred milligrams have been made at one time. For reasons of economy and sensitivity, the method of synthesis has been so modified as to incorporate as much as possible of the $I^{131}$ into the product. The progress of the synthesis is controlled by radioactive counts on the intermediate products.

**Isotopic Synthesis.**—To the radioactive iodine,[20] in solution, in the form of iodide ion, is added sufficient potassium iodide to make a total of 25 mg. The solution is adjusted to a *p*H above 7 and evaporated to a volume of less than 0.5 ml. The sample is transferred quantitatively, with the aid of several small portions of water, to a Pyrex test-tube and the volume is reduced to about 0.2 ml. A few small crystals of sodium sulfite are added. After cooling, an equal volume of concentrated hydrochloric acid is added followed by 25 mg. of diazobenzenesulfonic acid. After the initial evolution of nitrogen the sample is warmed to complete the reaction. The tube is cooled again and another 15 mg. each of diazobenzenesulfonic acid and potassium iodide are added and allowed to react as before. The reaction mixture is then saturated with sodium chloride and cooled, whereupon the sodium salt of *p*-iodophenylsulfonic acid crystallizes out. The crystals are centrifuged down and washed with brine. The combined mother liquor and washings are warmed and about 40 mg. of non-isotopic sodium iodophenylsulfonate, in solution in a small volume of water, is added. Upon cooling, the added sodium salt crystallizes out carrying down residual isotopic analog. This is also centrifuged down and washed with brine and the procedure repeated. The separate batches of sodium salt are dried and then each is dissolved in about one ml. of phosphorus oxychloride containing a substantial excess of phosphorus pentachloride. The batches are pooled and the mixture is heated gently to ensure reaction. The reaction mixture is transferred to a separatory funnel containing ice-water and about 50 ml. of benzene. Small portions of benzene are used to facilitate the transfer from the test tubes to the funnel. At this point, approximately 200 mg. of pure non-isotopic pipsyl chloride is added. The benzene layer is washed several times with cold water to remove excess phosphorus halides. The rate of hydrolysis of pipsyl chloride is negligible, under these conditions, as is indicated by the absence of any appreciable amounts of radioactivity in the wash water. The benzene solution is dried over anhydrous sodium sulfate and the drying agent is washed with benzene until it is substantially free of radioactivity.

The combined benzene solution is evaporated to a small volume and transferred to a cold finger micro-distillation apparatus. The benzene is evaporated in a stream of air and the pipsyl chloride is distilled onto the cold finger at 150° at a few mm. of mercury pressure. The distilled material is washed into a vessel with a minimum of benzene. At this point more non-isotopic pipsyl chloride

(17) C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, p. 109.

(18) C. Weygand, *ibid.*, p. 112.

(19) W. Lenz, *Ber.*, **10**, 1136 (1877).

(20) The radioactive iodine used in the early part of the work was obtained through the kindness of Dr. Robley D. Evans of the Department of Physics at the Massachusetts Institute of Technology. The $I^{131}$ used more recently in this investigation was supplied by the Clinton Laboratories on allocation from the U. S. Atomic Energy Commission. An irradiation unit containing approximately 100 millicuries of $I^{131}$ was used for each isotopic synthesis. The $I^{131}$ was separated from the tellurium by a procedure developed in this Laboratory (M. Levy, A. S. Keston and S. Udenfriend, THIS JOURNAL, **70**, 2289 (1948)). Isotopic pipsyl chloride was prepared at approximately six-week intervals.

may be added to make a desired specific activity. The pipsyl chloride must be completely dissolved and thoroughly mixed to ensure isotopic homogeneity. Recrystallization may be achieved by adding petroleum ether to the benzene and concentrating the solution. The small amount of residual solvent is then drawn off with a capillary pipet and the crystals are dried at 70° for about one hour. The reagent has been successfully used even when the last recrystallization was omitted.

**The Synthesis of Pipsyl Amino Acids for Use as Carriers.**—In the case of the monobasic amino acids, an excess of amino acid, in aqueous solution, is heated with pipsyl chloride in the presence of enough sodium bicarbonate to neutralize the acids formed during the reaction. Efficient stirring must be provided and the temperature maintained near boiling until the pipsyl chloride has all reacted. Potassium chloride is then added to precipitate some dipipsyl impurities which have very insoluble potassium salts and the reaction mixture is treated with activated charcoal and filtered. Crystals of the derivative generally appear after acidification and cooling of the filtrate. If they do not, the compound may be extracted into ether or ethyl acetate and then returned to a small volume of alkali. Upon acidification, the crystalline derivative will then appear. The derivatives may be recrystallized either from hot water or from a mixture of acetone and water. The crystals are dried at 105°. The properties of a number of derivatives are given in Table III.

## Discussion

Hevesy and Hobbie[21] in 1932 were the first to use isotopes to overcome the difficulties of analytical methods which required the quantitative isolation of a pure sample from a mixture. They developed a microanalytical method for the analysis of lead in ores which involved adding a measured trace amount of radium D, which is isotopic with lead, to the dissolved ore and then separating a pure sample of lead from the mixture by standard chemical procedures. The total amount of lead present in the sample at the start of the analysis was then found by dividing the amount of lead isolated by the fraction of radioactivity recovered. The use of isotopically prepared organic compounds, in a manner similar to radium D in the analysis of lead, has come to be known as the isotope dilution method.[22,23,24]

The analysis of radioactive constituents in a mixture by carrier techniques has been a commonplace for a long time in the fields of radioactivity and its biological applications. The simplest statement of the new method described here is that the compounds of interest are converted into radioactive substances by direct chemical binding with a radioactive reagent.

The isotopic derivative method, presented here, has much higher sensitivity than the isotope dilution technique, being operable below the microgram level, and has the inherent specificity and accuracy characteristics of isotopic methods. One isotopic reagent suffices for the determination of many compounds. It is also possible to check analytical values with many reagents of different types. The use of large amounts of carrier makes possible rigorous isotopic purification. The use of large amounts of racemic carrier, moreover, enables one to estimate simultaneously both forms of an optically active compound, eliminating any errors that might arise due to racemization during preparation. The method may be made optically specific by using the appropriate enantiomorph as the carrier. Furthermore, the estimation of naturally occurring compounds whose syntheses present difficulties may be accomplished, since it is usually easier to prepare a derivative as a carrier than to synthesize the compound itself in isotopic form.

The significance of co-precipitation to the problem of the purification of isotopic compounds has been emphasized above. Co-precipitation is a phenomenon familiar to inorganic chemists.[25] It is evidently common in mixtures of related organic compounds also. We suggest that more attention should be paid to it in all tracer studies in which the tracer is isolated from a complex mixture and then purified.

The isotopic derivative method may also be applied where quantitative conversion to a derivative is not achieved. The addition of a trace amount of the compound to be determined, labelled with a second isotope which can be distinguished from that used in the reagent, enables one to calculate and correct for the extent of conversion to the derivative.

Pipsyl chloride has been applied to the determination of peptides in partial hydrolysates of proteins[26] and pipsyl chloride containing $S^{35}$ as the isotopic label has been made and used as an indicator in the application of the procedure to paper chromatography.[5] The application of the procedure to the systematic analysis of proteins, using both the carrier technique and paper chromatography, is now in progress.

## Summary

A new principle for the application of isotopes to the determination of organic compounds is introduced and its application to the determination of amino acids is presented.

A mixture is treated with an isotopic reagent to form quantitatively an isotopic derivative of the desired amino acid. A large excess of the unlabelled derivative is added as carrier and purified to constant isotope concentration. Knowing the specific radioactivity of the purified carrier and of a suitably prepared standard and also the fraction of carrier remaining after purification, one can calculate the quantity of amino acid present in the original mixture.

As reagent *p*-iodophenyl sulfonyl chloride (pipsyl chloride) containing $I^{131}$ was used.

(21) G. Hevesy and R. Hobbie, *Z. anal. Chem.*, **88**, 1 (1932).

(22) R. Schoenheimer, S. Ratner and D. Rittenberg, *J. Biol. Chem.*, **130**, 703 (1939).

(23) H. H. Ussing, *Nature*, **144**, 977 (1939).

(24) D. Rittenberg and G. L. Foster, *J. Biol. Chem.*, **133**, 737 (1940).

(25) I. M. Kolthoff and V. A. Stenger, "Volumetric Anal.," Vol. I, 2nd ed., 1942, pp. 182–205.

(26) M. Levy and E. Slobodiansky, *Federation Proc.*, **7**, 168 (1948).

The method has extremely high sensitivity, being operable below the microgram level, and has the inherent specificity and accuracy characteristic of isotope techniques.

Recoveries of added amounts of glycine, alanine and proline from a mixture of twelve synthetic amino acids are reported to demonstrate the accuracy and specificity of the analytical procedure.

Values are reported for the glycine, alanine and proline contents of the crystalline proteins β-lactoglobulin, human hemoglobin, aldolase and phosphoglyceraldehyde dehydrogenase.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TENNESSEE AGRICULTURAL & INDUSTRIAL STATE COLLEGE]

# Preparation and Reactions of Several Chlorine Substituted Phenoxyacetyl Chlorides

BY CARL M. HILL, MYRON B. TOWNS AND GILBERT SENTER

Chemical investigation involving study of the several phenoxy acetic acids and their derivatives has been chiefly concerned with their insecticidal and herbicidal activity. Of the six phenoxy substituted acetic acids (phenoxy, 2-chlorophenoxy, 4-chlorophenoxy, 2,4-dichlorophenoxy, 2,4,5-trichlorophenoxy and 2,4,6-trichlorophenoxy) the derivatives of the two trichloro acids described in this paper are not reported in the literature. It was of interest, therefore, to investigate the preparation and properties of these derivatives and to establish their identification.

Inasmuch as the phenyl esters (except phenyl phenoxyacetate) of the six acids mentioned above are not described in the literature, these were prepared and identified.

## Experimental

**Acids.**—The 2,4,5- and 2,4,6-trichlorophenoxyacetic acids were obtained from Dow Chemical Company and were purified by recrystallization from chloroform; 2,4,5-trichlorophenoxyacetic acid, m. p. 152–153° (uncor.) (lit.,[1] m. p. 154–55°), neut. equiv. calcd. for $C_8H_5O_3Cl_3$ 255.5, found, 257.7; 2,4,6-trichlorophenoxyacetic acid, m. p. 177–178° (uncor.), (lit.,[1,2] m. p., 190°, 177°), neut. equiv. found 256.0.

**2,4,5-Trichlorophenoxyacetyl Chloride.**—Into a round-bottomed flask equipped with a condenser set for reflux was placed 64 g. of 2,4,5-trichlorophenoxyacetic acid. One hundred and nineteen grams of purified thionyl chloride were added dropwise to the acid over a period of twenty-four hours. At the end of this time, the reaction mixture was refluxed on a steam-bath for two hours. The excess thionyl chloride was removed by distillation at atmospheric pressure. Distillation of the residue from a modified Claisen flask, under reduced pressure, gave 54.8 g. (80.0%) of 2,4,5-trichlorophenoxyacetyl chloride; b. p. 165–167° (6 mm.). This product was a waxy, white solid with a cocoanut-oil odor; m. p., 78–79° (uncor.).

*Anal.* Calcd. for $C_8H_4O_2Cl_4$: ionizable Cl, 12.94. Found: Cl, 12.46.

**2,4,6-Trichlorophenoxyacetyl Chloride.**—This compound was prepared by the method described for 2,4,5-trichlorophenoxyacetyl chloride using 64 g. of 2,4,6-trichlorophenoxyacetic acid; yield 61.6 g. (90.0%). This product was a waxy, white solid; b. p. 147–150° (5 mm.), m. p., 55–56° (uncor.).

*Anal.* Calcd. for $C_8H_4O_2Cl_4$: ionizable Cl, 12.94. Found: Cl, 13.03.

(1) Synerholm and Zimmerman, *Contrib. Boyce Thompson Institute*, **14**, 91 (1945); *Chem. Abst.*, **39**, 1474 (1946).

(2) Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).

Both chlorides were analyzed for ionizable chlorine according to the following procedure: Fifty ml. of ethanol, 15 ml. of 2 *M* potassium hydroxide and 0.5 g. of the acid chloride were refluxed for twenty minutes in an erlenmeyer flask attached to a water-cooled condenser. The solution was allowed to cool, after which 50 ml. of distilled water was added through the head of the condenser. The solution was transferred to a 400-ml. beaker and the washings from the flask were added. After acidifying the solution with 1:1 nitric acid, the chlorine was precipitated with 0.5 *M* silver nitrate. The solution was then heated, with stirring, and the precipitated silver chloride filtered. The precipitate was washed on filter with 1:1 nitric acid followed by ethanol, dried and weighed as silver chloride.

### Amides

**2,4,5-Trichlorophenoxyacetamide.**—To 0.5 g. of 2,4,5-trichlorophenoxyacetyl chloride was added a slight excess of concentrated ammonia and the mixture heated over a water-bath until precipitation of the amide was complete. The crude amide was filtered and recrystallized from dilute ethanol. The pure product was a white solid; m. p. 173–174° (uncor.), yield 0.50 g. (97.5%).

*Anal.* Calcd. for $C_8H_6O_2Cl_3N$: N, 5.50. Found: N, 5.81.

**2,4,6-Trichlorophenoxyacetamide.**—This amide was prepared in the manner described for the 2,4,5-trichlorophenoxyacetamide, starting with 0.5 g. of 2,4,6-trichlorophenoxyacetyl chloride. This product was a white crystalline solid; m. p. 195–196° (uncor.), yield 0.50 g. (98.0%).

*Anal.* Calcd. for $C_8H_6O_2Cl_3N$: N, 5.50. Found: N, 5.59.

### Ethyl Esters

**Ethyl 2,4,5-Trichlorophenoxyacetate.**—To 5 g. of 2,4,5-trichlorophenoxyacetyl chloride was added a slight excess of 95% ethanol. The mixture was heated under reflux for two hours, allowed to cool, and washed with a saturated solution of sodium bicarbonate and then with water. The crude ester was extracted with diethyl ether and the ethereal solution dried over anhydrous calcium chloride. After removal of the ether, the crude ester was recrystallized from dilute ethanol. This product was a white crystalline solid; m. p. 63–64° (uncor.), yield 5.1 g. (89%), sap. equiv. calcd. for $C_{10}H_9O_3Cl_3$ 283.6, found 281.0.

**Ethyl-2,4,6-Trichlorophenoxyacetate.**—Five grams of 2,4,6-trichlorophenoxyacetyl chloride was used; yield 2.8 g. (85%). This ester was a white crystalline solid; m. p. 33–34° (uncor.), sapn. equiv. found, 280.0.

### Anilides

**2,4,5-Trichlorophenoxyacetanilide.**—A solution of 5 g. of 2,4,5-trichlorophenoxyacetyl chloride and 15 ml. of chloroform was placed in an erlenmeyer flask. To this was added a slight excess of pure aniline. The reaction mixture was heated under reflux for thirty minutes and then allowed to cool. The crude anilide was filtered off

and recrystallized from dilute ethanol. This pure anilide was a white crystalline compound; m. p. 176–177° (uncor.), yield 4.4 g. (67%).

*Anal.* Calcd. for $C_{14}H_{10}O_2Cl_3N$: N, 4.25. Found: N, 4.52.

**2,4,6-Trichlorophenoxyacetanilide.**—This compound was prepared according to the procedure described for 2,4,5-trichlorophenoxyacetanilide using 5 g. of the corresponding acyl chloride. This anilide was a white crystalline solid; m. p. 107–108° (uncor.), yield 4.1 g. (63%).

*Anal.* Calcd. for $C_{14}H_{10}O_2Cl_3N$: N, 4.25. Found: N, 4.20.

### Phenyl Esters

**Phenyl Phenoxyacetate.**[3]—To 5 g. of phenoxyacetyl chloride in an erlenmeyer flask was added dropwise an alkaline solution containing an equivalent amount of phenol dissolved in 10% sodium hydroxide. The reaction mixture was heated over a steam-bath for thirty minutes and then cooled. The ester crystallized out and was purified by recrystallization from dilute ethanol. The white crystalline product melted at 56–57° (uncor.); yield 5.0 g. (73%), sapn. equiv. calcd. for $C_{14}H_{12}O_2$ 228.0, found 224.0.

**Phenyl 2-Chlorophenoxyacetate.**—This phenyl ester was prepared from the corresponding acyl chloride according to the procedure described for phenyl phenoxyacetate. Five grams of the acyl chloride gave 4.9 g. (80%) of phenyl 2-chlorophenoxyacetate, a white crystalline solid; m. p., 58–59° (uncor.); sapn. equiv. calcd. for $C_{14}H_{11}O_3Cl$, 262.7, found, 262.2.

**Phenyl 4-Chlorophenoxyacetate.**—Used 5 g. of 4-chlorophenoxyacetyl chloride. This phenyl ester melted at 73–74° (uncor.); yield, 4 g. (63.5%); sapn. equiv. calcd. for $C_{14}H_{11}O_3Cl$, 262.7, found, 276.0.

**Phenyl 2,4-Dichlorophenoxyacetate.**—This compound was prepared from 5 g. of 2,4-dichlorophenoxyacetyl chloride by the method described for phenyl phenoxyacetate. Recrystallization of the ester from dilute ethanol gave 5.1 g. (82%) of product; m. p., 100–101° (uncor.); sapn. equiv. calcd. for $C_{14}H_{10}O_3Cl_2$ 297.2, found 301.5.

**Phenyl 2,4,5-Trichlorophenoxyacetate.**—A solution of 5 g. of the acyl chloride and an equivalent amount of phenol dissolved in 10% sodium hydroxide was treated as described for the preparation of phenyl phenoxyacetate. Recrystallization from dilute ethanol gave 4 g. (70%) of white crystalline product; m. p., 116–117° (uncor.), sapn. equiv. calcd. for $C_{14}H_9O_3Cl_3$ 331.6, found 336.0.

**Phenyl 2,4,6-Trichlorophenoxyacetate.**—Five grams of 2,4,6-trichlorophenoxyacetyl chloride and an equivalent amount of phenol were used in alkaline solution. The resulting phenyl ester was recrystallized from dilute ethanol. The yield of ester was 4.5 g. (75%); m. p. 84.5–85° (uncor.), sapn. equiv. found 332.0.

Determination of the saponification equivalents of the six phenyl esters presented several experimental difficulties. Because of the formation of phenol upon acidification of the hydrolytic mixture, certain experimental errors were introduced which rendered the usual procedure employed for determination of saponification equivalents inaccurate and unreliable.

Therefore, the following procedure was employed. An accurately weighed sample (0.2 to 0.5 g.) of the phenyl ester was introduced into an erlenmeyer flask and a measured excess of 0.25 *N* sodium hydroxide solution added. The flask was then attached to a water cooled condenser and the mixture refluxed for six to eight hours or until the ester disappeared. At the end of this time, the mixture was allowed to cool and a calculated excess of 0.25 *N* hydrochloric acid was added from a buret. At this point the total volume of the mixture was noted. The excess acid was then backtitrated with standard alkali to the end point of phenolphthalein as indicator.

The titration error due to the production of phenol was corrected by weighing out the theoretical amount of pure phenol as was present in the weighed sample of phenyl ester, and preparing an aqueous solution of the same molar concentration and volume as that of the saponification mixture after addition of the excess standard acid. The aqueous phenolic solution was then titrated with 0.25 *N* sodium hydroxide solution to the end point of phenolphthalein. The number of milliequivalents thus obtained was subtracted from the total number of milliequivalents of standard alkali used in saponification of the phenyl ester.


## Summary

The preparation of 2,4,5- and 2,4,6-trichlorophenoxyacetyl chlorides from the corresponding acids has been reported. The reaction of these acyl chlorides with ammonia, aniline, ethanol and phenol has been investigated.

The phenyl esters chlorophenoxy-, 2-chlorophenoxy-, 4-chlorophenoxy-, 2,4-dichlorophenoxy-, 2,4,5-trichlorophenoxy- and 2,4,6-trichlorophenoxy acetate were prepared.

Several new compounds were prepared and identified.


NASHVILLE, TENNESSEE RECEIVED AUGUST 5, 1948

(3) Morel, *Bull. soc. chim.*, [3] **21**, 967 (1899); m. p. 58°.

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[CONTRIBUTION FROM THE G. W. CARVER FOUNDATION, TUSKEGEE INSTITUTE]

# The Preparation and Properties of Some Branched-Chain Alkyl Bromomethyl Ethers

BY HAROLD W. LUCIEN[1] AND CLARENCE T. MASON[2]

The importance of the halomethyl ethers as intermediates in synthesis, and the greater reactivity of the bromomethyl ethers[3] make necessary the present investigation to extend the knowledge of the branched-chain bromomethyl ethers.

The Henry synthesis and its modifications[4–7] are carried out by saturating equimolar quantities of an alcohol–aldehyde mixture with a hydrogen halide. In the present work branched-chain bromoethers were prepared by the Henry synthesis,[4] Wedekind's adaptation,[7] and two new modifications of Henry's method. When pre-

(1) A part of this article is taken from the thesis presented to the graduate faculty of Tuskegee Institute by Harold W. Lucien, in partial fulfillment of the requirement for the degree of Master of Science. Presented at the September, 1948, Meeting of the American Chemical Society, St. Louis, Mo.

(2) Director of Research, George W. Carver Foundation, Tuskegee Institute, Alabama.

(3) Hamonet, *Compt. rend.*, **138**, 814 (1904).

(4) Henry, *Bull. acad. roy. Belg.*, [3] **25**, 439 (1938).

(5) Karvonen, *Acad. sci. Fennicae*, **3A**, 1 (1912); *C. A.*, **14**, 2175 (1920).

(6) Blair and Henze, THIS JOURNAL, **54**, 399 (1932).

(7) Wedekind, German patent 135,310, Aug. 31, 1901; *Chem. Zentr.*, **73**, II, 1164 (1902).

TABLE I

PHYSICAL CONSTANTS OF SOME BRANCHED-CHAIN ALKYL ETHERS

| Ether, 1-bromomethoxy | B. p. °C. | Mm. | Yield, % | Analyses Calcd. | Br, % Found | $d^{25}_4$ | $n^{25}D$ | Molar Refraction Calcd. | Molar Refraction Found | Lv cal./g. |
|---|---|---|---|---|---|---|---|---|---|---|
| -1-Methylethane | 75–76 | 196 | 70(a), 85(c), 87(d) | 52.15 | 52.21 | 1.3454 | 1.4251 | 30.080 | 30.849 | 68.7 |
| -2-Methylpropane | 52–53 | 30 | 79(a), 96(c), 98(d) | 47.83 | 47.85 | 1.2350 | 1.4400 | 34.698 | 35.887 | 60.1 |
| -3-Methylbutane | 128–129 | 247 | 80(a), 96(c), 98(d) | 44.13 | 44.21 | 1.2013 | 1.4489 | 39.316 | 40.769 | 56.9 |
| -2-Methylbutane | 67–68 | 16 | 79(a), 91(c), 98(d) | 44.13 | 44.19 | 1.2291 | 1.4671 | 39.316 | 40.892 | 64.2 |
| -1-Methylpropane | 106–108 | 357 | 75(a), 97(d) | 47.83 | 47.86 | 1.2550 | 1.4453 | 34.698 | 35.799 | 58.1 |
| -1-Methylhexane | 68–69 | 4 | 76(a), 92(c), 96(d) | 38.22 | 38.39 | 1.1295 | 1.4537 | 48.552 | 50.109 | 58.4 |
| -1-Methylheptane | 71–72 | 3 | 77(a), 93(c) | 35.82 | 35.91 | 1.1009 | 1.4562 | 53.170 | 54.894 | 75.4 |

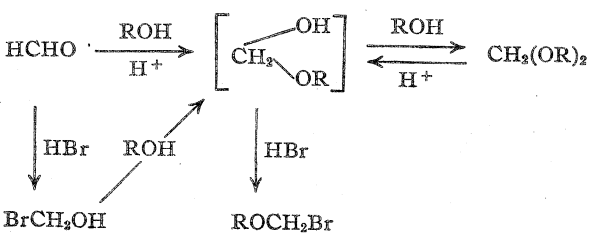
[a] By Henry's synthesis. [c] By Wedekind's method modified by using calcium chloride during the preparation. [d] From molar quantities of bromomethanol and an alcohol with hydrogen bromide.

pared by known methods the yields reported for straight-chain ethers were not achieved, due, in part, to the easier formation of alkyl halides. A mixture composed of the bromomethyl ether, formals and alkyl halides was isolated from Henry's synthesis. Unless the amount of water was reduced during these preparations, an excess of hydrogen bromide was necessary to complete the reaction.

The use of molar quantities of calcium chloride in conjunction with the Wedekind modification of Henry's synthesis boosted yields by about 15%. From the reaction of the alcohol with bromoethanol, yields of the order of 97% were obtained. Contaminated bromomethyl tertiary alkyl ethers were isolated in small amounts by all of the methods employed, but their preparation in high yields does not appear imminent.

The ease of preparation, yield, boiling point, refractive index and stability of the bromoethers prepared increase with molecular weight; the density and heat of vaporization[8] vary in an inverse manner. The exaltation increases with carbon content, being about 0.2 times the number of carbon atoms. These properties are summarized in Table I.

The formation of bromoethers from the reaction between an alcohol and bromomethanol appeared to take place by way of a hemiformal as an intermediate. It was not possible to isolate nor identify the compound suspected to be a hemiformal, due to the ease of formal formation. It was possible to obtain a bromoether from the reaction between a formal, paraformaldehyde, and hydrogen bromide.[9] The reactions encountered suggest the mechanism




(8) Calculated by substituting $p$ and $T$ data in the Clapeyron-Clausius equation.

(9) $ROCH_2OR + 2HBr + HCHO \rightarrow 2ROCH_2Br + H_2O$.

## Experimental

All alcohols and paraformaldehyde were obtained from Fisher Scientific Co. and were of the highest grade of purity. Bromomethanol was prepared according to Henry[10] and di-isobutyl formal was prepared by the method of Favre.[11]

**Bromomethyl Alkyl Ethers. A. By the Henry Synthesis.**[4]—Into a three-neck flask fitted with thermometer, stirrer and an inlet and outlet tube for hydrogen bromide, were placed one mole of the alcohol and 80 ml. of 37–38% formaldehyde solution. The flask was cooled to −5° and hydrogen bromide bubbled through the mixture until an excess of 1 mole accumulated in the flask. During the addition, the temperature was not allowed to rise above 25°. The crude bromoether was separated from the aqueous layer and dried for two hours over anhydrous calcium chloride. The products which resulted were amber in color, fumed on contact with air, and were lachrymatory. After drying, the crude bromoether was placed in an apparatus arranged for reduced pressure distillation, and the excess hydrogen bromide removed at 20 mm. pressure by bubbling nitrogen through the mixture. The product was distilled under reduced pressure.

**B. By Wedekind's Modification**[7] **of the Henry Synthesis.**—Procedure A was modified by substituting 30.0 g. of paraformaldehyde for 80 ml. of a 37–38% formaldehyde solution.

**C. By a Modification of the Wedekind Procedure.**—Procedure B was modified by using molar quantities of calcium chloride to remove the water as it was formed, and using only 1 mole of hydrogen bromide to 1 mole of alchohol and 30 g. of paraformaldehyde. The resulting product was decanted from the solid material and the latter extracted three times with 25-ml. portions of isopropyl ether. After the removal of ether by distillation, the bromoether was combined with the extract and purified as in procedure A.

**D. By the Reaction between Bromomethanol and an Alcohol.**—Into a 500-ml. erlenmeyer flask containing 74.1 g. (1 mole) of isobutyl alcohol was placed 111.1 g. (1 mole) of bromomethanol. The temperature rose to 50° and after an hour the mixture had cooled and two water-insoluble layers remained. The bottom layer was more dense than water, the top layer was less dense than water, and constantly decomposed to the more dense product and an aqueous solution. The total water-insoluble portion was dried and purified as before and yielded 153.1 g. (91.6%) 1-bromomethoxy-2-methylpropane, b. p. 51–53° at 30 mm., $n^{25}D$ 1.4402, $d^{25}_4$ 1.2352.

*Anal.* Calcd. for $C_5H_{11}BrO$: Br, 47.83; *MR*, 34.698. Found: Br, 47.94; *MR*, 34.889.

Experiment D was repeated to find some indication of hemiformal formation in the top layer which was constantly changing to bromomethyl isobutyl ether, but all attempts to isolate a hemiformal from this layer resulted in the isolation of di-isobutyl formal, b. p. 164–166°,

(10) Henry, *Rec. trav. chim.*, **23**, 16 (1904).

(11) Favre, *Compt. rend.*, **119**, 285 (1894).

$n^{25}D$ 1.4003, $d^{25}_4$ 0.8389. The product obtained also had a mixed boiling point with di-isobutyl formal (Favre,[11] b. p. 164.5°) of 164–166°.

The general procedure developed for the preparation of the bromoethers was similar to method **D**. Equimolar quantities of bromomethanol and an alcohol were intimately mixed and reduced pressure was applied to the flask containing the mixture. At the first indication of the formation of water, the use of reduced pressure was discontinued and the reaction was allowed to proceed of its own accord.

**E. By the Reaction between a Formal, Paraformaldehyde and Hydrogen Bromide.**—Into a 250-ml. round-bottom flask, cooled by running tap water and containing 50.6 g. (0.5 mole) of di-isobutyl formal, was placed 15 g. of paraformaldehyde. Hydrogen bromide was bubbled through the mixture until two layers separated, and thereafter for five minutes. The product of the reaction was isolated as in procedure **A** and yielded 76.8 g. (91.5%) of bromomethyl isobutyl ether, b. p. 40–42° at 23 mm., $n^{25}D$ 1.4401, $d^{25}_4$ 1.2350.

*Anal.* Calcd. for $C_5H_{11}BrO$: Br, 47.83; *MR*, 34.698. Found: Br, 47.91; *MR*, 35.887.

**The Identification of the Alkyl Portions of the Bromomethyl Alkyl Ethers.**—A 10-g. sample of the purified bromoether was hydrolyzed by refluxing with 20 ml. of a 10% solution of sodium hydroxide for thirty minutes. The alcohol obtained was isolated and the 3,5-dinitrobenzoate prepared. The ester obtained was compared with that obtained from the known alcohol by melting point and mixed melting point determinations.

**Acknowledgment.**—The authors wish to express gratitude to the Research Corporation for a Frederick Gardner Cottrell grant which helped to support this investigation.

## Summary

The bromomethyl ethers of seven branched-chain alcohols in the $C_3$ to $C_1$ range have been prepared. The physical constants determined include the boiling point, density, refractive index and the heat of vaporization. Evidence suggests the possibility that these bromomethyl alkyl ethers are formed in the Henry synthesis by way of a hemiformal as an intermediate.

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RECEIVED JULY 12, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

# The Two-Step Reduction–Oxidation of Thiaxanthone-5-dioxide and Thiaxanthenol-5-dioxide[1]

BY HANS HEYMANN

In connection with another investigation the synthesis of the acetate of thiaxanthenol-5-dioxide was required. The interesting color phenomena exhibited by this ester, by the related alcohol and by the corresponding ketone prompted the study reported here. Carl Graebe[1a] had noted that thiaxanthone-5-dioxide gives blue solutions when heated with zinc and alkali or on heating with alcoholic potassium hydroxide; he observed that the color disappeared on continued heating with zinc and base. Ullmann and Glenck[2] found that the compound can be vatted with alkaline dithionite to give colored solutions. Recently Amstutz and his collaborators have again noted color phenomena akin to those seen by the earlier workers, and have voiced the suggestion that the colors appearing during the reduction of thiaxanthone-5-dioxides are due to semiquinone intermediates.[3] The same thought had occurred to us and we wish to present substantiation of the hypothesis in the present paper.[4]

(1) A preliminary report of this work was presented to a meeting of the Oregon Academy of Science on Jan. 17, 1948, in Salem, Oregon.

(1a) Graebe and Schulthess, *Ann.*, **263**, 11 (1891).

(2) Ullmann and Glenck, *Ber.*, **49**, 2509 (1916).

(3) Amstutz, Fehnel and Hunsberger, THIS JOURNAL, **70**, 133 (1948).

(4) Our work had been in progress for over a year when Dr. Amstutz's publication appeared. In his friendly reply to our inquiry Dr. Amstutz informed us that he does not intend to investigate, at the present time, the oxidation–reduction properties of the thiaxanthone dioxides.

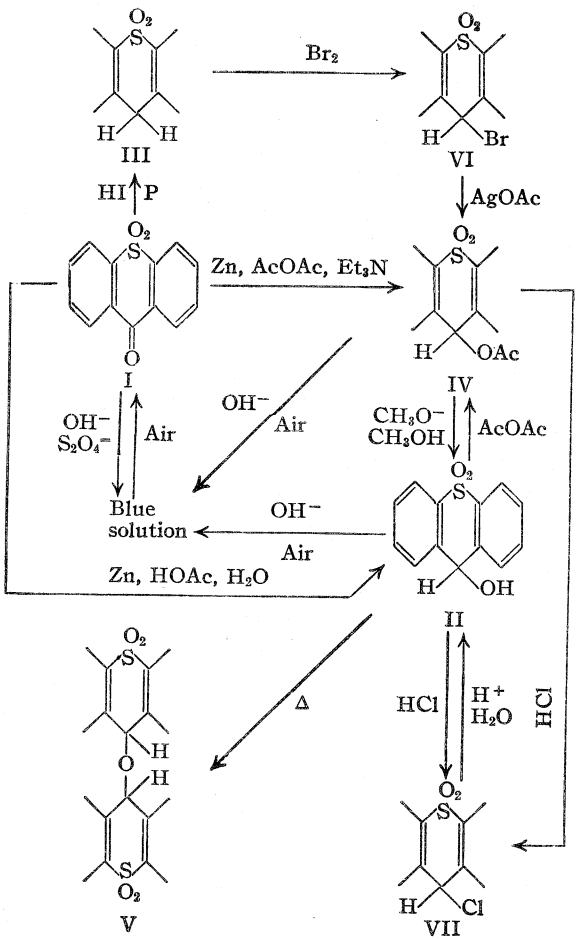
## A. Preparative Part

The synthetic reactions are summarized in the accompanying flow sheet. The ketone I was obtained according to well-known procedures.[1,2] Reduction to thiaxanthenol-5-dioxide was achieved smoothly by means of zinc dust in 80% acetic acid, conditions under which substituted sulfone-ketones like I may be reduced to the corresponding thiaxanthene-5-dioxides.[3] The alcohol II melts sharply when heated relatively rapidly (*ca.* 0.5° per minute), but the behavior of a sample that is permitted to resolidify after melting indicates that a change accompanies protracted heating: the alcohol is transformed into the ether V, much as benzhydrol upon distillation goes to benzhydryl ether.

The carbinol II may be acetylated smoothly with acetic anhydride in pyridine to yield the acetate IV, and the same compound is conveniently prepared by reductive acetylation of I in the presence of little triethylamine. Larger amounts of base lead to the formation of small quantities of a yellow by-product of unknown nature. The acetate IV was also obtained by displacement with silver acetate of the bromine atom in 10-bromothiaxanthene-5-dioxide (VI), which was the sole product of the action of bromine in carbon tetrachloride on III. The correlation described confirms the assignment of the bromine atom to position 10.

The conditions of hydrolysis or displacement of

FLOW SHEET




the acetate group in IV were investigated briefly because (see below) IV and the alcohol II appeared to be indistinguishable as far as their oxidation behavior in alkaline medium is concerned. When a warm solution of IV in acetic acid was treated with concentrated hydrochloric acid the insoluble 10-chlorothiaxanthene-5-dioxide (VII) crystallized instantaneously; when the mixture was boiled for two hours, during which much hydrogen chloride escaped, the alcohol II was formed in a not clean-cut reaction. Thus the bond from position 10 to the oxygen atom must be rather tenuous, as one would expect, and it is natural that the alcohol II yields the chloride as easily as does the acetate when subjected to the same conditions. The formation of the alcohol II from the chloride presumably involves a slow solvolysis, as encountered in the benzhydryl halide series. Sulfuric acid in aqueous acetic acid or in aqueous alcohol hydrolyzes IV rapidly but the reaction is not smooth, the yield is poor, and the product is generally contaminated with the ether V; presumably the insolubility of VII and the greater apparent affinity of the chlorine atom for position 10 prevent side reactions from occurring with hydrogen chloride.

Next the acetate IV was exposed to prolonged action of sodium benzoate in alcoholic solution in order to learn whether a weakly nucleophilic agent would attack at position 10, although the observations cited argue against this possibility and, indeed, only the unchanged acetate (63%) was isolated after boiling for forty-eight hours. However, sodium methoxide in practically oxygen-free absolute methanol and under rigid exclusion of oxygen from the air rapidly produced II in 87% yield. Had position 10 been attacked by the base the methyl ether of II should have been the product. Thus one may conclude that under basic and acidic conditions IV is rapidly hydrolyzed to II.

### B. Study of the Reduction–Oxidation Equilibrium

The alcohol II and the acetate IV both develop an intense blue color when their solutions in alcohol are treated with alkali. In the case of the acetate hydrolysis no doubt precedes color formation. The blue tint is decolorized on shaking with air, returns after a short time, may be discharged again, etc., until finally the solution remains colorless and contains the ketone I. In an experiment of this sort, using aqueous pyridine as the solvent, the ketone was isolated in 93% yield; the mother liquor had a pale orange color owing to the occurrence of a non-identified and apparently negligible side-reaction. Color formation is virtually suppressed by thorough expulsion of oxygen from both the solution of the alcohol II and from the alcoholic alkali before mixing. When, however, oxygen-free alcoholic potash is added to an oxygen-free solution of equimolar amounts of I and II the intense blue color appears immediately. The blue species described here is no doubt identical with the coloration seen by Graebe.[1] Since alcoholic potash alone is capable of producing the color from I upon heating, and since this must involve a reducing action exerted by ethoxide ion, we tried to isolate acetaldehyde from such a blue solution, but without success. Probably the small amounts of aldehyde present are rapidly aldolized in the strongly basic medium. However, even in neutral solutions and at room temperature I oxidizes alcohol at a measurable rate: an alcoholic solution of I had acquired a strong odor of acetaldehyde after having stood for about a month; the aldehyde was flushed from the solution by nitrogen and identified by means of a solid derivative.

By scanning the adsorption spectrum of the blue material as it exists in aqueous pyridine solutions of varying alkalinity (0.025, 0.14, 0.9 $M$ in hydroxide ion) we found absorption bands at 370 and 570 m$\mu$, separated by an absorption minimum at 475 m$\mu$. The spectral curves have approximately the same shape; for the least alkaline sample the ratio $D_{570}:D_{475}$ is somewhat smaller than for the more alkaline solutions ($D$ refers to log $I_0/I$). However, in view of the

rather crude experimental technique employed the difference of the ratios described may not be significant.

The color intensity of the oxidation–reduction system increases markedly with rising *p*H, at constant concentration. This intensification was demonstrated objectively by colorimetry with the aid of a suitably modified Thunberg tube in which equimolar amounts of I and II were brought together with aqueous alkaline pyridine in the absence of oxygen. The relative optical density of a system containing, before contact with alkali, $8.4 \times 10^{-3}$ mole/l. of each I and II varied as 1:2.5:8.0 as the hydroxide concentration changed from 0.027 to 0.14 to 0.91 *M*.

There is evidence that besides the blue species a red entity exists in the oxidation–reduction system. Samples at low alkalinity appear purplish rather than blue, particularly in aqueous dioxane solution, and the smaller ratio $D_{570}:D_{475}$ mentioned above conceivably indicates an increased absorption at 475 mμ. Furthermore, when samples of the blue system are subjected, in an inert atmosphere, to controlled oxidation by means of ferricyanide solution or simply by means of air-saturated buffer, the color changes from blue to purple to pure pink before it is discharged completely. Spectroscopic examination of the red body was not very satisfactory because of the low concentration and high air-sensitivity of the compound; none the less, an absorption maximum between 470 and 480 mμ was recognized.

In sealed-glass vessels the blue solutions appear to be unchanged over long periods of time, but on heating at 110° for two days the color is discharged and in the resulting solution sulfite and xanthone (10–15%) were found, besides a small amount of unchanged I. The course of this interesting cleavage is not known at present.

Rapid neutralization with acid of the blue solution led to a mixture from which pure I and pure II were isolated, but there was no evidence of the presence of any other compound, in contradistinction to Bachmann's findings regarding the colored solutions of metal ketyls in aprotic solvents[5] from which high yields of the corresponding pinacols were obtained by acid decomposition.

The observations related so far strongly indicate that the colored body is an intermediate between I and II differing in oxidation level from these substances by one additional or one lacking electron, respectively, that the relative amount of the intermediate increases with rising *p*H, and that the intermediate comprises a blue and a red species. The intermediate may be considered to be a new type of semiquinone, derived from a simple ketone, to be added to the list of well-known one-step intermediates in two-electron oxidation–reduction reactions. However, more definite and more conclusive information was desirable, and we considered that an apparently mobile system like that of I and II might be susceptible to electrochemical investigation.

The fundamental studies of Michaelis[6] and of Elema[7] have shown how to interpret potentiometric titration curves obtainable from mobile, reversible oxidation–reduction systems with particular reference to the detection of one-electron steps in multi-electron reactions. We found that the system under discussion did, indeed, give rise to stable potentials on oxidative titration with ferricyanide in a medium containing 30% by volume of pyridine or dioxane; inclusion of such a large proportion of organic solvent was required by the low solubility of I. The potentials are established with practicable rapidity only at alkali concentrations greater than about 0.01 *M*. Tables I and II summarize the results obtained by potentiometric titrations; the symbols used are those introduced by Michaelis.[6] $E_m$ is the mean normal potential, referred to the normal hydrogen electrode, for the over-all reaction $I \leftrightarrows II$; $E_{i25}$ and $E_{i75}$ are the index potentials, *i. e.*, the numerical differences between $E_m$ and the e. m. f. of the galvanic chain at 25 and 75% completion of the oxidation. The index potential serves as a convenient measure of the degree to which the theoretical mid-point slope $RT/2F$ of a titration curve for a two-electron change is modified by the participation of two one-electron reactions. Knowledge of $E_i$ permits computing the amount of semiquinone in equilibrium with the reduced and the oxidized forms, and therewith $E_1$ and $E_2$, the normal potentials of the first and the second one-electron steps.

Table I shows the results obtained in a series of oxidative titrations in pyridine-containing media covering a *p*H-range from the most alkaline phosphate buffer capable of existence through various concentrations of sodium hydroxide to about 1 *N* tetramethylammonium hydroxide. The last-named base was employed because pyridine is not miscible with sodium hydroxide more concentrated than about 0.4 *M*. $E_i$ is seen to increase with rising alkalinity indicating that the two-step change becomes more and more prevalent at higher basicity.

Species intermediate in oxidation level between alcohols and ketones must have an odd electron and they may also bear an ionic charge, *i. e.*, they are neutral or ion-radicals and such radicals may exist in equilibrium with their dimers. If they do, the shape of the titration curve should depend on the total concentration of the oxidation-reduction system.[6] As experiments 6 and 7, 10 and 11, and 15 and 16 in Table I show, dimerization does not appear to take place to a degree detectable within the limits of the experimental accuracy.

(5) Bachmann, THIS JOURNAL, **55**, 1179 (1933).

(6) For a recent review see Michaelis, *Ann. N. Y. Acad. Sci.*, **40**, 39 (1940).

(7) Elema, *J. Biol. Chem.*, **100**, 149 (1933).

In the experiments referred to by Table I the ionic strength underwent a more than ten-fold change; the alkaline agent employed was not the same for all runs, and the reproducibility of the measurements was not satisfactory. Therefore, another series of titrations was carried out, so designed as to employ the same alkaline agent throughout, and by incorporation in the medium of suitable amounts of potassium chloride the ionic strength was held constant at 1.4 for all runs. Furthermore, the temperature and the alkalinity were controlled more carefully. Dioxane was substituted for pyridine as the organic solvent, because dioxane permitted the use of higher concentrations of alkali hydroxide. Runs 1a to 6a, and 1b to 6b in Table II, represent two independent series of determinations, carried out with separate sets of reagents, and the results are seen to be reasonably well reproducible. Runs 7a are duplicate determinations of the a-series, and runs 8a and 9a, agreeing with one another, again show the absence of measurable dimerization of the semiquinone. Runs 2c to 5c were carried out in the absence of potassium chloride, thus involving a variation of the ionic strength from 0.03 to 0.3. It is of interest to note that with increasing alkalinity the hydrogen ion activity as well as $E_m$ diverge more and more from the values observed in series a and b, but that the values for $E_i$ are very nearly alike for solutions of the same molarity of alkali hydroxide, irrespective of the ionic strength. In another case[8] $E_i$ varied appreciably with the ionic strength of the medium.

The dependence of $E_m$ upon alkalinity is a consequence of the fact that I and II differ by two protons in addition to their disparate state of oxidation. Clark and Cohen have formulated the relation[9] between bends in an $E_m$ *versus* $p$H curve and the $pKa$ values of the protolytic dissociations pertaining to the species involved in the oxidation–reduction equilibrium. It is of great interest to construct a potential-$p$H diagram for the three potentials $E_1$, $E_2$ and $E_m$ of the system under discussion. The quantity referred to as $p$H in this article was calculated in the usual way from the e. m. f. of a cell consisting of the saturated calomel electrode and of the system hydrogen, colloidal palladium, platinum immersed in the fully reduced oxidation–reduction system, as recommended by Michaelis. The question of the significance of $p$H values of this nature is involved; all of the values are considerably higher than those to be expected from purely aqueous solutions of equal molarity. However, it seems not inconceivable to us that $p$H values calculated from potentials measured in such solvents as we have used might, up to a certain point, constitute a self-consistent $p$H scale which has a consistent relation to the normal potentials of a oxidation–reduction system involving protolytic equilibria. In the hope of detecting the presence of such dissociations and of gaining qualitative information about the nature of the colored intermediate we have plotted the experimental results in Fig. 1.

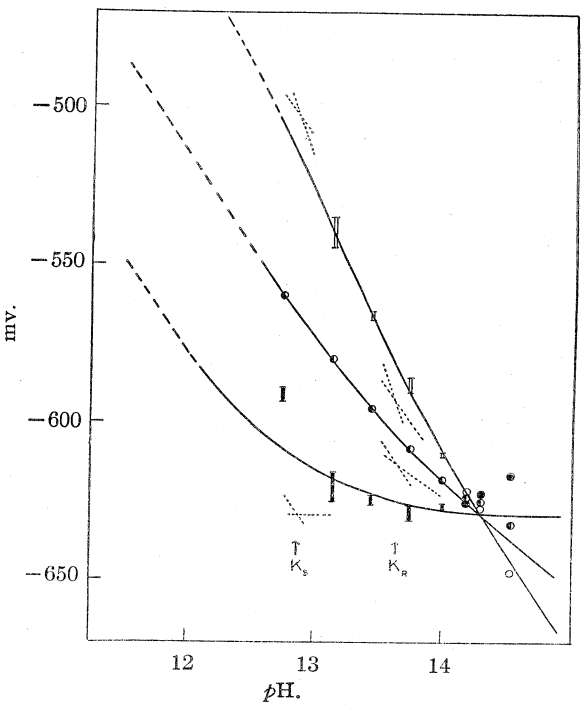



Fig. 1.—The three normal potentials of the oxidation–reduction system from oxidative titrations in aqueous dioxane. The lines drawn are theoretical curves: ○, $E_1$; ◐, $E_m$; ●, $E_2$.

Figure 1 contains the more reliable data, those obtained in the experiments with aqueous dioxane as the solvent. On this graph we have drawn an $E_m$-curve that begins with a slope of 59 mv. per $p$H unit at the low-alkalinity end of the plot and and gradually bends over to a slope of 29 mv. as one passes to higher values of $p$H. Continuations of the straight-line portions of the curve intersect at a point labelled $K_R$. The curve drawn is a *theoretical* curve of the type characteristic of oxidation–reduction systems, in which the reduced form differs from the oxidized form by two protons and two electrons; a bend like the one drawn occurs when $p$H approaches and passes through $pK_a$ of the first dissociable proton.[10] However, inspection of the experimental points shows that the steepest slope realized by measurement is only 55 mv. Since in well-studied cases of the dependence of oxidation–reduction potentials upon $p$H the non-linear portion of the curves extends over one to two $p$H units, a range comparable to that covered by all of the measurements in Table II, we consider it plausible that owing to the im-

(8) Michaelis and Fetcher, THIS JOURNAL, **59**, 2460 (1937).

(9) W. M. Clark and Cohen, U. S. Pub. Health Repts., **38**, 933 (1923).

(10) In view of the unknown relation between the normal $p$H scale and our "$p$H" values the usual interpretation that the $p$H at the intersection equals $pK_a$ is, of course, inadmissible.

mobility of the equilibrium at low alkalinities our measurements could not be extended to reach the region where the slope becomes equal to the theoretical value of 59 mv. Even at the lowest $p$H used, we feel, the over-all reaction is to be represented by both of the following equilibria,[11] with the second equilibrium becoming more and more prevalent as the alkalinity increases. Since $RH_2$ (II) dissolves readily to give a colorless solution in 30% aqueous dioxane containing

$$RH_2 \rightleftharpoons T + 2H^+ + 2e^-$$
$$RH^- \rightleftharpoons T + H^+ + 2e^-$$

potassium hydroxide in 1.4 $M$ concentration, when air is excluded and the system is kept in the reduced state by means of dithionite, whereas in the absence of potassium hydroxide the solubility of II in the same solvent is small, we do not doubt the reality of the acidic function of $RH_2$ implied in the $E_m$ curve.

At the flatter end of the $E_m$ curve the experimental points seem to deviate from the theoretical curve in a minor way. However, as the alkali concentration is increased with concomitant reduction of the potassium chloride concentration, the potential at the liquid junction $KCl_{satd.}$ KOH, KCl no doubt changes by greater and greater increments, and introduces a larger and larger error into the potential measurements. We hope to show presently that the values of $E_m$ and $p$H may be trusted up to a $p$H of 14 to 14.2 (0.2 to 0.3 $M$ potassium hydroxide); there is reason to think that beyond that point the seemingly fair agreement of the data with the theoretical curve is spurious.

The *index potentials* should be reliable regardless of any error caused by the liquid junction potential, because they are relative values that depend only on the shape of the titration curves and not on the absolute values of the mid-point potentials. Consequently the values of the semiquinone formation constant $k = (S)^2/(R)\times(T)$ are significant, and so are the values for $E_2 - E_1$ computable from $k$. Unfortunately most of our values for $E_2 - E_1$ had to be calculated in that region where small variations of $E_i$ cause a large uncertainty in the value of this potential difference; nonetheless we feel that to the left of $p$H 14 the data for $E_2$ and $E_1$ conform at least qualitatively to the theoretical curves which we have drawn for these two potentials in Fig. 1. From this agreement we draw the conclusion that the values for $E_m$ and $p$H may also be fairly reliable within the same region.

The slope of the $E_2$-curve changes from 59 mv. to zero at a region labelled $K_S$, which corresponds to a transition from the first to the second of the following equilibria. In the region of

$$SH \rightleftharpoons T + H^+ + e^-$$
$$S^- \rightleftharpoons T + e^-$$

zero slope the semiquinone differs from the ketone I merely by one additional electron. Because of the proximity of $K_S$ and $K_R$ as drawn in Fig. 1 the bends in the theoretical $E_1$-curve are not clearly visible; we have tried to indicate changes from slope 59 to 118 and back to 59, corresponding to the equilibria

$$RH_2 \rightleftharpoons SH + H^+ + e^-$$
$$RH_2 \rightleftharpoons S^- + 2H^+ + e^-$$
$$RH \rightleftharpoons S^- + H^+ e^-$$

The theoretical $E_2$-curve continues beyond $p$H 14 with a slope of zero, and the other two curves are drawn accordingly. The experimental values of $E_2$ and $E_1$, calculated by adding $\pm(E_2-E_1)/2$ to the measured value of $E_m$ diverge markedly from the lines; indeed, $E_2$ seems to rise again. We have considered the possibility that this might indicate a second acidic dissociation of the semiquinone, involving a species $SOH^{--}$. This idea is not acceptable on electrochemical grounds and on the basis of other considerations; *e. g.*, it is inconceivable that $S^-$, a negative ion, should act as a Lewis acid to accept a hydroxyl ion when T (I), which does not bear any charge, shows no signs whatever of such a dissociation. Furthermore, in the light of the great stability of the S-form relative to $R$ and $T$ in the region under discussion ($k$ for runs 8a and 9a equals 3.2–3.5) existence of the semiquinone as $SOH^{--}$ is excluded because any structural expression of such an entity implies that it would be of very high energy. Thus we believe that the theoretical system of curves approximates the true situation; the experimental points deviate because beyond $p$H 14.2 both $E_m$ and $p$H are falsified by increasingly larger errors. For instance, in runs 8a and 9a $E_2 - E_1$ equals 31 mv.; the curves drawn differ by this amount at "$p$H" 14.80, where the $E_m$-curve has a value of $-647$ mv. This is taken to mean that the potential measurements upon which $p$H and $E_m$ are based must have been in error by $+15$ to $+16$ mv.[12]

The data of Table I give rise to a plot of similar pattern (not included in this article). Although the experimental points show considerable scatter, which is to be expected in view of the variable conditions in this series of experiments, we believe that the plot corroborates the conclusions we have drawn from Fig. 1.

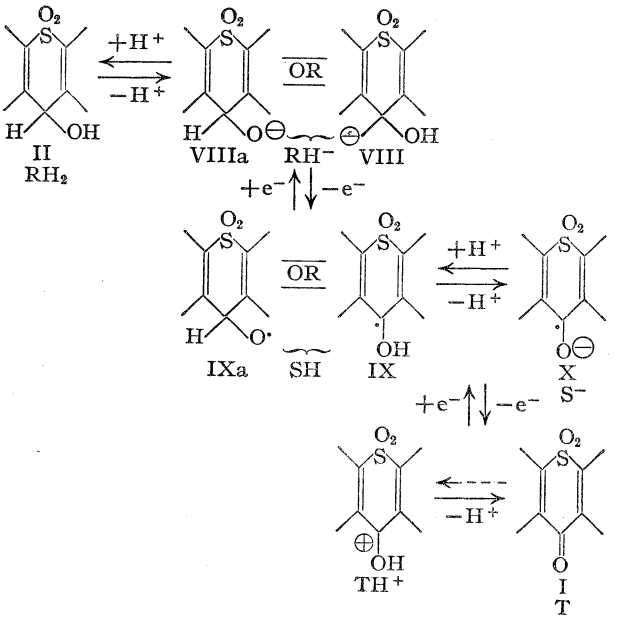
We do not intend to attach quantitative significance to the values of $K_R$ and $K_S$ which, in any

(11) It is convenient, in slight modification of existing usage,[6,9] to use the letters T, S and R for general reference to the oxidized, semiquinone and reduced forms in an oxidation-reduction equilibrium, and to indicate charges and dissociable protons by means of the usual symbols and by the letter H, respectively, attached to these letters in discussions of protolytic equilibria. Thus a reduced form with two dissociable protons can give rise to the species $RH_2$, $RH^-$ and $R^{--}$.

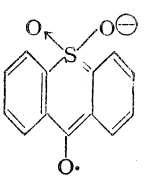
(12) We are indebted to Dr. L. Michaelis for the suggestion that the possibility of measuring index potentials in highly alkaline media may be used to extend the $p$H scale toward the alkaline side similarly to its extension to strongly acid media by Michaelis and Granick, THIS JOURNAL, 64, 1861 (1942).

case, would be hard to interpret, nor do we believe that the relative positions of these bends on the graph should be taken as precise. We do feel, however, that the data and the interpretation attempted make probable in a qualitative way the actual existence of the several protolytic and oxidation–reduction equilibria discussed. The colorimetric measurements agree with the view that $S^-$ is the blue entity, the relative amount of which increases rapidly as one approaches the region where most of the reduction–oxidation system exists, at half-oxidation, as the semiquinone form. The purplish appearance of the solution at lower alkalinity is quite possibly due to SH, the conjugate acid of the semiquinone, which may perhaps be identified with the red species described before. If one ascribes greater tinctorial power to $S^-$ than to SH, which appears to be a reasonable assumption (*cf.* formulas IX and X), the preponderance of the blue color even at low alkalinity becomes understandable, although in this region SH must be present in concentrations comparable to, or greater than, those of $S^-$. A region where the solution was of a pure pink at the midpoint of the titration was not realized experimentally, and the appearance of the pink color only at the extreme ends of the oxidation process is puzzling. Since no reversion of the pink to purple was visible within thirty minutes, we do not believe that sluggish establishment of the equilibrium near the end-point is the cause; on the other hand, the ratio $(S^-)/(SH)$ should be independent of the total concentration of the S-form for any given *p*H. At this time we cannot offer an adequate explanation for the phenomenon.

We have formulated the species involved in the equilibria considered in this discussion in the accompanying set of structures, which are so arranged that horizontal displacements correspond to protolytic equilibria, vertical ones to oxidation–reduction changes. The species $TH^+$ is included for the sake of clarity; there is no reason to believe that it is present and therefore the appropriate equilibrium arrow is shown as a broken line. Both VIII and VIIIa must be considered as expressions for $RH^-$ and the present work does not furnish conclusive evidence in favor of either one. The known mobility of the hydrogen atom in benzohydryl ethyl ether[13] as well as such phenomena as the ready isomerization oxanthrone–anthrahydroquinone might be cited as precedent supporting the carbanion structure VIII. Such an ion would be expected to be stabilized by resonance to a considerable degree, but it might also be expected to show some color, which was not observed in the alkaline solution of $RH_2$. The intrinsic greater mobility of a proton bound to oxygen argues in favor of structure VIIIa, but when one considers the formulations IXa and IX for SH, which results from $RH^-$ by loss of one electron, formula IX alone seems capable of accounting for the small but definite stability of this free radical. Since the formation of IX is best understood if VIII is




assumed to be its precursor, we consider the carbanion formula VIII preferable to the alkoxide structure VIIIa. The stable form of the semiquinone, $S^-$, is formulated as the ion-radical structure X. Species $S^-$ should be represented by two structures showing the usual resonance of a metal ketyl grouping; furthermore, both the charge and the lone electron must be thought of as distributed over the lateral rings so that for X one has to consider at least 13 additional structures (excluding Kekule resonance) of comparable energy. In most of the known cases of stable semiquinones one can write limiting structures in which the charge and the lone electron are distributed to both of two atoms other than carbon, such as nitrogen or oxygen, so that a state of more or less equivalent resonance exists. We should like to raise the question whether in a formulation of $S^-$ structures involving distribution of the charge and of the lone electron to the sulfone oxygens ought to be considered, *e. g.*, structures like XI.



XI

This consideration touches upon the problem whether sulfur is capable of expanding its valence shell with utilization of a 4s or 3d orbital without a great increase in the energy of the system. Although this problem has recently been discussed in

(13) Wooster and Dean, THIS JOURNAL, **57**, 113 (1937).

TABLE I

OXIDATIVE TITRATIONS OF II IN AQUEOUS PYRIDINE AT 24–28°

The buffers were made by mixing 15 cc. of pyridine with 35 cc. of an alkali solution of the composition listed and adding potassium chloride to a total concentration of 0.07 *M*

| Expt. | Molarity × $10^3$ | Alkali solution | *p*H | $E_i$ 25%, mv. | $E_i$ 75%[a] mv. | $E_m$, mv. |
|---|---|---|---|---|---|---|
| 1 | 3.3 | 33.2 cc. of 0.03 *M* disodium phosphate and 1.8 cc. of 1 *M* NaOH[b] | 11.85 ± 0.15 | 14.8 (?)[c] | | −520.7 |
| 2 | 0.67 | 0.02 *M* NaOH | 12.47 ± 0.11 | 17.6 | | −549.5 |
| 3 | Same | Same | 12.43 ± 0.10 | 17.2 | | −551.2 |
| 4 | 0.67 | 0.036 $Me_4NOH$ | 12.87 ± 0.03 | 15.5 (?) | 16.7 | −564.3 |
| 5 | 1.7 | Same | 12.88 ± 0.09 | 16.9 | 16.3 | −566.8 |
| 6 | 3.3 | 0.1 *M* NaOH | 13.08 ± 0.06 | 17.4 | | −588.9 |
| 7 | 0.67 | Same | 13.08 ± 0.06 | 17.4 | | −588.9 |
| 8 | 0.67 | 0.2 *M* NaOH | 13.44 ± 0.04 | 18.3 | 18.2 | −597.0 |
| 9 | 3.3 | 0.5 *M* NaOH | 13.80 ± 0.1 | 20.6 | | −609.8 |
| 10 | 0.33 | 0.6 *M* NaOH | 13.82 ± 0.04 | 20.9 | 20.5 | −610.4 |
| 11 | 3.3 | Same | 13.86 ± 0.04 | 19.3 | 20.3 | −611.8 |
| 12 | 1.7 | 0.51 *M* $Me_4NOH$ | 13.86 ± 0.03 | 23.9 | 24.0 | −611.9 (?) |
| 13 | 1.7 | 0.8 *M* $Me_4NOH$ | 14.09 ± 0.02 | 29.1 | 29.4 | −616.1 |
| 14 | 1.7 | 1 *M* $Me_4NOH$ | 14.35 ± 0.05 | 36.5 | 36.0 | −621.0 |
| 15 | 0.33 | 1.3 *M* $Me_4NOH$[b] | 14.38 ± 0.05 | 44.8 | 41.7 | −623.4 |
| 16 | 3.3 | Same[b] | 14.38 ± 0.05 | 43.3 | 41.5 | −625.3 |
| 17 | 1.7 | 1.3 *M* $Me_4NOH$ | 14.35 ± 0.05 | 46.3 | 43.0 | −628.9 |
| 18 | Same | Same | 14.35 ± 0.04 | 45.8 | 44.9 | −629.4 |

[a] When only one value for $E_i$ is listed this was obtained from the straight line of a plot of the e. m. f. *versus* the logarithm of the ratio % oxidized/(100 − % oxidized). The important section of such plots deviated only negligibly from linearity. [b] No potassium chloride was added in these runs. [c] Owing to the slowness of the equilibrium this run required six hours for completion and $E_{i\ left}$ differed by three to four mv. from $E_{i\ right}$. The value listed pertains to the left-hand side; it is not considered reliable.

TABLE II

OXIDATIVE TITRATIONS OF II IN AQUEOUS DIOXANE AT 24.5 ± 0.5°

In all experiments except no. 9a the concentration of II was $10^{-3}$ *M*; in run 9a it was $3 \times 10^{-3}$ *M*. The buffer consisted of 16 cc. of dioxane and 35 cc. of an alkali solution of the composition listed.

| Expt. | Composition of alkali solution KOH *M* | KCl *M* | *p*H | $E_i$ 25%, mv. | $E_i$ 75%, mv. | $E_m$, mv. |
|---|---|---|---|---|---|---|
| 1a | 0.02 | 1.98 | 12.75 ± 0.07 | 16.1 | 16.5 | −560.6 |
| 1b | Same | Same | 12.72 ± 0.08 | 16.2 | 16.0 | −559.0 |
| 2a | 0.041 | 1.96 | 13.15 ± 0.04 | 15.9 | 15.8 | −579.2 |
| 2b | Same | Same | 13.12 ± 0.03 | 15.6 | 15.4 | −580.6 |
| 2c | Same | ... | 13.16 ± 0.04 | 15.6 | 15.7 | −580.0 |
| 3a | 0.08 | 1.92 | 13.45 ± 0.03 | 16.6 | 16.3 | −594.2 |
| 3b | Same | Same | 13.40 ± 0.02 | 16.3 | 16.5 | −596.4 |
| (3bb) | Same | Same | 13.37 ± 0.01 | 16.0 | 16.3 | −592.5[a] |
| 3c | Same | ... | 13.41 ± 0.01 | 16.4 | 16.3 | −592.3 |
| 4a | 0.16 | 1.84 | 13.76 ± 0.03 | 17.4 | 17.8 | −608.2 |
| 4b | Same | Same | 13.73 ± 0.02 | 17.0 | 17.2 | −608.5 |
| 4c | Same | ... | 13.68 ± | 17.4 | 17.9 | −602.9 |
| 5a | 0.33 | 1.67 | 13.98 ± 0.03 | 19.3 | 19.3 | −618.2 |
| 5b | Same | Same | 14.00 ± 0.01 | 19.5 | 19.6 | −618.7 |
| 5c | Same | ... | 13.90 ± | 19.2 | 19.1 | −609.9 |
| 6a | 0.49 | 1.51 | 14.19 ± 0.03 | 20.8 | 21.2 | −624.2 |
| 6b | Same | Same | 14.17 ± 0.01 | 20.9 | 20.9 | −623.8 |
| 6c | Same | ... | 14.06 ± 0.01 | 20.8 | 21.0 | −614.8 |
| 7a | 0.65 | 1.35 | 14.30 ± 0.03 | 21.8 | 22.4 | −625.1 |
| | | | 14.27 ± 0.03 | 21.9 | 22.4 | −625.3 |
| 8a | 1.31 | 0.69 | 14.52 ± 0.02 | 27.1 | 27.3 | −632.2 |
| 9a | 1.31 | 0.69 | 14.53 ± 0.01 | 26.8 | 27.2 | −633.1 |

[a] Run 3bb was carried out by retitrating the sample used in run 3b after the reduction for the final measurement of *p*H. The same amount of ferricyanide was consumed; possibly the slight change in the medium is responsible for the rise of 3 mv. of $E_m$.

several places[14] the question remains open. The remarkable stability of the ion-radical X may have some bearing on this point.

Finally we should like to consider the slow step in the oxidation–reduction equilibrium manifest during air oxidations and visible during titrations in the lower *p*H region. Here each addition of a portion of oxidizing agent discharges the blue color immediately; the tint returns after a short period of time and reaches a maximum density. Simultaneously the e. m. f. becomes constant with time. Apparently the conversion of S to T is fast and the regeneration of S is slow. The process most likely to be time-consuming is the dissociation of $RH_2$ to $RH^-$, because a number of carbon–hydrogen dissociations on record are known to be slow, and it is reasonable to assume that $RH^-$ rather than $RH_2$ is the species that is being oxidized by ferricyanide or by T to give SH and then $S^-$. The observation that at low *p*H the potentials are established very slowly agrees with this interpretation.

## Experimental[15]

### A. Preparative Part

**Thiaxanthenol-5-dioxide (II). (a) By Reduction of I.**—A solution of 8.9 g. of I in 150 cc. of glacial acetic acid and 30 cc. of water was boiled for five minutes with 10 g. of zinc dust, filtered, and diluted with much water when

(14) (a) Bordwell and Albisetti, THIS JOURNAL, **70**, 1558 (1948); (b) Doering and Levy, Acidity of a Bicyclic Trisulfone, presented at the 112th meeting of the American Chemical Society, New York, N. Y., September, 1947; (c) Woodward and Eastman, THIS JOURNAL, **68**, 2229 (1946). There earlier references may be found.

(15) All melting points are corrected.

7.48 g. of a hydrate of II separated. Recrystallization from 400 cc. of benzene yielded 6.6 g. (73.5%) of large prisms of II, m. p. 184.2–186.2°, and another 0.5 g. (6%) was obtained from the mother liquors. The pure alcohol melts at 186–187.5°; the melting point is somewhat uncertain because on slow melting the alcohol partly changes to the ether V.

**(b) By Alkaline Hydrolysis of IV in Methyl Alcohol.**—Into a glass-stoppered flask equipped with gas-inlet and outlet tubes fitted with stopcocks was placed a small test-tube containing 1 g. of IV, 50 cc. of absolute methanol (commercial) and 1.15 g. of sodium. Contact between the contents of the test tube and the solvent was avoided. After the metal had dissolved oxygen-free nitrogen was passed through the liquid for twenty-five minutes; then the system was closed and the acetate was caused to fall into the methoxide solution. The solid dissolved and a very faint lavender color developed. After the mixture had stood at room temperature for one hour 10 cc. of 6 *N* hydrochloric acid was added quickly, followed by 200 cc. of water. The excess acid was neutralized with bicarbonate and 800 mg. (87.3%) of II was collected, m. p. 186.5–187°.

**(c) By Acid Hydrolysis of IV.**—This reaction proceeds rapidly in hot solutions, but the product is contaminated with the chloride VII when hydrochloric in acetic acid is used, and with the ether V in the case of sulfuric acid.

*Anal.* Calcd. for $C_{13}H_{10}O_3S$: C, 63.40; H, 4.09. Found: C, 63.29, 63.55; H, 4.11, 4.23.

**10-Bromothiaxanthene-5-dioxide (VI).**—To a solution of 10.4 g. of III in 1 l. of carbon tetrachloride was added 7.6 g. of bromine dissolved in the same solvent, and the mixture was boiled for one and three-quarters of an hour. The bromide began to crystallize during this period; it was obtained in the form of a tan powder. The yield was 12.25 g. (87.6%). The material may be recrystallized from hot dioxane; it darkens at 260° but does not melt.

*Anal.* Calcd. for $C_{13}H_9O_2SBr$: C, 50.50; H, 2.93; Br, 25.85. Found: C, 50.85; H, 3.19; Br, 25.83, 26.83.

**10-Chlorothiaxanthene-5-dioxide (VII).**—To the solution of 0.4 g. of IV in 7.5 cc. of hot glacial acetic acid was added 2.5 cc. of concentrated hydrochloric acid. After a few seconds VII began to separate; heating was continued for one and one-half minutes, then the mixture was cooled and filtered. Water precipitated a small additional amount of VII from the filtrate. The yield was 0.35 g. (95%); recrystallization from benzene yielded shiny prisms that melt with discoloration at 253–258°. The compound gives a strong Beilstein test.

The alcohol II is converted to the same substance when treated as described.

*Anal.* Calcd. for $C_{13}H_9O_2SCl$: C, 58.98; H, 3.43. Found: C, 59.49, 58.95; H, 3.67, 3.51.

**10-Acetoxythiaxanthene-5-dioxide (IV).—(a) By reductive acetylation.**—To a mixture of 0.5 g. of I and 0.5 g. of zinc dust was added 5 cc. of acetic anhydride and one drop of triethylamine. The mixture became warm during five minutes and then cooled off again. It was heated for five minutes on the steam-bath, filtered, and decomposed with water at 100°. The product separated as a colorless solid weighing 0.52 g. (88%), m. p. 154–156°. Recrystallization from benzene or from alcohol yields the pure acetate, m. p. 155.6–157°. The substance may appear in the form of needles or leaflets, and of hexagonal plates; occasionally a sample resolidifies after melting as described and remelts at 158–158.5° or 159–160°. The use of larger amounts of base during the acetylation leads to contamination of the product by a small quantity of an unidentified yellow substance.

**(b) From the Bromide VI.**—A mixture of 12.25 g. of VI, 7 g. of silver acetate, and 100 cc. of glacial acetic acid was stirred on the steam-bath for one-quarter of an hour. After filtration water was added and the whitish product was collected. Recrystallization from alcohol afforded 8.4 g. (73.5%) of pure IV, m. p. 154.8–156.8°.

Acetylation of II in the usual manner with pyridine and acetic anhydride gave IV in 99% yield.

*Anal.* Calcd. for $C_{15}H_{12}O_4S$: C, 62.48; H, 4.19. Found: C, 62.46, 62.53; H, 4.33, 4.45.

**Ether of Thiaxanthenol-5-dioxide (V).**—The alcohol II (0.2 g.) was heated in an oil-bath at 197 ± 5° for one-half hour when the melt solidified to a compound melting at 262–272° with discoloration. The solid was recrystallized from glacial acetic acid (15 cc.) which deposited 0.14 g. (72%) of a colorless crystal powder having the composition of V and melting at 280–283° with darkening.

*Anal.* Calcd. for $C_{26}H_{18}O_5S_2$: C, 65.80; H, 3.82. Found: C, 65.95, 65.66; H, 4.00, 3.93.

**Solubility of II in Alkali.**—To 20 mg. of II contained in a small ampoule was added 1 cc. of a mixture of 1.5 cc. of dioxane, 3.5 cc. of potassium hydroxide and 66 mg. of sodium dithionite. The vessel was sealed, and the blue color that had developed disappeared soon. The solid dissolved within a few minutes of agitation at room temperature. When the vessel was opened the blue color reappeared rapidly.

When 20 mg. of II was treated similarly with 1 cc. of 30% aqueous dioxane, partial solution occurred only on heating, and most of the material crystallized again on cooling to room temperature.

### B. Study of the Oxidation Reduction Equilibrium

**Alkaline Cleavage of the Oxidation Reduction System.**—A mixture of 100 mg. of each ketone I and alcohol II, 5 cc. of pyridine and 10 cc. of 0.6 *N* sodium hydroxide was sealed into a pyrex glass ampoule, without any special precautions to keep out oxygen from the air. The deep blue liquid was heated at 110° for two days at the end of which the color had faded to a very pale yellow. The originally homogeneous solution had separated into two phases, one of which had a volume of about 2 cc. and appeared to be a concentrated alkaline solution of sodium silicate. On dilution with water a white solid separated, which was collected, dried, and extracted with benzene. A residue of silica was left undissolved; the filtrate contained 22 mg. of a white compound melting at 174–176°, which after recrystallization melted at 175.4–176° and did not depress the melting point of authentic xanthone.

The alkaline pyridine–water filtrate was freed of pyridine under reduced pressure and a small amount of solid separated, identified as I by its color reaction with zinc and alcoholic potash. On acidification of the filtrate a strong odor of sulfur dioxide was observed, but no other identifiable fission products were isolated.

**Acid Decomposition of the Blue Solution.**—To 40 cc. of ethanol in an erlenmeyer flask equipped with a ground-glass stopper was added 1.9 g. of sodium, while the flask was cooled with ice. After dissolution of the metal 0.5 g. each of I and II was added rapidly and the flask was stoppered. After agitation with slight warming for fifteen minutes most of the material had dissolved and the liquid was a dark inky blue. The material was poured rapidly into 6 cc. of acetic acid and the flask was rinsed with a few additional cc. of the same acid. By filtration of the solution, dissolution of the precipitated sodium acetate with water, collection of the organic material precipitated by more water, and finally removal of the organic solvents under reduced pressure and recrystallization from ethanol of the deposited organic material, four crops of I totalling 242 mg., m. p. 187.2–188.6°, were obtained.

The ethanolic mother liquor was diluted with water and the precipitated solid was collected and dried. Owing to mechanical loss the weight of this fraction is not known precisely but estimated at 200 to 250 mg. On recrystallization from benzene 50 mg. of II was obtained, m. p. 186–187° alone or when mixed with authentic II.

Although only a fraction of the total material was accounted for, the conclusion is justified that no significant amounts of the pinacol could have been present because this substance should have appeared among the least

soluble, high-melting fractions, yet no trace of such a compound was detected at any point during the separation.

**Air Oxidation of II.**—To a solution of 500 mg. of II in 4 cc. of pyridine and 3 cc. of water was added 7 cc. of 1 *N* tetramethylammonium hydroxide. An inky blue coloration resulted at once and white crystals were being deposited. The solution was agitated for seven minutes when the blue color had disappeared permanently. The pale orange liquid was filtered from the solid which weighed 460 mg. (93%), m. p. 186–187.8°.

**Colorimetry.**—A Thunberg tube was equipped with gas inlet tubes fitted with stopcocks and extending to the bottom of the main compartment and of the side-arm. Into the side-arm was placed 0.5 cc. of a solution containing $8.4 \times 10^{-3}$ mole/l. of each I and II in pyridine; the main compartment contained 4.5 cc. of a pyridine-buffer mixture. Hydrogen was passed through for ten minutes, admitted through an all-glass train; then the vessel was closed, inserted into a Klett colorimeter (red filter, no. 66) and the galvanometer was zeroed. The liquids were mixed, the tube was replaced in the same position and the optical density was read as usual. The results are as follows:

| Alkali *M* | Optical density |
|---|---|
| 0.027 | 0.106 |
| .11 | .265 |
| .91 | .850 |

**Spectrophotometry.**—Flat-bottomed ampoules drawn from a piece of 16-mm. pyrex tubing were filled with pyridine-alkali mixtures as used in runs 4, 8 and 17 in Table I and pure nitrogen was bubbled through the liquid for ten minutes. The ampoule was closed with a rubber cap and a small amount of a strong solution (about 0.01 *M*) of II in pyridine was added by means of a syringe and hypodermic needle. The oxygen contained in the pyridine solution as well as oxygen remaining in the buffer mixture caused the immediate appearance of the blue color of the semiquinone. When the intensity appeared suitable the ampoule was sealed; some heat decomposition near the neck of the ampoule could not be avoided. After several attempts samples suitable for spectrophotometry were obtained; the degree of oxidation or the concentration of the oxidation–reduction system are, of course, not known. The ampoules were placed into the cell holder of a Beckman spectrophotometer and the place for the blank solvent was occupied by an ampoule filled with pyridine-alkali. In spite of the optically most unsatisfactory shape of the ampoules the optical densities appeared to be reproducible within about ±1% of their numerical values on successive measurements when the cell holder was shifted from and restored to its rest position in the instrument. The results are listed.

| Alkali *M* | λmax. (mμ) | *D* max. | λmin. (mμ) | *D* min. | λmax. (mμ) | *D* max. | $\frac{D_{370}}{D_{475}}$ |
|---|---|---|---|---|---|---|---|
| 0.027 | 370 | 1.76 | 475 | 0.258 | 570 | 0.79 | 2.54 |
| .14 | 370 | 2.9 | 475 | .431 | 570 | 1.46 | 3.39 |
| .91 | 370 | 2.9 | 475 | .509 | 570 | 1.29 | 3.06 |

The columns labelled *D* refer to the optical density registered; the densities at 370 mμ are so high that their quantitative significance is very small.

The red form in aqueous dioxane was studied in the presence of 0.11 mole/liter potassium hydroxide in a square Corex glass cell equipped with a ground-in glass-stopper, into which the liquid was forced by nitrogen pressure from a titration cell where it had been obtained by careful oxidation of a blue solution with air-saturated buffer. No change in color was visible after such a pink solution had stood in the titration cell under nitrogen for one-half hour. Because of the low concentration and the sensitivity of the system, some air oxidation could not be avoided during the transfer, and the optical density of the solution finally secured in the cell was very low: at the absorption maximum at 470 and 480 mμ the sample had an optical density of only 0.051. The red form could also be seen during the potentiometric titrations, although, as shown by a separate experiment, the palladium colloid tends to obscure the color.

Existence of the red form could be demonstrated not only at the *p*H mentioned but also at lower and higher alkalinity. On the basis of visual inspection the red form seems to make a greater contribution to the total color at low alkalinity, but apart from the somewhat debatable spectroscopic data there is no objective evidence for this subjective estimation of color.

**Potentiometry.**—The procedure was based on Michaelis' recommendations.[16] The nitrogen was purified by passage through Fieser solution followed by lead acetate solution and a 25-cm. section of copper filings heated to 450°. The gas was conducted to the titration cell through all-glass connections made flexible by means of a ball-and-socket joint, and proved to be inert toward moist white phosphorus. The cell was equipped with two electrodes of shiny platinum (*ca.* 1 sq. cm.), gas outlet, buret, etc., and an externally operated electromagnetic stirrer was found to be a convenient means of agitation. A sleeve-type saturated calomel half-cell was used to complete the galvanic chain. Potentials were measured with a type K-2 potentiometer and a Leeds and Northrup box-type galvanometer having a sensitivity of $1.7 \times 10^{-8}$ amp. per mm.

The pyridine used as a solvent was purchased from the Barrett Company, New York ("Barrett refined") and purified by distillation through a Widmer column. The dioxane was purified by the customary treatment with hydrochloric acid and then sodium metal.

Stock solutions of II appeared to be stable for a week or two when pyridine was the solvent. After this length of time they were generally discarded because of the appearance of a faint yellow tinge. No discoloration was noticeable with dioxane solutions, but some change did take place within a month of standing. As a rule, only fresh solutions were used.

The composition of the reaction media is listed in Tables I and II. At the beginning of a run the added II was partly or wholly oxidized to I by the oxygen contained in the solvents. Colloidal palladium was added and hydrogen was passed in until the blue color had been discharged and the potential of the chain had become constant and equal to within 0.1 mv. for the two electrodes; the *p*H was computed from the e. m. f. thus observed. Some difficulty was experienced in the most alkaline media because of premature coagulation and deactivation of the colloid. The e. m. f. would reach a maximum value, keep this value for a few minutes, and then, while hydrogen was still being admitted, the potential would begin to drift away from its steady position. An additional amount of palladium would generally restore the e. m. f. close to its previous steady value, and there is no reason to doubt that this potential does correspond to equilibrium conditions. At the highest alkalinities it was sometimes found difficult to expel the hydrogen from the system prior to the beginning of the oxidative titration, presumably owing to retention of the gas by the coagulated palladium. If in such cases a reasonable rise of the potential could not be achieved within about one-half hour after the addition of the first few per cent. of oxidizing agent the run was discarded. Three kinds of palladium colloid were investigated; a commercial product ("Baker Colloid 46"), a colloid stabilized with gum arabic[17] and one containing sodium protalbinate.[18] The last-named preparation, obtained according to Paal's original recommendation by reduction of palladous chloride with hydrazine, proved to be the most satisfactory for our purposes. The sodium protalbinate had been made from a sample of commercial egg albumin.

(16) See Weissberger, "Physical Methods of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1946, p. 1085 ff.

(17) Wohl and Mylo, *Ber.*, **45**, 340 (1912).

(18) Paal and Amberger, *ibid.*, **37**, 134 (1904).

The oxidizing agent was potassium ferricyanide, used in aqueous buffer solutions for the pyridine runs; the concentrations were chosen so that from 3 to 5 cc. of oxidizing solution was added to the 50-cc. volume containing the oxidation–reduction system in the titration cell. In the dioxane runs the ferricyanide was dissolved freshly for each experiment in the same solvent mixture that was used as buffer in the titration cell; the volumes added were between 3 and 4 cc. for 50 cc. of buffer containing the oxidation–reduction system.

In most runs the potentials were established about as rapidly as the potentiometer could be adjusted, and the potentials registered by the two electrodes agreed with one another within ±0.1 mv. or better, except in the regions of 0 to 5% and 95 to 100% completion. The potentials were stable with time and in general showed no noticeable drift. At the lower alkalinities potentials were established more and more sluggishly and, particularly toward the end-point, long periods of waiting became necessary. In such cases it was advantageous to use the return of the blue color as a guide rather than to wait for the potential to fall to a constant value.

Finally the *p*H was measured again after addition of more palladium colloid, and the tables give the average of the initial and final *p*H value together with the deviation of these figures from the average. In all cases the higher *p*H is the initial one.

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## Summary

1. Thiaxanthenol-5-dioxide and several of its derivatives have been prepared and characterized.

2. The existence of a mobile, two-step oxidation–reduction equilibrium between thiaxanthenol-5-dioxide and thiaxanthone-5-dioxide in alkaline solution has been established. By optical, chemical and electrochemical means it was shown that the colored entity in this equilibrium is a semiquinone.

3. The structure of the semiquinone is discussed with particular reference to potential *vs.* *p*H diagrams.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC CO.]

# The Relative Reactivities of Chloromethyltrimethylsilane and Chloromethylpentamethyldisiloxane

BY GEORGE F. ROEDEL

When chloromethyl siloxanes are treated with alkaline reagents, Si–C cleavage of the $-SiCH_2Cl$ group occurs to form methyl chloride.[1] It has been claimed that the cleavage is accompanied by a competitive hydrolysis of the C–Cl bond.[1] On the other hand no Si–C cleavage of the $-SiCH_2Cl$ group was reported when chloromethyltrimethylsilane was treated with basic reagents.[2] Since methyl chloride, the cleavage product, reacts with the alkaline reagents used in the previous work cited, it was not clearly established that hydrolysis of the C–Cl bond in chloromethyl siloxanes occurs to any significant degree nor that Si–C cleavage is absent with chloromethyltrimethylsilane. In an effort to establish these points and to further elaborate the effect of silicon-bonded oxygen on the behavior of the functional group attached to the silicon, the reactivities of $(CH_3)_3SiCH_2Cl$ (I) and $(CH_3)_3SiOSi(CH_3)_2CH_2Cl$ (II) have been compared in this paper.

The activating effect of oxygen bound to silicon has previously been shown by Sommer, Bailey, Strong and Whitmore.[3] They found markedly greater reactivity of the C–Cl bond in α-chloroethyldiethylsilanol as compared with α-chloroethylmethyldiethylsilane toward such reagents as sodium ethoxide in ethanol and potassium acetate in glacial acetic acid.

Whitmore and Sommer[2] found that chloromethyltrimethylsilane (I) with sodium iodide in dry acetone gave a good yield of the corresponding iodide. In this study chloromethylpentamethyldisiloxane (II) was found to behave similarly with this reagent to also give the iodide in good yield.

$$(CH_3)_3SiOSi(CH_3)_2CH_2Cl + NaI \longrightarrow (CH_3)_3SiOSi(CH_3)_2CH_2I + NaCl$$

III

Neither α-chloroethyldiethylsilanol,[3] nor I, nor II reacts with aqueous or ethanolic silver nitrate. Iodomethyltrimethylsilane is also unreactive with silver nitrate reagents,[2] but iodomethylpentamethyldisiloxane (III) reacts readily with ethanolic silver nitrate to precipitate silver iodide.

Both chloro-(II) and iodomethylpentamethyldisiloxane (III) readily form Grignard reagents in a similar manner to chloro-(I) and iodomethyltrimethylsilane.[2]

The Si–C bond of the chloromethylsilyl group, $-SiCH_2Cl$, is not split by sulfuric acid at room temperature. This was shown by adding small amounts of I and II to methyl siloxane systems of known functionality and equilibrating with sulfuric acid.[4] The viscosities of the oils obtained

(1) Krieble and Elliott, THIS JOURNAL, 68, 2291 (1946).
(2) Whitmore and Sommer, *ibid.*, 68, 481 (1946).
(3) Sommer, Bailey, Strong and Whitmore, *ibid.*, 68, 1881 (1946).
(4) Roedel, *Anal. Chem.*, 20, 705 (1948).

showed that the change in functionality which would have accompanied cleavage of the Si–C bond did not occur.

The greater reactivity of the $-SiCH_2Cl$ group when oxygen is also bonded to the silicon is shown by the results tabulated in Table I. The reactivity of chloromethylpentamethyldisiloxane (II) was significantly greater than that of chloromethyltrimethylsilane (I) with sodium ethoxide in absolute ethanol and potassium acetate in glacial acetic acid. This behavior parallels closely the greater reactivity of α-chloroethyldiethylsilanol as compared to α-chloroethylmethyldiethylsilane with the same reagents.[3] With potassium hydroxide in *n*-butanol the difference in reactivity between I and II was slight.

TABLE I

RELATIVE REACTIVITIES OF CHLOROMETHYLTRIMETHYLSILANE AND CHLOROMETHYLPENTAMETHYLDISILOXANE

| Reagent[a] | Reaction, % $(CH_3)_3SiCH_2Cl$ (I) | Reaction, % $(CH_3)_3SiOSi(CH_3)_2CH_2Cl$ (II) |
|---|---|---|
| 2.0 *M*-$C_2H_5ONa$/abs. $C_2H_5OH$ | 36 | 91 |
| ($1^2/_3$ hours reflux) | (35-1-0)[b] | (59-29-3) |
| 1.0 *M*-$CH_3CO_2K$/glacial $CH_3CO_2H$ | 2 | 76 |
| ($1^3/_4$ hours reflux) | (2-0-0) | (76-0-0) |
| 1.0 *M*-KOH/moist $C_4H_9OH$ | 77 | 90 |
| ($1^3/_4$ hours reflux) | (67-10-trace) | (47-43) |
| 1.0 *M*-KOH/moist $C_4H_9OH$ | 77 | 80 |
| (1 hour reflux) | (71-6-0) | (62-17-1) |

[a] Molar ratio of $C_2H_5ONa$, $CH_3CO_2K$ and KOH to $(CH_3)_3SiCH_2Cl$ or $(CH_3)_3SiOSi(CH_3)_2CH_2Cl$ was 2:1. [b] Figures in parentheses give % reaction determined for the reaction flask, trap 1 and trap 2, respectively.

Since it had previously been shown that alkaline reagents react with chloromethyl siloxanes to form methyl chloride,[1] provision was made for determining any methyl chloride which formed and escaped from the reaction mixtures. This was effected by using bubbler traps filled with sodium ethoxide in absolute ethanol. The reaction between methyl chloride and sodium ethoxide in absolute ethanol is rapid and complete when the reagent is warm. The decrease in concentration of the sodium ethoxide in the traps is a measure of that methyl chloride which formed and escaped from the reaction mixture.

Since methyl chloride does not react with 1.0 *M* potassium acetate in glacial acetic acid, the fact that all of the sodium ethoxide remained unreacted in the traps is good evidence that no –Si–C cleavage of the $-SiCH_2Cl$ group in I or II occurs with this reagent. This evidence indicates the reaction to be entirely bimolecular nucleophilic substitution on the methylene carbon as suggested by Whitmore and Sommer.[2]

With sodium ethoxide in absolute ethanol and potassium hydroxide in *n*-butanol, however, formation of methyl chloride shows that Si–C cleavage of the $-SiCH_2Cl$ group occurs with both I and II. The trap figures are minimum figures for the Si–C splitting, since methyl chloride can react with both reagents.

It is not shown in this work whether hydrolysis of the C–Cl bond accompanies cleavage of the Si–C bond in chloromethyl siloxanes. However, the inadequacy of a chloride ion determination in the reaction vessel as sole measure of a C–Cl hydrolysis reaction is established. The cleavage product methyl chloride reacts readily with alkaline reagents, and the amount which escapes from the reaction zone varies with the experimental conditions.[5] Actually determining the presence or absence of a hydrolytic reaction is not readily accomplished. Isolation of ethoxymethylpentamethyldisiloxane, the expected product of the hydrolytic reaction of II with sodium ethoxide in absolute ethanol, was attempted but was unsuccessful. Rearrangement of siloxane bonds during the reaction produces a series of methyl siloxanes[1] that make isolation by fractional distillation difficult. Even were it proved that no ethoxymethylpentamethyldisiloxane were present in the reaction product, the possibility would still exist that it formed but was in turn subjected to Si–C cleavage of the $Si-CH_2OC_2H_5$ group by the reagent. Such a cleavage would presumably produce methyl ethyl ether, but this is also the product of the methyl chloride–sodium ethoxide reaction.

However, the reaction of sodium ethoxide in absolute ethanol with chloromethyltrimethylsilane (I) has been elaborated. The chief attack is at the methylene carbon (1). Of the total reaction, however, 5–10% is attack at the silicon

$$(CH_3)_3SiCH_2Cl + C_2H_5ONa \xrightarrow{C_2H_5OH} \underset{\text{IV}}{(CH_3)_3SiCH_2OC_2H_5} + NaCl \quad (1)$$

with resultant Si–C bond cleavage. This cleavage reaction is primarily reaction (2) but some Si–C cleavage of the $-SiCH_2OC_2H_5$ group of

$$(CH_3)_3SiCH_2Cl + C_2H_5OH \xrightarrow{C_2H_5ONa} (CH_3)_3SiOC_2H_5 + CH_3Cl \quad (2)$$

(5) When 1.95 g. of chloromethylpentamethyldisiloxane and 9.9 cc. of 2.0 *M* sodium ethoxide in absolute ethanol were allowed to react in a 25-cc. test-tube, the methyl chloride detected in the trap system varied with the rate of reflux. Vigorous reflux for one hour and forty minutes gave a total reaction of 91%. The methyl chloride escaping to the trap system represented 32% of the reaction. Gentle reflux for a similar period produced 90% total reaction with methyl chloride caught in the traps representing but 21%. In these reactions a hot bath was raised around the reaction tube. In another experiment 150 g. of chloromethylpentamethyldisiloxane and 755 cc. of 2.0 *M* sodium ethoxide in absolute ethanol were allowed to react in a one liter round-bottomed flask, the mixture being heated to reflux by means of a heating mantle over a forty-five minute period and continued at reflux for four hours. Methyl chloride which escaped from the reaction mixture was not determined but an extent of reaction of 86% in the reaction flask indicates that under such conditions much less methyl chloride escapes. It is, however, possible that when the temperature is raised slowly the course of the reaction is changed and less Si–C cleavage occurs.

ethoxymethyltrimethylsilane (IV) may also occur. The evidence for these conclusions consists of (a) the isolation and characterization of ethoxymethyltrimethylsilane (IV), (b) the determination of the amount of monofunctional methyl siloxane, $(CH_3)_3SiO_{1/2}$, in the product, (c) the measurement of methyl chloride evolved, and (d) the identification of hexamethyldisiloxane and IV in the product by means of the mass spectrometer.

## Experimental

**Preparation of Chloromethylpentamethyldisiloxane (II) and Chloromethyltrimethylsilane (I).**—The method described by Krieble and Elliott[6] was employed in preparing chloromethylpentamethyldisiloxane, $n^{20}D$ 1.4102, b.p. 151–152°.

Chloromethyltrimethylsilane[2] was made by treating a mixture of chloromethylmethyldichlorosilane[1] and chloromethyldimethylchlorosilane[1] with methylmagnesium bromide.[7] Dibutyl ether was used as the solvent. The chloromethyltrimethylsilane used for the comparative reactivity experiments had these properties: b.p. 98.2–98.7° (747 mm.), $n^{20}D$ 1.4169, Cl, 28.4, 28.5 (calcd. for $C_4H_{11}SiCl$, 28.9 Cl).

**Iodomethylpentamethyldisiloxane (III).**—The technique employed for the preparation of III followed in detail that used by Whitmore and Sommer in the preparation of iodomethyltrimethylsilane.[2] From the reaction of 65.5 g. (0.44 mole) of dry sodium iodide and 49.5 g. (0.25 mole) of chloromethylpentamethyldisiloxane (II) and 500 cc. of dry acetone was obtained upon fractionation 54.5 g. (0.19 mole) of iodomethylpentamethyldisiloxane, b.p. 77° (20 mm.), 187° (757 mm.), $n^{20}D$ 1.4575. The yield was 76%.

*Anal.* Calcd. for $C_6H_{17}Si_2OI$: I, 44.0. Found: I, 43.6, 43.6.

**Reactions with Silver Nitrate.**—One gram of chloromethylpentamethyldisiloxane was added to 25 cc. of 20% aqueous silver nitrate. No precipitate formed even after five minutes of boiling. The result was the same when a saturated ethanol solution of silver nitrate was used. Treating chloromethyltrimethylsilane with the same reagents likewise produced no reaction.

One gram of iodomethylpentamethyldisiloxane with 25 cc. of 20% aqueous silver nitrate showed only faint opalescence after five minutes of boiling. In ethanolic silver nitrate at room temperature a faint turbidity developed in a few seconds and after five minutes a curdy precipitate of silver iodide had settled.

**Grignard Reagents from Chloro- and Iodomethylpentamethyldisiloxane: $(CH_3)_3SiOSi(CH_3)_2CH_2MgCl$ and $(CH_3)_3SiOSi(CH_3)_2CH_2MgI$.**—A mixture of 3.9 g. (0.02 mole) of chloromethylpentamethyldisiloxane, 0.5 g. (0.02 mole) of magnesium turnings and 10 cc. of dry ethyl ether was placed in a 125-cc. flask topped by a reflux condenser and a Drierite–Ascarite tube. Reaction began upon adding a crystal of iodine and heating at gentle reflux for fifteen minutes. After twenty hours the customary titration indicated an 80% yield of $(CH_3)_3SiOSi(CH_3)_2CH_2MgCl$.

A mixture of 2.9 g. (0.01 mole) of iodomethylpentamethyldisiloxane, 0.24 g. (0.01 mole) of magnesium turnings and 5 cc. of dry ethyl ether was allowed to react as above. The reaction began readily without the application of heat. After twenty hours, titration showed a 93% yield of $(CH_3)_3SiOSi(CH_3)_2CH_2MgI$.

**Chloromethyltrimethylsilane and Chloromethylpentamethyldisiloxane with Sulfuric Acid.**—The general technique of equilibrating methyl silicone oils with sulfuric acid has been described by Patnode and Wilcock.[8] It has also been shown that the relationship existing between the viscosity of equilibrated methyl silicone oils and their functionality can be used as a sensitive analytical tool for the determination of mono- and trifunctional methyl siloxane units in an otherwise difunctional methyl siloxane system.[4]

To 18.0 g. of an equilibrated methyl silicone oil (A) composed of mono- and difunctional units was added 0.042 g. of chloromethyltrimethylsilane. The mixture was then equilibrated as has been described[4] by shaking for forty-eight hours with 0.7 cc. of concentrated sulfuric acid to yield oil B. Oil C was prepared by merely dissolving 0.030 g. of chloromethyltrimethylsilane in 12.0 g. of A. The viscosities obtained lie within the experimental range of accuracy. Had the $-CH_2Cl$ groups been completely split from the Si, the mono-functional groups, $(CH_3)_3SiO_{1/2}$, resulting would have lowered the viscosity of oil B to 200 centistokes.[9] It was also found that chloromethyltrimethylsilane could be purified of –SiOSi– containing compounds by shaking with concentrated sulfuric acid. Compounds containing the siloxane linkage dissolved in the acid; the chloromethyltrimethylsilane separated as a second phase. No pressure buildup was noted during such operations to indicate volatile decomposition products.

| Oil | Viscosity, centistokes-100°F. |
|---|---|
| A | 242 |
| B | 239 |
| C | 241 |

A similar technique was used to check chloromethylpentamethyldisiloxane. Hexamethyldisiloxane and chloromethylpentamethyldisiloxane were equilibrated with octamethylcyclotetrasiloxane, contact with 1.2 cc. of concentrated sulfuric acid being effected for forty-eight hours. The amount of each disiloxane added was equivalent to 1.10 mole per cent monofunctional units. The greater viscosity of the oils prepared with chloromethylpentamethyldisiloxane is believed due to the greater polarity of the C—Cl bond. If no viscosity increase is attributed to the presence of C—Cl bonds, the cleavage of the Si—C bond of the —Si—$CH_2Cl$ group in chloromethylpentamethyldisiloxane was at most 2%. This derives from the fact that a methyl silicone oil composed of mono- and difunctional units has a viscosity of 258 centistokes at 100 °F. when the monofunctional unit content is 1.08 mole per cent.[9] The drop in monofunctionality of from 1.10 to 1.08 mole per cent would require but 2% cleavage to a difunctional unit.

| Wt. $[(CH_3)_2SiO]_4$, g. | Wt. chain stopper, g. | Viscosity (centistokes-100°F.) |
|---|---|---|
| 30.0 | 0.363 $(CH_3)_3SiOSi(CH_3)_3$ | 242 |
| 30.0 | .443 $(CH_3)_3SiOSi(CH_3)_2CH_2Cl$ | 257 |
| 30.0 | .441 $(CH_3)_3SiOSi(CH_3)_2CH_2Cl$ | 259 |

**Measurement of Evolved Methyl Chloride.**—Isolation and identification of methyl chloride as the volatile cleavage product of chloromethyl siloxanes has been reported by Elliott and Krieble.[1,6] A readily effected quantitative method of determining methyl chloride evolved is bubbling the gases through sodium ethoxide in absolute ethanol. To the 25-cc. erlenmeyer flask in which the reactions of Table I were run was attached a 45-cm., water-cooled, Liebig reflux condenser. The condenser outlet was in turn connected to a pair of traps (25 cm., 1 cm. diameter) arranged in series with an Ascarite–Drierite tube at the trap outlet. All connections were glass tubing and ground glass joints since rubber absorbs methyl chloride. Into each trap was pipeted 9.9 cc. of 2.0 *M* sodium ethoxide in absolute ethanol. The first trap was heated by the vapors of refluxing acetone to increase the speed of reaction. The final trap was allowed to stand overnight before titration.

(6) Krieble and Elliott, THIS JOURNAL, **67**, 1810 (1945).
(7) Whitmore, Sommer and Gold, *ibid.*, **69**, 1976 (1947).
(8) Patnode and Wilcock, *ibid.*, **68**, 358 (1946).
(9) D. F. Wilcock, private communication.

When 54.9 cc. (0°, 760 mm.) of methyl chloride was bubbled into the trap system from a gas buret over a one and a half hour period, 94% of the methyl chloride reacted in trap 1. A negligible amount of methyl chloride was indicated in trap 2. In this experiment trap 2 was not allowed to stand before titration. The extent of reaction ($CH_3Cl + NaOC_2H_5 \rightarrow CH_3OC_2H_5 + NaCl$) was determined by diluting with water and titrating with standard sulfuric acid using phenol red as an indicator. Turbidity due to sodium chloride separation was marked after only 5 cc. of methyl chloride had been added.

**Reaction of Chloromethyltrimethylsilane and Chloromethylpentamethyldisiloxane with Reagents of Table I.**—The experimental setup was that described above. The reagent (9.9 cc.) and I or II were charged to the 25 cc. erlenmeyer flask, the molar ratio of sodium ethoxide, potassium hydroxide or potassium acetate to I or II being two. Heat was supplied by raising a hot silicone oil-bath around the reaction flask. The temperature of each reaction was the reflux temperature of the reaction mixture. At the conclusion of reaction the system was swept with a slow stream of nitrogen. For sodium ethoxide in absolute ethanol and potassium hydroxide in moist butanol the extent of reaction in the erlenmeyer flask and the methyl chloride evolved were then determined by dilution with water and titration with 0.990 *N* sulfuric acid employing a phenol red indicator. Twenty-five per cent. of the titrations were checked against Volhard chloride determinations with excellent agreement. For potassium acetate in glacial acetic acid the extent of reaction was determined by Volhard chloride analysis; no methyl chloride entered the traps. Blanks were titrated for the volume of alkaline reagents pipeted into the reaction flask and traps.

To check on the efficiency of the water condenser, 1.2 g. of chloromethyltrimethylsilane (I) was refluxed in the system with 10 cc. of moist butanol for one hour. Nitrogen was then swept through the system for one hour as the mixture cooled (nitrogen inlet just above neck of erlenmeyer flask). Only a very faint opalescence developed when the diluted trap I contents were tested with silver nitrate.

**Reaction of Chloromethyltrimethylsilane (I) with Sodium Ethoxide in Absolute Ethanol.**—To a 250-cc. round-bottomed flask were charged 210 cc. of 1.91 *M* sodium ethoxide (0.40 mole) in absolute ethanol and 24.5 g. (0.20 mole) of I ($n^{20}D$ 1.4179, Cl, 29.0%).[10] The condenser and trap system described above were attached. The reaction was continued for four hours at reflux. Titration showed 0.10 mole sodium ethoxide had reacted in the flask, an extent of reaction of 50%. The amount of sodium ethoxide reacted with in traps 1 and 2 was 0.0041 and 0.0004 mole, respectively. This increases the extent of reaction 2% and shows that a minimum of 4% of the total reaction was the cleavage reaction forming methyl chloride. Upon dilution of the reaction product with 1 l. of water, 18.5 g. of a water immiscible phase was separated. This reaction product contained 2.4% by weight of monofunctional methyl siloxane units [0.0054 mole $(CH_3)_3SiO_{1/2}$]. Thus 5% of the chloromethyltrimethylsilane which reacted was subjected to Si—C bond cleavage. Analysis of the reaction product in the mass spectrometer showed the typical main peak for hexamethyldisiloxane (mass number 147). Also the presence of ethoxymethyltrimethylsilane was indicated by significant peaks at mass numbers 103 and 117, corresponding to the fragments $(CH_3)_3SiCH_2O$ and $(CH_3)_2SiCH_2OC_2H_5$, respectively.

A similar experiment was performed on a larger scale. To a 1-liter round bottomed flask were charged 750 cc. of 2.01 *M* sodium ethoxide (1.51 moles) in absolute ethanol and 94.3 g. of I ($n^{20}D$ 1.4176, Cl, 28.2 %). After four hours at reflux, 0.50 mole of sodium ethoxide had reacted in the reaction flask, an extent of reaction of 67%. The amount of reaction in traps 1 and 2 was 0.0042 and 0.0010 mole of sodium ethoxide, respectively. The cleavage reaction resulting in methyl chloride formation is at least 1% of the total reaction. The reaction product was diluted with 2 l. of water and 85 g. of a water immiscible phase (A) separated. Upon washing free of alkali and drying with anhydrous sodium sulfate, A was analyzed by the gel test method[4] and found to have a monofunctional methyl siloxane unit concentration of 3–5% by weight. This represents 0.042 mole $(CH_3)_3SiO_{1/2}$ and shows that Si–C cleavage constituted 8% of the total reaction. Seventy-two grams of the water immiscible phase (A) was then shaken with concentrated sulfuric acid for one-half hour and 25 g. of a sulfuric acid insoluble layer (B) separated. B upon washing and drying was found to have a $n^{20}D$ of 1.4174 and represented unreacted chloromethyltrimethylsilane. The sulfuric acid solution was run slowly into 2 l. of water with cooling and 30 g. of an immiscible phase (C) separated. After drying with anhydrous sodium sulfate, a gel test analysis[4] showed the presence of 21% by weight of monofunctional methyl siloxane units. Degradation of some ethoxymethyltrimethylsilane to $(CH_3)_3SiO_{1/2}$ apparently occurred during solution in sulfuric acid. To rid C of most of these methyl siloxane units (presumably present as hexamethyldisiloxane boiling at 100°) a methyl silicone oil incorporating the $(CH_3)_3SiO_{1/2}$ units in a polymeric system was prepared.[11] Twenty-five grams of C was added to 475 g. of octamethylcyclotetrasiloxane and the solution equilibrated.[3,6]. Before fractional distillation 75 cc. of xylene was added to reduce the viscosity. Three fractions boiling from 102.3–102.9° had the same refractive index ($n^{20}D$ 1.3940) and were combined (5.4 g.). Analysis showed this material to be ethoxymethyltrimethylsilane (IV).

*Anal.* Calcd. for $C_6H_{16}OSi$: C, 54.5; H, 12.2; mol. wt., 132.2. Found: C, 54.5; H, 12.0; mol. wt., 130 and 134.

**Acknowledgment.**—The author is indebted to Dr. Paul Zemany for the mass spectrometer analyses, Mr. Lester Bronk for the Volhard chloride determinations, Miss Mary Caldwell for the micro combustion analysis and the Schenectady Works Laboratory for Parr chlorine and viscosity determinations.

## Summary

The reactivities of chloromethyltrimethylsilane and chloromethylpentamethyldisiloxane have been compared.

The replacement of an alkyl group attached to the Si holding the chloromethyl group by a trimethylsiloxy group greatly enhances the reactivity to such reagents as potassium acetate in glacial acetic acid and sodium ethoxide in absolute ethanol.

The reaction of sodium ethoxide with chloromethyltrimethylsilane results primarily in attack on the chloromethyl carbon and formation of ethoxymethyltrimethylsilane, a silicon containing ether. A small amount of Si–C cleavage of the $-SiCH_2Cl$ group also occurs. With chloromethylpentamethyldisiloxane the same reagent causes considerable attack at the Si resulting in Si–C cleavage of $-SiCH_2Cl$ group to form methyl chloride. This may be the sole reaction in this system.

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(10) The chloromethyltrimethylsilane was in addition checked both in the General Electric Nier Type (60 degree) mass spectrometer and by the gel test method.[4] In the mass spectrometer the main peak for hexamethyldisiloxane is the fragment of mass number 147, corresponding to $(CH_3)_2SiOSi(CH_3)_3$. No 147 hump appeared when I was run. Also the gel test showed no monofunctional, $(CH_3)_3SiO_{1/2}$ units, present.

(11) Scott, THIS JOURNAL, 68, 2294 (1946).

[CONTRIBUTION FROM MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

# Chloromethylmethylpolysiloxanes

BY JOHN L. SPEIER

The availability of chlorochloromethylmethylsilanes[1] has prompted the preparation of the linear polymers derived from these and their linear copolymers containing dimethyl or trimethylsiloxy units. The compounds prepared may be regarded as the chlorinated derivatives of the open chain dimethylsiloxanes with trimethylsiloxy end-groups described by Hunter[2] and others.[3,4,5] Data concerning these compounds are to be found in Table I.

TABLE I

CHLOROMETHYLMETHYLSILOXANE POLYMERS

| $x$ = | B. p. °C. | B. p. Mm. | $n^{25}D$ | $d^{25}_4$ | Mol. ref. Found | Mol. ref. Theory[6] | Cs. viscosity 0°C. | Cs. viscosity 99.4°C. | F. p., °C. | Chlorine, % Found | Chlorine, % Calcd. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Series I—$ClCH_2SiMe_2O(Me_2SiO)_xSiMe_2CH_2Cl$ | | | | | | | | | | | |
| 0[1] | 110 | 40 | 1.4363 | 1.034 | 58.5 | 58.50 | 3.54 | 0.76 | −90 | | |
| 1 | 142 | 40 | 1.4283 | 1.020 | 77.1 | 77.24 | 4.55 | 1.00 | −79 | 23.16 | 23.23 |
| 2 | 168 | 40 | 1.4231 | 1.008 | 95.9 | 95.88 | 5.61 | 1.20 | −94 | 18.74 | 18.69 |
| 3 | 190 | 40 | 1.4200 | 1.002 | 114.8 | 114.52 | 6.80 | 1.41 | −85 | 15.86 | 15.64 |
| 4 | 223 | 40 | 1.4173 | 0.996 | 133.2 | 133.30 | ... | .. | −77 | 13.41 | 13.44 |
| Series II—$Me_3SiO(MeSiCH_2ClO)_xSiMe_3$ | | | | | | | | | | | |
| 0[2] | 62 | 225 | 1.3748 | 0.757 | 48.9 | 48.92 | 0.87 | | | | |
| 1 | 102 | 40 | 1.4058 | 0.918 | 72.5 | 72.48 | 2.46 | 0.70 | −85 | 13.15 | 13.09 |
| 2 | 162 | 40 | 1.4212 | 1.006 | 95.5 | 95.88 | 6.02 | 1.18 | −77 | 18.72 | 18.70 |
| 3 | 210 | 40 | 1.4311 | 1.063 | 118.9 | 119.36 | 9.83 | 1.67 | −85 | 21.60 | 21.80 |
| 4 | 251 | 40 | 1.4375 | 1.100 | 142.2 | 142.8 | 21.17 | 2.68 | −77 | 23.24 | 23.78 |
| Series III—$ClCH_2Me_2SiO(MeSiCH_2ClO)_xSiMe_2CH_2Cl$ | | | | | | | | | | | |
| | | | | | | | 55.8° | | Si, % Found | Si, % Calcd. | Mol. wt. Found | Mol. wt. Calcd. |
| 1 | 176 | 40 | 1.4465 | 1.112 | 81.8 | 82.07 | 2.75 | 1.44 | 24.8 | 24.75 | 341 | 340 |
| 2 | 167 | 5 | 1.4520 | 1.157 | 104.4 | 105.57 | 4.97 | 2.45 | 25.2 | 25.03 | 440 | 448 |
| 3 | 210 | 5 | 1.4553 | 1.182 | 128.2 | 129.01 | 8.00 | 3.61 | 25.2 | 25.18 | 560 | 557 |

## Experimental Part and Discussion

The polymers of series I were prepared by refluxing for two hours in aqueous alcoholic solution, chlorochloromethyldimethylsilane (178 g., 1.24 moles) and hexamethylcyclotrisiloxane (46 g., 0.62 mole). The products of the reaction were washed with water, dried over calcium chloride and distilled.

The polymers of series II were prepared by refluxing for three and one-half hours an aqueous alcoholic solution of hexamethyldisiloxane (162 g., 1 mole), and dichlorochloromethylmethylsilane (163.5 g., 1 mole) followed by washing with water, drying over calcium chloride and distilling.

The polymers of series III were prepared by copolymerizing chlorochloromethyldimethylsilane (2 moles) and dichlorochloromethylmethylsilane (1 mole). The mixture of chlorosilanes was added to aqueous alcohol and shaken. The products were then given the same treatment afforded series I and II.

Despite the fact that three different methods were used to form the three series of polymers the molar distribution of products was the same in each case as nearly as can be determined by distillation analysis.

Also of interest is the fact that only in the case of series I was the slightest trace of cyclic polymers detected in the mixtures. This is surprising in view of the findings of Scott[7] and Wilcock[8] who found that cyclic compounds form when methylpolysiloxane systems were "equilibrated." Perhaps this difference is due to the differences in methods of "equilibrating" or it may be due to an influence of the chloromethyl group which hinders the formation of cyclic polymers. In series I, an indication of the presence of about 2 ml. of hexamethylcyclotrisiloxane, b. p. about 133°, was detected.

A curious fact is that each of the members of series I possesses very nearly the same specific refraction and energy of activation for viscous flow.

The chlorine contents of the compounds of series I and II were determined by heating the chloride with a known excess of potassium hy-

(1) Krieble and Elliott, THIS JOURNAL, **67**, 1810 (1945).
(2) Hunter, Warrick, Hyde and Curry, *ibid.*, **68**, 2284 (1946).
(3) Patnode and Wilcock, *ibid.*, **68**, 358 (1946).
(4) Hurd, *ibid.*, **68**, 364 (1946).
(5) Wilcock, *ibid.*, **68**, 691 (1946).
(6) Warrick, *ibid.*, **68**, 2455 (1946).
(7) Scott, *ibid.*, **68**, 2294 (1946).
(8) Wilcock, paper presented at 110th meeting of the American Chemical Society, Chicago, Ill., Sept., 1946.

droxide in diethylene glycol in a closed bottle at about 150–175°, followed by titrations of the excess alkali with standard acid. Series III formed gels when treated in this way. Titration of the excess alkali in the gel was difficult and led to variable results. Therefore, the molecular weights of the members of series III were determined ebulliometrically. The values given are those obtained by extrapolation to zero concentration.

The viscosities were obtained in a carefully calibrated Fenske pipet.

## Summary

Three series of open chain chloromethylmethylpolysiloxanes were prepared and characterized. The boiling points, index of refraction, density, viscosity and freezing point of the polymers were determined.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

# Some Aminodibenzothiophenes

BY HENRY GILMAN AND JOHN F. NOBIS

In connection with studies concerned with antimalarial and antituberculous compounds, some substituted dibenzothiophenes[1] were prepared.

2-Acetyldibenzothiophene[2] is an important starting material for the preparation of 2-amino- and 2-acetaminodibenzothiophenes. 2-Aminodibenzothiophene can be prepared in excellent yields by a Beckmann rearrangement of the oxime of 2-acetyldibenzothiophene followed by hydrolysis of the resulting acetamino compound. This amine can also be prepared by the nitration and reduction of the parent heterocycle, but the over-all yields are lower, although catalytic reduction of the 2-nitro compound gives high yields of the amine.

2,8-Diacetyldibenzothiophene[3] was prepared and was found to be a suitable intermediate in the preparation of 2,8-diaminodibenzothiophene. Formation of the dioxime of the diacetyl compound, treatment of the dioxime with phosphorus pentachloride, and hydrolysis of the resulting diacetamino compound (m. p. 304–305°) gave a good yield of the 2,8-diamino compound (m. p. 199.5–200°). These same melting points were recently reported.[4] The older literature reported the melting point of the diamino compound to be 178°[5] and 194°,[3] and the melting point of the diacetamino derivative as 237°[5] and 254°.[3]

In order to confirm the structure of the 2,8-diaminodibenzothiophene, an authentic specimen was prepared by nitration of 2-nitrodibenzothiophene followed by catalytic reduction of the resulting 2,8-dinitrodibenzothiophene. Acetylation of this diamino compound gave 2,8-diacetaminodibenzothiophene. The melting points of the latter two compounds were in agreement with the melting points of the compounds obtained from 2,8-diacetyldibenzothiophene, and mixed melting points were not depressed.

The oxidation of 2,8-diacetaminodibenzothiophene to the 5-dioxide was accomplished with either hydrogen peroxide or hypochlorous acid where it had been previously reported[4] that hydrogen peroxide oxidation was not possible.

The authors are grateful to Parke, Davis and Company for arranging for pharmacological tests, the results of which will be reported elsewhere.

## Experimental

**2-Nitrodibenzothiophene.**—Since the previous directions[6] could not be duplicated to give the reported 40% yield, the following procedure was developed. To 10 g. (0.054 mole) of dibenzothiophene dissolved in 80 cc. of glacial acetic acid at 30° was added 10 cc. of fuming nitric acid (d., 1.51) over a period of thirty minutes. When the addition was complete the reaction mixture was stirred at room temperature for one hour and filtered. The yellow solid was refluxed for several hours with 100 cc. of 95% ethanol and the insoluble 2-nitrodibenzothiophene removed by filtration. The yield of product was 3.5 g. (28%) melting at 186–187°.

**2,8-Dinitrodibenzothiophene.**—The following procedure was worked out from the brief directions reported previously.[5] To 18 cc. of fuming nitric acid (d., 1.51) in 25 cc. of glacial acetic acid was added 7.2 g. (0.031 mole) of 2-nitrodibenzothiophene in small portions. When the addition was complete an additional 10 cc. of fuming nitric acid was added dropwise. The reaction mixture was stirred for one hour and poured into water; the resulting yellow product was recrystallized from glacial acetic acid to give 4 g. (47%) of product melting at 320–330°. Recrystallization from dioxane gave 3.2 g. (38%) of the dinitro compound melting at 339–340° (previously reported, 324–325°[5]).

One attempt to prepare this compound by direct nitration of dibenzothiophene gave only 12% of the 2-nitrodibenzothiophene.

**2-Aminodibenzothiophene-5-dioxide.**—2-Nitrodibenzothiophene-5-dioxide was prepared in 88% yield by refluxing the 2-nitro compound with an excess of hydrogen peroxide.[6] The crude product was recrystallized from dioxane and from acetone to give pure material melting at 255–256°. A mixture of 9 g. (0.034 mole) of this nitro compound, 23 g. of granular tin metal, 115 cc. of hydrochloric acid, and 100 cc. of ethanol was refluxed for one hour, cooled, and the amine hydrochloride removed by filtration. An 87% yield of the amine (m. p. 274–276°) was obtained by treatment of the salt with ammonium

(1) Gilman and Avakian, THIS JOURNAL, **68**, 1514 (1946); Gilman and Nobis, *ibid.*, **67**, 1479 (1945).

(2) (a) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); (b) Burger and Bryant, *ibid.*, **4**, 119 (1939).

(3) Burger, Wartman and Lutz, THIS JOURNAL, **60**, 2628 (1938).

(4) Neumoyer and Amstutz, *ibid.*, **69**, 1920 (1947).

(5) Courtot and Pomonis, *Compt. rend.*, **182**, 893 (1926).

(6) Cullinane, Davies and Davies, *J. Chem. Soc.*, 1435 (1936).

hydroxide. Recrystallization from methanol gave 4.7 g. (59%) of product melting at 278–280°.

*Anal.* Calcd. for $C_{12}H_9O_2NS$: S, 13.84. Found: S, 13.50.

**2-Acetyldibenzothiophene.**—Conflicting reports[2] exist concerning the preparation and yield of this compound. The following procedure was developed.

One hundred and twenty grams (0.64 mole) of dibenzothiophene in 900 cc. of dry carbon disulfide was treated with 52 g. (0.64 mole) of acetyl chloride.[2a] The reaction product was distilled at reduced pressure (b. p. 183–185° (1 mm.)) to give 112.5 g. (78%) of crude compound. This material was refluxed for two hours with two successive 500-cc. portions of ether to give the desired 2-acetyldibenzothiophene melting at 109–110°. Recrystallization from methanol gave 60 g. (41%) of material melting at 111–111.5°.

**2-Aminodibenzothiophene. A. From 2-Nitrodibenzothiophene.**—A suspension of 13.5 g. (0.059 mole) of 2-nitrodibenzothiophene and one and one-half teaspoonfuls of Raney nickel catalyst in 150 cc. of absolute ethanol was hydrogenated at 50 p. s. i. The reaction was complete in eighteen hours; there was obtained 3.7 g. of amine melting at 133°. Dilution of the filtrate gave 7 g. of product melting at 129–131°, making a total yield of 91%. Reduction of the 2-nitro compound with tin and hydrochloric acid gave only a 66% yield of 2-aminodibenzothiophene melting at 125–126°.

B. **From 2-Acetyldibenzothiophene.**—Eighteen grams (0.075 mole) of the oxime of 2-acetyldibenzothiophene was treated with phosphorus pentachloride,[2a] yielding 2-acetaminodibenzothiophene quantitatively. This crude product was refluxed with 500 cc. of 1:1 hydrochloric acid for four hours and filtered hot. The residue was extracted with two liters of boiling water and the combined extracts were treated with ammonium hydroxide to give 10.7 g. (72%) of product melting at 129–131°.

**2,8-Diacetyldibenzothiophene Dioxime.**—2,8-Diacetyldibenzothiophene was prepared by an adaptation of the method of Burger, Wartman and Lutz.[3] To a mixture of 22.6 g. (0.1 mole) of 2-acetyldibenzothiophene and 53 g. (0.4 mole) of aluminum chloride in 500 cc. of dry carbon disulfide was added 7.8 g. (0.1 mole) of acetyl chloride over a period of ten minutes. The reaction mixture was refluxed for six hours, poured into an ice–hydrochloric acid mixture, and filtered; the crude yield was quantitative. The white solid was washed with 50 cc. of benzene and recrystallized from 95% ethanol to give 20.5 g. (76%) of pure product melting at 206–208°.

A mixture of 26.8 g. (0.1 mole) of 2,8-diacetyldibenzothiophene, 27.2 g. (0.4 mole) of hydroxylamine hydrochloride, 60 cc. of pyridine, and 250 cc. of absolute ethanol was refluxed for three hours. The solution was evaporated to one-half the volume and the remaining liquid poured into 1600 cc. of water. There was obtained, subsequent to filtration and washing with water, 28.5 g. (95%) of 2,8-diacetyldibenzothiophene dioxime melting at 266–267°.

**2,8-Diacetaminodibenzothiophene. A. From 2,8-Diacetyldibenzothiophene Dioxime.**—To 26.7 g. (0.09 mole) of the dioxime in 500 cc. of benzene was added 60 g. (0.287 mole) of phosphorus pentachloride at such a rate as to cause gentle refluxing. When the reaction had subsided, the mixture was poured onto ice and the suspension made alkaline with sodium carbonate. There was obtained 25 g. (93.5%) of crude diacetamino compound melting at 240–280°. (When this rearrangement was effected with hydrogen chloride[3] a 30% yield of crude product was obtained melting at 220–280°.) The crude diacetamino compound was hydrolyzed in the usual manner. The yield was 13.7 g. (76%) of 2,8-diaminodibenzothiophene melting at 197–198°. Two recrystallizations from 95% ethanol raised the melting point to 199.5–200°. A mixed melting point with 2,8-diaminodibenzothiophene obtained by reduction of 2,8-dinitrodibenzothiophene was not depressed.

*Anal.* Calcd. for $C_{12}H_{10}N_2S$: S, 14.95. Found: S, 14.90.

One-tenth gram (0.0004 mole) of 2,8-diaminodibenzothiophene in 25 cc. of benzene was refluxed for one hour with a few drops of acetic anhydride. There was obtained 0.11 g. (92%) of the diacetamino compound melting at 299–301°. Recrystallization from dilute ethanol gave a melting point of 303°.

*Anal.* Calcd. for $C_{16}H_{14}O_2N_2S$: N, 9.39. Found: N, 9.44.

B. **From 2,8-Diaminodibenzothiophene.**—2,8-Diaminodibenzothiophene (m. p. 194–196°) was prepared in 46% yield by catalytic reduction of 2,8-dinitrodibenzothiophene in the manner previously described for the preparation of 2-aminodibenzothiophene. (Reduction of the 2,8-dinitro compound with tin and hydrochloric acid gave a 35% yield of impure material.) A mixed melting point with the material obtained from the Beckmann rearrangement was not depressed.

One-tenth gram (0.0004 mole) of this diamine was treated with acetic anhydride to give 0.1 g. of 2,8-diacetaminodibenzothiophene (m. p., 301–302°) after recrystallization from dilute methanol. A mixed melting point with the material prepared from 2,8-diacetyldibenzothiophene dioxime was not depressed.

**2,8-Diacetaminodibenzothiophene-5-dioxide.**—One gram (0.003 mole) of 2,8-diacetaminodibenzothiophene was dissolved in 20 cc. of glacial acetic acid by warming to 70°. To this solution was added 2 cc. of 30% hydrogen peroxide; the temperature was slowly raised to 93°. At the end of three hours, during which time an additional 2 cc. of hydrogen peroxide was added, the reaction mixture was poured onto ice. There was obtained 1 g. (95%) of dioxide melting at 330–331°. This material was refluxed first with 75 cc. of 95% ethanol and then with 100 cc. of dioxane to give a melting point of 356–357°. This oxidation method had been previously reported[4] to give no isolable product.

*Anal.* Calcd. for $C_{16}H_{14}O_4N_2S$: S, 9.70. Found: S, 9.65.

**2,8-Diaminodibenzothiophene-5-dioxide.**—A mixture of 0.8 g. (0.002 mole) of 2,8-diacetaminodibenzothiophene-5-dioxide and 100 cc. of 18% hydrochloric acid was refluxed for thirty minutes. The clear solution was diluted with an equal volume of water and filtered hot. Treatment of the filtrate with ammonium hydroxide gave 0.6 g. of material melting at 306–308°. Recrystallization from 95% ethanol gave 0.3 g. (51%) of the 2,8-diamino compound melting at 327–328°.

In another preparation, 10 g. (0.034 mole) of crude 2,8-diacetaminodibenzothiophene was suspended in 300 cc. of glacial acetic acid at 80° and 100 cc. of freshly prepared sodium hypochlorite solution[7] was added over a period of fifteen minutes. The reaction mixture was poured into one liter of water and a quantitative yield of crude dioxide was obtained by filtration. This crude product was refluxed for two hours with 300 cc. of 18% hydrochloric acid and allowed to stand overnight. The insoluble material was extracted with two one-liter portions of water and the combined extracts were treated with decolorizing carbon. Neutralization of the filtrate with ammonium hydroxide precipitated 4 g. (48% based on the 2,8-diacetaminodibenzothiophene) of 2,8-diaminodibenzothiophene-5-dioxide melting at 325–326°.

*Anal.* Calcd. for $C_{12}H_{10}O_2N_2S$: S, 13.0. Found: S, 13.4.

**4-Methoxydibenzothiophene-5-dioxide.**—An 85% yield of this dioxide was obtained by refluxing 4-methoxydibenzothiophene[2a] with an excess of hydrogen peroxide. After recrystallization from 95% ethanol the melting point was 191–192°.

*Anal.* Calcd. for $C_{13}H_{12}O_3S$: S, 13.00. Found: S, 13.33.

**Reaction of Dibenzothiophene with Aluminum Halides.**—In attempts to obtain a dibenzothiophenecarboxylic acid, dibenzothiophene was heated with various aluminum halides in sealed tubes under a variety of conditions. No

(7) Weijlard, THIS JOURNAL, 67, 1031 (1945).

acid was obtained by carbonation of the reaction mixtures, although 2-dibenzofurancarboxylic acid was isolated in similar reactions with dibenzofuran.[8]


## Summary

New procedures are given for the preparation of some aminodibenzothiophenes and aminodibenzothiophene-5-dioxides. Additional proof is presented for the structure of 2,8-diacetyldibenzothiophene.


AMES, IOWA RECEIVED JULY 26, 1948

(8) Gilman and Haubein, *ibid.*, **67**, 1033 (1945).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

# The Alcoholysis of Sugar Derivatives

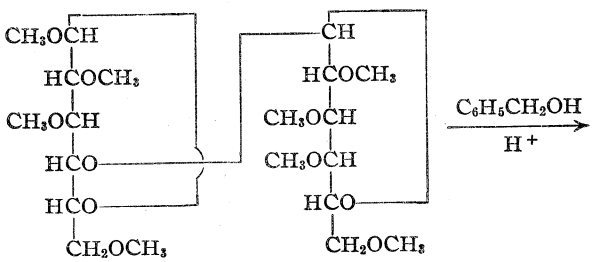
BY ELMER E. COMBS,[1] CHESTER M. MCCLOSKEY, ROBERT L. SUNDBERG AND GEORGE H. COLEMAN[2]

The study of the alcoholysis reaction was undertaken in this Laboratory with the object of developing a method for the preparation of 2,3,6-trimethylglucose. The method was found to be satisfactory enough to warrant investigation of a larger field than originally planned with the object of obtaining a practical method of separation of the alcoholysis products of methylated disaccharides.

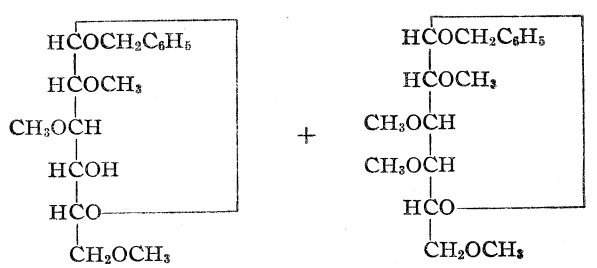
Berner[3] investigated the methyl alcoholysis of sucrose and other carbohydrates. From sucrose he obtained glucose and methyl fructofuranoside. Voss and Wachs[4] investigated the reaction rates of alcoholysis, acetolysis and hydrolysis of phenyl glucosides and found that the length of time required for completion of the reaction increased in the order mentioned with the reaction constant for methyl alcoholysis being over one-hundred times as great as that for hydrolysis. Methyl alcohol was used by the above workers and by others[5]; however, the use of methyl alcohol had the disadvantage that the hydrolysis rate of the methyl glycoside approximated that of the original compound. Considerable decomposition of the free sugars sometimes resulted during hydrolysis making it difficult to obtain crystalline compounds.

Richtmyer[6] studied the conditions under which benzyl glycosides are cleaved by catalytic hydrogenation. He found that palladium catalysts in glacial acetic acid, at room temperature and atmospheric pressure were capable of cleaving benzyl glycosides giving a quantitative yield of the free sugar. Methylated benzyl glycosides have been shown to be capable of distillation under high vacuum.[7,8] Studies of the benzyl alcoholysis of methyl α-fructofuranoside and of fructose have been described.[9] In view of these findings benzyl alcohol was selected for use in this investigation of the alcoholysis reaction.

The general procedure of benzyl alcoholysis is illustrated using methyl heptamethyl-β-lactoside.




Methyl heptamethyl-β-lactoside




Benzyl 2,3,6-trimethyl-D-glucoside

Benzyl 2,3,4,6-tetramethyl-D-galactoside

The benzyl glycosides obtained were distilled under vacuum and the separate fractions redistilled. In eleven runs the yield of the benzyl tetramethylglycoside averaged 87.7% and the yield of the benzyl trimethylglycoside averaged 46.1%. The lower yield of the trimethyl fraction was probably due to its higher boiling point and to the fact that it was subjected to high temperatures of distillation for a longer period of time. For this reason smaller runs generally gave better percentage yields than did larger runs. After separation the benzyl glycosides were catalytically reduced to the free sugar using palladium–charcoal catalyst in glacial acetic acid. In every case a nearly quantitative yield of the free sugar was obtained.

The methylated disaccharides used in this in-

(1) Abstract of a portion of the dissertation submitted to the Graduate College of the State University of Iowa by Elmer E. Combs in partial fulfillment of the requirement for the degree of Doctor of Philosophy. Deceased Nov. 13, 1948.

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(3) Berner, *Ber.*, **66B**, 1076 (1933).

(4) Voss and Wachs, *Ann.*, **522**, 240 (1936).

(5) Coleman, Rees, Sundberg and McCloskey, THIS JOURNAL, **67**, 381 (1945).

(6) Richtmyer, *ibid.*, **56**, 1633 (1934).

(7) Hess and Hwang, *Ber.*, **72B**, 1906 (1939).

(8) Hess and Gramberg, *ibid.*, **72B**, 1898 (1939).

(9) Purves and Hudson, THIS JOURNAL, **59**, 49–56, 1170–1174 (1937).

TABLE I

PHYSICAL CONSTANTS OF BENZYL GLYCOSIDES

| | | Boiling point, °C. | Mm. | $n^{25}D$ | $[\alpha]^{25}D$ in $CHCl_3$ ($c$, 2) | Analyses, % Calculated C | Calculated H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Benzyl 2,3,4,6-tetramethyl-D-galactoside | 114–116 | 0.020 | 1.4980 | 80.3 | 62.6 | 8.0 | 62.79 | 8.23 |
| 2 | Benzyl 2,3,4,6-tetramethyl-D-glucoside | 110–111 | .014 | 1.4936 | 76.1 | 62.6 | 8.0 | 63.05 | 8.01 |
| 3 | Benzyl 2,3,4-trimethyl-D-glucoside | 133–134 | .025 | 1.5080 | 173 | 61.5 | 7.7 | 61.31 | 8.07 |
| 4 | Benzyl 2,3,6-trimethyl-D-glucoside | 127–128 | .020 | 1.5110 | 74.9 | 61.5 | 7.7 | 63.30 | 7.89 |
| 5 | Benzyl 2,4,6-trimethyl-D-glucoside | 132–133 | .014 | 1.5110 | 92.5 | 61.5 | 7.7 | 62.13 | 8.31 |

vestigation and the benzyl glycosides obtained therefrom were as follows: methyl heptamethyl-$\beta$-lactoside → benzyl 2,3,6-trimethylglucoside + benzyl 2,3,4,6-tetramethylgalactoside. Methyl heptamethylmaltoside → benzyl 2,3,6-trimethylglucoside + benzyl 2,3,4,6-tetramethylglucoside. Methylheptamethyl-$\beta$-cellobioside→benzyl 2,3,6-trimethylglucoside + benzyl 2,3,4,6-tetramethylglucoside. Methyl heptamethyl-$\beta$-melibioside→benzyl 2,3,4-trimethylglucoside + benzyl 2,3,4,6-tetramethylgalactoside.

Of these four benzyl glycosides none has been previously reported.[10] The physical constants of the four glycosides were determined. The effect of temperature on the rate of the reaction was investigated over the range of 25 to 150°. The higher temperatures were found to cause decomposition and side reactions; 100° was selected as the optimum temperature. It was found that the reaction would not occur in the absence of an acid catalyst and that the rate of the reaction was dependent on the acid concentration. However, high acid concentrations (5% and greater) were to be avoided as causing decomposition and side reactions. The optimum concentration was found to be 2.5%.

*p*-Toluenesulfonic acid monohydrate was the catalyzing acid used in this investigation. It was sufficiently strong for the purpose and was easily removed by extraction with aqueous ammonia. It was found to cause no harmful side reaction. Dibenzyl ether was usually formed under the reaction conditions, but this did no harm. Hydrochloric acid was first used as the catalyst, but was discontinued as it reacted quickly with the benzyl alcohol to give benzyl chloride, making it difficult to determine the length of effective reaction. The benzyl alcoholysis of methyl heptamethyl-$\beta$-lactoside was completed in two hours as compared to twenty-two hours for the hydrolysis.

The benzyl alcoholysis procedure was applied to several monosaccharides for reference purposes, these being trimethyllevoglucosan, 2,3,4,6-tetramethylglucose and 2,4,6-trimethylglucose. In general the reaction conditions and the reaction rates were the same as for the dissacharides.

(10) The benzyl glycoside which had been reported by Hess and Gramberg (ref. 8) was a benzyl 2,3,6-trimethyl-$\beta$-D-glucoside; it was quite impure, with a methoxyl content 3.5% too high due to the presence of some trimethylglucose. Its rotation of $[\alpha]^{20}D$ +8.3° is quite different from the value +74.9° reported by the present authors.

## Experimental

**Alcoholysis of Methyl Heptamethyl-$\beta$-lactoside.**—A mixture of 30 g. of methyl heptamethyl-$\beta$-lactoside and 9 g. of *p*-toluenesulfonic acid monohydrate was dissolved in 300 ml. of benzyl alcohol contained in a 500-ml. round-bottomed flask. The flask was heated in an oil-bath at 100° for two hours at atmospheric pressure followed by two hours at aspirator pressure. The solution was cooled and 1 l. of chloroform added. The resulting solution was extracted with 250 ml. of water containing 30 ml. of concd. ammonium hydroxide followed by two extractions with 250 ml. of water. The chloroform layer was dried over potassium carbonate and the solvent distilled off at 0.5 to 1.0 mm. pressure. The amber colored oil was fractionated under reduced pressure through a 10-inch externally heated column packed with platinum gauze, giving two principal fractions. Each fraction was then redistilled separately. The physical constants given are for the redistilled fractions.

Fraction 1: Benzyl 2,3,4,6-tetramethyl-D-galactoside, yield 26 g. (80%), b. p. 114–116° at 0.02 mm., $n^{25}D$ 1.4980, $[\alpha]^{25}D$ 80.3 in chloroform ($c$, 2). *Anal.* Calcd. for $C_{17}H_{26}O_6$; C, 62.6; H, 8.0. Found: C, 62.7; H, 8.23. Catalytic hydrogenation, using palladium-charcoal as the catalyst, gave a quantitative yield of sirupy 2,3,4,6-tetramethyl-D-galactose. On standing at 0° for several days, about 25% of the material crystallized out; m. p. 70.2° (cor.)

Fraction 2: Benzyl 2,3,6-trimethyl-D-glucoside, yield 17.5 g. (51%), b. p. 127–128° at 0.02 mm., $n^{25}D$ 1.5110, $[\alpha]^{25}D$ 74.9 in chloroform ($c$, 2). *Anal.* Calcd. for $C_{16}H_{24}O_6$: C, 61.5; H, 7.7. Found: C, 63.30; H, 7.89. Catalytic hydrogenation of 12.9 g. of this compound in glacial acetic acid gave 6.7 g. of crystalline 2,3,6-trimethyl-D-glucose (73%).

**Alcoholysis of Other Methylated Sugars.**—All other methylated disaccharides and monosaccharides mentioned above were subjected to the same benzyl alcoholysis procedure as described for octamethyl lactose. The properties of the benzyl glycosides obtained are summarized in Table I.

Compounds 3 and 5 in Table I were obtained in crystalline form from their respective sirupy distillates in approximately 75% yield. Compound 3, m. p. 79–80.2 cor.; compound 5, m. p. 90.6–91.1° cor. Compounds 1, 2, and 4, being sirups, are probably mixtures of the $\alpha$- and $\beta$-forms, with considerable $\alpha$ as evidenced by the positive rotation. Compound 3, being crystalline, seems to be definitely an $\alpha$-form. Compound 5 should also be an $\alpha$-form, the $\beta$-form having been described by Richtmyer.[11]

**Catalytic Reduction of Benzyl Glycosides.**—The general procedure used in reduction of the glycosides is illustrated by the following example. A solution of 12.9 g. of benzyl 2,3,6-trimethyl-D-glucoside in 50 ml. of glacial acetic acid with palladium–charcoal catalyst (0.5 g. of palladium chloride and 3 g. of charcoal) absorbed the theoretical amount of hydrogen overnight (hydrogen pressure 3–4 atm.). The catalyst was filtered off and the reaction flask and catalyst washed with water. The combined filtrate and washings were evaporated under reduced pressure to a sirup. Toluene (250 ml.) was added and removed under reduced pressure. Ether was added to

(11) Richtmyer, THIS JOURNAL, 61, 1831 (1939).

the residue which crystallized. Crystallization was completed on standing for several days at 0°; yield 6.7 g. (73%).

In addition to reduction of benzyl glycosides this method was successfully applied to the reduction of the benzyl group from 3-benzyl 2,4,6-trimethyl-D-glucose without reduction of the aldehydic group. The 2,4,6-trimethyl-D-glucose was crystallized from carbon tetrachloride, m. p. 126°. When mixed with an authentic sample of 2,4,6-trimethyl-D-glucose, the melting point was not depressed.

## Summary

1. A new method of separation of the cleavage products of methylated disaccharides has been developed. This involves conversion of the methylated disaccharide to two benzyl glycosides, treatment with benzyl alcohol in the presence of an acid, separation of the glycosides by fractionation under high vacuum, and reduction of the benzyl glycosides to give the methylated monosaccharides.

2. This method gives good yields (85%) of the tetramethyl monosaccharides and fair yields (50%) of the trimethyl monosaccharides.

3. Two new crystalline benzyl glycosides, (presumably α-forms) have been prepared; benzyl 2,3,4-trimethyl-D-glucoside, and benzyl 2,4,6-trimethyl-D-glucoside. Three new sirupy benzyl glycosides (presumably mixtures of the α- and β-forms) have been prepared: benzyl 2,3,4,6-tetramethyl-D-galactoside, benzyl 2,3,4,6-tetramethyl-D-glucoside, and benzyl 2,3,6-trimethyl-D-glucoside.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, CALIFORNIA]

# Aluminum Monolaurate and Proposed Structures for Aluminum Soaps[1]

BY CHARLES G. McGEE[2]

The chemistry of aluminum soaps has long been in confusion. It has been stated: that only mono soaps exist,[3,4] that only a basic compound intermediate between mono- and di-soaps exists together with various sorption products,[5] and that the mono- as well as the di- and tri-soaps all exist.[6] Di-soaps have been prepared by several authors,[7,8,9] while efforts to prepare tri-soaps[10,11] failed.

It is the purpose of this paper to present evidence concerning the existence of aluminum mono-soaps. In the course of this work, no compounds were prepared having a ratio of exactly one molecule of fatty acid per atom of aluminum, but the preparations obtained had approximately one to one ratios and were stable under a wide variety of conditions. It is believed that these are true compounds, of the nature of co-polymers, and that as a result exact stoichiometric composition is not necessarily to be expected. Products containing from 1.2–0.8 molecules of fatty acid per aluminum atom will be referred to as aluminum mono-soaps.

(1) Study conducted under Contract OEMsr-1057 between Stanford University and the Office of Emergency Management, recommended by Division 11.3 of the National Defense Research Council, and supervised by Prof. J. W. McBain.

(2) Present address: Stanford Research Institute, Stanford, California.

(3) Alexander, reports to Div. 11.3, NDRC.

(4) Galley and Puddington, *Can. J. Research*, **B26**, 155–160 (1948).

(5) Eigenberger and Eigenberger-Bittner, *Kolloid Z.*, **91**, 287 (1940).

(6) Lawrence, *J. Inst. Petroleum*, **31**, 312 (1945). British Petroleum Warfare Board Memo No. 368.

(7) Ostwald and Rideal, *Kolloid Z.*, **69**, 185 (1934).

(8) Markowicz, *Färber Ztg.*, **34**, 326 (1928).

(9) Smith, Pomeroy, McGee and Mysels, THIS JOURNAL, **70**, 1053 (1948).

(10) McBain and McClatchie, *ibid.*, **54**, 3226 (1932).

(11) Licata, *Drugs, Oils & Paints*, **51**, 148 (1936).

The materials used in this study are those used in the previously reported work.[8] Analysis was carried out by ashing or by a split analysis in which the aluminum was determined by a standard procedure using 8-hydroxyquinoline and the fatty acid determined by precipitation and weighing.

## Aluminum Mono-Soaps

**Preparation from Aluminum Di-soaps, Accompanied by Alcoholysis.**—In the course of an investigation on the free acid content of commercial aluminum soaps, it was noted that the use of hot methanol for extraction gave much higher results than when acetone was employed. Analysis of these residues indicated that they approximated the composition then expected for a compound of the formula $Al(OH)_2$-fatty acid.

However, this reaction was repeated on samples of aluminum dilaurate prepared by Smith, *et al.*[9] Exhaustive treatment with hot methanol gave products containing 1.2–1.0 molecules of fatty acid per aluminum atom. The initial reaction is always accompanied by a marked physical change in the soap from a powder to a plastic mass. The reaction required several minutes at the boiling point of the methanol, and many days at room temperature. The plastic product contained large amounts of methanol and much free fatty acid. It gradually hardened over a period of several days, after which it was ground up and retreated with the methanol. During later treatments, it frequently reconsolidated.

To examine this assumed reaction, a weighed sample of aluminum dilaurate was treated with methanol, and the weight of fatty acid liberated and the loss in weight of the soap were determined. It was found that after drying *in vacuo*

over phosphorus pentoxide, the aluminum soap retained one molecule of methanol per molecule of soap initially present and lost one molecule of fatty acid. This indicates that methanolysis, analogous to hydrolysis, takes place. Similar reactions were observed with ethanol and higher alcohols, and with a solution of 10% water in acetone.

**Direct Preparation of Aluminum Mono-soaps.**—Aluminum mono-soaps were prepared directly in methanol by adding aqueous ammonium hydroxide to a solution of aluminum nitrate and lauric acid in hot methanol. If an excess of ammonia was added quickly, a finely divided product, which often consolidated on further treatment with hot methanol, was obtained. Most of these products contained distinctly more than one molecule of lauric acid per aluminum atom, even after they had been washed free of salts with methanol. Continued treatment with hot methanol, or methanol plus water, was necessary to bring the acid content down. Extraction with acetone did not alter the acid content. The material began to decompose at 250° without melting; at 270° it softened to a brown transparent mass.

Aluminum mono-soaps were prepared from aluminum hydroxide by precipitating the hydroxide in aqueous solution, washing it with water and then methanol, and finally adding a solution of lauric acid in methanol and heating. A slow reaction took place, leading to the formation of a gummy mass similar to that obtained in the other reactions.

An attempted direct precipitation in water yielded a mixture of at least two products, one containing 1.5 molecules of lauric acid per aluminum atom and soluble in a benzene–acetone mixture, the other containing about 0.6 molecule of lauric acid per aluminum atom, insoluble in benzene–acetone and unaffected chemically by it.

**Direct Conversion of Monolaurate to Dilaurate by Reaction with Lauric Acid.**—Shreve, Pomeroy and Mysels[12] had found that no water was formed in the benzene distillation of a mixture of aluminum monolaurate and lauric acid. They concluded that no reaction forming dilaurate had taken place. Later evidence showed that the monolaurate may have contained methoxyl groups. Reaction with lauric acid would have produced methanol, which would not have been detected in the benzene distillation. Hence, the reaction was reinvestigated, using acetone as a solvent. A large excess of lauric acid was employed, the mixture was refluxed, the acetone evaporated and the mixture dried over phosphorus pentoxide. It was then extracted repeatedly with cold acetone until the acetone was substantially free of fatty acid. Analysis of the residue showed that it contained 1.9 molecules of lauric acid per aluminum atom, indicating that substantial conversion to dilaurate had taken place.

**Behavior of Aluminum Monolaurate toward Organic Solvents.**—Aluminum laurates containing less than 1.2 molecule of lauric acid per aluminum atom are not noticeably soluble in the common organic solvents at room temperature. At its boiling point (171°), butyl cellosolve dissolved a fair amount, the solution gelling upon cooling. The residue from this treatment retained the composition of the original material.

Certain mixed solvents were effective in dissolving certain aluminum mono-soaps, methanol–benzene in particular. The solubility varied greatly with the composition of the soap. No solvents were found for products containing less than one molecule of lauric acid per aluminum atom. Treatment with solvents for fatty acids did not reduce the acid content of these materials.

**The Nature of Aluminum Mono-soaps.**—The question immediately arises as to whether these materials are true compounds or merely sorption products of lauric acid on hydrous alumina. The evidence seems strongly in favor of true compounds. Treatment of di-soaps with methanol always yields products having about one molecule of lauric acid per aluminum atom. Extended treatment with organic solvents does not significantly lower the acid content further. Treatment of aluminum hydroxide with lauric acid gives a product similar in every way to that from the degradation of dilaurate. With some products, solution can be effected in methanol–benzene mixtures from which the dissolved material can be precipitated by the addition of excess of methanol or acetone. The precipitated material is similar to the original material. Mono-soap was converted by reaction with lauric acid into di-soap which is a well-defined compound.[9]

**The Structure of Aluminum Mono-soaps.**—A rational structure for the aluminum mono-soaps can be built up on the basis of the known preference of aluminum for octahedral coördination. Each fatty acid ion will occupy two adjacent corners of the octahedron with hydroxyl (or methoxyl) groups in the other four. In order to maintain electrical neutrality, each of the hydroxyl groups must be shared. If neighboring aluminum ions share edges of the octahedra, long chains of the type shown in Fig. 1 will be formed. Structures based on corner and face sharing seem much less probable. The suggested structure would be expected to produce a non-crystalline material, as is observed. Powder X-ray diffraction photographs yield only diffuse halos, even after prolonged heating of the solid in methanol.

Low solubility is conferred by the high molecular weight and by a mechanism analogous to vulcanization. An aluminum hydroxide octa-

(12) Shreve, Pomeroy and Mysels, *J. Phys. and Coll. Chem.*, **51**, 963 (1947).

Fig. 1.

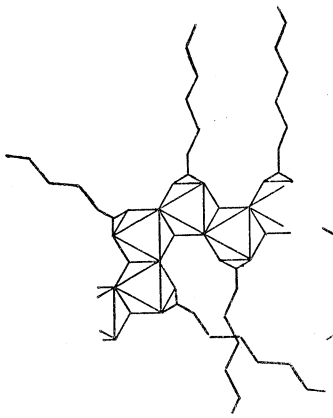
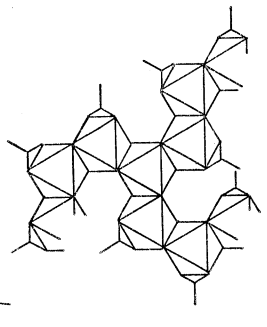


Fig. 2.



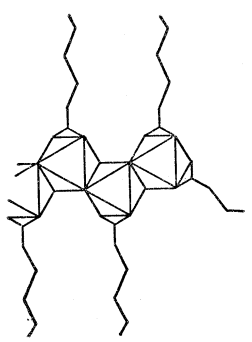


Fig. 3.

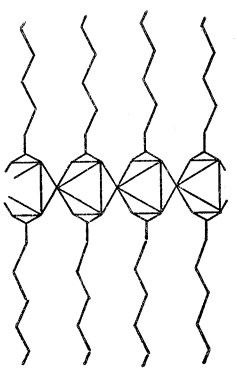


Fig. 4.

hedron can join three chains by sharing its edges with three molecules of mono-soaps as in Fig. 2.

If the chains terminate in di-soap molecules as in Fig. 3, it will be seen that the composition of the material may vary from that of a di-soap to aluminum hydroxide, depending upon the chain length and degree of cross linking. Since products containing close to one molecule of fatty acid per aluminum atom were obtained under a fairly wide variety of conditions, it seems probable that chains of mono-soap molecules predominate and that the term mono-soap is justified when referring to these materials. The high ratio of fatty acid to aluminum found in many cases may be due to incomplete conversion and/or failure to extract completely the free acid.

The physical behavior of these substances is similar in many respects to certain high polymers. They are much more soluble in mixed than in single solvents (although this is true of ordinary sodium soaps also), they are soluble in butyl cellosolve, they lack a definite melting point, they are frequently elastic and sometimes sticky when not free from solvent. They give gels in solvents and their solutions show very high viscosity.

## Structure of Aluminum Di-soaps

Some of the physical properties of aluminum di-soaps are also polymer-like, but they have not been reported with a fibrous X-ray structure. Ross and McBain[13] found by X-ray diffraction that they are crystalline and suggested a structure in analogy with that of sodium soaps.

An alternative suggestion is shown in Fig. 4. Here the two carboxyl groups occupy four of the coördinating positions while the two remaining positions contain hydroxyl ions which are shared to form a chain. This structure has been proposed by Grey[14] who, however, did not note that these chains would have to end in charged groups. It will be seen from Fig. 5a that a chain ending as shown will possess a net charge of minus one-half on the terminal group, while a chain ending as in Fig. 5b or 5c will possess a charge of plus one-half. This is an important feature of this structure, for it provides a reasonable mechanism for the observed association of aluminum di-soaps in dilute solutions.[14,15]

Fig. 5a.

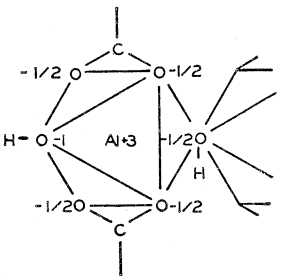
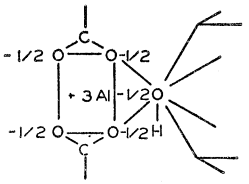



Fig. 5b.



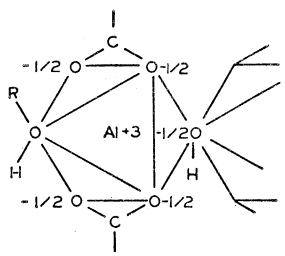




Fig. 5c.

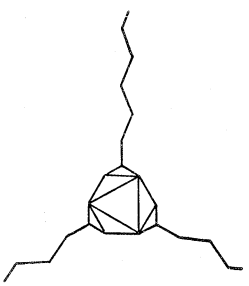


Fig. 6.

The suggested structure for aluminum di-soaps permits a much more regular arrangement of the molecules than did the structure for mono-soaps. Adjacent di-soap chains would be held together by both van der Waals forces between the hydrocarbon chains and hydrogen bonds between the hydrogen of the shared hydroxyl ions and the oxygen atoms of the carboxyl groups. The observed melting points may correspond to the breaking of these two forces, leaving the individual aluminum soap chains intact, since the molten soap possesses extremely high viscosity. In aluminum di-soap–hydrocarbon systems, the forces holding the hydrocarbon chains together

(13) Ross and McBain, *Oil and Soap*, **23**, 214 (1946).

(14) Grey, *Trans. Faraday Soc.*, **42B**, 197 (1946).

(15) McBain and Working, *J. Phys. and Colloid Chem.*, **51**, 947 (1947).

would be largely eliminated, leaving only the hydrogen bonds holding the aluminum soap chains to one another. Hence, the gel–jelly transition, which was found[16] to be largely independent of temperature for different aluminum di-soaps in a given solvent, may be a melting process taking place with only the hydrogen bonds left.

The effects of various substances upon aluminum di-soap in hydrocarbon systems can be interpreted on the assumption of the above model. Compounds which can coördinate with the aluminum ion will reduce the chain length and hence the viscosity, and usually increase the rate of solution or gelation of soap. Alcohols, water, amines and higher fatty acids all show this behavior.[17] Lower fatty acids increase the time required for gelation. This might be due to metathesis and resultant precipitation of less-soluble aluminum di-soaps on the surface of the particles, or simply to the possibility that although the rate of solution was increased, the dissolving chains were broken down by the acid so that some time had to elapse before the concentration of long chains was sufficient to gel the system.

McBain and Working[15] found that in benzene, the viscosity of aluminum di-soap solutions often increases with increasing temperature. This might be due to unfolding of chains, thus increasing the asymmetry of the particles. There were long time aging effects present, however, and what the situation would be at equilibrium is not clear. Mysels[18] reported no increase in viscosity with increase in temperature in cyclohexane, but observed very long time effects in the aging of the systems which sometimes led to anomalous results. His observations fit in well with the picture of reorganizing long chains.

McBain and Working[15] also found by osmometry that aluminum dilaurate was associated in benzene solutions as dilute as 0.001% by weight. The degree of association was found to increase very rapidly with increased concentration, but the effect of moisture was not examined. The jellies of aluminum dilaurate are very sensitive to moisture,[19] and it is possible that residual moisture in the soap and benzene gave rise to the apparent decreased association in the dilute solutions.

The dilaurate is characterized by a modest degree of crystallinity, solubility in hydrocarbons, reversible association, formation of jellies from gels at well-defined temperatures, and instability in the presence of water and alcohols. On the other hand, the monolaurates had low crystallinity, very low solubility in hydrocarbons, formation only of gels, no jellies, and stability in the presence of alcohols. These properties are reasonably in accord with the proposed structures based upon identical principles for both compounds.

(16) McBain, Mysels and Smith, *Trans. Faraday Soc.*, **42B**, 173 (1946).

(17) Smith, Rogers and Mysels, communication.

(18) Mysels, *J. Colloid Sci.*, **2**, 375 (1947).

(19) McRoberts and Schulman, *Nature*, **162**, 101 (1948).

### Aluminum Tri-soaps

Attempts to prepare tri-soaps by treating an aluminum alcoholate with a fatty acid have failed.[10,11] A structure analogous to those suggested for mono- and di-soaps, Fig. 6, in which the oxygen atoms of three carboxyl groups occupy the six coördination positions, would appear stable. It gives a reasonable explanation of the failure of attempts to prepare tri-soaps, since the molecule would be expected to possess a solubility very similar to that of the fatty acid; in fact, because of the shape of the molecule and the resultant difficulty of fitting into a compact crystal lattice, the tri-soap might be a liquid, miscible with the solvents used to extract the free acid. Hence, if produced, it would be found with the free acid and not in the residue, as assumed by previous workers.

### Detailed Preparation of Aluminum Monolaurates

**From Aluminum Dilaurate and Methanol.**—Four grams of aluminum dilaurate was boiled with 100 ml. of methanol for ten minutes. The methanol was removed by filtration and the solid was then washed with a 20-ml. portion of methanol and three 15-ml. portions of acetone. Evaporation of the methanol yielded a considerable quantity of lauric acid. The solid was dried in a vacuum desiccator. On ashing it was found to contain 8.4% aluminum; theoretical of $Al(OH)_2L$ is 10.4%; theoretical for $Al(OH)L_2$ is 6.1%. On repeating the treatment with methanol the aluminum content rose to 9.2%.

**From Aluminum Dilaurate in Benzene Solution and Methanol.**—A 2-g. portion of a monolaurate prepared from dilaurate and methanol was dissolved in 30 ml. of benzene by wetting it with methanol, adding the benzene and heating. An excess of methanol was added to the solution, reprecipitating the aluminum soap as an elastic material containing a large amount of solvent. This material was dried and analyzed. It contained 8.8% aluminum and had a ratio of 1.1 laurate to 1 aluminum.

**From Aluminum Dilaurate and Methanol with a Material Balance.**—1.677 g. of aluminum dilaurate (6.28% aluminum; theory 6.10%) was placed in a weighed 50-ml. centrifuge tube; 20 ml. of dried methanol was added and the tube was stoppered. It was allowed to stand overnight at room temperature; 10 ml. more of methanol was added, the solid was separated by centrifuging and 20 ml. of the supernatant liquid was pipetted out, transferred to another weighed tube and evaporated. An additional 20 ml. of dried methanol was added to the solid and the process repeated. After the third treatment the alcohol was raised to its boiling point to hasten the removal of the acid.

It was found that 0.669 g. (3.34 mmoles.) of lauric acid had been removed from the dilaurate. The dilaurate had lost only 0.538 g. The differ-

ence, 0.131 g. (3.8 mmoles.) represents the amount of methanol retained by the aluminum soap after drying in a vacuum over phosphorus pentoxide. It is slightly above the 3.34 mmoles. of acid extracted, but in good agreement with the 3.79 mmoles. of dilaurate originally present. It is probable that the extracted acid is low, due to the clumping of the particles during the experiment, and subsequent failure to extract completely the freed acid.

**By Precipitation in Methanol.**—37.5 g. (0.1 mole) of $Al(NO_3)_5 \cdot 9H_2O$ and 20 g. (0.1 mole) of lauric acid was dissolved in 200 ml. of boiling methanol; 20 ml. of concentrated ammonium hydroxide was added as quickly as possible. A very voluminous precipitate formed and 600 ml. of methanol were added to disperse the product. It was washed repeatedly with hot methanol and finally with acetone. After drying it contained 10.0% aluminum. It was treated with two portions of boiling methanol, after which it contained 10.6% aluminum. A small portion of this material was sealed in an evacuated capillary and heated. It began to decompose at 250° without melting. At 270° it softened to a brown transparent mass.

**From Aluminum Hydroxide and Lauric Acid.**—2.41 g. (0.01 mole) of $AlCl_3 \cdot 6H_2O$ was dissolved in 30 ml. of distilled water and a slight excess of ammonia was added. The aluminum hydroxide was centrifuged off and washed four times with methanol; 6.0 g. (0.03 mole) of lauric acid was then added and the mixture was heated to 70°. A gelatinous white precipitate formed which began to clump together after a few minutes. Within fifteen minutes it had formed a soft plastic mass, similar to that formed by treating dilaurate with methanol. This was dried, ground under methanol, and washed twice with hot methanol. During the second wash it again clumped together. It was washed with acetone and dried. It contained 7.8% aluminum and had almost 1.4 molecules of laurate per atom of aluminum.

**Acknowledgment.**—The author wishes to acknowledge the stimulating direction of Professor J. W. McBain, the many thought-provoking discussions with Drs. K. J. Mysels and G. H. Smith, and the financial assistance of the Colgate–Palmolive–Peet Company during the latter portion of this work.

## Summary

The preparation and properties of aluminum mono-soaps have been described. It has been suggested that aluminum mono-soaps are polymers in which the repeating units are alumina octahedra joined by sharing edges, with the carboxyl groups occupying the remaining positions.

The structure of aluminum di-soaps has also been discussed. A polymer structure has been suggested in which alumina octahedra are joined by sharing two opposite corners, which carboxyl groups occupying the remaining four. An attempt has been made to correlate such a structure with the known properties of the di-soaps.

Aluminum tri-soaps have likewise been discussed. Possible structures have been suggested and reasons for failure hitherto to prepare them have been considered.

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[CONTRIBUTION FROM COLGATE–PALMOLIVE–PEET CO.]

# The Autoxidation of Methyl Oleate

BY JOHN ROSS, ARTHUR I. GEBHART AND J. FRED GERECHT

It has been shown that autoxidation of olefinic compounds involves, in effect, addition of a molecule of oxygen with formation of a hydroperoxide group on a carbon atom adjacent to an olefinic group. Farmer, *et al.*, further developed this view and suggested a free radical chain reaction mechanism.[1]

Autoxidation, of the various resonance forms of methyl oleate, *via* such mechanism, should give rise to the structures:

$CH_3(CH_2)_6CH_2CH{=}CHCH(OOH)(CH_2)_6COOCH_3$,
$CH_3(CH_2)_6CH{=}CHCH(OOH)CH_2(CH_2)_6COOCH_3$
$CH_3(CH_2)_6CH_2CH(OOH)CH{=}CH(CH_2)_6COOCH_3$,
$CH_3(CH_2)_6CH(OOH)CH{=}CHCH_2(CH_2)_6COOCH_3$

We have examined autoxidation of methyl oleate with oxygen in the presence of ultraviolet light at 35° and found evidence that such is the case.[2]

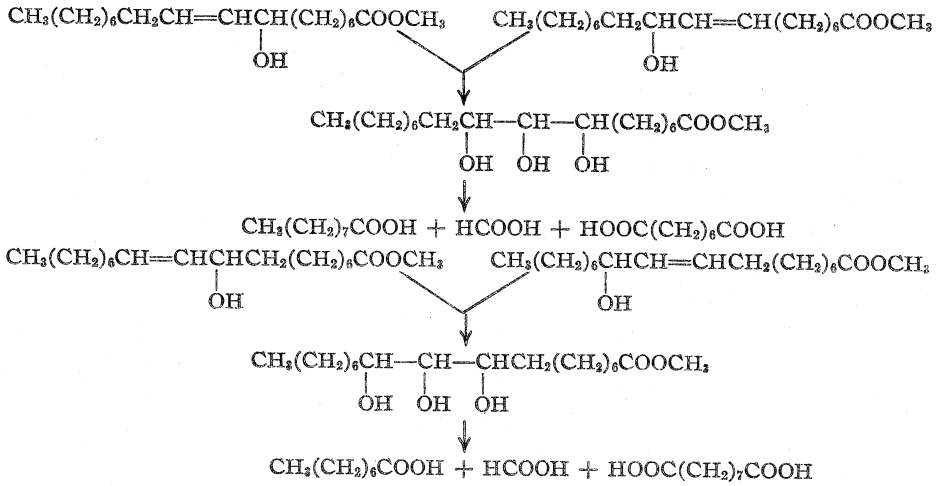
The position of the hydroperoxide group was determined as follows: The mixture of hydroperoxides of methyl oleate was reduced to methyl hydroxyoleates, hydrogenated to methyl hydroxystearates, and oxidized to methyl ketostearates. After saponification, 9- and 10-ketostearic acids were isolated pure by fractional crystallization. The 8- and 11-ketostearic acids were not isolated pure, but their presence was demonstrated by conversion to suberic and nonane dicarboxylic acids, respectively, by hydrolysis of the amides obtained by Beckmann transformation of the oxime.

Evidence for the position of the ethylenic

(1) W. A. Waters, *Ann. Repts. on Progress Chem. (Chem. Soc. London)*, 130, **42**, 1945 (1946).

(2) Farmer, *et al.*, *J. Chem. Soc.*, 545 (1943), in a study of autoxidation of methyl oleate did not identify structurally any of the products of oxidation but later felt that all four hydroperoxides were probably present. In his examination of substituted cyclohexenes the structural evidence presented for the existence of four position isomers appears doubtful.

double bond was sought as follows: Dihydroxylation of the mixed hydroxy methyl oleates by performic acid gave two trihydroxy stearates, namely, 8,9,10- and 9,10,11-trihydroxystearic esters. Periodic oxidation of the mixed trihydroxystearic acids gave suberic and azelaic acids.




However, performic acid treatment of the mixed hydroxy oleates yields only 50% of trihydroxystearates. The remainder of the material suffered oxidative fission giving among other products, suberic, azelaic and sebacic acids. The appearance of appreciable amounts of acidic material is quite unusual under these conditions. Performic acid has been used with great success upon simple olefinic compounds to give almost theoretical yields of the monoformate of the dihydroxy derivative. Furthermore, ricinoleic ester under these conditions gives a 96% yield of 9,10,-12-trihydroxystearic ester[3] so that it appears that a non-adjacent hydroxy olefinic compound behaves normally according to the literature. The behavior of performic acid with olefinic compounds having a hydroxy group on a carbon atom directly adjacent to the olefinic group does not seem to have been examined previously. Compounds of this structure have been found to give abnormal products with other reagents. The explanation of the formation of suberic, azelaic and particularly sebacic acid must await further examination of this reaction of performic acid upon hydroxy olefins.

The relative proportion in which the isomeric hydroperoxides are formed in the case of oleic ester is of great interest. Our examination yielded the different substitution products in the order $C_{10} > C_{11} > C_8 > C_9$. However the preparation of the pure concentrated hydroperoxide and hydroxy olefinic ester undoubtedly involved selective crystallization.

Recently[4] we had occasion to examine the addition of olefinic esters to maleic anhydride and found that the main products were those in which addition occurred to the carbon atoms originally carrying the olefinic linkage, the latter in the final product taking up a position at the adjacent carbon atoms. There is insufficient evidence at present for regarding this addition reaction as proceeding by free radical chain mechanism.[5]

Writers in this field have introduced the term "methylenic reactivity" to describe substitution or reaction at or involving a methylene group adjacent to an olefinic linkage. We would suggest that the older term "allylic reactivity" is more inclusive and descriptive of the dynamic implications.

## Experimental

**Purification of Methyl Oleate.**—Commercial red oil or crude oleic acid (5600 g.) was heated at 200° with maleic anhydride (950 g.) for three hours in a carbon dioxide atmosphere.[6] After cooling, 4 liters of methanol containing 40 ml. of concentrated sulfuric acid was added and the solution refluxed for two hours. After standing overnight, 4 liters of water was added and the mixture was extracted with petroleum ether. The extract was washed with potassium carbonate solution to remove acidic material, dried, and the solvent removed. The esters were distilled at 2 mm. pressure, collecting up to 170° in order to leave the maleic anhydride condensation product of polyolefinic esters in the still residue. This crude methyl oleate was then fractionated through a modified Fenske column, 100 cm. long, and a total of 2550 g. of a fraction boiling 161.2–161.8° at 1.1 mm. pressure collected. Analysis showed this to be approximately 93% methyl oleate and 5% methyl linoleate. Using the procedure of Swern, Knight and Findley,[7] this crude ester was fractionally crystallized at low temperature in acetone solution, yielding a total of 1835 g. of methyl oleate having the analysis: *Anal.* Calcd. for $C_{19}H_{38}O_2$: I. V., 85.6; T. V., 85.0 (*cf.*[8]). Found: I. V., 85.7; T. V., 85.5. By spectrophotometric analysis it was

(3) Swern, Billen, Findley and Scanlan, THIS JOURNAL, 67, 1788 (1945).

(4) Ross, Gebhart and Gerecht, *ibid.*, 68, 1373 (1946).

(5) W. G. Bickford, G. S. Fisher, Lillian Kyame and C. E. Swift, *J. Am. Oil Chem. Soc.*, 24, 7, 254 (1948), since this present paper was written have shown that addition occurs at carbon atom 8, 9, 10 and 11.

(6) We felt that maleic anhydride treatment offered a rapid method for eliminating polyunsaturates when present in large amounts. As a result of further work we cannot say that there are necessarily any advantages in this treatment provided a good sample of oleic acid is available.

(7) D. Swern, H. B. Knight and T. W. Findley, *Oil and Soap*, 21, 133 (1944).

(8) Mehlenbacher, *Chem. Eng. News*, 22, 606 (1944).

estimated that this sample of ester contained 0.09% linoleic and 0.04% linolenic esters.

**Structure of Methyl Oleate Used.**—In order to be certain that no isomerization of the methyl oleate had occurred as a result of the maleic anhydride or any prior treatment, a sample (14.8 g.) was converted to methyl dihydroxystearate by performic acid.[3] A yield of 15.3 g. of solid dihydroxystearic acid, m. p. 93–93.5°, was obtained. The theoretical yield was 15.8 g. Swern, *et al.*, report m. p. 94°. Periodic oxidation of the above dihydroxystearic acid[9] gave only azelaic acid in the dicarboxylic acid fraction.

**Autoxidation of Methyl Oleate.**—In a liter thin-wall pyrex erlenmeyer flask connected to an oxygen reservoir, 300 g. of methyl oleate was shaken for twenty-four hours at 35° while being irradiated with ultraviolet light from a 500-watt Hanovia lamp with a type L burner. The oxygen pressure during this time averaged about 9 cm. of mercury above atmospheric. In this manner a peroxide value[10] of 250 milliequivalents per kg. was obtained which corresponded to about 4% of total methyl oleate oxidized. A total of 4570 g. of methyl oleate was oxidized in this manner.

Methyl oleate was separated from the mixture containing methyl hydroperoxido-oleate by crystallizing twice at −72° from a 10% solution in acetone,[11] whereby 158 g. of oil was obtained analyzing 70.1% methyl hydroperoxido-oleate.

**Methyl Hydroxyoleate.**—To a solution of 157 g. of the above 70% methyl hydroperoxido-oleate in a mixture of 1600 ml. of chloroform and 2400 ml. of acetic acid there was added a saturated solution of potassium iodide (200 g. in 150 ml. water) and the mixture was vigorously stirred for five minutes. Saturated aqueous sodium sulfite solution was then added and stirring continued until the liberated iodine had been destroyed, when the mixture was transferred to a separatory funnel and allowed to separate. The chloroform layer was drawn off, washed with 2% aqueous potassium carbonate until neutral, dried, and the solvent removed *in vacuo*. There was obtained 154 g. of a light brown oily liquid which according to hydroxyl determination[12] contained 70.3% methyl hydroxyoleate. By crystallization twice from 1500 ml. of petroleum ether at −60° and −40°, respectively, there was obtained 63 g. of ester containing 98.3% methyl hydroxyoleate according to hydroxyl value and 91.4% as calculated from iodine value. The ester showed an epoxide content of 1.2% by the method of Nicolet and Poulter.[13] By periodic acid oxidation, this ester also showed the presence of 2.5% of methyl dihydroxystearate. These amounts of epoxide and dihydroxystearate are of such low an order that they can be ignored. Making corrections for these it appears that the product contained 91.2% methyl hydroxyoleate.

**A. Methyl Hydroxystearate.**—Sixteen grams of the above methyl hydroxyoleate was hydrogenated at 50° and 600 p. s. i. of hydrogen with Raney nickel catalyst. After filtering off catalyst and removing solvent 16.0 g. of hydroxystearic esters was obtained.

**Methyl Ketostearates.**—The above hydroxystearic esters were dissolved in 50 ml. of glacial acetic acid and a solution of 3.98 g. of chromic oxide ($CrO_3$) in 24 ml. of 90% acetic acid was added over a period of one hour at 30–35° with stirring. Two hours later the mixture was poured into water and extracted with petroleum ether. After washing and drying, the solvent was removed and 16.0 g. of mixed ketostearic esters was obtained.

**Separation and Identification of Ketostearic Acids.**—The above mixed esters were saponified and the acids obtained fractionally crystallized using 20% acetone in petroleum ether (b. p. 35–50°) as solvent.

**9-Ketostearic acid** was obtained as fine needles, m. p. 82°, and separated first as the least soluble isomer, yield 0.5 g. This was identified by mixed melting point with a known sample of 9-ketostearic acid (see B below). It also gave a semicarbazone, m. p. 118–120°, which was identical with the semicarbazone of 9-ketostearic acid.

**10-Ketostearic acid** was obtained as thick needles or large rhombic prisms, m. p. 72–73°, yield about 5.0 g. This was identified by mixed melting point with a known sample of 10-ketostearic acid by preparation and comparison of the semicarbazone, m. p. 101–103°, as well as by isolation of sebacic acid, m. p. 133°, from the products of Beckmann transformation of the oxime.

**11-Ketostearic acid** was not isolated in the pure state. The next series of crystal crops (5.0 g.) consisted of fine short needles mixed with rhombs of 10-ketostearic acid. A quantity of the rhombs was separated manually with the aid of a microscope and by preferential solubility of the fine needles in cold solvent, but the concentrated material still contained some rhombic (and probably needle form) 10-ketostearic acid. Therefore 3 g. of this product was converted to the oxime and submitted to the Beckmann transformation and from the products of hydrolysis there was isolated sebacic acid (0.4 g.) and nonanedicarboxylic acid (0.2 g.), m. p. 109–110° when recrystallized from water at 65°.

*Anal.* Calcd. for $C_{11}H_{20}O_4$: neut. equiv., 108. Found: neut. equiv., 108. The above nonanedicarboxylic acid was identified by mixed melting point with a sample, m. p. 110–111°, prepared by the method of V. Braun and Danziger,[14] from nonane-1,9-diol prepared from diethyl azelate by the method of Chuit.[15]

**8-Ketostearic acid** was likewise not isolated in the pure state. The fourth series of crystal crops and final mother liquors were combined and 3.5 g. converted to the oxime and submitted to the Beckmann transformation. From the hydrolysis products of the amides there was isolated some nonane dicarboxylic acid (0.1 g.) sebacic acid (0.1 g.) and 0.1 g. of suberic acid, m. p. 139–140°, when recrystallized from acetone.

*Anal.* Calcd. for $C_8H_{14}O_4$: neut. equiv., 87. Found: neut. equiv., 87.7.

The suberic acid was identified by mixed melting point with a known sample.

**B. Preparation of 9- and 10-Ketostearic Acids.**—Ten grams of methyl 9,10-epoxystearate[16] was dissolved in 700 ml. of ethanol and the solution carefully neutralized to phenolphthalein with caustic soda; 3.5 g. of Raney nickel was added and hydrogenation carried out on a shaking machine at 25°; 600 ml. of hydrogen at S. T. P. was absorbed. After filtering, the solvent was removed and 10 g. of hydroxy ester was recovered. This ester was oxidized with 14 ml. of a solution of chromic acid in acetic acid containing 0.16 g. of chromic oxide per ml., stirring for one hour at 30–35° and two hours at room temperature. The oxidation mixture was then poured into 300 ml. of water and the product extracted with petroleum ether. About 10 g. of methyl ketostearate was obtained as a pale yellow liquid. This was saponified and the keto acids recovered.

The keto acids were fractionally crystallized from acetone–petroleum ether mixture (1:2).

9-Ketostearic acid was obtained as lustrous plates, m. p. 81.5°, yield 0.21 g. Behrend[17] obtained this acid, m. p. 83°, and proved the structure by obtaining azelaic acid, decanoic acid, ω-aminoöctanoic acid and nonylamine through the Beckmann transformation of the oxime.

The semicarbazone of 9-ketostearic acid, which was prepared and crystallized from alcohol, melted at 118–120°.

*Anal.* Calcd. for $C_{19}H_{37}O_3N_3$: N, 11.83. Found: N, 11.7.

(9) J. Ross, A. I. Gebhart and J. F. Gerecht, THIS JOURNAL, **67**, 1275 (1945).

(10) C. H. Lea, *J. Soc. Chem. Ind. (London)*, **65**, 289 (1946).

(11) C. E. Swift, F. G. Dollear and R. T. O'Connor, *Oil and Soap*, **23**, 355 (1946).

(12) C. L. Ogg, W. C. Porter and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945).

(13) B. H. Nicolet and T. C. Poulter, THIS JOURNAL, **52**, 1186 (1930).

(14) V. Braun and Danziger, *Ber.*, **45**, 1975 (1912).

(15) Chuit, *Helv. Chim. Acta*, **9**, 265 (1926).

(16) Findley, Swern and Scanlan, THIS JOURNAL, **67**, 412 (1945).

(17) Behrend, *Ber.*, **29**, 808 (1896).

10-Ketostearic acid was obtained as needles or rhombic prisms, m. p. 71°, yield 8.5 g. This acid gave a semicarbazone, m. p. 101–103°, crystallized from alcohol.

*Anal.* Calcd. for $C_{19}H_{37}O_3N_3$: N, 11.83. Found: N, 11.9.

Baruch[18] obtained this acid, m. p. 75°, and proved its structure. A sample of our keto acid, m. p. 71°, was converted to the oxime and by Beckmann transformation yielded sebacic acid, m. p. 133°.

**C. Beckmann Transformation on Oxime of 12-Ketostearic Ester.**—In order to ascertain the conditions for the Beckmann transformation upon long chain ketoximes the following examination was carried out. This is described in detail since to our knowledge it has not been previously reported for this readily available compound.

**Methyl 12-Hydroxystearate.**—Methyl ricinoleate, b. p. 189–191° at 1 mm. pressure, was prepared by fractional distillation of methyl esters of castor oil acids. The ester (227 g.) was hydrogenated directly using Raney nickel catalyst in a shaking bomb at 100° and 600 p. s. i. initial hydrogen pressure. The product was dissolved in 250 ml. of methanol, filtered and crystallized at 0°. After recrystallization from methanol 194 g. of pure methyl 12-hydroxystearate was obtained, m. p. 57–58°.

**Methyl 12-Ketostearate.**—The above ester (60 g.) was dissolved in 160 ml. of glacial acetic acid at 30° and 11.1 g. of chromic anhydride dissolved in 50 ml. of 80% acetic acid was gradually added with stirring. The reaction mixture was stirred for an additional two hours and then poured into water and the solid ester extracted with Skellysolve F, washed, dried and recovered. After recrystallization from methanol 52 g. of methyl 12-ketostearate, m. p. 45–46°, was obtained.[19]

**Oxime of Methyl 12-Ketostearate.**—The above ester (12 g.) was dissolved in 90 ml. of 80% alcohol, and solutions of 6.7 g. of hydroxylamine hydrochloride in 30 ml. of 80% alcohol and 10 g. of sodium acetate in 30 ml. of 80% alcohol were added, when the mixture was refluxed for two and one-half hours and then stood at 30° overnight. The alcohol was then distilled off and the residual oil taken up in ether, washed and dried. The oxime was obtained as 12 g. of oil and was not further purified.

**Beckmann Rearrangement of Oxime.**—The above crude oxime was added to 60 ml. of concentrated sulfuric acid and heated on steam-bath one hour. After cooling, the reaction mixture was poured into water. The solid amides which were filtered and washed weighed 12 g.

**Hydrolysis of Amides.**—This was carried out by heating the above amides with 60 ml. of 20% caustic potash in a bomb at 175–200° for three hours. The hydrolysis products were isolated in the order: (a) Monocarboxylic acid, by steam distillation of acidified hydrolysis mixture. Recovered 1.5 g. of *n*-heptanoic acid. *Anal.* Calcd. for $C_7H_{14}O_2$: neutral equivalent, 130. Found: neutral equivalent, 131. The *p*-toluidide had m. p. 80°. Reported *n*-heptanoic-*p*-toluidide, m. p. 81°. (b) Dicarboxylic acid, by ether extraction of acidified hydrolysis mixture after removal of (a). Recovered 6 g. of decane dicarboxylic acid. This was recrystallized from ethylene dichloride and had m. p. 127–128°. Reported m. p. was 127–128°. *Anal.* Calcd. for $C_{12}H_{22}O_4$: neutral equivalent, 115. Found: neutral equivalent, 116.5. (c) Amine, by making alkaline aqueous liquor from (b) and extraction with ether. Recovered 1 g. hexylamine, b. p. 127–128°. Reported b. p. 129–130°. (d) Amino acid, by acidifying the alkaline solution from above with acetic acid, adding ammonia until just alkaline and filtering the amino acid which precipitated as a solid (1.5 g.). This ω-aminoundecanoic acid recrystallized from water and had m. p. 183–184°.

*Anal.* Calcd. for $C_{11}H_{23}O_2N$: N, 6.96. Found by Kjeldahl: N, 6.80.

It was found that for the Beckmann rearrangement of the oximes of these keto acids concentrated sulfuric acid was more reliable than phosphorus pentachloride in ether and good yields of amides were obtained without any reversion to the keto acid, which sometimes occurred with the phosphorus pentachloride.

**D. Action of Performic Acid on Methyl Hydroxyoleates.**—Performic acid was prepared using the method of Swern, *et al.*[3] To 20 g. of 98% methyl hydroxyoleates dissolved in 320 ml. of 98% formic acid, 40.2 ml. of hydrogen peroxide (32%) was added. The reaction temperature was not allowed to exceed 40°. When the temperature began to drop the reaction mixture was left overnight at room temperature. The product was poured into water, saturated with sodium chloride and the separated oil extracted with ether. The ether solution was washed with water, then with acidified ferrous sulfate solution to remove peroxide and finally with 2% potassium carbonate to remove acidic material.

The neutral ether-soluble portion was recovered as an oil which was deformylated by refluxing in 150 ml. of methanol containing 1% sulfuric acid. This reaction mixture was poured into water and the solid which precipitated was taken up in ether, washed free of acid and dried. Evaporation of the ether yielded 10.6 g. of white solid which was crude methyl trihydroxystearates. This was purified by extraction with one liter of petroleum ether for forty-five minutes, cooling and filtering. There was obtained 5.6 g. of insoluble solid which by periodate analysis was 96% pure methyl trihydroxystearates. A portion was saponified and converted to the acid which melted at 115–120°.

*Anal.* Calcd. for $C_{18}H_{36}O_5$: neutral equivalent, 332. Found: neutral equivalent, 338.

Calcd. for $C_{18}H_{33}O_2(OH)_3$: hydroxy equivalent, 110.7. Found: 112.5.

The acidic fraction of this reaction was recovered as 10 g. of thick liquid material upon acidification and extraction of the potassium carbonate washings above. These acid esters were saponified with alcoholic caustic potash and the acids were recovered. The monocarboxylic acids were separated by steam distillation. A total of 5.0 g. of volatile acids was collected which after fractional redistillation in vacuum were found to boil from 87–100° at 0.7 mm. and these fractions had neutral equivalents varying from 153–167.

The material non-volatile with steam was taken up in 500 ml. of boiling water and filtered. A small amount (0.7 g.) of solid insoluble in water proved to be trihydroxystearic acid. The filtrate was fractionally crystallized and the following acids were separated and identified.

**Sebacic Acid.**—This separated at 60° from the water solution. A yield of 1.0 g. was obtained which upon recrystallizing from a 50% mixture of dioxane and water had m. p. 131–132.5°. *Anal.* Calcd. for $C_{10}H_{18}O_4$: neutral equivalent, 101. Found: neutral equivalent, 101. It gave a diphenacyl ester m. p. 81°.[20] The identity was proved by mixed melting point of the acid and the diphenacyl ester with pure specimens, respectively.

**Azelaic Acid.**—This separated at 25° from the water solution. A yield of 2.6 g. of acid was obtained which melted at 105–106° after recrystallization from benzene and then methyl acetate. *Anal.* Calcd. for $C_9H_{16}O_4$: neutral equivalent, 94. Found: neutral equivalent, 93. Identity was confirmed by mixed melting points of acid and diphenacyl ester (m. p. 70–71°) with pure specimens, respectively.

**Suberic Acid.**—This was obtained upon concentration of the aqueous mother liquor. Yield was approximately 1.1 g. after recrystallization from acetone, m. p. 140–141°. *Anal.* Calcd. $C_8H_{14}O_4$: neutral equivalent, 87. Found: neutral equivalent, 86. Its identity was confirmed by mixed melting points of acid and diphenacyl ester (m. p. 107.5°) with pure specimens of these.

**Periodate Oxidation of Above Mixed Trihydroxystearic Acids.**—Six grams of the above acid was dissolved in 60 ml.

(18) Baruch, *Ber.*, **27**, 174 (1894).

(19) Rene and Perrotte, *Compt. rend.*, **199**, 358 (1934).

(20) Huntress-Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, New York, N. Y., 1941, pp. 143, 150, 153.

of ethanol and treated with 8.5 g. of periodic acid in 60 ml. of ethanol with cooling and then kept at room temperature for thirty minutes.

The reaction mixture was poured into water and extracted with ether. The acid half-aldehydes were separated from the normal aldehydes by aqueous carbonate washing of the ether extract, and were subsequently separately oxidized to the carboxylic acid by treatment with peracetic acid.[9] There was thus recovered 2.47 g. of liquid monocarboxylic acids which were not further examined.

From the carbonate extract there was obtained 2.81 g. of mixed dicarboxylic acids after oxidation of the half aldehydes. These acids were separated by maceration with anhydrous ether. The portion insoluble in ether (0.6 g.) was washed with benzene and then crystallized from acetone to give a pure acid which was identified as suberic acid, m. p. 140–141° by mixed melting point with an authentic sample. *Anal.* Calcd. for $C_8H_{14}O_4$: neut. equiv., 87.0. Found: neut. equiv., 88.0.

The ether soluble fraction was crystallized from water and then from methyl acetate. 0.58 g. of pure acid was obtained which was identified by analysis and mixed melting point with a known sample as azelaic acid, m. p. 105–106°. *Anal.* Calcd. for $C_9H_{16}O_4$: neut. equiv., 94. Found: neut. equiv., 95.


## Summary

1. The products of autoxidation of methyl oleate at 35° in the presence of ultraviolet light have been examined.

2. The position of substitution of the hydroperoxido groups has been determined by conversion to the corresponding ketostearic acids. Substitution has been shown to occur at carbon atoms $C_8$, $C_9$, $C_{10}$ and $C_{11}$.

3. Evidence has been obtained that a double bond shift occurs in the formation of two of the above hydroperoxido substitutions so that in all four compounds the olefinic group is adjacent to the hydroperoxido group. In the peroxidation and double bond shift only the carbon atoms $C_8$, $C_9$, $C_{10}$ and $C_{11}$ are involved.

4. The products identified strongly support a chain reaction mechanism sequence involving allylic resonance of the two free radicals initially possible.


JERSEY CITY, N. J. RECEIVED JUNE 28, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

# Oxidation of Some Aliphatic Alcohols with Chromic Acid

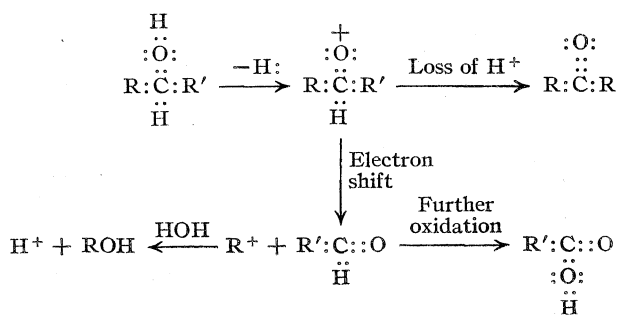
BY WILLIAM A. MOSHER AND ESLEY O. LANGERAK[1]

Mosher and Whitmore[2] recently reported the isolation of *t*-amyl alcohol from the chromic acid oxidation of methyl-*t*-amylcarbinol and isopropyl-*t*-amylcarbinol and *t*-butyl alcohol from the oxidation of methyl-*t*-butylcarbinol. A tentative mechanism involving the new concept of an intermediate containing an electronically-deficient oxygen atom was proposed. Work has been continued on this general problem by a careful search for anomalous oxidation products from other secondary aliphatic alcohols.

The secondary alcohols referred to above all have a neopentyl carbon in the alpha position to the hydroxyl-bearing carbon atom. It is probably due to the weak electron-attracting power of this type of group[3] and to the "steric strain"[4] that the splitting occurs to any appreciable extent. The first extension of the above work was to study the oxidation of secondary alcohols which had carbon atoms of lower substitution in the alpha position. The oxidation of ethyl-*s*-butylcarbinol with chromic anhydride in 80% aqueous acetic acid gave 63% of the corresponding ketone, 1% *s*-butyl alcohol, and about 1% methyl ethyl ketone probably formed by the oxidation of some of the *s*-butyl alcohol. The similar oxidation of methyl-*n*-amylcarbinol gave 83% of the corresponding ketone and a trace of *n*-amyl acetate presumably formed from the esterification of the corresponding alcohol or carbonium ion.

The question of the second part of the molecule formed by the split has been clearly answered in the case of *n*-propyl-*t*-butylcarbinol. The oxidation of this alcohol gave 41% of the corresponding ketone, 4% *n*-butyraldehyde and a corresponding amount of *t*-butyl alcohol. Traces of aldehyde have been isolated in other aliphatic alcohol oxidation but further oxidation to acid appears to be the usual course.

In the case of secondary aliphatic alcohols it would appear that some cleavage at the carbon alpha to the hydroxyl-bearing carbon is a general phenomenon. The amount of cleavage observed decreases as the electron attracting power of the group increases and the steric strain decreases. The proposed mechanism is written below in generalized form for any secondary alcohol.




(1) F. G. Cottrell Research Fellow in chemistry.

(2) Mosher and Whitmore, THIS JOURNAL, **70**, 2544 (1948).

(3) Whitmore and Bernstein, *ibid.*, **60**, 2626 (1938).

(4) H. C. Brown, *et al.*, *ibid.*, **66**, 435 (1944).

From the above mechanism it will be seen that the split of the molecule to yield carbonium ion and aldehyde occurs at the position beta to the position of electron deficiency. The electrons in this particular position are the most accessible to the oxygen atom. The position of the split, as well as the extent of splitting, is in complete harmony with the findings of Whitmore and Stahly[5] and Whitmore and Mosher.[6] This "beta-effect," discussed by Dean Whitmore[7] in 1944, has its physical basis in the fact that the beta electrons are the closest electrons to the deficient atom in which the deficient atom does not already have a part interest.

This work was possible through a Frederick G. Cottrell Grant from the Research Corporation, which we gratefully acknowledge.

## Experimental

**Preparation of Alcohols.**—Methyl-*n*-amylcarbinol was obtained from Carbide and Carbon Chemical Corporation. Ethyl-*s*-butylcarbinol and *n*-propyl-*t*-butylcarbinol were prepared by the Grignard reaction from the appropriate starting materials. Materials were purified by fractionation through a Whitmore–Lux[8] total condensation, partial take-off type column packed with single turn glass helices,[9] and equivalent to 20 theoretical plates.

**Oxidation.**—(a) All secondary alcohols were oxidized in the following manner exemplified with ethyl-*s*-butylcarbinol: a solution of 80 g. (0.8 mole) of chromic anhydride in 50 ml. of water and 125 ml. of glacial acetic acid was added dropwise to a stirred solution of 168 g. (1.4 mole) of the carbinol in 100 ml. of glacial acetic acid over a period of 5.75 hours. The temperature was kept below 30° at all times. The oil layer formed on dilution of the reaction mixture was separated, washed with bicarbonate solution, and then with water. The aqueous layer was steam distilled and the oil layer, after washing as before, was combined with the main portion. The dried oil layers were fractionated through a column of 20 theoretical plates. From the distillation charge of 133 g. the following cuts were obtained: I (1.5 g., 0.9%), 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic derivative of methyl ethyl ketone 116–117°; II (1.4 g., 0.8%), phenylurethan, m. p. and mixed m. p. with a derivative of *s*-butyl alcohol 64–65°; III (100.1 g., 63%), ethyl *s*-butyl ketone, 2,4-dinitrophenylhydrazone m. p. 78°. Unchanged carbinol (11.0 g., 7%) was recovered. Still residue, 8.1 g., was a dark viscous liquid.

(b) Methyl-*n*-amylcarbinol distillation charge 220 g. The corresponding ketone and *n*-amyl acetate boil very close together. The acetate was isolated from the proper fractions by removing the ketone as the bisulfite addition compound and the final traces as the semicarbazone. After drying over anhydrous sodium sulfate a trace (0.08 g., 0.03%) of *n*-amyl acetate, $n^{20}D$ 1.4039, characteristic odor, was isolated; 192 g. (83.2%) of methyl *n*-amyl ketone, 2,4-dinitrophenylhydrazone m. p. and mixed m. p. 74°, was obtained; 7.6 g. (3.4%) unoxidized carbinol was recovered. Still residue was 14.3 g.

(c) *n*-Propyl-*t*-butylcarbinol: No glacial acetic acid was used in order to facilitate isolation of any aldehydes or acids. The carbinol was added dropwise to a vigorously stirred aqueous solution of chromic anhydride. Distillation charge 180 g.; 6.8 g. (4%) of *n*-butyraldehyde, 2,4-dinitrophenylhydrazone m. p. and mixed 122–123°, and a corresponding amount of *t*-butyl alcohol, isolated as the chloride, were obtained. The main fraction (67.3 g., 40.8%), 2,4-dinitrophenylhydrazone m. p. 123–124°, consisted of the corresponding ketone; 50 g. (30.3%) of unoxidized carbinol, phenylurethan m. p. 70–71°, was recovered. Still residue amounted to 21.6 g.

(5) Whitmore and Stahly, THIS JOURNAL, **55**, 4153 (1933); **67**, 2158 (1945).

(6) Whitmore and Mosher, *ibid.*, **68**, 281 (1946).

(7) Whitmore, Organic Division, American Chemical Society, New York, N. Y., September, 1944.

(8) Whitmore and Lux, THIS JOURNAL, **54**, 3448 (1932).

(9) Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933).

## Summary

1. The chromic acid oxidation of ethyl-*s*-butylcarbinol yields the expected ketone, but also small amounts of *s*-butyl alcohol and methyl ethyl ketone.

2. Methyl-*n*-amylcarbinol in acetic acid solution gives a trace of *n*-amyl acetate.

3. Oxidation of *n*-propyl-*t*-butylcarbinol gives small amounts of *t*-butyl alcohol and *n*-butyraldehyde in addition to the expected ketone.

NEWARK, DELAWARE RECEIVED JULY 6, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL AND COLLOIDAL CHEMISTRY, THE HEBREW UNIVERSITY]

# A Reaction between Resorcinol and Glycine

BY N. LICHTENSTEIN, J. DOBKIN AND EVA HEIMANN-HOLLAENDER

Glycine dissolves with the evolution of carbon dioxide when heated in melted resorcinol at 175–185°. A colorless, crystalline substance can be isolated from the product which remains after the excess resorcinol is removed with ether. The elementary composition and chemical properties of this substance correspond to those to be expected of N-(*m*-hydroxyphenyl)-glycine anhydride (I).

The substance is insoluble in sodium bicarbonate solution, but dissolves readily in dilute sodium hydroxide. It gives positive color reactions with Millon reagent, with 2,6-dichloroquinonechlorimide,[1] and with diazotized sulfanilic acid. The picric acid reaction for diketopiperazines[2] is positive, whereas the fluorescein reaction for resorcinol and the ninhydrin color reaction give negative results. Van Slyke amino determination and titration in acetone according to Linderstrøm–Lang failed to reveal the presence of a free amino group.

Benzoylation of our substance converted it into a corresponding monobenzoyl derivative which was insoluble in dilute sodium hydroxide and gave no color reaction with Millon reagent.

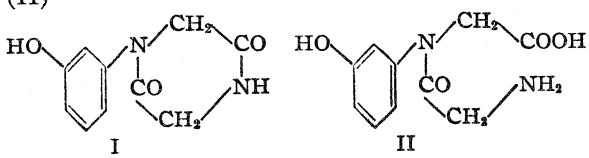
The substance was hydrolyzed with hydrochlo-

(1) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).

(2) E. Abderhalden and E. Komm, *Z. physiol. Chem.*, **139**, 181 (1924).

ric acid. When the hydrolysate was evaporated to dryness, dissolved in absolute alcohol and saturated with hydrogen chloride, glycine ethyl ester hydrochloride crystallized out.

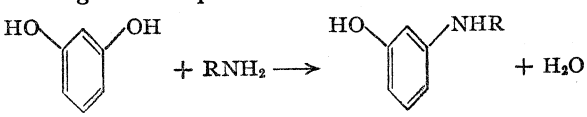
It is known that the glycine anhydride ring can easily be opened by treatment with sodium hydroxide to form glycylglycine. In a similar manner, we succeeded in opening the substituted diketopiperazine ring of our substance by treating it with sodium hydroxide and we were able to isolate in good yield a product whose C, H, N and amino N content correspond to the values theoretically expected of glycyl-N-(*m*-hydroxyphenyl)-glycine (II)




Finally, the same substance as that obtained from glycine was isolated after treating glycylglycine with hot resorcinol under similar conditions.

On heating with resorcinol at 175–185°, glycine anhydride could be recovered unchanged.

The formation of N-(*m*-hydroxyphenyl)-glycine anhydride from glycine and resorcinol may be explained as follows. It is known[3] that resorcinol reacts on heating with ammonia or with amines according to the equation




In a similar manner glycine may be assumed to react with resorcinol, yielding N-(*m*-hydroxyphenyl)-glycine. Heating would lead to the decomposition of a considerable part of this substance into carbon dioxide and *m*-methylaminophenol and the latter is thereafter removed with ether. An analogous decarboxylation of N-phenylglycine "on rapid distillation" is described by Bischoff and Hausdörfer.[4] A portion of the N-(*m*-hydroxyphenyl)-glycine, however, reacts with a second molecule of glycine to yield our substance (I). Similarly, glycylglycine would react primarily with resorcinol to give N-(*m*-hydroxyphenyl)-glycylglycine, which then forms the corresponding substituted diketopiperazine (I) by losing one molecule of water. However, we have not yet succeeded in isolating any of the hypothetical intermediary products mentioned above.

## Experimental

**Preparation of N-(*m*-Hydroxyphenyl)-glycine Anhydride (I).**—One hundred grams of resorcinol was heated in an oil-bath at a bath temperature of 175°. Twenty grams of glycine was added to the melted resorcinol, and the mixture was heated for an hour at 175–185° (bath temperature) with occasional stirring. The glycine soon dissolved with the evolution of gas bubbles. When the evolved gas was introduced into an aqueous solution of barium hydroxide, a precipitate was formed which was free of organic matter and which dissolved in diluted acids with the formation of gas bubbles. The clear hot solution was poured into a porcelain mortar. The solidified mass was treated with dry ether, the ether drawn off by suction and the residue washed with ether and dried; yield, 16 g. This material was repeatedly boiled with several portions of absolute alcohol, using the total volume of 1600 cc. of alcohol. The pooled filtered alcoholic extracts were concentrated to about 100 cc. and allowed to stand overnight. The brownish precipitate was filtered by suction, washed with a little absolute alcohol and dried; yield, 9 g. This substance was boiled with about 40 parts of water and filtered through a hot water funnel. The filtrate was boiled with *carbo animalis* and refiltered. On cooling, a precipitate in the form of yellowish needles appeared. It was filtered by suction, washed with water and dried. On recrystallization of the substance from 100 parts of 70% alcohol 3 g. of a colorless, crystalline substance was obtained in the form of glittering needles. The substance gives a red color reaction when boiled with Millon reagent. A deep orange color appears when diazotized sulfanilic acid and soda are added to its aqueous solution. With dichloroquinone chlorimide[1] and borate buffer (*p*H 9.2) a blue color is formed. The diketopiperazine reaction of Abderhalden and Komm[2] is positive. The ninhydrin color reaction and the fluorescein test for resorcinol are negative. The Linderstrøm-Lang titration value and the amino value according to Van Slyke are 0. The substance is insoluble in cold aqueous sodium bicarbonate but dissolves readily in dilute sodium hydroxide.

For analysis, the substance was twice recrystallized from 70% alcohol and dried *in vacuo* over phosphorus pentoxide at 100°.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.2; H, 4.9; N, 13.6. Found: C, 58.5; H, 4.7; N, 13.5.

The substance has no definite melting point. It decomposes at 265–270° after previous darkening.

**N-(*m*-Benzoyloxyphenyl)-glycine Anhydride.**—One gram of N-(*m*-hydroxyphenyl)-glycine anhydride was treated with 45 cc. of 0.1 *N* sodium hydroxide (about 0.9 mole) and filtered. The filtrate was cooled in a mixture of ice and water and 0.6 g. of benzoyl chloride was added drop by drop with constant stirring. The colorless precipitate was filtered by suction, repeatedly washed with cold water and dried; yield, 900 mg. For analysis, the substance was recrystallized twice from a small amount of absolute alcohol, m. p. 171° (uncor.). *Anal.* Calcd. for $C_{17}H_{14}N_2O_4$: N, 9.03. Found: N, 9.08. The substance is insoluble in dilute sodium hydroxide and gives no color reaction with Millon reagent.

**Acid Hydrolysis of N-(*m*-Hydroxyphenyl)-glycine Anhydride.**—One gram of N-(*m*-hydroxyphenyl)-glycine anhydride was boiled with 15 cc. of hydrochloric acid (1:1) for fifteen to twenty hours. The hydrolyzate was evaporated to dryness in a vacuum desiccator over sulfuric acid and soda lime. α-Amino carboxyl determination (Van Slyke's ninhydrin method) showed that at least the greatest part of the substance was completely hydrolyzed. The evaporated hydrolyzate was dissolved in a small amount of absolute alcohol and saturated with dry hydrogen chloride. On standing, about 200 mg. of glycine ethyl ester hydrochloride crystallized out. *Anal.* Calcd.: N, 10.0; Cl, 25.4. Found: N, 10.1; Cl, 25.5.

**Glycyl-N-(*m*-hydroxyphenyl)-glycine (II).**—Two grams of N-(*m*-hydroxyphenyl)-glycine anhydride was dissolved in 40 cc. of *N* sodium hydroxide and allowed to stand for three days at 30°. Forty cc. of *N* hydrogen chloride was added, and the solution was evaporated to dryness *in vacuo*. The substance obtained was treated with 100 cc. of absolute alcohol and filtered the next day. The remaining product was dissolved in 4 parts of hot water, and the precipitate which formed on cooling was again recrystallized from water. Eight hundred and fifty mg. of a

(3) Beilstein's "Handbuch der organ. Chemie," **6**, 799, 806, 807 (1923).

(4) C. A. Bischoff and A. Hausdörfer, *Ber.*, **25**, 2270 (1892).

reddish, crystalline substance free of chlorine were obtained in this manner. The substance was dried *in vacuo* at 100° over phosphorus pentoxide. It gives positive color reactions with ninhydrin, with diazotized sulfanilic acid and with dichloroquinone chlorimide.

*Anal.* Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.6; N, 12.5; amino-N, 6.3. Found: C, 53.4; H, 5.6; N, 12.6; amino-N, 6.3 (Linderstrøm-Lang titration).

The substance has no definite melting point.

**Formation of N-(*m*-Hydroxyphenyl)-glycine Anhydride from Glycylglycine and Resorcinol.**—To 25 g. of melted resorcinol was added 5 g. of glycylglycine. The mixture was heated for three hours in an oil-bath at a bath temperature of 175–185°. The limpid, hot solution was poured into a porcelain mortar and the solidified material was treated with ether. (No gas formation was observed on heating the dipeptide with resorcinol). After removing the ether by suction the remaining substance was washed with ether and dried; yield, 7.4 g. Five grams of this product was extracted with ethyl acetate for twenty-four hours in a Soxhlet apparatus. The yellowish product which appeared in the extract was filtered by suction, washed with ethyl acetate and dried. The substance (1.1 g.) was recrystallized from 30 cc. of water to which *carbo animalis* was added. On cooling, 250 mg. of a colorless substance was obtained in the form of glittering needles. The Millon reaction was positive. *Anal.* Found: N, 13.2. On benzoylation of 200 mg. under the conditions previously described and on recrystallization from alcohol 170 mg. of a product was obtained whose melting point (171°) was identical with the melting point of the product obtained by benzoylation of N-(*m*-hydroxyphenyl)-glycine anhydride. The m. p. of a mixture of the two substances was also 171°.

*Anal.* Calcd. N, 9.0. Found: N, 9.2.

**Treatment of Glycine Anhydride with Hot Resorcinol.**—Glycine anhydride was heated for three hours with 5 parts of resorcinol at 175–185° in a similar manner to the treatment of glycine or glycylglycine. It dissolved in a short time. After solidification, the reaction mixture was treated with ether. The material obtained after drawing off the ether was boiled with 96% alcohol, filtered, washed with alcohol and dried. The product so obtained (80% of the original material) gave no color reaction with Millon reagent. It was recrystallized from water. *Anal.* Calcd. for glycine anhydride: N, 24.6. Found: N, 24.5.

## Summary

N-(*m*-Hydroxyphenyl)-glycine anhydride was isolated after treating glycine with hot resorcinol at 175–185°. The same product is formed when glycylglycine is heated with resorcinol.

Treating with sodium hydroxide converts N-(*m*-hydroxyphenyl)-glycine anhydride into glycyl-N-(*m*-hydroxyphenyl)-glycine.

JERUSALEM, PALESTINE RECEIVED FEBRUARY 25, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Preparation of 3,3′-Dibromobiphenyl and its Conversion to Organometallic Compounds

BY H. R. SNYDER, CLAY WEAVER[1,2] AND CLIFFORD D. MARSHALL

Although the reactions of various dibromobiphenyls with magnesium[3,4] and with an alkyllithium[5] have been reported, 3,3′-dibromobiphenyl appears to have escaped such investigation. Since symmetrical difunctional organometallic compounds related to biphenyl have been of interest to us as possible intermediates[6] in the synthesis of biphenyldiboronic acids,[7,8,9] the behavior of 3,3′-dibromobiphenyl toward magnesium, lithium and *n*-butyllithium has been examined.

3,3′-Dibromobiphenyl was prepared from *o*-nitrobromobenzene by reduction to the hydrazo compound, rearrangement to the benzidine, and deamination of the tetrazonium salt with hypophosphorous acid.[10] The hydrazo compound and the benzidine thus prepared were found to have melting points quite different from those observed on samples, obtained by processes involving the bromination of azobenzene[11] and of N,N′-diacetylbenzidine,[12] which have been considered[13] to have the structures of 2,2′-dibromohydrazobenzene and 3,3′-dibromobenzidine, respectively. The bromination of N,N′-diacetylbenzene was repeated, and a dibromobenzidine identical with our sample was the only product isolated in a pure state from the reaction mixture. In a Sandmeyer reaction with cuprous bromide the tetrazonium salt from our dibromobenzidine gave a product possessing the same melting point as the tetrabromobiphenyl[14] prepared by van Roosmalen from a dibromobenzidine obtained by the direct bromination method. Furthermore, our compounds had the expected compositions and yielded 3,3′-dibromobiphenyl of the correct properties.[15]

3,3′-Dibromobiphenyl did not react with magnesium under the usual conditions of Grignard preparations, but it did react in the presence of ethylmagnesium bromide. The difunctional Gri-

(1) du Pont Post-Doctorate Research Assistant, 1941–1942.

(2) Present address: Experimental Station, E. I. du Pont de Nemours and Company, Incorporated, Wilmington, Delaware.

(3) Case, THIS JOURNAL, **58**, 1246 (1936).

(4) Malinovskii and Pokrovskii, *Trudy Gor'kov. Gosudarst. Pedagog. Inst.*, No. 5, 51–53 (1940) [*C. A.*, **37**, 3077 (1943)].

(5) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2332 (1940).

(6) Khotinsky and Melamed [*Ber.*, **42**, 3094 (1909)] first prepared boronic acids from alkyl borates and Grignard reagents.

(7) Snyder and Weaver, THIS JOURNAL, **70**, 232 (1948).

(8) Snyder, Weaver and Parmerter, *ibid.*, **70**, 773 (1948).

(9) Snyder and Meisel, *ibid.*, **70**, 774 (1948).

(10) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 262.

(11) Janowsky and Erb, *Ber.*, **20**, 364 (1887).

(12) Levenstein, German Patent 97,101, *Chem. Zentr.*, **69**, II, 522 (1898); see *Frdl.*, **5**, 75 (1901).

(13) Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, Oxford, 1934, pp. 429, 440.

(14) van Roosmalen, *Rec. trav. chim.*, **53**, 371 (1934).

(15) Ullmann, *Ann.*, **332**, 57 (1904).

gnard reagent so formed separated from the ether as a heavy oil. Because of the separation, and because of the presence of ethylmagnesium bromide in the solutions, it was not convenient to determine the extent of reaction of the dibromobiphenyl by titration. Carbonation of such solutions produced the known 3,3′-biphenyldicarboxylic acid which was further characterized as the methyl ester.[16,17] Since the yield of once-recrystallized dicarboxylic acid was moderately good (40%), the conversion of the dibromo compound to the Grignard reagent must have been high. When the Grignard preparation was carried out with only one equivalent of magnesium, both the mono- and difunctional organometallic compounds were formed, as shown by the conversion to 3′-bromo-3-biphenylcarboxylic acid and 3,3′-biphenyldicarboxylic acid. 3,3′-Dibromobiphenyl could not be induced to react with metallic lithium; however, it did react with *n*-butyllithium to produce the difunctional organometallic compound, the presence of which was demonstrated by carbonation.

## Experimental[18]

**2,2′-Dibromohydrazobenzene.**—The method of preparation was patterned after that used by Lukashevich[19] for the synthesis of the chloro analog. A mixture of 20 g. of *o*-nitrobromobenzene and 5 ml. of 50% aqueous sodium hydroxide was stirred at 60°, and zinc dust was added intermittently in small portions such that the temperature remained at 70–80°. After 15 g. of zinc had been added, the sludge was diluted with 50 ml. of water and 30 ml. of 20% aqueous sodium hydroxide. Then 20 g. of zinc was added rapidly, and the mixture was stirred at 70–80° until it was nearly colorless. The cooled mixture was poured slowly into 200 ml. of 25% sulfuric acid at 10°; the mixture was stirred for a few minutes and then filtered. The dry solid was extracted with three 30-ml. portions of ether, and the residue from the evaporation of the ether was recrystallized from petroleum ether (b. p. 40–60°), diluted with a little benzene, to give 10.8 g. (57%) of the hydrazo compound melting at 97–98°.

*Anal.* Calcd. for $C_{12}H_{10}Br_2N_2$: C, 42.1; H, 2.95. Found: C, 42.4; H, 3.30.

**3,3′-Dibromobenzidine.**—Method A: A solution of 4 g. of 2,2′-dibromohydrazobenzene in 50 ml. of ether was added slowly with shaking to 25 ml. of cold concentrated hydrochloric acid. Shaking was continued for one hour, and the dihydrochloride was separated by filtration and washed with ether. A suspension of the white product (wt., 4 g.) in excess 10% aqueous sodium hydroxide was heated on the steam-bath for one hour. The free base was extracted from the cooled mixture with ether, and the extracts were dried over calcium sulfate. The benzidine, recovered from the ether extracts, was recrystallized from ethanol to give 3 g. (75%) of a nearly white solid melting at 127–129°.

*Anal.* Calcd. for $C_{12}H_{10}Br_2N_2$: C, 42.1; H, 2.95. Found: C, 42.3; H, 3.27.

For the preparation of larger quantities of the dihydrochloride, essentially the same procedures were used but the intermediate hydrazo compound was not isolated. The yield of 3,3′-dibromobenzidine dihydrochloride from 61 g. of *o*-nitrobromobenzene was 35–40 g. (57–65%).

Method B: To a well-stirred suspension of 2.68 g. of N,N′-diacetylbenzidine in 100 ml. of water containing a trace of ferric bromide, 3 ml. of bromine was added over a two-hour period. The mixture was stirred for fifteen hours more and then permitted to stand for three days, at the end of which time a brown solid was removed by filtration, washed with water, and added to 40 ml. of 42% sulfuric acid. This mixture was gently refluxed for eighteen hours, cooled, diluted with water, and made alkaline with solid sodium carbonate. A dark solid was collected and extracted with ether. After treatment of the combined extracts with Darco, the ether was removed under reduced pressure. The dark solid so obtained was dissolved in a small amount of alcohol; careful addition of concentrated ammonia to the alcoholic solution produced, first, a very dark precipitate which was removed and discarded, and second, a light brown precipitate, which after separation and washing was dissolved in dilute sulfuric acid. This acidic solution, after decolorization with Darco, was made alkaline with ammonia and gently heated on a steam-bath for several minutes. A cream-colored precipitate was collected and washed with water; it was dissolved in alcohol and to the hot, filtered solution water was added to incipient cloudiness. From the cooled solution a finely crystalline precipitate was collected and washed with cold alcohol–water solution. The solid melted at 128–130° either alone or when mixed with a sample made by Method A, while admixture with benzidine caused a large depression in melting point.

**3,3′,4,4′-Tetrabromobiphenyl.**—The procedure employed was essentially that of van Roosmalen[14]; a portion of 3,3′-dibromobenzidine prepared by Method A was used in the reaction. The product, recrystallized from benzene, melted at 166.5–168.5° (lit.[14] 169°).

**3,3′-Dibromobiphenyl.**—A mixture of 42 g. of 3,3′-dibromobenzidine dihydrochloride and 50 ml. of concentrated hydrochloric acid was diluted with 25 g. of ice and 25 ml. of water and tetrazotized by the addition of a solution of 14 g. of sodium nitrite in 50 ml. of water. The mixture was stirred for one hour after the addition of the nitrite and was then allowed to settle. The clear supernatant solution was added to 330 g. of 30% hypophosphorous acid at 10°; the small amount of residual solid was treated with 10 ml. of concentrated hydrochloric acid and sufficient sodium nitrite to cause complete solution, and this solution was also added to the hypophosphorous acid. The mixture was allowed to stand in the refrigerator for thirty hours and then in the room, with occasional shaking, for twenty hours. The mixture was then extracted with five 50-ml. portions of ether. The combined ether extracts were washed with two 50-ml. portions of 5% sodium hydroxide, followed by 50 ml. of water. The extracts were dried over potassium carbonate and the oil remaining after evaporation of the ether was distilled from a short-necked flask with a very wide side tube.[20] The yield of nearly colorless oil (b. p. 130–140° (2 mm.)), which soon solidified, was 22.0–25.2 g. (71–81%). A sample recrystallized from ethanol melted at 52–52.5° (lit.,[15] 53°).

**3,3′-Biphenyldicarboxylic Acid.**—From the difunctional Grignard reagent: To 3.12 g. of 3,3′-dibromobiphenyl, 0.58 g. of magnesium, and 12 ml. of anhydrous ether, contained under a nitrogen atmosphere in a 3-necked 50-ml. flask equipped with a mercury sealed stirrer and a condenser, there was added an ethylmagnesium bromide solution prepared from 0.76 ml. of ethyl bromide, 0.28 g. of magnesium and 4 ml. of dry ether. After the mixture had been gently refluxed for eight hours, a heavy dark red oil had formed. The content of the flask was poured, portionwise with stirring, onto an excess of powdered Dry Ice contained in a flask toward whose mouth a vigorous stream of nitrogen was directed. After the carbonated mixture had been hydrolyzed with 20 ml. of 6 *N* sulfuric acid, a light yellow solid was removed by filtration and washed with several small portions of ether and

(16) Ullmann, *Ann.*, **332**, 71 (1904).

(17) Bulow and von Reden, *Ber.*, **31**, 2576 (1898).

(18) All melting points uncorrected.

(19) Lukashevich, *Anilinokrasochnaya Prom.*, **4**, 605 (1934) [(*C. A.*, **29**, 2527 (1935)].

(20) The flask was of the type recommended by Koelsch, "Organic Syntheses," **20**, 20 (1940).

then with water (wt. of solid 1.60 g.). The ether layer of the filtrate was extracted with two 20-ml. portions of 5% sodium bicarbonate; acidification (congo red) of the combined bicarbonate washes with sulfuric acid gave a small amount of light yellow precipitate, which was collected and washed with water.

The solution of the two above precipitates in dilute sodium carbonate was decolorized with Darco. Acidification (congo red) of the solution with sulfuric acid produced a flocculent white solid, which was collected and washed with water. Recrystallization from dioxane gave a white powdery solid (wt. 0.97 g., 40%) melting at 330–332° (lit. 339–341°,[17] 356–357°[16]) and containing no halogen.

From 3,3′-biphenyldilithium: To an ice-cold *n*-butyllithium solution in 24 ml. of dry ether, prepared from 0.56 g. of lithium and 3.4 g. of *n*-butyl chloride, contained in the apparatus described above and under an atmosphere of nitrogen, 2.34 g. of 3,3′-dibromobiphenyl in 12 ml. of dry ether was added by means of a dropping funnel over a thirty-minute period. The mixture was cooled and stirred for four hours and was then gently refluxed for one hour. After carbonation of the mixture, the acid was isolated and purified as above, m. p. 330.5–332° (wt. 0.83 g., 46%).

**Dimethyl Ester of 3,3′-Biphenyldicarboxylic Acid.**—The procedure of Bulow and von Reden[17] was employed. The dimethyl ester so obtained melted at 97.5–99 (lit.[17] 100–101).

**3′-Bromo-3-biphenylcarboxylic Acid.**—To 3.20 g. of 3,3′-dibromobiphenyl, 0.24 g. of magnesium and 20 ml. of dry ether, contained in the apparatus previously described and under an atmosphere of nitrogen, approximately 0.005 mole of ethylmagnesium bromide in 5 ml. of dry ether was added; the mixture was stirred and gently heated for seven hours. The reaction mixture was carbonated and hydrolyzed as before.

From the hydrolysis mixture, 0.31 g. of light yellow solid (m. p. above 300°) was removed by filtration and washed with several small portions of ether. The separated ether layer was extracted with two 20-ml. portions of 5% sodium bicarbonate, then with two 20-ml. portions of 5% sodium hydroxide.

The combined sodium bicarbonate washes were decolorized with Darco, and acetic acid was added until the solution was almost neutral to litmus. A precipitate (A, wt. 0.59 g.) was collected and washed with water. Acidification (congo red) of the filtrate from A with sulfuric acid gave a second precipitate (B, wt. 0.13 g.). Similar treatment of the sodium hydroxide extracts with acetic acid gave a precipitate (C, wt. 0.37 g.); on further acidification of the filtrate no appreciable precipitate was obtained.

A portion of C was dissolved in dilute sodium carbonate and decolorized with Darco. Acidification of the filtered solution gave a white solid which was removed by filtration, washed with water and dried. The solid, which contained bromine, was recrystallized twice from benzene to give 3′-bromo-3-biphenylcarboxylic acid, melting at 190–191°.

*Anal.* Calcd. for $C_{13}H_9O_2Br$: C, 56.34; H, 3.27. Found: C, 56.76; H, 3.54.

Precipitate A consisted primarily of the monobasic acid as shown by its almost complete liquefaction at a temperature of 190° and by its separation into the mono- and dibasic acids by stepwise acidification of its solution in dilute sodium carbonate. Precipitate B was primarily the dibasic acid as shown by the melting point, roughly determined as above 300°.

## Summary

3,3′-Dibromobiphenyl has been synthesized from *o*-nitrobromobenzene by zinc–alkali reduction to 2,2′-dibromohydrazobenzene, rearrangement of the hydrazo compound to 3,3′-dibromobenzidine, and deamination of the benzidine by reaction of the tetrazonium salt with hypophosphorous acid. A dilithium compound and a difunctional Grignard reagent were prepared from 3,3′-dibromobiphenyl. From the monofunctional Grignard reagent the new 3′-bromo-3-biphenylcarboxylic acid was obtained.

The melting points of the 2,2′-dibromohydrazobenzene and 3,3′-dibromobenzidine prepared in this work do not agree with those of substances previously considered to have these structures.

URBANA, ILLINOIS RECEIVED JULY 26, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Stereochemical Course of Amine Replacement Reactions. Some Reactions of *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide

BY H. R. SNYDER AND JAMES H. BREWSTER[1]

Quaternary ammonium compounds containing benzyl groups can be used in the benzylation of the anions of such salts as sodiomalonic ester,[2] sodium cyanide,[3] sodium phenolate,[3,4] and the sodium salts of carboxylic acids[3] or of sulfur containing acids.[3,5] These reactions appear to be completely analogous to the formation of benzyl alcohol[6] and benzyl chloride[7] by thermal decomposition of quaternary benzylammonium hydroxides and chlorides, and it would be expected that all of these processes occur by similar mechanisms.

Evidence has been presented to show that both methanol and benzyl alcohol are formed from benzyltrimethylammonium hydroxide by reactions having $S_N2$ mechanisms.[8,9] Reactions proceeding by such mechanisms occur with complete inversion of configuration when they take place at an asymmetric carbon atom; other mechanisms result in partial or complete racemization or in retention of configuration.[10] Read and

(1) Present address: Department of Chemistry, University of Chicago, Chicago, Illinois.

(2) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

(3) von Meyer, *Abhandl. math.-phys. Klasse sachs. Gesellschaft Wiss.*, **31**, 179 (1908); [*Chem. Zentr.*, **80**, II, 1800 (1909)].

(4) Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926); [*C. A.*, **20**, 3695 (1926)].

(5) Snyder and Speck, THIS JOURNAL, **61**, 668, 2895 (1939).

(6) von Braun, *Ann.*, **382**, 1 (1911).

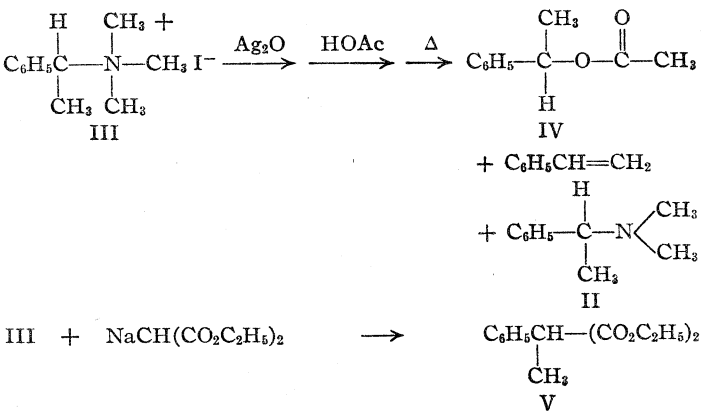
(7) Michler and Gradmann, *Ber.*, **10**, 2078 (1877).

(8) Hughes and Ingold, *J. Chem. Soc.*, 69 (1933).

(9) Hughes, Ingold and Patel, *ibid.*, 526 (1933).

(10) Cowdrey, Hughes, Ingold, Masterman and Scott, *ibid.*, 1252 (1937).

Walker[11] concluded that Walden inversion occurred in the formation of *d*-neopiperitol from *l*-piperityltrimethylammonium hydroxide. Accordingly it would be anticipated that an optically active quaternary salt containing an α-substituted benzyl group would alkylate the various reagents mentioned above to give products of configuration opposite to that of the original salt. The present work was undertaken to test this assumption. Optically active forms of α-phenylethyltrimethylammonium salts were chosen for the experiments because the configurational relationships of a large number of compounds containing the α-phenylethyl group have been established.[12] These relationships may be summarized in the statement that in the α-phenylethyl series optically active halo, hydroxy, amino, dimethylamino and acetoxy compounds which have the same sign of rotation have the same configuration.




α-Phenylethylamine (I) was resolved by means of malic and tartaric acids.[13] The optical purity of the *d*-(+)-form ($[\alpha]^{25}D$ +36.24°, $[\alpha]^{22}D$ +36.60°) was estimated to be no more than 97.5%, on the basis of the rotation observed by Marckwald and Meth[14] ($[\alpha]^{22}D$ 37.70°), and to be no less than 94.5%, on the basis of the rotation found by Holmberg[15] ($[\alpha]^{19}D$ 38.73°). The optically active primary amine was methylated by means of formaldehyde and formic acid. N,N-Dimethyl-α-phenylethylamine (II) has a high rotation ($[\alpha]^{26}D$ +61.76°) and might be a useful resolving agent; it forms a methiodide (III) which is dextrorotatory in water.

A water solution of the methiodide (III) was treated with silver oxide and then with acetic acid; the solution of the quaternary acetate was distilled to dryness. From the distillate there was obtained 1-(−)-α-phenylethyl acetate (IV) (26.3%) ($[M]^{28}D$ −185.1 in benzene) having an estimated optical purity of 95.4%, based on the value of Levene and Marker[16] ($[M]^{25}D$ −194 in benzene). Thus, inversion of configuration occurred to the extent of 98–100%, strongly indicating an $S_N2$ mechanism for the reaction. Styrene (33.1%) and *d*-(+)-II (12.1%) were also obtained from this degradation.

Sodiomalonic ester can be alkylated by the racemic salt (III) in diethyl carbitol solution. When the optically active methiodide was employed, the α-methylbenzylmalonic ester (V) formed was optically inactive. A small amount of weakly dextrorotatory II was also obtained, suggesting that the quaternary salt was largely racemized before it could participate in the alkylation reaction.

When an aqueous solution of III and sodium cyanide was distilled to dryness none of the desired hydratroponitrile could be isolated from the distillate, which appeared to consist mainly of styrene.

## Experimental

***d*-(+)-α-Phenylethylamine (I).**—*dl*-α-Phenylethylamine (60 g., 0.50 mole) was resolved by the successive use of *l*-malic acid and *d*-tartaric acid[13] to give 16.1 g. (53.7%) of *d*-(+)-α-phenylethylamine, $n^{20}D$ 1.5264; $d^{20}_4$ 0.951; $[\alpha]^{25}D$ +36.24°, $[\alpha]^{22}D$ +36.60° (*l* = 1 dcm.).

***dl*- and *d*-(+)-N,N-Dimethyl-α-phenylethylamine[17] (II).**—The general method of "Organic Syntheses"[18] for the methylation of amines was found to be applicable to α-phenylethylamine. *dl*-N,N-Dimethyl-α-phenylethylamine, b.p. 92–94° (30 mm.), $n^{20}D$ 1.5023, $d^{20}_4$ 0.908 (lit.[12c] $n^{14}D$ 1.5025, $d^{16}_4$ 0.8986), was obtained in 75% yield, and *d*-(+)-N,N-dimethyl-α-phenylethylamine, $n^{20}D$ 1.5025, $d^{20}_4$ 0.908, $[\alpha]^{26}D$ +61.76° (*l* = 1 dcm.), in 64.5% yield.

***dl*- and *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide (III).**—To a solution of N,N-dimethyl-α-phenylethylamine (60.0 g., 0.40 mole) in ether (100 ml.) was added slowly a solution of methyl iodide (64.0 g., 0.45 mole) in ether (100 ml.). After fifteen minutes the mixture had solidified. The flask was cooled under the tap several times during the succeeding two hours and then let stand at room temperature for fourteen hours. The white solid was collected by filtration and washed with two 100-ml. portions of ether. After it had been dried in the air and finally in a vacuum desiccator (continuous pumping for twenty-four hours) the solid weighed 111 g. (95%).

In a similar manner, *d*-(+)-α-phenylethylamine (9.5 g., 0.064 mole) was converted to its methiodide, 17.0 g. (92%), m. p. 157° $[\alpha]^{26}D$ + 11.88 (in water) (*c* = 1.-2627) [lit.[19] m. p. 157.0–157.5°, $[\alpha]^{26}D$ + 19.60° (in alcohol) (*c* = 2.5)].

**Degradation of *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Acetate.**—The still moist, thoroughly washed silver oxide prepared from 11.0 g. of silver nitrate

(11) Read and Walker, *J. Chem. Soc.*, 308 (1934).

(12) (a) Levene, Rothen and Kuna, *J. Biol. Chem.*, **120**, 777 (1937); (b) Levene and Rothen, *ibid.*, **127**, 237 (1939); (c) Campbell, Houston and Kenyon, *J. Chem. Soc.*, 93 (1947); (d) Bergmann, *Helv. Chim. Acta.*, **20**, 590 (1937); (e) Hughes, Ingold and Scott, *J. Chem. Soc.*, 1201 (1937); (f) Ott, Zinnius, Wegler, Beischer and Packendorf, *Ann.*, **488**, 186 (1931); (g) Wegler and Ruber, *Ber.*, **68**, 1055 (1935).

(13) Ingersoll, in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(14) Marckwald and Meth, *Ber.*, **38** 808 (1905).

(15) Holmberg, *ibid.*, **45**, 999 (1912).

(16) Levene and Marker, *J. Biol. Chem.*, **97**, 379 (1932).

(17) Stevens, *J. Chem. Soc.*, 2107 (1930).

(18) Icke, Wisegarver and Alles, "Organic Syntheses," Vol. XXV, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

(19) Biilmann, Jensen and Jensen, *Bull. soc. chim.*, [5] **3**, 2295 (1936).

was added slowly, and with good stirring, to a warm (50°) solution of *d*-(+)N,N,N-trimethyl-α-phenylethylammonium iodide (11.64 g., 0.04 mole) in water (100 ml.). The precipitate of silver iodide was broken up continuously to expose fresh silver oxide until the precipitate as a whole was light brown in color. The silver oxide–silver iodide precipitate was removed by filtration and washed with four 50-ml. portions of water. The combined filtrate and wash water was treated with glacial acetic acid (30 g., 0.50 mole), and concentrated to a thick sirup on a steam cone at the water pump.

This oil was transferred, while still warm, to a 50-ml. distilling flask with a wide low-set side arm. Two 1-ml. portions of water and two 1-ml. portions of glacial acetic acid were used in this transfer. The solution in the distilling flask was then distilled at 34 mm. pressure with a Woods metal-bath to heat the bulb of the flask. Most of the excess water and[5] acetic acid distilled below 80° (bath temperature 130° or less). When the bath temperature reached 170–175°, vigorous ebullition occurred and the entire contents of the flask distilled smoothly and rapidly (vapor temperature, 80–110°). The distillate had a strong odor of acetic acid, and weighed 9.5 g.

The distillate was dissolved in ether (50 ml.) and extracted with three 50-ml. portions of water and then with two 25-ml. portions of 5% aqueous sodium bicarbonate. The five aqueous washings were combined (A).

The ether solution was distilled at atmospheric pressure and then at water pump pressure. Fractions which distilled at 69–71° (30 mm.) and at 118–119° (30 mm.) were collected.

The lower-boiling fraction, identified as styrene, weighed 1.38 g. (33.1%); $n^{20}D$ 1.5455, dibromide, m. p. 73–74° (lit., b. p. 145–145.8°[20] ($n^{20}D$ 1.5463,[20] dibromide m. p. 74–75°).[21]

The higher-boiling fraction was 1-(−)-α-phenylethyl acetate; it weighed 1.72 g. (26.3%); $n^{20}D$ 1.4953 (after two further distillations); $[\alpha]^{28}D$ −112.9° (in benzene) ($c$ = 0.1196); $[\alpha]^{28}D$ −112° (homogeneous) ($l$ = 1 dcm.) (capillary); $[M]^{28}D$ −185.1° (lit., b. p. 104° (23 mm.),[12d] $n^{20}D$ 1.49432,[22] ($[M]^{25}D$ −194°).[16]

To the combined aqueous extracts (A) was added 15 ml. of 37% hydrochloric acid. The solution was then evaporated to dryness on a steam cone at the water pump. The white solid was taken up in four 3-ml. portions of water, and these solutions were combined and treated with a solution of sodium hydroxide (10 g.) in water (15 ml.). A vigorous evolution of a basic gas, probably trimethylamine, occurred and an organic liquid separated. The aqueous mixture was extracted three times with 10-ml. portions of ether. The ether was distilled at atmospheric pressure, and the residue was distilled at 31 mm. to yield *d*-(+)-N,N-dimethyl-α-phenylethylamine, b. p. 95–96° (31 mm.), 0.72 g. (12.1%), $n^{20}D$ 1.5021, $[\alpha]^{27}D$ + 59.04 (homog.) ($l$ = 1 dcm.).

**Alkylation of Malonic Ester with *d*-(+)-N,N,N-Trimethyl-α-phenylethylammonium Iodide.**—It was found that absolute diethyl carbitol[23] is a superior solvent for the alkylation of sodiomalonic ester with quaternary salts containing the α-phenylethyl group, for styrene formation was much lower in non-protonic solvents than in the more acidic solvents, such as alcohol. Diethyl carbitol is a polyfunctional ether, and as such has greater solvent powers than dibutyl ether.

Sodium (0.51 g., 0.022 mole) was converted to sodium sand in dry xylene. This operation was carried out in a 50-ml. round-bottomed flask with a ground joint and a gas-inlet side-arm. The xylene was decanted from the sodium sand, and was immediately replaced by about 15 ml. of absolute diethyl carbitol. This was in turn decanted from the sodium, and fresh absolute diethyl carbitol (25 ml.) was added at once. The flask was then fitted with a two-necked adapter bearing a reflux condenser and a small Hershberg stirrer. Diethyl malonate (8.0 g., 0.05 mole) was added slowly to the well-cooled, stirred suspension of sodium sand. After the initial vigorous reaction had subsided and most of the sodium had gone into solution, the cooling-bath was removed, and the reaction allowed to proceed at room temperature. Sodiomalonic ester is quite soluble in diethyl carbitol and the reaction was complete within an hour. Powdered dry *d*-(+)-N,N,N-trimethyl-α-phenylethylammonium iodide (8.73 g., 0.03 mole) was added rapidly. A source of nitrogen was attached to the gas-inlet side-arm of the flask, and the system was flushed out with nitrogen.

The flask was heated by means of an oil-bath. While the contents of the flask were vigorously stirred the oil-bath was maintained at a temperature of 130–140° for twenty-four hours. The temperature of the bath was raised to 150° and held there for one-half hour. During all of this heating only a slow evolution of trimethylamine was noted.

To the cooled mixture in the flask was added 10% hydrochloric acid (20 ml.) and benzene (25 ml.). The organic layer was separated from the acidic aqueous layer.

The benzene solution was extracted with two 50-ml. portions of 5% sodium bicarbonate solution and then with three 25-ml. portions of 37% hydrochloric acid. Diethyl carbitol is wholly extracted from the benzene by this procedure. The benzene solution was distilled, finally under reduced pressure. The fraction boiling at 118–120° (1 mm.) was collected; it consisted of α-methylbenzylmalonic ester (V) 0.93 g. (17.5%), $n^{20}$ 1.4752. This material was optically inactive.

The substituted malonic ester was saponified by the use of 50% potassium hydroxide. The malonic acid so formed melted at 144–145°.[24]

The aqueous solution obtained when hydrochloric acid was added to the reaction mixture was made strongly basic by the addition of 10% sodium hydroxide. The liquid which separated was taken up in ether. The ether solution was evaporated and the residue was distilled. The fraction boiling at 95–96° (30 mm.) was collected; weight 0.72 g. (24.2%), $n^{20}D$ 1.5003, $[\alpha]^{27}D$ + 19.06 (homog.) ($l$ = 1 dcm.). The material was largely racemized N,N-dimethyl-α-phenylethylamine.

## Summary

1(−)-α-Phenylethyl acetate has been prepared from *d*-(+)-N,N,N-trimethyl-α-phenylethylammonium iodide by amine replacement. Essentially complete Walden inversion occurred, indicating an $S_N2$ mechanism for the replacement reaction.

Although the quaternary salt can be used in the alkylation of malonic ester, extensive racemization occurs during the long heating period required.

URBANA, ILLINOIS RECEIVED JULY 30, 1948

(20) Waterman and deKok, *Rec. trav. chim.*, **53**, 1133 (1934).

(21) Evans and Morgan, THIS JOURNAL, **35**, 57 (1913).

(22) Naves, *Helv. Chim. Acta*, **27**, 261 (1944).

(23) Snyder and Brewster, THIS JOURNAL, **70**, 4320 (1948).

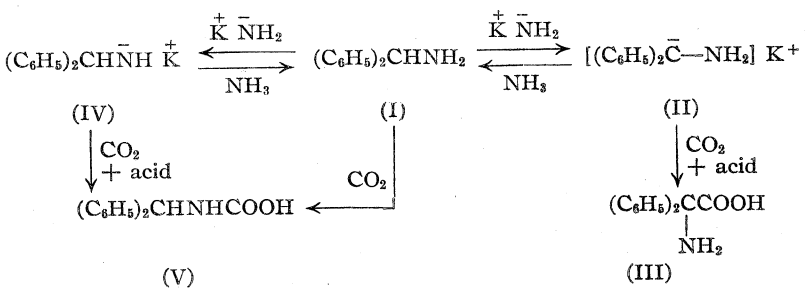
(24) Fischer and Schmitz, *Ber.*, **39**, 353, 2210 (1906).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Metalation and Carbonation of Benzohydrylamine and Derivatives Using Potassium Amide[1]

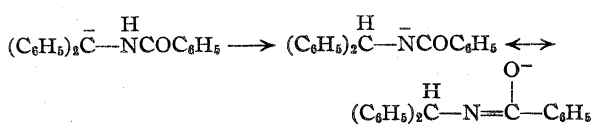
BY CHARLES R. HAUSER, INA C. FLUR AND SIMON W. KANTOR

Because nitrogen is more negative than carbon, the amino hydrogens of methylamine are more acidic than the methyl hydrogens and, with a sufficiently strong base, the amino hydrogens would presumably be ionized preferentially. However, because of the well-known activating effect of the phenyl group, the methylene hydrogens of benzylamine and especially the methinyl hydrogen of benzohydrylamine might be expected to approach or even surpass the amino hydrogens in acidity. Actually, both of these amines produce red colored solutions with potassium amide in liquid ammonia indicating the formation of the corresponding carbanions. Confirmation of the presence of the carbanion (II) from benzohydrylamine (I) has been obtained by carbonation of the potassium salt to form the amino acid (III). However, similar carbonation of the salt from benzylamine has yielded no carboxylic acid. Even with the potassium salt of benzohydrylamine, carbonation has produced the amino acid (III) only under special conditions; frequently the corresponding carbamic acid (V) is obtained. The formation of (V) indicates that the anion of the potassium salt is partly the amide ion (IV), although (V) may also be formed from the free amine. The interconversion of anions (II) and (IV) is considered to involve reaction with the solvent and amide ion, although it might conceivably occur intramolecularly involving the shift of a proton.




The conditions required for the formation of the amino acid (III) are somewhat difficult to define. This product has been obtained twice in yields of 33% and 42% by evaporating the liquid ammonia in the presence of ether and treating the resulting ether suspension with Dry Ice; these are the conditions employed previously in the carbonation of potassium diphenylmethide.[2] However, attempts to duplicate these results have failed; instead of the amino acid, the carbamic acid (V) was obtained. A more certain way of obtaining the amino acid is to evaporate the liquid ammonia rapidly and then to carbonate an ether suspension of the residue. Apparently, as the liquid ammonia is evaporated, salt (II) is converted to salt (IV): this conversion appears to be minimized by the rapid evaporation of the solvent. However, even with some liquid ammonia present, carbonation has given only the carbamic acid. Similarly, carbethoxylation with diethyl carbonate in liquid ammonia has given only the carbamic acid ethyl ester. With these reactions in liquid ammonia solution, especially with the relatively slow carbethoxylation, a steric factor may be important in that the less-hindered amide ion (IV) may react faster than the carbanion (II), the equilibrium shifting in favor of the former.

The two derivatives of benzohydrylamine, N-isopropylbenzohydrylamine[3] and N-phenylbenzohydrylamine,[4] produce red colored solutions with potassium amide in liquid ammonia but, rather surprisingly carbonation of the ether suspension of the residue, obtained on the evaporation of the ammonia, yielded neither the amino acid nor the carbamic acid, most of the amine being recovered. N - Benzoylbenzohydrylamine[5] reacts with potassium amide in liquid ammonia to produce a red colored solution which gradually lightens to pink and finally becomes colorless after four to five minutes. Apparently some of the carbanion is formed but it is soon converted to the amide ion, thus




It is obvious that derivatives of benzohydrylamine in which both of the hydrogens are substituted can produce only the carbanion. An interesting derivative of this type is benzalbenzohydrylamine (VI) the carbanion of which reacts on carbonation as if it had resonance form (VIIB) rather than (VIIA) since (VIII) is produced apparently exclusively. The acid corresponding to (VIII)

(1) Part of the work reported in this paper was carried out in connection with a contract with the Office of Naval Research.

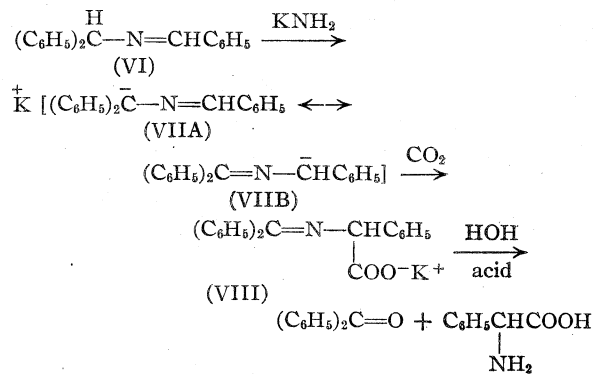
(2) Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).

(3) This compound (b. p. 170–171° at 19 mm.) was prepared in 72% yield from benzohydrylamine and isopropyl iodide by the method of Leeuw, *Rec. trav. chim.*, **30**, 250 (1911).

(4) This compound was obtained as its hydrochloride as described by Busch and Rinck, *Ber.*, **38** [2], 1767 (1905).

(5) This compound was prepared in 97% yield by the Schotten–Baumann method; see Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 88.

was not isolated but its hydrolysis products, benzophenone and *dl*-α-aminophenylacetic acid, were obtained in good yields on acidification of the reaction mixture.



Benzohydrylidenebenzohydrylamine[6] produces a red colored solution with potassium amide in liquid ammonia but the color disappears on replacing the ammonia with ether and the carbonation fails.[7]

It should be pointed out that also certain important syntheses involve metalations of the system, CHNH. One of these consists in the metalation of benzoyl[8] or acetyl[9] aminomalonic ester, followed by alkylation and hydrolysis to form α-amino acids. Application of certain of the ideas discussed above to such syntheses is contemplated.

## Experimental[10]

**Benzohydrylamine.**—This amine has been prepared on a half mole scale from benzophenoneoxime both by reduction with sodium in ethanol and by hydrogenation over Raney nickel. The former method in which the very small scale procedure of Jones and Hurd[11] was adapted gave a satisfactory yield (85%) but the process was somewhat difficult to carry out on the large scale. The hydrogenation in which the general procedure of Adkins[12] was adapted gave equally good yields (85–92%) and it was more convenient.

The oxime (109 g., 0.55 mole) in 600 ml. of 95% ethanol was hydrogenated over Raney nickel at 1000–1300 pounds pressure at 75°. After removal of the catalyst and alcohol, the residue was dissolved in ether. The ether solution was washed with dilute sodium hydroxide, then with water and dried over solid sodium hydroxide. The amine, after removal of the solvent, distilled at 134–135° at 3.5 mm. and at 125–127° at 1 mm.

**Carbonation of Benzohydrylamine.**—To a stirred solution of 0.075 mole of potassium amide in about 200 ml. of liquid ammonia[13] was added 9.15 g. (0.05 mole) of benzohydrylamine. The solution became red immediately. The ammonia was evaporated rapidly using a steam-bath. When all the liquid ammonia was gone, the black residue was heated on the steam-bath for fifteen minutes. The bath was removed and 200 ml. of anhydrous ether was added with constant stirring. An excess of powdered Dry Ice was then added and the mixture stirred for two hours. When the excess Dry Ice was gone, 200 ml. of water was added and after shaking, the aqueous layer was filtered. Carbon dioxide was then bubbled into the aqueous alkaline solution until neutral to *p*H paper. The precipitate was filtered off and washed with methanol or ethanol to dissolve carbamic acid leaving the amino acid, α,α-diphenylglycine, m. p. 238°, in 31% yield. After several washings with ether and alcohol the melting point was raised to 243–245° dec. (reported m. p. 245–246° dec.).[14] The amino acid was further identified by conversion to benzilic acid, m. p. 150°.[15] In two other runs the pure amino acid, m. p. 243–245°, was obtained in 10% yield. Evaporation of the original ether extract of the mixture generally yielded a considerable amount of recovered benzohydrylamine. The recovered amine plus the carbonated product usually accounted for 80–90% of the starting material.

When the residue obtained on the evaporation of the liquid ammonia was suspended in anhydrous dioxane, a red color was produced but, on carbonation, only a 5% yield of the amino acid (m. p. 238°) was obtained. There was obtained a 50% yield of the carbamic acid, m. p. 89–91° (reported m. p. 91°).[16]

When the liquid ammonia solution was evaporated on a steam-bath as anhydrous ether was added at such a rate as to maintain a constant volume, the amino acid (m. p. 238°) was obtained in 42% yield on immediate carbonation and in 34% yield when the ether suspension was refluxed for two hours before carbonation. However, two attempts to duplicate the first result and one attempt to duplicate the latter have failed; instead of the amino acid the carbamic acid was obtained in yields up to 40%.

When the liquid ammonia solution of the potassium salt of benzohydrylamine was allowed to evaporate to a volume of 50 ml. and the contents of the flask then poured on an excess of powdered Dry Ice, only the carbamic acid (26%) was obtained.

When a mixture of 0.05 mole each of benzohydrylamine and diethylaminomagnesium bromide in ether[17] was refluxed for six hours and powdered Dry Ice then added, no carbonation product could be isolated. Most of the amine was recovered. The amine was similarly recovered when equivalent amounts of methylmagnesium iodide and benzohydrylamine were refluxed for one hour and then carbonated.

**Carbonation of Benzalbenzohydrylamine.**—To a stirred solution of 0.2 mole of potassium amide in 200 ml. of liquid ammonia was added 27.1 g. (0.1 mole) of benzalbenzohydrylamine (m. p. 100°).[18] The solution became red immediately. The liquid ammonia was evaporated as sufficient ether was added to maintain constant volume and the resulting red suspension was carbonated in the usual manner. After stirring with water, the aqueous layer was acidified with dilute acetic acid. The solid was filtered off and washed with water; it weighed 22.7 g. and melted over a considerable range. This solid was stirred thoroughly with 50 ml. of ether and the mixture filtered. The precipitate was identified as *dl*-α-aminophenylacetic

(6) This compound was prepared by the method of Ingold and Wilson, *J. Chem. Soc.*, 1502 (1933).

(7) The destruction of the red colored carbanion presumably involves reversion to benzohydrylidenebenzohydrylamine and potassium amide. Similar reversions on replacement of the liquid ammonia by an inert solvent have been observed with sodium triphenylmethide (Kraus and Rosen, THIS JOURNAL, **47**, 2739 (1925)) and with sodium diphenylmethide (see ref. 2) but not with potassium triphenylmethide or potassium diphenylmethide. We have observed the reversion with potassium sym-tetraphenylethide. The tendency for the reversion appears to be dependent both on the metallic cation and on the carbanion. The tendency is greater with sodium ion than with potassium ion and apparently with carbanions which have a greater capacity for resonance.

(8) Redeman and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(9) Dakin, *ibid.*, **154**, 549 (1944); Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945); Albertson and Archer, *ibid.*, **67**, 308 (1945).

(10) All melting points are uncorrected.

(11) Jones and Hurd, THIS JOURNAL, **43**, 2438 (1921).

(12) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 92.

(13) Hauser, Shivers and Skell, THIS JOURNAL, **67**, 409 (1945); Shivers, Hudson and Hauser, *ibid.*, **65**, 2051 (1943).

(14) Biltz and Seydel, *Ann.*, **391**, 226 (1912).

(15) Jena, *ibid.*, **155**, 80 (1870).

(16) Leuckart and Bach, *Ber.*, **19**, 2130 (1886).

(17) Hauser and Walker, THIS JOURNAL, **69**, 295 (1947).

(18) Michaelis and Linow, *Ber.*, **26**, 2169 (1893).

acid, m. p. 255–257° (after sublimation *in vacuo*) (reported m. p. 255–256°, subl.);[19] the yield was 10.7 g. (71%). The acetyl derivative melted at 197.5–198.5° (reported 198.5).[20] The ether filtrate was evaporated yielding 12 g. (66%) of benzophenone. The semicarbazone melted at 163–164° (reported m. p. 164°).[21]

## Summary

1. Benzohydrylamine and certain of its derivatives react with potassium amide in liquid ammonia to form red colored solutions indicating the formation of the corresponding carbanions.

2. Carbonation of the potassium salt of benzohydrylamine has given the corresponding α-amino acid.

3. Carbonation of the carbanion of benzalbenzohydrylamine gives the N-benzohydrylidene α-phenylglycine instead of N-benzal α,α-diphenylglycine.

(19) Zelinsky and Stadnikoff, *Ber.*, **39**, 1726 (1906).

(20) Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p. 112.

(21) See ref. 5, p. 264.

DURHAM, NORTH CAROLINA RECEIVED AUGUST 2, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

# Allylic Rearrangements. XXV. Reaction of the Sodium Derivative of Allylbenzene with α-Haloacetic Acids

BY TOD W. CAMPBELL AND WILLIAM G. YOUNG

The sodium derivative of allylbenzene, which has been the subject of recent investigations[1] undergoes reactions which can best be expressed[1c] as nucleophilic attacks by the resonating anion

$$\left[C_6H_5\overset{\curvearrowleft}{C}H{=}CH{-}\overset{\curvearrowright}{CH_2} \longleftrightarrow C_6H_5\overset{\curvearrowright}{CH}{-}CH{=}\overset{\curvearrowright}{CH_2}\right]^- Na^+$$

I II

Since most reactions studied in which steric effects are not serious lead to mixtures of products derived from both of the principal resonance forms of the allylbenzene anion, it seemed odd that the reaction with simple halides[1a] gave, at least principally, products derived from form II above.

In an attempt to clarify the issue, the reaction of sodium allylbenzene with a series of α-haloacetate ions was examined. This particular series was chosen since it should be possible to determine the effect of (a) steric hindrance, (b) polarization and (c) the nature of the ion being displaced, on the manner in which the resonating allylbenzene carbanion reacts in displacement reactions. When the chosen reactants were mixed, a rapid reaction ensued. From the reaction product was isolated a mixture of carboxylic acids, whose formation can be represented by the equation

$$\left[\begin{matrix}\text{I}\\ \updownarrow \\ \text{II}\end{matrix}\right] + XCR_2CO_2^- \xrightarrow{\begin{matrix}X = Cl, Br\\ R = H, CH_3\end{matrix}}$$

$$C_6H_5CH{-}CH{=}CH_2 + C_6H_5{-}CH{=}CH{-}CH_2CR_2CO_2^-$$

$$\quad\quad |$$

$$\quad\quad CR_2CO_2^-$$

All possible combinations of X and R were examined. The individual acids produced were separated and carefully characterized, principally as benzylamine salts.[2] The composition of the original mixtures was estimated to about ± 2% from the characteristic absorption spectrum[3] for the conjugated system.

From the results listed in Table IV, it will be seen that the polarizing effect of the carboxylate ion adjacent to the carbon atom being attacked is probably more important than simple steric hindrance, since the unsubstituted α-haloacetate ions are certainly less hindered than a compound such as α-methallyl chloride.[1a] It will be noted that the addition of methyl groups on the α-haloacetate ions leads to an increasing amount of the product arising from the primary form of the carbanion, as might be predicted from steric effects.[1c] It is also interesting to note that in this series the nature of the halogen being displaced definitely affects the composition of the mixture obtained from the resonating carbanion, the effect becoming more apparent as the number of methyl groups is increased. This effect of the halogen being displaced on the products has not been noted before in any of the reactions of sodium allylbenzene.

## Experimental Part

All melting points are uncorrected.

**Reaction of the Sodium Derivatives of Allylbenzene with α-Haloacetic Acids—General Method.**—The sodium derivative was prepared in 300 ml. of liquid ammonia in the usual manner[1] from 0.1 *M* of allylbenzene. The solution was forced over as rapidly as possible (by the vapor pressure of the liquid ammonia solvent) into a two-liter three-necked flask containing 0.05 mole of the appropriate α-haloacetic acid dissolved in 20 ml. of ether (anhydrous). The flask was equipped with a stirring device and a wide outlet tube to provide for escape of the ammonia vapors. The characteristic red color of the sodium derivative was discharged rapidly. After evaporation of the solvent, water was added, and the carboxylic acids were separated from the non-acidic material. Table I is a résumé of results obtained by this method. Data are averages of several experiments.

(1) (a) Levy and Cope, THIS JOURNAL, **66**, 1684 (1944); (b) Campbell and Young, *ibid.*, **69**, 688 (1947); (c) *ibid.*, **69**, 3066 (1947).

(2) Buehler, Carson and Edds, *ibid.*, **57**, 2181 (1935).

(3) Campbell, Linden, Godshalk and Young, *ibid.*, **69**, 880 (1947).

TABLE I

PRODUCTION OF ACIDS BY COUPLING OF AN α-HALOACETIC ACID WITH SODIUM ALLYLBENZENE

| α-Haloacetic acid | Equivalent weight of mixture Theory | Observed | Yield,[a] % of mixed acids | Abs. spectrum of mixture[b] $\epsilon_{284}^{Max.}$ | $\epsilon_{294}^{Max.}$ |
|---|---|---|---|---|---|
| $ClCH_2CO_2H$ | 176 | 177 | 43 | 647 | 440 |
| $ClCH(CH_3)CO_2H$ | 190 | 189 | 54 | 784 | 545 |
| $ClC(CH_3)_2CO_2H$ | 204 | 203 | 40 | 1100 | 742 |
| $BrCH_2CO_2H$ | 176 | 176 | 74 | 650 | 450 |
| $BrCH(CH_3)CO_2H$ | 190 | 188 | 67 | 927 | 663 |
| $BrC(CH_3)_2CO_2H$ | 204 | 204 | 72 | 1270 | 919 |

[a] Yield based on α-haloacetic acid. [b] Maximum deviation in values of maximum averaged was 5%, mean deviation about 2%.

**Identification of Acidic Components of the Reaction Mixture from Bromoacetic Acid and Sodium Allylbenzene.**—The mixture of acids, obtained in 74% yield, was partially separated by filtration of the chilled product. The solid separated in this manner from the residual oil was recrystallized several times from ligroin. It formed shining white scales, m. p. 90°, which was identified as 4-phenyl-3-pentenoic acid by its melting point and the melting point (162°) of its dibromide.[4] Its equivalent weight was 176 (calculated for $C_{11}H_{12}O_2$, 176), and it yielded benzoic and succinic acids on ozonization. The benzylamine salt[2] of 4-phenyl-3-pentenoic acid melted at 108°.

*Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47. Found: C, 76.40; H, 7.61.

The oily mixture of acids remaining after filtration was dissolved in four times its volume of benzene, and an equivalent amount of potassium hydroxide was added as a 25% solution in methanol. The solid which precipitated was filtered off and found to be nearly pure potassium 4-phenyl-3-butenoate. This separation was purely fortuitous and was not expected. The residual solution was treated with dilute sulfuric acid, dried, and the solvent removed. The oily acid remaining gave a benzylamine salt melting at 97–98°.

*Anal.* Calcd. for $C_{18}H_{21}NO_2$; C, 76.29; H, 7.47. Found: C, 76.26; H, 7.55.

The oily acid was converted by hydrogenation to a solid acid, m. p. 58°. The benzylamine salt of the latter melted at 96–97°.

*Anal.* Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.94; H, 8.21. The hydrogenated acid was shown to be β-phenylvaleric acid (see below), thus the liquid acid was β-vinylhydrocinnamic acid. It could not be 2-phenyl-2-pentenoic acid, since the absorption spectrum of the liquid acid indicated that the double bond was out of conjugation with the benzene ring.[3]

**Synthesis of β-Phenylvaleric Acid.**—β-Ethylcinnamic acid, m. p. 94°, was synthesized through the Reformatsky reaction from propiophenone and ethyl bromoacetate.[5] Its benzylamine salt melted at 139–140°. *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47. Found: C, 76.34; H, 7.43. This acid (19.70 g.) absorbed 2740 ml. of hydrogen at 750 mm. and 23° (theory 2750) over platinum oxide in ethyl acetate. The acid melted at 58° after recrystallization from warm (35°) methanol, to which water had been added to the cloud point. Its benzylamine salt melted at 96.5°. Neither the melting point of the acid, nor the melting point of the benzylamine salt, was depressed by addition of the corresponding product obtained by hydrogenation of β-vinylhydrocinnamic acid described above.

**Separation of the Reaction Products from α-Bromopropionic Acid and Sodium Allylbenzene.**—The methods described above could not be used to separate this mixture of acids. Benzylamine was added to the mixture, and the mixture of solid benzylamine salts was fractionally crystallized. It was possible to isolate the spectroscopically pure benzylamine salt of the *secondary* acid, α-methyl-β-vinylhydrocinnamic acid, m. p. 145.5°, by fractional crystallization from ethyl acetate. *Anal.* Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.35; H, 7.87. The benzylamine salt of the primary acid could not be obtained optically pure, by direct recrystallization.

The residual impure benzylamine salt, which was rich in the primary acid, was dissolved in glacial acetic acid. An equivalent amount of bromine in acetic acid was added, followed by dilution with water, to give an oily dibromo-acid and a solid dibromo-acid. The solid was isolated and purified by recrystallization from aqueous ethanol; long, lustrous needles, m. p. 133°. This solid dibromo-acid was refluxed with zinc dust in isopropyl alcohol. The resulting oily acid was isolated and converted to a benzylamine salt, which was recrystallized from Skellysolve C, giving long needles, m. p. 119°. *Anal.* Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.58; H, 7.92. The absorption spectrum[3] of the salt indicated that it was derived from the primary acid.

**Separation of Acids Derived from the Sodium Derivative of Allylbenzene and α-Bromoisobutyric Acid.**—The primary acid was obtained by filtration of the partially solidified mixture. It was obtained optically pure on recrystallizing from methanol–water. It formed massive prisms, m. p. 104°. Its benzylamine salt melted at 145.5°. *Anal.* Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09. Found: C, 77.23; H. 8.28. The secondary form of the acid could not be obtained spectroscopically pure.

**Absorption Spectra of the Pure Acids Derived from the Primary Form of the Allylbenzene Carbanion.**—The absorption spectra of these acids and their benzylamine salts were taken on the Beckmann ultraviolet spectrophotometer and are tabulated in Table II.

TABLE II

| Acid | Absorption spectra of acid 293 Max. | 284 Max. | 250 Max. | Absorption spectra of benzylamine salt 293 Max. | 284 Max. | 250 Max. |
|---|---|---|---|---|---|---|
| $C_6H_5CH{=}CHCH_2CH_2CO_2H$ | 791 | 1120 | 18,470 | 820 | 1260 | 17,020 |
| $C_6H_5CH{=}CH{-}CH_2CH(CH_3)CO_2H$ | (850)[a] | (1250)[a] | (18,800)[a] | 850 | 1385 | 18,500 |
| $C_6H_5CH{=}CHCH_2C(CH_3)_2CO_2H$ | 978 | 1380 | 19,030 | 971 | 1498 | 19,980 |

[a] Estimated values from benzylamine salt.

**Composition of Original Reaction Mixture by Spectral Analysis.**—From the extinction coefficients quoted above, the percentage composition was calculated from the formula

$$(\%\text{ of Compound I}) = \frac{\epsilon_{molar}^{mixture}}{\epsilon_{molar}^{Pure\ I}} \times 100$$

TABLE III

| α-Haloacetic acid | Composition of mixture $x$ = Cl, per cent from anion primary | secondary | Composition of mixture $x$ = Br, per cent from anion primary | secondary |
|---|---|---|---|---|
| $XCH_2CO_2H$ | 57.2 | 42.8 | 57.6 | 42.4 |
| $XCH(CH_3)CO_2H$ | 63.4 | 36.6 | 76.0 | 24.0 |
| $XC(CH_3)_2CO_2H$ | 77.2 | 22.8 | 93.3 | 6.7 |

(4) Fichter and Bauer, *Ber.*, **31**, 2002 (1898).

(5) Shriner, "The Reformatsky Reaction" in "Organic Reactions," Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1942, p. 1.

where (I) is derived from the primary form of the allylbenzene carbanion. It was assumed that the acid derived from the secondary form of the allylbenzene carbanion would have extinction coefficients of approximately zero at 294 mμ, 20 at 283 mμ and $\epsilon_{molar}^{mixture}$ was accordingly corrected. The results are tabulated in Table III.

## Summary

1. Sodium allylbenzene has been prepared and allowed to react with a series of α-haloacetic acids to give mixtures of substituted γ-benzalbutyric and hydrocinnamic acids.

2. The observed results have been discussed with regard to the possible influences which may alter the course of the reaction.

LOS ANGELES, CALIF. RECEIVED AUGUST 2, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

# Perfluoro-2-butyne and its Hydrogenation Products

BY ALBERT L. HENNE AND WILLIAM G. FINNEGAN

Preceding articles have reported fluorinated compounds with a $CF_3$ group adjacent to another function, double bond, acid, alcohol or halide. A compound, $CF_3C{\equiv}CCF_3$, with a triple bond flanked by two $CF_3$ groups has now been prepared[1] and examined. In line with our expectations, the triple bond is so sluggish that it does not appreciably accept halogens at room temperature; it is however very sensitive to alkaline oxidation, and breaks quantitatively to give two moles of trifluoroacetic acid. In addition, it easily accepts one mole of hydrogen on Raney nickel to yield $CF_3CH{=}CHCF_3$, presumed to be the *cis*-isomer; it takes up two molecules of hydrogen with equal facility to form $CF_3CH_2$-$CH_2CF_3$.

**Preparation of $CF_3C{\equiv}CCF_3$.**—A three-liter flask heated on an electric nest is equipped with a sealed stirrer and a reflux condenser of the "down draft and overflow return" type the outlet of which leads to a Dry Ice-cooled receiver. This type of condenser permits high rates of reflux without flooding; it receives vapors at its top and syphons the condensate from its bottom back to the boiler. The flask is loaded with six moles (420 g.) of zinc dust, six moles (1380 g.) of dried and distilled $CF_3CCl{=}CClCF_3$[2] and 900 ml. of absolute alcohol. Constant stirring and refluxing is maintained for ten days, with a liquid temperature of about 40°. At the end of this period, distillation is performed until the liquid in the flask reaches 78°; the distillate is combined with the reaction product which had been collected in the chilled receiver during the ten-day period. Rectification of this combined material yields 477 g. (49.1% conversion, 54.4% net yield) of $CF_3C{\equiv}CCF_3$, b. p. −24.7° to −24.5°; 5 g. of an intermediate fraction, b. p. −20° to +24°; 14 g. of impure $CF_3CH_2CH_2CF_3$, b. p. 25° to 27°; 322 g. of impure $CF_3CCl{=}CH$-$CF_3$ (mixed *cis* and *trans*), b. p. 31 to 37°; 31.5 g. of an intermediate cut; and 140 g. of recovered $CF_3CCl{=}CClCF_3$, b. p. 65 to 67°. The material balance is thus 90%. Refractionation of the (−20 to +24°) intermediate yielded 4 g. of a compound boiling within one degree of 6°; this will be referred to as "the 6° cut." Wojcik[1] mentions a (0 to +5°) cut, and states that it is "a $C_4F_6$ isomer."

The main reaction product was quantitatively oxidized in a sealed vessel by the procedure previously reported[3] to give 1.74 moles of trifluoroacetic acid per mole of $CF_3C{\equiv}CCF_3$, identified as its amide. The next most important product, $CF_3CCl{=}CHCF_3$, was found identical with a by-product obtained in the preparation of $CF_3$-$CCl{=}CClCF_3$ and previously reported[2] as "presumably $CF_3CCl{=}CFCF_3$" on account of its ability to yield two moles of trifluoroacetic acid when oxidized. Recalculation of the atomic refraction $AR_F$ for fluorine on this new basis gave the excellent value of 1.07.

**Hydrogenation of $CF_3C{\equiv}CCF_3$.**—In a one-liter pressure vessel, 3.43 moles (556 g.) of $CF_3C{\equiv}CCF_3$ was hydrogenated by means of 3.5 moles of hydrogen at an initial pressure of 100 atm. and with 5 g. of Raney nickel and 10 ml. of absolute alcohol as catalyst. Reduction started at room temperature and proceeded rapidly with a large evolution of heat. A leak caused some material loss. The reduced material was distilled from the pressure vessel (heated to 50°) directly into a receiver cooled with Dry Ice. Rectification of this distillate gave 100 g. of recovered $CF_3C{\equiv}CCF_3$, and 368 g. of material boiling from 0 to +33°. The latter material was refractionated to give 119 g. of $CF_3CH_2CH_2CF_3$ and 191 g. of $CF_3CH{=}CHCF_3$. The material balance in the reduction step was only 83% on account of the leakage; the distillation steps had a material balance of 90%.

**Identification.**—The saturated derivative $CF_3CH_2CH_2CF_3$ was analyzed for fluorine: 68.6% calcd., 68.2% found. The identity of the olefin and that of the alkyne are derived from the facts that both yielded two molecules of $CF_3CO_2H$ on oxidation, and were transformed into the analyzed

(1) Others have also obtained this derivative recently: W. T. Miller, Cornell, and E. T. McBee, Purdue, private communications; Wojcik, American Chemical Society fall meeting, New York, N. Y., 1947.

(2) Henne and Trott, THIS JOURNAL, **69**, 1820 (1947).

(3) Henne and Zimmerschied, *ibid.*, **69**, 281 (1947).

paraffin by acceptancy of one mole and two moles of hydrogen, respectively; this was done quantitatively in independent, conventional experiments, using Raney nickel, and differing only by the amount of hydrogen supplied. The Bayer (potassium permanganate) test was positive while the bromine in carbon tetrachloride negative for both the alkyne and the alkene.

**Physical Tests.**—All three compounds are soluble in light paraffins, toluene, carbon tetrachloride, acetone, alcohol and ether as far down as −25°; they are also soluble in acetic acid above its freezing point. At −78° the alkyne was insoluble in all those solvents which were still liquid, while the olefin and the paraffin were not observed. In concentrated sulfuric acid, all three were insoluble at room temperature.

A dielectric constant measurement on the alkyne at −30°, by the heterodyne beat procedure showed a value comparable to that of a saturated straight-chain paraffin, indicative of a substantially zero dipole moment. The olefin, however, had a dielectric constant of approximately 20.8 at +20°, as compared to 4.3 for ether and 80.0 for water. This indicates a substantial dipole moment and the *cis*-configuration was therefore assigned to this compound.

The alkyne boils remarkably low; a contrast between hydrocarbons and their perfluorinated derivatives emphasizes the fact that the fluorinated derivatives are less associated, probably not at all.

Contrasting boiling points.

| | | | |
|---|---|---|---|
| $CH_3CH_2CH_2CH_3$ | − 0.4° | − 1.4° | $CF_3CF_2CF_2CF_3$ |
| $CH_3CH{=}CHCH_3$ | + 1.0° | + 0.4° | $CF_3CF{=}CFCF_3$ |
| $CH_3C{\equiv}CCH_3$ | +27.2° | −24.6° | $CF_3C{\equiv}CCF_3$ |

Addition of hydrogen to the triple bond affects the molecular weight negligibly but permits hydrogen bonding[4] in the resulting product, and the boiling point rises consequently by nearly 50°.

| | | | |
|---|---|---|---|
| $CF_3C{\equiv}C{-}CF_3$ | −24.6° | +24.6° | $CF_3CH_2CH_2CF_3$ |

The importance of hydrogen bonding is also shown by the fact that both $CF_3CH{=}CHCF_3$ and $CF_3CH{=}CClCF_3$ boil at nearly the same temperature (33° and 34°, respectively) in spite of their different masses, a case similar to that of $CHF_3$ and $CClF_3$ (−82° and −81°). An additional example is the contrast between $CF_3CH{=}CClCF_3$ and $CF_3CF{=}CFCF_3$, boiling about +35° and 0°, respectively, in spite of their almost identical molecular masses.

**Physical Properties.**—Conventional physical measurements[5] were made after repurification, with the accuracy claimed by the decimals shown in the table:

| Compound | $CF_3C{\equiv}CCF_3$ | $CF_3CH{=}CHCF_3$ | $CF_3CH_2CH_2CF_3$ | $CF_3CH{=}CClCF_3$ |
|---|---|---|---|---|
| B. p., °C., 760 mm. | − 24.6 | +33.2 | +24.6 | + 34.4 |
| F. p., °C. | −117.4 | −90.5 | −53.7 | −106.1 |
| $d_4$ | | 1.4128 at 0° | 1.3702 at 0° | 1.4909 at 20.0° |
| $n_D$ | | 1.2825 at 2.2° | 1.2732 at 3.0° | 1.2996 at 20.0° |
| $AR_F$ | | 1.16 | 1.12 | 1.07 |

The atomic refraction for fluorine, $AR_F$, was computed in the conventional way by subtracting from the experimental molecular refraction the customary increments for C, H, Cl and double bond.

**Infrared Spectrum.**—Infrared adsorption spectra were taken on the alkyne, *cis*-alkene and the 6° by-product in order to obtain information as to the structure of the 6° by-product. Inasmuch as the alkyne is symmetrical, it would show only C–F bond absorption in the infrared, and any other absorption would be attributable to the 6° material present as an impurity. The alkyne and 6° cut absorption curves are indeed essentially the same.

Strong C–F bond absorption was noted from 7 to 10 microns with the C—F bond overtone at 4.2 microns for all three compounds. A major C—H bond stretching band was obtained at 3.35 microns with the alkene and a smaller one at the same place with the 6° cut. This latter is probably due to $CF_3{-}CH{=}CH{-}CF_3$ (*trans*) or $CF_3{-}CH_2{-}CH_2{-}CF_3$ as impurities in the 6° cut, as this absorption is not present in the alkyne absorption curve. A strong absorption from 6.4 to 7.1 microns in the alkene, absent in the alkyne and 6° cut curves, could be attributed to hydrogen bonding. A very strong absorption at 5.95 microns in the alkene curve is attributed to C=C; this absorption is absent in the alkyne curve and is present to a smaller degree in the 6° cut curve. Thus the 6° by-product is contaminated with olefinic material similar in nature to the *cis*-alkene; this is probably the *trans*-alkene.

The alkyne and 6° cut curves show five bands from 6 to 7 microns with the strongest at 6.4 microns; these bands are absent in the alkene curve and could thus be attributed to components of an allenic type of structure. Two absorption peaks at 4.7 and 4.85 microns, respectively, appear in the alkyne and 6° cut curves, but only the 4.7 micron peak appears in the olefin. The 4.7 micron peak is attributed to partial allenic character of the following types: $CF_3{\cdots}C{\cdots}C{\cdots}CF_3$, $CF_3{\cdots}CF{\cdots}C{=}CF_2$, and $CF_3{\cdots}CH{\cdots}CH{\cdots}CF_3$.

(4) The term "hydrogen bonding" is used in extension of the conventional cases, on the basis that fluorinated compounds containing hydrogen invariably boil higher than the perfluoro compounds: $CH_2F_2 > CF_4$; $CHF_2CO_2H > CF_3CO_2H$; $CHF_2COCl > CFCOCl$; etc. . . . The hydrogen is attached to an electronegative group ($CF_2$) instead of electronegative atom (O).

(5) Weissberger, "Techniques of Organic Chemistry," Interscience Publishers, New York, N. Y., Vol. I, New York, N. Y., 1945. For freezing point, Mair, Glasgow and Rossini, *J. Research Natl. Bur. Standards*, **26**, 591 (1941).

The peak at 4.85 microns could be attributed to absorption of the C=C=C structure.

Because of the symmetry of the alkyne and similarities between the absorption curves of the alkyne and 6° by-product curves, and because of the almost complete dissimilarity between these and the alkene absorption curves, the following conclusions are drawn.

(1) The impurity of the alkyne is essentially the 6° by-product material.

(2) The 6° by-product material is probably the perfluorinated methylallene, $CF_3—CF=C=CF_2$, obtained by rearrangement of the alkyne by zinc chloride during its synthesis.

## Summary

The preparation and physical properties of $CF_3C\equiv CCF_3$, $CF_3CH=CHCF_3$, $CF_3CH_2CH_2CF_3$ and $CF_3CH=CHClCF_3$ are reported.

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[CONTRIBUTION FROM ST. OLAF COLLEGE]

# Preparation and Reactions of α,β-Dichlorovinyltrichlorosilane

BY C. L. AGRE

Recently several publications[1] have disclosed the addition of trichlorosilane and related silanes to ethylenic and acetylenic hydrocarbons under the activation of peroxide, ultraviolet light, or elevated temperature below the decomposition point of the reactants. The results, in general, are illustrated by the addition of trichlorosilane to propylene and to acetylene to yield, respectively, *n*-propyltrichlorosilane and 1,2-bis-(trichlorosilyl)-ethane. The yields of the products varied appreciably and were dependent both on the experimental conditions and on the nature of the reactants. Silicon tetrahalides were reported not to add to the unsaturated materials.

The present investigation, based in part on work done several years ago, is somewhat parallel to the above efforts but differs primarily in that the reaction was carried out at a temperature appreciably above the decomposition temperature of the unsaturated compound charged to the apparatus. Preliminary experiments showed that trichloroethylene and trichlorosilane, in the presence of a peroxide catalyst, gave very little addition product under the experimental conditions employed. It was thought worthwhile, however, to pass the mixture through a hot tube at atmospheric pressure to determine the effect of the greatly elevated temperature. The reaction thus would be run under conditions amenable to commercial practice should interesting products be obtained. It was observed that at a temperature of about 500° a mixture of trichloroethylene and trichlorosilane evolved hydrogen chloride and gave a good yield of a product identified as α,β-dichlorovinyltrichlorosilane. The reaction can be explained simply according to the equations

$$Cl_2C=CHCl + HSiCl_3 \longrightarrow Cl_2HCCHClSiCl_3 \quad (1)$$
$$Cl_2HCCHClSiCl_3 \longrightarrow HCl + ClHC=CClSiCl_3\ I \quad (2)$$

It is more likely, however, that hydrogen chloride first is eliminated from the trichloroethylene to give dichloroacetylene. In the absence of trichlorosilane, and to a very limited extent in its presence, the dichloroacetylene almost instantaneously polymerizes to give hexachlorobenzene in a manner parallel to the formation of benzene from acetylene. However, the dichloroacetylene preferentially adds to trichlorosilane to give the observed product I.

$$Cl_2C=CHCl \longrightarrow HCl + ClC\equiv CCl \quad (3)$$
$$ClC\equiv CCl + HSiCl_3 \longrightarrow ClHC=CClSiCl_3\ I \quad (4)$$

In similar manner, I is obtained in low yield from *s*-tetrachloroethane and trichlorosilane. The first step apparently is the elimination of hydrogen chloride[2] to form trichloroethylene, which then reacts as indicated above.

It is reported[3] that a halogen atom in a position beta (as contrasted to alpha and gamma) to $-SiCl_3$ has unusual activity and upon titration reacts as illustrated in the example

$$ClCH_2CH_2SiCl_3 + 4NaOH \longrightarrow CH_2=CH_2 + Si(OH)_4 + 4NaCl \quad (5)$$

It was obviously of interest to determine if the beta-chlorine atom in I would have similar activity. Titration of I with standard base showed the presence of three active chlorine atoms, which are the three chlorine atoms attached to silicon. The presence of the ethylenic bond in the side chain has, in the customary manner, deactivated the adjoining chlorine atoms to the extent that the beta-chlorine atom does not have the unusual activity observed in the saturated analog, β-chloroethyltrichlorosilane.

The silane I reacts with ethylmagnesium bromide in the expected manner to give α,β-dichlorovinyltriethylsilane (II)

$$ClHC=CClSiCl_3 + 3C_2H_5MgBr \longrightarrow ClHC=CClSi(C_2H_5)_3\ II \quad (6)$$

(1) (a) Sommer, Pietrusza and Whitmore, THIS JOURNAL, **69**, 188 (1947); (b) Burkhard and Krieble, *ibid.*, **69**, 2687 (1947); (c) Barry, *ibid.*, **69**, 2916 (1947); (d) Miller and Schreiber, U. S. Patent 2,379,821 (1945); (e) Pietrusza, Sommer and Whitmore, THIS JOURNAL, **70**, 484 (1948).

(2) British Patent 575,530; *Chem. Abst.*, **41**, 6891 (1947).

(3) (a) Sommer and Whitmore, THIS JOURNAL, **68**, 485 (1946); (b) Sommer, Dorfman, Goldberg and Whitmore, *ibid.*, **68**, 488 (1946).

The inactivity of the β-chlorine atom is apparent in this reaction also. This is in contrast to the saturated analogs for it is reported[4] that a saturated side chain having a beta-halogen atom is separated from the silicon atom as follows

$$ClCH_2CH_2SiCl_3 + 4CH_3MgX \longrightarrow CH_2{=}CH_2 + (CH_3)_4Si \quad (7)$$

Alcohols react with I to give the anticipated esters without any effect on the beta-chlorine atom as follows

$$ClHC{=}CClSiCl_3 + 3ROH \longrightarrow ClHC{=}CClSi(OR)_3 \quad (8)$$

In this manner the esters in which R was methyl and *n*-butyl were prepared.

Trichlorosilane adds to I in a sealed tube in the presence of a peroxide catalyst to give a product believed to be 1,2-bis-(trichlorosilyl)-1,2-dichloroethane (III) according to the equation

$$HSiCl_3 + ClHC{=}CClSiCl_3 \longrightarrow Cl_3SiCHClCHClSiCl_3 \text{ III} \quad (9)$$

This structure is assigned to the product because the addition should be similar to the addition of two molecules of trichlorosilane to acetylene[1b] with the formation of 1,2-bis-(trichlorosilyl)-ethane. Product III is interesting in that it has two chlorine atoms in positions beta, respectively, to the two $-SiCl_3$ units and thus should be very reactive. Titration with standard base shows the presence of seven active chlorine atoms. Hydrolysis and fission probably occur

$$Cl_3SiCHClCHClSiCl_3 + 7NaOH \longrightarrow Si(OH)_4 + CHCl{=}CHSi(OH)_3 + 7NaCl \quad (10)$$

Direct reaction of III with methanol gives rise to a vigorous evolution of hydrogen chloride and a product which boils over a wide range and has less than the anticipated chlorine content. The reaction proceeds satisfactorily by reaction of III and methanol in the presence of pyridine as an acid acceptor. Under these conditions, the two beta-chlorine atoms are not affected and the product obtained is the expected 1,2-bis-(trimethoxysilyl)-1,2-dichloroethane.

$$Cl_3SiCHClCHClSiCl_3 + 6CH_3OH \longrightarrow (OCH_3)_3SiCHClCHClSi(OCH_3)_3 \quad (11)$$

Hydrolysis of III in ether by the addition of water gave a completely water-soluble product since no residue remained on evaporation of the ether layer. Titration of a portion of the aqueous solution showed that slightly over seven of the total of eight chlorine atoms in III had been removed as hydrogen chloride. Evaporation of the water left a powdery, white resin which gradually lost chlorine on prolonged heating. The analytical data do not fit well any proposed product obtained by the hydrolysis of III, but they show that the reaction is deep-seated and probably involves more than the mere hydrolysis of the six chlorine atoms attached to silicon.

The various reactions enumerated above leave very little question relative to the structure of product I. However, to prove more definitely its structure, I was made by the addition of trichlorosilane to dichloroacetylene in a sealed tube in the presence of peroxide catalyst. Extreme precautions must be observed in the handling of dichloroacetylene for, as reported,[5] it explodes violently in the presence of oxygen. Furthermore, it appears to be unstable even in the absence of oxygen because a severe explosion was encountered while approximately fifteen grams of dichloroacetylene in a well stoppered Carius tube was standing in a bath at about −10°. No difficulty was encountered in its preparation even at temperatures much higher than reported[5] as being safe. The relatively pure dichloroacetylene does not react with trichlorosilane at room temperature in the absence of a catalyst but does add essentially completely under the influence of a peroxide at moderate temperature. In view of the observation that the product thus obtained is identical with I prepared pyrolytically from trichloroethylene and trichlorosilane, the structure of I as given previously is correct.

In agreement with observations previously mentioned in the attempted addition of silicon tetrahalides to unsaturated hydrocarbons, no appreciable (if any) addition occurred when attempts were made to add silicon tetrachloride and silicon tetrabromide to trichloroethylene in a heated tube.

Hydrolysis of I gives rise to a resinous product, probably initially according to the following steps

$$ClHC{=}CClSiCl_3 \longrightarrow ClHC{=}CClSi(OH)_3 \longrightarrow ClHC{=}CClSiO_{1.5} \text{ IV} \quad (12)$$

The initial resin was obtained in nearly the theoretical quantity for IV and was clear and tough. However, prolonged heating at 110° caused a gradual loss in weight, probably in part due to the loss of hydrogen chloride, until finally the resinous product became colored and brittle. Analysis of this final resinous product showed the presence of more silicon and less chlorine than required by the formula IV.

Both to aid in the proof of the structure of I and also to observe the possible activity[3] of the beta-chlorine atom in the saturated chain, I was chlorinated and the product was studied.

$$ClCH{=}CClSiCl_3 + Cl_2 \longrightarrow Cl_2HCCCl_2SiCl_3 \text{ V} \quad (13)$$

Titration of V, α,α,β,β-tetrachloroethyltrichlorosilane, gave results which showed that four chlorine atoms had reacted quantitatively and, therefore, proved that one chlorine atom attached to a carbon atom had been removed as well as the three chlorine atoms on the silicon.

(4) Sommer, Goldberg, Dorfman and Whitmore, THIS JOURNAL, **68**, 1083 (1946).

(5) (a) Ott, Ottmeyer and Packendorff, *Ber.*, **63B**, 1941 (1930); (b) Ott, *ibid.*, **75B**, 1517 (1942); (c) Ott and Packendorff, *ibid.*, **64B**, 1324 (1931).

$$Cl_2HCCCl_2SiCl_3 + 4NaOH \longrightarrow HClC{=}CCl_2 + Si(OH)_4 + 4NaCl \quad (14)$$

In this experiment the trichloroethylene was recovered by steam distillation of a sample of V treated with excess alkali. The fission of the side chain is therefore directly parallel to that mentioned previously.

Similarly, the bromination of silane I proceeded as follows to give $\alpha,\beta$-dibromo-$\alpha,\beta$-dichloroethyltrichlorosilane, VI

$$ClHC{=}CClSiCl_3 + Br_2 \longrightarrow ClBrHCCClBrSiCl_3 \text{ VI} \quad (15)$$

Titration of VI gave 36.5% active halogen, calculated as chlorine, which agrees closely with the removal of the three chlorine atoms attached to silicon plus one additional halogen atom. This had been anticipated because here too the presence of the beta-halogen atoms would cause a C–Si fission on treatment of the silane with alkali. Since both a bromine atom and a chlorine atom are beta to the silicon atom, the beta-elimination could proceed by the removal of either of the halogen atoms along with the silicon. Consideration of the C–Cl and C–Br bond energies[6] would lead one to predict the preferential fission of the C–Br linkage. This actually was observed because titration of VI with base proceeded as

$$ClBrHCCClBrSiCl_3 + 4NaOH \longrightarrow ClHC{=}CClBr + Si(OH)_4 + 3NaCl + NaBr \quad (16)$$

The aqueous phase, after the titration, was tested for the bromide ion in the customary manner and a positive test was observed. The 1,2-dichlorobromoethylene obtained in this experiment was identified on the basis of the properties reported in the literature[7] and the appreciable difference between these data and those recorded for the alternate possibility, 1,2-dibromochloroethylene.

Hydrolysis of V and VI, respectively, in ether by the addition of water resulted in the formation of clear, tough resins after heating at about 55° for twenty-four hours or more. These appeared to be formed (by comparing the actual weight with the calculated weight) as follows

$$ClHCXCXClSiCl_3 \longrightarrow ClXHCCXClSiO_{1.5} \text{ (X is Cl or Br)} \quad (17)$$

Prolonged heating of the resins at 110° in the presence of air caused a gradual loss of weight, development of a yellow color, and change from tough to rather brittle residues. Analyses indicate that some loss of halogen occurred when the resins were heated.

## Experimental

**Trichloroethylene and Trichlorosilane in Heated Tube.**—The furnace employed was a commercially available combustion unit with a heated portion about seven inches in length. This was used to heat a Pyrex tube, 9 mm. internal diameter, fitted with a separatory funnel to feed the charge and with a condenser attached to a receiver set in a salt–ice mixture. The tube ordinarily was unpacked but was indented to provide more intimate contact of the charge for better heat transfer. The temperature recorded was that observed on the inbuilt thermocouple in the furnace near the surface of the tube and represents approximately the temperature in the middle portion of the tube.

During three hours a mixture of trichloroethylene (35 g.) and of trichlorosilane (25 g.), both freshly distilled, was passed through the tube at about 490°. The liquid product was amber in color and weighed 50.3 g. Distillation through an 8 inch packed column gave the following cuts:

| Cut | B. p., °C. | Weight | Si, % | Titrable chlorine, % | Calcd. weight product I |
|---|---|---|---|---|---|
| 1 | 35–78 | 6.6 g. | .. | 62.9 | 0.0 g. |
| 2 | 78–155 | 26.5 | .. | 28.1 | 16.2 |
| 3 | 155–169 | 11.3 | 12.2 | 48.1 | 11.3 |
| 4 | 169–190 | 1.8 | 11.8 | 46.1 | 1.9 |
| 5 | Residue | 2.5 | .. | .. | .. |
| | | | | | 29.4 g. |

Analysis of Cut 1 indicated that 5.3 g. of trichlorosilane was recovered, so 19.7 g. was used. Analyses of the various cuts indicated a total yield of adduct I of 29.4 g., or 87.5% yield of $\alpha,\beta$-dichlorovinyltrichlorosilane I based on unrecovered charge. The hydrogen chloride evolved was determined by titration to weigh 7.0 g., compared with a theoretical yield of 6.5 g. Redistillation of the above product combined with similar cuts from other runs gave a colorless liquid, b. p. 159° (729 mm.), with slight decomposition, 52° (8 mm.), $n^{20}D$ 1.4942. Active chlorine was determined by direct titration with standard base, total chlorine[8] by fusion with sodium peroxide followed by potentiometric titration, and the silicon by acid digestion of the sample followed by ignition to constant weight.

*Anal.* Calcd. for $C_2HSiCl_5$: active Cl, 46.2; total Cl, 77.6; Si, 12.15. Found: active Cl, 46.5; total Cl, 77.1; Si, 12.21.

**Trichloroethylene and Trichlorosilane in Sealed Tube.**—A mixture of freshly distilled trichlorosilane (7.0 g.) and trichloroethylene (12.0 g.), together with 1.5 g. of a 30% solution of diacetyl peroxide in dimethyl phthalate, was sealed into a tube and was heated at 65–85° for six hours. Distillation of the product gave 14.5 g. of recovered charge, b. p. 36–88°, and 3.5 g. of a fuming liquid which boiled at 89–240°. This product, together with similar material (8.5 g.) from parallel runs using benzoyl peroxide as the catalyst, was distilled to give the following fractions.

| Cut | B. p., °C. | Weight, g. | Si, % | Active Cl, % |
|---|---|---|---|---|
| 1 | 83–100 | 4.0 | 1.2 | 5.5 |
| 2 | 100–155 | 4.1 | 2.9 | 12.1 |
| 3 | 155–195 | 2.2 | 7.1 | 24.2 |
| 4 | 195–245 | 1.0 | 4.0 | 13.9 |

Since the anticipated adduct, $C_2H_2Cl_6Si$, should have 10.4% silicon and 39.7% active chlorine, it is evident that the product obtained in low yield was only partly organosilicon compounds.

**Reaction of I with Alcohols.**—Anhydrous methanol (15 g.) was added dropwise to silane I (21.0 g.) contained in a 50-cc. Claisen flask. Reaction was vigorous and hydrogen chloride was evolved. The mixture was refluxed gently for fifteen minutes after addition was completed. Distillation gave 14.5 g. of liquid which boiled at 181–188°. Two redistillations through a 6-inch packed column gave 8.0 g. (40%) of $\alpha,\beta$-dichlorovinyltrimethoxysilane, b. p. 104–106° (50 mm.), $n^{20}D$ 1.4421.

*Anal.* Calcd. for $C_5H_{10}O_3SiCl_2$: total Cl, 32.7; Si, 12.92. Found: total Cl, 33.2; Si, 12.95.

(6) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 53.

(7) Swarts, *Chem. Zentr.*, I, 588 (1899). The following properties are recorded: b. p. 112–113°, $n^{16}$ 1.5190.

(8) All total chlorine analyses were made by Mr. R. W. Perlich and his co-workers at the Minnesota Mining and Manufacturing Co.

A portion of this product (0.4760 g.) was placed in a porcelain crucible, water (2 cc.) and 1 drop of concd. hydrochloric acid were added, and the mixture was evaporated to dryness and the residue was heated at 175° for one hour. The resin thus formed was glassy and was moderately tough. Its weight of 0.318 g. amounted to 67% of the original charge, whereas the expected resin, $CHCl{=}CClSiO_{1.5}$, should weigh 67.8% of the charge.

Parallel reaction of I (20.0 g.) with *n*-butanol (25.0 g.) gave on redistillation 15.5 g. (53%) of α,β-dichlorovinyltributoxysilane, $CHCl{=}CClSi(OC_4H_9)_3$, boiling at 163–165° (10 mm.), $n^{20}D$ 1.4434.

*Anal.* Calcd. for $C_{14}H_{28}O_3SiCl_2$: total Cl, 20.7; Si, 8.17. Found: total Cl, 21.2; Si, 8.27.

The resin obtained by hydrolysis of this ester initially was a tough glass but gradually became colored and brittle upon prolonged heating in an oven at 110°.

**Reaction of I with Ethylmagnesium Bromide.**—Ethyl magnesium bromide in ether was prepared from ethyl bromide (47 g.) and magnesium (11 g.). The slow addition of I (20.0 g.) in ether to the cooled Grignard reagent resulted in the formation of a precipitate. After refluxing for two hours, the mixture was cooled and was hydrolyzed in the customary manner. Distillation of the dried ether solution gave 13.2 g. (73%) of α,β-dichlorovinyltriethylsilane, $ClHC{=}CClSi(C_2H_5)_3$, b. p. 97–99° (14 mm.), $n^{20}D$ 1.4780.

*Anal.* Calcd. for $C_8H_{16}SiCl_2$: total Cl, 33.6. Found: total Cl, 33.1.

**Reaction of I with Trichlorosilane.**—Trichlorosilane (13 g.), silane I (6.3 g.), and benzoyl peroxide (0.2 g.) were placed in a sealed tube and heated at 70–80° for sixty-five hours. Distillation gave 3.9 g. (40%) of product, 1,2-bis-(trichlorosilyl)-1,2-dichloroethane III, boiling at 98–103° (4 mm.), $n^{20}D$ 1.5158, plus some foreshot and tailings of approximately the same boiling point. Titration of active chlorine gave 67.35% chlorine, while seven active chlorine atoms would indicate 67.7% chlorine.

*Anal.* Calcd. for $C_2H_2Si_2Cl_8$: total Cl, 77.7; 7 active Cl, 67.7; Si, 15.3. Found: total Cl, 77.4; 7 active Cl, 67.4; Si, 15.6.

**Reaction of III with Methanol.**—In a 250-cc. Erlenmeyer flask were placed dry ether (50 cc.), anhydrous methanol (5.5 g.), and anhydrous pyridine (12.2 g.). Silane III (7.03 g.) in about 50 cc. of dry ether was slowly added. Reaction was instantaneous, heat was evolved, and there separated a lower liquid layer which soon became a dough-like mass. The mixture was warmed at 35° for one hour, was cooled, and the ether solution was decanted. The residue in the flask was washed twice with ether, and the combined ether layers were distilled to remove the ether. The distilled ether was shaken with slightly acidic (HCl) distilled water to decompose any methyl orthosilicate possibly formed and the ether was then evaporated to leave no residue of silica. The liquid residue left after distillation of the ether was distilled twice to give 3.7 g. (56%) of 1,2-bis-(trimethoxysilyl)-1,2-dichloroethane, b. p. 140–146° (10 mm.), 121° ( 1 mm.), $n^{22}D$ 1.4406.

*Anal.* Calcd. for $C_8H_{20}Si_2Cl_2O_6$: total Cl, 21.2; Si, 16.7. Found: Total Cl, 20.9; Si, 16.9.

**Resin Formation from III.**—Silane III (1.7745 g.) in about 50 cc. of dry ether was extracted carefully with four 15-cc. portions of water. Evaporation of the residual ether solution left only 0.0573 g. of residue, so practically all of the resin was water-soluble. Titration of an aliquot portion of the combined aqueous layers indicated 1.231 g. of chlorine, or 69.3% of the weight of the charged silane III, whereas seven active chlorine atoms require 67.7% chlorine. Evaporation of the water left 0.756 g. of a white powder of resinous nature. Analyses showed the presence of 32.7% silicon and 15.2% chlorine.

Silane III (1.6105 g.) in 25 cc. ether was treated carefully in a beaker with about 2 cc. of distilled water. After the vigorous reaction had subsided, the ether was evaporated at a maximum temperature of 70° and the residue was maintained at this temperature for three hours. The resin amounted to 54.5% of the original III and contained 24.1% chlorine. The resin was heated at 110° for an additional forty-nine hours. The product, corrected for removed samples, amounted to 47.8% of the original III and contained 17.3% chlorine.

**Reaction of Dichloroacetylene with Trichlorosilane.**—A 250-cc. distillation flask was filled to the neck with sodium hydroxide pellets, analytical grade, and was immersed in an oil-bath maintained at about 260°. Air was removed by passage of a slow stream of dry natural gas. During ninety minutes, trichloroethylene (20 cc.) was added dropwise from a separatory funnel through an open tube extending to the bottom of the reaction flask. The dichloroacetylene, unconverted trichloroethylene, and some water distilled from the flask and were caught in a 50-cc. Claisen flask in an ice–salt mixture. Trichlorosilane (3 cc.) was added to this flask to remove the small amount of water. The dichloroacetylene was then slowly distilled into the bottom of a Carius tube with constricted neck placed in a salt–ice mixture. The water-bath employed for heating the flask can advantageously be raised to about 75° toward the end of the distillation because the dichloroacetylene does not readily distill completely. The receiver was then clamped to prevent entrance of air and was separated from the long delivery tube leading from the intermediate Claisen flask. Only slight hazard is ordinarily encountered in dismantling the apparatus, although it is best to continue the flow of gas (preferably nitrogen) until all residual dichloroacetylene has escaped. The dichloroacetylene plus any small amount of contaminant in the Carius tube weighed 7 g. To this was added trichlorosilane (10 cc.) containing 0.7 cc. of a 30% solution of diacetyl peroxide in dimethyl phthalate. The tube was sealed and then was heated at 70° for sixty-five hours. On several occasions tubes exploded at this stage, so extreme precautions are necessary. Distillation gave 4.7 g. (28%) of a liquid, b. p. 87–92° (55 mm.), $n^{20}D$ 1.4988, identified as α,β-dichlorovinyltrichlorosilane, I.

*Anal.* Calcd. for $C_2HSiCl_5$: active Cl, 46.2; Si, 12.15. Found: active Cl, 45.7; Si, 11.9.

In addition to more material approximating the above product, there was 3.4 g. of liquid boiling at 76–126° (10 mm.) with only 32.8% active chlorine.

**Resin Formation from I.**—Silane I, 4.7 g., was placed in about 20 cc. of ether and was shaken carefully twice with 25 cc. of water. The ether was evaporated at a maximum temperature of 50° to leave an oil which soon changed to a clear glass. The residue gradually decreased in weight during prolonged heating at 110° as follows with the recorded percentages being the ratios of residue to the original charge of I.

| Hours at 110° | Residue, % | Nature |
|---|---|---|
| 0 | 63.8 | Liquid |
| 1 | 56.0 | Clear glass, tough |
| 22 | 45.8 | |
| 75 | 37.0 | |
| 215 | 35.2 | Yellow, brittle |

Analyses of the final sample indicated 32.3% silicon and 17.6% chlorine. In view of the fact that the inital resin, $ClHC{=}CClSiO_{1.5}$, should amount to 64.2% of the charge and contain 19.0% silicon and 40.8% chlorine, it is evident that the resin lost a large portion of its chlorine.

***s*-Tetrachloroethane and Trichlorosilane in Hot Tube.**—A mixture of *s*-tetrachloroethane (26.5 g.) and trichlorosilane (26.0 g.) was passed through a tube at 500° during ninety-five minutes. The product was a dark, mobile liquid which weighed 35.5 g. Distillation through a Claisen flask gave mainly recovered charge plus 3.3 g. of a liquid, b. p. 157–167°, $n^{19}D$ 1.4928. The yield of α,β-dichlorovinyltrichlorosilane amounted to a maximum of 15% under these experimental conditions.

**Addition of Chlorine to α,β-Dichlorovinyltrichlorosilane.**—The silane I (8.5 g.) and chloroform (10.0 g.) were placed in a Pyrex test-tube. The tube was immersed in ice and dry chlorine (1.2 g.) was absorbed to give a yellow

solution. Immediate and vigorous reaction occurred when the tube was removed from the ice and was exposed to full sunlight. The solution was recooled, additional chlorine (1.4 g.) was added, and the reaction again was effected by exposure to sunlight. The tube again was cooled and chlorine (0.5 g.) was added. As expected, the yellow color remained after this third brief exposure to the sun since an excess amount of chlorine (theory was 2.6 g.) had been added. The tube was allowed to stand stoppered at room temperature for three days. After this period the yellow color was gone so addition was complete and possibly some substitution of hydrogen by chlorine had occurred. The chloroform was removed by distillation and the colorless residual liquid was distilled through a modified Claisen flask. The main fraction (7.9 g., 71%) boiled at 104–106° (17 mm.) and is $\alpha,\alpha,\beta,\beta$-tetrachloroethyltrichlorosilane, V, $n^{27}D$ 1.5149.

*Anal.* Calcd. for $C_2HSiCl_7$: total Cl, 82.6; titrable Cl, 47.0 (4 Cl); Si, 9.1. Found: total Cl, 84.3; titrable Cl, 46.5; Si, 9.3.

**Removal of Side Chain from V.**—Silane V (6.0 g.) was placed in a distillation flask, distilled water was added, and then sufficient sodium hydroxide pellets were added to make the mixture definitely basic. Steam distillation gave a lower organic layer of about 1.2 cc. of colorless liquid. The dried liquid was distilled to give 1.45 g. of trichloroethylene, b. p. 85–88° (739 mm.), $n^{27}D$ 1.4740, which properties coincide well with the accepted values.

*Anal.* Calcd. for $C_2HCl_3$: total Cl, 81.0; Found: total Cl, 81.6.

**Addition of Bromine to I.**—Bromine (7.0 g., calcd. 6.95 g.) was added to I (10.0 g.) in a chloroform (15 g.) and the solution was allowed to stand in the laboratory for twenty-four hours. Since the red color still persisted, the tube was placed in direct sunlight for one day. Analysis of the reaction mixture showed that about 0.15 g. of bromine still remained. Distillation gave 3.8 g. of foreshot, boiling at 59–119° (10 mm.), and 11.0 g. (65%) of product, $\alpha,\beta$-dichloro-$\alpha,\beta$-dibromoethyltrichlorosilane, VI, b. p. 118–120° (10 mm.), $n^{25}D$ 1.5595.

*Anal.* Calcd. for $C_2HSiCl_5Br_2$: active halogen as Cl, 36.3; total halogen as Cl, 63.7; Si, 7.15. Found: active halogen as Cl, 36.5; total halogen as Cl, 63.7; Si, 6.9.

The aqueous solution after titration was acidified with nitric acid, boiled to about half its volume, cooled, and filtered. Fresh chlorine water was added to the solution which then was shaken with carbon tetrachloride. A definite brown color showed the presence of bromide ions in the water and indicated that, in part at least, the beta-bromine had been removed.

**Side Chain Removal from VI.**—Silane VI (6.0 g.) was placed in a 250-cc. Claisen flask and was steam distilled from sodium hydroxide solution. The lower organic layer of about 2 cc. was distilled from a small modified Claisen flask to give about 2 g. of 1,2-dichlorobromoethylene,[7] b. p. 109–112°, $n^{16}D$ 1.5198.

*Anal.* Calcd. for $C_2HCl_2Br$: total halogen as Cl, 60.4. Found: total halogen as Cl, 60.1.

**Resin Formation from V.**—Silane V (0.954 g.) was placed in a 50-cc. beaker and 1 cc. of distilled water suspended in ether was added. Vigorous reaction occurred, hydrogen chloride was evolved, and a lower liquid layer separated. The ether was evaporated and the residue was heated overnight at 55°. The resin was clear and tough, and weighed 0.678 g. (theory is 0.693 g.). Continued heating at 55° for twenty-four hours reduced the weight to 0.65 g. The total chlorine content was 57.0% in comparison with the required 64.9% for $C_2HSiCl_4O_{1.5}$.

**Resin Formation from VI.**—Silane VI (1.7433 g.) in dry ether as above was treated slowly with about 2 cc. of water to give a vigorous reaction and separation of a lower liquid layer. The ether was evaporated and the residue was heated for seventy hours at 55°. The resin weighed 1.315 g. (theoretical is 1.375 g.), and was tough and colorless. The residue was heated at 110° for twenty-four hours to leave a yellow, fairly tough resin which weighed 1.2489 g. Additional heating for twenty-four hours at 110° left 1.1618 g. of resin. After a total heating at 110° for one hundred hours there remained a yellow, brittle resin weighing 1.1279 g. The total halogen amounted to 45.1% as compared to a value of 46.1% for $ClBrHCCBrClSiO_{1.5}$.

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## Summary

1. Trichlorosilane and trichloroethylene react in a hot tube at about 500° to give $\alpha,\beta$-dichlorovinyltrichlorosilane and hydrogen chloride.

2. Trichlorosilane adds to dichloroacetylene in the presence of a peroxide catalyst to give $\alpha,\beta$-dichlorovinyltrichlorosilane.

3. $\alpha,\beta$-Dichlorovinyltrichlorosilane reacts with alcohols and with ethylmagnesium bromide to replace the chlorine atoms attached to the silicon atom.

4. $\alpha,\beta$-Dichlorovinyltrichlorosilane adds trichlorosilane to give 1,2-bis-(trichlorosilyl)-1,2-dichloroethane, which by alkaline titration is shown to have seven active chlorine atoms.

5. $\alpha,\beta$-Dichlorovinyltrichlorosilane adds chlorine and bromine, respectively, to give $\alpha,\alpha,\beta,\beta$-tetrachloroethyltrichlorosilane and $\alpha,\beta$-dichloro-$\alpha,\beta$-dibromoethyltrichlorosilane. Titration in each instance showed the presence of four active halogen atoms.

6. Alkaline hydrolysis of $\alpha,\alpha,\beta,\beta$-tetrachloroethyltrichlorosilane gives trichloroethylene. Alkaline hydrolysis of $\alpha,\beta$-dibromo-$\alpha,\beta$-dichloroethyltrichlorosilane gives 1,2-dichlorobromoethylene.

7. Resins formed by the hydrolysis of the above polyhalogenated silanes lose halogen on prolonged heating in air at 110°.

NORTHFIELD, MINN. RECEIVED AUGUST 5, 1948

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

# Quantitative Studies on Lithium Aluminum Hydride Reactions[1]

BY F. A. HOCHSTEIN[2]

The reactions of lithium aluminum hydride closely resemble those of Grignard reagents.[3,4,5,6,7] These agents appear to differ principally in the more aggressive behavior of the hydride, resulting in a lessening of side-reactions and of steric influences. An analytical procedure employing lithium aluminum hydride may, therefore, be more generally useful than the Zerewitinoff procedure which was so elegantly refined on a macro scale by Kohler and co-workers.[8,9]

Results obtained in the determination of active hydrogen in alcohols, glycols, phenols and amines are satisfactory. Benzyl alcohol, *n*-amyl alcohol,

TABLE I

COMPARISON OF HYDRIDE METHOD AND ZEREWITINOFF METHOD FOR ENOLIZABLE COMPOUNDS

| Compound | Solvent | Active hydrogen, found By $LiAlH_4$ | By $CH_3MgI$ |
|---|---|---|---|
| Aceto-phenone | None | 0.03–0.05 | 0.12[a] |
| | Dibutyl ether | .02– .03 | |
| | Diamyl ether | | .15,[b] 0.12[a] .13–0.23[c] |
| | Dioxane | .38– .42 | .78[a] |
| Acetomesit-ylene | None | .02– .03 | |
| | Dibutyl ether | .01– .03 | |
| | Diamyl ether | | .73[d]–0.99[b] |
| | Dioxane | .10– .13 | |
| | Xylene | | 1.03[e] |
| Ethyl aceto-acetate | None | .67– .73 | |
| | Dibutyl ether | .57– .74 | 1.00[f] |
| | Diamyl ether | | 0.92,[g] 0.95[h] |
| | Dioxane | .74– .78 | |
| | Pyridine | | .87[h] |
| Ethyl malonate | None | .45– .46 | |
| | Dibutyl ether | .52 | 1.00[f] |
| | Pyridine | | 1.70[k] |
| Indane-dione | Dioxane | .23– .30 | |
| | Ethyl morpholine | 1.17–1.18 | |

[a] Lieff, Wright and Hibbert, THIS JOURNAL, **61**, 865 (1939). [b] Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927). [c] Hollyday and Cottle, *Ind. Eng. Chem., Anal. Ed.*, **14**, 774 (1942). [d] R. G. Kadesch, Ph.D. Thesis, University of Chicago, 1941. [e] Smith and Guss, THIS JOURNAL, **59**, 804 (1937). [f] Fuchs, Ishler and Sandoff, *Ind. Eng. Chem., Anal. Ed.*, **12**, 507 (1940). [g] Hibbert and Sudborough, *J. Chem. Soc.*, **85**, 933 (1904). [h] Zerewitinoff, *Ber.*, **41**, 2223 (1908). [k] Fischer and Walter, *ibid.*, **60**, 1987 (1927).

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Chicago, Illinois, meeting, April, 1948.

(2) U. S. Rubber Company Fellow, 1947–1948.

(3) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947).

(4) Nystrom and Brown, *ibid.*, **69**, 2548 (1947).

(5) Krynitsky, Johnson and Carhart, *ibid.*, **70**, 486 (1947).

(6) Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

(7) Hochstein and Brown, *ibid.*, **70**, 3484 (1948).

(8) Kohler, Stone and Fuson, *ibid.*, **49**, 3181 (1927).

(9) Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930).

TABLE II

DETERMINATION OF VARIOUS REDUCIBLE GROUPS[n]

| Compound | Active $H_2$ found | Moles $LiAlH_4$ consumed | Temp., °C. | Solvent[p] |
|---|---|---|---|---|
| I Carbonyl group (theor.: No active hydrogen; 0.25 mole $LiAlH_4$) | | | | |
| Cyclopentanone | 0 | 0.227–0.238 | 75–90 | A |
| | 0 | .245 | 24 | B |
| Xanthone | 0 | .248– .255 | 26 | B |
| | 0 | .278 | 100 | B |
| Benzoin | 1.02[a] | .480[b] | 25 | B |
| Benzil | 0 | .512– .514[b] | 25 | B |
| II Esters (theor.: no active hydrogen; 0.5 mole $LiAlH_4$) | | | | |
| Ethyl benzoate | 0 | 0.491–0.500 | 28 | A |
| Butyl carbitol acetate | 0 | .492– .495 | 25 | A |
| Stearin | 0 | 1.495[c] | 26 | B |
| | | 1.520[c] | 90 | B |
| Palmitin | 0 | 1.483[c] | 27 | B |
| | | 1.515[c] | 75 | B |
| β-Propiolactone | 0 | 0.520 | 95 | B |
| γ-Valerolactone | 0 | .475– .490 | 28 | A |
| α-Angelica lactone | 0.10 | .497– .510 | 90 | B |
| | 0.10 | .388 | 27 | B |
| β-Angelica lactone | 0 | .478– .519 | 90 | B |
| Di-*n*-butylcarbonate | 0 | .685– .751[d] | 25 | A |
| | | .735[d] | 80 | A |
| Protocatechualdehyde carbonate | 0 | .875[a] | 27 | B |
| | 0 | 1.015[a] | 80 | B |
| l-Tyrosine ethyl ester | 2.0–2.4[m] | 0.95–1.10[e] | 90 | B |
| Coumarin | 0 | .640 | 100 | B |
| III Acids (theor.: 1.0 active hydrogen; 0.75 mole $LiAlH_4$) | | | | |
| Benzoic | 0.99–1.02 | 0.503–0.517 | 25 | A |
| | 1.02 | .595 | 25 | B |
| | 1.02–1.03 | .753–0.758 | 75–90 | B |
| Stearic | 1.00–1.01 | .613–0.615 | 25 | A |
| | 1.02 | .765 | 75 | B |
| | 1.00 | .809–0.838 | 75–85 | A |
| Salicylic | 2.01[f] | ..... | 28 | A |
| Triphenylacetic | 1.04–1.05 | .81–0.84[k] | 100 | B |
| Phthalic anhydride | 0[g] | .96–0.99[c] | 85–90 | A |
| IV Amides (theor.: 1.0 active hydrogen; 0.75 mole $LiAlH_4$) | | | | |
| Benzamide | 1.96[f] | ..... | 34 | B |
| Ethyl benzamide | 0.985–1.01 | 0.715–0.81 | 90 | B |
| | .985–0.995 | ..... | 29 | A |
| | 1.005 | .334 | 24 | B |
| Methyl formanilide | 0.03[g] | .517[b] | 90 | B |
| | ..... | .453 | 27 | B |
| Phthalimide | .96–1.00 | .48–0.42[h] | 25 | B |
| | 1.96–2.03 | 1.17–1.19[h] | 95 | B |
| N-Phenyl glutarimide | 0.0[g] | 1.01 | 100 | B |
| N-Phenyl succinimide | .0[g] | 1.01 | 90 | B |
| Urea | 4.4[j] | ..... | 100 | B |
| V Oximes (theor.: 1.0 active hydrogen) | | | | |
| Acetaldoxime | 1.04 | 0.49 | 25 | B |
| Benzophenone oxime | 1.04 | .275 | 25 | B |
| | 1.04 | .505 | 80 | B |
| VI Miscellaneous Compounds | | | | |
| Benzoyl peroxide | 0.93–1.025[a] | 1.725–1.50[c] | 100 | A |
| Triphenylaceto-nitrile[k] | 0[g] | 0.20–0.28[b] | 80–100 | B |
| Nitrobenzene | 2.25–2.55[f] | ..... | 70–75 | A, B |
| 2-Nitrobutane | 2.5–2.7[m] | ..... | 75 | A, B |
| | 3.2[m] | 1.65[c] | 70 | B |

TABLE II (*Continued*)

| Compound | Active $H_2$ found | Moles $LiAlH_4$ consumed | Temp., °C. | Solvent |
|---|---|---|---|---|
| *o*-Nitroaniline | 3.3[i] | ..... | 29 | A |
| | 4.5[i] | ..... | 75 | A |
| | 5.1[i] | ..... | 30 | B |
| Azoxybenzene | 1.04[a] | 0.58[b] | 75 | B |
| Fluorene | < 0.03 | ..... | 75 | A |
| Triphenylmethane | < 0.06 | ..... | 75 | A |
| Naphthalene | ... | < 0.05 | 100 | B |

[a] 1.0 active hydrogen calcd. [b] 0.5 mole $LiAlH_4$ calcd. [c] 1.5 mole $LiAlH_4$ calcd. [d] 0.75 mole $LiAlH_4$ calcd. [e] 1.25 mole $LiAlH_4$ calcd. [f] 2.0 active hydrogen calcd. [g] No active hydrogen calcd. [h] Nature of reaction not known. [i] 4.0 active hydrogen calcd. Very small sample used, so percentage error was large. [k] Red color at end of reaction, which disappears on hydrolysis. [m] 3.0 active hydrogen calcd. [n] Reaction time ten to twenty minutes. [y] A = dibutyl ethers; B = N-ethylmorpholine.

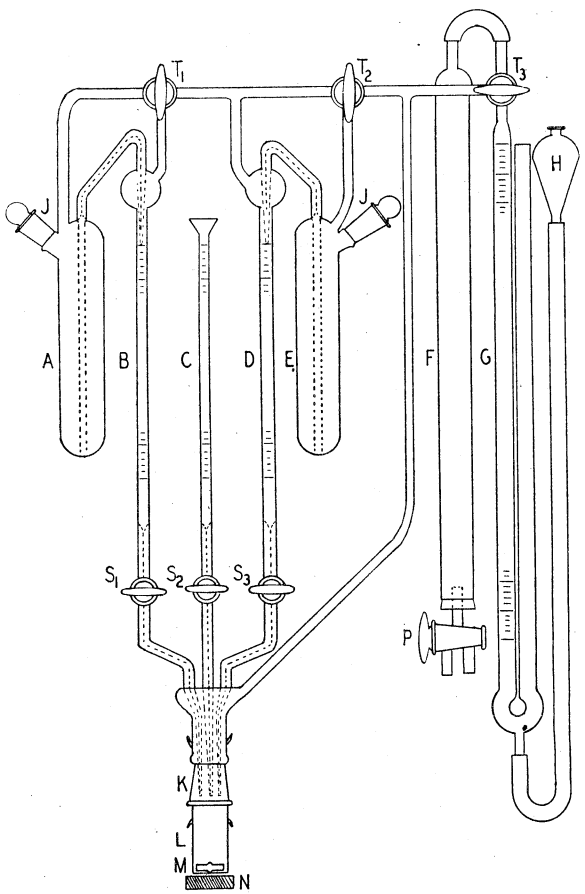



Fig. 1.—Apparatus for measurement of active hydrogen and of $LiAlH_4$ consumption: A, E, 125 ml. reservoirs; B, 2 ml. reagent buret; C, 2 ml. hydrolyzing agent buret; D, 5 ml. solvent buret; F, nitrogen drying tube, packed with phosphorus pentoxide on pumice; G, 25 ml. gas measuring buret; H, mercury reservoir; J, 14/30 ⅀ filling ports; K, 24/40 ⅀ female joint; L, 12 ml. reaction flash, with 24/40 ⅀ male joint; M, glass covered iron stirrer; N, rotating magnet; P, three-way stopcock, for nitrogen; $S_1$, $S_2$, $S_3$, 1 mm. capillary bore stopcocks; $T_1$, $T_2$, $T_3$, three-way 6 mm. stopcocks.

β-naphthol, thio-β-naphthol, 2,4,6-tribenzylphenol, benzylaniline, diphenylamine and dibenzylamine gave values indicating 1.00 active hydrogen, with an average deviation of ±0.015. Phenylethylene glycol, 1,6-hexanediol, hydroquinone, aniline and *n*-butylamine gave values indicating 2.00 active hydrogen, with an average deviation of ±0.010. Water, in N-ethylmorpholine solution, gave values indicating 1.7 to 1.9 active hydrogen.

TABLE III

REACTIONS OF $LiAlH_4$ WITH UNSATURATED COMPOUNDS[a]

| Compound | Active hydrogen found | Moles $LiAlH_4$ consumed Found | Calcd.[b] | Temp. °C. |
|---|---|---|---|---|
| Allyl alcohol[c] | 1.01 | 0.41 | 0.25 | 95 |
| Cinnamyl alcohol | 1.01 | .365 | .25 | 25 |
| | 1.01 | .496–0.521 | .25 | 95 |
| Cinnamic acid[c] | 1.03 | .794 | .75 | 28 |
| | 0.97–1.03 | .92–1.02 | .75 | 80 |
| Phenylpropiolic acid | 1.03 | .89 | .75 | 27 |
| | 1.03–1.06 | 1.09–1.11 | .75 | 100 |
| Maleic anhydride | 0 | 0.90–0.91 | 1.00 | 100 |
| Benzalacetophenone | 0 | .266 | 0.25 | 25 |
| | 0 | .494 | .25 | 90 |
| *p*-Benzoquinone[d,e] | 0.50–0.52 | .46–0.49 | .50 | 27 |
| | .74–0.84 | .49 | .50 | 25 |
| | .86 | .485 | .50 | 75 |
| Phenanthraquinone[e] | .85 | .481 | .50 | 25 |
| | .76 | .52 | .50 | 70 |
| Acenaphthenequinone | .13–0.25 | .45–0.48 | .50 | 80 |
| Perinaphthenone | 0 | .28–0.39 | .25 | 27 |
| | 0 | .31 | .25 | 80 |
| Benzanthrone | 0.26[e] | .35 | .25 | 26 |
| | 0.50–0.68 | .41–0.42 | .25 | 90 |

[a] Reactions carried out in N-ethylmorpholine. Reaction time ten to fifteen minutes. [b] Assuming no reduction of carbon–carbon double bonds. [c] Reaction time sixty minutes. [d] Dibutyl ether solvent. [e] 1.0 mole active hydrogen calcd.

TABLE IV

REDUCING OF VARIOUS COMPOUNDS BY $LiAlH_4$[a]

| Compound | Reaction time, hr. | Yield, % | Product |
|---|---|---|---|
| Fluorenone | 1/4 | 99 | 9-Fluorenol |
| Perinaphthenone | 1/4 | 23 | Perinaphthene |
| Benzalacetophenone | 1/4 | 65 | Phenylstyrylcarbinol |
| α-Angelica lactone | 24 | 65 | γ-Acetylpropanol |
| β-Angelica lactone[b] | 4 | 10 | 2,4-Pentanediol[c] |
| Coumarin | 24 | 50 | 3-(*o*-Hydroxyphenyl)-propanol |
| | | 10 | *o*-Hydroxycinnamyl alcohol[d] |
| 1-Tyrosine ethyl ester[b] | 2 | 60 | 2-Amino-3-(*p*-hydroxyphenyl)-propanol[e] |
| Benzophenone oxime[b] | 7 | 60 | Benzhydrylamine[f] |

[a] Reductions carried out in ether at 35° unless otherwise specified. [b] Reductions carried out in tetrahydrofuran at 65°. [c] Isolated as diacetate, $d^{20}_{20}$ 1.028, $n^{20}D$ 1.4294. [d] New compound. Colorless needles from benzene, m. p. 110.5–111.5°. *Anal.* Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.71; act. $H_2$ 1.33%; Br. No., 108. Found: C, 72.0; H, 6.52; act. $H_2$, 1.37%; Br. No., 118. Dibenzoate (act. $H_2$ 0.0%), rectangular plates from methanol, m. p. 92.5–93.5°. [e] New compound: isolated as triacetyl derivative; white needles from alcohol m. p. 118–119°. *Anal.* Calcd. for $C_{15}H_{19}O_5N$: N, 4.78. Found: N, 4.76, 4.89. $[\alpha]^{25}D$, + 1.95° (in ethanol). 2-Amino-3-(*p*-hydroxyphenyl) propanol sulfate, m. p. 272–7° (decomp.). *Anal.* Calc. for $(C_9H_{13}NO_2)_2H_2SO_4$: $SO_4$, 22.2. Found: $SO_4$, 22.3. [f] 20% of oxime recovered unchanged.

Further data, with reference to types of compounds which undergo reduction as well as replacement of active hydrogen, are presented in Tables I–III. The agreement with the theory is in general within the limits of experimental error.

It was occasionally desirable to run larger scale reactions in order that reaction products might be investigated. Some of these are described in Table IV, the procedures having been described previously.[4]

## Experimental

Early experiments were carried out with the usual type of micro-scale Grignard machine,[10] the reactions being performed in air. Erratic results, due to a slow reaction of the hydride with oxygen and the consequent liberation of hydrogen, were remedied by carrying out the operations in an atmosphere of nitrogen. Difficulties encountered because of the leaking and fouling of the three-way stopcock were overcome by a modification of the apparatus. Dioxane, anethole and N-methylmorpholine are less satisfactory than dibutyl ether as a solvent, while N-ethylmorpholine is the most satisfactory solvent used to date. Pyridine cannot be used since it is reduced by the reagent.

The design of the apparatus is shown in Fig. 1. It may be noted that if an accuracy of better than one per cent. is desired, the design should be altered to minimize the free space in the head of the reaction vessel and in the connections to the gas buret, and also that the latter should be maintained at constant temperature.

The operation of the apparatus is similar in principle to that described by Soltys.[10] A weighed sample is placed in the reaction vessel, L, the apparatus is flushed with dry nitrogen, and the desired quantity of solvent is added from the buret, D. The gas buret is levelled at zero, and with stirring by the magnetic bar, M, the desired quantity of lithium aluminum hydride solution (taken in 20–30% excess) is added from buret, B. The evolution of hydrogen from compounds containing active hydrogen is usually complete in one to ten minutes at room temperature; reduction reactions may require a longer time, or may require heating. After measurement of the hydrogen gas volume, the excess hydride is decomposed by the addition, from buret, C, of 1.0 ml. of a mixture of amyl alcohol in two volumes of dibutyl ether. Complete decomposition of the reagent may require some time; usually fifteen minutes at room temperature is adequate.

**Reagents.**—Stock solutions of lithium aluminum hydride were prepared by shaking 2 g. of the compound[11] with 200 ml. of dibutyl ether for fifteen minutes or longer, allowing the mixture to settle and filtering the supernatant liquid through sintered glass, all operations being conducted under nitrogen. This yields a clear solution, 0.20–0.25 molar in $LiAlH_4$, which slowly deposits a white precipitate and deteriorates at a rate of less than 1% per month when stored under dry nitrogen.

The solvents, N-ethylmorpholine and dibutyl ether, were first dried over calcium hydride, then treated with lithium aluminum hydride (2 g. per l.) at 90–100° for two hours, and were then distilled at 20 mm. pressure. After placing the solvent in the reservoir, control runs were made on the basis of which the calculated quantity of lithium aluminum hydride solution was added to the solvent contained in the reservoir and the mixture heated to 70° for one hour. With this procedure the quantity of hydrogen liberated from 1 ml. of solvent by the addition of hydride solution could be made smaller than 0.05 ml.

Cylinder nitrogen was used without purification, other than drying over phosphorus pentoxide.

The test compounds were purified by conventional procedures but with special care to exclude moisture. In the recrystallization of solids it was necessary to avoid the use of hydroxylic solvents. Liquids were dried over calcium hydride where possible, otherwise over Drierite.

**Acknowledgments.**—Dr. Weldon G. Brown offered much helpful advice in the development of this method; he supplied many of the compounds tested in the apparatus.

## Summary

The quantitative aspect of the reaction of lithium aluminum hydride with several types of organic compounds has been investigated. It is shown that lithium aluminum hydride may be used as a reagent for the determination of active hydrogen, and reducible groups.

(10) Soltys, *Mikrochemie*, **20**, 107 (1937). See also Niederl and Niederl, "Micromethods of Quantitative Organic Elementary Analysis," J. Wiley and Sons, Inc., New York, N. Y., 1938, p. 206.

(11) Lithium aluminium hydride was prepared in this Laboratory by the method of Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

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# An Empirical Expression for the Melting Points of the Straight-Chain Dicarboxylic Acids

BY JOHN G. ERICKSON

It was pointed out by Baeyer[1] in 1877 that the melting points of the unsubstituted aliphatic dibasic acids are of an oscillatory nature, that is, the melting points of successive members of the series are alternately high and low. The melting points converge to an asymptotic value, the melting points of the acids with an even number of carbon atoms decreasing and the melting points of the acids with an odd number of carbon atoms increasing with the length of the carbon chain. The convergence value for the dibasic acids is 123°.

(1) Baeyer, *Ber.*, **10**, 1286 (1877).

This oscillation is not peculiar to the melting points of the dicarboxylic acids; other homologous series, including aliphatic monobasic acids and their α-hydroxy derivatives, α,α′-dibromodicarboxylic acids, dinitriles, glycols, diamines, dialdehydes, alcohols and paraffins, show similar oscillatory effects and other physical properties, including solubilities, molecular volumes, optical rotatory powers and dissociation constants are affected. However, the oscillatory or "alternating" effect is much the most pronounced with the dicarboxylic acids and has attracted the most atten-

tion with these compounds. The effect has been discussed by a number of persons[2] and explanations have been offered. A good summary of the conclusions reached is given by Ralston.[3]

King and Garner[4] have fitted a mathematical expression to the melting points of the ethyl esters of the saturated straight-chain monocarboxylic acids. This is a series which shows a slight alternating effect in the sense that, while the melting points for both even and odd numbered esters increase with the length of the carbon chain, the differences between successive members of the series are alternately relatively large and small. These differences become small as the chain becomes long so that, plotted as melting point *vs.* length of chain, the even and odd numbered esters give two curves which rise and tend to converge as the carbon chain increases in length. King and Garner found that the melting points could be represented by the following equation: for esters of even acids

$$T_m = \frac{0.7630n + 0.63}{0.00179n + 0.01475}, \text{ up to } n = 20$$

and

$$T_m = \frac{0.7081n - 3.28}{0.001796n - 0.0012} \text{ above } n = 20$$

for esters of odd acids

$$T_m = \frac{0.8389n - 5.58}{0.00224n - 0.00904}$$

$T_m$ represents the melting points and $n$, the number of carbon atoms in the acid.

This paper reports an expression which shows the alternating effect and convergence for the dicarboxylic acids and reproduces their melting points, from glutaric acid on, with a fair degree of accuracy. It is of a type quite different from that of King and Garner and takes the form of a single sequence, applicable over the entire range of values. It may be expressed:

$$(T_m)_n = ab^{cd_{n-1}} + e = ad_n + e$$
$$(T_m)_{n+1} = ab^{cd_n} + e = ad_{n+1} + e$$
$$(T_m)_{n+2} = ab^{cd_{n+1}} + e = ad_{n+2} + e, \text{ etc.}$$

where $(T_m)_n$ represents the melting point of a dibasic acid, $(CH_2)_n(COOH)_2$, where $n$ is greater than two, and $a$, $b$, $c$ and $e$ are constants whose values are: $a = 100.00$, $b = 0.09500$, $c = 0.85000$, $e = 80.000$. Each term in the $d_n$ sequence, $d_n = b^{cd_{n-1}}$, $d_{n+1} = b^{cd_n}$, $d_{n+2} = b^{cd_{n+1}}$, etc., is calculated from the preceding one. The initial term for this sequence is $d_2 = 0.87300$.

(2) (a) Biach, *Z. physik. Chem.*, **50**, 61 (1905); (b) Falk and Nelson, THIS JOURNAL, **32**, 1637 (1910), and *J. prakt. Chem.*, **88**, 101 (1913); (c) Pauly, *Ann.*, **383**, 260 (1911), and *Z. anorg. Chem.*, **119**, 271 (1921); (d) Tammann, *ibid.*, **109**, 221 (1920), and **115**, 288 (1921); (e) Stark, *ibid.*, **119**, 292 (1921); (f) Meerwein, *Ann.*, **419**, 121 (1921); (g) Cuy, *Z. anorg. Chem.*, **115**, 273 (1921); (h) Fairweather, *Phil. Mag.*, [7] **1**, 944 (1926); (i) Normand, Ross and Henderson, *J. Chem. Soc.*, 2632 (1926); (j) Nekrassow, *Z. physik. Chem.*, **128**, 203 (1927); (k) Malkin, *Nature*, **127**, 126 (1931); (l) King and Garner, *J. Chem. Soc.*, 1368 (1936).

(3) Ralston, "Fatty Acids and their Derivatives," John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 324 and 353.

(4) King and Garner, *J. Chem. Soc.*, 1449 (1934); ref. 21.

The results are summarized in Table I, where calculated and reported values are given. The reported values were taken from Beilstein, fourth edition, Vol. II and its first and second supplements except where otherwise noted. The reported values which fit the calculated values best are given first, followed by other reported values in parentheses. The experimental values to which this expression was fitted were, with two exceptions ($C_{11}$ and $C_{21}$ acids), the highest values reported for each acid since it was felt, in the absence of other generally applicable criteria, that

TABLE I

MELTING POINTS OF THE DIBASIC ACID, $(CH_2)_n(COOH)_2$

| $n$ | $d_n$ | $T_m$ (calcd.) | $T_m$ (observed) | |
|---|---|---|---|---|
| 3 | 0.17435 | 97.4 | 97.5 | (97, 97-98, 98, 98-99) |
| 4 | .70550 | 150.6 | 150.6 | (149-149.5, 150, 151, 152, 153, 153-153.5) |
| 5 | .24376 | 104.4 | 105 | (103, 105-106, 105-105.5) |
| 6 | .61401 | 141.4 | 141 | (140, 144) |
| 7 | .29273 | 109.3 | 109 | (106, 106.2, 106.5, 107, 107.5, 107-108) |
| 8 | .55672 | 135.7 | 134.5 | (130-132,[a] 133-133.5) |
| 9 | .32828 | 112.8 | 111 | (100-101, 109, 110, 124) |
| 10 | .51849 | 131.8 | 129 | (123, 124, 124-125, 124.5-125.5, 125.5-127, 126.5-127, 127, 127-128,[b] 127.8-128) |
| 11 | .35438 | 115.4 | 114 | (112, 112-113, 113, 113.5) |
| 12 | .49212 | 129.2 | 126.5 | (123, 124, 125.8) |
| 13 | .37358 | 117.4 | 114.6-114.8 | (111,[c] 113, 113-114) |
| 14 | .47356 | 127.4 | 125 | (123, 123-124, 124, 124-124.2) |
| 15 | .38770 | 118.7 | 118 | (116-117) |
| 16 | .46038 | 126.0 | 124.6-124.8[d] | (118, 124, 124.2-124.6[e]) |
| 17 | .39807 | 119.8 | 119-120.5 | (119.2) |
| 18 | .45092 | 125.1 | 124-125[f] | (123,[c] 123.8-124.2,[e] 125.7-125.9[g]) |
| 19 | .40568 | 120.6 | 118-120 | (117-117.5, 117.7-117.9, 123[c]) |
| 20 | .44411 | 124.4 | 123.5-124.5[h] | (120-122,[i] 121, 123.75, 123-124, 124,[j] 122.5-124.5,[k] 125.7-126.3,[l] 126.9-127.1,[g] 123) |
| 21 | .41221 | 121.2 | 127.5[m] | |
| 22 | .43834 | 123.8 | 126.9-127.1[g] | (128-130[n]) |
| 23 | .41601 | 121.6 | | |
| 24 | .43502 | 123.5 | 123.5 | |
| 25 | .41878 | 121.9 | | |
| 26 | .43262 | 123.3 | | |
| 27 | .42080 | 122.1 | | |
| 28 | .43087 | 123.1 | 123.25 | |
| 29 | .42228 | 122.2 | | |
| 30 | .42960 | 123.0 | | |
| 31 | .42311 | 122.3 | | |
| 32 | .42889 | 122.9 | 123 | |

[a] Korshak and Rafikov, *C. A.*, **39**, 4592 (1945). [b] Walker, *J. Chem. Soc.*, 1304 (1940). [c] Chuit and Hauser, *Helv. Chim. Acta*, 12, 850 (1929). [d] Ruzicka, Plattner and Widmer, *Helv. Chim. Acta*, **25**, 1086 (1942). [e] Siina, *C. A.* **32**, 499 (1938). [f] Ruzicka, Plattner and Widmer, *Helv. Chim. Acta*, 25, 604 (1942). [g] Siina, *C. A.* **33**, 7278 (1939). [h] Zetsche and Bähler, *Helv. Chim. Acta*, **14**, 632 (1931). [i] Ross, Gebhart and Gerecht, THIS JOURNAL, **67**, 1275 (1945). [j] Zetsche and Bähler, *Helv. Chim. Acta*, **14**, 846 (1931). [k] Drake, Carhart and Mozingo, THIS JOURNAL, **63**, 617 (1941). [l] Siina, *C. A.* **34**, 7638 (1940). [m] Flaschenträger and Halle, *Z. physiol. Chem.*, **190**, 120 (1930). [n] Ruzicka and Stoll, *Helv. Chim. Acta*, **16**, 493 (1933).

the highest melting points would correspond to compounds of the greatest purity. In view of this, it is not surprising that most of the values which agree most closely with the calculated values are also the highest reported values. It will be seen that, in general, the difference between the calculated and observed values for an acid is considerably less than the range of values reported for the acid. The large difference, 6.3°, between calculated and observed melting points for the $C_{23}$ acid may be attributed to the fact that this acid was isolated from a naturally occurring wax and the difficulties of purifying long-chain compounds when contaminated with compounds of nearly the same properties are rather great. The melting points for the $C_{26}$, $C_{39}$ and $C_{34}$ acids were taken from the very careful work of Fairweather[2h] and definitely fix the convergence value of the series as 123°.

## Summary

An empirical expression, which takes the form of a mathematical sequence is proposed for the melting points of the unsubstituted dicarboxylic acids. It is shown that this expression reproduces the melting points of these acids satisfactorily.

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[CONTRIBUTION FROM THE METCALF RESEARCH LABORATORY OF BROWN UNIVERSITY]

# Properties of Electrolytic Solutions. XXXVII. The Conductance of Some Long Chain Salts in Acetone–Water Mixtures[1]

BY HOWARD S. YOUNG,[2] PHILIP F. GRIEGER[3] AND CHARLES A. KRAUS

## I. Introduction

The effect of added methanol on the conductance of several long chain electrolytes (principally *n*-octadecyltrimethylammonium salts) in aqueous solution has been described in preceding numbers of this series.[4,5,6]

Based on the form of their conductance curves in water and mixtures of water with other solvents, long chain salts may be divided into three classes: I, the conductance curve exhibits a breakpoint in water as well as in mixtures of water with other solvents; II, the curve exhibits a maximum in water as well as in its mixtures; and III (an intermediate case), the curve exhibits a breakpoint in water and a maximum in mixtures containing sufficient additive.

Solutions of the octadecyltrimethylammonium ion have been measured in combination with seven different gegenions in methanol–water mixtures. Of these, the bromide, nitrate and oxalate fall into Class I; the chloride, bromate, iodate and formate fall into Class III. Of the octadecylpyridonium salts measured, the bromide and nitrate fall into Class I, the chloride falls into Class III and the iodate into Class II.

In the present investigation, the conductance of three octadecyltrimethylammonium salts (oxalate, formate and bromate) was measured in acetone–water mixtures (0 to 30% acetone by weight) in order to compare the effects of added acetone with those observed with methanol. Although the measurements with acetone are less extensive than those with methanol,[3,4] they permit of an adequate comparison in the case of several salts.

Among other things, it was of interest to determine whether salts in acetone–water mixtures fall into the methanol–water classification groups. It was also of much interest to determine whether or not the critical phenomenon (breakpoint or maximum) may be correlated with the physical constants of the solvent mixtures, such as dielectric constant.

## II. Experimental

**Apparatus and Procedure.**—The details appertaining to these have been fully described in earlier numbers of this series.[4] All measurements were made at 25 ± 0.01°.

**Salts.**—The salts were identically the same as those used in a previous investigation.[5]

**Solvents.**—Water was prepared according to the technique already described[4]; its specific conductance was in the neighborhood of $1 \times 10^{-6}$.

**Acetone.**—Commercial acetone was treated by the silver hydroxide method described by Werner.[7] The water introduced in this treatment was removed by refluxing over anhydrous potassium carbonate. The carbonate was removed by filtration, and the acetone was fractionally distilled from activated alumina. It was freshly distilled from activated alumina immediately before use. The lowest specific conductance obtained in this manner was $6 \times 10^{-9}$.

## III. Results

In Tables I, II and III are recorded selected values of the equivalent conductance, Λ, as a func-

(1) This paper is based on a portion of a thesis presented by Howard S. Young in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in the Graduate School of Brown University, June, 1948.

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(4) Evers and Kraus, THIS JOURNAL, **70**, 3049 (1948).

(5) Grieger and Kraus, *ibid.*, **70**, 3803 (1948).

(6) Brown, Grieger and Kraus, *ibid.*, **71**, 95 (1949).

(7) Werner, *Analyst*, **58**, 335 (1933).

TABLE I

CONDUCTANCE OF *n*-OCTADECYLTRIMETHYLAMMONIUM OXALATE IN WATER–ACETONE MIXTURES AT 25°

| $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ |
|---|---|---|---|---|---|---|---|---|---|
| Water | | 13.89% Acetone | | 9.91% Acetone | | 20.69% Acetone | | 28.84% Acetone | |
| $\kappa_0 = 0.89 \times 10^{-6}$, $d = 0.9971$, $D = 78.48$ | | $\kappa_0 = 0.76 \times 10^{-6}$, $d = 0.9783$, $D = 71.0$ | | $\kappa_0 = 0.84 \times 10^{-6}$, $d = 0.9834$, $D = 73.2$ | | $\kappa_0 = 0.56 \times 10^{-6}$, $d = 0.9685$, $D = 67.2$ | | $\kappa_0 = 0.98 \times 10^{-6}$, $d = 0.9564$, $D = 62.6$ | |
| 0.779 | 88.60 (14) | 1.101 | 68.33 (8) | 0.808 | 71.90 (15) | 1.177 | 61.78 (6) | 1.177 | 57.40 (11.0) |
| 0.935 | 82.75 | 1.234 | 68.73 | 1.039 | 72.80 | 1.327 | 61.73 | 1.391 | 56.68 |
| 1.086 | 65.50 | 1.433 | 68.29 | 1.181 | 73.04 | 1.542 | 61.58 | 1.655 | 56.15 |
| 1.328 | 48.32 | 1.781 | 60.15 | 1.439 | 62.46 | 2.010 | 61.30 | 2.166 | 55.45 |
| 1.503 | 40.33 | 2.059 | 48.97 (4) | 1.620 | 52.59 | 2.237 | 61.14 (2) | 2.373 | 55.24 (3) |
| 1.803 | 31.63 | 2.531 | 37.20 | 1.899 | 42.22 | 2.570 | 59.54 | 2.661 | 55.13 |
| 2.284 | 24.55 | 2.929 | 31.04 | 2.134 | 35.93 | 2.884 | 54.02 | 3.237 | 54.63 |
| 3.536 | 17.12 (4) | 3.521 | 25.27 | 2.499 | 29.77 (5) | 3.360 | 44.74 | 3.734 | 53.79 |
| 5.037 | 13.82 | 4.012 | 22.18 | 2.790 | 26.34 | 3.767 | 38.47 (1) | 4.196 | 52.82 (1) |
| 5.632 | 13.11 | 4.870 | 18.71 (2) | 3.216 | 22.85 | 4.378 | 31.95 | 4.831 | 50.14 |
| 6.588 | 12.23 | 6.805 | 15.02 | 3.601 | 20.62 | 4.910 | 27.89 | 5.778 | 43.01 |
| 8.479 | 11.19 (1) | 8.190 | 13.68 | 4.165 | 18.39 | 5.718 | 23.62 | 6.562 | 37.45 |
| | | 10.71 | 12.40 (0.5) | 4.677 | 16.93 (2) | 6.529 | 20.75 | 7.884 | 30.59 (0.5) |
| | | | | 5.428 | 15.45 | 7.796 | 17.81 (0.5) | 10.69 | 22.60 |
| | | | | 6.277 | 14.28 | 10.06 | 15.01 | | |
| | | | | 7.674 | 13.08 | | | | |
| | | | | 10.70 | 11.78 (0.6) | | | | |

TABLE II

CONDUCTANCE OF *n*-OCTADECYLTRIMETHYLAMMONIUM FORMATE IN WATER–ACETONE MIXTURES AT 25°

| $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ |
|---|---|---|---|
| 10.00% Acetone | | 13.89% Acetone | |
| $\kappa_0 = 0.97 \times 10^{-6}$ | | $\kappa_0 = 0.76 \times 10^{-6}$ | |
| $d = 0.9833$, $D = 73.1$ | | $d = 0.9783$, $D = 71.0$ | |
| 1.303 | 57.69 (9.0) | 1.390 | 55.52 (7) |
| 1.490 | 58.22 | 1.543 | 55.59 |
| 1.847 | 59.23 | 1.738 | 55.73 |
| 2.171 | 62.68 | 1.913 | 56.02 |
| 2.635 | 66.78 | 2.134 | 56.71 (3) |
| 3.087 | 68.22 | 2.325 | 57.83 |
| 3.881 | 66.62 | 2.580 | 59.49 |
| 4.551 | 63.65 | 2.906 | 61.15 |
| 5.666 | 57.92 (0.5) | 3.441 | 62.76 (1) |
| 6.668 | 54.12 | 3.952 | 62.87 |
| 8.134 | 49.09 | 4.702 | 61.51 |
| 11.57 | 41.71 (0.2) | 5.215 | 59.99 |
| | | 6.003 | 57.56 |
| | | 8.074 | 51.22 (0.2) |

TABLE III

CONDUCTANCE OF *n*-OCTADECYLTRIMETHYLAMMONIUM BROMATE IN 10.00% ACETONE AT 25°

| $10^2\sqrt{C}$ | $\Lambda$ | $10^2\sqrt{C}$ | $\Lambda$ |
|---|---|---|---|
| $\kappa_0 = 0.97 \times 10^{-6}$, $d = 0.9833$, $D = 73.1$ | | $\kappa_0 = 0.97 \times 10^{-6}$, $d = 0.9833$, $D = 73.1$ | |
| 1.280 | 60.71 (9) | 3.028 | 66.87 |
| 1.480 | 60.91 | 3.703 | 62.70 |
| 1.663 | 61.28 | 4.245 | 58.42 (1) |
| 1.821 | 61.85 | 5.152 | 51.58 |
| 2.023 | 63.71 | 6.015 | 46.34 |
| 2.331 | 66.31 | 7.404 | 40.18 |
| 2.609 | 67.83 (2) | 10.33 | 32.88 (0.3) |

tion of the square root of equivalent concentration, $C$, for *n*-octadecyltrimethylammonium oxalate, formate and bromate, respectively. The numbers in parentheses in the tables are the percentage solvent correction; they are included to indicate the magnitude of this correction. The solvent composition is given in weight per cent. The following data are included for the solvents: specific conductance, $\kappa$; density, $d$[8]; and dielectric constant, $D$.[9] In computing the equivalent concentration, the densities of the solutions were assumed equal to those of the pure solvents[3]; no buoyancy corrections were applied.

In Figure 1, $\Lambda$ is plotted against $\sqrt{C}$ for *n*-octadecyltrimethylammonium oxalate in acetone–water mixtures. Earlier results[4] with water as solvent are included in the figure for comparison. In Figs. 2 and 3 are shown similar plots for the formate and the bromate. Previous results[4,10] with water and water–methanol mixtures as solvents are also plotted for purposes of comparison.

## IV. Discussion

As may be seen from an inspection of Figs. 1, 2 and 3, the effect of added acetone on the conductance of octadecyltrimethylammonium salts in water is similar to that of methanol. In methanol–water mixtures, the oxalate shows the simple breakpoint phenomenon (Class I); an analogous situation prevails in acetone–water mixtures. Similarly, the bromate and formate, which exhibit a maximum in $\Lambda$ in methanol–water mixtures (Class III), likewise exhibit a maximum in acetone–water mixtures.

The low value of the breakpoint concentration of octadecyltrimethylammonium oxalate in water and the wide range of concentration over which it is displaced on addition of added solvents render this salt particularly useful in any attempt to correlate the breakpoint concentration with the

(8) Determined with a Weld type specific gravity bottle. Good agreement was found with the results of McElroy, THIS JOURNAL, **16**, 618 (1894).

(9) Albright, *ibid.*, **59**, 2098 (1937).

(10) Carignan, Thesis, Brown University, 1947.

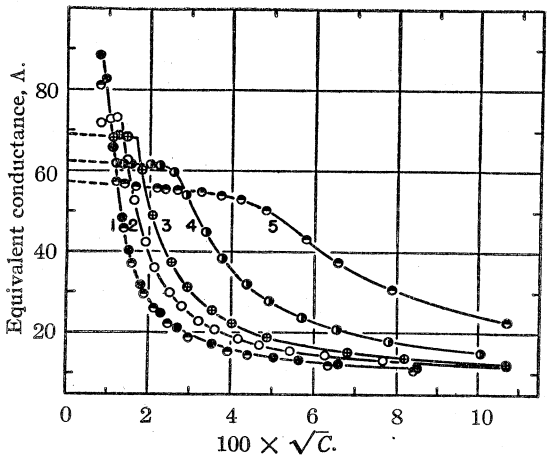



Fig. 1.—Octadecyltrimethylammonium oxalate in: water (1); acetone: (2) 9.9%; (3) 13.9%; (4) 20.7%; (5) 28.8%.

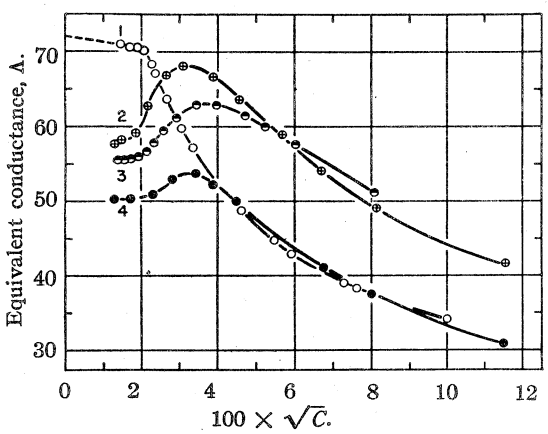



Fig. 2.—Octadecyltrimethylammonium formate in: water (1); acetone: (2) 10.0%; (3) 13.9%; methanol: (4) 19.4%.

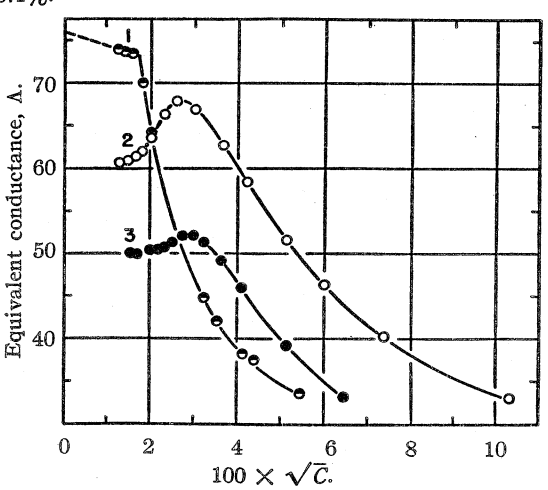



Fig. 3.—Octadecyltrimethylammonium bromate in: water (1); acetone (2) 10.0%; methanol (3) 20.7%.

physical properties of the solvent mixtures. For smaller additions of acetone or methanol, the breakpoint remains quite sharp, but, for larger additions, for example, 28.8% acetone, the breakpoint concentration can only be approximated.

Breakpoint concentrations for octadecyltrimethylammonium oxalate in acetone–water and methanol–water mixtures are given in Table IV.[11]

The composition of the solvent is given in terms of both weight per cent. and mole per cent. of additive. The reciprocal of the dielectric constant of the solvent (column 3) and the logarithm of the breakpoint concentration (column 5) are also given.

TABLE IV

BREAKPOINT CONCENTRATION, $C_b$, OF *n*-OCTADECYLTRIMETHYLAMMONIUM OXALATE IN ACETONE–WATER AND METHANOL–WATER MIXTURES

| Wt. % org. comp. | Mole % org. comp. | $10^2/D$ | $10^2\sqrt{C_b}$ | $4 + \log C_b$ |
|---|---|---|---|---|
| | | Acetone | | |
| 0 | 0 | 1.274 | 0.8 | −0.19 |
| 9.91 | 3.30 | 1.366 | 1.2 | +0.158 |
| 13.9 | 4.76 | 1.408 | 1.6 | .408 |
| 20.7 | 7.48 | 1.488 | 2.3 | .724 |
| 28.8 | 11.1 | 1.597 | 3.6 | 1.123 |
| | | Methanol | | |
| 20.7 | 12.7 | 1.435 | 1.64 | 0.428 |
| 30.2 | 19.5 | 1.529 | 2.6 | .828 |
| 40.1 | 27.3 | 1.642 | 4.2 | 1.246 |

Inspection of Table IV will show that on a weight per cent. basis, acetone increases the breakpoint concentration more than does methanol. The relationship is shown clearly in Fig. 4

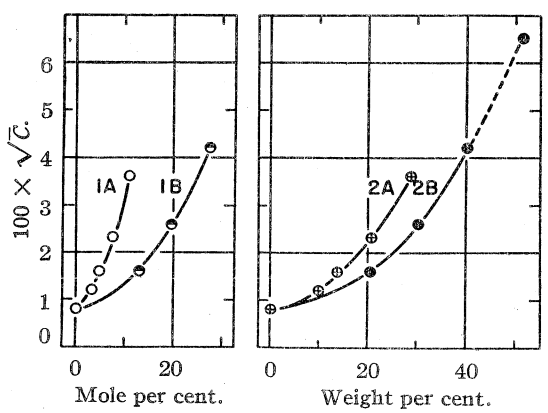



Fig. 4.—Square root of breakpoint concentration for octadecyltrimethylammonium oxalate as function of composition for: water–acetone mixtures (A); water–methanol mixtures (B); Composition: mole per cent, curves 1; weight per cent, curves 2.

(11) The breakpoint concentration of the oxalate in water has not been evaluated experimentally. However, according to Dakin, THIS JOURNAL, **63**, 1007 (1941), the conductance of the oxalate ion is known to be 74.1 and that of the octadecyltrimethylammonium ion[4] 18.3, yielding a value of approximately 92 for the equivalent conductance of the oxalate. If a line be drawn from the Λ axis from the point corresponding to this value and according to the theoretical slope, its intersection with the extension of the experimental curve at higher concentration should give an approximate value of the breakpoint. This procedure leads to the value $\sqrt{C} = 0.8 \times 10^{-2}$.

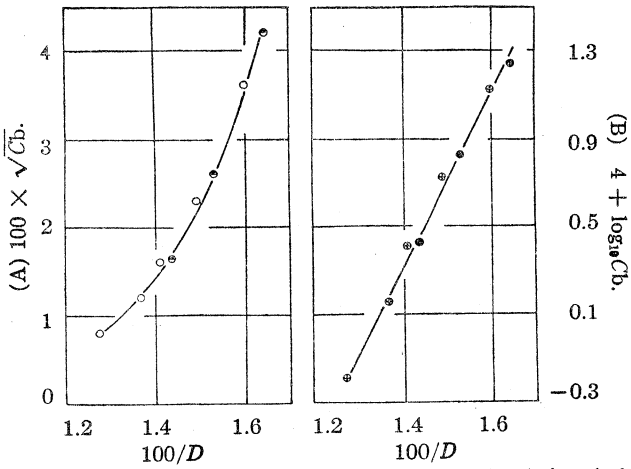



Fig. 5.—Breakpoint concentration of octadecyltrimethylammonium oxalate as a function of reciprocal of dielectric constant $1/D$; (A) $100\sqrt{Cb}$, ○ acetone, ◒ methanol; (B) $\log_{10}Cb$, ⊕ acetone, ● methanol.

where the square root of the breakpoint concentration is plotted as a function of solvent composition (1, mole per cent., and 2, weight per cent. of additive). Curves A relate to acetone and Curves B to methanol. The divergence of the curves is greater on a mole than on a weight per cent. basis. It will be noted that the change in the breakpoint concentration, for a given amount of additive, increases with increasing additive content of the solvent.

The results for acetone and methanol can be brought to substantial coincidence by plotting the breakpoint concentration as a function of the reciprocal of the dielectric constant. In Fig. 5A, the square root of the breakpoint concentration is plotted as a function of the reciprocal of the dielectric constant of the mixtures. It will be noted that the points for the two solvents lie on the same curve within the limit of experimental error. In Fig. 5B, the logarithm of breakpoint concentration is plotted as a function of the reciprocal of dielectric constant. Here the points lie on the same straight line within the experimental error.

The coincidence of the values for the two solvents, when plotted as a function of $1/D$, would seem to indicate a possible connection between the breakpoint phenomenon and the dielectric constant of the solvent medium. However, such a coincidence in the present instance may be purely fortuitous. Thus, Brown[6] has shown that, with dodecylammonium chloride, methanol increases the breakpoint concentration while isopropyl alcohol and *t*-butanol decrease it.

Specific differences between acetone and methanol are more apparent in the cases of the bromate and formate than in that of the oxalate. In 10.1% methanol, the bromate does not show a maximum, while in 15.1% methanol, a maximum occurs: Λ starts to rise at about $C = 3.2 \times 10^{-4}$ and reaches its largest value at $C = 6.2 \times 10^{-4}$; the peak in Λ is about two units high.[4] The highest peak for the bromate comes at about 20% methanol (Curve 3, Fig. 3) and is about 2.5 Λ-units high. In contrast, the bromate in 10.0% acetone shows a maximum starting at $C = 2.4 \times 10^{-4}$, the largest value of Λ comes at $C = 7.3 \times 10^{-4}$, and the peak is 7 Λ-units high.

Similarly, in the case of the formate, the maximum phenomenon is more pronounced in acetone–water mixtures than it is in methanol–water mixtures. Thus, in 19.4% and 23.5% methanol, the peak for the formate is about 3.5 and 2.5 Λ-units high,[5] respectively, while for the same salt in 10.0 and 13.9% acetone the maximum is 10.7 and 7.5 Λ-units high, respectively.

In 10% acetone, the formate exhibits a higher peak than the bromate; similarly, in a given methanol–water mixture, the formate gives rise to a more pronounced maximum than does the bromate.

As far as the present investigation goes to show, it appears that a salt which exhibits a maximum in Λ in a methanol–water mixture will also show a maximum in an acetone–water mixture, but in the latter case, the start of the rise in Λ comes at a somewhat lower concentration and the height of the peak is markedly greater (perhaps by a factor of two or three). However, the salt concentration corresponding to the maximum value of Λ is about the same in the two solvent mixtures.

## V. Summary

1. Measurements have been made on the conductance of octadecyltrimethylammonium oxalate in water–acetone mixtures (0 to 28.8% acetone by wt.), *n*-octadecyltrimethylammonium formate in 10.0 and 13.9% acetone and *n*-octadecyltrimethylammonium bromate in 10.0% acetone, all at 25°.

2. In water–acetone mixtures, the oxalate shows the breakpoint phenomenon; the critical concentration increases with increasing acetone content of the solvent. The results in water–acetone mixtures are similar to those previously obtained with water–methanol mixtures.

3. The curves obtained by plotting the square root of the breakpoint concentration of octadecyltrimethylammonium oxalate against the reciprocal of the dielectric constant of the solvent for water–acetone and water–methanol mixtures nearly coincide.

4. The logarithm of the critical concentration is a linear function of the reciprocal of the dielectric constant for the oxalate in water–acetone and water–methanol mixtures.

5. *n*-Octadecyltrimethylammonium formate and bromate show maxima in conductance curves for water–acetone as well as for water–methanol mixtures. The peaks for acetone are higher than for methanol.

PROVIDENCE, R. I. RECEIVED AUGUST 31, 1948

# Unit Cell Dimension of Face-centered Cubic Chromium Hydride and Space Groups of Two Chromium Hydrides

BY CLOYD A. SNAVELY[1] AND DALE A. VAUGHAN[1]

Chromium metal normally assumes the body-centered cubic crystalline arrangement. However other crystalline arrangements have been reported for electrodeposited chromium. A hexagonal close-packed structure was first reported in 1926,[2] and an $\alpha$-manganese type structure was reported in 1931.[3] Several workers have identified the hexagonal structure since 1926, but there has been no corroboration of the $\alpha$-manganese type structure. Recently one of the present authors presented additional data[4] which show that the hexagonal structure in electrodeposited chromium is actually a chromium hydride, with the hydrogen in interstitial positions in the hexagonal close-packed lattice. In addition, the existence of a face-centered cubic hydride of chromium was reported. It is desired to present here additional recent work which provides a more precise value for the lattice parameter of the face-centered cubic hydride, and to suggest structures for the chromium hydrides.

The initial studies of the F.C.C. hydride of chromium were made with an X-ray spectrometer, with which it was possible to determine the lattice of a given sample in the form of an electroplate, and to follow any structural changes occurring over a period of time. The data gave definite proof of the existence of the new phase. However, to avoid the well-known pitfalls of the spectrometer method as to errors in intensity of the diffraction maxima resulting from grain size or orientation, and to obtain a complete pattern of the new compound, samples were prepared for study by the powder X-ray diffraction method.

The F.C.C. hydride was deposited from an aqueous plating bath originally made up to contain 1021 g./l. of $CrO_3$, 3.4 g./l. of $SO_4$ and 20 g./l. of cane sugar. The sugar was added to the bath last as a sirup, and had the effect of reducing to the trivalent state from 7 to 10% of the contained chromium. The bath was refrigerated to $5 \pm 4°$ during plating operations. The current density was approximately 0.8 amp./sq. in. Disks of brass $\frac{1}{2}$ in. in diameter and 0.020 in. thick were used as cathodes. The anode was cut from antimonial lead sheet. Plating was continued for periods of from six to twelve hours to provide thick deposits which could be handled easily. After plating, the samples were dropped into dilute nitric acid to dissolve the brass backing disk. Care was necessary in this step, as the heat generated was sufficient to decompose the hydride if the acid was too concentrated. The chromium hydride, which was not attacked by the acid, was then rinsed, dried and crushed into fine particles. It was so brittle that the crushing was easily carried out in a glass beaker, using a glass rod as a pestle. This provided a satisfactory sample for powder X-ray diffraction studies.

The powder photograms were taken with unfiltered chromium radiation ($\lambda$Ka = 2.29090 Å.) in a 114.6 mm. camera of the Buerger design. The data obtained from the diffraction pattern of the new "structure compound," corrected for systematic errors by extrapolation, gave 3.8605 ± 0.0005 Å. for the unit cell dimension. A more precise value could not be obtained owing to the fact that the diffraction maxima were broader than those usually obtained from a material as friable as is this compound. This broadening is believed to be the result of either or both of two factors, namely, small particle size and variations in lattice spacing resulting from variations in the number of interstitially placed hydrogen atoms. The intensities of the diffraction maxima are the same as those of a face-centered cubic metal.

Westgren[5] compiled much of the available data on the metal hydrides, which show that the hydrides are interstitial solid solutions of variable hydrogen content within certain definite composition limits. Westgren concluded that the hydrogen atoms occupy the second largest interstices in the metal lattice, since spatial considerations show that the largest interstice would provide too much space for the accepted value of the hydrogen radius. With few exceptions, hydrides of compositions ranging between $M_2H$ and MH tend to adopt the H.C.P. crystal arrangement. Those of formula MH to $MH_2$ tend to adopt the F.C.C. arrangement. Thus, a complete composition range between the limits $M_2H$ and $MH_2$ is possible, and the crystalline arrangement is governed by the composition.

In the case of $Cr_2H$–CrH, the metal atoms fall in a hexagonal close-packed arrangement with the hydrogen occupying the second largest interstitial positions.[4] However, the metal atoms are not in actual contact with each other, but bond through the hydrogen atoms. Two space groups are possible. If the chromium atoms have true holohedral symmetry, the space group is $D_{6h}^4$-$C6/mmc$. However, if the chromium atoms assume hemihedral symmetry, the space group is $C_{6v}^4$-$C6mc$. These two space groups are indistinguishable by X-ray diffraction methods, and it is only necessary for our purposes to consider one, *e. g.*, the latter. The chromium atoms assume hexagonal positions as H atoms enter the allowed interstitial point positions specified below, until these are filled, whereupon the addition of another hydrogen atom will cause an unstable structure due to the proximity of two hydrogen atoms. If more hydrogen atoms are present than will be included in the H.C.P. structure, the metal atoms assume a face-centered cubic structure which will accept two hydrogen atoms for each chromium atom. The space group becomes $T_d^2$-$F43m$ (or $O_h^5$-$Fm3m$ if all of

(1) Research Engineer, Battelle Memorial Institute, Columbus Ohio.

(2) Ollard and Bradley, *Nature*, **117**, 122 (1926).

(3) Sasaki and Sekito, *Trans. Electrochem. Soc.*, **59**, 437 (1931)

(4) Snavely, *Electrochem. Soc.*, Preprint 92-35 (1947).

(5) Westgren, *J. Franklin Inst.*, **212**, 577 (1931).

the equivalent positions are filled). In both of the postulated structures, the apparent radius of the hydrogen atom is 0.39 Å. which is in the lower range of values obtained from calculations for previously reported hydrides. Postulated point positions for CrH and $CrH_2$ structures[6] are

CrH $C_{6v}^4$-*C*6mc. Wurtzite Hemihedral
Cr at 2(b) 00Z; $1/3, 2/3, 1/2 + Z$ where $Z = 0$
H at 2(b) 00Z; $1/3, 2/3, 1/2 + Z$ where $Z = 3/8$

$CrH_2$ $O_h^5$-*F*m3m Fluorite–Holohedral
Cr at 4(a) 000; $0\ 1/2\ 1/2$; $1/2\ 0\ 1/2$; $1/2\ 1/2\ 0$
H at 8(c) $1/4\ 1/4\ 1/4$; $1/4\ 3/4\ 3/4$; $3/4\ 1/4\ 3/4$; $3/4\ 3/4\ 1/4$
$3/4\ 3/4\ 3/4$; $3/4\ \overline{1/4}\ \overline{1/4}$; $\overline{1/4}\ 3/4\ \overline{1/4}$; $\overline{1/4}\ \overline{1/4}\ 3/4$

The important result of the discovery of these hydrides of chromium is that the radius of the chromium atom no longer constitutes an anomaly within the family of metals. Recent discussions of the chromium atom radius[7,8] have treated the hexagonal hydride as a normal H.C.P. allotropic form of the metal. A somewhat complicated postulate regarding behavior of the electrons in the outer rings was advanced to explain the very large apparent radius (1.35 Å.) of the atom in the H.C.P. arrangement. With the introduction of the hydride concept, the chromium atoms may be considered to undergo only the normal radius change of 3% in passing from the F.C.C or H.C.P. hydride phases to the B.C.C. metallic phase ($r = 1.25$ Å.). The interstitially placed hydrogen atoms expand the metal lattice in both hydride phases and the Goldschmidt correction[9] of 3% provides a radius value of 1.28 Å. which appears to satisfy the X-ray data for these phases.

(6) International Tables for the Determination of Crystal Structures.

(7) Hume-Rothery, "The Structure of Metals and Alloys," 1936.

(8) Pauling, THIS JOURNAL, **69**, 542 (1947).

## Summary

1. A determination of the lattice parameter of F.C.C. chromium hydride is reported. The new value is $a = 3.8605 \pm 0.0005$ Å.

2. Structures are postulated for the F.C.C. and H.C.P. chromium hydrides.

3. Argument is presented to refute the concept that chromium is allotropic.

(9) Goldschmidt, *Z. physik. Chem.*, **133**, 397 (1928).

RECEIVED AUGUST 13, 1948

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[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

# Heat Capacities at Low Temperatures and Entropies of Vanadium Carbide and Vanadium Nitride

BY C. H. SHOMATE[1] AND K. K. KELLEY[2]

In previous papers from this laboratory, Anderson[3] has reported low-temperature heat-capacity measurements of vanadium and three of its oxides and Shomate[4] has reported similar data for vanadium di- and trichlorides. The present paper reports heat capacity measurements throughout the temperature range 50.4 to 298.16°K. and entropies at 298.16°K. of vanadium carbide and vanadium nitride. No similar data for either of these substances are in the literature.

**Materials.**[5]—The starting material for the preparation of vanadium carbide was vanadium containing 8% carbon and only a trace of other impurities. An intimate mixture of this material was made with Norblack sufficient to comply with the formula VC. The mixture was heated in vacuum at 1300 to 1350° for a total of twenty-six hours. After twelve and twenty-two hours heating, the product was analyzed and reground, and minor adjustment was made in the composition. The final product was uniform and showed no signs of incomplete reaction, which also was confirmed by the X-ray diffraction pattern.[6] No free carbon was evident on solution in 1:3 nitric acid. The product was analyzed for vanadium by permanganate titration, after fusion in a mixture of sodium bisulfate and potassium nitrate, and for carbon by absorbing and weighing the carbon dioxide evolved on combustion in pure oxygen in the presence of red lead oxide. The results were 80.90% vanadium and 19.04% carbon, as compared with the theoretical 80.92% and 19.08%, respectively.

Vanadium containing carbon, as mentioned above, also was the source material for the preparation of vanadium nitride. A 5:1, by volume, mixture of purified nitrogen and hydrogen was passed over the finely ground carburized vanadium at 1200° for twenty-eight hours. This gas mixture slowly replaced carbon by nitrogen, the carbon being carried out of the hot zone evidently by free radical formation with hydrogen. At seven-hour intervals, the reaction mixture was cooled, removed from the furnace, and reground. After twenty-eight hours of treatment, the product contained 0.76% carbon and an excess of nitrogen. It then was heated for eight hours at 1100° in a stream of pure hydrogen. The final product was analyzed for vanadium by permanganate titration, after burning to oxide and fusing in sodium bisulfate. The average result was 78.24% vanadium, as compared with the theoretical 78.43%. Combustion analysis for residual carbon gave only 0.05%. The X-ray diffraction pattern showed no evidence of materials other than vanadium nitride.

**Heat Capacities.**—The heat capacities were measured with apparatus previously described.[7] The results, expressed in defined calories (1 cal. = 4.1833 int. joules) per mole, are listed in Table I and are plotted against temperature in Fig. 1.

(1) Formerly chemist, Pacific Experiment Station, Bureau of Mines.

(2) Supervising Engineer, Pacific Experiment Station, Bureau of Mines.

(3) Anderson, THIS JOURNAL, **58**, 564 (1936).

(4) Shomate, *ibid.*, **69**, 220 (1947).

(5) The preparations and analyses of these substances were conducted by A. E. Salo, formerly chemist, Pacific Experiment Station, Bureau of Mines.

(6) X-Ray diffraction examinations of both substances were made by E. V. Potter, formerly physicist, Salt Lake City Station, Bureau of Mines.

(7) Kelley, Naylor and Shomate, Bureau of Mines Technical Paper 686, 1946, 34 pp.

The molecular weights accord with the 1947 International Atomic Weights. The samples of carbide and nitride weighed 284.19 g. and 351.29 g., respectively, corrected to vacuum.

The heat capacity curves follow a normal course, the nitride curve being higher at all temperatures. The difference in heat capacity ranges from 0.6 cal./deg./mole at 50°K. to 1.1 cal./deg./mole at 298.16°K. At the lowest points measured the heat capacity of the carbide is just on the verge of following the $T^3$-law, while an additional 20° lower temperature would be required to bring the nitride heat capacity to this region. Values of the heat capacities at 298.16°K., as read from smooth curves, also are included in Table I.

TABLE I

MOLAL HEAT CAPACITY OF VC (MOL. WT., 62.96)

| T, °K. | $C_p$, cal./deg. | T, °K. | $C_p$, cal./deg. | T, °K. | $C_p$, cal./deg. |
|---|---|---|---|---|---|
| 52.5 | 0.5895 | 115.1 | 3.132 | 216.2 | 6.326 |
| 56.5 | .7180 | 125.2 | 3.525 | 226.0 | 6.555 |
| 60.2 | .8504 | 135.1 | 3.894 | 235.8 | 6.774 |
| 64.3 | 1.007 | 145.6 | 4.265 | 246.1 | 6.988 |
| 68.5 | 1.175 | 155.3 | 4.595 | 256.2 | 7.202 |
| 72.7 | 1.351 | 165.5 | 4.921 | 266.1 | 7.382 |
| 77.0 | 1.532 | 175.5 | 5.237 | 276.2 | 7.577 |
| 85.0 | 1.871 | 185.6 | 5.527 | 286.3 | 7.762 |
| 94.7 | 2.287 | 195.9 | 5.809 | 297.0 | 7.955 |
| 104.4 | 2.696 | 205.8 | 6.062 | 298.16 | (7.970) |

MOLAL HEAT CAPACITY OF VN (MOL. WT., 64.96)

| | | | | | |
|---|---|---|---|---|---|
| 52.6 | 1.272 | 115.1 | 4.255 | 216.1 | 7.483 |
| 56.7 | 1.484 | 125.1 | 4.649 | 226.1 | 7.727 |
| 60.9 | 1.702 | 135.0 | 5.036 | 235.8 | 7.925 |
| 65.1 | 1.925 | 145.6 | 5.413 | 246.1 | 8.159 |
| 69.4 | 2.150 | 155.5 | 5.759 | 256.1 | 8.379 |
| 73.5 | 2.365 | 165.4 | 6.085 | 266.0 | 8.546 |
| 80.0 | 2.688 | 175.3 | 6.415 | 276.0 | 8.727 |
| 84.8 | 2.917 | 185.6 | 6.700 | 286.1 | 8.899 |
| 94.7 | 3.376 | 195.9 | 6.980 | 296.3 | 9.053 |
| 104.5 | 3.809 | 205.8 | 7.244 | 298.16 | (9.080) |

**Entropies.**—The entropies were calculated in the usual manner, the portion between 52.00 and 298.16°K. being obtained by numerical integration of a plot of $C_p$ against log $T$ and the portion below 52.00°K. being obtained by extrapolation. The latter was accomplished by the empirical use of Debye functions, $D(476/T)$ and $D(351/T)$, respectively, for the carbide and nitride. These functions fit the measured data to within 0.02 cal./deg./mole, or better, at temperatures below 70 and 80°K., respectively. The results of the entropy calculations are in Table II. It is noteworthy that the extrapolated portions of the entropies are only 3.0 and 5.3% of the totals at 298.16°K.

TABLE II

ENTROPIES AT 298.16°K. (E. U./MOLE)

| | VC | VN |
|---|---|---|
| 0–52.00°K. (extrapolated) | 0.20 | 0.47 |
| 52.00–298.16°K. (measured) | 6.57 | 8.44 |
| $S^\circ_{298.16}$ | 6.77 ± 0.03 | 8.91 ± 0.04 |

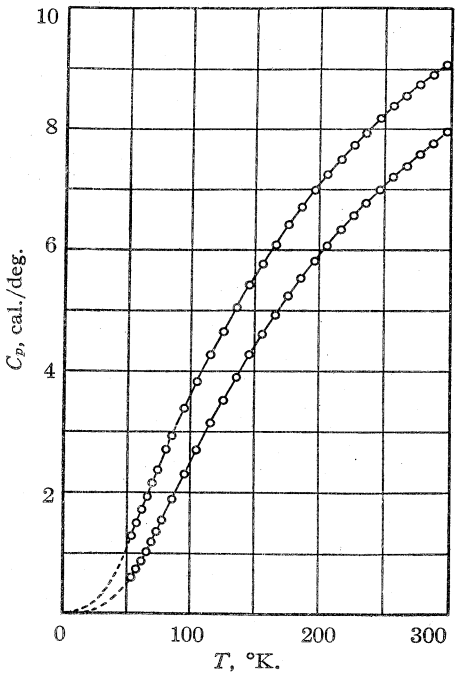



Fig. 1.—Molal heat capacities: upper curve, VN; lower curve, VC.

The results in Table II and the entropies of the elements[8] ($S^\circ_{298.16}$ = 7.0 ± 0.1 for V, $S^\circ_{298.16}$ = 1.36 ± 0.03 for C, and $S^\circ_{298.16}$ = 45.79 ± 0.01 for $N_2$) yield $\Delta S^\circ_{298.16}$ = −1.6 ± 0.1 for the entropy of formation of vanadium carbide from the elements and $\Delta S^\circ_{298.16}$ = −21.0 ± 0.1 for the entropy of formation of vanadium nitride from the elements.

## Summary

The heat capacities of vanadium carbide and vanadium nitride were measured throughout the temperature range 50.4 to 298.16°K.

The entropies of vanadium carbide and nitride are, respectively, $S^\circ_{298.16}$ = 6.77 ± 0.03 and $S^\circ_{298.16}$ = 8.91 ± 0.04. The corresponding entropies of formation from the elements are $\Delta S^\circ_{298.16}$ = −1.6 ± 0.1 and $\Delta S_{298.16}$ = −21.0 ± 0.1.

BERKELEY, CALIFORNIA RECEIVED AUGUST 2, 1948

(8) Kelley, Bureau of Mines Bulletin 434, 1941, 115 pp.

[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

# High Temperature Heat Contents of Vanadium Carbide and Vanadium Nitride

BY E. G. KING[1]

In a recent paper, Shomate and Kelley[2] reported low temperature heat capacity data for vanadium carbide and vanadium nitride, but with the exception of three measurements of vanadium nitride between 273 and 732°K. by Sato,[3] no high temperature heat content values have been available for these substances. This paper reports the results of high temperature heat content measurements covering the temperature range from 298 to 1611°K.

## Materials and Method

The materials used in the present work were identical with those employed by Shomate and Kelley.[2] Reference is made to their paper for the description of methods of preparation, chemical analyses and X-ray examinations.

The heat content measurements were made by the "drop" method, for which apparatus and experimental procedure have been described[4] previously. The calorimeter was calibrated electrically in terms of international joules and conversion to calories was made by the relation, 1 cal. = 4.1833 int. joules.

During the measurements the samples were contained in platinum–rhodium alloy capsules, the heat contents of which were determined by separate experiments. The capsules, after being filled with sample, were evacuated of air, filled with helium, and then quickly sealed gas-tight by platinum welding.

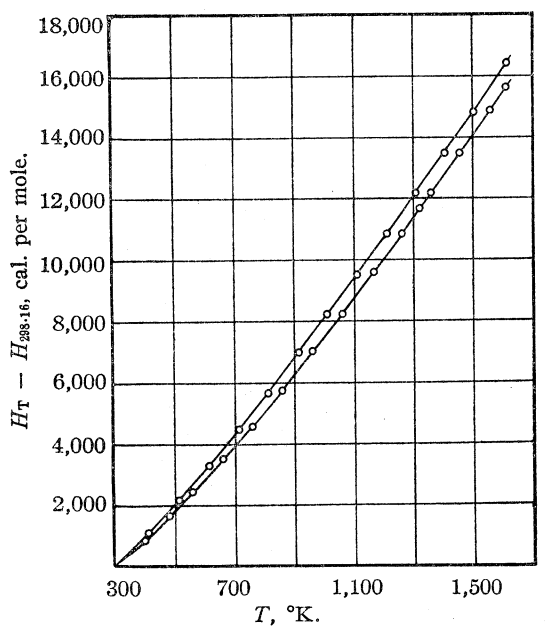



Fig. 1.—High temperature heat contents: upper curve, VN; lower curve, VC.

The weights of materials used in the measurements were 17.1426 g. of vanadium carbide and 19.3105 g. of vanadium nitride, corrected to vacuum by means of the densities, 5.93 g./cc. and 6.21 g./cc., respectively. The heat content of the empty capsule averaged about 12% of the total heat content in each instance.

## Results

The experimental results, covering the temperature range 298° to 1611°K., are listed in Table I and shown plotted against temperature in Fig. 1. In Table I, $T$, °K., is the temperature of the sample immediately before dropping into the calorimeter, and $H_T - H_{298.16}$ is the heat liberated per gram mole in cooling from this temperature to 298.16°K. The molecular weights are in accord with the 1947 International Atomic Weights.

TABLE I

HEAT CONTENTS ABOVE 298.16°K. (EXPERIMENTAL VALUES)

| VC (mol. wt. = 62.96) | | VN (mol. wt. = 64.96) | |
|---|---|---|---|
| $T$, °K. | $H_T - H_{298.16}$, cal./mole | $T$, °K. | $H_T - H_{298.16}$, cal./mole |
| 397.2 | 855 | 408.1 | 1,105 |
| 476.9 | 1,660 | 511.0 | 2,195 |
| 557.2 | 2,435 | 609.6 | 3,310 |
| 657.4 | 3,500 | 709.8 | 4,475 |
| 756.4 | 4,570 | 807.7 | 5,685 |
| 858.1 | 5,765 | 910.0 | 6,970 |
| 958.1 | 7,000 | 1006.8 | 8,220 |
| 1057.0 | 8,220 | 1106.6 | 9,520 |
| 1162.9 | 9,580 | 1206.6 | 10,840 |
| 1258.1 | 10,810 | 1306 | 12,170 |
| 1319 | 11,620 | 1406 | 13,490 |
| 1359 | 12,150 | 1503 | 14,830 |
| 1458 | 13,470 | 1611 | 16,400 |
| 1558 | 14,870 | | |
| 1611 | 15,620 | | |

Measurements at temperatures above 1611°K. were invalidated by the progressive development of embrittlement, which finally produced leaks in the platinum–rhodium alloy capsules. The occurrence of a leak was readily detectable by weighing the capsule and contents after each of the higher temperature determinations, because of resulting oxidation of the sample. The capsules remained gas-tight for all determinations listed in Table I.

It is evident from Fig. 1 that the behavior of these substances is normal in all respects. The heat content of vanadium nitride is the higher throughout the measured temperature range, thus extending the similar observation of Shomate and Kelley[2] for low temperatures. The three previous determinations of Sato[3] for vanadium nitride deviate from the present work and merit no weight in comparison. The deviations are, respectively,

(1) Chemist, Pacific Experimental Station, Bureau of Mines.

(2) Shomate and Kelley, THIS JOURNAL, **71**, 314 (1949).

(3) Sato, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **34**, 241 (1938).

(4) (a) Southard, THIS JOURNAL, **63**, 3142 (1941); (b) Kelley, Naylor and Shomate, U. S. Bureau of Mines Technical Paper 686, 1946.

−1.4% at 373°K., +2.2% at 578°K., and +4.9% at 732°K., the temperatures being those reported by Sato.

Table II gives heat content values read from smooth curves at 100° intervals, together with the corresponding entropy increments above 298.16°K. The latter were computed from and exactly match the former.

TABLE II

HEAT CONTENTS AND ENTROPIES ABOVE 298.16°K. (SMOOTH VALUES)

| | VC | | VN | |
|---|---|---|---|---|
| $T$, °K. | $H_T - H_{298.16}$, cal./mole | $S_T - S_{298.16}$, cal./deg./mole | $H_T - H_{298.16}$, cal./mole | $S_T - S_{298.16}$, cal./deg./mole |
| 400 | 890 | 2.55 | 1,010 | 2.91 |
| 500 | 1,850 | 4.70 | 2,080 | 5.30 |
| 600 | 2,870 | 6.55 | 3,200 | 7.34 |
| 700 | 3,950 | 8.22 | 4,370 | 9.14 |
| 800 | 5,090 | 9.74 | 5,590 | 10.76 |
| 900 | 6,280 | 11.14 | 6,850 | 12.25 |
| 1000 | 7,510 | 12.43 | 8,130 | 13.60 |
| 1100 | 8,770 | 13.64 | 9,430 | 14.84 |
| 1200 | 10,060 | 14.76 | 10,750 | 15.99 |
| 1300 | 11,380 | 15.81 | 12,090 | 17.06 |
| 1400 | 12,720 | 16.80 | 13,450 | 18.07 |
| 1500 | 14,080 | 17.74 | 14,820 | 19.01 |
| 1600 | 15,450 | 18.63 | 16,200 | 19.90 |

High temperature heat content equations were derived by the method of Shomate[5]; using all the data of Table I and the molal heat capacities[2] at 298.16°K., $C_{p,\ 298.16} = 7.970$ for vanadium carbide and $C_{p,298.16} = 9.080$ for vanadium nitride. The resulting equations, which follow, fit the measured data to within an average deviation of 0.3% in each instance.

$$\text{VC: } H_T - H_{298.16} = 9.18T + 1.65 \times 10^{-3}T^2 + 1.95 \times 10^5T^{-1} - 3538$$

$$\text{VN: } H_T - H_{298.16} = 10.94T + 1.05 \times 10^{-3}T^2 + 2.21 \times 10^5T^{-1} - 4096$$

The corresponding molar heat capacity equations are:

$$\text{VC: } C_p = 9.18 + 3.30 \times 10^{-3}T - 1.95 \times 10^5T^{-2}$$

$$\text{VN: } C_p = 10.94 + 2.10 \times 10^{-3}T - 2.21 \times 10^5T^{-2}$$

## Summary

High temperature heat contents above 298.16°K. of vanadium carbide and vanadium nitride were measured from about 400° to 1611°K. A table of heat content and entropy increments above 298.16°K. is reported, and heat content and heat capacity equations are derived.

(5) Shomate, THIS JOURNAL, **66**, 928 (1944).

BERKELEY, CALIFORNIA RECEIVED SEPTEMBER 16, 1948

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[CONTRIBUTION FROM THE PACIFIC EXPERIMENT STATION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

# Low-Temperature Heat Capacity and High-Temperature Heat Content of Ammonium Vanadate

BY S. S. TODD[1] AND J. P. COUGHLIN[1]

Ammonium vanadate is the commercially most readily obtainable, substantially pure, vanadium-containing substance and frequently is the source material in the preparation of other vanadium compounds. Consequently, considerable interest attaches to its properties. This paper reports the results of low temperature heat capacity measurements in the temperature range 51.4 to 298.16°K. and of high temperature heat content measurements in the temperature range 298.16 to 550°K. No previous similar data are available for this substance.

**Material.**—Ammonium vanadate of 96.7% purity was dissolved in hot concentrated hydrochloric acid until saturation, diluted by two volumes of distilled water, and filtered. The filtrate was heated to boiling, oxidized with ammonium persulfate in the presence of a small amount of nitric acid, and again filtered. The oxidized solution was neutralized with ammonium hydroxide in the presence of an excess of ammonium chloride. The precipitated ammonium vanadate was filtered off, washed several times with 1:40 ammonium hydroxide and once with distilled water, and finally dried for twenty-four hours at 75 to 80°. The product was analyzed by dissolving in 10% sulfuric acid, reducing the vanadium with sulfur dioxide, expelling excess sulfur dioxide by bubbling with a stream of carbon dioxide, and titrating with 0.1 $N$ potassium permanganate. The analysis gave 43.55% vanadium content, which is the theoretical value for ammonium vanadate.

(1) Chemist, Pacific Experiment Station, Bureau of Mines.

## Measurements and Results

Both the low temperature heat capacity and high temperature heat content measurements were made by means of previously described[2] apparatus and methods. The defined calorie (1 cal. = 4.1833 int. joules) is used throughout. All weighings were corrected to vacuum and the molecular weight of ammonium vanadate is taken as 116.99 in accordance with the 1947 International Atomic Weights. The ice point is taken as 273.16°K.

A 41.810 g. sample was employed in the low temperature heat capacity measurements. The measured results are given in Table I and are plotted against temperature in Fig. 1. The heat capacity curve is normal, there being no indication whatever of the transition encountered in similar measurements of the ammonium halides[3,4,5] and

(2) Kelley, Naylor and Shomate, U. S. Bureau of Mines, Tech. Paper 686, 1946, 34 pp.

(3) Simon, *Ann. Physik* (4), **68**, 241 (1922).

(4) Simon Simson, and Ruhemann, *Z. physik. Chem.*, **129**, 344 (1927).

(5) Extermann and Weigle, *Helv. Phys. Acta*, **15**, 455 (1942).

TABLE I

LOW-TEMPERATURE HEAT CAPACITY OF $NH_4VO_3$

| T, °K. | $C_p$, cal./deg./mole | T, °K. | $C_p$, cal./deg./mole | T, °K. | $C_p$, cal./deg./mole |
|---|---|---|---|---|---|
| 53.5 | 6.041 | 115.1 | 15.32 | 216.6 | 25.50 |
| 57.6 | 6.703 | 124.9 | 16.58 | 226.7 | 26.19 |
| 62.0 | 7.397 | 136.2 | 17.96 | 236.6 | 26.87 |
| 66.3 | 8.059 | 146.3 | 19.07 | 246.2 | 27.59 |
| 70.8 | 8.776 | 156.0 | 20.09 | 256.3 | 28.29 |
| 75.7 | 9.583 | 166.2 | 21.13 | 266.5 | 28.91 |
| 80.1 | 10.29 | 176.3 | 22.12 | 276.5 | 29.62 |
| 84.2 | 10.90 | 186.3 | 22.98 | 286.8 | 30.19 |
| 95.1 | 12.55 | 196.2 | 23.86 | 296.8 | 30.87 |
| 104.8 | 13.91 | 206.7 | 24.68 | 298.16 | (30.91) |

ammonium sulfate.[6] In this respect the substance behaves similarly to both hydrated and anhydrous ammonium–aluminum sulfate.[6] (The heat capacity value at 298.16°K., included in Table I, was read from a smooth curve.)

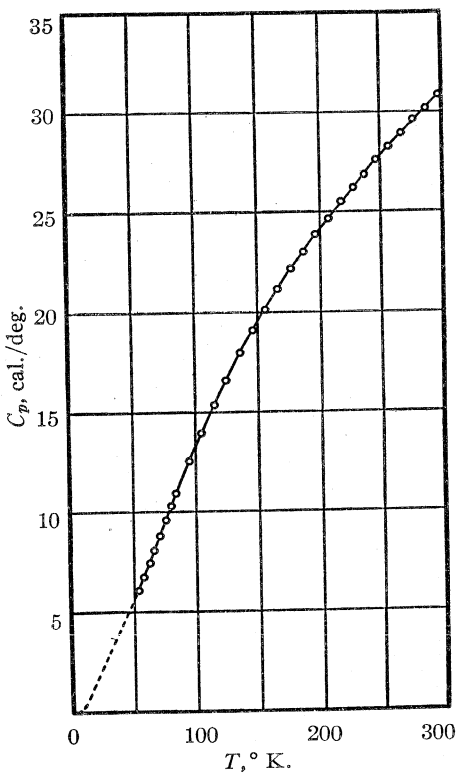



Fig. 1.—Molal heat capacity at low temperatures of ammonium vanadate.

The entropy of ammonium vanadate, obtained from these heat capacity measurements, is $S^\circ_{298.16} = 33.6 \pm 0.3$ cal./deg./mole. Of this amount, 30.00 is the measured portion between 51.00 and 298.16°K., and 3.61 is the extrapolated portion between 0 and 51.00°K. The former was obtained by numerical integration of a plot of the measured heat capacity against log $T$. The latter was obtained from the following empirical sum of Debye and Einstein functions, which represent the measured heat capacity over the entire experimental range to within 1%

$$D\left(\frac{125}{T}\right) + 3E\left(\frac{331}{T}\right) + 3E\left(\frac{919}{T}\right).$$

Combination of this entropy value and the entropies of the elements[7] leads to $\Delta S^\circ_{298.16} = -132.3$ as the entropy of formation of ammonium vanadate. Bichowsky and Rossini[8] give $\Delta H_{293.16} = -283{,}500$ cal. per mole as the heat of formation. (The correction of the latter value to 298.16°K. is negligible.) The free energy of formation from the elements is, therefore, $\Delta F^\circ_{298.16} = -244{,}050$ cal. per mole.

TABLE II

HIGH TEMPERATURE HEAT CONTENTS OF $NH_4VO_3$

| T, °K. | $H_T - H_{298.16}$, cal./mole | T, °K. | $H_T - H_{298.16}$, cal./mole | T, °K. | $H_T - H_{298.16}$, cal./mole |
|---|---|---|---|---|---|
| 351.7 | 1785 | 525.7 | 8,460 | 569.3 | (10,730) |
| 401.5 | 3625 | 554.7 | (9,795) | 576.8 | (10,920) |
| 452.8 | 5575 | 564.1 | (10,320) | 597.4 | (12,290) |
| 502.7 | 7510 | | | | |

A 4.3485-g. sample of ammonium vanadate was used in the high temperature heat content measurements. During measurement the substance

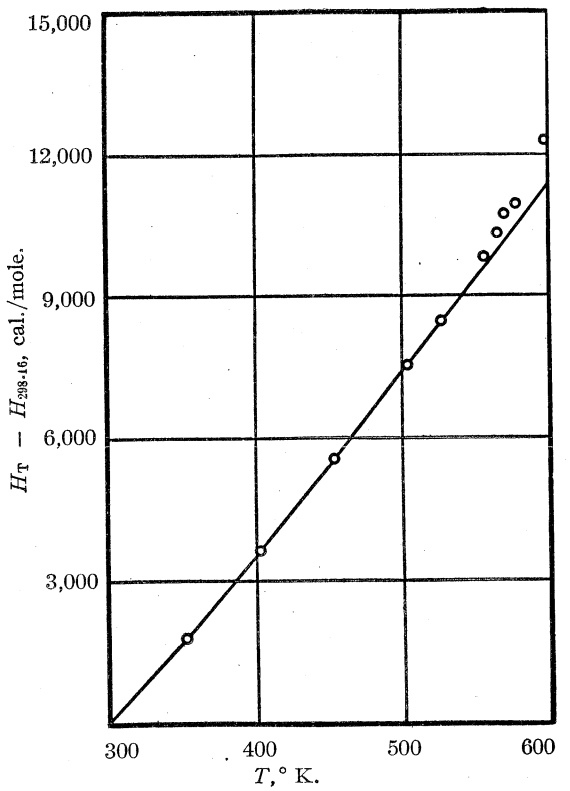



Fig. 2.—High temperature heat content of ammonium vanadate.

(6) Shomate, THIS JOURNAL, 67, 1096 (1945).

(7) Kelley, U. S. Bureau of Mines, Bull. 434, 1941, 115 pp.

(8) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936.

was contained in a platinum–rhodium capsule which was sealed gas tight by gold soldering. The heat content of the capsule was determined by separate measurements. The experimental results are listed in Table II and are plotted in Fig. 2.

The substance behaved satisfactorily up to about 550°K. Above that temperature the results are somewhat discordant and become progressively too high. This is attributed to beginning of thermal decomposition of the substance, which is confirmed by the fact that the gas pressure within the platinum–rhodium capsule became large enough to cause rupture at 610°K. All values in parentheses in Table II show decomposition effects. Between 298.16 and 550°K., the results are represented to within an average deviation of 0.8% by the equation

$$H_T - H_{298.16} = 45.42T + 12.90 \times 10^5 T^{-1} - 17{,}869$$

The corresponding molal heat-capacity equation is

$$C_p = 45.42 - 12.90 \times 10^5 T^{-2}$$

These equations, however, should not not be employed for extrapolation to higher temperatures.

Table III gives smooth values of the high-temperature heat content and corresponding entropy increments above 298.16°K.

TABLE III

HEAT CONTENT AND ENTROPY INCREMENTS FOR AMMONIUM VANADATE ABOVE 298.16°K.

| $T$, °K. | $H^\circ_T - H^\circ_{298.16}$, cal./mole | $S^\circ_T - S^\circ_{298.16}$, cal./deg./mole |
|---|---|---|
| 350 | 1730 | 5.35 |
| 400 | 3580 | 10.29 |
| 450 | 5480 | 14.76 |
| 500 | 7420 | 18.85 |
| 550 | 9390 | 22.61 |

## Summary

The low temperature heat capacity of ammonium vanadate was measured throughout the temperature range 51.4 to 298.16°K. The entropy is $S^\circ_{298.16} = 33.6 \pm 0.3$ cal./deg./mole.

The high temperature heat content of ammonium vanadate was measured throughout the temperature range 298.16 to 550°K. Thermal decomposition precluded obtaining satisfactory results at higher temperatures. Heat content and entropy increments above 298.16°K. are tabulated.

BERKELEY, CALIFORNIA RECEIVED AUGUST 2, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# Thermodynamic Data on the Cadmium Chloride Complexes Determined from the Solubility of Cadmium Ferricyanide

BY EDWARD L. KING[1]

In this paper data on the solubility of cadmium ferricyanide in solutions containing chloride ion will be presented. It is possible to interpret these data in terms of the formation of the cadmium chloride complexes: $CdCl^+$, $CdCl_2$ and $CdCl_3^-$. These complexes have been studied previously by I. Leden[2] and others.[3] The solubility measurements have been carried out at several temperatures making it possible to calculate heats of formation and entropies of the several complex species as well as the several equilibrium constants.

## Experimental Work

**Preparation of Solutions Used in These Experiments.**—All solutions were prepared using doubly distilled water, the second distillation being from an alkaline permanganate solution. Analytical reagent grade chemicals were used in all cases without further purification. In the preparation of the sodium perchlorate solution, equivalent amounts of perchloric acid and sodium carbonate were mixed.

**Preparation of the Cadmium Ferricyanide.**—The solid used in the solubility measurements was prepared by precipitating cadmium ferricyanide at room temperature from a freshly prepared dilute solution of potassium ferricyanide by the addition of cadmium nitrate solution. The solid separates as a very finely divided yellow material. Analyses of the material used in the solubility measurements as well as several other samples of solid precipitated in the presence of a low (less than 0.1 *M*) excess of potassium ferricyanide or in the presence of an excess of cadmium nitrate were performed. The solid was decomposed by heating with concentrated sulfuric acid. The iron and cadmium were then separated by isopropyl ether extraction of iron as described by Swift.[4] The iron was analyzed iodometrically[5] and cadmium was determined gravimetically by conversion to the sulfate. The ratio of cadmium to iron in the five different samples analyzed ranged from 1.47 to 1.52 with an average of 1.49. Thus the finely divided yellow solid is $Cd_3\{Fe(CN)_6\}_2 \cdot xH_2O$. The degree of hydration of the solid was not determined as in no case was the solid dried and weighed; only the ratio of cadmium to iron was determined.

**Solubility Measurements.**—Before using the $Cd_3\{Fe(CN)_6\}_2 \cdot xH_2O$ in a solubility determination, it was washed several times with a dilute solution of sodium perchlorate. Then each portion was washed with a solution of the composition to be used in the solubility experiment. The solubility equilibrium is established very rapidly; in no experiment was a slowness detected even though in the experiments at 47.5° samples were removed after two minutes stirring. In several experiments equilibrium was approached from the supersaturated side as well as from the other side. Because of the high rate of solution, it was possible to carry out the measurements in open vessels; no errors due to evaporation would be expected. The

(1) Present address: Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

(2) Leden, *Z. physik. Chem.*, **188A**, 160 (1941).

(3) Reference 2 contains a comprehensive review.

(4) E. H. Swift, "A System of Chemical Analysis," Prentice Hall, New York, N. Y., 1946, pp. 291–298.

(5) E. H. Swift, *op. cit.*, pp. 298–300.

solid was stirred with the solution in 40 ml. test-tubes with a mechanical stirrer in a thermostat. At two or three different times, aliquots of solution and suspended solid were removed, delivered into a centrifuge cone and centrifuged to remove the suspended solid, which otherwise settled exceedingly slowly upon standing. By using 15 ml. centrifuge cones which were centered in the cups for 50-ml. cones by use of a rubber stopper with the appropriate sized hole, it was possible to jacket the cone with the thermostat media. Only in the case of the experiments at 47.5° was real trouble experienced during centrifugation in keeping the solution at the approximate temperature of the experiment. In these experiments at 47.5°, hot air was blown into the centrifuge (International Clinical model) through the small hole in the lid. Even with this device, the solution temperature would drop several degrees during the centrifugation. Because the saturated solution at 47.5° will be supersaturated at room temperature, a measured aliquot of the solution from the centrifugation was diluted for analysis.

The concentration of dissolved cadmium ferricyanide was determined by measurement of the ferricyanide concentration by means of light absorption. The absorption at several wave lengths in the region 4200 to 4600 Å. was determined with a Beckman Quartz Spectrophotometer. This proved to be a convenient method of analysis at the concentrations under consideration.

## Experimental Results and Discussion

In practically all experiments two or three portions of saturated solution were removed at various times. The average variation in the concentrations in the successive aliquots in a given experiment was 1.7% for the experiments at 0.0° and 25.0°, while in the experiments at 47.5° it was 3%. The greater variation in the experiments at 47.5° is due no doubt to the temperature variations during centrifuging. The results of the solubility experiments are presented in Table I and also in Fig. 1.

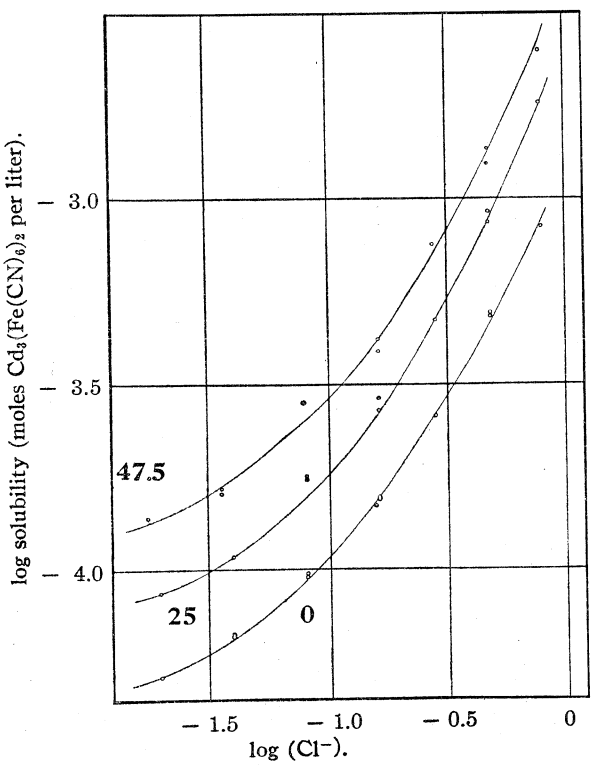



Fig. 1.—Solubility of $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$ in solutions containing chloride ion at 0, 25 and 47.5°.

**The Equilibria which are Consistent with Solubility Data.**—The equations for the net reactions occurring when $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$ dissolves in a solution containing chloride ion are

$$1/3Cd_3(Fe(CN)_6)_2 \cdot xH_2O + nCl^- = CdCl_n^{+2-n} + 2/3Fe(CN)_6^{=} + x/3H_2O \quad (1)$$

$n = 0, 1, 2, 3$

The equilibrium constants for these reactions are

$$K_n = (CdCl_n^{+2-n})(Fe(CN)_6^{=})^{2/3}/(Cl^-)^n$$

The equilibrium constants for the reactions of cadmium ion to form the several complex species

$$Cd^{++} + nCl^- = CdCl_n^{+2-n} \quad (2)$$

TABLE I

SOLUBILITY OF $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$

All solutions: 2.96 $M$ $Na^+$; 0.04 $M$ $H^+$; $\{3.00 - (Cl^-)\}$ $M$ $ClO_4^-$

| Total concentration of $Cl^-$, mole/liter | Observed solubility,[c] moles $Cd_3(Fe(CN)_6)_2$ per liter × $10^5$ 0.0°C. | 25.0°C. | 47.5°C.[b] |
|---|---|---|---|
| 0.000 | 4.0, 3.75 | 6.8, 6.5 | 9.9, 9.4 |
| .018 | | | 13.8 |
| .020 | 5.15 | 8.65 | |
| .036 | | | 16.0, 16.5 |
| .040 | 6.6, 6.7 | 10.8, 10.8 | |
| .080 | 9.5, 9.7 | 17.8, 17.4 | 26.8 |
| .154 | 14.8[a] | | |
| .160 | 15.6, 15.4 | 28.9, 26.8 | 38.7, 41.7 |
| .280 | 25.9 | 46.9 | 75 |
| .480 | 49, 48 | 83, 92 | 124, 137 |
| .800 | 84 | 182 | 251 |

[a] In this experiment $(H^+) = 0.15$ $M$, $(Na^+) = 2.85$ $M$. [b] In all experiments at 47.5° $(H^+) = 0.02$ $M$, $(Na^+) = 2.98$ $M$. [c] When two figures are given they are the results of two independent experiments.

are related to the $K$'s for the solubility reactions in the following manner

$$\beta_n = \frac{(CdCl_n^{+2-n})}{(Cd^{++})(Cl^-)^n} = \frac{K_n}{K_0}$$

It is seen that $K_0$ is the cube root of the solubility product constant for $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$.

The solubility experiments were all carried out at constant ionic strength made up of sodium ion, hydrogen ion, perchlorate ion and chloride ion. In the solutions in which the solid is most soluble, the increased ionic strength due to the ferricyanide ion and the various complexes is of the order of one per cent. of the total. The approximation has been made that the activity coefficients of the various species are not affected at constant ionic strength when the medium is varied from 3.0 $M$ $ClO_4^-$ to 2.20 $M$ $ClO_4^-$, 0.80 $M$ $Cl^-$. Thus the equilibrium constants presented will all be concentration equilibrium constants for a solution of ionic strength of 3.00.

**The Value of $K_0$, the Cube Root of the Solubility Product Constant for $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$.**—The values of $K_0$ at the several tempera-

tures can be determined from the results of single experiments at each temperature. This is the measurement of the solubility in the absence of chloride ion. It is seen that $K_0 = S^{5/3} \times 3 \times (2)^{2/3} = 4.76\ S^{5/3}$ where $S$ is the solubility of $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$. Using the values of the solubility of $3.85 \times 10^{-5}$, $6.65 \times 10^{-5}$ and $9.7 \times 10^{-5}$ mole per liter, values of $K_0$ calculated are $2.1 \times 10^{-7}$, $5.2 \times 10^{-7}$ and $9.7 \times 10^{-7}$ at 0°, 25° and 47.5°, respectively.

In the interpretation of the data on the solubility in the presence of chloride ion it is necessary to know that at the concentration of ferricyanide present, no soluble cadmium ferricyanide complexes exist. This was checked in a simple experiment. A solution of $9.1 \times 10^{-4}$ *M* cadmium nitrate in 2.69 *M* sodium perchlorate–0.04 *M* perchloric acid was added with rapid stirring to a solution of the composition: $3.8 \times 10^{-3}$ *M* potassium ferricyanide, 2.96 *M* sodium perchlorate and 0.04 *M* perchloric acid. At a point in the addition of the cadmium solution when the concentration of cadmium was less than $6 \times 10^{-5}$ *M*, precipitation had already occurred. This leads to an upper limit of $K_0$ of $1.4 \times 10^{-6}$ at 25°. This is 2.7-fold higher than calculated from the solubility of the pure salt but would still lead to the result that no more than one per cent. of the cadmium (II) dissolved in a solution of 0.80 *M* chloride ion is present as a ferricyanide complex.

From the values of the equilibrium constants at the three temperatures, it is possible to calculate the heat of solution of $Cd_3\{Fe(CN)_6\}_2 \cdot xH_2O$ in a solution of ionic strength 3.0. When log $K_0$ is plotted *vs.* $1/T$, an approximately straight line results with a slope which corresponds to a $\Delta H$ of solution of 17.2 ± 0.7 kcal. per formula weight of $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$.

**The Dependence of the Solubility upon Hydrogen Ion Concentration.**—In eq. (1) for the net reaction which occurs when cadmium ferricyanide dissolves in a solution containing chloride ion, neither the cadmium chloride complex ion nor ferricyanide ion are shown with attached hydrogen ion. One would expect $CdCl_nH^{+3-n}$ to be a strong acid since hydrochloric acid is strong and the presence of the metal ion would cause an acid strengthening. Kolthoff and Tomsicek[6] have presented data which indicate that ferricyanide ion exists as such at hydrogen ion concentrations as high as $6 \times 10^{-3}$ *M*. In one of the solubility measurements run at 0°, the hydrogen ion concentration was 0.15 *M* instead of 0.04 *M* (see Table I and Fig. 1). It is seen that this experimental point is on the same smooth curve as are the other data. If the species of ferricyanide present in a solution of this hydrogen ion concentration range were $HFe(CN)_6^{=}$, a 3.7-fold change in hydrogen ion concentration would give rise to a change in solubility by a factor of 1.7. Therefore, these data indicate that at a hydrogen ion concentration as high as 0.15 *M*, ferricyanide exists as $Fe(CN)_6^{=}$.

**The Values of the Several Equilibrium Constants.**—It is possible to calculate the various equilibrium constants by a variety of methods. The method which best uses all of the data in the chloride ion concentration range in which the appropriate constant is most relevant is the method of Leden[2] and Connick.[7] A few obvious modifications of the method of Leden make it suitable for the treatment of these solubility data.

It was found necessary to assume the presence in solution of the species $Cd^{++}$, $CdCl^+$, $CdCl_2$ and $CdCl_3^-$ in order to explain the solubility data. It was not necessary to assume the presence of $CdCl_4^{=}$. The values of $K_n$, the equilibrium constants for reactions (1), are given in Table II. The curves in Fig. 1 are calculated using these equilibrium constants and the solubility product constants discussed earlier. Included in Table II are the values of $K_n$ at 25° calculated from Leden's values[2] of $\beta_n$ and the value of $K_0 = 5.2 \times 10^{-7}$.

TABLE II

EQUILIBRIUM CONSTANTS FOR REACTIONS

$$1/3\ Cd_3\{Fe(CN)_6\}_2 \cdot x\ H_2O + n\ Cl^- = CdCl_n^{+2-n} + 2/3\ Fe(CN)_6^{=} + x/3\ H_2O$$

| Temperature, °C. | $K_1 \times 10^5$ | $K_2 \times 10^5$ | $K_3 \times 10^5$ |
|---|---|---|---|
| 0.0 | 0.57 ± 0.04 | 3.7 ± 0.3 | 1.6 ± 0.3 |
| 25.0 (this work) | 1.3 ± 0.15 | 8.0 ± 1 | 13 ± 3.0 |
| (Leden) | 2.0 | 8.8 | 13.5 |
| 47.5 | 3.5 ± 0.5 | 13.0 ± 3.0 | 28 ± 4 |

It should be noted that in the case of the bromide and iodide complexes of cadmium, complexes which involve four halide ions are observed.[2] The chloride complexes appear to be less stable to an extent such that at 0.8 *M* $Cl^-$, the species $CdCl_4^{=}$ is not present at appreciable concentrations.

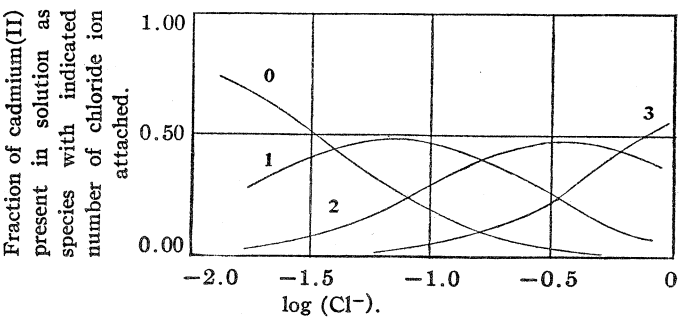



Fig. 2.—Distribution of cadmium (II) among the various complex species at 25°.

The overlapping of the chloride ion concentration ranges in which the various complexes are most important is clearly shown in Fig. 2. In systems where such an overlapping occurs, it is possible to fit the experimental data, unless they

(6) Kolthoff and Tomsicek, *J. Phys. Chem.*, **39**, 955 (1935).

(7) R. E. Connick, private communication.

are exceedingly accurate, with an appreciable range of values for each equilibrium constant. This accounts for the rather large uncertainty shown in values in Table II.

**The Heats of Formation and Entropies of the Several Complexes.**—It is possible to obtain heats of formation of the complex species $CdCl^+$, $CdCl_2$ and $CdCl_3^-$ from the ions $Cd^{++}$ and $Cl^-$ by considering the values of $\beta_n$ as a function of temperature. These data are plotted in Fig. 3. The vertical lines in this figure indicate the ranges of values of $\beta_1$, $\beta_2$ and $\beta_3$ which are consistent with the experimental inaccuracies. Heats of reaction (2) at 25° have been calculated from the slope of these curves. These values are given in the first column of Table III. It is seen that all of the complexes except $CdCl_2$ are formed endothermically. Their stability is due to the entropy increase which occurs upon their formation. Unlike association reactions in the gas phase which are associated with a decrease in entropy, these association reactions of ions in solution are accompanied by an increase in entropy. This is due to the greater freedom of motion of the solvent molecules in the field of the complex compared to their freedom in the field of the several reacting ionic species.

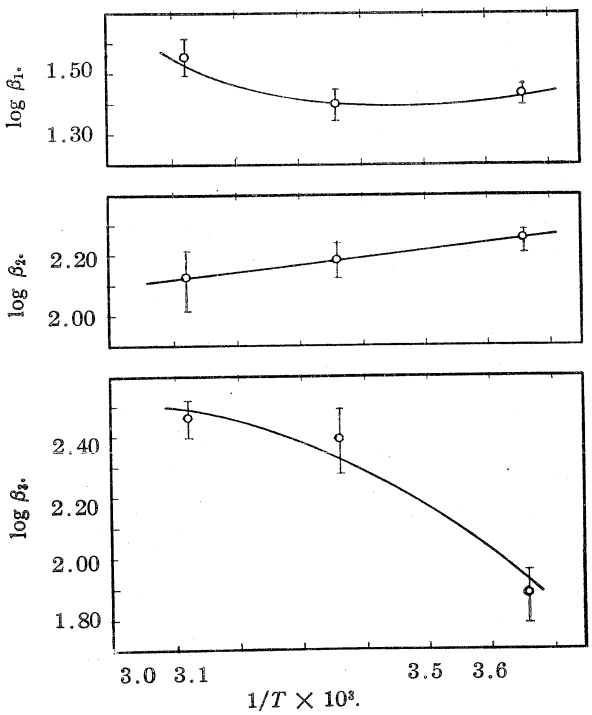



Fig. 3.—Values of $\beta_n$ at various temperatures.

The entropies of the several complex species can be calculated from the $\Delta S$ of the reactions for their formation and the known entropies of cadmium and chloride ions. The entropies of these two ions are given by Latimer, Pitzer and Smith[8] as $-16.4$ for $Cd^{++}$ and $+13.5$ for $Cl^-$. The results of these calculations are given in the last column of Table III. In these calculations the entropies used are for the hypothetical one molal solution while the entropy change is for a hypothetical one molal solution in which the ionic strength is 3.0. The use of the two sets of quantities without correction to the same standard state is the best one can do in view of lack of data regarding the effect of ionic strength changes on the entropy.

TABLE III

VALUES OF HEAT, FREE ENERGY AND ENTROPY CHANGES FOR THE REACTIONS: $Cd^{++} + nCl^- = CdCl_n^{+2-n}$

| Reaction for the formation of | $\Delta H/T$, cal./mole deg. | $-\Delta F/T$, cal./mole deg. | $\Delta S$ cal./mole deg. | $S$ complex |
|---|---|---|---|---|
| $CdCl^+$ | 2.1 | 6.4 | 8.5 | 5.6 |
| $CdCl_2$ | −3.7 | 10.1 | 6.4 | 17.0 |
| $CdCl_3^-$ | 15.5 | 11.0 | 26.5 | 50.7 |

The entropy of the species $CdCl_3^-$ is quite large. That it is probably larger than one would expect is realized if the entropy change for the reaction

$$CdCl_2 + Cl^- = CdCl_3^-$$

is considered. This entropy change is +20.2 entropy units. If the entropy change arises largely from the change in the polarization of water by ionic charges, it might be expected to be small. However Frank and Evans[9] have pointed out that other factors play an important role in determining entropies of dissolved species.

It is very desirable to have more data on the entropies of complex ions in solution such that correlations could be made.

## Summary

The solubility of $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$ has been determined in aqueous solution containing various concentrations of chloride ion at 0.0°, 25.0° and 47.5°. These data have been interpreted on the basis of there being present in solution the species: $Cd^{++}$, $CdCl^+$, $CdCl_2$ and $CdCl_3^-$. The complex species $CdCl_4^{=}$ is not appreciably stable in solutions in which the chloride ion concentration is 0.8 $M$.

The $\Delta H$ of solution of $Cd_3(Fe(CN)_6)_2 \cdot xH_2O$ has been found to be 17.2 ± 0.7 kcal. per formula weight.

The heats and entropies of formation of the several complex species have been calculated by considering the variation of the various equilibrium constants with temperature.

CAMBRIDGE, MASS. RECEIVED JULY 14, 1948

(8) Latimer, Pitzer and Smith, THIS JOURNAL, **60**, 1829 (1938).

(9) Henry S. Frank and Marjorie W. Evans, *J. Chem. Phys.*, **13**, 522 (1945).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, WYANDOTTE CHEMICALS CORPORATION]

# The Hydrogenation of Sodium Bicarbonate to Sodium Formate

BY LESTER G. LUNDSTED

The hydrogenation of an aqueous solution of potassium bicarbonate to potassium formate in 70% yield over a palladium-black catalyst by Bredig and Carter[1] suggested the probability that a similar reaction could be carried out with the cheaper sodium bicarbonate over some of the more recently developed hydrogenation catalysts.

In order to select a suitable catalyst for this study, thirteen catalysts were tested in a preliminary way by attempting to hydrogenate a 5% aqueous solution of sodium bicarbonate. Under the conditions chosen, ten catalysts showed some activity for the reaction while three, copper chromium oxide and manganese and iron chromites, displayed no activity. In Table I will be found a list of the catalysts tested, the conditions used and the percentage of sodium formate found in the products based on the starting sodium bicarbonate. The percentages of sodium formate given are not necessarily the maximum obtainable over individual catalysts since optimum conditions were not determined. This was shown by two experiments with the Universal Oil Products Hydrogenation Catalyst in which the sodium formate in the products was increased from 24 to 75% by an increase in reaction time from two and one-half to eight and one-half hours.

TABLE I

PRELIMINARY TESTS OF CATALYSTS FOR THE HYDROGENATION OF SODIUM BICARBONATE[a]

| Catalyst | Time, hr. | Sodium formate, % |
|---|---|---|
| U. O. P. hydrogenation catalyst | 2.5 | 24.2 |
| Nickel chromite | 1.0 | 45.5 |
| Copper and nickel | 5.0 | 63.5 |
| Zinc chromite | 6.0 | 14.0 |
| Nickel on kieselguhr | 4.0 | 16.0 |
| Copper chromium oxide | 5.0 | 0.0 |
| Raney nickel | 6.0 | 49.0 |
| Ruffert nickel pellets | 5.0 | 64.6 |
| Ruffert nickel | 6.0 | 77.0 |
| Nickel (from $Ni(OOCH)_2$) | 1.0 | 16.0 |
| Boron phosphate on charcoal | 3.0 | 9.1 |
| Iron chromite | 6.0 | 0.0 |
| Manganese chromite | 1.3 | 0.0 |

[a] The tests were carried out under 1800 p. s. i. g. initial hydrogen pressure at a temperature of 200° using 4 g. of catalyst and 600 ml. of a 5% aqueous sodium bicarbonate solution.

The effect of variations in the reaction conditions on the percentage of sodium formate found in the products is shown in Table II for a series of studies with the Ruffert nickel catalyst in a wax support. Over the ranges studied an increase in either the quantity of catalyst or the hydrogen pressure increased the rate of hydrogenation as shown by the higher percentages of sodium formate in the products at the end of one hour. Longer reaction times increased the percentage of sodium formate found in the products when other conditions were such as to favor a low rate of reaction since under such conditions side reactions appeared to be at a minimum. Increasing the concentration of the sodium bicarbonate solution lowered the percentage of sodium formate in the products, although the actual quantity of sodium bicarbonate hydrogenated was greater. In such cases, an increased period of reaction served to raise the percentage of sodium formate in the products. An increase in the reaction temperature increased the rate of the reaction, but when the temperature became too high, side reactions increased to an extent which left little sodium formate in the product.

TABLE II

EFFECT OF VARIABLES ON THE HYDROGENATION OF SODIUM BICARBONATE OVER RUFFERT NICKEL CATALYST

| Expt. | Variable | Catalyst, g. | Conc. of solution.,[1] % | Temp., °C. | Pressure | Time, hr. | Sodium formate, % |
|---|---|---|---|---|---|---|---|
| 58 | Catalyst | 2 | 5 | 200 | 2000 | 1 | 52 |
| 42 | concn. | 4 | 5 | 200 | 2200 | 1 | 67 |
| 44 | | 6 | 5 | 200 | 1700 | 1 | 72 |
| 58 | Time | 2 | 5 | 200 | 2000 | 1 | 52 |
| 55 | | 2 | 5 | 200 | 2000 | 2 | 69 |
| 61 | | 2 | 5 | 200 | 2000 | 3 | 70 |
| 63 | Pres. | 2 | 5 | 200 | 850 | 1 | 42 |
| 58 | | 2 | 5 | 200 | 2000 | 1 | 52 |
| 56 | | 2 | 5 | 200 | 3000 | 1 | 74 |
| 57 | | 4 | 5 | 200 | 1000 | 1 | 47 |
| 42 | | 4 | 5 | 200 | 2200 | 1 | 67 |
| 54 | | 4 | 5 | 200 | 2800 | 1 | 78 |
| 59 | Temp. | 4 | 5 | 150 | 2000 | 1 | 14 |
| 42 | | 4 | 5 | 200 | 2000 | 1 | 67 |
| 43 | | 6 | 5 | 200 | 2000 | 1 | 71 |
| | | 6 | 5 | 250 | 2000 | 1 | 10 |
| 67 | | 8 | 5 | 150 | 2000 | 1 | 16 |
| 64 | | 8 | 5 | 200 | 2000 | 1 | 58 |
| 42 | Soln. | 4 | 5 | 200 | 2000 | 1 | 67 |
| 62 | concn. | 4 | 16⅔ | 200 | 2000 | 1 | 54 |
| 66 | | 4 | 16⅔ | 200 | 2000 | 2 | 62 |

Similar results can also be expected over other catalysts although the allowable variation in reaction conditions and the magnitude of the effect on the percentage of sodium formate in the product will differ from one catalyst to another.

## Experimental

**Materials Used.**—The sodium bicarbonate used was a U. S. P. grade manufactured by Wyandotte Chemicals Corporation.

(1) Bredig and Carter, *Ber.*, **47**, 541 (1914).

**Catalysts Preparation.**—The U. O. P. hydrogenation catalyst was obtained from Universal Oil Products Company, Riverside, Illinois. Raney nickel was purchased as an aqueous suspension from the Gilman Paint and Varnish Company, Chattanooga, Tennessee. The Ruffert nickel pellets and nickel catalyst supported in wax were obtained from The Ruffert Chemical Division of the Seymour Manufacturing Company.

Copper chromium oxide,[2] nickel on kieselguhr,[3] nickel chromite[4] and zinc chromite[5] were prepared and used according to standard methods. Iron chromite and manganese chromite were prepared according to the method used for zinc chromite.

The boron phosphate on charcoal catalyst was prepared by mixing 58 g. of phosphoric acid (85%) and 30.9 g. of boric acid in 100 ml. of distilled water with vigorous stirring and heating at 85° for one hour. The mixture was evaporated to dryness with constant stirring on a hot-plate, the residue taken up in 200 ml. of distilled water and heated to boiling until a homogeneous suspension was obtained.

Fifteen grams of Darco activated charcoal were added with vigorous stirring and the suspension evaporated to dryness. The resulting cake was dried at 120° for twelve hours and then ground up for use.

The nickel–copper catalyst was prepared by dissolving 145.3 g. of nickel nitrate hexahydrate and 120.8 g. of cupric nitrate trihydrate in 1500 ml. of distilled water at 85°. One hundred seventy ml. of ammonium hydroxide, diluted with two parts of water, were added with vigorous mechanical stirring over a period of ten minutes while the temperature was maintained at 80–85°. Stirring and heating were continued fifteen minutes after which the suspension was filtered on a Büchner funnel. The residue was washed three times by alternate suspension in hot water and filtration. After the last filtration the residue was sucked as dry as possible on the filter and then dried in an oven at 110° for three days. Before use the catalyst was reduced in a slow hydrogen stream at 450° for forty-five minutes.

Nickel formate was obtained from the Harshaw Chemical Company, Cleveland, Ohio. Before use, it was reduced at 350° in a slow hydrogen stream for one hour and then transferred directly to the reactor.

**Method of Reaction.**—The hydrogenations were carried out in a rocking bomb of 1200 ml. void according to the method of Adkins.[6] The reaction product was washed from the bomb with distilled water, made up to a known volume and aliquots analyzed for sodium formate by the method of Blackadder.[7] Additional aliquots were acidified and used for the determination of Duclaux constants to demonstrate the presence of formic acid in the acidified product.

(2) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 13.

(3) *Ibid.*, p. 19.

(4) Adkins, Richards and Davis, THIS JOURNAL, **63**, 1320 (1941).

(5) Sauer and Adkins, *ibid.*, **59**, 1 (1937).

## Summary

Sodium bicarbonate, in aqueous solution, has been converted to sodium formate by hydrogenation over ten different catalyst. Nickel-containing catalysts appear to be the most effective type among those tested. Catalyst concentration, hydrogen pressure, reaction temperature, reaction time and solution concentration have been shown to effect the conversion of sodium carbonate to sodium formate over a nickel catalyst.

(6) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 40.

(7) Treadwell and Hall, "Analytical Chemistry," Vol. II, Ninth English Edition, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 561.

WYANDOTTE, MICHIGAN RECEIVED SEPTEMBER 15, 1948

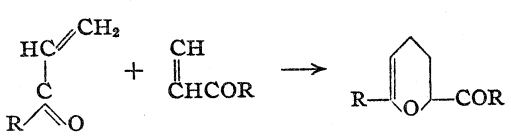
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[CONTRIBUTION NO. 56 FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TENNESSEE]

# The Thermal Dimerization of Acrylonitrile[1]

BY EUGENE C. COYNER[2a] AND WILLIAM S. HILLMAN[2b]

Various carbonylenic compounds, such as acrolein and methyl vinyl ketone, have been found by Alder and co-workers[3] to undergo thermal dimerization to give up to 55 per cent. yields of dihydropyran derivatives of the type represented by structure I.



R = H or $CH_3$ I

The present work was initiated with a view to carrying out this type of reaction with a nitrogen-containing analog, acrylonitrile, which it was thought, might correspondingly give a dihydropyridine derivative. However, under the optimum conditions found for the thermal dimerization of acrylonitrile, the only dimeric products isolated were not heterocyclic in nature, but were found to be *cis*- and *trans*-1,2-dicyanocyclobutane. Both products, upon hydrolysis, gave *trans*-1,2-cyclobutanedicarboxylic acid, whose structure was established by conversion to the known dihydrazide and by its resolution into the *d* and *l* forms.

(1) Abstracted from a thesis by William S. Hillman submitted in partial fulfillment of the requirements for the M.S. degree.

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(3) Alder, Offermanns and Rueden, *Ber.*, **74B**, 905 (1941); Alder and Rueden, *ibid.*, 920.

## Experimental

**1,2-Dicyanocyclobutane.**—All runs were carried out in an externally heated steel bomb of 250 cc. capacity under autogenous pressures (20–130 atmospheres). About 0.1 g. of hydroquinone was added to inhibit chain polymerization. Representative reaction conditions and the yields of acrylonitrile dimer obtained are given in Table I.

TABLE I

DIMERIZATION OF ACRYLONITRILE

| | | | | | | |
|---|---|---|---|---|---|---|
| Acrylonitrile | 53[a] g. | 53 g. | 53 g. | 100 cc. | 100 cc. | 100 cc. |
| Benzene, cc. | 100 | 100 | 100 | | | |
| Temp., °C. | 245–250 | 275–280 | 295–304 | 195–200 | 200–210 | 245–265 |
| Time, hours | 7.5 | 2.0 | 0.5 | 24 | 3.5 | 0.8 |
| Dimer, g. | 1.5 | 2.6 | 2.4 | 5.5 | 1.2 | 2.8 |

[a] A glass liner was used.

No significant differences in results were observed whether or not benzene was added or a glass liner was used. The dimerization reaction became excessively slow below 190°, and decomposition which produced carbonaceous residues occurred extensively above 300°.

After the heating cycle was completed, the reaction mixtures, which usually possessed a strong ammoniacal odor, were fractionally distilled. Unreacted acrylonitrile and the solvent, if any, were distilled at atmospheric pressure, and the residue was then distilled *in vacuo* through a 16 in. Vigreux-type column. The product was obtained in three colorless fractions of approximately the same weight.

TABLE II

FRACTIONS OF 1,2-DICYANOCYCLOBUTANE

| Fraction number | B. p. at 3–4 mm. | M. p., °C. | Analyses C, % | H, % | N, % | Molecular weight[a] |
|---|---|---|---|---|---|---|
| 1 | 108–115° | <0 | 67.54 | 5.91 | 26.55[b] | 106 |
| 2 | 120–125° | 27 | | | | 104 |
| 3 | 140–145° | 62 | 67.58 | 5.55 | 26.39 | 101 |
| Calcd. for $C_6H_6N_2$: | | | 67.90 | 5.70 | 26.40 | 106 |

[a] Determined ebullioscopically in benzene. [b] By difference.

It is probable that fractions 1 and 3 are the relatively pure *cis* and *trans* forms and that fraction 2 is a mixture of the two. All three fractions failed to react with bromine in carbon tetrachloride.

***trans*-1,2-Cyclobutanedicarboxylic Acid.**—Fractions 1,2 and 3 (see Table II) gave nearly identical yields (*ca.* 70–80%) of *trans*-1,2-cyclobutanedicarboxylic acid, m.p. 129–130°,[4] upon hydrolysis in excess alcoholic potassium hydroxide or in 10% hydrochloric acid.

A typical alkaline hydrolysis was carried out as follows: To a solution of 10 g. of potassium hydroxide dissolved in 80 cc. of 70% ethyl alcohol was added 6 g. of fraction 1 of the dinitrile, m.p. < 0°. A bright blue color developed immediately which turned dark green in a few seconds and after a few minutes disappeared, leaving a colorless solution which was heated under reflux for twenty-four hours under a slow stream of nitrogen. The alcohol was then removed by distillation. The residue was made acidic with hydrochloric acid and was extracted with three 100 cc. portions of ether. Upon evaporation of the ether, a viscous liquid was obtained which solidified on cooling to give 5 g. (73%) of crude acid, m.p. 120–125°. After one recrystallization from concentrated hydrochloric acid it melted at 129–130°.

A typical hydrolysis with hydrochloric acid was carried out as follows: Five grams of dinitrile, fraction 2, m.p. 27°, was boiled under reflux with 100 cc. of 10% hydrochloric acid. The reaction mixture was extracted with ether and the ether was removed by evaporation. The yield of acid, m.p. 123–127°, was 5.6 g. (82%). After one recrystallization from concentrated hydrochloric acid it melted at 129–130°.

The isolation of only the *trans* isomer is not to be unexpected, since this acid is the more stable. Thus, if *cis*-1,2-cyclobutanedicarboxylic acid is heated in concentrated hydrochloric acid it is converted into the *trans* isomer.[4] The *cis* dinitrile should be even more susceptible to isomerization.

*Anal.* Calcd. for $C_6H_8O_4$: C, 49.99; H, 5.60; neutral equivalent, 72. Found: C, 49.88; H, 5.55; neutral equivalent, 74.

The corresponding dihydrazide, *trans*-1,2-cyclobutanedicarboxdihydrazide, m.p. 219–220°, was prepared by the method of Buchman, *et al.*[5]

*Anal.* Calcd. for $C_6H_{12}O_2N_4$: C, 41.85; H, 7.02; N, 32.53. Found: C, 41.90; H, 7.07; N, 32.19.

(4) Bode, *Ber.*, **67B**, 332 (1934).

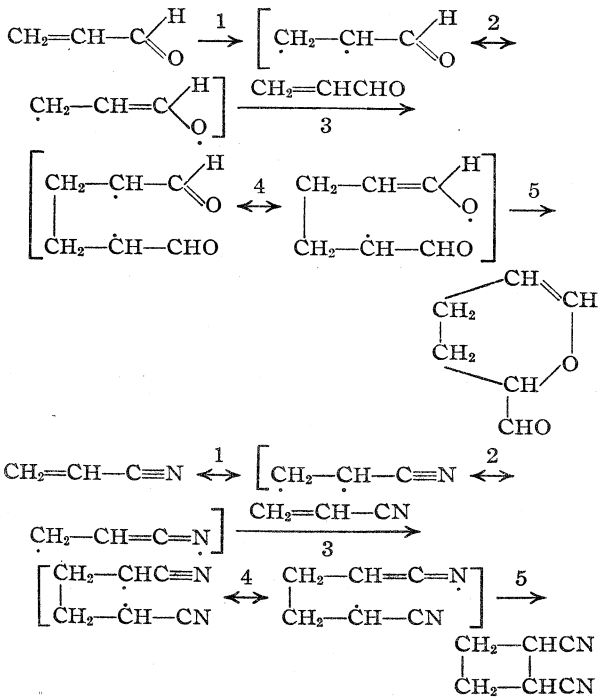
(5) Buchman, Reims, Skei and Schlatter, THIS JOURNAL, **64**, 2696 (1942).

**Resolution of *trans*-1,2-Cyclobutanedicarboxylic Acid.**—The resolution was carried out by the procedure of Goldsworthy,[6] but, by employing a simple modification, a purer sample of the *l* isomer was obtained. To a solution of 7 g. of quinine in 25 cc. of ethyl alcohol was added a solution of 3 g. of *d,l-trans*-1,2-cyclobutanedicarboxylic acid in 200 cc. of water. The alcohol was then evaporated by boiling the mixture for forty-five minutes and the total volume was made up to 650 cc. with boiling water. The solution was cooled to 35° and the precipitated impure *l*-salt was removed by filtration. It was redissolved in hot water and allowed to crystallize at room temperature. The purified *l*-salt was removed by filtration and dried in air; it weighed 4 g. It was dissolved in 200 cc. of water and made alkaline with ammonium hydroxide. The solution was cooled to 0° and the quinine was removed by filtration. The filtrate was made acid with hydrochloric acid and extracted with ether. The ether extract was evaporated to dryness, leaving 0.5 g. of impure *l-trans*-cyclobutane-1,2-dicarboxylic acid which, after one recrystallization from benzene, melted at 114–117°. The specific rotation was −150° at 28° in water. This is a higher specific rotation than that reported by Goldsworthy[6] (−124.3° at 30°), and thus represents a more complete resolution.

The mother liquor from the initial crystallization was concentrated to one-third of the original volume and the *d*-acid, in less pure condition, was separated as outlined above for the *l*-form. The melting point was 115–117° and the specific rotation at 28° was found to be +104°.

## Discussion of Mechanism

Although the type of product obtained upon the thermal dimerization of acrylonitrile is quite different from the heterocyclic compounds obtained by Alder, *et al.*,[3] from oxygen analogs, such as acrolein, it is probable that the mechanisms of the reactions involved are quite similar, as illustrated below:



According to Hurd,[7] the primary effect of heat

(6) Goldsworthy, *J. Chem. Soc.*, **125**, 2012–2013 (1924).

(7) Hurd, *Ind. Eng. Chem.*, **26**, 54 (1934).

upon the C=C of an olefin is the rupture of one bond giving rise to a divalent radical C—C. In the examples given above this process is represented by step 1. The splitting of one electron pair of the double bond is doubtless facilitated in the compounds illustrated by resonance involving one of the unpaired electrons (process 2).

The establishment of a covalent bond between β-carbon atoms, as represented in step 3, is to be expected for two reasons. First, the most reactive center in the activated molecule (the di-radical) is the β-carbon atom, since the resonance involving the odd electron associated with the α-carbon atom and the oxygen atom in acrolein or the nitrogen atom in acrylonitrile (process 2) should make any reaction involving that electron less likely. Second, the new di-radicals thus formed can exist in four resonating forms, as partially illustrated by process 4, and hence are stabilized to some extent, whereas, if the initial union were between α-carbon atoms, no such resonance could occur. Similar considerations have been advanced by Koelsch and Boekelheide[8] to account for the orientations observed in the coupling of aryl radicals with α,β-unsaturated compounds.

The final phase of the reaction (step 5) is a cyclization process. In the case of acrolein a relatively stable six-membered heterocyclic ring is formed. With acrylonitrile, however, the distribution of the odd electrons which would be required for the formation of a six-membered ring produces the linear configuration C=C=N, and the resulting distance between the atoms bearing the odd electrons is too great for electron pairing bond formation. The final electron pairing reaction therefore takes place between the two α-carbon atoms.

(8) Koelsch and Boekelheide, This Journal, **66**, 413 (1944).

## Summary

1. Acrylonitrile has been thermally dimerized to give low yields of 1,2-dicyanocyclobutane.

2. It is proposed that this reaction occurs by an electron pairing mechanism.

3. A similar mechanism is advanced for the thermal dimerization of acrolein and related carbonylenic compounds.

Knoxville, Tennessee Received June 25, 1948

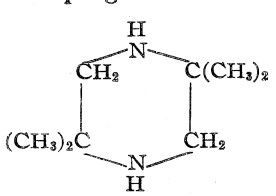
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[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

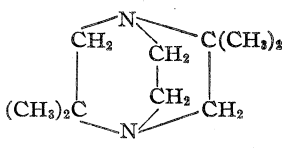
# 2,2,5,5-Tetramethylpiperazine and Derivatives

By S. M. McElvain and Everett H. Pryde[1]

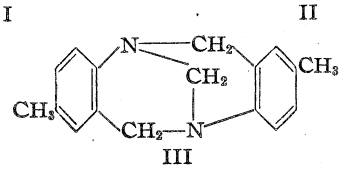
The preparation of 2,2,5,5-tetramethylpiperazine (I) was undertaken in the hope that by bridging its nitrogens with an ethylene radical the bicyclic structure (II), which contains asymmetric nitrogen atoms comparable in structure to those of Troeger's base (III), might be obtained and resolved into its optical antipodes. The resolution of III[2] is the only recorded successful separation of a *dl*-mixture into its component optical isomers, the asymmetry of which is due to trivalent nitrogen atoms. Although the synthesis of II has not been achieved and further work in this direction is in progress in this Laboratory, the preparation of I and the properties of certain of its derivatives seem of sufficient interest to report at this time.



I



II



III

The preparation of the dihydrochloride[3] and the N,N'-dinitroso derivative[4] of I in low yields have been reported, but none of these procedures appeared adaptable to the production of substantial quantities of I. For this reason it seemed that 2,2,5,5 - tetramethyl - 3,6 - diketopiperazine (IV), if it could be obtained readily, offered a better approach to I.

The preparation of the diketopiperazine (IV) in 34% yield by heating methyl α-aminoisobutyrate[5] and in 23% yield from the ethyl ester[6] have been reported; however the requisite methyl ester was obtained in yields that left much to be desired.[5] The preparation of IV from N-(α-aminoisobutyryl)-α-aminoisobutyric acid also has been reported.[7] The ester approach[5] to IV was investigated in the present work and, although a method of preparation of methyl α-aminoisobutyrate in good yield was developed, the product resulting from heating this ester contained only about 3% of

(1) S. B. Penick and Company Fellow, 1947-1948.

(2) Prelog and Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).

(3) (a) Reihlen, *et al.*, *Ann.*, **493**, 20 (1932); (b) Drew and Head, *J. Chem. Soc.*, 49 (1934).

(4) Conant and Aston, This Journal, **50**, 2783 (1928).

(5) Franchimont and Friedman, *Rec. trav. chim.*, **27**, 197 (1908).

(6) Jacobson, This Journal, **68**, 2628 (1946).

(7) Abderhalden and Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926); Levene and Steiger, *J. Biol. Chem.*, **93**, 595 (1931).

IV; the major reaction product was α-aminoisobutyric acid.

Recently Sannié[8] reported the preparation of certain diketopiperazines in 60–70% yields by heating α-amino acids in ethylene glycol; however, he found that such amino acids as α-aminoisobutyric acid, in which the amino group is on a tertiary carbon, gave negative results. In the present work it was found that the latter amino acid could be made to undergo this cyclization in the higher boiling diethylene glycol, and a procedure has been developed for the preparation of IV in 40% yield.

The reduction of certain diketopiperazines to the corresponding piperazines in low yields (15–17%) by sodium in amyl alcohol has been effected[9]; however, much higher yields (57–86%) of pyridines and pyrrolidines have been obtained from the reduction of 2-piperidones and 2-pyrrolidones with sodium in butyl alcohol, using a 10:1 ratio of sodium to reductant.[10] Following the latter procedure yields of 24% of I and 40% of half reduced product V were obtained from IV in the present work. The yield of I was improved somewhat by the use of higher ratios of sodium to IV, but with such ratios the manipulation of the reaction mixtures became more difficult. The hydrogenation of IV to I over a copper–chromium oxide catalyst was much more successful. In spite of the insolubility of IV in all of the ordinary solvents, it could be hydrogenated in a dioxane suspension to I in 87% yield.

Attempts to prepare the bicyclic structure II by the catalytic intramolecular alkylation[11] of the 4-nitrogen of VI—obtained together with some of the 1,4-di-(β-hydroxylethyl) derivative, VIa, from the reaction of I with ethylene oxide—with the 1-hydroxyethyl substituent were unsuccessful. At temperatures up to 200°, VI was recovered unchanged; at 250° some of VI was recovered, but the major portion of it lost the 1-substituent and reverted to the original piperazine I.

The bicyclic compound, 1,4-diazobicyclo-(2,2,-2)-octane, the unmethylated homolog of II, has been prepared in low yields by heating (a) diethanolamine hydrochloride (2%)[12] and (b) 1-(β-chloro- (or-bromo)-ethyl)-piperazine dihydrohalides (20–25%)[13]; and by treatment of 1-(β-chloroethyl)-piperazine with aqueous alkali.[13] However, an attempt to effect a similar cyclization of 1-(β-bromoethyl)-piperazine by the latter procedure was unsuccessful.[14]

When the corresponding 1-(β-bromoethyl) derivative of I (VIIa) was added to an aqueous sodium hydroxide solution, it dissolved immediately, but within a few seconds a precipitate began to separate. The amount of this precipitate was dependent upon the dilution of the solution with respect to VIIa, *i. e.*, the more dilute the solution the less the amount of precipitate. This insoluble material was separated into the dimer (IX, *n* is 1), m. p. 123–125, the trimer (IX, *n* is 2), m. p. 160–167°, and a higher melting (above 260°), insoluble material, which is, presumably, a more complex polymer (IX, $n > 2$). From the aqueous alkaline solution only VI was isolated; the yields of this compound increased, as those of the insoluble products (IX) decreased, with the dilution of the solutions of VIIa.

The chloro derivative (VII) showed an interesting and significant variation in behavior. When an aqueous alkali solution was added to an aqueous solution of VII, there was an immediate precipitation of the free base, due to the neutralization of the hydrochloride functions. This precipitate, however, rapidly returned to solution and from the resulting clear solution the polymers IX began to separate. All of these changes occurred within approximately one minute after the salt VII was added to the alkaline solution.

This behavior indicates that the free bases of VII and VIIa are preferentially converted into the ethyleneimmonium ion[15] (VIII) rather than the bicyclic structure II; VIII then reacts with water to produce VI (if the solution is sufficiently dilute) or intermolecularly to produce the polymer IX. In the case of the bromo derivative (VIIa), the formation of VIII is so rapid that there is no evidence of the intermediate free base; but with the less reactive chloro compound, the free base of VII is momentarily precipitated before it cyclizes to the soluble ion (VIII) that undergoes the subsequent reactions.

When the salts VII and VIIa were heated alone or in suspension in Stanolind oil, 77–88% of one equivalent of hydrogen halide was evolved at 220–240°. However, investigation of the remaining salt in a search for the bicyclic compound II yielded only the piperazine I. Whether or not the formation of this product involved the quaternary ion VIII could not be determined; it is possible that a salt of I could form from VII by dehydrohalogenation followed by the loss of acetylene.

## Experimental

**Methyl α-Aminoisobutyrate.**—A mixture of 51.5 g. (0.5 mole) of α-aminoisobutyric acid, prepared by the hydrolysis of 5,5-dimethylhydantoin,[16] and 600 ml. (15.3 mole) of methanol was treated with hydrogen chloride until 30 g. (0.82 mole) had been absorbed. The resulting solution was refluxed on a steam-bath for sixteen hours, after which time 150 g. of Drierite was added. Throughout this experiment, the solutions were protected from atmospheric moisture with calcium chloride drying tubes.

(8) Sannié, *Bull. soc. chim.*, [5] **9**, 487 (1942).

(9) Gavrilov, *ibid.*, [4] **37**, 1651 (1925); Abderhalden, *et al.*, *Z. physiol. Chem.*, **135**, 180 (1924).

(10) Koelsch, THIS JOURNAL, **65**, 2093 (1943).

(11) *Cf.* Adkins, *et al.*, *ibid.*, **60**, 1033 (1938); *ibid.*, **61**, 3499 (1939).

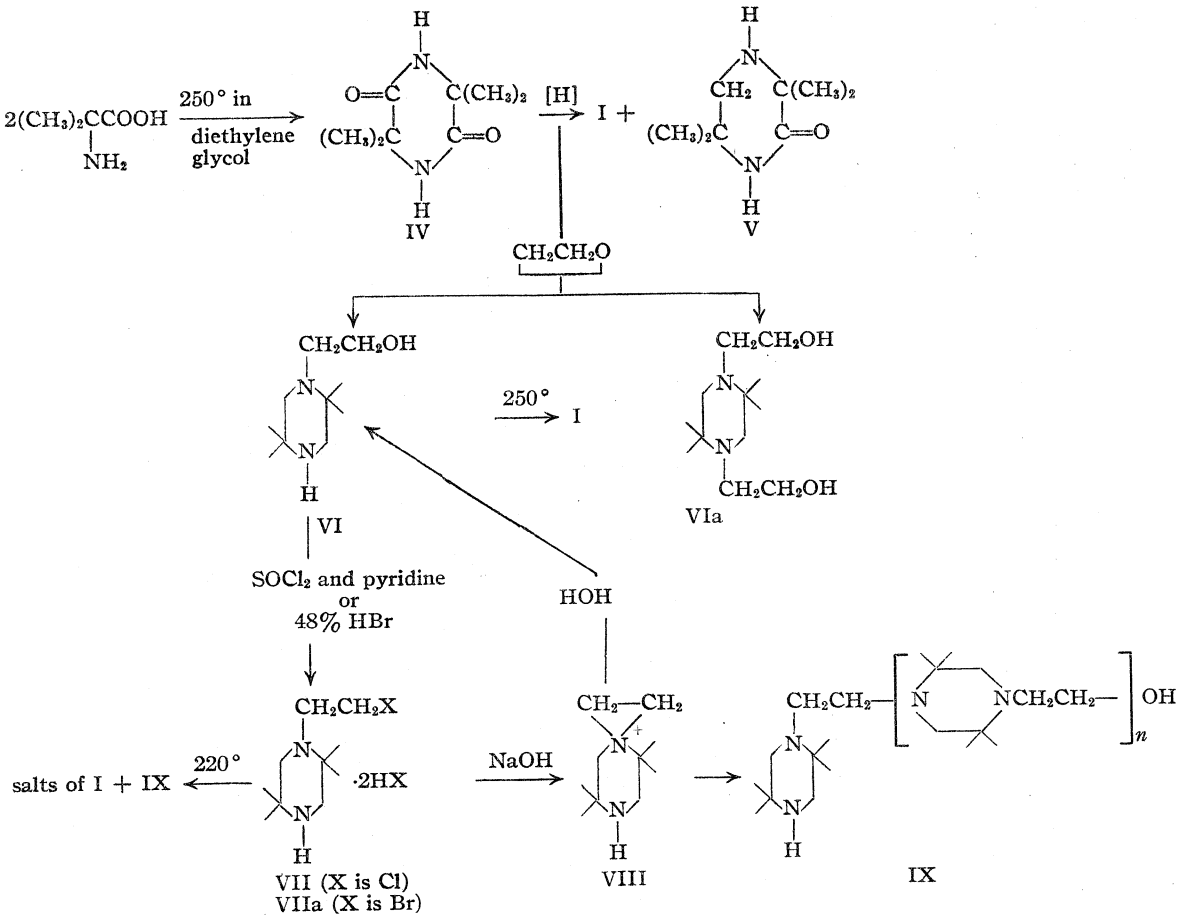
(12) Hromatka, *Ber.*, **75**, 1302 (1942).

(13) Hromatka and Engel, *ibid.*, **76**, 712 (1943); in procedure (b) a loss of the 1-substituent occurred and piperazine formed to the extent of 12–60%.

(14) Prelog, *et al.*, *Ann.*, **535**, 37 (1938).

(15) *Cf.* Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947); Cohen, Artsdalen and Harris, *ibid.*, **70**, 281 (1948).

(16) Bucherer and Steiner, *J. prakt. Chem.*, **140**, 305 (1934).




After filtering off the Drierite, the methanol and excess hydrogen chloride were removed under vacuum until the residue was solid; it then was placed in a vacuum desiccator over potassium hydroxide until completely dry. A quantitative yield of methyl α-aminoisobutyrate hydrochloride, m. p. 179–182° dec., and which contained 23.2% chlorine (calcd. 23.1%), was obtained. The ester hydrochloride after recrystallization from absolute alcohol and ether melts at 182–183° dec.[5]

The free ester was liberated from its salt by adding a solution of sodium methoxide in dry methanol (from 14 g. of sodium and 200 ml. methanol) to a sirup of the ester hydrochloride in methanol until the solution was alkaline to phenolphthalein. After filtering off the sodium chloride, the methanol solution was distilled in a modified Claisen flask at atmospheric pressure. A 64% yield of methyl α-aminoisobutyrate, b. p. 133–134°, was obtained.

**2,2,5,5-Tetramethyl-3,6-diketopiperazine (IV).**—To 200 ml. of diethylene glycol contained in an open 500-ml. long-neck, round-bottom flask was added 100 g. of crystalline α-aminoisobutyric acid, which had been ground and passed through a 20-mesh screen (a larger crystal size caused prolongation of the heating time). The glycol was refluxed at such a rate that the water formed in the reaction was driven out as steam. During four hours of heating, the temperature at reflux gradually increased from 210 to 234°, and all the acid had gone into solution. The diketopiperazine crystals which formed when the solution was allowed to cool to room temperature were collected on a filter and washed with methanol until free from glycol; the yield was 16 g.

To the filtrate was added another 100 g. of α-aminoisobutyric acid and the mixture heated as above. After five hours, the temperature of the vapors above the refluxing glycol had increased to 249°, and only a small amount of insoluble material remained. After the solution had cooled, 47.5 g. of IV was collected. Two repetitions of this procedure, using 75 g. and 50 g. of acid in the same glycol filtrate, yielded 31.5 g. and 16.5 g. of diketopiperazine, respectively. Smaller quantities of acid were employed in these latter runs to insure complete solution of the acid in the glycol. After these four runs, the diethylene glycol solution was dark brown and viscous, and not suitable for further use. The total yield of the diketopiperazine (IV) from 325 g. of α-aminoisobutyric acid was 111.5 g. (41.6%).

Undoubtedly, some acid and diketopiperazine are lost through sublimation from the diethylene glycol. In an effort to determine the fate of the remainder of the acid not recovered as IV, the diethylene glycol solution from the above runs was diluted with methanol and benzene. No precipitate separated; any acid or diketopiperazine that was in solution would have been precipitated by this change in solvent. When the diethylene glycol solution was distilled, 7% of its weight was recovered as methyl α-aminoisobutyrate; 42% as diethylene glycol, b. p. 75–120° (0.4 mm.), $n^{25}D$ 1.4483; 27% as material, b. p. 160–198° (0.3 mm.), $n^{25}D$ 1.4630–1.4760; and 16% remained as residual tar. The latter two materials were not investigated further. The methyl ester was formed from the methanol used to wash the diketopiperazine crystals and which was added to the diethylene glycol filtrate. That portion of the acid not recovered probably was in the form of glycol esters.

The diketopiperazine (IV) does not melt, even in a sealed capillary tube, below 400°, but sublimes in the temperature range 360–370° (cor.) in an open capillary and at about 390° in a sealed capillary. Many sublimation tem-

peratures have been reported,[6] varying from 210 to 260°, all of which are much lower than those found for IV in the present work. The diketopiperazine is much less volatile than α-aminoisobutyric acid (sublimation temperature 300–320°). The sublimation temperatures now reported for these compounds are those ranges in which the rate of sublimation suddenly increases as the compounds are heated. The diketopiperazine (IV) is insoluble in water, and relatively insoluble in most organic solvents. It dissolves to the extent of about 0.2% in hot 95% ethyl alcohol, 0.4% in hot butanol, 3% in hot glacial acetic acid, 10% in diethylene glycol at 250°, but less than 0.5% at room temperature. Recrystallization from this latter solvent, followed by leaching with hot water, gives a very pure product.

*Anal.* Calcd. for $C_8H_{14}N_2O_2$: C, 56.47; H, 8.23; N, 16.47; mol. wt., 170. Found: C, 56.66; H, 8.33; N, 15.96; mol. wt. (in acetic acid), 170, 177.

When α-aminoisobutyric acid was heated in diphenyl ether or diphenyl amine, the acid sublimed from the liquid and no diketopiperazine was found. Apparently, a polar solvent such as diethylene glycol, is necessary to keep the acid from volatilizing at the temperature required for its condensation to IV.

When methyl α-aminoisobutyrate hydrochloride was heated in a distilling flask, only a small amount of a semi-solid distillate, from which was recovered some of the original acid, was obtained. No trace of diketopiperazine was found. When methyl α-aminoisobutyrate was heated in a glass lined bomb at 200° it was converted to a solid, only 3% of which (IV) was insoluble in water. Evaporation of the aqueous solution yielded only α-aminoisobutyric acid.

**2,2,5,5-Tetramethylpiperazine (I) and 2,2,5,5-Tetramethyl-3-ketopiperazine (V) (a).**—A mixture of 34 g. (0.2 mole) of IV, 15 g. of copper–chromium oxide catalyst[17] and 50 ml. of dioxane were placed in a steel bomb, which then was filled with hydrogen to 3500 p. s. i. The hydrogenation was carried out at 250° for sixteen hours. The dioxane solution, after separation from the catalyst by centrifuging, was distilled and two fractions, b. p. 85–168° (a liquid) and 168–173° (a crystalline solid), collected. Hydrogen chloride was added to the first fraction, and the dioxane evaporated. The free base (I) was liberated from the remaining salt with 50% sodium hydroxide and extracted with benzene; the benzene solution then was distilled and yielded 10.5 g. of crystalline I, which, when combined with the second fraction, gave a total yield of 22 g. (77%) of I.

After recrystallization from absolute ether, **2,2,5,5-tetramethylpiperazine** (I) is obtained as a white, crystalline, fairly volatile solid, m. p. 85–87° with previous softening at 83°. It boils at 168–171° and has a pleasant ammoniacal odor. It is very soluble in water and all organic solvents. In contrast to the unsubstituted piperazine, the tetramethylpiperazine is not hygroscopic and does not react with carbon dioxide of the atmosphere.

*Anal.* Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.70. Found: C, 67.40; H, 13.13; N, 19.71.

**2,2,5,5-Tetramethylpiperazine dihydrochloride** was prepared by passing hydrogen chloride through a solution of I in dioxane and evaporating the dioxane. This dihydrochloride is very soluble in water, but insoluble in all organic solvents, and no means for recrystallization was found. It does not melt below 350°, but begins to darken at 310°.

*Anal.* Calcd. for $C_8H_{20}Cl_2N_2$: Cl, 32.96. Found: Cl, 32.45.

**1,4-Dibenzoyl-2,2,5,5-tetramethylpiperazine** was prepared from I in 92% yield by the usual Schotten–Baumann procedure. When recrystallized from absolute ethanol, it melted 273–276°.

*Anal.* Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48. Found: C, 75.26; H, 7.82.

From the residue, remaining after the distillation of I from the hydrogenation products, was obtained 3.1 g. 5% of **2,2,5,5-tetramethyl-3-ketopiperazine** (V), which after recrystallization from toluene melted at 153–156° and boiled at 250–258°. This compound is soluble in water, ether, alcohol and benzene.

*Anal.* Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.33; N, 17.93. Found: C, 61.17; H, 10.17; N, 18.12.

**2,2,5,5-Tetramethyl-3-ketopiperazine hydrochloride** was prepared by passing hydrogen chloride through a solution of 0.5 g. of V in 30 ml. of dioxane and evaporating the dioxane. After recrystallization from alcohol–ether, 0.5 g. (81%) of the hydrochloride, m. p. 305–308° dec., was obtained.

*Anal.* Calcd. for $C_8H_{17}ClN_2O$: Cl, 18.4. Found: Cl, 18.2.

The hydrogenation of V, as described above for IV, gave the piperazine I in 87% yield.

The yields of I and V varied from 87% and 0% to 36% and 42%, depending on the purity of IV. The former high yield of I was obtained with a sample of IV that had been recrystallized from diethylene glycol. With less pure samples of IV, *i. e.*, those obtained by washing the crude product with methanol or water, the yields of V became significant.

(b) **The Reduction of IV with Sodium in Butanol.**—To 400 ml. of hot, absolute butanol and 25 g. (0.147 mole) of IV, contained in a three-neck, three-liter round-bottom flask equipped with a stirrer and a large bore condenser, was added 90 g. (3.48 mole) of sodium over a period of approximately ten minutes. To prevent the formation of solid sodium butoxide, another 600 ml. of butanol was added portionwise during the reduction. The solution was kept at reflux by heating on sand-bath until all the sodium had reacted. About 300 ml. of water was added then, and, after cooling, the water layer separated and 115 ml. of concentrated hydrochloric acid was added to the butanol solution. The aqueous layer was extracted with benzene to determine if any reduced product remained in it, but only a negligible amount was found. The acidified butanol layer was steam distilled to remove the butanol. To the remaining aqueous acid solution of the piperazine salt (about 750 ml.) was added 200 ml. of 50% sodium hydroxide, and the solution was extracted five times with 100 ml. portions of benzene. From the remaining aqueous layer was recovered 3 g. (12%) of the insoluble diketopiperazine (IV). The benzene solution was distilled to yield 5.0 g. (24%) of I in the fraction boiling at 165–210°, and 9.2 g. (40%) of V in the fraction boiling at 210–250°.

**1-(β-Hydroxyethyl)-2,2,5,5-tetramethylpiperazine (VI).**—In a 10-inch length of 15-mm. Pyrex tubing sealed at one end was placed 11.36 g. (0.08 mole) of I. The neck of the tube was drawn out for sealing, and, after chilling the tube in Dry Ice, 2 ml. (1.85 g., 0.042 mole) of ethylene oxide was added, and the tube sealed. The tube then was heated with shaking for two hours at 150°.

The combined contents of three of such tubes was distilled through an eight-inch Vigreux column to yield 18.8 g. of I and 15.5 g. (66% based on the ethylene oxide) of VI, b. p. 240–247°, which after recrystallization from petroleum ether (b. p. 60–68°), melted at 78–83°.

*Anal.* Calcd. for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.21; H, 11.91; N, 14.63.

From the residue (4.5 g.) of this distillation, after treatment with Norit and recrystallization from toluene, was isolated 1.83 g. (13% based on the ethylene oxide) of **1,4-di-(β-hydroxyethyl)-2,2,5,5-tetramethylpiperazine** (VIa), m. p. 110–115°. After a second recrystallization from toluene, VIa melted at 113–116°.

*Anal.* Calcd. for $C_{12}H_{26}N_2O_2$: C, 62.56; H, 11.38; N, 12.16. Found: C, 62.21; H, 11.42; N, 12.55.

When a ratio of 1.5 moles of I to one mole of ethylene oxide was used in one experiment, 54% of VI and 41% (based on the ethylene oxide) of VIa were obtained.

**1-(β-Hydroxyethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride.**—Hydrogen chloride was passed through a

(17) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wis., 1937, p. 112.

solution of 5 g. of VI in 100 ml. of dioxane until no further precipitate was formed. The dioxane was evaporated in a stream of air, and the residue dried overnight in a vacuum desiccator. This dihydrochloride had no definite melting or decomposition point, but began to darken at about 200°. As it is very soluble in water but insoluble in organic solvents, it was not possible to recrystallize it. However, analysis showed the compound to be quite pure.

*Anal.* Calcd. for $C_{10}H_{23}ClN_2O$: Cl, 27.36. Found: Cl, 27.18.

**1-(β-Chloroethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride (VII).**—In a 200-ml. round-bottom flask were placed 5.0 g. of the dihydrochloride of VI, 5.8 ml. of freshly distilled thionyl chloride, 2.2 ml. of pyridine, and 50 ml. of benzene. The flask was attached to a condenser fitted with a calcium chloride tube, and the solution heated to gentle reflux. After the first two to three hours of refluxing the flask was removed, and the large lumps which had formed were crushed to a powder. The flask then was replaced, and the refluxing continued for twenty hours. At the end of this time, the solution was filtered while hot. The solid on the filter was washed with benzene and absolute ethanol, after which it was placed in a 200 ml. flask, 25 ml. of absolute ethanol added, and any large lumps were broken into a powder. The alcoholic suspension was refluxed for fifteen minutes and filtered. The solid on the filter was washed with absolute ethanol and then absolute ether. After drying in a vacuum desiccator for several hours, the weight of the white powder was 5.57 g. (74.6%).

*Anal.* Calcd.: ionic Cl, 25.55; total Cl, 38.31. Found: ionic Cl (Volhard), 25.11; total Cl (Stepanow), 37.83.

**1-(β-Bromoethyl)-2,2,5,5-tetramethylpiperazine Dihydrobromide (VIIa).**—To a 50-ml. round-bottom flask were added 5 g. of VI and 25 ml. of 48% hydrobromic acid. An all-glass still head and condenser was attached to the flask, and the solution was distilled slowly for three to four hours, during which time the distilled material was replaced by hydrobromic acid. The solution then was allowed to reflux for sixteen hours, after which it was slowly distilled until the residue was a sludge. Acetone was added, and the insoluble product filtered off. After drying in a vacuum desiccator, the resulting white salt (VIIa) weighed 8.8 g. (80%).

*Anal.* Calcd. for $C_{10}H_{23}Br_3N_2$: Total Br, 58.32. Found: Br, 55.5.

The Volhard procedure gave the same halogen values as those obtained with the Stepanow procedure.

**Attempted Preparation of 2,2,5,5-Tetramethyl-1,4-diazabicyclo-(2,2,2)-octane (II). (a) By Catalytic Intramolecular Alkylation of VI.**—In a 150-ml. glass-lined bomb were placed 5.0 g. of VI, 2.0 g. of copper–chromium oxide catalyst and 20 ml. of dioxane. The bomb was filled with hydrogen and heated in various experiments at temperatures ranging from 200 to 250° for two to four hours. At the end of the heating period, the catalyst was removed from the dioxane solution by centrifuging, and the solution distilled. The recovery of VI varied from 63 to 78%; in the case of the lower recovery of VI (250°), a 13% yield of I was obtained. Repetition of the experiment at 250° using nitrogen instead of hydrogen in the bomb gave 62% of VI and 30% of I. With a nickel catalyst at 150°, 90% of VI was recovered; at 250° a 51% yield of I was obtained. There was no evidence that any di-tertiary amine (II) had formed in any of these experiments.

**(b) From 1-(β-Bromoethyl)-2,2,5,5-tetramethylpiperazine Dihydrobromide (VIIa).**—Experiments in which aqueous solutions of VIIa were treated with aqueous sodium hydroxide solutions are listed in Table I.

In experiment A, the solution containing 2.5 g. of VIIa was overlaid with ether, and 5% aqueous sodium hydroxide was added with shaking. The layers were separated, and the ether distilled from a steam-bath. Water was added to the residue from the ether solution, and the insoluble polymer, m. p. 113–120°, was separated by filtration. The filtered aqueous solution was distilled, and the distillate was found to contain 0.0006 mole of base (16% calculated as VI). This titrated solution was evaporated to dryness, treated with benzoyl chloride and 5% sodium hydroxide, and filtered. The filtrate from this treatment was distilled, and the resulting distillate showed no titratable basicity, indicating the absence of any of the di-tertiary amine II.

Table I

Reaction of Aqueous Solutions of VIIa with Alkali

| Experiment | % Solution of VIIa in water: Original | Final[a] | Moles NaOH per mole VIIa | Recovery, % as: VI | IX |
|---|---|---|---|---|---|
| A | 10 | 6 | >3[b] | 16 | 70 |
| B | 10 | 6 | 3 | 16 | 30 |
| C | 0.3 | 0.3[c] | 3 | 72 | 7 |
| D | 24 | 8 | 3 | .. | 65 |

[a] After addition of the aqueous sodium hydroxide solution. [b] An excess of 5% aqueous sodium hydroxide added. [c] The amount of water added with the alkali in this case did not change the original percentage significantly.

In B and C, the polymer was separated by filtration, after which 50% sodium hydroxide was added to the aqueous filtrate, which then was extracted with benzene. Distillation of the benzene solution gave the quantities of VI listed in Table I. No other amine was present.

In D, 4.8 g. of VIIa (54.6% bromine content) in 15 ml. of water was treated with 46 ml. of 0.706 *N* (three equivalents) sodium hydroxide solution. After four hours, the solution was filtered, and the insoluble material leached with water to remove occluded inorganic salts; no attempt was made to identify the products in the aqueous filtrates. After drying the insoluble product in an oven at 70°, it (1.88 g.) was treated with 75 ml. of absolute ethanol, and 1.12 g. of insoluble material, m. p. above 260°, was separated from the alcoholic solution. The alcoholic solution was evaporated to dryness and treated with petroleum ether (b. p. 60–68°), and 0.1 g. of an insoluble material, m. p. 160–170°, was separated. The petroleum ether solution was concentrated and chilled; 0.47 g. (11%) of the dimer IX ($n = 1$), m. p. 112–133°, separated. After one recrystallization from petroleum ether, this dimer, **1-β-(2,2,5,5-tetramethylpiperazino)-ethyl-2,2,5,5-tetramethyl-4-(β-hydroxyethyl)-piperazine,** melted at 121–129°. After another recrystallization, it melted at 123–125.5°.

*Anal.* Calcd. for $C_{20}H_{42}N_4O$: C, 67.76; H, 11.94; mol. wt., 354.5. Found: C, 67.54; H, 12.20; mol. wt. (Rast), 346.

The material melting at 160–170°, which was insoluble in petroleum ether, had a molecular weight and gave analytical values corresponding to those calculated for the trimer IX ($n$ is 2). The yield of this product amounted to 2% of the theoretical.

*Anal.* Calcd. for $C_{30}H_{62}N_6O$: C, 68.92; H, 11.95; mol. wt., 522. Found: C, 68.12; H, 12.43; mol. wt. (Rast), 511.

The major portion of the polymer, which was insoluble in ethanol and melted above 260°, was too insoluble in all solvents to permit a molecular weight determination. Although its properties indicated it to be a higher polymer IX, ($n > 2$), its analyses (C, 67.7%; H, 12.7%) were not satisfactory for such a structure (for higher values of $n$ the calcd. values for IX approach the limiting values: C, 71.5; H, 12.5, the calcd. values for IX minus water). Because of its refractory nature, this polymer was not investigated further.

When an aqueous solution of the chloro-dihydrochloride (VII) was treated with alkali in the manner described above, there was a momentary turbidity, indicating precipitation of the free base, but the solution cleared within five seconds. Within one minute a gelatinous precipitate began to separate. From such solutions the polymers

(IX) were obtained in quantities approximating those shown in Table I for the bromo compound, VIIa.

(c) **From Heating 1-(β-Chloroethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride (VII).**—This salt was heated alone and suspended in Stanolind mineral oil. The results of four such experiments are given in Table II.

TABLE II

PYROLYSIS OF VII

| Run | Condition | Temp., °C. | Time, min. | Mole HCl/mole VII evolved | I, %, recovered |
|---|---|---|---|---|---|
| 1 | Alone | 230–245 | 30 | 0.82 | 69 |
| 2 | Alone | 210–240 | 35 | .82 | 76.3 |
| 3 | In oil | 180–220 | 80 | .77 | 56.3 |
| 4 | In oil | 213–220 | 80 | .88 | 29.4 |

A typical experiment (run 3) follows: In a 200-ml. three-neck, round-bottom flask fitted with a stirrer, a thermometer, an air inlet and an outlet leading to 50 ml. of water in an erlenmeyer flask were placed 5 g. of VII and 50 ml. of Stanolind mineral oil. The flask was heated in a metal-bath and the hydrogen chloride evolved collected in water and titrated periodically with standard alkali. Above 180° the evolution of hydrogen chloride was steady. After the evolution of hydrogen chloride slowed, the oil suspension was diluted with petroleum ether (b. p. 60–68°), filtered, and the insoluble solid washed with petroleum ether; it weighed 3.48 g. after drying. The solid was dissolved in water, and the solution filtered; 0.06 g. of insoluble material remained. To the aqueous solution was added 5% sodium hydroxide solution; no precipitate formed. The solution was distilled until the distillate was no longer alkaline. Titration of the distillate with standard 1 *N* hydrochloric acid against methyl orange showed the presence of sufficient base to amount to 56.3% of I. Conversion of the salt, remaining from evaporation of the titrated solution, to the dibenzoyl derivative of I, m. p. 273–276°, identified this base as the reaction product. The filtrate from the preparation of the benzoyl derivative was distilled and a non-alkaline distillate obtained, indicating the absence of any of the tertiary, bicyclic amine II.

## Summary

The preparation of 2,2,5,5-tetramethyl-3,6-diketopiperazine (IV) from α-aminoisobutyric acid is described. This diketopiperazine has been converted to 2,2,5,5-tetramethylpiperazine (I) and 2,2,5,5-tetramethyl-3-ketopiperazine (V) by catalytic hydrogenation over copper–chromium oxide as well as by reduction with sodium in butanol.

Attempts to convert the 1-(β-hydroxyethyl)- and the 1-(β-haloethyl)-2,2,5,5-tetramethylpiperazines to the tetramethyl-1,4-diazabicyclo-(2,2,2)-octane (II) were unsuccessful. The hydroxy compound lost the 1-substituent and reverted to I; the 1-haloethyl derivatives in aqueous alkaline solution yielded the 1-hydroxyethyl derivative and polymers (IX) *via* an intermediate ethylene immonium ion, or when heated as salts, lost the 1-substituent to form the piperazine I.

MADISON, WISCONSIN RECEIVED SEPTEMBER 25, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

# The Synthesis of Some Isomeric Dimethyl-hydroxymethylpyridines. 3,4-Didesoxypyridoxin

BY RAYMOND P. MARIELLA AND JOHN L. LEECH[1]

Recent interest in antibiotics has led us to investigate the effect of the variation of the substituents in pyridoxin on possible anti-pyridoxin activity.

It has been shown by Ott[2] that 4-desoxypyridoxin was a powerful competitor to pyridoxin in the chick, and that methoxypyridoxin[3] exhibited similar activity, but to a lesser extent. Recently,[4] 5-deshydroxymethylpyridoxin was shown to be a weak inhibitor of pyridoxin in *Saccharomyces Cerevisiae*, while more recent work with 4-deshydroxymethylpyridoxin[5] has shown that this compound also exhibited very weak anti-pyridoxin properties.[6]

In the present work 2,3-dimethyl-5-hydroxymethylpyridine (VII), and 2,4-dimethyl-5-hydroxymethylpyridine (III) (3,4-didesoxypyridoxin) were synthesized as shown in Fig. 1.

As might be expected, VII exhibited neither pyridoxin nor anti-pyridoxin activity, but III did show weak anti-pyridoxin activity when tested against *Neurospora Sitophila*.[7]

From our work and previously cited work, it would appear that those structures similar to pyridoxin (with one or two groups removed) can exhibit this effect of anti-vitamin activity, and this could be explained on the basis of failure of the organism to differentiate between the vitamin and the similar molecule. With this reasoning, however, it would be difficult to explain why 3-amino-5-aminomethyl-4-ethoxymethyl-2-ethylpyridine has turned out to be the most potent anti-pyridoxin compound yet reported.[4] Work on the synthesis of other compounds related to pyridoxin is continuing in this Laboratory and will be reported soon.

**Acknowledgement.**—The authors wish to thank the Graduate School for a grant which made some of this work possible.

(1) Taken in part from a Master of Science thesis of John L. Leech.

(2) Ott, *Proc. Soc. Exp. Biol. Med.*, **61**, 125 (1946).

(3) Ott, *ibid.*, **66**, 215 (1947).

(4) Reported by Martin, Avakian and Moss at the April, 1948, meeting of the American Chemical Society.

(5) Perez-Medina, Mariella and McElvain, THIS JOURNAL, **69**, 2574 (1947).

(6) Private communication from Professor S. M. McElvain.

(7) These experiments were conducted by the Biochemical Group of the Lilly Research Laboratories, Indianapolis, Indiana.

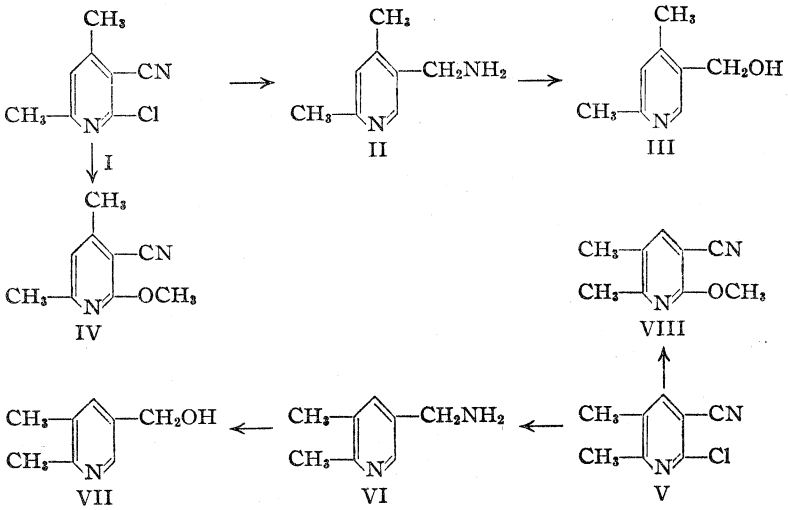



Fig. 1.

## Experimental[8]

**3-Cyano-4,6-dimethyl-2(1)-pyridone.**—This was prepared from acetylacetone and cyanoacetamide.[9] The product was obtained as colorless needles, m. p. 286° (uncor.).

*Anal.* Calcd. for $C_8H_8N_2O$: N, 18.9. Found: N, 18.9.

**2-Chloro-3-cyano-4,6-dimethylpyridine (I).**—An intimate mixture of the two solids, 43 g. of the above pyridone and 66 g. of phosphorus pentachloride, was heated until gentle refluxing began, and the refluxing was continued for two hours. The generated phosphorus oxychloride was removed under reduced pressure, and the remaining brown solid broken up, mixed with ice, and made basic with concentrated sodium hydroxide. The black mixture was then steam distilled, and a yellow solid came over with the water, 37 g. (77%), m. p. 91–94°. After several recrystallizations from alcohol–water, white plates were obtained, m. p. 94.5–95.0°.

*Anal.* Calcd. for $C_8H_7ClN_2$: N, 16.8. Found: N, 16.6.

**3-Cyano-4,6-dimethyl-2-methoxypyridine (IV).**—Sodium methoxide was prepared by adding 0.35 g. of sodium to 25 cc. of methyl alcohol. To this solution, 1.0 g. of chloropyridine (I) was added, and the resulting solution was refluxed for twenty-four hours. The methyl alcohol was removed on a steam cone, and the yellow solid which remained was extracted with anhydrous ether, and the insoluble sodium chloride filtered off. Evaporation of the ether left 0.45 g. (46%) of product, m. p. 93–94°. The material was further purified by sublimation, m. p. 93.5–94.0°. A mixed m. p. with the chloro compound (I) was depressed 30°.

*Anal.* Calcd. for $C_9H_{10}N_2O$: N, 17.3. Found: N, 17.0.

**5-Aminomethyl-2,4-dimethylpyridine Dihydrochloride (II).**—To a solution of 5.54 g. of 2-chloro-3-cyano-4,6-dimethylpyridine (I) in 125 cc. of absolute ethyl alcohol were added in order, a solution of 1.18 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid, 15 cc. of 15% hydrogen chloride in absolute alcohol, and 3 g. of Norit. The suspension was shaken with hydrogen at twenty pounds pressure for two hours, after which time the uptake of hydrogen had ceased. Another solution of 1.10 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid was added and the reduction resumed. After an additonal six hours, the hydrogen absorption had stopped. The catalyst and support were filtered, washed well with absolute alcohol and then water. The water solution was taken to dryness and contained no solid. The alcohol solution was evaporated to 10 cc., cooled in ice, and 1.45 g. of starting compound, m. p. 91°, was obtained. The filtrate was concentrated then to 2 cc. and 50 cc. of absolute alcohol added. This caused the precipitation of 2.09 g. (41% based on recovered starting material) of a voluminous white solid. Recrystallization from a concentrated hydrochloric acid and absolute alcohol mixture, gave small prisms, m. p. 204–206°.

*Anal.* Calcd. for $C_8H_{14}Cl_2N_2$: N, 13.4. Found: N, 13.8.

**2,4-Dimethyl-5-hydroxymethylpyridine Hydrochloride (III).**—To a solution of 2.2 g. of 5-aminomethyl-2,4-dimethylpyridine dihydrochloride (II) in 10 cc. of water was added a solution of 40 cc. of concentrated hydrochloric acid in 80 cc. of water, and the resulting solution was heated to 95°. A solution of 4.5 g. of sodium nitrite in 10 cc. of water was then added, all at once, with vigorous shaking, and the temperature was maintained at 90–95° until all the gas had evolved. The solution was then evaporated to dryness and the remaining white crystalline residue extracted with three 20-cc. portions of boiling absolute alcohol. After filtering off the insoluble sodium chloride, the combined extracts were evaporated to dryness, leaving a yellow solid, 1.6 g. (87%). Subsequent recrystallizations from alcohol–dioxane gave a white product, m. p. 215–220°, which did not give the correct analytical figures. Treatment with acetyl chloride (20 cc.), refluxing one hour, boiling the resulting solution to dryness, and recrystallization of the residue from alcohol–dioxane gave beautiful white plates, m. p. 225–227°.

*Anal.* Calcd. for $C_8H_{12}ClNO$: N, 8.1. Found: N, 8.2.

**2-Chloro-3-cyano-5,6-dimethylpyridine (V).**—An intimate mixture of 20 g. of 3-cyano-5,6-dimethyl-2(1)-pyridone,[10] and 37 g. of phosphorus pentachloride was heated until gentle refluxing began, and the mixture treated in the manner described above for the isomer. The product from the steam distillation was a water-insoluble oil. This oil was extracted with ether, the ether layer dried with anhydrous sodium sulfate, and the ether then removed on a steam cone. The resulting liquid was distilled *in vacuo*, and 16 g. (71%) b. p. 141.5–142.5° at 12 mm., of colorless liquid was collected, $n^{20}D$ 1.5496.

*Anal.* Calcd. for $C_8H_7ClN_2$: N, 16.8. Found: N, 16.3.

**3-Cyano-5,6-dimethyl-2-methoxypyridine (VIII).**—To a sodium methoxide solution, prepared by adding 0.35 g. of sodium to 25 cc. of methyl alcohol, was added 1.0 g. of 2-chloro-3-cyano-5,6-dimethylpyridine (V), and the resulting solution treated in the manner described above for its isomer. Evaporation of the ether from the ether extraction left a wine-colored liquid. This was distilled *in vacuo* and a colorless liquid collected, 0.71 g. (73%), b. p. 145° at 17 mm., $n^{20}D$ 1.5278.

*Anal.* Calcd. for $C_9H_{10}N_2O$: N, 17.3. Found: N, 17.5.

**5-Aminomethyl-2,3-dimethylpyridine Dihydrochloride (VI).**—To a solution of 5.12 g. of 3-cyano-2-chloro-5,6-dimethylpyridine (V) in 75 cc. of absolute alcohol was added in order a solution of 1.55 g. of palladium chloride in 3 cc. of concentrated hydrochloric acid, 15 cc. of a 15% solution of hydrogen chloride in absolute alcohol and 3 g. of Norit. The resulting solution was shaken with hydrogen at fifty pounds pressure for three hours, at which time

(8) Microanalyses by Misses Guy, Hobbs and Hines.

(9) Wagtendonk and Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).

(10) Mariella, THIS JOURNAL, **69**, 2670 (1947).

the hydrogen absorption had ceased. Another solution of 1.00 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid was added and the reduction resumed. After six additional hours, the hydrogen uptake had again ceased. The catalyst and support were filtered, washed well with absolute alcohol and then water. The aqueous solution was taken to dryness on a steam cone and contained no organic material. The alcohol layer was evaporated to 2 cc. and 50 cc. of absolute alcohol added, causing the precipitation of 3.7 g. (58%) of product as voluminous white crystals, m. p. 204–207°. This material was very hygroscopic. Recrystallization from alcohol–ether gave small white needles. After drying at 100° and 1 mm. for six hours the m. p. was 216–218°.

*Anal.* Calcd. for $C_8H_{14}Cl_2N_2$: N, 13.4. Found: N, 13.3.

**2,3-Dimethyl-5-hydroxymethylpyridine and Hydrochloride (VII).**—To a solution of 2.3 g. of 5-aminoethyl-2,3-dimethylpyridine dihydrochloride (VI) in 10 cc. of water was added a solution of 40 cc. of concentrated hydrochloric acid in 80 cc. of water, and the resulting solution heated to 95°. A solution of 4.5 g. of sodium nitrite in 10 cc. of water was then added all at once, with vigorous shaking. The temperature was maintained at 85–90° until the gas evolution had ceased. The solution was then evaporated until a semi-crystalline mass remained. Attempts to obtain the crystalline hydrochloride by the method described for its isomer failed, as a liquid was always obtained. This liquid hydrochloride was then added to 10 cc. of water containing 1 g. of sodium bicarbonate. The water was removed *in vacuo*, and the residue extracted with three 15-cc. portions of boiling absolute alcohol. After filtering off the inorganic salts, the combined alcoholic extracts were concentrated until an oil remained. This was distilled and a colorless liquid, 0.45 g. (30%), b. p. 108° at 0.5 mm., was obtained.

*Anal.* Calcd. for $C_8H_{11}NO$: N, 10.2. Found: N, 9.9.

The hydrochloride was finally prepared by dissolving this free base in 100 cc. of dry ether and passing in dry hydrogen chloride gas as a voluminous white solid separated out. This was very hygroscopic. A sample dried at 40° and 1 mm. for seventy-two hours had a m. p. 103–106°.

## Summary

2,3-Dimethyl-5-hydroxymethylpyridine and 2,4-dimethyl-5-hydroxymethylpyridine (3,4-didesoxypyridoxin) have been synthesized. The former compound exhibited neither vitamin nor anti-vitamin activity, while the latter compound proved to be a weak antagonist for pyridoxin.

EVANSTON, ILL. RECEIVED JULY 30, 1948

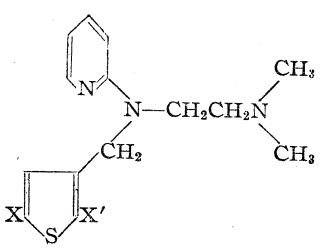
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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

# 3-Substituted Thiophenes. III. Antihistaminics of the N-(3-Thenyl)-ethylenediamine Series[1]

BY E. CAMPAIGNE AND WILLIAM M. LESUER[2]

Recently it has been discovered that incorporation of the thiophene nucleus in antihistaminic compounds leads to desirable properties.[3–6] The work of Clapp, *et al.*,[5] indicates that the inclusion of a halogen atom on the thiophene ring improves the therapeutic ratio. Continuing a study of the properties of 3-thienyl analogs of physiologically active compounds,[7–9] attention was turned to the antihistaminic series. The preparation of four N-substituted dimethylaminoethylaminopyridines, containing the 3-thenyl and halogen-substituted 3-thenyl nucleus are described in this paper. The compounds prepared were: I, N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thenyl)-ethylenediamine; II, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-chloro-3-thenyl)-ethylenediamine; III, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-bromo-3-thenyl)-ethylenediamine; and IV, N,N-dimethyl-N′-(2-pyridyl)-N′-(2,5-dichloro-3-thenyl)-ethylenediamine.




I, X = H, X′ = H
II, X = H, X′ = Cl
III, X = H, X′ = Br
IV, X = Cl, X′ = Cl

These compounds were readily synthesized by the reaction of the sodio-derivative of 2-dimethylaminoethylaminopyridine with the appropriate 3-thenyl bromide, obtained when the proper 3-methylthiophene reacted with N-bromosuccinimide.[7] In order to produce the corresponding halogenated compounds, it was necessary to extend the N-bromosuccinimide reaction to the halogenated 3-methylthiophenes, and characterize the halogenated thenyl bromides. As was expected, it was found that blocking the active 2-position with a halogen greatly improved the yield of side-chain bromination with N-bromosuccinimide. The reactions carried out in the preparation of the four antihistaminics and intermediates are outlined in the accompanying diagram. In each case the thenyl bromide was converted to the hexamethylenetetramine salt, the salt steam distilled to obtain the aldehyde, which was then oxidized to the acid with silver oxide.

The chlorination of 3-methylthiophene with sulfuryl chloride[10] was extended to the preparation

(1) Taken from part of the thesis submitted by William M. LeSuer in partial fulfilment of the requirements for the degree Doctor of Philosophy at Indiana University, June, 1948.

(2) Sterling-Winthrop Fellow in Chemistry, 1947. Present address: Lubrizol Corporation, Cleveland, Ohio.

(3) Weston, THIS JOURNAL, **69**, 980 (1947).

(4) Lee, Dinwiddie and Chen, *J. Pharm.*, **90**, 83 (1947).

(5) Clapp, *et al.*, THIS JOURNAL, **69**, 1549 (1947).

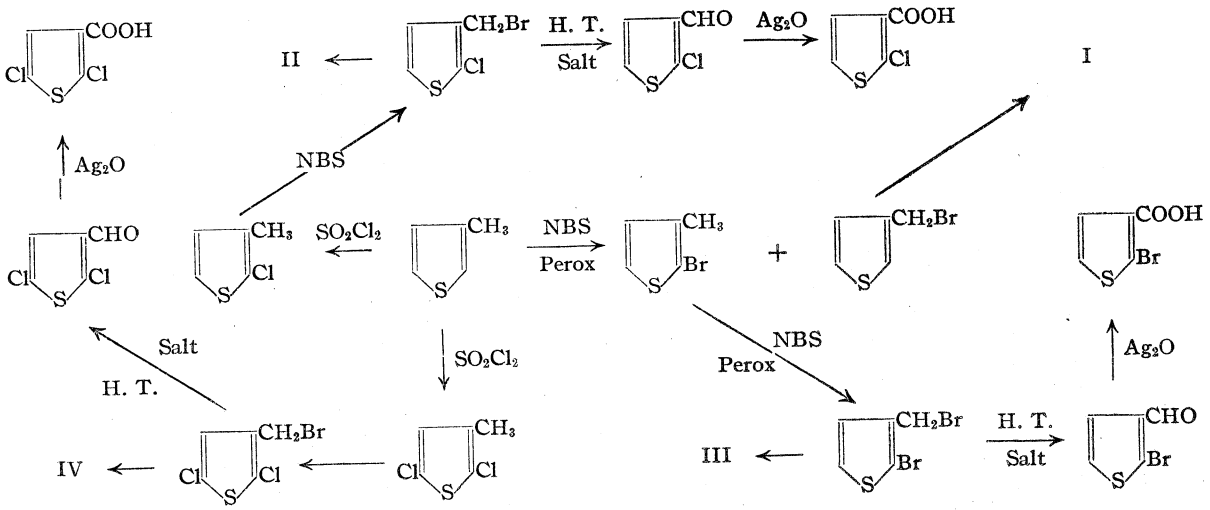
(6) Kyrides, Meyer and Zienty, *ibid.*, **69**, 2239 (1947).

(7) Campaigne and LeSuer, *ibid.*, **70**, 1555 (1948).

(8) Campaigne, *et al.*, *ibid.*, **70**, 2611 (1948).

(9) Campaigne and LeSuer, *ibid.*, **70**, 3498 (1948).

(10) Campaigne and LeSuer, *ibid.*, **70**, 415 (1948).




of 2,5-dichloro-3-methylthiophene, which was found to be produced in good yield by this reaction.

The pharmacological data on these compounds will be published elsewhere by Dr. A. M. Lands, of the Sterling–Winthrop Research Institute.

## Experimental

**2-Chloro-3-thenyl Bromide.**—A solution of 66 g. (0.5 mole) of 2-chloro-3-methylthiophene[10] in 150 ml. of carbon tetrachloride was mixed with 88.5 g. (0.5 mole) of N-bromosuccinimide and 1.0 g. of benzoyl peroxide was added. After refluxing for eight hours, the mixture was cooled and filtered to remove succinimide. The succinimide was washed with 50 ml. of carbon tetrachloride, and the combined filtrates fractionated under reduced pressure. A highly lachrymatory oil was collected at 85–92° (1–2 mm.), and amounted to 81 g. (0.37 mole, 75%). The main portion distilled at 88° (1 mm.), and a sample of this fraction ($n^{22}D$ 1.6119), was used for analyses.

*Anal.* Calcd. for $C_5H_4BrClS$: S, 15.16. Found: S, 15.19.

**Hexamethylenetetramine Salt of 2-Chloro-3-thenyl Bromide.**—To 37.2 g. (0.18 mole) of 2-chloro-3-thenyl bromide in 50 ml. of chloroform was added 25 g. (0.18 mole) of hexamethylenetetramine, and the mixture was shaken. Separation of the salt began immediately, but the mixture was refluxed for one hour to ensure complete reaction. After cooling the salt was filtered, washed with ether, and air dried; yield, 52 g. (84%). Recrystallization of the salt from ethanol yielded beautiful white needles which melted at 165°.

*Anal.* Calcd. for $C_{11}H_{16}N_4BrClS$: S, 9.12. Found: S, 8.80.

**2-Chloro-3-thenaldehyde.**—A solution of 40 g. (0.14 mole) of the hexamethylenetetramine salt of 2-chloro-3-thenyl bromide in 150 ml. of hot water was rapidly steam distilled until 750 ml. of distillate was collected. The distillate was acidified with hydrochloric acid, extracted with three 75-ml. portions of ether, and the extract dried over Drierite. After removing the ether, the residue solidified on cooling. It was dissolved in high-boiling petroleum ether, and crystallized at Dry Ice temperature. After filtering, the crystalline material was transferred to a small flask and distilled in vacuum. The product was a colorless oil, b. p. 100–102° (1–2 mm.), and weighed 4.2 g. (0.029 mole, 25%). It crystallized on standing at room temperature, m. p. 25°, $n^{20}D$ 1.5908.

*Anal.* Calcd. for $C_5H_3OClS$: S, 21.87. Found: S, 21.58.

The 2,4-dinitrophenylhydrazone of 2-chloro-3-thenaldehyde was formed readily by the usual procedure, giving orange needles from chloroform, which melted at 214°.

*Anal.* Calcd. for $C_{11}H_7O_4N_4ClS$: S, 9.81. Found: S, 9.98.

**2-Chloro-3-thenoic Acid.**—A solution of 0.5 g. (0.0034 mole) of 2-chloro-3-thenaldehyde in 5 ml. of ethanol was added to a thoroughly shaken suspension of silver oxide, produced by adding 0.35 g. of sodium hydroxide to 1.0 g. of silver nitrate in 25 ml. of water, and the mixture shaken for thirty minutes. The free silver was removed by filtering, washed with water, and the filtrate acidified with concentrated hydrochloric acid. The white precipitate was recrystallized from water, yielding 0.42 g. (0.0025 mole, 75%) of 2-chloro-3-thenoic acid, which melted at 163°.

*Anal.* Calcd. for $C_5H_3O_2ClS$: S, 19.72. Found: S, 19.84.

**2-Bromo-3-thenyl Bromide.**—The 2-bromo-3-methylthiophene used for this preparation was obtained as a by-product in the bromination 3-methylthiophene with N-bromosuccinimide.[7] The compound was separated by treating the mixture produced in the bromination reaction with hexamethylenetetramine in chloroform, thus removing the 3-thenyl bromide salt. The unreacted 2-bromo-3-methylthiophene and chloroform was accumulated from a number of such preparations and fractionated. The 2-bromo-3-methylthiophene was collected from 172–174°[11] and redistilled in vacuum, b. p. 52° (3 mm.). A solution of 88.5 g. (0.5 mole) of 2-bromo-3-methylthiophene in carbon tetrachloride was treated with 0.5 mole of N-bromosuccinimide and 1.0 g. of benzoyl peroxide, as described above. The product was collected at 105–120° (7 mm.), the main portion coming over at 113° (7 mm.) ($n^{20}D$ 1.6241) and weighed 84.2 g. (0.328 mole, 65%).

*Anal.* Calcd. for $C_5H_4Br_2S$: S, 12.82. Found: S, 12.79.

**Hexamethylenetetramine Salt of 2-Bromo-3-thenyl Bromide.**—This salt was formed in the usual manner from 0.32 mole of 2-bromo-3-thenyl bromide in 75% yield (94 g.). When recrystallized from ethanol, the salt melted at 171–172°.

*Anal.* Calcd. for $C_{11}H_{16}N_4Br_2S$: S, 8.09. Found: S, 7.77.

**2-Bromo-3-thenaldehyde.**—Produced by the steam distillation of 50 g. of the hexamethylenetetramine salt, the aldehyde solidified on standing, after the ether used to extract it was removed. Two recrystallizations from high-boiling petroleum ether yielded 3.7 g. (15%) of white needles, which melted at 34°.

(11) Steinkopf, *Ann.*, **515**, 273 (1935), reported the boiling point of this compound to be 175° (729 mm.).

*Anal.* Calcd. for $C_5H_3OBrS$: S, 16.78. Found: S, 17.00.

The 2,4-dinitrophenylhydrazone of 2-bromo-3-thenaldehyde crystallized from chloroform in orange needles, which melted at 230.5°.

*Anal.* Calcd. for $C_{11}H_7O_4N_4BrS$: S, 8.64. Found: S, 8.65.

**2-Bromo-3-thenoic Acid.**—One gram (0.005 mole) of 2-bromo-3-thenaldehyde was shaken with silver oxide, and the acid worked up in the usual manner. Recrystallization from a 4:1 water–ethanol mixture yielded 0.84 g. (78%) of slender white needles, which melted at 178–179°.

*Anal.* Calcd. for $C_5H_3O_2BrS$: S, 15.49. Found: S, 15.54.

**2,5-Dichloro-3-methylthiophene.**—To 296 g. (3.0 moles) of 3-methylthiophene was added dropwise 810 g. (6.0 moles) of sulfuryl chloride over a period of three hours. Spontaneous refluxing soon began and continued throughout the addition. When spontaneous refluxing subsided, heat was applied and the mixture refluxed two hours longer, and then fractionally distilled. The yield of 2-chloro-3-methylthiophene, b. p. 50° (16 mm.), $n^{20}D$ 1.5408, was 31 g. (0.235 mole, 8%). The main product, 2,5-dichloro-3-methylthiophene, distilled at 44° (1 mm.), 65° (11 mm.), $n^{20}D$ 1.5560, and weighed 316 g. (1.89 moles, 63%). The higher boiling products were not identified.

*Anal.* Calcd. for $C_5H_4Cl_2S$: S, 19.2. Found: S, 19.6.

**2,5-Dichloro-3-thenyl Bromide.**—A solution of 83.5 g. (0.5 mole) of 2,5-dichloro-3-methylthiophene was treated, as previously described, with an equivalent portion of N-bromosuccinimide and 1.0 g. of benzoyl peroxide. A violent reaction occurred when heating was begun, and it was necessary to cool externally at first to control the reaction. After refluxing ten hours, the yellow filtrate was concentrated and the product fractionated in vacuum. The yield of 2,5-dichloro-3-thenyl bromide, b. p. 104.5–106° (4 mm.), $n^{20}D$ 1.6177, was 84.7 g. (0.345 mole, 69%).

*Anal.* Calcd. for $C_5H_3BrCl_2S$: S, 13.03. Found: S, 12.92.

The hexamethylenetetramine salt of 2,5-dichloro-3-thenyl bromide was obtained in 90% yield; recrystallized from methanol, m. p. 178–80° (dec.).

*Anal.* Calcd. from $C_{11}H_{15}N_4BrCl_2S$: S, 8.30. Found: S, 8.56.

**2,5-Dichloro-3-thenoic Acid.**—Steam distillation of a solution of 42 g. (0.109 mole) of the hexamethylenetetramine salt of 2,5-dichloro-3-thenyl bromide yielded a small amount of oil having an almond odor. The crude aldehyde was oxidized with silver oxide, and the crude acid crystallized from a 50:50 water–ethanol mixture, yielding 2.3 g. (0.0125 mole, 11.4%) of 2,5-dichloro-3-thenoic acid, which melted at 146.5–147.5°.[12]

**Dimethylaminoethylaminopyridine Derivatives.**—The syntheses of all of the antihistaminic compounds were conducted in essentially the same manner. The procedure for the preparation of the 3-thenyl derivative is described, and the physical constants and yields of all are tabulated in Table I. To a stirred suspension of 3.12 g. (0.08 mole) of sodamide in 50 ml. of dry tolene was added dropwise 12 g. (0.073 mole) of 2-dimethylaminoethylaminopyridine.[13] The mixture was refluxed for two hours, cooled to 50°, and 21 g. (0.12 mole) of 3-thenyl bromide was added dropwise. When the reaction subsided, the brownish-orange mixture was refluxed one-half hour longer, cooled, and poured into 150 ml. of water. Three layers formed, water, toluene and a black oil which contained none of the desired product, but was probably the quaternary salt resulting from the reaction of 3-thenyl bromide with the dimethylamine group. The toluene layer was separated, extracted with 5% hydrochloric acid, and the hydrochloric acid layer saturated with potassium carbonate. The free base was extracted with ether, dried and fractionated. In this way, 6 g. (0.023 mole, 31.4%) of a yellow oil boiling at 169–172° (1 mm.) was obtained.

TABLE I

PROPERTIES OF THE 3-THENYL-DIMETHYLAMINOETHYLAMINOPYRIDINES

| Compounds | Yield, % | B. p., °C. (1 mm.) | $n^{20}D$ | Formula | Anal. S, % Calcd. | Found |
|---|---|---|---|---|---|---|
| I | 31.4 | 169–172 | 1.5915 | $C_{14}H_{19}N_3S$ | 12.27 | 12.24 |
| II | 28 | 156–158 | 1.5950 | $C_{14}H_{18}N_3ClS$ | 10.84 | 11.33 |
| III | 20 | 177–179 | 1.6590 | $C_{14}H_{18}N_3BrS$ | 9.42 | 9.14 |
| IV | 38 | 179–181 | 1.5968 | $C_{14}H_{17}N_3Cl_2S$ | 9.71 | 10.01 |

The monohydrochloride of N,N-dimethyl-N'-(3-thenyl-)-N'-(2-pyridyl)-ethylenediamine was prepared in the following manner from a larger quantity of the base.[14] 106 g. of the free base was dissolved in 500 ml. of isopropyl alcohol and 34 ml. of concentrated hydrochloric acid was added. After shaking, the reaction mixture was allowed to crystallize. After thorough cooling in an ice–methanol mixture, the salt was collected and washed on the filter with low-boiling petroleum ether. The salt was dried in an oven at 70°, giving 91 g. of a white solid, m. p. 169.5–170°. A second crop of 13 g. was obtained by concentrating the filtrate, making the total yield 86%.

*Anal.* Calcd. for $C_{14}H_{20}N_3SCl$: Cl, 11.93; S, 10.76; N, 14.12. Found: Cl, 11.80; S, 10.79; N, 13.97.

**Acknowledgment.**—The authors gratefully acknowledge the coöperation and financial support of this research by the Sterling–Winthrop Research Institute.

## Summary

Four new compounds containing the 3-thenyl and halogen-substituted 3-thenyl radical, have been synthesized for testing for antihistaminic activity.

The peroxide-catalyzed reaction of N-bromosuccinimide with halogen substituted 3-methylthiophenes has been shown to give good yields of the corresponding 3-thenyl bromides.

Several new 3-substituted thiophene derivatives, containing the methyl, bromomethyl, aldo and carboxyl group in the 3-position, have been synthesized and characterized.

BLOOMINGTON, IND. RECEIVED JUNE 7, 1948

(12) Hartough and Conley, THIS JOURNAL, **69**, 3096 (1947), reported 147–148° for the acid prepared by oxidation of 2,5-dichloro-3-acetylthiophene.

(13) Generously supplied by Dr. C. M. Suter of the Sterling-Winthrop Research Institute.

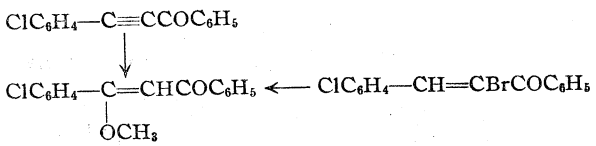
(14) We are indebted to Mr. B. F. Tullar of the Sterling-Winthrop Research Institute for the preparation of this salt.

[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

# β-Alkoxy Derivatives of 2-Chlorochalcone

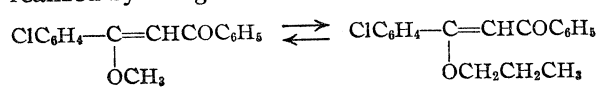
BY CHARLES L. BICKEL

Earlier reports from this Laboratory described the preparation of β-methoxy-2-chlorochalcone either by the addition of methanol to *o*-chlorophenylbenzoylacetylene[1] or by the action of methanol and potassium hydroxide on α-bromo-2-chlorochalcone.[2] β-Ethoxy-2-chlorochalcone and



β-propoxy-2-chlorochalcone have now been prepared by the addition of the appropriate alcohol to *o*-chlorophenylbenzoylacetylene.

In the presence of potassium hydroxide, these alkoxy derivatives can be converted one into the other by the use of the proper alcohol as solvent and reagent. For example, β-methoxy-2-chlorochalcone is converted into β-propoxy-2-chlorochalcone when treated with propanol-1 and potassium hydroxide, and the reverse reaction is realized by using methanol and the base.



These interconversions bear a resemblance to the interchange of esters but a closer examination indicates that the resemblance is only superficial. Ester interchange is catalyzed by a trace of a base while the interconversions herein described may proceed in the presence of a quantity of base exceeding one equivalent of the β-alkoxy compound. The reaction corresponding to the saponification of an ester, the liberation of the enol form of the β-diketone, apparently does not occur since the compound thus liberated would be cleaved by the base. Moreover, ester interchange is catalyzed by acids but β-alkoxychalcones are converted cleanly into β-diketones by the action of acids.

This investigation was assisted by a generous grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

## Experimental

**Preparation of β-Alkoxy Derivatives from *o*-Chlorophenylbenzoylacetylene.**—The preparation of β-methoxy-2-chlorochalcone from *o*-chlorophenylbenzoylacetylene appeared in an earlier paper.[1] Application of the same general procedure gave the ethoxy and propoxy derivatives.

β-Ethoxy-2-chlorochalcone is extremely soluble in ether, appreciably soluble in low-boiling petroleum ether, crystallizes as stout colorless prisms and melts at 39°.

*Anal.* Calcd. for $C_{17}H_{15}O_2Cl$: C, 71.2; H, 5.28. Found: C, 70.5, 71.0; H, 5.33, 5.22.

β-Propoxy-2-chlorochalcone is very soluble in ether, sparingly soluble in low-boiling petroleum ether, crystallizes as long fibrous white needles resembling glass wool and melts at 55°.

*Anal.* Calcd. for $C_{18}H_{17}O_2Cl$: C, 71.8; H, 5.71. Found: C, 71.5; H, 5.77.

Each of the above new compounds was converted quantitatively into *o*-chlorodibenzoylmethane by concentrated hydrochloric acid.[2]

**Interconversion of β-Alkoxy Compounds.**—The same general procedure was employed in all cases and can be illustrated by the following conversion of β-methoxy-2-chlorochalcone into β-propoxy-2-chlorochalcone.

A solution of 20 g. of the methoxy compound in 50 ml. of propanol-1, containing 1.5 g. of potassium hydroxide pellets, was heated on a steam-bath for five hours. The resulting solution was cooled, water added to a pronounced turbidity, the turbid mixture seeded with the propoxy compound and placed in the refrigerator until crystallization was complete. During the crystallization, water was added from time to time in sufficient quantity to produce turbidity but not enough to precipitate the product as an oil. The solid was filtered, washed with a cold mixture of propanol and water, and then washed thoroughly with water. The dry product weighed 19 g. and melted at 53–55°, recrystallization from ether and petroleum ether giving 18.5 g. of pure white needles melting at 55°.

The yields in the conversions varied from 60 to 90%. The highest yields were realized in the preparation of the methoxy compound, undoubtedly due to its higher melting point and lower solubility; the lowest yield was obtained in the preparation of the ethoxy compound which is very low melting and has a marked tendency to separate as an oil. However, in each case the residual oily product was converted into *o*-chlorodibenzoylmethane by the action of concentrated hydrochloric acid, indicating the absence of side reactions.

**Action of Potassium Hydroxide and Methanol on the Methoxy Compound.**—In order to test the action of an excess of potassium hydroxide on an alcoholic solution of the alkoxy derivatives, a solution containing 5.00 g. of β-methoxy-2-chlorochalcone, 1.5 g. of potassium hydroxide pellets and 50 ml. of methanol was refluxed for ten hours. A recovery of 4.95 g. of the starting material was realized.

**Action of Potassium Hydroxide and Methanol on *o*-Chlorodibenzoylmethane.**—A solution containing 5 g. of *o*-chlorodibenzoylmethane, 1.5 g. of potassium hydroxide and 50 ml. of methanol was refluxed for ten hours. The extent of cleavage was about 50%, both benzoic acid and *o*-chlorobenzoic acid appearing in the cleavage products.[2]

## Summary

The interconversion of certain β-alkoxy derivatives of 2-chlorochalcone is reported.

EXETER, NEW HAMPSHIRE RECEIVED AUGUST 16, 1948

(1) Bickel, THIS JOURNAL, **69**, 74 (1947).

(2) Bickel, *ibid.*, **68**, 866 (1946).

[CONTRIBUTION FROM NATIONAL BUREAU OF STANDARDS]

# Mass Spectra of Some Cyclic and Straight Chain Fluorocarbons[1]

BY FRED L. MOHLER, EVELYN G. BLOOM, J. H. LENGEL AND C. E. WISE

The Mass Spectrometry Section of the Bureau of Standards has measured the mass spectra of some pure fluorocarbons prepared by George H. Cady of the Chemistry Department of the University of Washington.[1a] This paper presents these measurements in comparison with the mass spectra of the corresponding hydrocarbons. Tables of the detailed mass spectral data have been published in the Catalog of Mass Spectral Data.[2]

## Experimental

Mass spectra were obtained with a 180° Consolidated mass spectrometer which has been described in detail elsewhere.[3] Recommended procedures were followed in obtaining the spectra except that it was necessary to use a magnet current in excess of the rated current to record the ions of high molecular weight. A magnet current of 1.3 amperes was used in the range from molecular weight 50 up to a value exceeding the molecular weight of the molecule. Mass spectra were measured with ionizing potentials of 50 volts and 70 volts but only the 70-volt spectra are reported here. The temperature of the ionization chamber was automatically maintained at 245° and the electron current to the collector (catcher) was automatically held at 9 microamperes.

Relative intensities in the mass spectrum are expressed on a scale of the peak of maximum height taken as 100 and peaks as small as 0.01 can be detected. The sensitivity is commonly expressed in terms of the current at the maximum peak in arbitrary units divided by the pressure in the gas reservoir. The ratio of this sensitivity to the sensitivity to normal butane at $43^+$ gives a value independent of the arbitrary units used and it is this relative sensitivity that is given here. The resolving power of our mass spectrometer was not sufficient to resolve completely unit mass differences beyond mass 150. This introduces a little uncertainty in reading the mass peaks of the heavier ions from cyclo-$C_5F_9H$.

The boiling points of the six fluorocarbons measured are listed in Table I. The first three of these compounds were carefully separated from impurities using an 82 theoretical plate fractionating column. The same column was used for cyclo-$C_5F_9H$ but traces of impurities probably remained. The last two compounds are of good quality but inferior to the first three. The mass spectrometer analysis showed no recognizable impurities in any of the perfluoro compounds. In the spectrum of cyclo-$C_5F_9H$ there is a small peak, 0.19% of the maximum peak, near mass 250. This could be $C_5F_{10}^+$ or $C_5F_{10}H^+$. The spectrum shows that it cannot be cyclo-$C_5F_{10}$ but a trace of a perfluoropentene is possible. Another possibility is that it is $C_5F_{10}H^+$ from $C_5F_{11}H$. This compound makes an unknown but probably small contribution to the pattern recorded in Table III.

TABLE I

BOILING POINTS OF FLUOROCARBONS

| Number | Substance | Boiling point, °C. |
|---|---|---|
| 1 | Cyclo-$C_5F_{10}$ | 22.5 |
| 2 | $n$-$C_5F_{12}$ | 29.3 |
| 3 | $i$-$C_5F_{12}$ | 30.1 |
| 4 | Cyclo-$C_5F_9H$ | 37.8 to 38.2 |
| 5 | Cyclo-$C_6F_{12}$ | 51 (sublimes) |
| 6 | $n$-$C_7F_{16}$ | 82.4 to 82.6 |

TABLE II

MASS SPECTRA OF CYCLOHEXANES

Sensitivity relative to $43^+$ of $n$-butane: $C_3F_5^+$, 1.37

| Ion | Rel. inten. | Ion | Rel. inten. | Ion | Rel. inten. | Ion | Rel. inten. |
|---|---|---|---|---|---|---|---|
| $C_6^-$ | | $C_6^-$ | | $C_3^-$ | | $C_3^-$ | |
| $H_{12}$ | 73.9 | $F_{12}$ | 0.70 | $H_7$ | 13.6 | $F_7$ | 0.02 |
| $H_{11}$ | 4.55 | $F_{11}$ | 3.77 | $H_6$ | 29.8 | $F_6$ | .48 |
| | | | | $H_5$ | 64.9 | $F_5$ | 100 |
| $C_5^-$ | | $C_5^-$ | | $H_4$ | 6.21 | $F_4$ | 2.53 |
| $H_{10}$ | 1.20 | $F_{10}$ | 0.05 | $H_3$ | 28.4 | $F_3$ | 15.0 |
| $H_9$ | 22.2 | $F_9$ | 20.9 | $H_2$ | 2.53 | $F_2$ | 2.96 |
| $H_8$ | 1.69 | $F_8$ | 0.16 | H | 1.05 | F | 1.07 |
| $H_7$ | 2.95 | $F_7$ | 2.71 | | | | |
| | | | | $C_2^-$ | | $C_2^-$ | |
| $C_4^-$ | | $C_4^-$ | | $H_5$ | 11.7 | $F_5$ | 5.59 |
| $H_8$ | 100 | $F_8$ | 0 | $H_4$ | 13.2 | $F_4$ | 29.2 |
| $H_7$ | 34.9 | $F_7$ | 21.4 | $H_3$ | 30.4 | $F_3$ | 2.14 |
| $H_6$ | 6.82 | $F_6$ | 3.96 | $H_2$ | 4.74 | $F_2$ | 1.23 |
| $H_5$ | 4.80 | $F_5$ | 2.06 | | | | |
| $H_4$ | 1.35 | $F_4$ | 1.54 | $C^-$ | | $C^-$ | |
| $H_3$ | 3.34 | $F_3$ | 0.57 | $H_3$ | 5.35 | $F_3$ | 70.3 |
| $H_2$ | 2.23 | $F_2$ | .36 | $H_2$ | 0.42 | $F_2$ | 5.15 |
| | | | | H | .08 | F | 21.8 |
| | | | | C | .05 | C | .03 |

The hydrocarbon mass spectra given for comparison with the fluorocarbons were obtained with National Bureau of Standards Samples of purity 99.85% and better. The tables omit some smaller peaks of less than 2% of the maximum peak.

## Results

When mass spectra of fluorocarbons are tabulated in the order of increasing or decreasing molecular weight the ions with different numbers of carbon atoms and of fluorine atoms alternate in a rather confusing disorder. For convenient comparison with the more familiar hydrocarbon spectra the ions containing the same number of carbon atoms have been grouped together in the following tables.

**Cyclohexanes.**—Table II gives the mass spectra of cyclohexane and the perfluoro compound. In the hydrocarbon molecule the molecule ion (parent ion) and ions $C_5H_9^+$, $C_4H_8^+$, $C_3H_5^+$ and $C_2H_3^+$ are relatively abundant. It is of interest that $CH_3^+$ has about the same intensity in cyclics as in molecules containing $CH_3$ terminal radicals.

In the fluorinated compounds the parent ion peaks are always very small indicating that the more probable ionization process is removal of $F^-$

(1) Paper presented before the Oregon meeting of the American Chemical Society, September 13–17, 1948.

(1a) The fluorinated pentanes used for this research were prepared under contract with the Office of Naval Research, Navy Department.

(2) Catalog of mass spectral data, American Petroleum Institute, Project 44, National Bureau of Standards.

(3) H. W. Washburn, H. F. Wiley, S. M. Rock and C. E. Berry, *Ind. and Eng. Chem., Anal. Ed.*, **15**, 54 (1943).

TABLE III

MASS SPECTRA OF CYCLOPENTANES

Sensitivity relative to $43^+$ of *n*-butane; $C_3F_5^+$ of $C_5F_{10}$, 1.73; $C_3F_5^+$ of $C_5F_9H$, 0.61

| Cyclo-$C_5H_{10}$ Ion | Rel. inten. | Cyclo-$C_5F_{10}$ Ion | Rel. inten. | Cyclo-$C_5F_9H$ Ion | Rel. inten. | Ion | Rel. inten. |
|---|---|---|---|---|---|---|---|
| $C_5^-$ | | $C_5^-$ | | $C_5^-$ | | $C_5^-$ | |
| $H_{10}$ | 29.3 | $F_{10}$ | 0.36 | | | $F_9H$ | 0.11 |
| $H_9$ | 1.07 | $F_9$ | 4.45 | $F_9$ | 0 | $F_8H$ | 4.26 |
| $H_8$ | 0.41 | $F_8$ | .02 | $F_8$ | 0.13 | $F_7H$ | 0.33 |
| $C_4^-$ | | $C_4^-$ | | $C_4^-$ | | $C_4^-$ | |
| $H_7$ | 29.0 | $F_7$ | 14.4 | $F_7$ | 0 | $F_6H$ | 20.7 |
| $H_6$ | 0.91 | $F_6$ | 0.93 | $F_6$ | 0.76 | $F_5H$ | 1.93 |
| $H_5$ | 1.86 | $F_5$ | .53 | $F_5$ | .74 | $F_4H$ | 1.34 |
| $C_3^-$ | | $C_3^-$ | | $C_3^-$ | | $C_3^-$ | |
| | | | | $F_7$ | .66 | $F_6H$ | 2.97 |
| $H_6$ | 100 | $F_6$ | .39 | $F_6$ | .53 | $F_5H$ | [a] |
| $H_5$ | 28.9 | $F_5$ | 100 | $F_5$ | 100 | $F_4H$ | 80.4 |
| $H_4$ | 7.33 | $F_4$ | 1.36 | $F_4$ | 1.06 | $F_3H$ | 1.62 |
| $H_3$ | 20.9 | $F_3$ | 9.65 | $F_3$ | 9.40 | $F_2H$ | 11.0 |
| $H_2$ | 3.16 | $F_2$ | 2.62 | $F_2$ | 2.87 | F H | 2.39 |
| H | 1.42 | F | 1.13 | F | 1.55 | H | 0.69 |
| $C_2^-$ | | $C_2^-$ | | $C_2^-$ | | $C_2^-$ | |
| $H_5$ | 4.56 | $F_5$ | 0.24 | $F_5$ | 5.59 | $F_4H$ | 0.60 |
| $H_4$ | 3.73 | $F_4$ | 23.8 | $F_4$ | 29.6 | $F_3H$ | 23.4 |
| $H_3$ | 14.7 | $F_3$ | 1.88 | $F_3$ | 1.34 | $F_2H$ | 2.62 |
| $H_2$ | 3.35 | $F_2$ | 1.28 | $F_2$ | 1.34 | FH | 1.64 |
| $C^-$ | | $C^-$ | | $C^-$ | | $C^-$ | |
| $H_2$ | 3.44 | $F_2$ | 16.2 | $F_2$ | 56.3 | $F_2H$ | 14.0 |
| $H_2$ | 0.51 | $F_2$ | 5.11 | $F_2$ | 6.19 | FH | 2.24 |
| H | .11 | F | 23.3 | F | 30.9 | H | 0.13 |

[a] Masked by isotope.

rather than an electron. Studies[4] of mass spectra and appearance potentials for simpler compounds such as carbon tetrafluoride support this view. Ions $C_6F_{11}^+$, $C_5F_9^+$, $C_4F_7^+$, $C_3F_5^+$, $C_2F_4^+$ and $CF_3^+$ are the most abundant ions in each carbon group.

**Cyclopentanes.**—Table III gives mass spectra of three cyclopentanes. There is a marked similarity between cyclo-$C_5F_{10}$ and cyclo-$C_6F_{12}$. The same ions $C_5F_9^+$, $C_4F_7^+$, $C_3F_5^+$, $C_2F_4^+$ and $CF_3^+$ are abundant in both spectra although in the cyclopentane $CF^+$ is greater than $CF_3^+$. There is a different type of similarity between the two hydrocarbons. In these the largest peaks in the first four carbon groups are the molecule ion and molecule ions which have lost $CH_3$, $C_2H_4$ and $C_3H_7$. As a result the larger peaks in the two spectra are different.

Substituting one hydrogen in the fluoro compound doubles the complexity of the spectrum and it is convenient to list the ions in two columns, one containing perfluoro ions and the other containing ions with one hydrogen (Table III). As noted above there are two sources of experimental uncertainty in the data on cyclo-$C_5F_9H$. A trace of $C_5F_{10}^+$ gives an unknown contribution and insufficient resolution gives some uncertainty in the height of peaks containing an H atom when there are seven or more fluorine atoms. The absence of $C_4F_7^+$ in the cyclo-$C_5F_9H$ spectrum shows that the $C_5F_{10}^+$ is not from cyclo-$C_5F_{10}$.

Table III shows a very close parallelism between ions of $C_5F_9H$ containing H and the corresponding ions of cyclo-$C_5F_{10}$. The occurrence of $C_3F_6H^+$ but no ion $C_3F_7^+$ from cyclo-$C_5F_{10}$ is an exception. Another exception is the fact that $CF^+$ is large but $CH^+$ is small. This is not surprising however as the $CH^+$ peak is of the same magnitude as is found in all hydrocarbons.

The perfluoro ions of cyclo-$C_5F_9H$ do not correspond closely to the ions of $C_5F_{10}$. The absence of ions $C_5F_9$ and $C_4F_7$ is a striking characteristic of the $C_5F_9H$ spectrum. It is suggestive that the abundance of $CF_3^+$ from $C_5F_9H$ is almost four times the abundance of $CF_2H^+$ for this is the *a priori* probability of finding H missing or present on one of the C atoms of cyclo-$C_5F_9H$. The chance of finding H missing or present on two adjacent carbon atoms is 3 to 2 while the ratio of $C_2F_4^+$ to $C_2F_3H^+$ is 2.52 to 2. In ions with more than two carbon atoms there is no evidence for such a relation.

**Normal and Isopentanes.**—Table IV shows the mass spectra of the normal pentanes and the isopentanes. In both the perfluoro compounds $CF_3^+$ is by far the largest peak which is quite unlike the hydrocarbon spectra. The difference in the $C_3F_7^+$ peaks is the most conspicuous difference in the perfluoro spectra while the $C_4H_9^+$ peaks are best for distinguishing the hydrocarbons. The largest peak in each carbon group of perfluoro-*n*-

TABLE IV

MASS SPECTRA OF NORMAL PENTANES AND ISOPENTANES

Sensitivity relative to $43^+$ of *n*-butane: $CF_3^+$ of *n*-$C_5F_{12}$, 2.59; $CF_3^+$ of *i*-$C_5F_{12}$, 2.77.

| Ion | Relative intensities of mass peaks: *n*-$C_5H_{12}$ | *n*-$C_5F_{12}$ | *i*-$C_5H_{12}$ | *i*-$C_5F_{12}$ |
|---|---|---|---|---|
| $C_5X_{12}$ | 8.79 | 0.03 | 6.19 | 0.00 |
| $C_5X_{11}$ | 0.51 | .77 | 1.82 | 1.72 |
| $C_4X_9$ | 12.6 | .27 | 54.0 | 0.87 |
| $C_4X_8$ | 2.20 | .26 | 16.8 | 1.04 |
| $C_4X_7$ | 2.87 | 3.25 | 4.71 | 4.53 |
| $C_3X_7$ | 100 | 9.73 | 100 | 0.19 |
| $C_3X_6$ | 57.9 | 1.10 | 86.0 | 1.76 |
| $C_3X_5$ | 40.5 | 6.54 | 67.3 | 8.32 |
| $C_3X_4$ | 2.37 | 0.35 | 3.38 | 0.51 |
| $C_3X_3$ | 14.2 | 2.06 | 21.5 | 2.76 |
| $C_3X_2$ | 1.55 | 0.44 | 2.40 | 0.53 |
| $C_2X_5$ | 24.4 | 29.5 | 45.7 | 16.4 |
| $C_2X_4$ | 6.00 | 7.18 | 6.17 | 3.51 |
| $C_2X_3$ | 34.6 | 0.64 | 42.2 | 0.52 |
| $C_2X_2$ | 3.30 | .45 | 4.11 | .38 |
| $CX_3$ | 4.65 | 100 | 8.40 | 100 |
| $CX_2$ | 0.55 | 3.12 | 1.05 | 2.12 |
| CX | .12 | 9.21 | 0.23 | 6.54 |
| C | .06 | 0.05 | 0.10 | 0.06 |
| X | .72 | .08 | 1.13 | .14 |

(4) V. H. Dibeler and F. L. Mohler, *J. Research Natl. Bur. Standards*, **40**, 25 (1948).

pentane is given by losing F, $CF_5$, $C_2F_5$, $C_3F_7$ and $C_4F_9$.

**Normal Heptane.**—Table V gives the mass spectra of the *n*-heptanes. Again as in *n*-pentane the largest peak in each carbon group of the fluorocarbon comes from losing F, $CF_5$, $C_2F_5$, $C_3F_7$, $C_4F_9$ and in addition $C_5F_{11}$ and $C_6F_{13}$. It was noted above that the perfluoro cyclics gave identical ions rather than losing identical masses in the dissociation. The ion $C_7F_{15}^+$ of mass 369 is probably the heaviest ion ever recorded on this type of mass spectrometer. The perfluoro-*n*-heptane, like the perfluoropentanes, differs from the hydrocarbon in that ionization by loss of $CF_3$ is very improbable and production of $CF_3^+$ most probable.

TABLE V

MASS SPECTRA OF NORMAL HEPTANES

Sensitivity relative to $43^+$ of *n*-butane; $CF_3^+$, 3.30

| Ion | Rel. inten. | Ion | Rel. inten. |
|---|---|---|---|
| $C_7^-$ | | $C_7^-$ | |
| $H_{16}$ | 13.1 | $F_{16}$ | 0 |
| $H_{15}$ | 0.01 | $F_{15}$ | 0.09 |
| $C_6^-$ | | $C_6^-$ | |
| $H_{13}$ | 1.90 | $F_{13}$ | 0.02 |
| $H_{12}$ | 0.16 | $F_{12}$ | 0 |
| $H_{11}$ | .03 | $F_{11}$ | 1.08 |
| $C_5^-$ | | $C_5^-$ | |
| $H_{11}$ | 44.0 | $F_{11}$ | 1.20 |
| $H_{10}$ | 17.2 | $F_{10}$ | .03 |
| $C_4^-$ | | $C_4^-$ | |
| $H_9$ | 47.8 | $F_9$ | 8.48 |
| $H_8$ | 26.3 | $F_8$ | 0.21 |
| $H_7$ | 10.5 | $F_7$ | 2.53 |
| $C_3^-$ | | $C_3^-$ | |
| $H_7$ | 100 | $F_7$ | 20.50 |
| $H_6$ | 24.1 | $F_6$ | 0.88 |
| $H_5$ | 51.9 | $F_5$ | 13.3 |
| $H_4$ | 3.23 | $F_4$ | 0.47 |
| $H_3$ | 18.8 | $F_3$ | 2.38 |
| $C_2^-$ | | $C_2^-$ | |
| $H_5$ | 46.0 | $F_5$ | 27.0 |
| $H_4$ | 7.83 | $F_4$ | 7.34 |
| $H_3$ | 39.3 | $F_3$ | 0.51 |
| $H_2$ | 3.22 | $F_2$ | .24 |
| $C^-$ | | $C^-$ | |
| $H_3$ | 4.88 | $F_3$ | 100 |
| $H_2$ | 0.42 | $F_2$ | 1.86 |
| H | .09 | F | 6.06 |

**Metastable Transitions.**—Mass spectra usually show some small diffuse peaks which are in general at non-integral masses. These arise from ions which dissociate after they have traversed the ion accelerating field and thus have less than the full kinetic energy of the initial ion before dissociation.[5] The apparent mass $m_a$ of these ions is related to the initial mass $m_i$ and the final mass $m_f$ by the equation

$$m_a = m_f^2/m_i$$

A survey of metastable ions in hydrocarbon spectra[6] shows that metastable transition peaks are only observed when both the initial and final ions give relatively large peaks.

The same phenomenon is observed in fluorocarbons and Table VI lists the observed metastable transitions. These are all small peaks amounting to a few tenths of a per cent. of the maximum peak at the most. The table shows that these transitions frequently recur in different compounds and that only two types of transition occur, losing CF and losing $CF_2$. The three metastable transitions found in cyclo-$C_5F_9H$ correspond to the three found in cyclo-$C_5F_{10}$ with H substituted for one of the fluorine atoms in both the initial and final ions. There is no correspondence between these transitions and the metastable transitions found in the corresponding hydrocarbons.

TABLE VI

METASTABLE TRANSITIONS IN FLUOROCARBONS

| Apparent mass | Transition | Compounds showing transition |
|---|---|---|
| 76.3 | $C_3F_5^+ \rightarrow C_2F_4^+ + CF$ | Cyclo-$C_5F_{10}$, cyclo-$C_6F_{12}$, *n*-$C_7F_{16}$ |
| 94.8 | $C_4F_7^+ \rightarrow C_3F_5^+ + CF_2$ | Cyclo-$C_5F_{10}$, cyclo-$C_6F_{12}$, *n*-$C_5F_{12}$ and *n*-$C_7F_{14}$ |
| 141.8 | $C_5F_9^+ \rightarrow C_4F_7^+ + CF_2$ | Cyclo-$C_5F_{10}$ |
| 189.9 | $C_6F_{11}^+ \rightarrow C_5F_9^+ + CF_2$ | Cyclo-$C_6F_{12}$ |
| 59.5 | $C_3F_4H^+ \rightarrow C_2F_3H^+ + CF$ | Cyclo-$C_5F_9H$ |
| 78.3 | $C_4F_6H^+ \rightarrow C_3F_4H^+ + CF_2$ | Cyclo-$C_5F_9H$ |
| 124.7 | $C_5F_8H^+ \rightarrow C_4F_6H^+ + CF_2$ | Cyclo-$C_5F_9H$ |

## Conclusion

No difficulties were encountered in obtaining spectra of these fluorocarbons and the experiments indicate that the mass spectrometer can be very useful in analysing fluorinated compounds up to and including heptanes. This will require accumulating data on mass spectra of pure fluorocarbons. The Mass Spectrometry Section of the Bureau of Standards will be glad of an opportunity to analyse any new fluorocarbons that may be made. An advantage of this method of analysis is that very small quantities, of the order of a milligram, are sufficient for full sensitivity.

WASHINGTON, D. C. RECEIVED JULY 30, 1948

(5) J. A. Hipple, R. E. Fox and E. U. Condon, *Phys. Revs.*, **69**, 347 (1946).

(6) Evelyn G. Bloom, Fred L. Mohler, J. H. Lengel and C. E. Wise, *J. Research Natl. Bur. Standards*, in press.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

# The Absorption Spectra of the Aminopyridines

BY LEIGH C. ANDERSON AND NELSON V. SEEGER

A study has been made of the ultraviolet absorption of the three aminopyridines and of some of their derivatives in order to obtain data which might be used to indicate their structure. Curves for the quantitative absorption of ether solutions of 2-aminopyridine, 3-aminopyridine, 2-(methylamino)-pyridine, 2-(dimethylamino)-pyridine and 1-methyl-2-pyridoneimine are presented in Fig. 1.

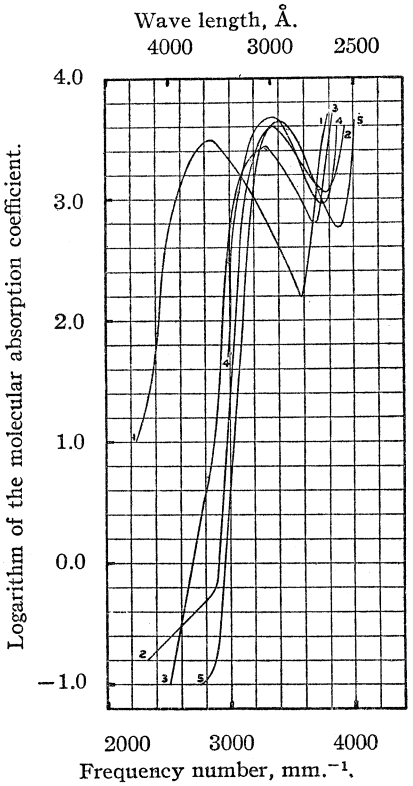
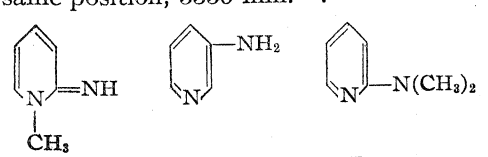



Fig. 1.—Absorption in ether solution of: 1, 1-methyl-2-pyridone-imine; 2, 3-aminopyridine; 3, 2-(dimethylamino)-pyridine; 4, 2-(methylamino)-pyridine; 5, 2-aminopyridine.

1-Methyl-2-pyridoneimine has a pyridone structure (I) and its ether solution is yellow in color with one broad absorption band at 2850 mm.$^{-1}$. 3-Aminopyridine and 2-dimethylaminopyridine can possess only a pyridine structure (II, III) and their ether solutions are colorless and have the peaks of the absorption bands at approximately the same position, 3350 mm.$^{-1}$.




I II III

The absorption curve of 2-aminopyridine has only the one broad band at 3350 mm.$^{-1}$ which is characteristic of the pyridine ring structure. If 2-aminopyridine existed in two tautomeric forms, two bands might be expected, one for the pyridone imine structure at approximately 2850 mm.$^{-1}$ and one for the pyridine structure at approximately 3350 mm.$^{-1}$. The absorption curves were determined for solutions having concentrations of nearly 40 g. per liter, yet only one band in the pyridine absorption region appeared. The conclusion drawn from these observations is that 2-aminopyridine possesses the pyridine structure exclusively and does not tautomerize in ether at room temperature.

The effect on the absorption curve of substituting a methyl group for an amino hydrogen is only minor. This is illustrated by the absorption curves of 2-(methylamino)-pyridine and 2-(dimethylamino)-pyridine. There is only a slight change in position of the peak and height of the band of 2-(methylamino)-pyridine when compared with 2-aminopyridine.

The possibility of tautomerization of 2-aminopyridine in a water type solvent was studied by determining the curve of the absorption spectrum of this compound in a dioxane–water solution as given in Fig. 2. In this case, 1-methyl-2-pyridoneimine in pure dioxane and 3-aminopyridine in a dioxane–water solution (72%:28% by volume) were used as reference compounds. The curves of 2- and 3-aminopyridines are very similar, both possessing the single broad band as was found in ether solution, indicating that only the pyridine structure is present.

In order to explain the fact that the dipole moment of 2-aminopyridine decreased with increasing temperature, Goethals[1] suggested that the equilibrium between tautomeric pyridine and pyridone forms was altered by changes in temperature. To study the supposed effect of temperature, absorption curves of 2-aminopyridine in dioxane–water solution were obtained at 65 and 80° by placing the absorption cells in an electrically-heated aluminum block. However, the absorption curves at these temperatures were found to be identical with the curves determined at room temperature.

2-Aminopyridine does not diazotize readily in dilute acid solutions. Since there appeared to be a possibility that tautomerization of 2-aminopyridine to the pyridoneimine structure would render the amine difficult to diazotize, the absorption curves of 2-aminopyridine in dilute sulfuric acid solutions were determined in order to attempt to establish the structure of 2-aminopyridine under

(1) Goethals, *Rec. trav. chim.*, **54**, 304 (1935).

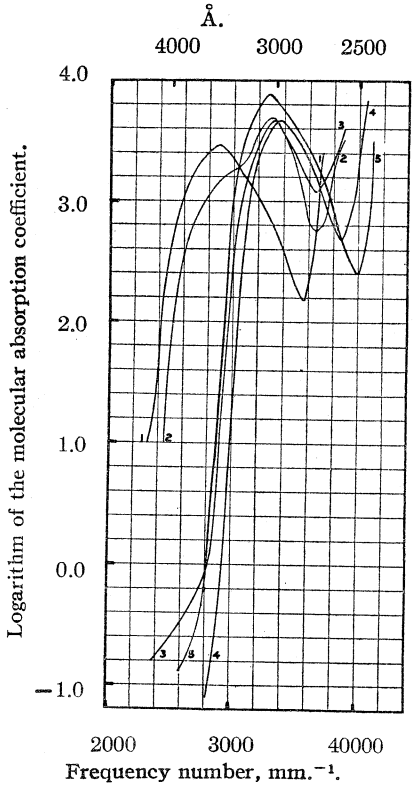
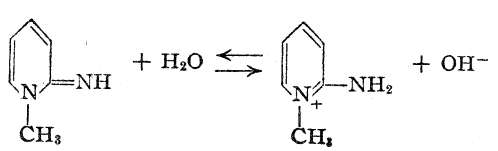



Fig. 2.—1, 1-Methyl-2-pyridoneimine in dioxane; 2, 1-methyl-2-pyridoneimine in 72%:28% dioxane–water; 3, 3-aminopyridine in 72%:28% dioxane–water; 4, 2-aminopyridine in 72%:28% dioxane–water at 25°, 65° and 80°; 5, 2-aminopyridine sulfate in 72%:28% dioxane–water.

conditions of diazotization. In Fig. 2, the absorption curve of 2-aminopyridine sulfate in dioxane–water solution (72%:28%) is given. It was found that the acid solutions have identical absorption curves over a wide range of acid concentration. No evidence of tautomerization can be observed from these curves since they contain only one absorption band characteristic of 2-aminopyridine. The curves of 2-aminopyridine in neutral and acid solutions are similar, although the curve in acid solution is slightly higher and broader. This fact has also been pointed out by Ley and Engelhardt.[2]

1-Methyl-2-pyridoneimine which is yellow, dissolves in water to form 1-methyl-2-aminopyridinium hydroxide which is colorless and strongly basic. The absorption curve of 1-methyl-2-pyridoneimine in 72%:28% dioxane–water shows clearly that in this solution an equilibrium is established as indicated by the following equation:




(2) Ley and Engelhardt, *Z. physik. Chem.*, **74**, 59 (1910).

This equilibrium is shifted to the right on the addition of more water to the solution in which case the color gradually disappears and the solution becomes more basic. The absorption band in the region of 2850 mm.$^{-1}$ appears to be a measure of the amount of 1-methyl-2-pyridoneimine present in the solution while the band at 3300 mm.$^{-1}$ appears to be a measure of the amount of pyridinium hydroxide. It will be noted that the latter band corresponds to the bands of 2- and 3-aminopyridines.

The absorption curve of 1-methyl-4-pyridoneimine (Fig. 3) was determined in 90%:10% dioxane–water solution because the compound was quite insoluble in pure dioxane. In the dioxane–water mixture the absorption curve of this compound shows the existence of an equilibrium similar to that found for the corresponding 1-methyl-2-pyridoneimine.

The absorption curves of the 2- and 4-compounds are very similar in shape but occur at different positions. The band for 1-methyl-2-pyri-

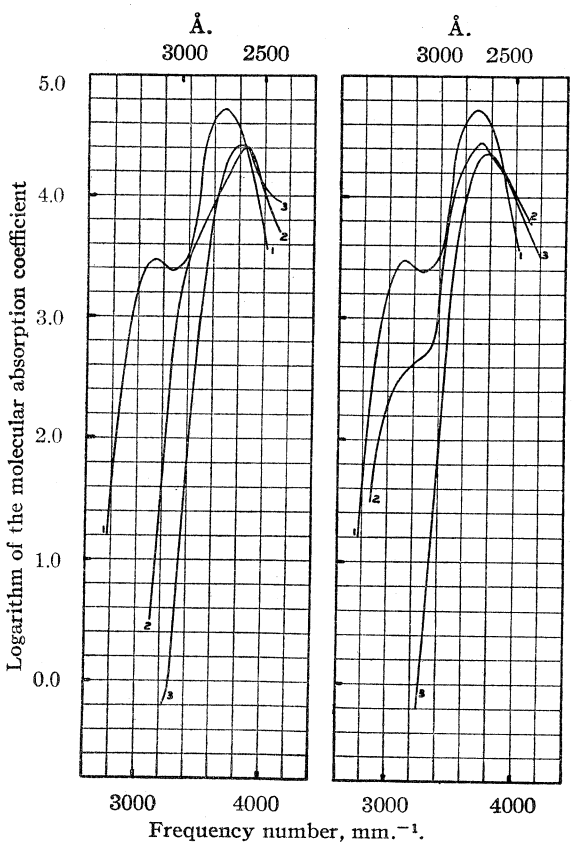



Fig. 3.—1, 1-Methyl-4-pyridoneimine in 90%:10% dioxane–water; 2, 4-(dimethylamino)-pyridine in 72%:28% dioxane–water; 3, 4-aminopyridine in 72%:28% dioxane–water.

Fig. 4.—1, 1-methyl-4-pyridoneimine in 90%:10% dioxane–water; 2, 1-methyl-4-pyridoneimine in 72%:28% dioxane–water; 3, 4-aminopyridine sulfate in 72%:28% dioxane–water.

doneimine lies at 2850 mm.$^{-1}$, whereas that for 1-methyl-4-pyridoneimine lies at 3150 mm.$^{-1}$, while the bands at 3300 mm.$^{-1}$ and 3700 mm.$^{-1}$ correspond, respectively, to the 2- and 4-aminopyridine structure.

Evidence for the structure of 4-aminopyridine has been determined in a manner similar to that used in the case of 2-aminopyridine. The curves for 4-aminopyridine and 4-(dimethylamino)-pyridine given in Fig. 3 were determined in 72%:28% dioxane–water solution due to the insolubility of 4-aminopyridine in ether. The curve for 4-aminopyridine has only a single band corresponding to the band for 4-(dimethylamino)-pyridine which is unable to tautomerize. From this evidence, it may be concluded that only the pyridine ring structure can be assigned to 4-aminopyridine, no evidence for tautomerization being shown.

The curve for the absorption spectrum of 4-aminopyridine sulfate in dioxane–water (72%:28%) (Fig. 4) indicates that sulfuric acid does not induce tautomerization of the 4-aminopyridine. Only the one band for the 4-substituted pyridine derivatives is observed, there being no bands corresponding to the 4-pyridoneimine structures. From these data it would appear that the difficulty in diazotizing 4-aminopyridine in acid solution is not due to a migration of an amine hydrogen to the ring nitrogen.

## Experimental

The absorption spectral data were obtained by methods which have been described.[3] The dioxane was fractionated by successive crystallizations and was finally distilled. All solvents were optically clear in the spectral region investigated.

**2-Aminopyridine.**—This amine was obtained by the action of ammonia on 2-bromopyridine.[4] After several recrystallizations from benzene–petroleum ether, it melted at 57–58°.

**1-Methyl-2-pyridoneimine.**—This compound resulted from the action of a concentrated solution of sodium hydroxide on the methiodide of 2-aminopyridine.[5] The product was extracted with ether and purified by distillation under reduced pressure; b. p. 108° (16 mm.).

**2-(Methylamino)-pyridine.**—This substance was prepared by the action of a concentrated aqueous methylamine solution on 2-bromopyridine in a sealed Pyrex tube heated to 150° for ten hours. After addition of alkali, the amine was extracted with ether and distilled; b. p. 200–201°. The picrate melted at 190°.

**2-(Dimethylamino)-pyridine.**—This compound, obtained by the action of dimethylamine on 2-bromopyridine[6] was purified by distillation; b. p. 196° (740 mm.). The picrate, recrystallized from absolute alcohol, melted at 182°.

**3-Aminopyridine.**—This amine was prepared by the action of ammonia on 3-bromopyridine using $CuSO_4 \cdot 5H_2O$ as a catalyst.[7] The product was extracted with ether and recrystallized from a benzene–petroleum ether solution; m. p. 64°.

**4-Aminopyridine.**—This substance was obtained by heating crude 4-pyridylpyridinium dichloride with concentrated aqueous ammonia.[8] After recrystallizing several times from water and treatment with norite, the product melted at 150°.

**1-Methyl-4-pyridoneimine.**—This imine was prepared by the action of concentrated sodium hydroxide on the methiodide of 4-aminopyridine. The product was extracted with hot benzene and the solvent evaporated; m. p. 150–151°. It liquefies in the air since it is very hygroscopic and soon becomes red in color.

**4-(Dimethylamino)-pyridine.**—This compound was obtained by heating crude 4-pyridylpyridinium dichloride with a concentrated aqueous solution of dimethylamine and was recrystallized from benzene; m. p. 114°.[9] The picrate melted at 204°.

## Summary

1. Curves for the absorption of visible and ultraviolet light by solutions of the aminopyridines and some of their derivatives in ether, dioxane, water and acid are presented.

2. No evidence was found for the presence of a pyridone structure for the 2- and 4-aminopyridines in the solutions studied.

3. The absorption spectra indicate the presence of tautomeric equilibria between pyridine and pyridone forms of 1-methyl-2- and 1-methyl-4-pyridoneimines in dioxane–water solutions.

ANN ARBOR, MICHIGAN RECEIVED JULY 26, 1948

(3) Anderson and Gomberg, THIS JOURNAL, **50**, 203 (1928).

(4) Hertog and Wibaut, *Rec. trav. chim.*, **55**, 125 (1936).

(5) Tschitschibabin, Konowalowa and Konowalowa, *Ber.*, **54B**, 818 (1921).

(6) I. G. Farbind A.-G., French Patent 802,105 (1936).

(7) Maier-Bode, German Patent 586,879 (1933).

(8) Koenigs and Greiner, *Ber.*, **64B**, 1054 (1931).

(9) Koenigs, Friedrich and Jurany, *ibid.*, **58B**, 2571 (1925).

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

# The Absorption Spectra of Some Methylpyridine Derivatives

BY LEIGH C. ANDERSON AND NELSON V. SEEGER

The structures of the 2- and 4-methylpyridines have not been definitely determined and one finds both the pyridine and pyridone–methide structures used for 2-methylpyridine. Tschitschibabin[1] postulated that both the 2- and 4-isomers existed as tautomeric mixtures of the two forms. Cartwright and Errera[2] presented evidence based on infrared absorption spectral curves of the 2- and 3-methylpyridines which indicated the existence of only the pyridine structure for the 2-isomer.

In order to obtain data which might be of value in determining the structure of 2-methylpyridine, the ultraviolet absorption curve of the compound was compared with that of 1-methyl-2-pyridonemethide in ether solution. The absorption curves are shown in Fig. 1. The pyridonemethide has two distinct bands at 2370 mm.$^{-1}$ and at 3620 mm.$^{-1}$ while 2-methylpyridine has only one band at 3850 mm.$^{-1}$. One would expect 2-methylpyridine to have an absorption curve with two bands if it consists of a tautomeric mixture of the 2-pyridonemethide and 2-methylpyridine forms and since it has only one band in the region where pyridine absorbs light, the conclusion must be drawn that only the pyridine ring structure can be assigned to it.

In the preceding paper, it was shown that 1-methyl-2-pyridoneimine reacted with water to give a quaternary ammonium hydroxide and there was a corresponding change from the pyridone–imine absorption type of curve to that of pyridine. The absorption curves of 1-methyl-2-pyridone in ether, hexane, 72% dioxane–28% water, and pure water are presented in Fig. 1. These curves show absorption in the same spectral region. Apparently there is little tendency to form the quaternary compound and this is also shown by the fact that a water solution of 1-methyl-2-pyridone reacts neutral to litmus. There is comparatively little change in absorption in these different types of solvent. There is a pronounced change in absorption, however, when the

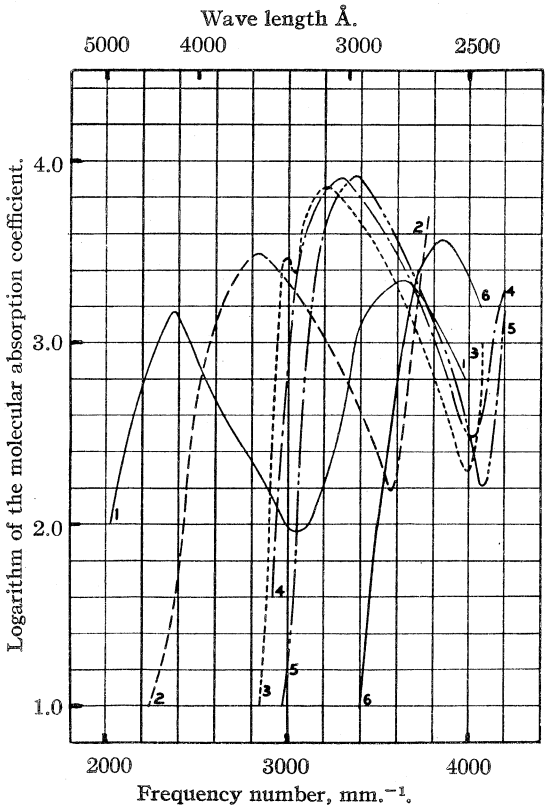



Fig. 1.—1, 1-Methyl-2-pyridonemethide in ether; 2, 1-methyl-2-pyridoneimine in ether; 3, 1-methyl-2-pyridone in ether and hexane; 4, 1-methyl-2-pyridone in 72%:28% dioxane–water; 5, 1-methyl-2-pyridone in water; 6, 2-methylpyridine in ether.

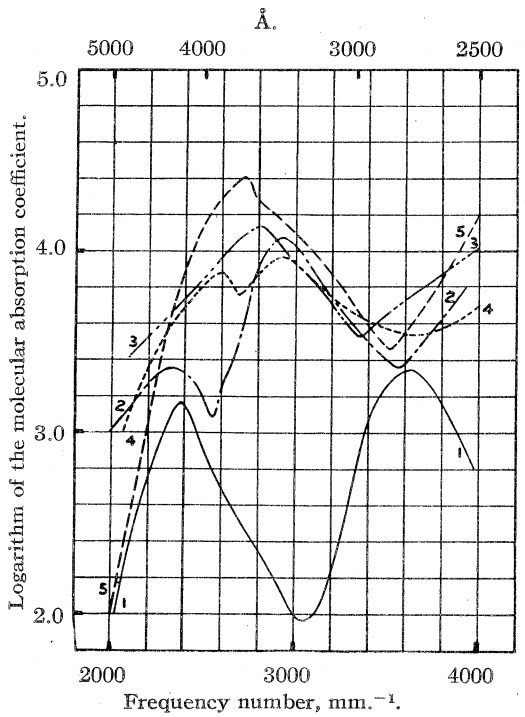



Fig. 2.—Absorption of ether solution of: 1, 1-methyl-2-pyridonemethide; 2, 1-methyl-2-pyridone-phenylmethide; 3, 1-methyl-2-pyridone-diphenymethide; 4, 1-methyl-4-pyridone-phenylmethide; 5, 1-methyl-4-pyridone-diphenylmethide.

(1) Tschitschibabin, *Ber.*, **60B**, 1607 (1927).

(2) Cartwright and Errera, *Compt. rend.*, **200**, 914 (1935).

ketonic oxygen is replaced by an imine group and a still more marked change when the oxygen is replaced by a methylene group.

Figure 2 presents the curves of the following compounds wherein the methide hydrogens of 1-methyl-2- and 1-methyl-4-pyridone methides have been replaced with phenyl groups.

The compound with two hydrogens on the methide group has two bands, one at the edge of the visible, the other in the ultraviolet. Each of the compounds having one hydrogen replaced by a phenyl group also has two absorption bands but they occur much closer to each other than in the unsubstituted compound, there being a shift of the ultraviolet band toward the visible and of the band in the visible region toward the ultraviolet. When both hydrogens of the methide group have been replaced, only one intense band is found. In Fig. 3 a comparison between the curves of 1-methyl-4-pyridonediphenylmethide and of diphenylquinomethane shows a very striking similarity. The maximum absorption for both compounds is in the same region, 2750 mm.$^{-1}$ for diphenylquinomethane and 2700 mm.$^{-1}$ for the pyridone. The intensities of the bands are also very similar.

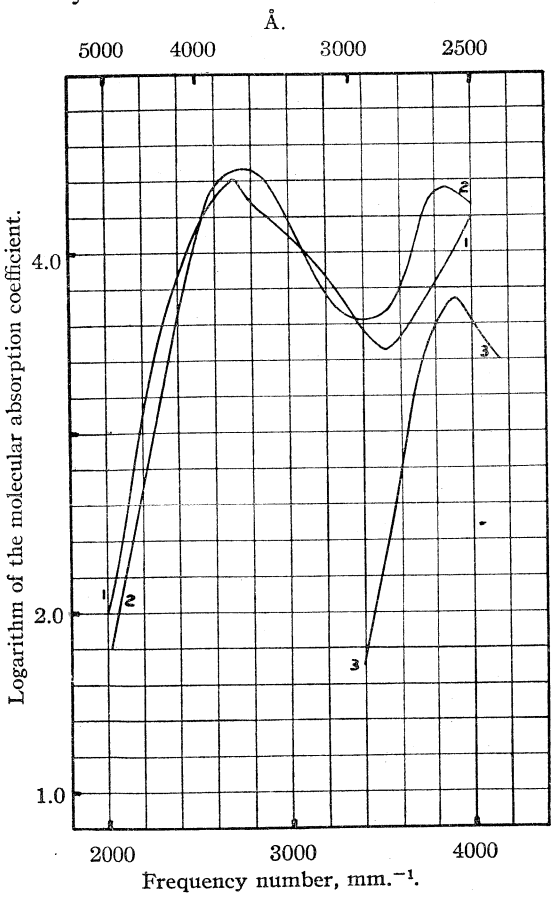



Fig. 3.—1, 1-Methyl-4-pyridone-diphenylmethide in ether; 2, diphenylquinomethane in ether; 3, 4-pyridyldiphenylcarbinol in dioxane.

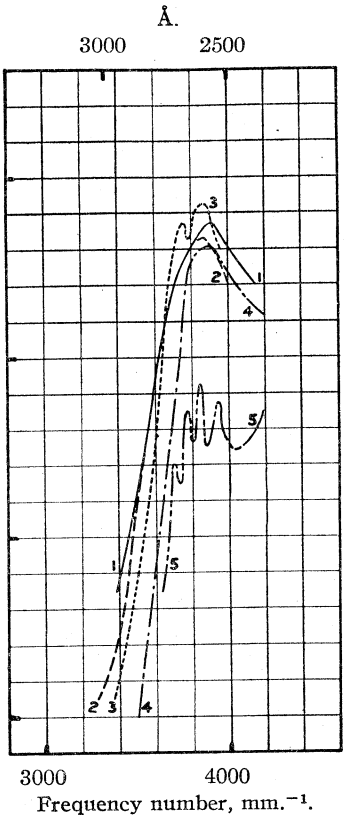



Fig. 4.—1, 4-Pyridyldiphenylcarbinol in dioxane; 2, 3-pyridyldiphenylcarbinol in ether; 3, 2-pyridyldiphenylcarbinol in ether; 4, pyridine in 72%:28% dioxane–water; 5, triphenylcarbinol in ether.

Figure 4 shows the curves of triphenylcarbinol, 2-pyridyldiphenylcarbinol and 3-pyridyldiphenylcarbinol in ether, 4-pyridyldiphenylcarbinol in dioxane, and pyridine in dioxane–water. Dioxane was used as a solvent for the 4-pyridyldiphenylcarbinol because the material was insoluble in ether. A comparison of the four carbinols shows that the replacement of a phenyl group by a pyridyl residue causes a considerable increase in the intensity of absorption. This increase is approximately the same regardless of the position of the pyridine substitution. The curves of the three pyridylcarbinols are strikingly similar to pyridine, the series of small bands in triphenylcarbinol being absent in the pyridylcarbinols except for the two peaks in 2-pyridyldiphenylcarbinol. Each of the pyridylcarbinols gives an intense red solution in concentrated sulfuric acid.

## Experimental

**2-Methylpyridine.**—Eastman Kodak Co. product was purified in the same manner as pyridine according to the method of Spiers and Wibaut[3]; b. p. 127°.

**1-Methyl-2-pyridonemethide.**—This compound was prepared by the action of concentrated potassium hydroxide on the methiodide of 2-methylpyridine[1]; it is a red oil which decomposes on distillation, even under reduced pressure.

(3) Spiers and Wibaut, *Rec. trav. chim.*, **56**, 579 (1937).

**1-Methyl-2-pyridone.**—This compound was prepared by the action of potassium ferricyanide on 1-methylpyridinium hydroxide according to the directions given in "Organic Syntheses"[4]; b. p. 250° (740 mm.).

**2-Pyridyldiphenylcarbinol.**—2-Pyridylmagnesium bromide, prepared by the method of Overhoff and Proost,[5] was added to an ether solution of benzophenone. The carbinol which resulted was recrystallized from alcohol; m. p. 103–104°.[6]

**1-Methyl-2-pyridone-diphenylmethide.**—2-Pyridyldiphenylmethane was prepared by the method of Tschitschibabin and Benewolenskaja.[7] It was recrystallized from a mixture of alcohol and water; m. p. 63°.

2-Pyridyldiphenylmethane was heated with methyl iodide in a sealed tube and the product was recrystallized from hot water; m. p. 222–224°. This methiodide upon treatment with concentrated potassium hydroxide solution gave 1-methyl-2-pyridone-diphenylmethide which crystallized from alcohol in long, dark red-violet needles; m. p. 147°.

**3-Pyridyldiphenylcarbinol.**—In order to prepare 3-pyridylmagnesium bromide, the procedure of Overhoff and Proost for the preparation of the 2-isomer had to be modified somewhat. A few drops of ethyl bromide were added to 8 g. of magnesium under 20 cc. of absolute ether. When the reaction had started, a mixture of 20 g. of redistilled Eastman 3-bromopyridine and 10 g. of ethyl bromide in 100 cc. of ether was added drop by drop with heating and constant stirring, a reddish brown precipitate being formed. The solution was boiled for two hours.

To obtain 3-pyridyldiphenylcarbinol, 36 g. of benzophenone in ether was added to the 3-pyridylmagnesium bromide solution and after some time the addition compound was decomposed with an ice-cold solution of ammonium chloride. The ether layer was extracted with dilute hydrochloric acid and the carbinol precipitated with ammonia. On recrystallization from ethyl acetate, the carbinol melted at 115–116°.

*Anal.* Calcd. for $C_{18}H_{15}ON$: N, 5.36. Found: N, 5.32.

The picrate of 3-pyridyldiphenylcarbinol was formed by adding a hot alcoholic solution of picric acid to a hot alcoholic solution of the carbinol; m. p. 195°.

*Anal.* Calcd. for $C_{18}H_{15}ON \cdot C_6H_3O_7N_3$: N, 11.42. Found: N, 11.46.

(4) Prill and McElvain, "Organic Syntheses," Vol. XV, John Wiley and Sons, New York, N. Y., 1935, p. 41.

(5) Overhoff and Proost, *Rec. trav. chim.*, **57**, 184 (1938).

(6) Proost and Wibaut, *ibid.*, **59**, 971 (1940).

(7) Tschitschibabin and Benewolenskaja, *Ber.*, **61B**, 551 (1928).

**4-Pyridyldiphenylcarbinol.**—A mixture of 2- and 4-benzylpyridines was obtained by the action of benzyl chloride and pyridine according to the directions of LaForge.[8] Following the procedure of Tschitschibabin[9] this mixture was oxidized with permanganate to the 2- and 4-benzoylpyridines. For the preparation of 4-pyridyldiphenylcarbinol, previous investigators[7] used pure 4-benzoylpyridine. However, this requires a tedious separation of the mixture of 2- and 4-benzoylpyridines by means of the picrate. Therefore, in this work, the mixture of benzoylpyridines was added directly to phenylmagnesium bromide forming a mixture of 2- and 4-pyridyldiphenylcarbinols. The 2-pyridyldiphenylcarbinol dissolved readily in ether and the 4-isomer which is insoluble in ether was filtered off. After two recrystallizations from ethyl acetate, the melting point was 234–235°.

**1-Methyl-4-pyridonediphenylmethide.**—4-Pyridyldiphenylmethane was prepared by the method of Tschitschibabin and Benewolenskaja using gaseous hydrogen iodide to reduce 4-pyridyldiphenylcarbinol; m. p. 125°. To obtain the methiodide, 4-pyridyldiphenylmethane was heated with methyl iodide in a sealed tube and the product recrystallized from alcohol; m. p. 159–161°. The methiodide was treated with concentrated potassium hydroxide and 1-methyl-4-pyridonediphenylmethide was formed; recrystallization from alcohol gave yellow needles, m. p. 113°.

**1-Methyl-2- and 4-Pyridonephenylmethides.**—Each of these compounds was prepared according to the directions of Decker[10] by the addition of a concentrated solution of potassium hydroxide to the methiodides of 2- and 4-benzylpyridines.

## Summary

1. Quantitative absorption spectral data indicate that 2-methylpyridine possesses only a pyridine structure in ether solution.

2. The absorption spectrum curve for 1-methyl-4-pyridonediphenylmethide in ether solution is very similar to the curve for diphenylquinomethane.

3. Curves for 2-, 3- and 4-pyridyldiphenylcarbinols show the presence of a pyridine structure only.

(8) LaForge, THIS JOURNAL, **50**, 2484 (1928).

(9) Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, **33**, 300 (1901).

(10) Decker, *Ber.*, **38**, 2494 (1905).

ANN ARBOR, MICHIGAN. RECEIVED JULY 26, 1948

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE AND THE DEPARTMENT OF CHEMISTRY OF THE MICHIGAN STATE COLLEGE]

# The Kinetics and Mechanism of the Uncatalyzed Alkylation of Phenol

BY HAROLD HART AND J. H. SIMONS

Although the alkylation of the aromatic nucleus has long been an important reaction to the organic chemist, there have been relatively few kinetic studies of the mechanism of this reaction. Ionic intermediates for this reaction have been postulated,[1,2] but some recent kinetic studies[3] on the hydrogen fluoride catalyzed alkylation of toluene with *t*-butyl chloride present strong evidence against any high energy intermediate for that reaction. These conclusions were based on the fact that various oxygen-containing (basic) promoters affected the rate only as a function of their concentration, and independent of the structure of the particular promoter, upon the retardation effect of hydrogen chloride, and upon the energy requirements for the reaction.

Following the discovery that phenols could be alkylated in the para-position with tertiary alkyl halides in the absence of any added catalysts[4,5]

(1) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 309.

(2) C. C. Price, *Chem. Rev.*, **29**, 44–51 (1941).

(3) (a) W. H. Pearlson and J. H. Simons, THIS JOURNAL, **67**, 352 (1945); (b) J. W. Sprauer and J. H. Simons, *ibid.*, **64**, 648 (1942).

(4) J. H. Simons and H. Hart, *ibid.*, **66**, 1309 (1944).

(5) (a) G. M. Bennett and F. M. Reynolds, *J. Chem. Soc.*, 131 (1935); (b) J. van Alphen, *Rec. trav. chim.*, **46**, 287 (1927).

we believed that it would be of interest to study the kinetics and mechanism of this reaction. A detailed study of the reaction has revealed several interesting facts which were not anticipated at the outset of the work.

It was found that the alkylation of phenol with *t*-butyl chloride is a homogeneous, quantitative reaction which proceeds at a measurable rate at convenient temperatures. The reaction could be readily followed by means of the increase in pressure due to the evolution of hydrogen chloride. Tertiary butyl chloride, *t*-amyl chloride, dimethylisopropylcarbinyl chloride and benzyl chloride were the halides used, and phenol and *p*-cresol were the phenols. The reactions were studied at several different temperatures in order to determine the activation energies. The effect of hydrogen chloride pressure, and of the diluents *p*-xylene, 1,4-dichlorobutane, ethylene dichloride, nitrobenzene and 1,4-dioxane was studied.

It is believed that the experimental results (a very high order rate dependency upon phenol concentration, low energies of activation, the lack of reactivity of anisole, and the very striking inhibitory power of dioxane) indicate the improbability of a simple ionic mechanism for this reaction, and a mechanism involving what has been termed the "amphoteric medium effect"[4] has been proposed which satisfactorily accounts for the experimental observations.

## Experimental

**Preparation of Materials.**—The phenol was Eastman Kodak Company material, which was fractionated at a pressure of approximately 100 mm. in a column packed with multi-turn glass helices, with approximately 20 theoretical plates. The phenol was further purified and samples prepared in the apparatus which is described below (see Fig. 1).

The *t*-butyl chloride was prepared from *t*-butyl alcohol and concentrated hydrochloric acid in the usual manner.[6] It was dried over anhydrous potassium carbonate and fractionated through a glass-helices packed column with approximately 30 theoretical plates. The middle cuts which boiled constantly at 52° and had a constant refractive index $n^{20}D$ 1.3850 were used in the sampling apparatus.

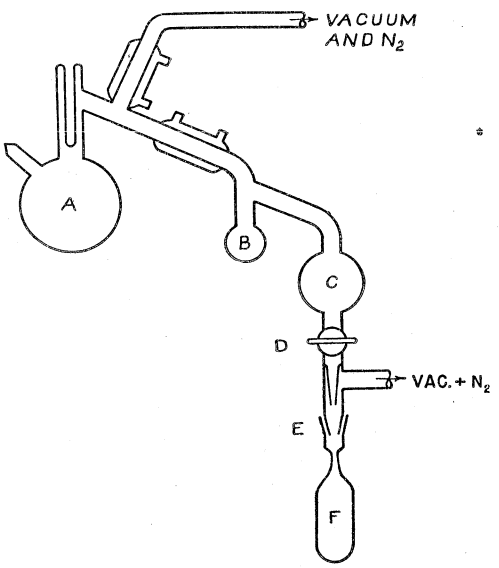



Fig. 1.—Diagram of the phenol sampling apparatus.

The *p*-cresol was Reilly Tar and Chemical Company's best grade of material. It was carefully fractionated in a manner similar to that used for the phenol. The *t*-amyl chloride was prepared and purified in a manner similar to that described above for *t*-butyl chloride. We are indebted to Dr. N. C. Cook for the dimethylisopropylcarbinyl chloride, which had been fractionated under reduced pressure in an efficient column.

Anhydrous hydrogen chloride was prepared by dropping concentrated hydrochloric acid on concentrated sulfuric acid, passing the gas through a concentrated sulfuric acid bubbler and a phosphorus pentoxide tube, and collecting the gas in a liquid air trap. The hydrogen chloride was degassed by alternate freezing, evacuation and thawing, and was then allowed to evaporate through (H) into bulb (B) in Fig. 2. It was stored there until used in the rate measurements as described below.

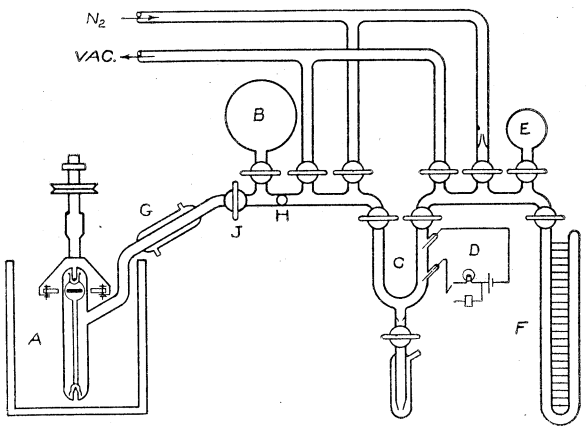



Fig. 2.—The rate measuring apparatus.

Aluminum triphenolate was prepared by dropping pieces of aluminum metal into hot phenol, which was contained in a round-bottomed flask equipped with a reflux condenser.[7] Once the reaction started, it was self-sustaining and the flame was removed. When a slight excess of the theoretical amount of aluminum was added, heat was again applied until the reaction was completed (no more evolution of hydrogen). The product was poured on Pyrex watch glasses and allowed to cool. It solidified almost immediately to a gray vitreous solid, which was readily pulverized to a grayish-white powder. This material was dried in an oven at 110° for eight hours before use.

The 1,4-dichlorobutane, ethylene dichloride, benzyl chloride, nitrobenzene, benzene, *p*-xylene and *p*-dioxane were all carefully fractionated (the last three over sodium) in packed columns. The samples were prepared in evacuated ampoules as described below. (The 1,4-dichlorobutane was kindly donated by the Electrochemical Division of E. I. du Pont de Nemours and Co.)

**The Quantitative Nature of the Reaction.**—The reaction between *t*-butyl chloride and phenol was demonstrated to be essentially quantitative. In Expt. 27 (see Table I) a determination of the quantitative nature of the reaction was made. After the reaction (carried out in *p*-xylene as a solvent) had reached essential completion (ninety hours at 40°), the volatile contents of the rate-determining apparatus were removed by evacuation with a Cenco Hy-

(6) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 144.

(7) H. Funk and E. Rogler, *Z. anorg. allgem. Chem.*, **252**, 323–328 (1944).

TABLE I

SUMMARY OF RATE DATE FOR THE ALKYLATION OF PHENOL WITH TERTIARY ALKYL HALIDES

| (1) Expt. | (2) *t*-RCl, mole | (3) Phenol, mole | (4) Diluent, mole | (5) Molarity of phenol | (6) Initial HCl pressure, mm. | (7) *T*, °C. | (8) $P_0$, mm. | (9) $P_f$, mm. | (10) *a* | (11) *b* | (12) *C* | (13) $t_{1/2}$ (min.) | (14) *n* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.01178B | 0.236 | | 10.54 | | 45 | 78.7 | 372.5 | 0.00854 | | 107.7 | 81.1 | |
| 2 | .01109B | .263 | | 10.52 | | 45 | 62.1 | 344.4 | .00914 | | 103.7 | 75.8 | |
| 3 | .01168B | .257 | | 10.59 | | 45 | 68.1 | 285.4 | .00907 | 0.1148 | 68.8 | 84.1 | |
| 4 | .00597B | .218 | | 10.83 | | 45 | 31.9 | 204.7 | .00812 | | 41.7 | 85.3 | |
| 5 | .00572B | .224 | | 10.87 | 392.2 | 45 | 415.9 | 562.6 | .00812 | | 21.5 | 85.4 | |
| 6 | .00592B | .238 | | 10.87 | 345.4 | 45 | 367.1 | 522.0 | .00800 | | 26.8 | 86.6 | |
| 7 | .00544B | .221 | | 10.86 | 195.9 | 45 | 217.2 | 366.1 | .00767 | | 17.4 | 90.4 | |
| 8 | .00673B | .236 | | 10.82 | 101.7 | 45 | 130.4 | 314.0 | .00832 | | 50.9 | 83.3 | |
| 9 | .01288B | .118 | | 9.83 | | 45 | 127.1 | 442.7 | .00558 | | 101.4 | 124.2 | 6.72 |
| 10 | .01485B | .110 | | 9.56 | | 45 | 142.1 | 547.1 | .00616 | .1271 | 139.9 | 121.9 | 5.43 |
| 11 | .01124B | .234 | | 10.51 | | 50 | 78.2 | 361.7 | .01107 | | 103.6 | 62.5 | |
| 12 | .01150B | .229 | | 10.50 | | 50 | 74.8 | 380.8 | .01379 | .1049 | 102.6 | 52.2 | |
| 13 | .01182B | .225 | | 10.42 | | 55 | 89.5 | 397.0 | .02053 | .1764 | 88.4 | 35.2 | |
| 14 | .01180B | .214C | | | | 45 | 46.7 | 310.2 | .00192 | | −360.1 | 361.9 | |
| 15 | .01094B | .229 | 0.0134DB | 9.87 | | 45 | 43.7 | 354.0 | .00727 | .0334 | 109.9 | 97.4 | 5.01 |
| 16 | .01267B | .187 | .0264DB | 8.85 | | 45 | 83.0 | 420.0 | .00536 | .0621 | 103.7 | 136.2 | 4.15 |
| 17 | .01256B | .164 | .0467DB | 7.65 | | 45 | 79.8 | 391.9 | .00218 | | −178.2 | 318.7 | 4.77 |
| 18 | .01028B | .115 | .0883DB | 5.35 | | 45 | 59.4 | 328.4 | .000454 | .000172 | −4631.0 | 1529.0 | 4.59 |
| 19 | .01410B | .178 | .0494E | 7.87 | | 45 | 137.8 | 460.7 | .00388 | .0442 | 48.8 | 188.4 | 3.66 |
| 20 | .01422B | .177 | .0291N | 8.65 | | 45 | 68.1 | 467.6 | .00791 | .0739 | 142.5 | 90.7 | 2.18 |
| 21 | .01278B | .168 | .0529N | 7.65 | | 45 | 64.7 | 399.6 | .00674 | | 120.8 | 102.9 | 1.81 |
| 22 | .01399B | .120 | .0962N | 5.38 | | 45 | 81.6 | 425.5 | .00257 | | −47.5 | 269.5 | 2.26 |
| 23 | .00937B | .166 | .0497N | 7.97 | | 35 | 47.0 | 275.2 | .00352 | −0.0280 | −52.2 | 187.4 | |
| 24 | .01260B | .188 | .0276X | 8.66 | | 45 | 59.9 | 395.8 | .00296 | | −24.7 | 210.5 | 5.46 |
| 25 | .01261B | .164 | .0431X | 7.62 | | 45 | 84.0 | 396.8 | .00127 | | −727.7 | 551.7 | 6.13 |
| 26 | .00917B | .161 | .0343X | | | 40 | 67.3 | 255.0 | .00157 | | −774.7 | 440.3 | |
| 27 | .01885B | .205 | .0334X | | | 40 | 106.4 | 544.5 | .00118 | | −561.7 | 588.3 | |
| 28 | .01690B | .217 | .0316X | | 156.4 | 40 | 203.9 | 622.8 | .00183 | | −144.5 | 378.3 | |
| 29 | .01151A | .247 | | | | 45 | 14.0 | 330.2 | .00555 | | 101.2 | 125.0 | |
| 30 | .01138A | .228 | | | | 45 | 9.3 | 332.0 | .00636 | 0.0626 | 108.2 | 113.9 | |
| 31 | .00942A | .231 | | | | 50 | 13.3 | 295.0 | .01094 | .1635 | 97.9 | 68.6 | |
| 32 | .00958A | .230 | | | | 50 | 15.0 | 298.1 | .01003 | .0968 | 100.6 | 72.7 | |
| 33 | .01088A | .237 | | | | 55 | 28.8 | 354.2 | .01122 | .0792 | 113.5 | 63.8 | |
| 34 | .01058H | .214 | | | | 45 | 9.2 | 320.0 | .00204 | .0887 | −302.4 | 425.7 | |
| 35 | .01769H | .229 | | | | 50 | 4.1 | 420.1 | .00305 | .2192 | 15.8 | 304.2 | |
| 36 | .01198H | .238 | | | | 55 | 10.2 | 355.0 | .00436 | .0939 | 78.8 | 174.6 | |
| 37 | .01406B | .174 | 0.0682D | | | 45 | | | | | | *a* | |
| 38 | .01085B | .176 | .0518D | | 91.4 | 45 | | | | | | *b* | |

The capital letters in columns (2), (3) and (4) have the following meanings: A = *t*-amyl chloride; B = *t*-butyl chloride; C = *p*-cresol; DB = 1,4-dichlorobutane; E = ethylene dichloride; H = dimethylisopropylcarbinyl chloride (2-chloro-2,3-dimethylbutane); N = nitrobenzene; X = *p*-xylene and D = 1,4-dioxane.

In column (14) experiments 37 and 38; [a] no rise in pressure after four hours, [b] a pressure rise of only 3 mm. was observed after seven hours.

Columns (1–4) are self-explanatory. The molarity of phenol in column (5) was obtained by using available data in the literature for the densities of the substances used in each experiment. The volume of each material was calculated (at the temperature of the experiment) and it was assumed that the solutions were perfect. This assumption probably did not introduce any appreciable error since in most cases one component comprised the majority of the solution. Once the total volume was calculated, the molarity of the phenol could be ascertained in the usual manner.

The values in column (6) represent the equilibrium pressure of hydrogen chloride that was added to the phenol before the *t*-butyl chloride was admitted to the reaction vessel. Column (7) indicates the temperatures of the experiments. The thermostat was kept at these temperatures ±0.01°. Columns (8) and (9) represent the initial and final equilibrium pressures, respectively. $P_0$ represents the vapor pressure of the tertiary halide plus that of phenol plus, in certain cases, the pressure of hydrogen chloride added before the start of the run, or the vapor pressure of the particular diluent employed. $P_f$ was determined experimentally in most cases, by allowing the experiment to proceed to completion. However, it could also be calculated by extrapolation of the straight line obtained by plotting $dP/dt$ *vs.* $P$ to $dP/dt = 0$. When the calculated and experimental values did not agree, the experimental value was used, and it was necessary to insert the constant *b* (column (11)) into the kinetic equation. The determination and significance of the data in columns (10–14) is discussed below. The values of *a*, *b* and *C* pertain to equation (2) below, $t_{1/2}$ is the reaction half-time, and *n* is the apparent order of the reaction with respect to phenol concentration.

Vac pump. A sodium carbonate absorption tube and a Dry Ice–acetone cold trap were placed in the line before the pump. In this manner, 98.1% of the chlorine was recovered as sodium chloride in the absorption tube, and no isobutylene was obtained in the cold trap. This indicates, therefore, that the alkylation is practically quantitative and little or no dehydrohalogenation of the *t*-butyl chloride occurs.

**The Henry's Law Constants for Hydrogen Chloride in Phenol.**—In order to ensure that no unusual solubility behavior of hydrogen chloride in the liquid phase would influence the kinetic interpretation, the Henry's law constants for hydrogen chloride in phenol were determined at 45, 50 and 55° over a total pressure range of 200 to 900 mm. of mercury. It was found that these constants, for a given temperature, varied less than ±3%, approximately the precision of the measurements. Thus, the increase in pressure due to evolved hydrogen chloride could be employed as a reliable method of following the reaction.

**Preparation of Samples.**—The samples of phenol, alkyl halides and diluents were prepared in such a manner as to exclude moisture. Small amounts of moisture would lead to incorrect data because of the generation of hydrogen chloride by hydrolysis of the alkyl halides. The phenol samples were prepared in the apparatus shown in Fig. 1. Approximately 500 g. of fractionated phenol and 10 g. of aluminum triphenolate (as a drying aid) were placed in the 1-l. distilling flask (A) through the side arm (against a counter-current of dry nitrogen). The side arm was then sealed off and the phenol was frozen in (A). It was degassed by alternate freezing, evacuation and thawing. The system was then evacuated, filled with dry nitrogen and re-evacuated several times to remove oxygen. It was finally left at about 50 mm. of mercury pressure with nitrogen and heat was applied at (A). About 75 ml. of phenol was collected in the 125 ml. receiver (B), and the distillation was discontinued. The system was then filled with dry nitrogen until the pressure was 5–10 mm. below atmospheric. Vessel (B) was sealed off and discarded. The system was re-evacuated and the distillation continued. The phenol used for samples was collected in (C).

The ampoule (F), made of 15 mm. tubing, was weighed with the female half of ground joint (E). The ampoule was then attached to the system at (E), evacuated, flushed with dry nitrogen and re-evacuated and sparked. The phenol in (C) was melted with a hot-air gun and was allowed to run through 4 mm.-bore stopcock (D) into the ampoule. The phenol was frozen in the ampoule, degassed, and then sealed off in vacuum at the constriction, leaving a capillary tip for breaking with the magnetic hammer. The two halves of the ampoule were weighed, giving the weight of the sample by difference.

When a diluent was used, the ampoule was not sealed off after the phenol was added. Instead, it was filled with dry nitrogen and weighed (a stopper was used before and after to prevent oxidation and absorption of moisture). The ampoule was then connected to a small system in which the diluent had been distilled *in vacuo* and degassed according to standard vacuum techniques. The diluent was then added to the phenol, the mixture frozen and the ampoule sealed under vacuum. The weight of the diluent was then obtained from the total weight by difference.

The tertiary halide samples were prepared in a manner similar to that described in reference 3a. Standard vacuum techniques were used for distilling the halides *in vacuo* and for degassing and sealing off the samples. Care was taken to keep oxygen and traces of moisture from the samples.

**Apparatus.**—A schematic diagram of the rate apparatus is shown in Fig. 2. The method of following the rate of the reaction is to add a known weight of tertiary alkyl halide to a known weight of phenol in a thermostatted vessel, and to measure the increase in pressure due to the evolution of hydrogen chloride in a constant volume system. In certain experiments hydrogen chloride was added to the phenol prior to the addition of the tertiary halide, and in certain experiments the phenol contained a diluent.

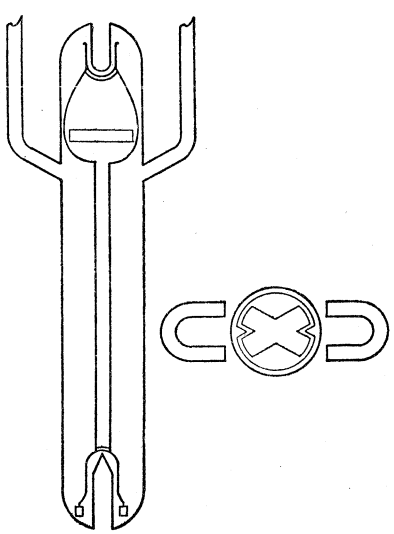


Fig. 3.—The reaction vessel.

An enlarged diagram of the reaction vessel is shown in Fig. 3. It consisted of 41 mm. tubing approximately 18 in. long, with a fulcrum extending up from the bottom and a guide tube extending down from the top. An all-glass stirrer was sealed inside the vessel. It rested on the glass fulcrum and had a tube at the top which prevented it from touching the walls of the vessel. An iron cross was sealed inside the bulb-like portion at the top of the stirrer, and the latter was operated by revolving two permanent horseshoe magnets outside the vessel, on a level with the iron cross. A bell-shaped device at the bottom of the stirrer carried four solid-glass paddles which served to stir the reaction mixture. Although there was no added lubrication, a speed of 300 r. p. m. or better was possible if the vessel was carefully constructed.

The reaction vessel contained three exit tubes immediately below the level of the bulb in the stirrer. Two of these led, through stopcocks, to the addition tubes from which the phenol and tertiary alkyl halide were added to the vessel. The third was connected to the rest of the rate apparatus. The entire reaction vessel was submerged in a thermostat.

The reagent addition tubes consisted merely of a tube which held the ampoule containing the reagent and a side-tube containing a nail sealed in glass which could break the capillary tip of the ampoule when activated with an electromagnet.

Since the reaction proceeded at a measureable rate only at elevated temperatures, it was necessary to have a condenser (G) (Fig. 2) to prevent the distillation of the reactants into the cooler parts of the system. The reaction side of the differential manometer (C) also contained a hydrogen chloride reservoir (B), lines to vacuum and dry nitrogen, and a line (H) to the hydrogen chloride generator.

The outside of the differential manometer contained an electric rest point signalling device (D) (see ref. 3a) which had both a light and a buzzer for indicating completion of the circuit. The rest of the system contained a one-liter buffer volume (E), a calibrated manometer (F) and lines leading to the vacuum and dry nitrogen sources for balancing the differential manometer. The nitrogen inlet contained a fine capillary to permit the increase in pressure on the outside of the differential manometer by very small increments.

The nitrogen source was a commercial cylinder. The nitrogen was dried over phosphorus pentoxide and the pressure was regulated by means of a mercury blowout valve set at approximately 200 mm. above atmospheric pressure. A Cenco Hy-Vac pump was the source of vacuum.

Approximately 90% of the volume of the reaction side of the system was thermostatted and the remainder of the system was at room temperature, which did not vary more than 3° during a single run.

**Measurement Procedure.**—When making measurements, the phenol was added to the reaction vessel, temperature and pressure equilibrium were established and hydrogen chloride was added in those cases in which its effect upon the reaction rate was being studied. Equilibrium was again established, the tertiary halide added, and time and pressure readings were made. The reaction was followed until at least 90% complete, and in many cases to essential completion.

The reagent addition tubes were sealed to the reaction vessel, the entire system evacuated, sparked, and checked for leaks. Mercury was then admitted to the differential manometer until contact was made with the upper tungsten lead. Both sides of the system were then filled with dry nitrogen and twice re-evacuated. This ensured the presence of very little oxygen in the system and therefore

very little oxidation of the phenol during the course of the reaction. (When the reaction was complete, the phenol solution was only very pale yellow.)

With the system evacuated, the phenol in the ampoule was melted (if not liquid already because of diluent), the tip broken with the magnetic hammer, and the phenol was admitted to the reaction vessel. The addition tube was gently flamed and analysis showed that less than 0.1% of the phenol remained in it. The stopcock to the addition tube was then closed and the stirrer started. After thirty to sixty minutes, the halide ampoule was broken, flamed, and the halide was admitted to the reaction vessel. The stopcock was opened for about thirty seconds; the stop watch was started at the initial opening of this stopcock.

For a few minutes after addition of the tertiary halide the pressure decreased, due to solution of the halide in the phenol. Thus, readings were taken on the "break" of the contact with the mercury. When solution was complete, however, and the pressure was increasing, readings were always taken on the "make" of contact. The rate curves (Figs. 4, 5) show only the rise in pressure.

Readings were taken as frequently as possible (about one every minute) at the beginning of the reaction and less frequently as the reaction proceeded. The points obtained were very self-consistent as is indicated by the curves in Figs. 4 and 5.

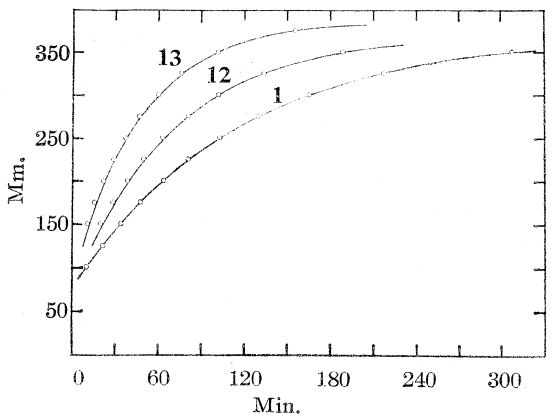



Fig. 4.—Typical rate curves for alkylation of phenol with *t*-butyl chloride at 45, 50 and 55°.

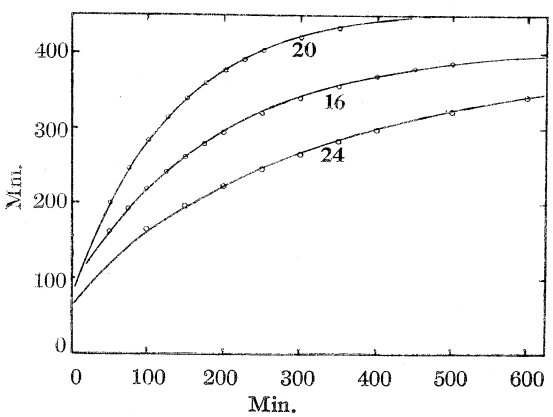



Fig. 5.—Typical rate curves for the alkylation of phenol with *t*-butyl chloride at 45° using various diluents.

When a run was completed, a break was made between stopcock (J) and condenser (G). The reaction vessel was thoroughly cleaned, dried, and re-sealed to the system for the subsequent run.

After completion of a run, the tertiary halide addition tube was removed *below* the stopcock. Ethanol was then admitted through the stopcock and the addition tube was rinsed several times with 95% ethanol. These rinsings were then analyzed for chloride by the Volhard procedure, allowing ten minutes after addition of the silver nitrate for complete reaction with the organic halide. In order to determine the weight of chloride actually used in the experiment, the weight of the alkyl halide in the ampoule was then corrected for the amount which remained behind. This correction was of the order of 1%.

## Results

Numerous kinetic experiments were carried out. Space requirements prohibit a complete tabulation of the data from each experiment. A summary of the essential results obtained from thirty-eight of the experiments is given in Table I. Columns (1)–(9) have been explained in the notes to that table. Time *vs.* pressure plots were made for each run (see Figs. 4 and 5 for typical curves). These curves show the consistency of the measurements in any one experiment. Only one experimental point out of every ten is indicated on these curves, for the sake of clarity in the drawings. The solid curve is drawn using equation (2) below, and employing for each experiment shown, the corresponding constants *a*, *b* and *C* from Table I. Thus, these drawings show the closeness of fit of the calculated curve and the experimental points. In order to determine these constants a spline was used to draw a smooth curve through the experimental points, and normals to these rate curves were drawn with a plane first-surface mirror held in a small frame at right angles to the plane of the curve. The normal was drawn when the curve itself and its image appeared to give no perceptible break.[8] The slope of the rate curve at various points was then determined as the negative recip-

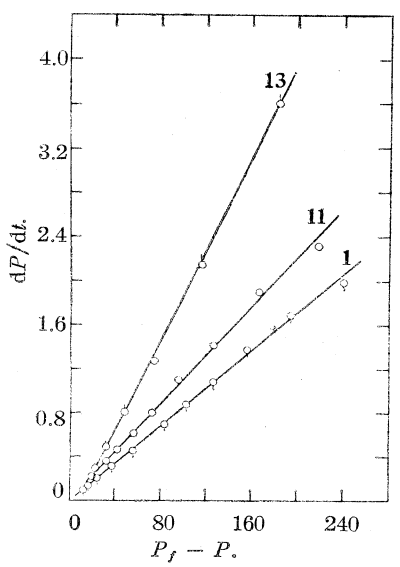



Fig. 6.—Typical derivative curves for the alkylation of phenol with *t*-butyl chloride.

(8) A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 88.

rocal of the slope of the normal. About ten slopes were measured for each curve, at regular intervals with respect to time, over the curve.

It was found that in all of the experiments, the equation

$$dP/dt = a(P_f - P) - b \qquad (1)$$

represented the data satisfactorily. In this equation $P$ represents the instantaneous total pressure, $P_f$ is the final equilibrium pressure, $t$ is the time, $dP/dt$ is the slope of the rate curve, and $a$ and $b$ are constants. Thus, when $dP/dt$ was plotted against $(P_f - P)$, straight lines were obtained (see Fig. 6). The best straight line was determined by the method of least squares, and the constants $a$ and $b$ obtained in this manner are given in columns (10) and (11) of Table I. This equation is essentially that for a first-order reaction (when $b = 0$) in which $a$ is a pseudo first-order rate constant. In some of the experiments, however, it was found that the straight lines did not go through the origin, and this small deviation is represented by $b$. This constant may arise because of the uncertainty of the zero time, and if we use half-times to compare different experiments we can do so independently of constant $b$.

Upon integration of (1), one obtains

$$1/a \ln [a(P_f - P) - b] + t = C \qquad (2)$$

The integration constant was determined by fitting the integrated equations to the original kinetic curves, using some experimental point near the half-time of reaction. These constants are given in column (12) of Table I. It was also possible then, after $a$, $b$ and $C$ were determined, to calculate the values of $P_0$ and of $t_{1/2}$ given in columns (8) and (13), respectively, of Table I.

The values of $n$, the apparent order of the reaction with respect to phenol, were determined only for the reaction between $t$-butyl chloride and phenol at 45°. They were obtained in the following manner. If one will plot $t_{1/2}$ *vs.* $M$, the molarity of phenol, using any theoretical order for the rate dependency of phenol (1st, 2nd, etc.) it is evident that in the region of $M = 9.5$ to 11.2 the curve is very nearly a straight line ($M = 11.2$ was taken as the molarity of pure phenol at 45°). The data of experiments 1, 2, 3, 4, 9 and 10 were then plotted ($t_{1/2}$ *vs.* $M$) and the best straight line was drawn through these points by the method of averages. This line, extrapolated to $M = 11.2$ gave a limiting theoretical value of $t_{1/2}$ (for zero $t$-butyl chloride concentration) of fifty-one and one half minutes.

It is well known[9] that

$$t \alpha \quad 1/a^{n'-1} \qquad (3)$$

where $t$ is the time required to complete a certain fraction of a reaction, $a$ is the initial concentration of reactants, and $n'$ is the total order of the reaction. In two different experiments, we then have that

$$t_1/t_2 = (a_2/a_1)^{n'-1} \qquad (4)$$

In the particular case of the reaction being studied, it is known that the reaction rate is first order with respect to the tertiary halide. The half-life is therefore independent of the halide concentration. Thus, since $n'$ in the above equation is the total order of the reaction, $n' - 1$ may be considered as the order of the reaction with respect to the phenol. Setting $n' - 1$ equal to $n$, the order with respect to phenol, expressing the concentrations $a$ as molarities $M$, and using as our reference value the half times $t_{1/2}$, we obtain the expression

$$t_{1/2}/t^0_{1/2} = (M^0/M)^n \qquad (5)$$

where $t^0_{1/2}$ is fifty-one and one half minutes at 45°, $t_{1/2}$ is the half-time for the particular experiment (column 13 of Table I) $M^0$ is 11.2 at 45°, $M$ is the molarity of the phenol for the particular experiment (column 5 of Table I). Values of $n$, the apparent order of the reaction with respect to phenol, could be calculated. These are the values given in column 14 of Table I.

The activation energies for the reaction of phenol with $t$-butyl chloride, $t$-amyl chloride and dimethylisopropylcarbinyl chloride were determined in the usual manner from rates at 45 and 55°. For the reaction in which nitrobenzene was used as the diluent the rate constant at 45° was corrected to the same phenol molarity as was used at 35° (see expt. 23) before calculating the Arrhenius energy of activation. The results of these calculations are given in Table II.

TABLE II

ENERGIES OF ACTIVATION FOR ALKYLATION OF PHENOL (45 to 55°)

| Chloride | $E$, kcal./mole |
|---|---|
| $t$-Butyl | 17.1 |
| $t$-Amyl | 14.8 |
| Dimethylisopropylcarbinyl | 15.9 |
| $t$-Butyl[a] | 13.0 |

[a] Using nitrobenzene as a diluent, $t = 35$ to 45°.

## Discussion of Results

All of the reactions which were studied were carried out with a large (ten to twenty-fold) excess of the phenol. Thus, the rate constants $a$ which were obtained, are pseudo first order rate constants, indicating that the reactions are all first order with respect to the tertiary alkyl halide. This is readily seen from the straight line relationship between the effective concentration of the tertiary halide $(P_f - P)$ and the over-all reaction rate $dP/dt$.

The determination of the order of the reaction with respect to phenol presents a more difficult problem. The amount of $t$-butyl chloride could not have been greatly increased, because too great a pressure rise for the system would have resulted. The tertiary halide could not be used in large ex-

(9) S. Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Company, Inc., 1940, pp. 1046–1047.

cess, as was the phenol, because of its low boiling point.

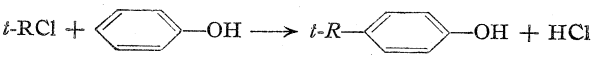
However, the order with respect to phenol was determined by using relatively small quantities of diluents of varying dielectric constants. The mathematical details of this determination were described above. The first diluent employed was *t*-butyl chloride itself, which has a dielectric constant nearly identical with that of phenol ($\epsilon_{t\text{-BuCl}} = 9.4$; $\epsilon_{C_6H_5OH} = 9.7$). Thus, in experiments 9 and 10 we see that only half of the usual quantity of phenol was employed (it still was present in ten-fold excess). Although the molarity of the phenol was only slightly lowered (from about 10.6 to 9.7) it is seen from Table I that the half-time was increased from approximately eighty-five to one hundred and twenty-three minutes. These results lead to a value of approximately 6 for $n$.

Other diluents which also have approximately the same dielectric constants as phenol are ethylene dichloride and 1,4-dichlorobutane ($\epsilon = 8.9$). These diluents did not interfere with the reaction and led to values of about 3.7 and 4.5 for $n$. From experiments 15 to 19 on Table I, one may note the very large change in the reaction half-time, although the change in dielectric constant of the medium was negligible. Thus, the principal reason for the rate differences is the change in phenol concentration. Although, in the case of the 1,4-dichlorobutane diluent, the phenol concentration was only halved, the half-time ($t_{1/2}$) was increased by 1500%. Two diluents with dielectric constants lower than that of phenol, and one greater were used. *p*-Xylene ($\epsilon = 2.3$) gave a value of $n = 5.8$ and nitrobenzene ($\epsilon = 35.4$) gave $n = 2$. The dioxane ($\epsilon = 2.4$) almost completely inhibited the reaction, and an explanation for this result is discussed below.

It can be seen from experiments 5, 6, 7 and 8 that the initial hydrogen chloride pressure has little or no effect upon the reaction rate for the *t*-butyl chloride–phenol reaction. This is a significant fact when one considers that the reaction being studied is one which is typical of those catalyzed by sulfuric acid, hydrogen fluoride or aluminum chloride. Because of the fact that the kinetic activity of hydrogen chloride did not have to be considered, we can interpret the change in reaction rate with temperature as due only to the increase in available thermal energy. The values for the activation energies are indicated in Table II. The values were determined over a very small temperature range (10°) and may be in error by as much as a kilocalorie.

The relative rates of reaction for the different halides are given by *t*-butyl > *t*-amyl >> dimethylisopropylcarbinyl >>> benzyl chlorides. The half times are approximately 84, 120, 425 and 1600 minutes, respectively, at 45°. (The run with benzyl chloride (not shown in Table I) proceeded very slowly and was not carried to completion, although its $t_{1/2}$ could be estimated at 1600 min.)

The main net reaction in each case is given by




but in the case of the dimethylisopropylcarbinyl chloride, dehydrohalogenation to the olefin may have taken place to a small extent. This was indicated by the fact that when the reaction was carried out on a large scale at reflux temperature using mole for mole quantities of phenol and halide, a 42% yield of the olefin was obtained. Of course in the kinetic experiments this was diminished considerably since lower temperatures were used, and the phenol was present in a twenty-fold excess. Dehydrohalogenation to the olefin was shown to be negligible in the case of *t*-butyl chloride (see section on the Quantitative Nature of the Reaction, in the experimental part).

Only one experiment (no. 14) was carried out using *t*-butyl chloride with *p*-cresol as the phenol. The reaction proceeded far more slowly than with phenol itself, $t_{1/2}$ being 362 minutes. This means that ortho alkylation proceeded at about one-eighth of the rate of para alkylation per ortho position. Thus, if rate were the only factor, one should obtain about 20% *o*-*t*-butylphenol from the alkylation of phenol.[9a] That none of this material has been isolated indicates that if formed at all, it rearranges to the more stable para isomer. (The synthesis and reactions of ortho-*t*-butylphenol are being investigated, and some of the results have been submitted for publication.)

Experiments were performed in which anisole was used as the aromatic nucleus to be alkylated. In all of these, the starting materials were recovered unchanged, indicating that the hydrogen attached to the oxygen atom in phenol is essential to mechanism of the reaction, in the absence of any added catalysts.

## Mechanism

In arriving at a mechanism for the reaction under study, the following facts must be explained: (1) first order rate dependency upon the tertiary halide, (2) a high power (approximately sixth order) rate dependency upon phenol, (3) the inhibitory power of dioxane and the effect of other diluents, (4) the low activation energy and (5) the lack of reactivity of anisole under similar conditions. There are several possible mechanisms which come to mind, one of which seems preferable to the others.

First, there is the possibility of formation of the phenyl *t*-alkyl ether as an unstable intermediate followed by the rearrangement of this ether in the presence of the generated hydrogen chloride to form the *p*-alkyl phenol.[10] In this case, the rate-

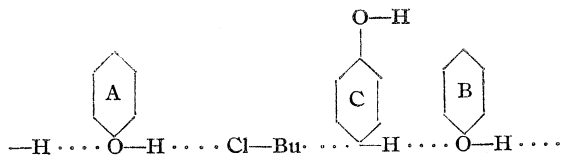
(9a) R. P. Perkins, A. J. Dietzler and V. T. Lundquist, U. S. Patent 1,972,599, claim about 1.2% *o*-*t*-butylphenol from *t*-butyl chloride and phenol using aluminum chloride as the catalyst at 50–200°.

(10) The authors are indebted to one of the referees for pointing out the work of Van Alphen (ref. 5b) on phenyl trityl and similar ethers.

determining step would have to be the formation of the ether since the reaction was not autocatalyzed by hydrogen chloride formed during the reaction, nor was it catalyzed by hydrogen chloride initially present in the phenol (see experiments 5–8, Table I). Rearrangement of the ether would have, therefore, to be intramolecular, since the involvement of five other phenol molecules in the transition state is indicated in the rate-determining (ether forming) step. If this were so, one would expect to obtain some *o*-*t*-butylphenol, which is not readily rearranged by concentrated hydrochloric acid,[11] and one would also expect that *p*-cresol would alkylate as readily or more so than phenol. Actually, the alkylation of *p*-cresol occurs only at one-eighth the rate of phenol, per ortho position. One might also expect the ether formation to be acid catalyzed, and it has been shown that this reaction is not catalyzed by hydrogen chloride. At any rate, one is hesitant to postulate an unstable intermediate if alternate mechanisms are more adequate.

Another possible mechanism involves the ionization of the tertiary alkyl halide to form a free or solvated carbonium ion, followed by attack of that ion upon the para position of the phenol. Since the reaction was carried out in a very large excess of phenol, it is likely that the ionization would have to be the rate-determining step. This would involve, then, the coördination of the chlorine with approximately five to six phenol molecules (either one hydroxyl of a phenol polymer or several hydroxyl groups of phenol molecules) in the ionization process. Such a mechanism could account for the observed facts, although one can show by calculations similar to those of Pearlson and Simons[3a] that the minimum energy required to form a solvated *t*-butylcarbonium ion in phenol at 45° is about 28 kcal. per mole. The experimentally determined activation energies are considerably lower than this value (14–17 kcal. per mole).

A third and preferred mechanism is here proposed, which we term the "amphoteric medium effect."[4] This mechanism involves a one-step, condensed phase reaction which makes use of the amphoteric properties of phenol. The mechanism rests on two important principles. Firstly, it is to be considered that the reaction has been studied in the liquid phase and that a large excess of phenol was present. This means that multiple collisions will be the rule, rather than the exception. The molecules are constantly in contact with and "colliding" with other molecules. The *t*-butyl chloride molecules can be considered, therefore, as essentially surrounded by phenol aggregates. Secondly, phenol is an amphoteric associated liquid which is readily capable of proton transfer in a manner analogous to that in water. The mechanism is schematically pictured below. The solid lines indicate the bonds prior to reaction, and the dotted lines indicate the shifts in the bonds




when reaction occurs. The rest of the phenol molecules (3 or 4) which are involved in the transition state may be represented as coördinated linearly to the phenol molecules A and B, or may aid in the making and breaking of bonds by the polymolecular attack on the chlorine and the para hydrogen. The most important point is that bonds are being made and broken simultaneously (because of the amphoteric properties of phenol) and that at no time need there be present a high energy intermediate capable of independent existence. This mechanism is in some respects similar to the acid–base catalysis of Lowry[12] and the termolecular mechanisms proposed recently by Swain.[13] This mechanism adequately explains all of the facts which are enumerated above in the first paragraph of this section.

## Summary

The reaction between tertiary alkyl chlorides and phenol was shown to be homogeneous and essentially quantitative when carried out in an excess of the phenol to form the alkyl phenol and hydrogen chloride.

The relative rates of reaction of *t*-butyl, *t*-amyl, dimethylisopropylcarbinyl and benzyl chlorides with phenol at 45° are 1:0.7:0.2:0.05. *p*-Cresol is alkylated in the ortho position at one-eighth the rate of para alkylation, per ortho position.

The rate of the reaction was first order with respect to the halide and essentially independent of the hydrogen chloride pressure. The rate was very highly dependent upon phenol concentration. The order with respect to phenol depended upon the diluent used: sixth order with *p*-xylene or *t*-butyl chloride diluent, 3.5 to 4.5 order with ethylene dichloride or 1,4-dichlorobutane, and second order with nitrobenzene as the diluent. The activation energies were experimentally determined between 45 and 55°, and were 14–17 kcal. per mole. Dioxane inhibited the reaction almost completely, and anisole would not react under conditions similar to those used with phenol in the absence of a catalyst.

The mechanism is discussed and the above facts are explained by a mechanism involving the amphoteric properties of phenol ("amphoteric medium effect").

Henry's law is obeyed within 3% by hydrogen chloride in phenol from 45 to 55° at pressures from 200 to 900 mm.

EAST LANSING, MICH.
STATE COLLEGE, PA.

RECEIVED MAY 29, 1948

(11) H. Hart, unpublished results.

(12) T. M. Lowry and I. J. Faulkner, *J. Chem. Soc.*, **127**, 2883 (1925).

(13) C. G. Swain, THIS JOURNAL, **70**, 1119 (1948); C. G. Swain and R. W. Eddy, *ibid.*, **70**, 2989 (1948).

[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

# Studies on the Schardinger Dextrins. The Preparation and Solubility Characteristics of Alpha, Beta and Gamma Dextrins[1]

BY DEXTER FRENCH, MELVIN L. LEVINE,[2] J. H. PAZUR AND ETHELDA NORBERG

A distinctive character of the Schardinger dextrins[3,4,5] which facilitates their separation from crude starch digests is their ability to form crystalline insoluble complexes with many liquids notably the hydrocarbons and halogenated hydrocarbons.[6] In a search for superior precipitants for the Schardinger dextrins, the authors have collected data on the precipitation efficiency of several organic liquids. The solubilities of the pure dextrins in water and aqueous propanol, and of the dextrin acetates in a few selected solvents have been measured. These data have been incorporated into a scheme for the separation and purification of the Schardinger dextrins which does not require the acetylation and saponification steps used by Freudenberg.[4] Aqueous propanol has been found doubly useful in the purification of the dextrins since it promotes sharp crystallization with a minimum of clouding or gum formation and the crystal forms of the individual dextrins are so characteristic that it is readily possible to identify the individual dextrin propanol complexes under the microscope (Figs. 1, 2, 3, 4).

That varying the enzymolysis conditions affects the total yield as well as the proportion of the Schardinger dextrins has been recorded by McClenahan, Tilden and Hudson.[5a] These observations have been corroborated and utilized so that the starch digestion is carried out under conditions most favorable for the individual compound sought. In particular, it has been possible to obtain the gamma dextrin which has hitherto been mentioned only by Freudenberg.[4] The modifications of enzymic and separative procedures are presented in detail in the experimental section.

## Experimental

**Preparation of the Schardinger Dextrins.**—In the early part of this study, enzyme digestion mixtures[5] were separated by the method of Freudenberg and Jacobi.[4a] In this way crude dextrin stocks were acquired and the individual compounds were purified by repeated crystallization. In later preparations the enzymolysis conditions have been varied according to the individual dextrin which is desired. In order to allow for differences in amount of enzyme, concentration of substrate and temperature of the reaction, it is convenient to describe the duration of enzymolysis in terms of *conversion periods*. A conversion period may be defined as that time of reaction between enzyme and substrate which under the conditions would be just sufficient to convert an equal weight of starch to the Tilden and Hudson end-point.[5b]

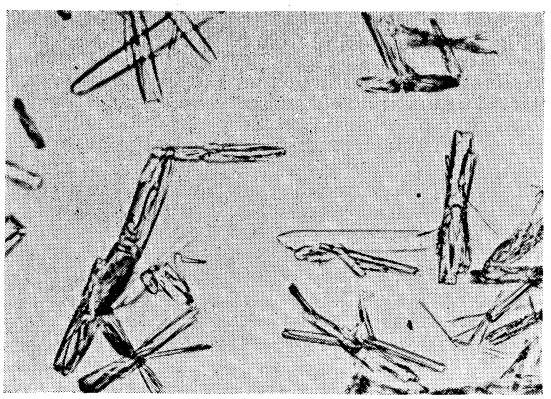


Fig. 1.—Alpha dextrin from 60% *n*-propyl alcohol, blade form.

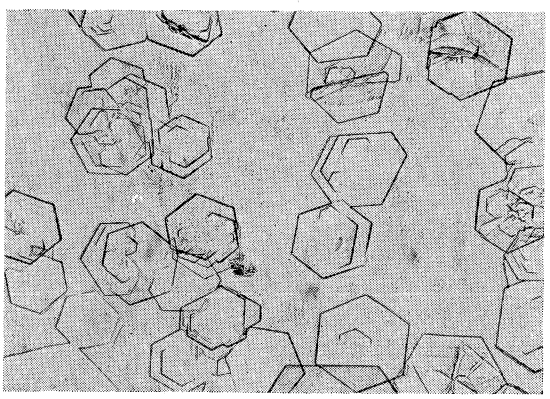


Fig. 2.—Alpha dextrin from 60% *n*-propyl alcohol, hexagonal form.

**Macerans Amylase.**—The enzyme used was prepared according to the directions of Tilden and Hudson.[5b] In order to prepare the gamma dextrin in good yield it is especially important that the enzyme be free from hydrolytic amylases. This can be determined by incubating a sample of starch with the enzyme for 50 conversion periods (using the conditions of the Tilden test, for example). At the end of this time the digest should show no more reducing power than the starch originally used, as indicated by copper or iron methods. Preparations with slight hydrolytic activity may be used for short conversions, as in the preparation of alpha dextrin.

**Alpha Dextrin.**—Enzymolysis of a 3–5% potato starch paste for 2–6 conversion periods in the absence of a dextrin

(1) Journal Paper No. J-1599 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project No. 964. Supported in part by a grant from the Corn Industries Research Foundation.

(2) Present address: Hawaiian Pineapple Co., Honolulu.

(3) Schardinger, *Zentr. Bakt. Parasitenk*, II **29**, 188 (1911).

(4) (a) Freudenberg and Jacobi, *Ann.*, **518**, 102 (1935); (b) Freudenberg, Plankenhorn and Knauber, *Chemistry & Industry*, 731 (1947). Substantially the same information is included in *Ann.*, **558**, 1 (1947), and FIAT Report No. 1096.

(5) (a) McClenahan, Tilden and Hudson, THIS JOURNAL, **64**, 2139 (1942); (b) Tilden and Hudson, *J. Bact.*, **43**, 527 (1942).

(6) Pringsheim, "Bacterial Degradation and Constitution of Starch," in "A Comprehensive Survey of Starch Chemistry," ed. Walton, The Chemical Catalog Co., Reinhold Publishing Corp., New York, N. Y., 1928, p. 35.

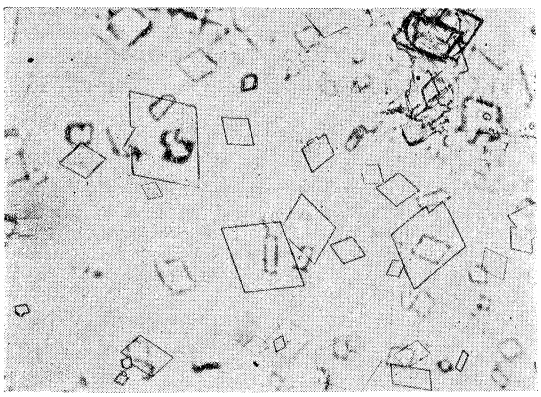


Fig. 3.—Beta dextrin from 60% *n*-propyl alcohol.

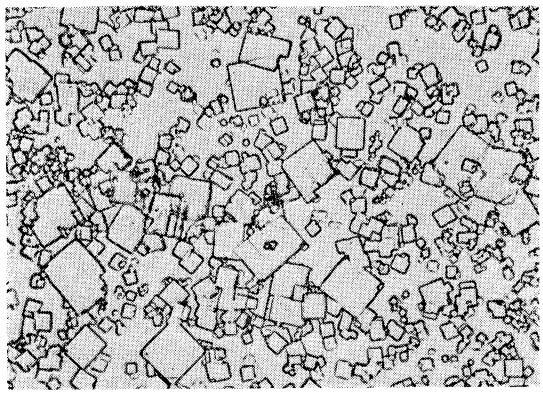


Fig. 4.—Gamma dextrin from 60% *n*-propyl alcohol.

precipitant (*i.e.*, the reaction mixture should be sterile or protected against microörganisms by a microbial inhibitor such as thymol) yields a mixture from which alpha dextrin can be readily obtained by concentration to about 15% solids, precipitation with trichloroethylene and centrifugation of the crystalline complex.[7] The crude precipitate is suspended in water, boiled to remove trichloroethylene, treated with carbon and filtered. After cooling and diluting to about 2% solids concentration, bromobenzene is added to effect precipitation of any beta or gamma dextrin which may be present. The mixture is best stirred with a mechanical stirrer or shaken overnight to insure complete equilibration with the bromobenzene. The resulting suspension is filtered with suction, the filtrate boiled down to about 40% of the original volume and the bromobenzene precipitate, which is usually small, worked up with beta–gamma crudes. The solution of crude alpha dextrin is now treated with trichloroethylene or tetrachloroethane by stirring or shaking overnight and the crystalline complex separated by suction filtration. The precipitate is air-dried, boiled with about 5 parts of water until the vapors are free from precipitant, clarified by filtration with carbon if necessary, treated with 1.5 volumes of *n*-propyl alcohol, and allowed to cool. The crystalline propyl alcohol complex is filtered off after several days and recrystallized by dissolving the air dry material in four parts of hot water and adding 1.5 volumes of propyl alcohol. The final crystallization may be carried out by dissolving the pure propanol complex in water, boiling off the propanol, concentrating the solution to about 35% solids and allowing to crystallize by evaporation at room temperature for a day or two. (Alcohol-free solutions of the dextrins should be guarded against mold growth by covering while hot.) The crystals are filtered and allowed to air dry. On drying in the vacuum oven the crystals lose about 10% moisture; the specific rotation of the anhydrous material is $[\alpha]_D + 150.5° \pm 0.5°$ (*c* 1, water).[8]

**Beta Dextrin.**—Enzymolysis of 3–5% paste of potato or waxy corn starch is carried out without a precipitant for 2–3 conversion periods. The digest, which is now very fluid, is clarified by filtration through diatomaceous earth, fresh enzyme added, layered over with toluene and enzymolysis allowed to proceed for 30–50 conversion periods. Beta dextrin–toluene complex separates during the digestion and to secure a maximum yield of dextrin the digestion vessel should be agitated from time to time to promote contact between the toluene and the enzymolysis mixture. After the conversion the precipitate is most conveniently separated by the supercentrifuge. The crude material is suspended in boiling water, toluene removed by boiling until there is no odor of toluene in the vapor, treated with carbon, and the boiling hot solution filtered with pressure through a clarifying filter.[9] The concentration at this point should not exceed 20–25% solids; higher concentrations give trouble through crystallization of the beta dextrin during filtration. If it is necessary to use suction filtration, this may be carried out at a concentration of 10% solids, and the filtrate concentrated by boiling to the 20–25% level. The filtrate should be perfectly clear; if not, it is filtered hot through successively finer filters, with carbon and filter aid if necessary. The resulting solution is allowed to cool, whereupon large crystals of beta dextrin are formed. After standing overnight in the cold, the crystals are filtered, washed, and purified by repeated crystallization from 4–5 parts of boiling water. In this way is obtained a product which is ash-free, completely soluble in water to give a clear solution, and which contains about 14% water of crystallization. After drying to constant weight at 70° in the vacuum oven, the rotation is $[\alpha]_D +162.5° \pm 0.5°$ (*c* 1, water)[8].

**Gamma Dextrin.**—The enzymolysis with potato or waxy maize starch is carried out in the same manner as described above for beta dextrin, except that after the initial brief conversion and clarification, the reaction is allowed to proceed in the absence of a precipitant for 30–50 conversion periods. Gamma dextrin is scarcely detectable in the early phases of the enzymolysis when the alpha dextrin concentration is at a maximum. If the reaction mixture is not sterile, thymol may be used to inhibit molds. When the conversion is complete, the mixture is concentrated to about one-fourth the original volume, stirred with trichloroethylene, and the precipitate separated by centrifugation (see ref. 7). The precipitate is dissolved in boiling water, clarified, concentrated to about 25% solids, and allowed to stand at room temperature a day or two. Seeding with beta dextrin may be advisable to promote fairly complete removal of this component. The precipitate is removed and the clear filtrate is diluted to about 3% solids. This solution is stirred overnight with bromobenzene and the resulting suspension filtered with suction. The precipitate is washed, dissolved in boiling water and boiled to remove the bromobenzene, concentrated to about 20% solids and treated with 1.5 volumes of *n*-propyl alcohol. After standing for a few days at room temperature, the crystals of gamma dextrin–propanol complex are removed by suction filtration and allowed to air dry. Gamma dextrin is best purified by dissolving the air-dry complex in 4 parts of boiling water, filtering with carbon if the solution is colored or turbid, and treating the resulting solution with 1.5 volumes of *n*-propyl alcohol. Recrystallization should be repeated until there is no evidence for alpha or beta dextrins in the 60% propanol mother liquors. Generally two or three recrystal-

(7) The Sharples Supercentrifuge is very useful for this type of separation.

(8) Specific rotations previously reported are: ref. 4a, alpha +148°, beta +158°, gamma +160°; ref. 4b, alpha 148 ± 2°, beta 158 ± 2°, gamma +169 ± 2°; ref. 5a, alpha +150.5 ± 0.5°, beta 162.5 ± 0.5°.

(9) Horm laboratory pressure filter, F. J. Horman and Co., Brooklyn, N. Y.

lizations are required. The propanol cannot be removed from this complex by either air or vacuum drying, but is readily removed by boiling in water. By concentrating a boiled aqueous solution to 40–50% solids and standing at room temperatures a few days, large clear crystals of gamma dextrin hydrate are formed. The crystals effloresce in air; the air dry material loses 8.3% of its weight on drying at 70° in the vacuum oven. The specific rotation of the anhydrous material is $[\alpha]_D + 177.4 \pm 0.5°$ ($c$ 1, water).[8]

**Identification of the Schardinger Dextrins.**—The dextrins form characteristic crystalline complexes with iodine and potassium iodide which permit the positive identification of alpha dextrin. If alpha dextrin is present to the extent of only 2–5% of the carbohydrate mixture, it forms blue-black hexagonal crystals when a solution containing a little 0.1 $N$ iodine in 0.1 $M$ potassium iodide is allowed to evaporate on a microscope slide.[3,5b] If the proportion of alpha dextrin is higher, needles exhibiting a colorless–blue-black dichroism are formed. These may be most readily identified by removing the polarizer of a microscope and rotating the analyzer, whereupon the crystals will be seen to alternate between blue-black and colorless. The hexagonal prisms described above exhibit a similar dichroism when turned over on a prism face. With the iodine–potassium iodide test the beta and gamma dextrins form brown to yellow complexes which are considerably less dichroic. No characteristics have been noted which enable the positive identification of the beta or gamma dextrin iodine complexes.

When the dextrins in 60% propyl alcohol are crystallized on a microscope slide, crystals of each complex can be readily identified. The crystallization is best carried out by allowing a drop of the 60% alcoholic solution to evaporate to dryness. A second drop is then placed on the slide and covered with a cover glass. Within a few minutes well-formed crystals will be observed. Alpha dextrin crystallizes as blade-shaped needles or hexagonal plates, beta dextrin as parallelograms, and gamma dextrin as square plates or rectangular rods. If the mixture contains some of each dextrin, it is usually possible to see each type of crystal. Particularly in the course of purification of the alpha and gamma dextrins it is worthwhile to examine the 60% propanol mother liquors for traces of other members of the dextrin series. Photographs of the dextrins as crystallized from 60% propanol are given in Figs. 1, 2, 3 and 4.

**Solubilities of the Dextrins in Water.**—Solutions containing 20% alpha dextrin, 5% beta dextrin or 35% gamma dextrin in water deposit crystals on standing at room temperature. Such solutions were allowed to equilibrate several days at room temperature with occasional shaking. The crystals were filtered off and the concentration of carbohydrate in the mother liquors was determined by measuring the rotations: alpha, 14.5 g./100 ml.; beta, 1.85 g./100 ml.; gamma, 23.2 g./100 ml.

**Solubilities of the Dextrins in 60% Propanol.**—Solutions of the pure alpha, beta and gamma dextrins were prepared by dissolving the air dry samples in four parts of hot water and adding six parts of anhydrous $n$-propyl alcohol. The solutions were shaken overnight and allowed to stand several days at room temperature. The suspensions were filtered and the concentration of carbohydrate in the filtrates determined by measuring the rotation. With alpha dextrin, at least three distinct crystalline forms, with different solubilities, were obtained. The solubilities ranged from 0.4 to 1.2 g./100 ml., with most frequent readings at about 0.8 and 1.1. With beta and gamma dextrins, no such variation was observed: beta, 0.54 g./100 ml.; gamma, 0.27 g./100 ml.

**Solubilities of the Dextrins in the Presence of Precipitants.**—Aqueous solutions of pure alpha, beta and gamma dextrins were treated with sufficient amounts of precipitants to form a distinct layer. Generally about 5 ml. of precipitant with 40 ml. of 0.3–0.5% dextrin was used. In some cases in which no precipitate was formed at this dextrin concentration, increasing amounts of dextrin were used. After equilibration by shaking overnight and standing for a few days at room temperature (*ca.* 27°) the precipitates were removed by filtration. The concentration of dextrin in the filtrate was determined by measuring the rotation. The results are presented in Table I.

TABLE I

SOLUBILITIES OF THE SCHARDINGER DEXTRINS IN THE PRESENCE OF PRECIPITANTS

| Precipitant | Alpha g./100 ml. | Beta g./100 ml. | Gamma g./100 ml. |
|---|---|---|---|
| Petroleum ether | | 0.12 | |
| Mineral oil | | .03 | |
| Cyclohexane | 0.15 | .06 | |
| Decalin | | .08 | |
| Benzene | .8 | .07 | |
| Toluene | .9 | .06 | 0.04 |
| *p*-Xylene | .9 | .02 | .06 |
| Ethylbenzene | | .03 | |
| *p*-Cymene | 3.3 | .04 | .17 |
| Naphthalene | | .03 | |
| Methyl iodide | | .06 | |
| Chloroform | 0.8 | .07 | |
| Carbon tetrachloride | | .10 | |
| Nitromethane | | Over .3 | |
| Carbon disulfide | .08 | .07 | |
| Ethylene dichloride | | .12 | |
| Ethylene dibromide | | .12 | |
| Trichloroethylene | .26 | .03 | .03 |
| Tetrachloroethane | .08 | .12 | .03 |
| Tetrachloroethylene | .7 | .004 | .01 |
| Tetrabromoethane | .10 | .02 | |
| Isoamyl iodide | | .10 | |
| Bromobenzene | 2.4 | .03 | .01 |
| Iodobenzene | | .03 | .03 |
| *p*-Chlorotoluene | | .02 | .05 |
| *o*-Bromotoluene | | .02 | .02 |
| *p*-Dichlorobenzene | | .18 | |
| α-Bromonaphthalene | | .02 | |
| Benzyl chloride | Over 1 | | |
| Nitrobenzene | Over 1 | .03 | .04 |
| Aniline | | Over .3 | .4 |
| Azobenzene | | .20 | |
| Butanol | | Over .3 | |
| Ethyl ether | | .66 | |
| Ethyl acetate | | Over .3 | |
| Benzyl alcohol | | Over .3 | |
| Cyclohexanol | 0.68 | | |
| Phenol | Over 1 | | |
| β-Phenylethanol | | 1.0 | |
| Thymol | | 0.14 | |

**Dextrin Acetates.**—The crude alpha dextrin, oven dry, was added in four equal parts at intervals to five parts of boiling acetic anhydride containing one-half part anhydrous sodium acetate. After the final addition the mixture was refluxed for thirty minutes, allowed to cool to room temperature, and poured with stirring into cracked ice and water. As the dextrin acetate hardened, the water was replaced. When all the acetic anhydride was destroyed, the dextrin acetate was broken and suction filtered. Pure beta and gamma dextrins were conveniently acetylated in the same manner. The crude alpha and beta acetates were crystallized from 10–15 parts of boiling toluene by cooling to room temperature. Gamma dextrin acetate was crystallized from 2–3 parts of hot butyl acetate. The dextrin acetates appear to crystallize with

solvent of crystallization which is lost on exposure to air, giving in some cases glasses which retain the exterior form of the original crystals. The specific rotations of the pure acetates were: alpha, $[\alpha]_D + 105.5 \pm 0.5°$ ($c$ 1, chloroform); beta, $[\alpha]_D + 122.0 \pm 0.5°$ ($c$ 1, chloroform); gamma, $[\alpha]_D + 138.5 \pm 0.5°$ ($c$ 1, chloroform).

**Solubility of Dextrin Acetates.**—The pure dextrin acetates were dissolved in about 15 parts of toluene, methanol, ethyl acetate and butyl acetate. If crystallization occurred on standing at room temperature, the mixtures were equilibrated for several days with frequent agitation and the concentration of material in the liquid phase determined by measuring the rotation as above. If crystallization did not occur, the solutions were evaporated until crystals separated or a glass was formed. After thorough equilibration the solubilities were determined as before. The values obtained are presented in Table II.

TABLE II

SOLUBILITIES OF THE SCHARDINGER DEXTRIN ACETATES

| Solvent | Alpha g./100 ml. | Beta g./100 ml. | Gamma g./100 ml. |
|---|---|---|---|
| Toluene | 0.22 | 0.24 | Very sol. |
| Methanol | 1.39 | 2.54 | Very sol. |
| Ethyl acetate | 8.84 | Very sol. | Very sol. |
| Butyl acetate | 0.67 | 17.8 | 11.0 |

## Summary

The preparation of pure Schardinger dextrins using differential precipitants and differential solubility in water and 60% propanol is described. For anhydrous gamma dextrin, $[\alpha]_D +177.4 \pm 0.5°$ ($c$ 1, water).[8] Characteristic crystal forms for the dextrins from 60% propanol are noted. The solubility behavior of the individual dextrins in water, 60% propanol and water saturated with various precipitants is reported.

AMES, IOWA RECEIVED SEPTEMBER 20, 1948

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[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

# Studies on the Schardinger Dextrins. II. Preparation and Properties of Amyloheptaose[1]

BY DEXTER FRENCH, MELVIN L. LEVINE[2] AND J. H. PAZUR[3]

In studying the behavior of starch it is clearly desirable to have available model compounds which may be expected to exhibit characteristic starch reactions without the difficulties and uncertainties associated with native starch. Lack of homogeneous amyloöligosaccharide of chain length intermediate between maltose and amylose has led to conflicting opinions on the mode of action of the amylolytic enzymes, the relationship between chain length and iodine coloration, etc. This paper describes the preparation and properties of a maltose homolog containing seven glucose residues per molecule: amyloheptaose. The biochemical properties of amyloheptaose will be reported subsequently.

Amyloheptaose may be conveniently prepared by the controlled acid hydrolysis of Schardinger's beta dextrin, cycloheptaamylose. Since this is a cyclic molecule containing seven[4] glucose units linked together by maltose bonds,[5] rupture of any one bond per cyclic molecule leads directly to the linear heptasaccharide of the amylose series. The experimental difficulty in confining hydrolysis to one glycosidic linkage per molecule is accentuated by the fact that the beta dextrin is considerably more resistant to acid hydrolysis than corresponding linear compounds.[6] In order to avoid extensive degradation of the amyloheptaose it was necessary to establish an experimental procedure based upon the rate constants for the decyclization reaction and the subsequent heptasaccharide breakdown. The separation of the heptasaccharide from large amounts of unchanged beta dextrin was accomplished by allowing the latter to crystallize in the cold and removing the last trace as the insoluble $p$-xylene complex.[7] The dilute hydrochloric acid used as hydrolysis catalyst was exactly neutralized with lithium carbonate and the resulting lithium chloride removed by repeated precipitation of the aqueous heptasaccharide solution with absolute ethanol. The complete details of the preparation are given in the experimental section.

## Reaction Kinetics Involved

A complete mathematical analysis of the kinetics of the hydrolysis of cycloheptaamylose ($\beta$)

$$\beta \longrightarrow \text{heptasaccharide} \longrightarrow \begin{matrix}\text{hexasaccharide}\\ \text{pentasaccharide}\\ \text{tetrasaccharide}\\ \text{trisaccharide}\\ \text{maltose and glucose}\end{matrix} \qquad (1)$$

is complicated and unnecessary for the purpose at hand. It was found expedient, however, to derive expressions for the amount of heptasaccharide (H) and the number of reducing hemiacetal groups (R) as a function of time. In setting up this system $k_1$ was defined as the rate constant for the destruction of $\beta$ and $k_2$ as the *average* rate constant for the destruction of the glycosidic bonds in all the open-chain molecules.[8]

(1) Journal Paper No. J-1600 of the Iowa Agricultural Experiment Station, Project No. 964. This work was supported in part by the Corn Industries Research Foundation.

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(4) French and Rundle, THIS JOURNAL, **64**, 1651 (1942).

(5) Freudenberg and Meyer-Delius, *Ber.*, **71**, 1596 (1938).

(6) (a) Cori, Swanson and Cori, *Federation Proc.*, **4**, 234 (1945). (b) Swanson and Cori, *J. Biol. Chem.*, **172**, 797 (1948), have come to similar conclusions using wholly different experimental and mathematical methods.

(7) French, Levine, Pazur and Norberg, THIS JOURNAL, **71**, 353 (1949).

(8) It is recognized that the rate of hydrolysis of the glycosidic bonds depends on such factors as the size of the molecule and the position of the bond within the molecule.

The rate of destruction of $\beta$ and the net rate of increase of H and R may then be expressed by the differential equations

$$d\beta/dt = -k_1\beta \quad (2)$$

$$dH/dt = k_1\beta - 6k_2H \quad (3)$$

$$dR/dt = k_1\beta + k_2(7\beta_0 - 7\beta - R) \quad (4)$$

with the corresponding solutions

$$\beta = \beta_0 e^{-k_1 t} \quad (5)$$

$$H = \beta_0 \frac{k_1}{(6k_2 - k_1)} [e^{-k_1 t} - e^{-6k_2 t}] \quad (6)$$

$$R = \beta_0 \left[7 - e^{-k_1 t} + \frac{6}{(k_2 - k_1)} (k_1 e^{-k_2 t} - k_2 e^{-k_1 t})\right] \quad (7)$$

The degree of purity of the amyloheptaose, assuming complete removal of unchanged beta dextrin and inorganic material, is $H/(\beta_0 - \beta)$.

Evaluation of $k_1$ was carried out by determining the initial rate of appearance of reducing groups (eqn. 4) as well as by recovery of unchanged beta dextrin after varying periods of hydrolysis; $k_2$ was approximated by plotting $R$ (eqn. 7) against $k_1t$ for trials values of $k_2/k_1$ and comparing with the observed reducing power.

Using $k_2/k_1$ thus determined, an extent of hydrolysis of 2% leads to an amyloheptaose of 95% purity. This limit was arbitrarily selected as a satisfactory compromise between purity of product and single-step yield.

## Properties of Amyloheptaose

A carefully purified batch of beta dextrin was hydrolyzed, using the principles outlined above, and 13.3 g. of amyloheptaose obtained. The product was a white glassy substance which has not yet crystallized. It is very soluble in water and insoluble in alcohol, forming a sirup when alcohol is added to an aqueous solution. It is only slightly sweet and the iodine coloration is scarcely noticeable. The observed rotation $[\alpha]_D$ +176° is somewhat lower than that calculated using Freudenberg's equation[9] and the customary constants for starch[10]: $[\alpha]_D$ +179.6°. The reducing power indicates a molecular weight of 1200 (alkaline ferricyanide method) or 1206 (iodine titration of aldoses) as compared with a calculated value of 1154. These discrepancies may be harmonized if one assumes that the glassy sample holds a small amount of difficultly removable water or other inert impurity (*i. e.*, about 3%). Chromatography of the amyloheptaose preparation failed to detect any glucose, maltose or trisaccharide although these substances are easily observed after more extensive hydrolysis of cycloheptaamylose.

The phenylhydrazone and potassium aldonate of amyloheptaose were prepared using standard procedures, and the nitrogen content of the phenylhydrazone and the potassium content of the aldonate were in good agreement with the values calculated for corresponding heptasaccharide derivatives.

(9) Freudenberg, Friedrich and Bumann, *Ann.*, **494**, 41 (1932).

(10) Levine, Foster and Hixon, THIS JOURNAL, **64**, 2331 (1942).

In studies to be reported subsequently it has been found that beta amylase degrades amyloheptaose to give a mixture of maltose and trisaccharide in the mole ratio of two to one. This indicates that the original oligosaccharide contains an odd number of glucose units, as beta amylase converts even-numbered amylose chains completely to maltose.[11] The mole ratio of maltose to trisaccharide as well as the increase in reducing power may be determined with sufficient precision to eliminate the possibility that the enzyme substrate was either a pentaose or a nonaose.

The chemical evidence concerning the identity and purity of the initial hydrolysis product of cycloheptaamylose, *i. e.*, amyloheptaose, is in harmony with the theoretical calculations within the experimental error of the methods used.

## Experimental

**Cycloheptaamylose.**—This substance was prepared using methods previously outlined[4,7] and had the following constants: water, 13.4%; $[\alpha]_D$ + 163.2 ± 0.5°, dry basis; ash by ignition, 0; ash by conductivity as sodium chloride, 0.005%.

**Determination of $k_1$.**—A ratio of one gram, dry weight, of cycloheptaamylose to 4 ml. of 0.001 *N* hydrochloric acid was uniformly used throughout all experiments and preparations in this paper. Tubes containing *ca.* 0.5 g. of cycloheptaamylose in 2 ml. of 0.001 *N* hydrochloric acid were stoppered and heated in a boiling water-bath for varying periods of time. The tubes were swirled occasionally to insure homogeneity of the reaction mixture. After a definite period of time a tube was removed, the contents transferred to a 300-ml. flask and the reducing power determined by the alkaline ferricyanide method.[10] The rate constant was calculated using the first term of eqn. 4 in integral form. After 180, 360, 540 min., $k_1 \times 10^5$ = 4.7, 6.5, 6.9.

Ten-gram samples of cycloheptaamylose dissolved in 40 ml. of 0.001 *N* hydrochloric acid were heated at 99° and after various periods of time the acid was neutralized and the mixtures were refrigerated. The crystals of cycloheptaamylose were collected quantitatively in weighed alundum filtering crucibles. The filtrates were treated with toluene by shaking twenty-four hours followed by refrigerating twenty-hour hours and the resulting precipitates collected in tared alundum crucibles. From the total dry weight of recovered cycloheptaamylose from each sample the $k_1$ values were calculated using eqn. 5: after 4,280, 7,130, 28,560 min., $k_1 \times 10^5$ = 4.0, 5.0, 4.6.

**Determination of $k_2/k_1$.**—The filtrate from the 28,560-minute sample above was collected quantitatively and the average molecular weight of the solids determined by iodine titration and specific rotation. From these figures the average number of reducing groups per mole of starting material was calculated to be 2.38. This value corresponded most closely to a value for $k_2/k_1$ of 0.64 on a plot of various values for $k_2/k_1$ in eqn. 7. Using $k_1 = 4.6 \times 10^{-5}$, $k_2 = 2.9 \times 10^{-5}$.

**Preparation of Amyloheptaose.**—A 100-g. sample of pure cycloheptaamylose was dissolved in 400 ml. of 0.001 *N* hydrochloric acid in a 1000-ml. flask fitted with a condenser. The flask was immersed in a boiling water-bath, 99°, and shaken frequently. After seven hours the flask was removed, the acid immediately neutralized with the calculated amount of lithium carbonate and the unhydrolyzed cycloheptaamylose allowed to crystallize on cooling to room temperature and refrigerating twenty-four hour. The crystals were removed by filtration and the remaining cycloheptaamylose removed by saturating the filtrate with *p*-xylene, shaking for twenty-four hours,

(11) Myrbäck and Leissner, *Arkiv Kemi, Mineral. Geol.*, **17A**, No. 18 (1943).

refrigerating twenty-four hours, and filtering off the precipitates. This final filtrate was then concentrated to one-fifth its original volume *in vacuo*. Six additional hydrolyses were carried to this stage and the concentrated filtrates combined. The resulting solution was again covered with *p*-xylene, shaken and refrigerated for twenty-four hour each, filtered, and the filtrate concentrated to a thin sirup *in vacuo*. In order to remove any lower saccharides and lithium chloride the amyloheptaose was precipitated by adding four volumes of absolute ethanol. The sirupy precipitate was taken up in a small amount of water and reprecipitated in like manner five times. Finally the precipitate was dehydrated with absolute ethanol to which a small amount of absolute butanol was added, filtered, and washed with dry butanol.[12] The material was finally dried to constant weight in the vacuum oven at 70°, $[\alpha]_D$ + 175.5° ($c$ = 2, water); another preparation, + 176.5°; theoretical, + 179.6°.[9,10] Molecular weight by alkaline ferricyanide,[10] 1200; by the Kline and Acree hypoiodite method,[13] 1206; theoretical, 1152.

**Potassium Amyloheptaonate.**—The method of Levine, Foster and Hixon[10] for the preparation of dextrinic acids was applied to 0.5 g. of amyloheptaose. After the final grinding and acetone extraction, the potassium salt was dried to constant weight and a weighed sample ashed with ammonium sulfate. The molecular weight was calculated from the potassium content: observed, K 3.34%, m. wt. 1167; calcd., m. wt. 1206.

**Amyloheptaose Phenylhydrazone.**—The phenylhydrazone was prepared by a modification of the method of Bergmann and Machemer[14] previously described.[10] Nitrogen was determined by the micro-Dumas method and the molecular weight of the derivative calculated assuming two atoms of nitrogen per molecule: observed, N 2.19%, 2.27%, m. wt. 1275, 1235; calcd., m. wt. 1242.

(12) The butanol was used to prevent condensation of water and consequent gumming of the amyloheptaose due to the evaporation of the ethanol during the filtration and drying.

(13) Kline and Acree, *Ind. Eng. Chem., Anal. Ed.*, **2**, 413 (1930).

(14) Bergmann and Machemer, *Ber.*, **63**, 322 (1930).

**Chromatographic Test for Lower Saccharides.**—A 20 mg. sample of the sugar was dissolved in 0.3 ml. of water and 4.8 ml. of absolute ethanol added. The resulting mixture was placed on a chromatographic column consisting of 12 g. of a 3:1 mixture of Florex XXX and Celite 535 as described by Lew, Wolfrom and Goepp.[15] The sugars were eluted with 90% ethanol and the concentration of sugar in the eluate determined colorimetrically by the diphenylamine method.[16] The rate of flow of the individual sugars was found to be sufficiently characteristic and the diphenylamine test sufficiently sensitive that an amount of glucose, maltose or trisaccharide as low as 0.01 mg./ml. could be readily detected.

On testing 20 mg. of amyloheptaose in this manner, there was no evidence whatsoever for contamination by glucose, maltose or trisaccharide. The column was then extruded, cut into 2-cm. portions and the individual portions extracted and tested for carbohydrate. The top 2-cm. portion was carbohydrate free, the next two 2-cm. portions contained carbohydrate, and the remainder of the column was carbohydrate free.

A cycloheptaamylose sample which was hydrolyzed for *ca.* 7000 minutes ($k_2t$ = 0.35) was similarly chromatographed, and glucose, maltose and trisaccharide were found to be present in sizable amounts (109 mg., 81 mg. and 62 mg.).

## Summary

Amyloheptaose has been prepared by controlled acid hydrolysis of cycloheptaamylose. The analytical constants of amyloheptaose, its potassium aldonate and its phenylhydrazone agree with those calculated for a heptasaccharide.

(15) Lew, Wolfrom and Goepp, THIS JOURNAL, **68**, 1449 (1946).

(16) See Oppel, *Biochem. Z.*, **229**, 85 (1930), and Davidson, Kermack Mowat and Stewart, *Biochem. Z.*, **30**, 433 (1936), for two modifications of the quantitative diphenylamine method.

AMES, IOWA RECEIVED SEPTEMBER 24, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RENSSELAER POLYTECHNIC INSTITUTE]

# The Reaction of Diethanolamine with Nitriles and Potassium Cyanide

BY WILLIAM H. RAUSCHER, IRVING S. GOLDSTEIN AND MAXWELL BRESLAU

Since ethanolamines have been used as agents for the reduction of organic compounds,[1] especially nitro compounds, it was though possible they might convert nitriles to amines. However, benzonitrile and benzyl cyanide, when refluxed with substantially dry diethanolamine, undergo hydrolysis rather than reduction to yield benzoic and phenylacetic acid, respectively, with concomitant evolution of ammonia. Maximum yields are obtained with a nitrile to diethanolamine ratio of 1:5 and a reflux period of forty-eight hours.

From larger scale runs, conducted in an attempt to isolate intermediate products, it was possible to obtain substantial quantities of water and piperazino-1,4-bis-(β-ethanol). It appears therefore that diethanolamine undergoes cyclization to the piperazine and water which effects hydrolysis of the nitrile. No other details of the mechanism have been established.

Under similar conditions, potassium cyanide yields ammonia and a mixture of potassium formate and succinate. The latter salt, the formation of which was unexpected, was always obtained in much larger amount than the formate. It was established that only a small amount of ammonia is evolved by refluxing diethanolamine alone and that the presence of a small amount of potassium cyanide in refluxing diethanolamine does not catalyze the evolution of ammonia from the amine or cause its cyclic dehydration to the piperazine. Potassium succinate was not formed by refluxing potassium formate with diethanolamine. The mechanism of the conversion of potassium cyanide to potassium succinate has not been determined.

(1) (a) M. Meltsner, C. Wohlberg and M. J. Kleiner, THIS JOURNAL, **57**, 2554 (1935); (b) C. B. Kremer, *ibid.*, **59**, 1681 (1937); (c) M. Meltsner, L. Greenstein, G. Gross and M. Cohen, *ibid.*, **59**, 2660 (1937); (d) C. B. Kremer and B. Kress, *ibid.*, **60**, 1031 (1938); (e) C. B. Kremer and A. Bendich, *ibid.*, **62**, 1279 (1940).

## Experimental

**Materials.**—Diethanolamine was the Carbide and Carbon Chemicals Corporation product purified by redistillation at 3 mm. Benzonitrile and benzyl cyanide were redistilled Eastman Kodak Co. products. Potassium cyanide was the C. P. grade. All melting points are corrected. Typical runs are described.

**Benzoic Acid from Benzonitrile.**—Five grams (0.05 mole) of benzonitrile and 27.5 g. (0.25 mole) of diethanolamine were refluxed for forty-eight hours in an apparatus employing standard taper joints. The condenser was water cooled. Evolved ammonia was swept out through the condenser into a measured quantity of standard acid by a gentle stream of purified air. At the end of forty-eight hours the reaction mixture was cooled and diluted with 100 ml. of water, complete solution taking place. The solid which appeared immediately on acidification with concentrated hydrochloric acid was removed by filtration and recrystallized from water. The filtrate was warmed for several hours on the steam-bath and cooled, but no additional solid was obtained; weight recrystallized acid 3.1 g. or a 52.4% yield; m. p. 121–122°; neut. equiv. 120.5; m. p. of *p*-nitrobenzyl ester 88–89°. The values for benzoic acid are: m. p. 121.4; neut. equiv. 122.1; m. p. *p*-nitrobenzyl ester 89°. During the reflux period ammonia evolved corresponded to 61% of the nitrogen of benzonitrile.

**Phenylacetic Acid from Benzyl Cyanide.**—Five grams (0.05 mole) of benzyl cyanide and 28 g. (0.25 mole) of diethanolamine were refluxed similarly for forty-eight hours. On adding 100 ml. of water complete solution took place. The solution was made acid with hydrochloric acid and warmed on the steam-bath for one hour. After cooling it was extracted three times with 50-ml. portions of ether. The solid recovered from the ether solution was recrystallized from petroleum ether; weight recrystallized acid 4.5 g. or a 77.4% yield; m. p. 76.5–77°; neut. equiv., 135; m. p. of *p*-nitrobenzyl ester 64.5–65°. The values for phenylacetic acid are: m. p. 76.7°; neut. equiv., 136.2; m. p. of *p*-nitrobenzyl ester 65°. During the reflux period evolved ammonia corresponded to 71% of the nitrogen of benzyl cyanide.

**Piperazino-1,4-bis-(β-ethanol).**—One-half mole (58.5 g.) of benzyl cyanide and 2.5 moles (260 g.) of diethanolamine were refluxed in a 3-necked, 500-ml. flask provided with a water cooled condenser and thermometers placed in the liquid and the vapor, standard taper joints being used. After several hours refluxing the liquid temperature fell to 145° and the vapor temperature to 101°, both temperatures remaining quite constant to the end of reflux. After forty-eight hours 36.5 g. of water were removed through a short Vigreux column at atmospheric pressure. On further distillation at 3 mm. considerable decomposition resulted and very little material could be distilled. On cooling overnight the remaining reaction mixture became a pasty solid. Pyridine was added with warming until it constituted about one third of the homogeneous solution resulting. On cooling the solution in the refrigerator a yellowish crystalline solid was obtained. It was removed and washed with pyridine and acetone. The dried product weighed 45 g. After several recrystallizations from acetone a colorless crystalline solid melting at 134.6–135.2° was obtained. As the identity of the material was not suspected at this time it was extensively investigated and the following data collected. *Anal.* C, 55.22, 55.10; H, 10.44, 10.23; N, 15.99, 16.1; neut. equiv. (using methyl red) 175.6, 175.0; weight of base combining with 1 mole of hydrochloric acid (gravimetric) 86.86, 86.88; per cent. chlorine in hydrochloride 28.67, 28.66; m. p. *p*-nitrobenzoate 158–160°. Piperazino-1,4-bis-(β-ethanol) has the following values. *Anal.* C, 55.14; H, 10.41; N, 16.08; m. p. 135–135.5°; mol wt. 174.2; weight combined with 1 mole hydrochloric acid 87.12; chlorine in dihydrochloride, 28.67; m. p. *p*-nitrobenzoate 158–158.5°.[2]

**Potassium Formate and Potassium Succinate from Potassium Cyanide.**—Thirty-three grams (0.5 mole) of potassium cyanide and 260 g. (2.5 moles) of diethanolamine were refluxed for forty-eight hours as in the 0.5 mole benzyl cyanide run described above. Evolved ammonia corresponded to 74.4% of the nitrogen of potassium cyanide. Soon after reflux began the liquid temperature was 238° but gradually fell to 156°, where it remained fairly constant. On cooling the reaction mixture became very viscous and crystals appeared. Sufficient absolute alcohol was added to permit the solid to be removed by filtration. This solid (A) was washed with absolute alcohol and dried in a vacuum desiccator to give 19.4 g. of product. The alcohol in the filtrate from (A) was removed by distillation and chloroform added as long as its addition gave evidence of the precipitation of a solid (B). Solid (B) was collected on a filter, washed with chloroform and dried in a vacuum desiccator to give 3 g. of material.

Solid (A) was shown to be potassium succinate from the following data: Solid (A) yielded an acid of m. p. 187–188°; neut. equiv., 60.1; mixed m. p. with authentic succinic acid 186–187°; *p*-bromophenacyl ester m. p. 212–213°; *p*-nitrobenzyl ester m. p. 86–87°. For succinic acid the values are: m. p. 188°; neut. equiv. 59.05; m. p. *p*-bromophenacyl ester 211°; m. p. *p*-nitrobenzyl ester 88°. The equivalent weight of solid (A) by the sulfate method was found to be 93.0, 92.5. The equivalent weight of potassium succinate is 97.1.

Solid (B) was shown to be potassium formate from the following data: m. p. 166–167°; m. p. of *p*-bromophenacyl ester 138–139°; equiv. wt. by sulfate method 86.0, 89.0. For potassium formate the values are: m. p. 167.5°; m. p. *p*-bromophenacyl ester 140°; equiv. wt., 84.

## Summary

By refluxing with substantially dry diethanolamine, benzonitrile and benzyl cyanide are hydrolyzed to the corresponding acids. Water required for the hydrolysis is apparently supplied by a cyclic dehydration of diethanolamine to piperazino-1,4-bis-(β-ethanol). In the case of potassium cyanide a substantial yield of potassium succinate and a small yield of potassium formate result. No mechanism is suggested for the formation of the succinate.

TROY, N. Y. RECEIVED AUGUST 20, 1948

(2) D. E. Adelson, L. G. MacDowell and C. B. Pollard, THIS JOURNAL, **57**, 1988 (1935).

# NOTES

## The Relation between Magneto-optic Rotation and Refractive Dispersion of Hydrocarbons

By A. Bondi

Inspection of data on the magneto-optic rotation (Verdet Constant, $V$) of hydrocarbons[1,2] suggested that they may be directly proportional to the refractive dispersion, $n_{\nu 1} - n_{\nu 2} = \Delta n$. The recent extensive and accurate data published by Foehr[3] make possible the quantitative comparison which is presented in Table I. It appears that $V/\Delta n$ is indeed very nearly independent of the hydrocarbon type at low molecular weights and substantially constant in the higher molecular weight range.

The greatest "exaltation" apparently occurs among the aromatic hydrocarbons, but too few measurements are available in this class of compounds to permit any valid generalization.

As a practical result this observation suggests that refractive dispersion and magneto-optic rotation may be used interchangeably. Since refractive dispersion data are usually more accessible[4,5] than Verdet constants, the ingenious scheme of (magneto-optic) hydrocarbon type analysis proposed by Foehr[3] may now be applied more extensively.

The theoretical background is contained in the Becquerel formula[6]

$$V = \gamma \frac{e}{2mc^2} \nu \frac{\partial n}{\partial \nu} \qquad (1)$$

where the universal factor $e/2mc.^2$ derives from the Larmor precession, $\nu$ = frequency of the light used, $\partial n/\partial \nu$ = refractive dispersion, $\gamma$ = "anomaly" factor. The constancy of the ratio $V/\Delta n$ thus means that for hydrocarbons $\gamma$ is a constant. For diamagnetic substances, according to Schütz[6]

$$\gamma = a_i + \frac{b}{2} \frac{\nu_i}{\Delta \nu_0} \qquad \text{if } \nu \ll \nu_i \qquad (2)$$

where $a_i$ = oscillator strength, $\nu_i$ = characteristic frequency of the electron transition which is active in the magneto-rotation and determines the dispersion of $V$ (as well as of the refractivity, v. i.), $\Delta \nu_0$ = multiplet splitting shift, and $b$ = a numerical factor of the order $-2/3$.[6] No data are yet available on the multiplet splitting term, $\Delta \nu_0$, of organic molecules, but it is likely to be equal for all hydrocarbons. Equation (2) therefore implies the existence of a linear relation between the oscillator strength and the characteristic frequency of the "dispersion-electron" of hydrocarbons.

As one can observe the constancy of $\gamma$ within other families of organic molecules,[6] this relation should hold more widely. The lack of reliable absolute intensity data, particularly in the vacuum ultraviolet where the characteristic absorption band of the saturated hydrocarbons is located, precludes a direct test of the postulate made. The constancy of $\gamma$ in spite of the wide variation in $\nu_i$ (0.8 to 2.5 $\times$ $10^{15}$ sec.$^{-1}$) and in $a_i$ encountered in the range of hydrocarbons reported in Table I suggests, however, that a relationship at least similar to the proposed one exists. (A plot of the oscillator strength $f_1$,[7] *versus* $\nu_1$ shows that the data lie on smoothly ascending curves, which are, however, characteristic of each family of (aromatic) hydrocarbons so tested, and not universal for all hydrocarbons as first hoped for.) The utility of Equation (2) for $\gamma$ = const. consists in the possibility of expressing the refractive dispersion of hydrocarbons as a function of $\nu_i$ alone, thereby facilitating the rational treatment of this easily determined physical property.

TABLE I

COMPARISON OF VERDET CONSTANT[a] AND REFRACTIVE DISPERSION[b] OF HYDROCARBONS

| Substance | $V_D \times 10^2$ | $V/\Delta n$[c] | $\Delta V/\Delta n$[d] |
|---|---|---|---|
| *n*-Pentane | 1.159 | 1.188 | 1.11 |
| *n*-Decane | 1.316 | 1.148 | 1.05 |
| *n*-Hexadecane | 1.359 | 1.12 | 1.03 |
| 11-*n*-Decyldocosane | 1.423 | 1.12 | 1.01 |
| Cyclopentane | 1.238 | 1.08 | 0.96 |
| Cyclohexane | 1.247 | 1.05 | .93 |
| 11-Cyclohexyl-*n*-heneicosane | 1.440 | 1.12 | 1.00 |
| 1,1-Dicyclohexyl-*n*-heptane | 1.443 | 1.11 | 0.99 |
| Benzene | 3.02 | 1.11 | 1.09 |
| Toluene | 2.726 | 1.065 | 1.11 |
| Ethylbenzene | 2.60 | 1.05 | .. |
| *n*-Propylbenzene | 2.46 | 1.015[e] | .. |
| *p*-Methylisopropylbenzene | 2.30 | 0.986[e] | .. |
| Diphenylmethane | 3.38 | 1.04 | .. |
| Naphthalene | 5.33 | 1.11 | .. |
| Methylnaphthalene | 4.48 | 0.94[e] | 1.105 |
| Average | .. | 1.08 av. deviation $\pm$0.05 | .. |

[a] From Ref. 3. [b] From Ref. 4 and 5. [c] $\Delta n = n_{G'} - n_C$. [d] $V = V_{4359} - V_D$. [e] These scattered values may be due to inaccurate refractive dispersion data.

(1) M. Scherer, "Pub. sci. tech. ministere de l'air," France, No. 50, (1934), p. 1–91. "Science of Petroleum," Vol. 2, London, 1938, p. 1220.

(2) S. Broersma, H. I. Waterman, J. B. Westerdijk and E. C. Wiersma, *Physica*, **10**, 97 (1943).

(3) E. G. Foehr, Ph.D. Thesis, Pennsylvania State College, 1944.

(4) R. E. Thorpe and R. G. Larsen, *Ind. Eng. Chem.*, **34**, 853 1942).

(5) W. J. C. de Kok and H. I. Waterman, *Chem. Weekblad*, **37**, 454 (1940).

(6) W. Schütz, "Magnetooptik" in Wien-Harms Handb. der Experimental physik, Vol. 16, Part 1, Leipzig, 1936. p. 80–141.

(7) From unpublished experimental data by Spectroscopic Department, Shell Development Co., Emeryville, Calif.

Since the dispersion of both the refractivity and the Verdet constant is governed by the term $\Sigma A_i/(\nu_i^2 - \nu^2)$, constancy of the ratio $\Delta V/\Delta n$ would be indicative of the fact that the electronic transitions responsible for both are identical. The data in the last column show that this expectation is essentially fulfilled, as has also been found for various aliphatic oxygen compounds.[8]

(8) W. J. Lewis and E. J. Evans, *Phil. Mag.*, **13**, 265 (1932).

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIF. RECEIVED MAY 24, 1948

## The Cryoscopic Behavior of 1,1-Dimethylcyclohexane Containing Certain Hydrocarbon Impurities[1]

BY G. L. EVANS,[2] K. W. GREENLEE, J. M. DERFER AND C. E. BOORD

A short investigation has been made concerning the cryoscopic behavior of 1,1-dimethylcyclohexane upon introduction of certain selected hydrocarbon impurities. This study was prompted by the observation that introduction of a small amount of *cis*-1,2-dimethylcyclohexane as an impurity in 1,1-dimethylcyclohexane caused an increase in the freezing point of the latter hydrocarbon, instead of the normal lowering. Although similar irregularities caused by solid solution formation have been observed in several binary hydrocarbon systems studied in detail by other workers,[3,4,5,6] it was thought that this new information would prove helpful because of the widespread reliance on cryoscopic data as criteria of purity.

The results of this investigation are summarized in Table I.

It will be noted that of the solutes used only *n*-heptane and *n*-butylcyclohexane produced normal freezing point lowering; *cis*-1,2-dimethylcyclohexane actually raised the freezing point, and the remaining solutes caused only a fraction of the normal lowering. In every case of abnormal behavior the apparent purity as calculated from the freezing point data was, of course, too high.

TABLE I

CRYOSCOPIC BEHAVIOR OF 1,1-DIMETHYLCYCLOHEXANE CONTAINING HYDROCARBON IMPURITIES

| Solute (impurity) | Total mole % impurity added | Freezing point (°C.) | Observed $\Delta t$ (°C.) | Expected[a] $\Delta t$ (°C.) | Actual purity[b] (mole %) | Apparent purity[a] (mole %) |
|---|---|---|---|---|---|---|
| None added | 0 | −35.83 ± 0.04 | .... | .... | 99.04 | ... |
| *cis*-1,2-Dimethylcyclohexane | 0.931 | −35.66 ± .05 | +0.17 | −2.25 | 98.11 | 99.11 |
| | 1.97 | −35.42 ± .07 | +0.41 | −4.79 | 97.07 | 99.21 |
| None added | 0 | −35.52 ± .04 | .... | .... | 99.17 | ... |
| *trans*-1,2-Dimethylcyclohexane | 0.648 | −35.58 ± .04 | −0.06 | −1.57 | 98.52 | 99.15 |
| | 1.33 | −35.69 ± .06 | −0.17 | −3.22 | 97.84 | 99.10 |
| None added | 0 | −36.21 ± .03 | .... | .... | 98.88 | ... |
| *trans*-1,4-Dimethylcyclohexane | 0.676 | −37.23 ± .02 | −1.02 | −1.66 | 98.20 | 98.4 |
| | 1.35 | −38.39 ± .05 | −2.18 | −3.29 | 97.53 | 97.98 |
| None added | 0 | −35.64 ± .02 | .... | .... | 99.12 | ... |
| Cyclohexane | 1.26 | −36.44 ± .04 | −0.80 | −3.05 | 97.86 | 98.79 |
| | 2.30 | −37.09 ± .03 | −1.45 | −5.59 | 96.82 | 98.52 |
| None added | 0 | −35.79 ± .03 | .... | .... | 99.06 | ... |
| 2,2,3-Trimethylbutane | 0.671 | −35.97 ± .03 | −0.18 | −1.62 | 98.39 | 98.98 |
| | 1.59 | −36.10 ± .05 | −0.31 | −3.85 | 97.47 | 98.93 |
| None added | 0 | −35.58 ± .04 | .... | .... | 99.15 | ... |
| *n*-Heptane | 0.798 | −37.49 ± .02 | −1.91 | −1.92 | 98.35 | 98.36 |
| | 1.19 | −38.36 ± .02 | −2.78 | −2.87 | 97.96 | 98.00 |
| None added | 0 | −35.74 ± .05 | .... | .... | 99.08 | ... |
| *n*-Butylcyclohexane | 0.643 | −37.25 ± .05 | −1.51 | −1.54 | 98.44 | 98.45 |
| | 1.04 | −38.23 ± .04 | −2.49 | −2.52 | 98.04 | 98.05 |

[a] These data were calculated from the approximate equation $\log_{10} p = 2 - (A/2.303)(t_{f_0} - t_f)$ where $p$ = purity (actual or apparent) in mole per cent., $t_{f_0}$ = freezing point at 100% purity $t_f$ = experimental freezing point (actual or expected) and $A = \Delta H_m^\circ/RT_{f_0}$ in which $\Delta H_m^\circ$ is the heat of fusion (per mole). Values for $t_{f_0}$ (−33.54°) and $A$ (0.0042 deg.$^{-1}$) had been given by the American Petroleum Institute Research Project 44 in Selected Values of Properties of Hydrocarbons (Circular of the National Bureau of Standards C461) Table 7z. [b] The original purity of each sample was calculated from its freezing point using the equation and data mentioned in footnote *a*, assuming that no impurity leading to abnormal behavior was already present. The subsequent (lower) purities were obtained from the original purities by subtracting the mole percentages of impurity added.

(1) An abstract of part of a dissertation submitted by George L. Evans in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry. The investigation was sponsored by the American Petroleum Institute (Research Project 45) in coöperation with The Ohio State University Research Foundation.

(2) Present address: E. I. du Pont de Nemours and Co., Inc., Experiment Station, Wilmington, Delaware.

(3) Smittenberg, Hoog and Henkes, THIS JOURNAL, **60**, 17 (1938).

(4) Took and Aston, *ibid.*, **67**, 2275 (1945).

(5) Fink, Cines, Frey and Aston, *ibid.*, **69**, 1501 (1947).

(6) Hirschler, King and Faulconer, paper presented before the Petroleum Division at the Chicago, Illinois, meeting of the American Chemical Society, April, 1948.

The ability to form mixed crystals (solid solutions) is common to all hydrocarbons having low heats and entropies of fusion, as has 1,1-dimethylcyclohexane. Such molecules rotate in the solid phase below their melting points and possess considerable mobility of structure, enabling solute molecules of similar size and shape to be accommodated in the crystal lattice without fusion of the crystal. Solute molecules such as *n*-heptane and *n*-butylcyclohexane which would interfere with the rotation cannot be incorporated into the crystal lattice of 1,1-dimethylcyclohexane, hence, solid solution formation does not occur, and normal cryoscopic behavior is observed. The fact that abnormal behavior occurs when 2,2,3-trimethylbutane is used as the solute confirms the idea that it is the over-all size and shape of the molecule rather than its molecular species which determines whether or not a solid solution will result.

### Experimental

**Hydrocarbons.**—The 1,1-dimethylcyclohexane and the hydrocarbons used as "impurities" were materials taken from the stock of the American Petroleum Institute Research Project 45 and were of good purity (99.0 mole % ± 0.5). When practicable, the 1,1-dimethylcyclohexane was separated from the "impurity" by fractional distillation at about 25-plate efficiency and re-used (after its freezing point had been checked) in the next determination, otherwise fresh solvent was used.

**Apparatus.**—The apparatus used in determining freezing points was essentially that described by Glasgow, Streiff and Rossini.[7] Temperatures were measured by means of a platinum resistance thermometer in connection with a Mueller resistance bridge (Leeds and Northrup, Type G-2). This thermometer was calibrated at the National Bureau of Standards.

**Acknowledgment.**—Grateful acknowledgment is made for the criticisms and suggestions of Drs. F. D. Rossini of the National Bureau of Standards and M. R. Cines of the Phillips Petroleum Company.

(7) Glasgow, Streiff and Rossini, *J. Research Natl. Bur. Standards*, **35**, 355 (1945).

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
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RECEIVED JULY 16, 1948

## The Reaction of Diazonium Salts with Some 2-Thiouracils

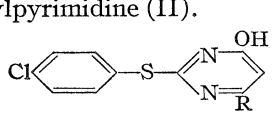
BY ELVIRA A. FALCO, GEORGE H. HITCHINGS AND PETER B. RUSSELL

Lythgoe, Todd and Topham[1] showed that pyrimidines suitably substituted in the 2,4-, 4,6- or 2,4,6-positions would undergo coupling with diazotized anilines in sodium carbonate or bicarbonate solution giving 5-phenylazo derivatives. They also investigated the structural conditions governing the coupling of pyrimidine derivatives. For this last purpose the dyes were not isolated, color being taken as an indication of coupling. They reported that 2-thiol-4,6-dihydroxy-, 2-thiol-4,6-diamino- and 2-thiol-4-hydroxy-6-methyl-pyrimidine underwent coupling.

In a recent paper Polonovski and Pesson[2] reexamined the reaction and arrived at the same general conclusions as the English authors regarding the nature of the products and the structural limitations of the reaction. They were, however, unable to couple 2-thiol-4-hydroxy-6-methylpyrimidine with diazonium salts, although they synthesized the brownish red 2-thiol-4-hydroxy-5-phenylazo-6-methylpyrimidine by condensation of thiourea with ethyl phenylazoacetoacetate.

Some time ago we examined the reactions of 2-thiol-4-hydroxypyrimidine and 2-thiol-4-hydroxy-6-methylpyrimidine with diazotized *p*-chloroaniline. When either of these compounds was allowed to react with the diazonium salt in carbonate or bicarbonate solution the following sequence of changes occurred. The solution turned pinkish red, solid separated and nitrogen was evolved. Examination of the solids revealed that they were not the expected 5-phenylazo compounds since on recrystallization from alcohol they were obtained colorless.

The product from 2-thiol-4-hydroxypyrimidine analyzed for $C_{10}H_7ON_2SCl$, while that from 2-thiol-4-hydroxy-6-methylpyrimidine gave analytical figures which agreed with the formula $C_{11}H_9ON_2SCl$. On heating with concentrated hydrochloric acid at 100° these compounds gave *p*-chlorothiophenol and uracil or 6-methyluracil, respectively. We concluded therefore that they were 2-(*p*-chlorophenylthio)-4-hydroxypyrimidine (I) and 2-(*p*-chlorophenylthio)-4-hydroxy-6-methylpyrimidine (II).




I, R = H
II, R = $CH_3$

The formation of *p*-chlorophenyl ethers of 2-thiolpyrimidines by this method is analogous to the formation of unsymmetrical diaryl and alkyl-aryl sulfides by the reaction of diazonium salts with the sodium salts of thiophenols or mercaptans.[3] In this instance the reaction proceeds *via* the diazosulfide (III) (R = alkyl or aryl). We did not isolate any product corresponding to III from the reaction of 2-thiolpyrimidines with

$$ArN_2^+X^- + RSNa \longrightarrow \underset{\text{III}}{ArN{=}NSR} \longrightarrow ArSR + N_2$$

diazonium salts. The fact that nitrogen is evolved in the cold would indicate that the 2-diazosulfides of pyrimidines are less stable than their aryl or alkyl analogs.

Unfortunately Polonovski's paper, no doubt unintentionally, gives the impression that previous students of the coupling reaction have been content to observe the appearance or non-appearance of a color reaction. In fact, Todd[1] demon-

(1) Lythgoe, Todd and Topham, *J. Chem. Soc.*, 315 (1944).

(2) Polonovski and Pesson, *Bull. soc. chim.*, [5] **15**, 688 (1948).

(3) Stadler, *Ber.*, **17**, 2675 (1884); Ziegler, *Ber.*, **23**, 2469 (1890).

strated by isolation and synthesis by alternative routes the nature of the coupling products in several instances and established the structural requirements for the occurrence of the reaction. Polonovski and Pesson have usefully extended these observations, but have failed to mention the considerable use to which the reaction already has been put in synthetic work.[4,5,6,7,8]

### Experimental

**2-(*p*-Chlorophenylthiol)-4-hydroxypyrimidine.**—Five grams of *p*-chloroaniline in 100 ml. of *N* hydrochloric acid was diazotized with 3.0 g. of sodium nitrite at 0°. Seven and one-half grams of sodium bicarbonate was added to the solution and then the whole was added rapidly with stirring to a solution of 5 g. of 2-thiol-4-hydroxypyrimidine in 4 l. of water. When the addition of the diazonium solution was complete, 10 ml. of a 15% solution of sodium carbonate was added. The solution turned pinkish in color, some gas was evolved and a solid began to form. After standing two hours the solution was neutralized with acetic acid and the solid filtered off. The pinkish powder (5.4 g.), after recrystallization from alcohol containing a little pyridine gave colorless octahedra, m. p. 243–245°.

*Anal.* Calcd. for $C_{10}H_7ON_2SCl$: C, 50.4; H, 3.0; N, 11.7. Found: C, 50.4; H, 2.9; N, 11.5.

**2-(*p*-Chlorophenylthio)-4-hydroxy-6-methylpyrimidine.**—To a solution of 5 g. of 2-thiol-4-hydroxy-6-methylpyrimidine in 3 l. of water was added a diazonium solution prepared from 8.9 g. *p*-chloroaniline (2 moles), followed by 16.6 ml. of a 15% solution of sodium carbonate. After standing for two hours, the solution was neutralized with acetic acid and the reddish solid was filtered off (8.3 g.). After washing with warm ethanol to remove some red material the substance was recrystallized from boiling ethanol. It formed colorless rectangular prisms, m. p. 223.5°.

*Anal.* Calcd. for $C_{11}H_9ON_2SCl$: N, 11.1. Found: N, 11.3.

**Hydrolysis of *p*-Chlorophenylthioethers with Hydrochloric Acid.**—One gram of each of the above compounds was refluxed with 25 ml. of 6 *N* hydrochloric acid for three hours. Steam distillation gave *p*-chlorothiophenol in about 75% yield, m. p. 53–54°; benzoyl derivative, m. p. 74–74.5°.[9] The acid solution on evaporation gave uracil or 6-methyluracil, according to the starting material, in about 80% yield. The compounds were identified by melting points, ultraviolet absorption spectra and analyses.

*Anal.* Calcd. for $C_4H_4N_2O_2$: C, 42.8; H, 3.6. Found: C, 42.5; H, 3.6. Calcd. for $C_5H_6N_2O_2$: C, 47.7; H, 4.8. Found: C, 47.6; H, 4.4.

The authors are indebted to Samuel W. Blackman for the microanalyses reported here.

(4) Baddiley, Lythgoe and Todd, *J. Chem. Soc.*, 318 (1944).
(5) Kenner, Lythgoe and Todd, *ibid.*, 652 (1944).
(6) Todd, *ibid.*, 647 (1946).
(7) King and King, *ibid.*, 731, 943 (1947).
(8) King, King and Spensley, *ibid.*, 1247 (1947).
(9) Daccomo, *Chem. Centr.*, **62**, II, 657 (1891).

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK RECEIVED AUGUST 5, 1948

## The Surface Area of Vermiculite

BY B. L. HARRIS

The surface area of vermiculite before and after exfoliation was measured by adsorption of nitrogen at −195° by the method of Brunauer, Emmett and Teller[1] in order to ascertain whether the area was large enough that the material might be used as a catalyst support. The area of the unexfoliated sample was measured by nitrogen adsorption and found to be 0.52 sq. m./g., giving a calculated average thickness of the platelets of 1.8 microns when the theoretical density of 2.13 is assumed. This indicates that the material was thoroughly fissured before exfoliation.

A sample of the vermiculite was exfoliated by heating for five minutes at 950°, resulting in a silvery-white accordion-like structure. The loss in weight on exfoliation was 19.6%. The surface area of this sample was 10.35 sq. m./g., giving a calculated platelet thickness of 0.091 micron. The structure of vermiculite consists of sheets of $(OH)_4Mg_6(Si, Al)_8O_{20}$ of 9.26 Å. thickness with alternate layers of 8 $H_2O$ spaced the order of 4.8 Å.[2] It was hoped that the platelet spacing might approximate this order of magnitude, resulting in a very large surface area. The smaller area, corresponding to a thickness some 200 times as great, agrees with the conclusion of Gruner that the structure collapses above 750° and that exfoliation is mechanical, due to the formation of steam.

(1) S. Brunauer, P. H. Emmett and Edward Teller, THIS JOURNAL, **60**, 309 (1938).
(2) J. W. Gruner, *Am. Mineral.*, **19**, 557 (1934).

DEPARTMENT OF CHEMICAL ENGINEERING
JOHNS HOPKINS UNIVERSITY
BALTIMORE 18, MARYLAND RECEIVED JULY 28, 1948

## The Interaction of Purified Antibody with Homologous Hapten. Antibody Valence and Binding Constant

BY HERMAN N. EISEN[1] AND FRED KARUSH[2]

As part of a study of the relation between protein structure and specificity we are investigating the properties of soluble complexes formed between purified antibody and homologous haptens. Rabbits were immunized with sheep serum coupled with diazotized *p*-arsanilic acid. Purified antibody, homologous to *p*-azophenylarsonic acid (R), was obtained[3] by treating pooled antisera with human erythrocyte stromata coupled with diazotized *p*-arsanilic acid (R-stromata). After several washings with 0.16 *M* sodium chloride, the antibody was eluted from R-stromata by acidification (*p*H 3.8) with acetic acid. The R-stromata was removed by centrifugation and the supernate, which contained the antibody, was neutralized. In the antibody solutions thus prepared at least 90% of the protein was specifically precipitable with R-stromata, in agreement

(1) Research Fellow, National Institute of Health.
(2) Investigation conducted during tenure of a Fellowship in Cancer Research of the American Cancer Society, recommended by the Committee on Growth of the National Research Council.
(3) K. Landsteiner and J. van der Scheer, *J. Exp. Med.*, **63**, 325 (1936).

with the observations of Campbell, *et al.*,[4] who also prepared purified antibody by exposure to acid *p*H (3.5). Controls involving the treatment with R-stromata of normal rabbit serum, a mixture of bovine γ-globulin and purified antibody, and bovine γ-globulin alone, showed no appreciable non-specific precipitation. Protein concentrations were determined by ultraviolet absorption[5]; the validity of this procedure was assured by low R-stromata blanks, and by the characteristic shape of the absorption curves.

The binding of homologous haptenic dye *p*-(*p*-hydroxyphenylazo)-phenylarsonic acid by purified antibody was determined by equilibrium dialysis. One ml. aliquots of an antibody solution of known protein concentration (0.15%) containing buffer and salt (*p*H 7.4, 0.01 *M* $PO_4$, 0.16 *M* NaCl) were placed inside 0.25-in. dialysis bags. These were equilibrated against equal volumes of hapten in buffered saline whose initial dye concentrations were accurately known. The free dye concentrations in equilibrium with the bound dye were determined by measuring the spectral absorption, at 440 mμ, of the outside solutions, after suitable dilution and adjustment to strongly alkaline *p*H. The concentrations of bound dye were calculated from the values for the free equilibrium and initial dye concentrations, the former ranging from $5 \times 10^{-6}$ *M* to $8 \times 10^{-5}$ *M*. This calculation required a correction, due to adsorption of dye on the dialysis bag, amounting to 11% of the free dye concentration. The following (which corresponds to the third point in Fig. 1) represents a typical calculation: initial dye concentration = $3.96 \times 10^{-5}$ *M*, free equilibrium dye concentration = $1.18 \times 10^{-5}$ *M*, concentration of bound dye = $1.35 \times 10^{-5}$ *M*, moles hapten bound per mole protein[6] (*r*) = 1.45.

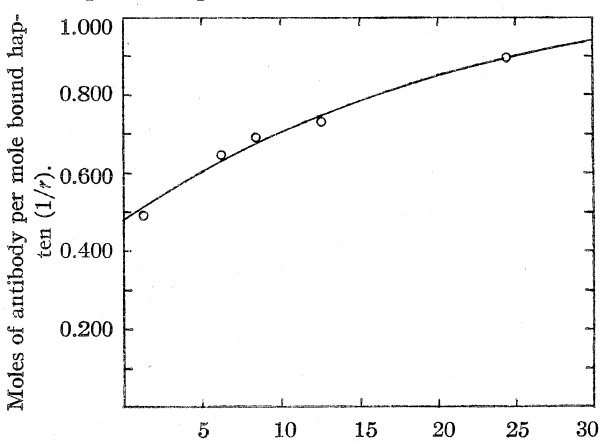



Fig. 1.

By plotting the reciprocal of moles hapten bound per mole antibody (1/*r*) against the reciprocal of free hapten concentration (1/*c*) the binding capacity is obtained from the extrapolated value of 1/*r*.[7] As could be anticipated from the known heterogeneity of antibodies,[3,8] the curve obtained was not linear. In such a situation the average intrinsic association constant can be shown to be equal to the value of 1/*c* at which one-half the binding sites are occupied, if it is assumed that the variation in the free energy of binding among the various sites can be described by a Gaussian distribution function.[9] Such an assumption has been made previously by Pauling, *et al.*,[8] to describe hapten inhibition data.

The binding data obtained at room temperature (29°) with the hapten indicated above are summarized in Fig. 1. Extrapolation yields a value of 2 for the binding capacity ("valence") of the antibody, within an accuracy of 10%. The value of the intrinsic association constant is $3.5 \times 10^5$, corresponding to $\Delta F^0 = -7.7$ kcal. per mole hapten.

Antisera prepared as in these experiments by Campbell, *et al.*,[4] contained about 1.0% antibody for R-group, whereas our yields of purified antibody correspond to an initial antibody concentration in antiserum of about 0.04%. Either our antisera were far less potent than Campbell's, or the antibody removed by our purification procedure comprised only a small fraction of the total antibody present in the antiserum, in which case the above association constant would measure the average binding energy of only the most reactive antibody molecules.

**Acknowledgment.**—We are indebted to Professor R. Keith Cannan for the laboratory facilities so generously made available to us during the conduct of this investigation.

(4) D. H. Campbell, R. H. Blaker and A. B. Pardee, THIS JOURNAL, **70**, 2496 (1948).

(5) H. N. Eisen, *J. Immunol.*, **60**, 77 (1948).

(6) Assuming a molecular weight for rabbit antibody of 160,000.

(7) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946)

(8) L. Pauling, D. Pressman and A. L. Grossberg, *ibid.*, **66**, 784 (1944).

(9) F. Karush and M. Sonenberg, *ibid.*, in press.

DEPARTMENTS OF CHEMISTRY AND MEDICINE
NEW YORK UNIVERSITY COLLEGE OF MEDICINE
NEW YORK 16, N. Y. RECEIVED SEPTEMBER 22, 1948

## Preparation and Properties of Several Cyclohexyl-alkyl-substituted Ketene Dimers

BY CARL M. HILL AND GILBERT W. SENTER

It has been demonstrated that tertiary aliphatic amines dehydrohalogenate acid halides with the formation of ketene monomers and dimers.[1] Sauer[2] has reported the dehydrohalogenation of several fatty acid halides by tertiary aliphatic amines to yield ketene dimers.

This paper describes the dehydrohalogenation of five omega-cyclohexyl-substituted acid chlorides (of type $C_6H_{11}\cdot(CH_2)_n\cdot COCl$) by triethylamine.

(1) Hanford and Sauer, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946, pp. 138–140.

(2) Sauer, THIS JOURNAL, **69**, 2444 (1947).

TABLE I

KETENE DIMERS

| -Cyclohexyl, ketene dimers | B. p. °C. | Mm. | Yield,[a] % | $n^{20}D$ | Formula | Mol. wt.[b] Found | Mol. wt.[b] Calcd. | Analyses, % Carbon Found | Carbon Calcd. | Hydrogen Found | Hydrogen Calcd. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ,ketene | 108–111 | 2 | 28 | 1.5001 | $C_{16}H_{24}O_2$ | 250.7 | 248.4 | 76.68 | 77.36 | 10.08 | 9.74 |
| ,methyl | 190–191 | 6 | 40 | 1.4925 | $C_{18}H_{28}O_2$ | 281.9 | 276.4 | 78.09 | 78.22 | 10.38 | 10.21 |
| β-, ethyl | 115–120 | 2 | 18 | 1.4850 | $C_{20}H_{32}O_2$ | 278.2 | 304.5 | 79.15 | 78.91 | 10.64 | 10.52 |
| γ-, propyl | 150–152 (m. p., 16–17) | 1 | 25 | 1.4860 | $C_{22}H_{36}O_2$ | 331.8 | 332.5 | 79.53 | 79.39 | 11.04 | 10.90 |
| δ-, butyl | 128–130 (m. p., 33–35) | 1 | 36 | .... | $C_{24}H_{40}O_2$ | 351.6 | 360.5 | 80.46 | 79.88 | 11.56 | 11.18 |

[a] Based upon the amount of unrecovered acid chloride. [b] Determined cryoscopically.

The ketene dimers thus formed have not been previously reported.

The dimers gave a negative test with silver nitrate; positive tests with potassium permanganate, and bromine. *p*-Nitrophenylhydrazine reacted with the dimers to yield the hydrazones.

### Experimental

The procedure followed in dehydrohalogenation of the the acid chlorides was similar to that reported by Sauer.[2] Equal molar quantities of acid chloride and triethylamine were allowed to react in dilute ether solution. Each dimer was isolated in its pure form by distillation under diminished pressure. A quantity of unreacted acid chloride was recovered from each experiment.

Analytical data and physical constants of the five ketene dimers are shown in Table I.

***p*-Nitrophenylhydrazones.**—The hydrazones were prepared according to the procedure described by McElvain.[3] The color of the hydrazones varied from lemon to deep orange.

Analytical data and physical properties of the hydrazones are given in Table II.

TABLE II

*p*-NITROPHENYLHYDRAZONES OF DIMERS

| -Cyclohexyl, ketene dimer | Hydrazone | N, % Found | N, % Calcd. | M. p.,[a] °C. | Yield, % |
|---|---|---|---|---|---|
| ,ketene | $C_{28}H_{34}O_4N_6$ | 16.29 | 16.21 | 102–103 d. | 19 |
| ,methyl | $C_{30}H_{38}O_4N_6$ | 14.89 | 15.38 | 104–105 d. | 41 |
| β-, ethyl | $C_{32}H_{42}O_4N_6$ | 14.05 | 14.63 | 110–111 d. | 53 |
| γ-, propyl | $C_{34}H_{46}O_4N_6$ | 14.10 | 13.95 | 113–114 d. | 44 |
| δ-, butyl | $C_{36}H_{50}O_4N_6$ | [b] | .... | 84–85 | 57 |

[a] Melting points are uncorrected. [b] Compound decomposed upon prolonged drying.

(3) McElvain, "Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 199.

DEPARTMENT OF CHEMISTRY
TENNESSEE A. AND I. STATE COLLEGE
NASHVILLE 8, TENNESSEE RECEIVED AUGUST 25, 1948

## The Preparation and Vapor Pressure of Bromopentachloroethane; the Vapor Pressures of Heptachloropropane and Dibromotetrachloroethane

BY TAKERU HIGUCHI,[1] NOBORU ENDOW[2] AND JOHN E. WILLARD

When confronted with a need for a sample of bromopentachloroethane we were not able to find any record of its preparation in the literature. We have prepared a sample by the photobromination of pentachloroethane at elevated temperature, using a technique similar to that previously employed in this laboratory for the preparation of bromotrichloromethane from chloroform and bromine.[3] The over-all reaction is

$$C_2Cl_5H + Br_2 \longrightarrow C_2Cl_5Br + HBr$$

Eastman Kodak Co. technical pentachloroethane was washed several times with concentrated sulfuric acid, with water, with 20% potassium hydroxide solution and again with water. After drying with phosphorus pentoxide, approximately 1 mole (125 cc.) was then mixed with one mole (55 cc.) of bromine and 75 cc. of carbon tetrachloride. This mixture was illuminated by two 500-watt Mazda projection bulbs placed next to the flask which was sealed to a water-cooled reflux condenser. The heat from the bulbs was sufficient to maintain the solution at or near the boiling temperature. Since the photobromination of chloroform has been found to be inhibited by both oxygen and water, the following precautions were taken to exclude gross amounts of these substances: (a) a slow stream of nitrogen was bubbled through the solution and allowed to pass out through the condenser throughout the course of the reaction; (b) 5 g. of phosphorus pentoxide was added to the reaction flask.

Initial attempts to prepare bromopentachloroethane by this method, from mixtures of bromine and pentachloroethane without carbon tetrachloride, led to a mixture of products. Because of the possibility that this might be the result of reactions favored by the relatively high temperature of the boiling point of the pentachloroethane (155°), carbon tetrachloride was added to reduce the boiling point.

After a week of continuous illumination the reaction solution solidified on cooling. The weight of this crude product was 200 g. Following three recrystallizations from small amounts of carbon tetrachloride large white crystals were obtained which melted with decomposition in the range of 180 to 200° when heated in sealed evacuated tubes. An estimate of the molecular weight and vapor pressure was obtained from this sample by measuring the gas pressure produced in a known volume by a weighed sample as a function of temperature. This was accomplished by placing the sample in an evacuated sealed bulblet in a sidearm of an evacuated thermostated flask which was connected to an open-end mercury manometer,[4] the middle section of which was made of flexible rubber suction tubing. The sample tube was broken with a glass-enclosed magnetic hammer. By means of a leveling bulb the mercury was maintained at an index mark on the glass side arm of the flask which connected with the manometer, thus maintaining a constant gas volume as the pressure

(1) Present address: Department of Pharmacy, University of Wisconsin, Madison, Wis.

(2) Present address: Hanford Engineer Works, General Electric Co., Richland, Wash.

(3) (a) Bohlmann and Willard, THIS JOURNAL, **64**, 1342 (1942); (b) Higuchi, Ph.D. Thesis, University of Wisconsin, 1943.

(4) The apparatus used in these determinations was constructed by Norman W. Rosenberg with the aid of funds from the National Youth Administration. Details of modifications and applications are given in the Masters' degree thesis of Noboru Endow filed with the Library of the University of Wisconsin in January, 1948.

changed due to vaporization of the sample. The pressure was read as the difference in heights of the mercury columns. The connection from the flask to the manometer entered the mineral oil thermostating-bath through a bushing in the bottom of the silver-soldered copper can and the index mark was viewed through a window in the side of the can. Experiments showed that no correction was necessary for the vapor pressure of mercury, thus indicating that the time required for the mercury vapor (which was always at a lower pressure than the organic vapor) to diffuse from the narrow side arm into the flask was long compared to the time involved in the experimental measurements.

Three experiments made on the freshly purified samples believed to be bromopentachloroethane gave linear plots of the logarithm of the sublimation pressure against the reciprocal of the absolute temperature over the temperature range of about 110 to 160°. A sharp break in the curve was found in each case at the temperature of total vaporization of the sample. The average molecular weights calculated for the totally vaporized system at the break in the curve were 280, 280 and 285 as compared to the theoretical value of 281 for $C_2Cl_5Br$. Chemical analysis of a sample of the compound by the Carius wet oxidation method combined with the Moser–Miksh iodide metathesis method gave the results:

| | Experimental | Theoretical ($C_2Cl_5Br$) |
|---|---|---|
| Bromine | 27.8 | 28.3 |
| Chlorine | 61.2 | 63.2 |

Samples of the compound prepared by the photobromination of pentachloroethane with radiobromine of known specific activity showed a specific activity corresponding to the formula $C_2Cl_5Br$.

The average vapor pressure of the $C_2Cl_5Br$ over the range tested is given by the relation $\log p = (-2.32 \times 10^3/T) + 6.33$, where $p$ is the pressure in cm. of Hg and $T$ is the absolute temperature.

**Heptachloropropane.**—A single series of measurements of the vapor pressure of $CCl_3CCl_2CHCl_2$ as a function of temperature with the apparatus described above gave a straight line plot of $\log p$ *vs.* $1/T$ for five points taken over the range of 140 to 200°. These data gave the expression $\log p = (-1.82 \times 10^3/T) + 5.11$. The sample used was obtained from the Eastman Kodak Company, which specified its melting point as 30°. The fact that the molecular weight of the sample calculated from the observed pressure at the temperature of total vaporization was 278 as compared to the theoretical value of 285 indicates that the sample was probably not highly impure. Prins,[5] Farlow[6] and Henne and Ladd[7] have reported values for the boiling point of $CCl_3CCl_2CHCl_2$ at several pressures. Their values are shown in Table I for comparison with those determined from the equation given above.

TABLE I

| Pressure, mm. | Obs. b. p., other workers, °C. | B. p. from vapor pressure equation, °C. |
|---|---|---|
| 10 | 110–113 (Farlow) | 83 |
| 32 | 137–140 (Farlow) | 122 |
| 43 | 147 (Prins) | 133 |
| 90 | 164 (Prins) | |
| | 163–166 (Henne and Ladd) | 165 |

The relation of $\log p$ to $1/T$ for Farlow's data is not in agreement with that for Prins' data and neither is in agreement with our vapor pressure determinations. These latter show a consistent relationship over a 60° range under conditions of measurement which have given agreement with well established values for the vapor pressure of carbon tetrachloride and have given consistent vapor pressure and molecular weight values for a number of compounds tested.

**Dibromotetrachloroethane.**—A similar determination of the vapor pressure of $C_2Cl_4Br_2$ gave the expression $\log p = (-2.74 \times 10^3/T) + 7.18$ over the range from 110 to 180°. These results are in satisfactory agreement with those of Carrico and Dickinson[8] who made similar measurements from 50 to 150°. At 50° they observed a pressure of 0.4 mm. while the value calculated from our data is 0.5 mm. At 150° they found 51 mm. and our data indicate 50 mm. Following complete vaporization of the $C_2Cl_4Br_2$, the vapor was heated to 215° without more than a few per cent. decomposition over the period of about half an hour, indicating greater thermal stability than that of the $C_2Cl_5Br$ reported above.

The work reported here was done as part of a program to which support was given by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(5) Prins, *J. prakt. Chem.*, **89**, 414 (1914).

(6) Farlow, "Organic Synthesis," **17**, 58 (1937).

(7) Henne and Ladd, THIS JOURNAL, **60**, 2491 (1938).

(8) Carrico and Dickinson, THIS JOURNAL, **57**, 1344 (1935).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

RECEIVED JUNE 22, 1948

## The Structure of Pellitorine[1]

BY MARTIN JACOBSON

The isolation from plant materials of several pungent N-isobutylamides of aliphatic unsaturated acids has been reported, namely, spilanthol (N-isobutyl-4,6-decadienamide) (I) from the flower heads of *Spilanthes oleraceae* Jacquin[2] and *S. acmella* Murr.,[3] pellitorine (the N-isobutylamide of a decadienoic acid) from the roots of *Anacyclus pyrethrum* DC.,[4] N-isobutyl-2,6,8-decatrienamide (II) from the roots of *Heliopsis longipes* (A. Gray) Blake[5]; and herculin (N-isobutyl-2,8-dodecadienamide) (III) from the bark of *Zanthoxylum clava-herculis* L.[6]

Gulland and Hopton[4] had identified pellitorine as an isomer of spilanthol, but they did not determine the positions of the double bonds in the molecule. In view of the insecticidal activity of compounds I,[3,7] II[5] and III,[6] and since preliminary tests in the laboratories of the Bureau of Entomology and Plant Quarantine had indicated that pellitorine was also insecticidal,[6] it was of considerable interest to determine the points of unsaturation in this compound, with a possible consequent correlation between insecticidal activity and molecular structure.

The procedure used in this Laboratory for isolating pure pellitorine eliminated the repeated fractional distillations found by Gulland and Hopton to be necessary for its purification. A Skelly-

(1) Report of a study made under the Research and Marketing Act of 1946.

(2) Gerber, *Arch. Pharm.*, **241**, 270 (1903); Asano and Kanematsu, *Ber.*, **65B**, 1602 (1932).

(3) Pendse, *et al.*, *Current Sci.*, **14**, 37 (1945); Gokhale and Bhide, *J. Indian Chem. Soc.*, **22**, 250 (1945).

(4) Gulland and Hopton, *J. Chem. Soc.*, 6 (1930).

(5) Jacobson, Acree and Haller, *J. Org. Chem.*, **12**, 731 (1947).

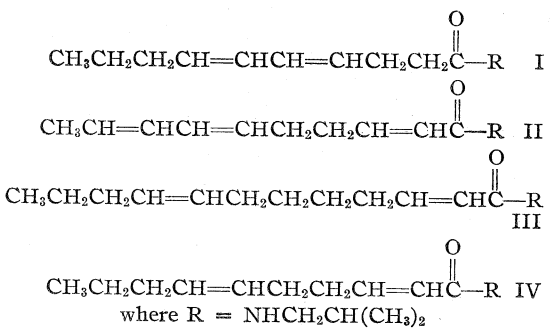
(6) Jacobson, THIS JOURNAL, **70**, 4234 (1948).

(7) Pendse, *et al.*, *J. Univ. Bombay*, **15A**, New Ser. Pt. 3, No. 20, 26 (1946).

solve A extract of dry pellitory root (*Anacyclus pyrethrum* DC.)[8] was extracted with nitromethane, and the neutral fraction of the nitromethane-soluble portion was distilled. One crystallization, from Skellysolve A, of the fraction boiling at 155–165° (0.3–0.5 mm.) gave pure pellitorine in 0.14% yield, based on dry root.

Oxidation of pellitorine with alkaline permanganate resulted in the isolation of butyric, succinic and N-isobutyloxamic acids, showing that the double bonds occupy the 2- and 6-positions. Pellitorine is therefore N-isobutyl-2,6-decadienamide (IV).

In tests[9] conducted with house flies (*Musca domestica* L.), a Deobase (refined kerosene) solution of pellitorine, used as a spray, showed paralyzing action equal to, and mortality somewhat greater than one-half that of pyrethrins tested at the same concentration.




### Experimental[10]

**Isolation of Pellitorine.**—6070 g. of finely ground, dry pellitory root was extracted in a Soxhlet extractor with Skellysolve A. The solution was concentrated to *ca.* 700 ml. and extracted three times with 150-ml. and twice with 100-ml. portions of nitromethane. The combined nitromethane solution was freed of solvent under reduced pressure, the residue (27 g. of reddish-brown oil) taken up in ethyl ether, and the ether solution washed thoroughly with water, 5% hydrochloric acid solution, 5% potassium hydroxide solution, and finally with water. After being dried over sodium sulfate, the ether solution of the neutral fraction was freed of solvent completely, and the remaining 20 g. (0.33% of the bark) of viscous reddish-yellow oil solidified rapidly.

Vacuum distillation of this material, in an atmosphere of nitrogen, gave 8.5 g. of pale-yellow oil, b. p. 155–165° (0.3–0.5 mm.), which was dissolved in a small quantity of Skellysolve A, cooled in ice–salt, and filtered. The yield was 8.4 g. (0.14% based on dry bark) of colorless, feathery needles of pellitorine, m. p. 72° (lit.[4] m. p. 72°).

**Oxidation of Pellitorine.**—To a stirred suspension of 5 g. of pellitorine in 500 ml. of water, maintained at 70°, 18.8 g. of finely powdered potassium permanganate (equivalent to 4 moles of oxygen) was added in small portions. When the reaction mixture had become colorless, the manganese dioxide was filtered and washed thoroughly with warm water. The combined aqueous filtrates were concentrated down to 70 ml. and made acid to congo red with sulfuric acid. The solution was steam-distilled to remove the volatile acids and then extracted with ether in a continuous extractor. The ether solution was freed of solvent, and the residue was extracted with three 10-ml. portions of boiling Skellysolve B. Cooling of the hydrocarbon solution caused the separation of 2.5 g. (77%) of colorless feathery needles, m. p. 106–107°, containing nitrogen.

*Anal.* Calcd. for $C_6H_{11}NO_3$: N, 9.66; neut. equiv., 145. Found: N, 9.65; neut. equiv., 145.

The substance was identified as N-isobutyloxamic acid by a mixed melting-point determination with an authenic sample, m. p. 107°, prepared by the procedure of Malbot.[11]

The insoluble residue from the Skellysolve B extraction was taken up in a small amount of ethyl acetate, cooled in ice–salt mixture, and filtered. One recrystallization from a small amount of the same solvent gave 1.8 g. (69%) of colorless crystals in the form of clusters of needles, m. p. 188–189°.

*Anal.* Calcd. for $C_4H_6O_4$: mol. wt., 118. Found: mol. wt. (titration), 118.

The product was identified as succinic acid by a mixed melting point determination with an authentic specimen, m. p. 189°, and by preparing the *p*-phenylphenacyl ester, m. p. 208°.

The solution of steam-volatile acids obtained above was neutralized with sodium hydroxide solution, concentrated to a small volume on the steam-bath, and acidified to congo red with sulfuric acid. Steam distillation gave Duclaux values of 17.9, 15.9 and 14.6, identical with those given for butyric acid.[12]

The acid was shown to be butyric acid by evaporating the neutral solution to dryness and then preparing the *p*-phenylphenacyl ester, m. p. and mixed m. p. with an authentic sample, 81–82°.

(8) Obtained from S. B. Penick & Co., New York, N. Y.

(9) These tests were made by W. A. Gersdorff and Miss S. F. McDuffie, of this Bureau.

(10) All melting points are corrected.

(11) Malbot, *Compt. rend.*, **104**, 229 (1887).

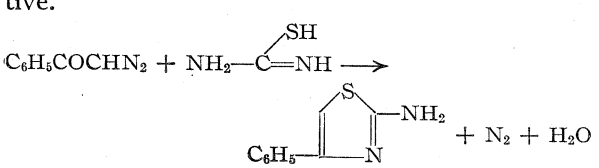
(12) McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945, p. 141.

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AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
BELTSVILLE, MARYLAND RECEIVED SEPTEMBER 30, 1948

## The Reaction of Diazoketones with Thioamide Derivatives[1]

BY L. CARROLL KING AND F. M. MILLER

Werner[2] found that the action of diazomethane on thiourea produced S-methylpseudothiourea. We have now observed that diazoketones react with thiourea and other thioamide derivatives to furnish substituted thiazoles. The reaction between diazoacetophenone and thiourea is illustrative.




The reaction is effected either by heating an intimate mixture of the reactants on the steam-bath, or by refluxing an alcoholic solution of the reaction components. The reaction in alcoholic solution is more satisfactory.[3]

Thiourea and ethyl diazoacetate react to give

(1) For previous papers dealing with the synthesis of thiazoles, see King and co-workers: (a) THIS JOURNAL, **67**, 2242 (1945); (b) *ibid.*, **68**, 871 (1946); (c) *ibid.*, **69**, 1813 (1947).

(2) Werner, *J. Chem. Soc.*, **115**, 1168 (1919).

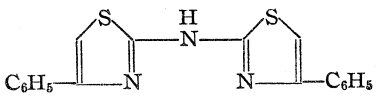
(3) A similar technique was employed for the preparation of quaternary salts from diazoacetophenone and salts of heterocyclic bases, King and Miller, THIS JOURNAL, **70**, 4154 (1948).

TABLE I

| Compound | Formula | Yield, % | M. p., °C. Found[c] | M. p., °C. Reported | Composition,[h] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|
| 2-Amino-4-phenylthiazole | $C_9H_8N_2S$ | 67[a] | 151–152 | 151–152[d] | ... | ... | .. | .. |
| Acetyl derivative | $C_{11}H_{10}ON_2S$ | | 213–214 | 214.5–215[d] | ... | ... | .. | .. |
| 2,4-Diphenylthiazole | $C_{15}H_{11}N_2S$ | 84[a] | 91–92 | 92–93[e] | [i] | [i] | .. | .. |
| 2-Amino-4-hydroxythiazole | $C_3H_4ON_2S$ | 34[a] | 233–238, dec. | [f] | 31.03 | 30.81 | 3.45 | 3.53 |
| bis-(4-Phenyl-2-thiazolyl)-amine | $C_{18}H_{13}N_3S_2$ | 40, 78[b] | 218–220 | [g] | 64.55 | 64.35 | 3.89 | 4.11 |
| Acetyl derivative | $C_{20}H_{15}ON_4S_2$ | | 132–133 | [g] | 63.16 | 63.45 | 4.25 | 4.14 |

[a] Based on the diazoketone. [b] The same compound was obtained with one or two molecular portions of diazoacetophenone, the latter giving the 78% yield, based on the dithiobiuret. [c] All melting points observed on a Fisher–Johns melting point block. [d] These compounds were compared with authentic material previously prepared in this Laboratory, reference 1.[a] [e] Hubacher, *Ann.*, **259**, 237 (1890). [f] Andreasch, *Monatsh.*, **8**, 424 (1887), reported a melting point of 208° (dec.) for this material prepared by a different method. The compound from the diazoketone reaction melted in this range above. Similar results were obtained by Allen and VanAllan, "Organic Syntheses," **27**, 71 (1947). [g] Not previously reported. [h] Analysis by Miss P. Craig. [i] Calcd.: N, 5.62. Found: N, 5.69.

2-amino-4-hydroxythiazole (pseudothiohydantoin). Thiourea and thiobenzamide yield with diazoacetophenone, 2-amino-4-phenylthiazole and 2,4-diphenylthiazole, respectively. With the same diazoketone dithiobiuret gives bis-(4-phenyl-2-thiazolyl)-amine (I).[4]



I

Evidence for the structure of I lies in the method of formation, the analysis of the compound and its N-acetyl derivative, and the fact that it was unaffected by both acid and alkaline hydrolytic conditions, contrary to the known sensitivity of the thioureido group.[5] Compound I was also prepared by the action of phenacyl bromide on dithiobiuret.

Data for the compounds prepared are listed in Table I.

This investigation was supported by a grant from the Abbott Fund of Northwestern University.

### Experimental

**Preparation of Materials.**—Diazoacetophenone was prepared as previously described.[3] Ethyl diazoacetate was prepared by the method of Curtius.[6] Thiobenzamide was prepared by suspending 60.5 g. (0.5 mole) of benzamide and 22.2 g. (0.10 mole) of phosphorus pentasulfide in 300 cc. of benzene and refluxing until the benzamide dissolved. The hot benzene solution was filtered and cooled, and the thiobenzamide collected. The material was recrystallized once from benzene m.p. 115–116°.[7] The dithiobiuret was a commercial sample, obtained through the courtesy of the American Cyanamid Company.

**Preparation of the Thiazoles.**—The techniques used will be illustrated by the following examples.

(a) **2-Amino-4-phenylthiazole.**—A solution of 1.46 g. (0.01 mole) of diazoacetophenone and 2.40 g. (0.012 mole) of thiourea in 20 cc. of absolute alcohol was refluxed for one hour. A portion of the alcohol was evaporated, a small amount of water and charcoal added, and the hot solution filtered and cooled. The separated material was collected and recrystallized from dilute aqueous alcohol.

(b) **bis-(4-Phenyl-2-thiazolyl)-amine.**—A solution of 2.92 g. (0.02 mole) of diazoacetophenone and 1.48 g. (0.011 mole) of dithiobiuret was refluxed for one hour in alcoholic solution. The product separated from the solution, was filtered and dissolved in excess acetone. Dilute aqueous alcohol was added and the acetone removed carefully on the steam-bath. The material crystallized on cooling and was recrystallized in the same manner.

bis-(4-Phenyl-2-thiazolyl)-amine was also prepared by refluxing 4.0 g. (0.02 mole) of phenacyl bromide and 1.50 g. (0.01 mole) of dithiobiuret in 25 cc. of alcohol for one hour. The separated material was suspended in alcohol and digested with ammonium hydroxide for one-half hour, filtered and washed with a small amount of alcohol. Recrystallization gave a material identical with that prepared above.

**Acetyl Derivatives of Thiazoles.**—These were prepared by the action of acetic anhydride on approximately 0.3 g. of the amino thiazole. The products were recrystallized from dilute aqueous alcohol.

**Attempted Hydrolysis of I.**—A solution of 0.1 g. of the material in 30 cc. of hot alcohol and 10 cc. of water was heated under reflux for three hours with 10 g. of barium hydroxide. Only the starting material was recovered, m.p. 217–218°.

Attempted acid hydrolysis performed in the same manner yielded identical results.

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(4) The descriptive literature of the American Cyanamid Company records the reaction of chloroacetone and dithiobiuret to produce 2-thioureido-4-methylthiazole. Attempts to obtain the analogous 2-thioureido-4-phenylthiazole were not successful.

(5) Mehta and Krall, *J. Indian Chem. Soc.*, **12**, 635 (1935), report the effects of acid and basic hydrolysis of phenylthiourea.

(6) Curtius, *J. prakt. Chem.*, **38**, 401 (1888).

(7) Gabriel and Heyman, *Ber.*, **23**, 158 (1890).

## The Verdet Constant of Certain Liquid Fluorocarbons

BY R. T. LAGEMANN

It is now known that certain fluorinated hydrocarbons possess some unusual physical properties. Although the density and viscosity are not particularly different from those of other liquids, the refractive index and ultrasonic velocity are both extraordinarily low. As an example, consider bis-(trifluoromethyl)-chlorononofluorocyclohexane. Here $n^{60}D$ is 1.3021,[1] only three liquids in Lange's "Handbook" have a lower value, and the ultrasonic velocity at 20° is 691.8 m./sec.,[1] also extremely low relative to other liquids. Since no values are known for the rotation of the plane of polarization of light by these liquids when placed in

(1) Lagemann, Woolf, Evans and Underwood, THIS JOURNAL, **70**, 2994 (1948).

a magnetic field (Verdet constant), it was considered of interest to measure the Verdet constant to note if it, too, was unusual. Indeed, such was found to be the case.

The eight fluorocarbons studied are listed in Table I along with the measured values of their Verdet constants at 25° and for 5893 Å. It will be noted that the Verdet constants for these fluorinated hydrocarbons are extraordinarily low. The lowest value, that belonging to hexadecafluoroheptane, is about one-half the lowest previous value listed for any compound in the "International Critical Tables."

TABLE I

VERDET CONSTANTS OF SOME LIQUID FLUOROCARBONS AT 25° AND FOR 5893 Å[a]

| Compound | Molecular weight | Density, 25°, g./cc. | Verdet constant, min./gauss-cm. |
|---|---|---|---|
| Hexadecafluoroheptane | 388 | 1.7208 | 0.003500 |
| (Trifluoromethyl)undecafluorocyclohexane | 350 | 1.7871 | .003751 |
| bis-(Trifluoromethyl)-decafluorocyclohexane | 400 | 1.8391 | .003950 |
| bis-(Trifluoromethyl)-chlorononofluorocyclohexane | 416 | 1.8711 | .005252 |
| Chlorotrifluoroethylene polymer | 713 | 1.9412 | .009093 |
| Chlorotrifluoroethylene polymer | 866 | 1.9681 | .009118 |
| Chlorotrifluoroethylene polymer | 911 | 1.9736 | .009168 |
| Fluorolube oil | 860 | 2.0081 | .004739 |

[a] The values of molecular weight and density found in this table were supplied by the Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee.

Enough data are present in Table I to enable a calculation to be made of the molecular magnetic rotation[2] (utilizing $MV/d$ for water at 25° and 5893 Å. as 0.2353). From this, values of the increment attributable to the fluorine atom may be made. For the cases presented here, the values vary, no doubt due to constitutive factors.

**Acknowledgments.**—It is a pleasure to acknowledge our indebtedness to Dr. Clifford Beck of the Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee, for the loan of the compounds studied and for data concerning them. The author is also indebted to the Department of Physics of Columbia University, particularly to Dr. Lucy Hayner, for permission to use the Faraday Effect equipment.

### Experimental

The measurements of the Verdet constant were made on the Faraday Effect apparatus of the Department of Physics, Columbia University. The procedures used were the same as those described by Slack[3] and the author[2] and will not be repeated here. The fluorocarbons were obtained through the courtesy of the Carbide and Carbon Chemicals Corporation, Oak Ridge, Tennessee, where they had been subjected to fractional distillation and their molecular weight and density measured.

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RECEIVED SEPTEMBER 29, 1948

(2) R. T. Lagemann, *J. Polymer Sci.*, **3**, 663 (1948).
(3) F. G. Slack, *Phys. Rev.*, **46**, 945 (1934).

## A Synthesis of Symmetric Phosphinic Acids

BY GENNADY M. KOSOLAPOFF

Michaelis and Wegner[1] were the first to employ the Grignard reaction in the synthesis of aromatic phosphinic acids under conditions which precluded the formation of by-products, by the reaction of aryl magnesium halides with N-piperidyl dichlorophosphate. Their lone paper on this subject, however, failed to state the yields obtained, although these were said to have been "good." Because of the relatively high cost of piperidine, it was thought that an equally good reagent might be found among the more available aliphatic dialkyl amines, which can be readily converted to the corresponding dichlorophosphates. This belief has been realized and excellent yields of some symmetric aromatic and aliphatic phosphinic acids have been readily attained by using N,N-diethylamine to block one reactive group of phosphorus oxychloride. The reaction, thus, may be extended to the aliphatic series, which has not been done previously.

### Experimental

The yields and the properties of the products are given in the table.

SYMMETRIC PHOSPHINIC ACIDS PREPARED

| Derivative | Yield, % | M. p., °C. | Equiv. weight Calcd. | Found |
|---|---|---|---|---|
| bis-*p*-tolyl | 75 | 131–132 | ..... | ....[1] |
| bis-*p*-anisyl | 79 | 179–180 | 278 | 275 |
| bis-*o*-anisyl | 74 | 227–228 | 11.15%[a] | 11.1%[a] |
| Di-*n*-butyl | 82 | 70.5–71 | 178 | 176 |

[a] % Phosphorus.

**bis-*p*-Tolylphosphinic Acid.**—N,N-Diethylamidodichlorophosphate (19 g., 0.1 mole) was added during one hour to a gently refluxing solution of *p*-tolylmagnesium bromide, prepared from 34.2 g. of *p*-bromotoluene and 4.8 g. of magnesium, in 300 ml. of dry ether. After refluxing for two hours, the mixture was hydrolyzed by means of ice-water and ammonium chloride, and the organic layer was treated with 250 ml. of concentrated hydrochloric acid. Ether was distilled from the mixture and the residue was refluxed for four hours. After cooling, the product was filtered and was recrystallized from dilute ethanol It formed long colorless needles. Michaelis and Wegner[1] reported its m. p. 130–132°.

**bis-*p*-Anisylphosphinic Acid.**—The same procedure, using 37.4 g. of *p*-bromoanisole for the Grignard reagent, yielded this acid in the form of short colorless needles.

**bis-*o*-Anisylphosphinic Acid.**—The same procedure using *o*-bromoanisole gave this substance, in the form of needles; this preparation was also checked by synthesizing the product from phosphorus oxychloride and the Grignard reagent by an earlier procedure.[2] The rather unexpectedly high melting point, in comparison with the *p*-isomer, may be caused by interaction of the oxygen atom of the *o*-methoxyl group, with the $PO_2H$ group.

**Di-*n*-butylphosphinic Acid.**—A procedure similar to the above was used with 57 g. of the dichlorophosphate and the Grignard reagent from 82.2 g. of *n*-butyl bromide and 14.58 g. of magnesium; the addition period was two hours and the reflux period was three hours. After hydrolysis by refluxing with hydrochloric acid, the bulk of the latter was distilled, the residue made strongly alkaline with sodium hydroxide, and the regenerated

(1) Michaelis and Wegner, *Ber.*, **48**, 316 (1915).
(2) Kosolapoff, THIS JOURNAL, **64**, 2982 (1942).

amine was steam distilled. The crude product m. p. 66–69°, was isolated by ether extraction and converted to the corresponding chloride (for separation from possible traces of butanephosphonic acid) by warming with 51.5 g. of phosphorus pentachloride followed by distillation; b. p. 156–157° at 28 mm. Hydrolysis of the chloride with warm water and crystallization from hexane gave the pure acid in the form of long silky colorless needles. This acid was previously reported by Plets[3] who prepared it by hydrolysis of either $R_2PCl_3$ or $R_2POCl$, which were, in turn, derived from dibutylchlorophosphine; he gave m. p. 31–32° for the acid. The higher melting point of the present preparation indicates either higher purity or, possibly, an isomeric form.

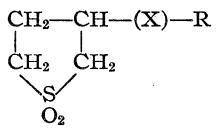
(3) Plets, dissertation, Kazan, U. S. S. R., 1938.

THE ROSS CHEMICAL LABORATORY
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AUBURN, ALABAMA RECEIVED SEPTEMBER 21, 1948

## Preparation and Properties of Tetramethylene Sulfones

BY MARLIN T. LEFFLER AND W. D. KRUEGER

In the course of a search for new types of chemotherapeutic agents, several cyclotetramethylene sulfones were prepared and studied. These were synthesized by the addition of amines, alcohols and mercaptans to 2,5-dihydrothiophene-1-dioxide (butadiene sulfone) in a manner similar to that described by Delfs.[1] The general formula, I, illustrates the types prepared and listed in Table I, where (X) is either –NH–, –O– or –S–, and R is an alkyl or substituted alkyl group.



(I)

It is of interest to note that while the addition of amines to butadiene sulfone does not generally require a catalyst, alcohols and mercaptans react best in the presence of an alkaline agent. Triton-B was found to be an effective catalyst; sodium and potassium hydroxides serve also. Worth emphasizing is the fact that strongly basic amines such as aliphatic amines, phenethylamine, etc., add readily to the double bond of butadiene sulfone but less basic amines, aniline and benzylamine for example, do not react to give any appreciable yield under similar conditions.

Through the courtesy of the Division of Chemotherapy for Tropical Diseases, National Research Council, the products described herein were tested for activity against a variety of tropical diseases. None was found to have any significant activity in amebiasis, filariasis, schistosomiasis or leischmaniasis.

We are indebted to Mr. E. F. Shelberg of the Microanalytical Department for the microchemical analyses.

### Experimental

The sample of 2,5-dihydrothiophene-1-dioxide (butadiene sulfone) used in this work was furnished by the Shell Development Company under the trade name "Sulfolene."

The tetrahydrothiophene-1-dioxides listed in Table I were prepared by the following general procedures:

**3-Amino Derivatives.**—A mixture of 0.5 mole of butadiene sulfone and 2 moles of the primary or secondary amine was stirred and heated at 70–80° for twenty-four hours. The excess amine was then removed by distillation *in vacuo* and the residue was dissolved in 300 ml. of anhydrous ether, which solution was treated with excess dry, gaseous hydrogen chloride to form the salt. The solid salts were removed by filtration and recrystallized to constant melting point from absolute alcohol.

**3-Substituted Ethers.**—A mixture of 0.5 mole of butadiene sulfone, 1.0 mole of the desired alcohol and 2 to 4 ml. of Triton-B was heated at 70–80° for twenty-four hours. At the end of this time the Triton-B was neutralized with concentrated sulfuric acid and the excess of the alcohol used was removed by distillation *in vacuo*. The residue was then distilled under reduced pressure. In the case of the 3-diethylaminoethoxy derivative, the product was converted to the phosphate by the addition of a slight excess of phosphoric acid (85%) to an alcoholic solution of

TABLE I

CYCLOTETRAMETHYLENE SULFONES, $CH_2(CH_2)(X)R$ / $CH_2CH_2$ / $SO_2$

| (X)—R | M. p., °C. | Yield, % | Formula | —Analyses, N, %— Calcd. | Found |
|---|---|---|---|---|---|
| | Amine Hydrochlorides | | | | |
| –$NHC_4H_9$-*n*·HCl | 148–149 | 73 (base) | $C_8H_{18}ClNO_2S$ | 6.15 | 6.14 |
| –$NHCH_2CH_2C_6H_5$·HCl | 188–189 | 41 | $C_{12}H_{18}ClNO_2S$ | 5.08 | 5.00 |
| –$NH(CH_2)_3N(C_2H_5)_2$·2HCl | 176–177[a] | 77 | $C_{11}H_{26}Cl_2N_2O_2S$ | 8.72 | 8.49 |
| –$NC_5H_{10}$(Piperidino)·HCl | 218–219 | 76 (base) | $C_9H_{18}ClNO_2S$ | 5.84 | 5.86 |
| | Ethers | | | | |
| –$O(CH_2)_2N(C_2H_5)_2$ | Phosphate: 132–133<br>Base: B. p. 175–181 (4 mm.) | 62 | $C_{16}H_{24}NO_7PS$ | 4.20 | 4.31 |
| –$SCH_2C_6H_5$ | 61–63 | 51 | $C_{11}H_{14}O_2S_2$ | C: 54.52 | 54.48 |
| | | | | H: 5.82 | 5.53 |
| –$S(CH_2)_2N(C_2H_5)_2$ | HBr: 122–123 | 48 | $C_{16}H_{22}BrNO_2S_2$ | 4.22 | 4.27 |

[a] Dihydrochloride precipitated by addition of excess alcoholic hydrogen chloride to an acetone solution of the base. Recrystallized from absolute alcohol.

(1) Delfs, U. S. Patent 2,219,006 (1940); 2,291,798 (1942).

the base. The phosphate was purified by recrystallization from a mixture of acetone and methanol (1:4).

**3-Substituted Thio-ethers.**—To a mixture of 0.2 mole of butadiene sulfone, 0.2 mole of the desired mercaptan and 75 ml. of water was added slowly and with good agitation 0.4 mole of powdered sodium hydroxide. During this addition, the temperature rose to and was held at 70–80°. Stirring was continued and the temperature was maintained at 70–80° for four hours longer. Then the reaction was cooled and extracted with two 250-ml. portions of ether. The combined ether extracts were washed with 150 cc. of water and dried over anhydrous magnesium sulfate.

In the case of the benzylthio ether, the product crystallized directly from the cold ether solution. It was purified further by recrystallization from dry ether. With the diethylaminoethyl thio-ether, the base was converted to the hydrobromide by treatment of the dry ether solution with gaseous hydrogen bromide. Purification was accomplished by recrystallizing the salt from absolute alcohol.

ABBOTT RESEARCH LABORATORIES
NORTH CHICAGO, ILLINOIS RECEIVED AUGUST 16, 1948

## Thermal Exchange Experiments with Radioactive Zinc

BY LEON LEVENTHAL[1] AND C. S. GARNER

Duffield and Calvin[2] have reported an intensive study of thermal exchange reactions of copper chelate compounds in pyridine, most of which reactions proceeded at measurable rates. Other exchange experiments of the type considered here include those of Drehmann[3] on manganese(II) ions with manganese acetylacetone and manganese benzoylacetone in methanol (half-times of exchange less than one hour), Sue and Yuasa[4] on vanadyl and vanadate ions with solid vanadium 8-hydroxyquinoline and solid vanadium cupferronate (relatively slow exchange), and Johnson and Hall[5] on nickel(II) ions with various nickel chelate compounds in acetone, methyl or ethyl cellosolve (rapid to slow exchanges).

We have examined the thermal exchange reactions of zinc ions with some zinc complex compounds of the kind referred to above, partly to find conditions under which the kinetics of such reactions might be studied and partly to learn which of these zinc compounds, if any, might be suitable for use in the Szilard–Chalmers method of concentrating radioisotopes.

Complete exchange of radioactive zinc was found between dipyridine zinc acetate and the following zinc complex compounds in pyridine solution at 25° after exchange times as short as thirty seconds in each case: zinc acetylacetone, zinc acetylacetone ethylenediimine, zinc benzoylacetone ammoniate, zinc nicotinylacetone and dipyridine zinc thiocyanate. In the case of the nicotinylacetone, the exchange solution in pyridine was 0.0034 $f$ in dipyridine zinc acetate and 0.0034 $f$ in the zinc chelate. In all other cases, the pyridine exchange solutions were 0.01 $f$ in the acetate and 0.01 $f$ in the complex compound. The acetylacetone exchange was also run at 0° without any apparent difference. Thus, it appears either that rapid exchange was induced by the separation procedure utilized or, more probably, that the above zinc complex compounds are comparatively unstable with respect to ionization or displacement reactions (stability apparently comparable with that of copper salicylaldehyde, copper salicylaldehyde anil, and copper salicylaldehyde methylimine in pyridine solution[2]). If the rapid exchange was not induced, the above zinc complex compounds would not be suitable for Szilard–Chalmers separations, at least in pyridine solution.

### Experimental

**Radiozinc Tracer.**—Several sections from a discarded copper cyclotron dee were obtained through the courtesy of Professor J. R. Richardson, to whom our thanks are hereby expressed. Since these copper parts had received lengthy deuteron and neutron bombardments and had been cooling for over a year, the principal activity in them was due to 250-day $Zn^{65}$, formed mainly by the reaction $Cu^{65}(d,2n)Zn^{65}$. Chemical separation and purification of the radiozinc was effected by a procedure similar to that outlined by Kamen,[6] giving a zinc fraction with the half-life and radiations characteristic of 250-day $Zn^{65}$.

**Procedure.**—Experiments were run in duplicate. All zinc compounds were synthesized and their identity established by chemical analyses. The pyridine was dried over potassium hydroxide and distilled through a column. Exchange mixtures were synthesized volumetrically from standardized stock solutions of the complex compounds and of radioactive zinc acetate in pyridine. After varying lengths of time the exchange mixtures were subjected to a separation procedure similar to that used by Duffield and Calvin[2] and consisting of the addition of water and chloroform followed by extraction of the complex compound into the chloroform–pyridine layer and of the acetate into the water–pyridine layer, re-extraction from each layer, then precipitation of zinc sulfide from the resulting extracts buffered with acetic acid–acetate mixtures. Since the zinc sulfide precipitates were found after drying to be of varying composition they were ignited to the oxide for weighing and subsequently mounted on filter paper discs. Both fractions from each experiment were counted in a reproducible geometry with a Geiger–Mueller counter and scale-of-64, the 0.45- to 1.14-Mev. gamma radiation associated with the decay of $Zn^{65}$ being counted through a compound absorber. The total activity in each experiment was of the order of 1000 counts per minute, and corrections for decay and changes in counter efficiency (by use of a standard $Zn^{65}$ aliquot) and for background were applied. The extent of exchange was calculated in the usual manner from the specific activities of the two fractions.

(1) Present address: Naval Radiological Defense Laboratory, San Francisco Naval Shipyard, San Francisco 24, California.

(2) R. B. Duffield and M. Calvin, THIS JOURNAL, **68**, 557 (1946).

(3) U. Drehmann, *Z. physik. Chem.*, **B53**, 227 (1943).

(4) P. Sue and T. Yuasa, *J. chim. phys.*, **41**, 160 (1944).

(5) J. E. Johnson and N. F. Hall, THIS JOURNAL, **70**, 2344 (1948).

(6) M. D. Kamen, "Radioactive Tracers in Biology," Academic Press, Inc., New York, N. Y., 1947, p. 246.

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RECEIVED SEPTEMBER 25, 1948

## Thermal Exchange Experiments with Radioactive Chromium

BY H. E. MENKER AND C. S. GARNER

The only published work on exchange reactions of chromium compounds is the observation of

TABLE I

THERMAL EXCHANGE OF LABELLED CHROMIUM (Cr*) BETWEEN CHROMIUM COMPOUNDS

| Ions | Composition, f. | $HClO_4$ f. | Temp. °C | Activity of Separated Fractions, net c./m:[a] Orig. act. | Orig. inact. | Std. aliq. | Exchange Time Hr. | Exchange % |
|---|---|---|---|---|---|---|---|---|
| $Cr(H_2O)_6^{+++}$, $Cr_2O_7^{--}$ | 0.010 $Cr^*(ClO_4)_3$, 0.0050 $K_2Cr_2O_7$ | 0.05 | Rm. | 4290 | 41 | 4333 | 72 | <2 |
| | | | | 1913 | 27 | 1952 | 456 | <3 |
| | | | 45.1 | 2645 | 108 | 2838 | 72 | 8 |
| | | | | 1840 | 129 | 1981 | 264 | 13 |
| | | | | 435[b] | 119[b] | 530 | 1200 | 43 |
| | | 2.0 | Rm. | 2509 | 23 | 2470 | 72 | <2 |
| | | | 45.1 | 2534 | 70 | 2838 | 72 | 5 |
| Cr(III), $Cr_2O_7^{--}$ | .0020 $Cr^*_2(SO_4)_3$,[c] .0020 $K_2Cr_2O_7$ | [d] | 25.1 | 310 | 1 | 354 | 72 | <1 |
| $Cr(OH)_4^-$, $CrO_4^{--}$ | .010 $Cr^*(ClO_4)_3$, .010 $K_2CrO_4$ | [e] | 25.1 | 2713 | 18 | 2838 | 72 | <3 |
| $Cr(H_2O)_6^{+++}$, $Cr(SCN)_6^{---}$ | .010 $Cr^*(ClO_4)_3$, .010 $K_3Cr(SCN)_6$ | 0.05 | Rm. | 1297 | 1 | 1300 | 72 | <1 |
| | | 2.0 | Rm. | 1363 | 1 | 1300 | 72 | <1 |
| $CrCl_2(H_2O)_4^+$, $Cr(SCN)_6^{---}$ | .0067 $Cr^*Cl_3$,[c] .0067 $K_3Cr(SCN)_6$ | [f] | 25.2 | 617 | 3 | 626 | 24 | <2 |
| $Cr(H_2O)_6^{+++}$, $Cr(CN)_6^{---}$ | .010 $Cr^*(ClO_4)_3$, .010 $K_3Cr(CN)_6$ | pH 3–4 | Rm. | 498 | 275 | 773 | 72 | 71 |
| $CrCl_2(H_2O)_4^+$, $Cr(CN)_6^{---}$ | .0049 $Cr^*Cl_3$,[c] .0049 $K_3Cr(CN)_6$ | [g] | 25.1 | 501 | 2 | ... | 72 | <2 |
| Cr(III), $Cr(CN)_6^{---}$ | .0080 $Cr^*(OOCCH_3)_3$,[c] .0080 $K_3Cr(CN)_6$ | [h] | 25.1 | 608 | 38 | 668 | 96 | 12 |
| $Cr(H_2O)_6^{+++}$, $Cr(C_2O_4)_3^{---}$ | .010 $Cr^*(ClO_4)_3$, .010 $K_3Cr(C_2O_4)_3$ | 0.025 | Rm. | 700 | 0 | 734 | 72 | <1 |
| $CrCl_2(H_2O)_4^+$, $Cr(C_2O_4)_3^{---}$ | .0050 $Cr^*Cl_3$,[c] .0050 $K_3Cr(C_2O_4)_3$ | [g] | 25.1 | 350 | 5 | 477 | 1 | <5 |

[a] Statistical counting error, taken as the square root of the sum of the squares of the standard deviations of sample and of background, was 1%. [b] Analyses gave same amount of chromium in each fraction, thus showing that oxidation of chromium(III) by perchloric acid is negligible under the experimental conditions. [c] Green form. [d] $H_2SO_4$ (pH 2–3). [e] 3.1 f. NaOH. [f] 0.067 f. HCl. [g] 0.050 f. HCl. [h] $CH_3COOH$ (pH 3–4).

Muxart, Daudel, Daudel and Haissinsky[1] that no appreciable exchange of radiochromium occurs between chromium(III) and dichromate ions in sulfuric acid solutions.

We have confirmed this observation and have extended the studies to exchange measurements in 2 *f* and 0.05 *f* perchloric acid and in 3.1 *f* sodium hydroxide. In addition, some exchange reactions of chromium(III) ions with hexathiocyanatochromate(III), hexacyanochromate(III), and trioxalatochromate(III) ions, respectively, have been investigated with radiochromium.

Table I summarizes the results. Appreciable exchange was observed only for Cr(III)—$Cr(CN)_6^{---}$ in low concentration of perchloric acid or acetic acid and for the pair hexaaquochromium(III) and dichromate ions in 0.05 *f* perchloric acid at 25° and 45°. In the latter case the exchange results obey approximately the exponential exchange law,[2,3] as is shown by Fig. 1. The half-time for the exchange under the stated conditions is 60 ± 6 days at 45° and greater than 430 days at 25°.

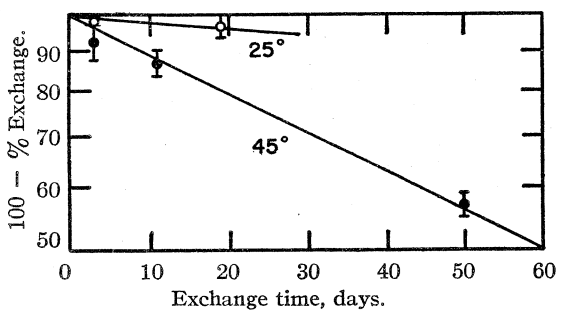



Fig. 1.—Hexaaquochromium(III)—dichromate exchange, 0.010 *f* $Cr^*(ClO_4)_3$, 0.0050 *f* $K_2Cr_2O_7$, 0.05 *f* $HClO_4$.

## Experimental

**Radiochromium Tracer.**—Radiochromium was prepared by the Cr(*n*, γ) reaction in the Oak Ridge pile and allocated by the U. S. Atomic Energy Commission. Chemical purification gave a chromium fraction with the half-life and radiation characteristics of 27-day $Cr^{51}$.

**Procedure.**—Experiments were run in duplicate. The exchange mixtures were synthesized volumetrically from the standardized stock reagent solutions, placed inside glass-stoppered flasks immersed in a thermostated bath, and subjected to chemical separation at the end of the exchange times. In the hexathiocyanatochromate (III) and hexacyanochromate (III) exchanges separation was effected by the addition of silver nitrate to precipitate $Ag_3Cr(SCN)_6$ and $Ag_3Cr(CN)_6$, respectively. Separation in the case of the trioxalatochromate (III) exchanges was achieved by the addition of barium chloride and ethanol to precipitate $Ba_3[Cr(C_2O_4)_3]_2$. In all other cases separation was brought about by precipitation of hydrous chromium(III) oxide. Both fractions in each exchange experiment were mounted and counted, in a few cases in the form precipitated (except for drying), but in most cases as $BaCrO_4$. Samples were suction-filtered onto Whatman No. 50 paper discs held in a cylindrical glass "chimney" device, then mounted on cardboard plates for counting. The 0.33-Mev gamma radiation associated with the decay of $Cr^{51}$ was generally used in the detection, the samples usually being counted through 108 mg./sq. cm. aluminum (to eliminate variable X-radiation) in a reproducible geometry with a Geiger–Mueller counter and scale-of-128. Corrections for decay and changes in counting efficiency (by use of a standard $Cr^{51}$ aliquot) and for background (~19 c./m.) were made.

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LOS ANGELES 24, CALIFORNIA RECEIVED OCTOBER 1, 1948

(1) R. Muxart, P. Daudel, R. Daudel and M. Haissinsky, *Nature*, **159**, 538 (1947).

(2) H. A. C. McKay, *ibid.*, **142**, 997 (1938).

(3) R. B. Duffield and M. Calvin, THIS JOURNAL, **68**, 557 (1946).

## Penicillin G as Electrolyte and Colloidal Electrolyte[1]

BY J. W. MCBAIN, HARRIETTE HUFF[2] AND A. P. BRADY[2]

There is disagreement concerning the state of aggregation of penicillin salts in aqueous solution. On the basis of surface tension and ultramicroscopic observations, Hauser, Phillips and Phillips[3] have reported sodium benzyl penicillinate (penicillin G) as a colloidal electrolyte. On the other hand, Kumler and Alpen[4] concluded from conductivity and surface tension measurements that both potassium and sodium salts of penicillin G are only molecularly dispersed in water. Since neither of those lines of evidence is conclusive, it seemed worth while to make other types of measurement on the solutions to decide between these opposing views. This note presents measurements of the conductivity, surface tension, freezing points, and dye solubilization at various concentrations of aqueous solutions; showing that sodium pencillin G above 0.25 m. is indeed a colloidal electrolyte, but that in lesser concentration it is an ordinary electrolyte. The authors[3,4] referred to were dealing with dilute solutions such as 0.017 mole/liter or 0.6%.

### Experimental

Crystalline sodium penicillin G was kindly furnished by Bristol Laboratories, Inc., of Syracuse, New York, and according to their analysis was 96.9% G with the remainder being F, dihydro F, and K.

The conductivity was measured at 2000 cycles in an oil thermostat at 25 ± 0.005° with a Dike–Jones type bridge using an oscillograph to detect the balance point. The conductivity water was about $0.8 \times 10^{-6}$ mho.

The crystalline penicillin and its solutions were stored in a refrigerator. With the exception of the solubilization measurements, all determinations were made with solutions less than six hours old and with less than half an hour at room temperature.

### Results and Discussion

The results are given in Table I and plotted in Figs. 1 and 2. The freezing point results are expressed in terms of $g$, the practical osmotic coefficient, the ratio of the lowering to the ideal lowering for a uni-univalent salt. Figure 1 also includes the results of solubilization measurements both with water and with isotonic salt solution as solvents. Both freezing point and solubilization show that sodium penicillin G aggregates in concentrated solution, but the critical concentration of 0.25 m. (8.26% G) is so high that it is of little interest biologically. Solubilization experiments in the presence of isotonic salt solution

TABLE I

OSMOTIC COEFFICIENT AT 0° AND EQUIVALENT CONDUCTIVITY AND SURFACE TENSION OF SODIUM PENICILLIN G SOLUTIONS AT 25°

| Concentration | | Osmotic coefficient, g. | Equivalent conductivity |
|---|---|---|---|
| Molal | Equiv./liter | | |
| 0.602 | 0.526 | 0.625 | 36.5 |
| .318 | .294 | .852 | 43.2 |
| .173 | .1652 | .924 | 50.0 |
| .0968 | .0942 | .950 | 53.5 |

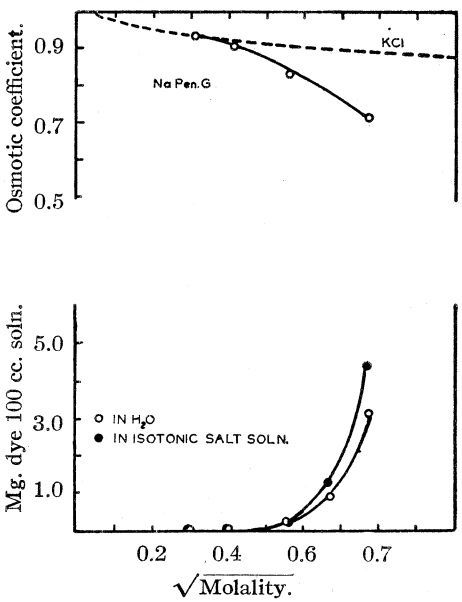



Fig. 1.—The osmotic coefficient $g$ of sodium penicillin G as compared with that of potassium chloride; also its solubilizing power in water and in isotonic salt solution (0.9% NaCl).

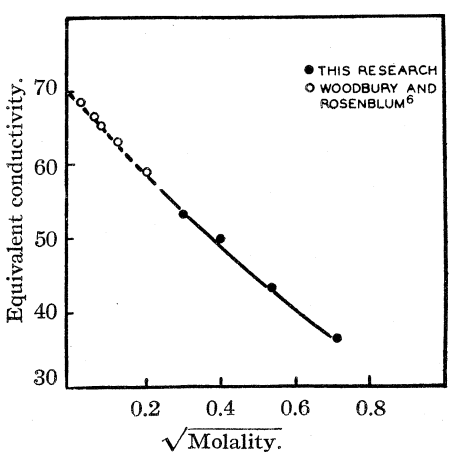



Fig. 2.—The equivalent conductivity of sodium penicillin G.

(1) This work was carried out under a contract between the Office of Naval Research and Stanford Research Institute, under the supervision of Professor J. W. McBain.

(2) Present address: Stanford Research Institute, Stanford, California.

(3) E. A. Hauser, J. W. Phillips, and R. G. Phillips, 22nd National Colloid Symposium, Cambridge 1948; *Science*, **106**, 616 (1947); also E. A. Hauser, American Chem. Soc. Meeting, Portland, September, 1948.

(4) W. D. Kumler and E. L. Alpen, Pacific Division Amer. Assoc. Adv. Sci., Berkeley, June, 1948; *Science*, **107**, 567 (1948).

show little effect upon critical concentration. The equivalent conductivity curve shows no break or a very doubtful one at the critical concentration, as expected for this type of polycyclic compound. Bile salts and sodium abietate, both shown to be colloidal electrolytes by freezing point measurements, give no break in the conductivity curve.[5,6] The conductivity curve determined here ties in satisfactorily with the data given by Woodbury and Rosenblum,[7] converted from 30 to 25° by assuming that the salt has the same temperature coefficient as that of the sodium ion.

The surface tension of these solutions is fairly low, but relatively independent of concentration and may easily result from small amounts of impurities.

(5) J. W. McBain and S. A. Johnston, *Proc. Roy. Soc. (London)*, **191A**, 129 (1942).

(6) I. M. Kolthoff and W. F. Johnson, *J. Phys. Chem.*, **50**, 440 (1946).

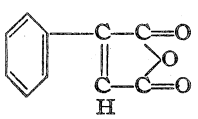
(7) D. T. Woodbury and C. Rosenblum, *J. Biol. Chem.*, **171**, 447 (1947).

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## A Preparation of Phenylmaleic Anhydride

BY LEONARD E. MILLER, HARLOW B. STALEY AND D. J. MANN

Although phenylmaleic anhydride (I) was first isolated in low yield as a by-product in the synthesis of phenylmalic acid by the reaction of phenylsuccinic acid with bromine and phosphorus tribromide,[1] no satisfactory procedure for the preparation of (I) has been reported.



I

When phenylsuccinic anhydride is permitted to react with N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide, phenylmaleic anhydride can be isolated in 57–64% yield.

The use of N-bromosuccinimide as a dehydrogenating agent for several hydroaromatic compounds has been reported recently by Barnes.[2]

### Experimental[3]

Phenylsuccinic anhydride,[4] m. p. 53–54°, was prepared in 78–84% yield from phenylsuccinic acid.[5]

Into a 500-ml., two-necked flask, equipped with a mechanical Hershberg stirrer (made of nichrome wire) and a condenser fitted with a drying tube, were placed 17.8 g. (0.1 mole) of N-bromosuccinimide, 8.8 g. (0.05 mole) of phenylsuccinic anhydride, 200 ml. of carbon tetrachloride and 0.1 g. of benzoyl peroxide. The reaction mixture was heated under reflux with stirring for twenty-four hours, during which time the solution became bromine-red in color and a precipitate of succinimide formed. After the mixture was cooled to room temperature, the insoluble succinimide was separated on a filter and washed with several portions of hot benzene until the washes no longer gave a positive Baeyer test with potassium permanganate (about 150 ml. of benzene were required). When cool, the combined benzene and carbon tetrachloride solutions deposited an additional small quantity of succinimide which was separated. The clear solution was concentrated by distillation to a volume of 30 ml. and was then placed in a refrigerator for two hours. The crystals of phenylmaleic anhydride which formed were separated and recrystallized from dry acetone–petroleum ether (high boiling); yield 2.1–2.3 g., m. p. 119–120° (reported, 119–119.5°[1]).

After the evaporation of the carbon tetrachloride filtrate to dryness under reduced pressure (water pump) in a two-bulb distillation apparatus, the residue was distilled under reduced pressure (1.0 mm.). At 60–70° a few drops of a yellow liquid were collected; this forerun was discarded. At 130–145° a yellow solid was collected. This material was recrystallized twice from dry acetone–petroleum ether (high boiling) (Norite) to give 2.1–2.3 g. of phenylmaleic anhydride, m. p. 119–120°. From the combined recrystallization filtrates, 0.8–1.0 g. of equally pure product was isolated. The total yield was 5.0–5.6 g. (57–64%).

The percentage yield was slightly lower (53–57%) when four times these amounts were used.

(1) Alexander, *Ann.*, **258**, 67 (1890).

(2) Barnes, THIS JOURNAL, **70**, 145 (1948).

(3) All m. p.'s and b. p.'s are uncorrected.

(4) Verkade and Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

(5) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1941, p. 451.

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URBANA, ILLINOIS RECEIVED SEPTEMBER 24, 1948

## Displacement-chlorination of Dimethylaminopropanol-2

BY N. L. WENDLER AND M. TISHLER

The reaction of methanesulfonyl chloride with dimethylaminopropanol-2 in an inert solvent was found to give rise to the *o*-mesylate hydrochloride (II) admixed to a greater or lesser extent with the hydrochloride of the propanolamine (I). The *o*-mesylate hydrochloride (II) could be obtained directly and in pure condition by conducting the reaction in a solvent mixture consisting of equal parts of chloroform and acetone.

The *o*-mesylate hydrochloride was titrated with one equivalent of alkali and was converted thereby to the free ester base, characterized as its picrate. When heated above its melting point for a short time the *o*-mesylate hydrochloride was converted smoothly by internal displacement into dimethylamino-2-chloropropane (III). The latter was isolated and identified as its picrate.

$$\underset{\text{(I)}}{CH_3CHOHCH_2N(CH_3)_2} \longrightarrow \underset{\text{(II)}}{CH_3CH(OSO_2CH_3)CH_2NH(CH_3)_2Cl} \xrightarrow{138^\circ} \underset{\text{(III)}}{CH_3CHClCH_2N(CH_3)_2}$$

### Experimental

**Dimethylaminopropanol-2 *o*-Mesylate Hydrochloride.**—To a stirred solution of 10.5 g. of dimethylaminopropanol-2 in 25 cc. of chloroform at 0° was added portion-wise a solution of 12.5 g. of methanesulfonyl chloride in 25 cc. of chloroform. The homogeneous solution was treated with

50 cc. of acetone and stored in the cold for twenty hours. During this time the *o*-mesylate hydrochloride crystallized. The crystals were collected, washed with cold 50% acetone-chloroform and dried in a vacuum desiccator over solid potassium hydroxide; yield 9.5–10 g. (40–45%), m. p. 126.5–128°. A small sample was recrystallized from acetone affording colorless micro-rhombs, m. p. 130–131°.

*Anal.* Calcd. for $C_6H_{16}O_3NSCl$: N, 6.44; Cl, 16.20; neut. equiv., 217.5. Found: N, 6.59; Cl, 16.10; neut. equiv., 226.

A sample of the *o*-mesylate hydrochloride was neutralized with aqueous potassium hydroxide at 0° and the oil which separated was extracted with ether–petroleum ether and dried over solid potassium hydroxide. The filtered solution was concentrated to dryness and the residue was converted to a picrate in ethyl acetate–ether solution. Recrystallization from ethyl acetate–ether afforded the picrate of the *o*-mesylate base as fine yellow needles, m. p. 90–91°.

*Anal.* Calcd. for $C_{12}H_{18}O_{10}N_4S$: C, 35.12; H, 4.39; N, 13.66; S, 7.81. Found: C, 35.39; H, 4.39; N, 13.67; S, 8.53.

**Dimethylamino-2-chloropropane from *o*-Mesylate Hydrochloride.**—*o*-Mesylate hydrochloride (II), 3.8 g., was sealed under vacuum in an ampule and heated in xylene vapor for four hours. The ampule was cooled. The contents were dissolved in an equal volume of water and treated with an excess of 50% aqueous potassium hydroxide solution. The oil which separated was extracted with petroleum ether, dried over solid potassium hydroxide and the solvent evaporated. The residue was converted to its picrate in ethyl acetate–ether solution and recrystallized from the same solvent as fine yellow needles, m. p. 101–103°. A mixed melting point with authentic picrate of dimethylamino-2-chloropropane was undepressed; yield 3.8–4.2 g. (70–75%).

*Anal.* Calcd. for $C_{11}H_{15}O_7N_4Cl$: Cl, 10.13; Found: Cl, 9.74.

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RECEIVED SEPTEMBER 29, 1948

## An Application of the Delépine Reaction to β-Bromopropionic Acid

BY N. L. WENDLER

A modification of the Delépine reaction[1] has been applied to β-bromopropionic acid for its conversion to β-alanine. A quaternary betaine-complex was formed between β-bromopropionic acid and hexamethylenetetramine according to a method applied by Schubert[2] to iodoacetic acid. This complex was subsequently decomposed by hydrochloric acid in ethanol to afford β-alanine in good yield and high state of purity.

$$(CH_2)_6N_4 + BrCH_2CH_2COOH \xrightarrow{HCO_3^-} [(CH_2)_6N_4]^+—CH_2CH_2COO^- \xrightarrow[C_2H_5O^+H_2]{} H_3NCH_2CH_2COOH$$

### Experimental

To a solution of 5 g. of β-bromopropionic acid[3] in 15 cc. of water and 10 cc. of ethanol was added 2.74 g. of sodium bicarbonate. After neutralization was complete, a solution of 4.57 g. of hexamethylenetetramine in 10 cc. of water was added and the resulting solution allowed to stand at room temperature for fifteen hours. At the end of this time, 50 cc. of ethanol was added to the point of faint turbidity followed by scratching, whereupon voluminous crystallization of colorless needles of the betaine-complex ensued. The crystals were chilled in ice for one to two hours and filtered, 9 g. A second crop afforded 0.5 g. yielding a total of 9.5 g. of material.

The betaine-complex (9.5 g.) was treated with 120 cc. of ethanol and 15 cc. of concentrated hydrochloric acid and refluxed for fifteen hours. The mixture was concentrated to dryness *in vacuo* at 50° and the residue extracted with several portions of ethanol. The filtered extract was concentrated to dryness and the residue boiled under reflux with 50–75 cc. of water for one-half hour. The cooled aqueous solution was treated portion-wise with an excess of silver oxide with stirring to remove chloride ion and subsequently filtered, and the filtrate saturated with hydrogen sulfide gas. The precipitated silver sulfide was removed by centrifugation followed by filtration. The colorless solution was concentrated *in vacuo* to a volume of a few cc. and diluted with ethanol to the point of crystallization. After chilling and filtering there was afforded 2.5 g. (85%) of β-alanine, m. p. 199–200° dec. A mixed melting point with known material was undepressed.

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RAHWAY, N. J.

RECEIVED SEPTEMBER 29, 1948

(1) Delépine, *Compt. rend.*, **120**, 501 (1895).
(2) Schubert, *J. Biol. Chem.*, **116**, 444 (1936).
(3) "Organic Syntheses," Vol. IV, p. 25.

## Explosive Properties of Metal Ammines[1]

BY W. R. TOMLINSON, K. G. OTTOSON AND L. F. AUDRIETH

The literature contains numerous references to the explosive nature of certain coördination compounds, but no generalization has thus far been formulated in which an effort has been made to relate chemical composition of such coördination compounds to explosive character. The experimental evidence which is presented below, together with information gleaned from the literature, demonstrates that metal compounds containing (a) coördinated ammonia and related nitrogen-containing donor molecules, and (b) coördinated and/or ionic groups of an oxidizing nature such as perchlorate, chlorate, nitrate, nitrite (or nitrato- and nitro-groups), will decompose violently under various conditions. As is known to be the case among substances classed as explosives, the sensitivity of various coördination compounds to impact, to friction, and to heat will vary widely; nevertheless, some of these same compounds can be caused to detonate when properly initiated. For this reason, due caution should be exercised in the preparation, handling and storage of compounds falling within the categories defined above.

It is significant that "metal nitrates with molecular ammonia" have been incorporated in explosive compositions containing ammonium nitrate as the principal ingredient.[2] Metallic chlorates and perchlorates containing coördinated hydrazine[3] have been found to be brisant and sensitive explosives. Other coördination compounds reported

(1) Publication of the material contained in this paper has been approved by the Ordnance Department of the United States Army.
(2) Cook, Davis and Lawson (to E. I. du Pont de Nemours and Co.), British Patent 544,582; *cf. Chem. Abstracts*, **36**, 6804 (1942).
(3) Friederich and Vervoorst, *Z. ges. Schiess.-Sprengstoffw.*, **21**, 49, 65, 84, 103, 123, 143 (1926).

TABLE I

THE EXPLOSIVE PROPERTIES[c] OF SOME METAL AMMINES

| Metal ammine[d] | Explosion temperature, °C.[c] | Impact sensitivity 2 kg. wt., cm. | Sand test-gm. Sensitivity to initiator, gm., required to cause complete explosion: Power Sand crushed | Mercury fulminate | Lead azide | Tetryl |
|---|---|---|---|---|---|---|
| Hexammine chromium(III) nitrate | 265 | 32 | 40.7 | 0.20 | .. | .. |
| Hexammine cobalt(III) perchlorate | 360 | 18 | 39.2 | .25 | .. | .. |
| Hexammine cobalt(III) iodate | 355 | 100 | 14.7 | .24 | .. | .. |
| Hexammine cobalt(III) nitrate | 295 | 50 | 35.9 | .27 | .. | .. |
| Hexammine cobalt(III) hexanitrocobaltate[a] | ... | 85 | 34.0 | .20 | .. | .. |
| Nitratopentammine cobalt(III) nitrate | 310 | 48 | 35.5 | .24 | .. | .. |
| Chloropentammine cobalt(III) perchlorate | 320 | 21 | 30.6 | .20 | .. | .. |
| Hexaurea chromium nitrate | 265 | 50 | 3.0 | .. | .. | .. |
| Thiocyanatopentammine cobalt(III) perchlorate | 325 | 55 | 20.1 | .. | .. | |
| Dithiocyanatotetrammine cobalt(III) perchlorate | 335 | 35 | 13.9 | .. | .. | . |
| Dichlorodiethylenediamine cobalt(III) perchlorate | 300 | 85 | 9.9 | .. | .. | .. |
| Dichlorodiethylenediamine cobalt(III) chlorate | 320 | ... | 13.7 | .. | .. | ..[b] |
| Trinitrotriammine cobalt(III) | 305 | 44 | None | .. | .. | .. |
| tris-Ethylenediamine cobalt(III) nitrate | ... | 61 | None | .. | .. | 0.4 |
| bis-Diethylenetriamine cobalt(III) perchlorate | 325 | 21 | 39.4 | .. | 0.07 | .. |
| Ammonium hexanitrocobaltate(III) | 230 | 33 | 19.0 | .30 | .. | .. |
| Tetrammine copper(II) nitrate | 330 | 19 | 17.2 | .. | .. | 0.19 |
| Mercuric fulminate | ... | 5 | 21.0 | .. | .. | .. |
| Lead azide | 335 | 10 | 18.0 | .. | .. | .. |
| TNT (*sym*-trinitrotoluene) | 470 | 95 | 42.0 | .24 | .. | .. |

[a] This compound was unstable. [b] Requires tetryl. [c] Exposure to the temperature cited causes very rapid decomposition, or explosion, in 5 seconds. [d] All oxalates, chromates, carbonates, sulfates, and non-oxygenated complexes tested were non-explosive (*e. g.*, hexammine cobalt(III) chromate, oxalate and chloride). No compounds containing explosive groupings (*e. g.*, azide) were tested. [e] For details of tests see Picatinny Arsenal Technical Report No. 1401, 18 March 1944; Bureau of Mines Technical Bulletin No. 346, "Physical Testing of Explosives" at the Bureau of Mines Explosives Experiment Station, Bruceton, Pa.

to be explosive include: hexammine cobalt(III) chlorite,[4] chlorate,[3] and perchlorate,[3,5] aquopentammine cobalt(III) chlorate and perchlorate,[5] trihydrazine cobalt(II) nitrate,[6] hexahydroxylamine cobalt(III) nitrate,[7] the tetrammineauric halides[8] and trinitrotriammine cobalt.[9] In light of the evidence available in literature, it seems quite probable that the explosions reported to have occurred during evaporation of filtrates from cobalt determinations were caused, as suggested by Broughton, Laing and Wentworth,[10] by the formation of complex nitro- or nitro-cobaltates(III).

Samples of a number of cobalt(III) and chromium(III) coördination compounds[11] were subjected to standard tests to determine explosion temperature, impact sensitivity, power and sensitivity to initiation (ease with which explosion can be effected). Results of these tests are compared in Table I with values for TNT, mercuric fulminate and lead azide, representing respectively a relatively insensitive high explosive and two very sensitive initiating agents.

The data show quite clearly that oxygenated coördination compounds, particularly those which are "oxygen balanced," vary quite widely with respect to their sensitivities to heat and impact. They represent an extremely wide range in explosive types. Since most of the compounds are capable of exploding sharply and powerfully, and in some cases with but slight provocation, they are to be considered exceedingly dangerous. Some possess sufficient sensitivity to propagate explosion under water; the use or presence of non-solvent liquids is therefore no guarantee of safety. In the absence of specific information the same considerations may be expected to apply also to other metal ammines containing oxidizing radicals such as those of silver, gold, cadmium, lead and zinc.

DOVER, NEW JERSEY RECEIVED JULY 2, 1948

(4) Levi, *Atti Lincei*, (5) **32**, I, 623 (1923).
(5) Salvadori, *Gazz. chim. ital.*, **40**, II, 17 (1910).
(6) Franzen and Meyer, *Z. anorg. Chem.*, **60**, 247, 274 (1908).
(7) Werner and Berl, *Ber.*, **38**, 897 (1905).
(8) Ephraim, "Inorganic Chemistry," 4 Ed., Nordeman Publishing Co., Inc., New York, N. Y., 1943, p. 311.
(9) Clark, Quick and Harkins, THIS JOURNAL, **42**, 2498 (1920).
(10) Broughton, Laing and Wentworth, *Anal. Chem.*, **19**, 72 (1947).
(11) The authors desire to acknowledge their indebtedness to Professor John C. Bailar, Jr., of the University of Illinois, for his help in furnishing many of the coördination compounds which were subjected to actual study or used for the preparation of related derivatives.

## Preparation of Radioactive $CO_2$ from $BaCO_3$[1]

BY NORMAN ZWIEBEL,[2] JOHN TURKEVICH AND WARREN W. MILLER

To obtain the $C^*O_2$ from $BaC^*O_3$ either for introduction into a reaction system for synthesis of a

(1) Work done at the Brookhaven National Laboratory under the auspices of the Atomic Energy Commission. The work was started by one of us (W. W. M.) while a member of the Laboratory of Nuclear Science, Massachusetts Institute of Technology.
(2) Present address: Pyridium Corporation, Yonkers, New York

labeled compound, or for transfer to a gas activity measuring device such as an ionization chamber or gas counter, it has been common practice to drop either concentrated phosphoric or sulfuric acid on the $BaCO_3$.[3] This procedure often involves the use of a stopcock in contact with concentrated acid, does not permit the ready attainment of high vacuum and may entail the formation of a crust of insoluble barium sulfate or phosphate around the active barium carbonate. In practice a still more disconcerting factor has been the spattering of the dry powder on contact with acid with the consequent sweeping of a portion of the sample out of the reaction vessel by the evolving gas. The direct thermal evolution of the $C^*O_2$ from $BaC^*O_3$ by roasting the dry salt in a quartz tube has also been used[4] but the temperature necessary is inconveniently high.

These difficulties may be surmounted by using a thermal reaction between dry solids to evolve the carbon dioxide. Acids such as potassium bisulfate are unsuitable as the reaction will produce water as well as carbon dioxide. Inorganic acid anhydrides such as boric oxide and the pyro salts melt at too high a temperature to be used in Pyrex apparatus. Organic anhydrides sublime under vacuum. A convenient reaction, however, is a metathetic one producing a thermally unstable carbonate such as the reaction between barium carbonate and lead chloride. Lead chloride was used because it can be readily obtained in an anhydrous state, and has a low melting point and vapor pressure. Silver chloride can also be used.

To obtain the total carbon dioxide from a barium carbonate sample, two procedures have been worked out. In the micro-procedure the weighed barium carbonate, from 5 to 200 mg., is dropped into a Pyrex test-tube with attached ground joint. Over this is layered 5 to 10 times its weight of dry powdered lead chloride, and then a wad of glass wool is pushed down on top. After attaching the tube to the vacuum system and pumping at 100°, the carbon dioxide is released by carefully melting the lead chloride with a micro burner. The reaction is known to be at least 98% complete from gas buret and activity measurements. The fusion temperature may be lowered by using a 50–50 mixture of $PbCl_2$–AgCl instead of pure lead chloride. The melt should not fill a full diameter of the reaction vessel or the latter may crack on cooling. For macro-quantities we have employed the following procedure. The two solids, one part by weight of barium carbonate and six parts by weight of lead chloride, were intimately mixed and ground together before placing the mixture in a reaction tube. The latter was connected to a standard vacuum system by means of a stopcock and a standard taper ground glass joint. The reaction mixture was pumped overnight at room temperature to a pressure of $10^{-5}$ mm. A tubular woven glass heating mantle was used as a heat source and the temperature was controlled by a Variac. Evolution of gas began at about 180° and each increment of temperature caused a more rapid evolution of gas which gradually decreased with time. It was found that the most convenient procedure was to raise the temperature to 400° as rapidly as possible (about twenty-five minutes) and maintain the reaction mixture at this temperature. The evolution of carbon dioxide was 65% complete in one hour from the start of heating, 80% in two hours and 96% complete in four hours. 3–9 g. of barium carbonate was employed in these experiments. Thus this reaction has been found to proceed at temperatures well below the fusion temperature and the system may therefore be used as a convenient, clean, "virtual" source of active carbon dioxide.

(3) (a) W. G. Dauben, J. C. Reid and P. E. Yankwich, *Ind. Eng. Chem., Anal. Ed.*, **19**, 828 (1947); (b) J. T. Kummer, THIS JOURNAL, **69**, 2239 (1947); (c) J. L. Huston and T. H. Norris, *ibid.*, **70**, 1968 (1948).

(4) M. G. Inghram, Atomic Energy Commission, MDDC 60, June, 1946.

BROOKHAVEN NATIONAL LABORATORY
UPTON, NEW YORK RECEIVED AUGUST 16, 1948

# COMMUNICATIONS TO THE EDITOR

## METALLIC ALUMINUM IN SOLUTION IN LIQUID AMMONIA

*Sir:*

It has long been generally accepted that the alkali metals, in dissolving in liquid ammonia, dissociate into alkali metal cations and free (solvated) electrons,[1] and that the latter impart the characteristic blue color to such solutions. The alkaline earth metals are known to dissolve similarly, although to a smaller extent.[2] Makishima[3] included the dissolution of electrons among electrode reactions which may occur at a cathode in liquid ammonia solutions, and Laitinen and Nyman[4] have very recently pointed out that, theoretically, all metals should be in some degree soluble in liquid ammonia. According to the hypothesis

(1) Kraus, THIS JOURNAL, **30**, 1323 (1908).

(2) Kraus, *ibid.*, **30**, 660 (1908).

(3) Makishima, *J. Faculty Eng. Tokyo Imp. Univ.*, **21**, No. 3, 115 (1938).

(4) Laitinen and Nyman, THIS JOURNAL, **70**, 3002 (1948).

of these latter authors, however, the solubility of metals less active than calcium should be exceedingly small.

On the basis of the reaction of metallic aluminum with solutions of alkali metal amides in liquid ammonia, Bergstrom[5] postulated that aluminum must be soluble in this solvent to a slight extent. There is no record in the literature, however, of any actual observation of a blue solution of metallic aluminum in ammonia, although Booth and Merlub-Sobel,[6] in a study of the electrolysis of aluminum iodide, reported the formation at the cathode of a transitory blue-black film which they suggested might be a subiodide or subnitride of aluminum.

In the course of an investigation, recently begun in this Laboratory, of the anodic oxidation of aluminum in solutions of various salts in liquid ammonia, we have carried out several electrolyses with aluminum iodide as electrolyte. In every such case, we have observed the appearance, in the immediate vicinity of the *cathode*, of a deep blue color. This color is at first impermanent, disappearing upon diffusion into the body of the solution with the concurrent formation of a white precipitate, and being regenerated at the cathode. On prolonged electrolysis, however, the rate of disappearance gradually decreases, and the entire solution eventually becomes dark blue. The most striking results were obtained in a solution containing 0.3 g. of aluminum iodide in 48 g. of ammonia, which was electrolyzed at $-33°$ in an atmosphere of nitrogen between a bright platinum cathode and a chemically pure aluminum anode, at a cathode current density of about 0.01 amp. per sq. cm.

We are unable to account for these results in terms of any hypothesis other than the following. The cathode reaction appears to consist of the dissolution of electrons, which are able to exist in the presence of a considerable concentration of $Al^{+++}$ ion. The blue solute, consisting therefore of ionized metallic aluminum, at first reacts rapidly with the solvent, liberating hydrogen and yielding an insoluble white derivative of aluminum amide; subsequently, however, the rate of this reaction decreases, so that an appreciable concentration of aluminum metal is able to persist in the solution for as much as fifteen minutes after the current is discontinued.

This phenomenon is being studied further, and will later be the subject of a more complete report.

ARTHUR W. DAVIDSON
JACOB KLEINBERG
WILLIAM E. BENNETT
ALBERT D. MCELROY

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF KANSAS
LAWRENCE, KANSAS

RECEIVED DECEMBER 10, 1948

(5) Bergstrom, THIS JOURNAL, **45**, 2788 (1923); **46**, 1545 (1924); *cf.* Fernelius and Watt, *Chem. Revs.*, **20**, 195 (1937).

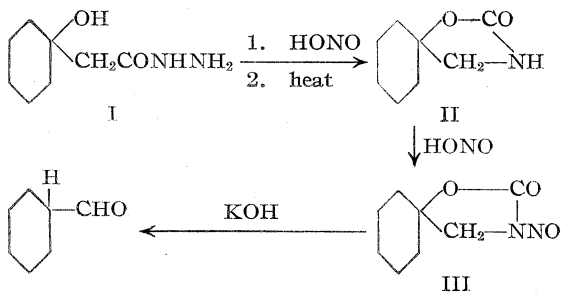
(6) Booth and Merlub-Sobel, *J. Phys. Chem.*, **35**, 3303 (1931).

## A NOVEL REACTION IN ORGANIC CHEMISTRY

*Sir:*

In connection with studies designed to develop a new approach to ring enlargement of cyclic ketones, an interesting new reaction has been discovered. When 3-nitroso-1-oxa-3-azaspiro[4,5]-decan-2-one, III, is treated with alkali, nitrogen is evolved immediately and hexahydrobenzaldehyde is produced. This aldehyde has been isolated in over 50% yield as the semicarbazone,[1,2] m. p. 172–173° after sintering at 166°.

The nitroso compound was prepared by the following series of reactions




Further studies as to the generality and mechanism of this reaction are under way in this Laboratory.

The author wishes to acknowledge a grant from the Research Corporation which has greatly assisted in this work.

**Hydrazide of 1-Cyclohexanolacetic Acid, I.**—This compound, m. p.[3] 102.2–104.4°, was prepared in 78% yield.

*Anal.* Calcd. for $C_8H_{16}O_2N_2$: C, 55.8; H, 9.4; N, 16.3. Found: C, 55.6, 55.8; H, 8.9, 8.7; N, 16.3, 16.4.

**1-Oxa-3-azaspiro[4,5]decan-2-one, II.**—The hydrazide, I, was dissolved in dilute hydrochloric acid and treated with a slight excess of sodium nitrite at 10–15°. The reaction mixture containing the resulting oily azide was slowly heated to 45° when decomposition began. Rapid stirring and temp. control near 50° are necessary to prevent violent decomposition. The cyclic urethan,[4] II, was isolated in 82% yield as colorless crystals, m. p. 101.0–102.4°.

*Anal.* Calcd. for $C_8H_{13}O_2N$: C, 61.9; H, 8.4; N, 9.0. Found: C, 61.8; H, 8.2; N, 9.3.[5]

On alkaline hydrolysis 1-aminomethylcyclohexanol (m. p. of N-benzoate,[6] 143–144°) was obtained.

**3-Nitroso-1-oxo-3-azaspiro[4,5]decan-2-one, III.**—II was converted into III, m. p. 82.8–83.2°, in 94% yield by nitrous acid.

*Anal.* Calcd. for $C_8H_{12}O_3N_2$: C, 52.2; H, 6.6; N, 15.2. Found: C, 52.3, 52.1; H, 6.3, 6.1; N, 15.5, 15.6.

**Semicarbazide of Hexahydrobenzaldehyde.**—To a solution of 1.84 g. of III in 15 cc. of alcohol was added drop-

(1) Melting points ranging from 167° to 176° for this derivative have been reported in Beilstein, "Handbuch der organischen Chemie," Julius Springer, Berlin, 1925, 4th ed., Vol. VII, p. 20.

(2) The author wishes to thank Mr. Abraham Kutner for preparing authentic samples.

(3) All melting points corrected.

(4) A similar cyclization has been reported [Schroeter, *Frdl.*, **10**, 1309 (1910–12)] but no details are mentioned and analyses for the products were not reported.

(5) This analysis by H. S. Clarke, Microanalytical Laboratories, Urbana, Illinois. Other analyses by Mrs. E. H. Klotz, O.S.U.

(6) M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, **26**, 288 (1943).

wise a slight excess of 50% potassium hydroxide. The evolution of nitrogen was quantitative. After warming to 60° the semicarbazone was prepared directly to yield 0.95 g. (56%) of semicarbazone, m. p. 172–173°, sintering at 166°.

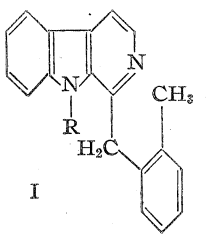
CHEMISTRY LABORATORY OF
THE OHIO STATE UNIVERSITY
COLUMBUS, OHIO MELVIN S. NEWMAN

RECEIVED DECEMBER 13, 1948

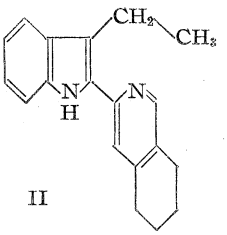
## THE STRUCTURE OF SEMPERVIRINE

*Sir:*

The alkaloid sempervirine, $C_{19}H_{16}N_2$, from *Gelsemium sempervirens*, Ait., is remarkable for its color and its high degree of unsaturation. In a recent elegant investigation, Prelog[1] has shown that the substance is transformed to the isomeric yobyrine (I, R = H) when heated with selenium, and to tetrahydroisoyobyrine (II) on treatment

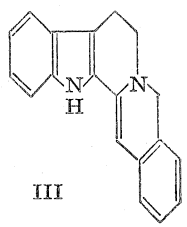



I

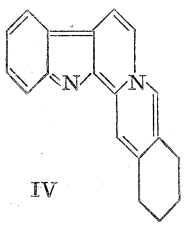



II

with Raney nickel. These results led to the proposal of structure (III) for sempervirine.

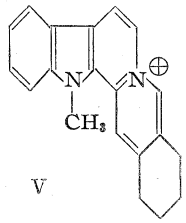



III

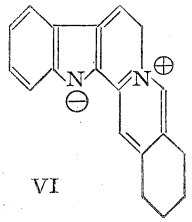



IV

We wish to propose a new structure (IV) for the alkaloid. In our view, the new formula is better in accord with the color of sempervirine, and with the formation from it of tetrahydroisoyobyrine. Beyond that we have been able to marshal new facts which provide further strong support for (IV). Thus, (i) the infrared spectrum of sempervirine *contains no band in the NH region*, while by contrast, all N-unsubstituted indole derivatives are characterized by an intense sharp band at 2.9 $\mu$; (ii) when sempervirine methochloride is heated with selenium, a new base, m. p. 103° [hydrochloride, m. p. 229°, picrate, m. p. 235°, (calcd. for $C_{26}H_{21}O_7N_5$: C, 60.58; H, 4.11. Found: C, 60.38; H, 4.15)], is formed, which is clearly N-methylyobyrine (I, R = Me), since its ultraviolet spectrum is nearly identical with that of yobyrine, and its infrared spectrum possesses no NH band.[2] These observations support the view that the metho-salts of sempervirine contain the cation (V). The expression IV implies of




V




VI

course an important contribution of the fully aromatic ionic structure (VI). Consideration of this fact makes understandable the formation of metho-salts of the structure (V), as well as the color of the alkaloid, and its high basicity ($pK_a$ 10.6). The formation from sempervirine of a mole of methane in the Zerewitinow determination can be attributed to the presence in (IV ⟷ VI) of a virtual (substituted) $\gamma$-picolinium system.

We wish to thank M. Raymond-Hamet (Paris) and Professor M.-M. Janot for their gracious gifts of sempervirine.

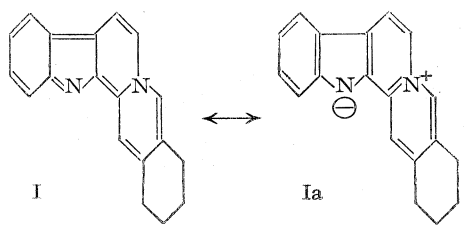
CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE 38, MASS. BERNHARD WITKOP

RECEIVED MAY 17, 1948

## THE SYNTHESIS OF SEMPERVIRINE METHOCHLORIDE

*Sir:*

It has been suggested on the basis of analytical and degradative evidence that the alkaloid sempervirine possesses the remarkable structure I ⟷ Ia.[1] We have now been able to provide conclusive evidence for the proposed structure through the synthesis of sempervirine metho-salts by an unambiguous route.




I ⟷ Ia

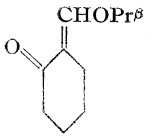
In model experiments, the lithium derivative of $\alpha$-picoline was condensed with isopropoxymethylene cyclohexanone[2] (II) [b. p. 64–65° (0.2 mm.), $n^{26}D$ 1.4980, calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.40]. From the acid-treated reaction-mixture, salts of the dehydroquinolizinium cation (III) were readily obtained (picrate, m. p. 237–238°, calcd. for $C_{19}H_{16}O_7N_4$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.41; H, 4.17; N, 13.36; per-

(1) Prelog, *Helv. Chim. Acta*, **31**, 588 (1948).

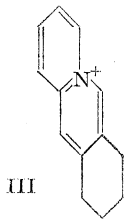
(2) More recently the nature of the base has been confirmed through direct comparison with a synthetic sample kindly supplied by Dr. Percy L. Julian.

(1) Woodward and Witkop, THIS JOURNAL, **71**, 379 (1949).

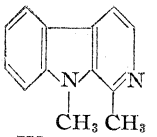
(2) Prepared from hydroxymethylene cyclohexanone by the method of Claisen, as reported by v. Auwers (*Ber.*, **71**, 2082 (1938)) and developed by Johnson and Posvic (THIS JOURNAL, **69**, 1361 (1947)).



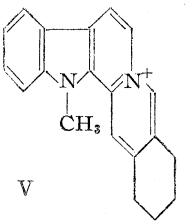

II




III




IV




V

chlorate, m. p. 187.1–187.8°, calcd. for $C_{13}H_{14}O_4NCl$: C, 55.05; H, 4.97. Found: C, 55.12; H, 5.05).

In a similar reaction, the use of the lithium derivative of N-methylharman[3] (IV) led to the smooth synthesis of salts of the methylsempervirinium cation (V). Synthetic samples of sempervirine methopicrate, m. p. 239–240°, and sempervirine methochloride, m. p. 330–332°, showed no depression in melting point on admixture with the corresponding salts of identical melting points prepared from natural sempervirine. The identity was further confirmed through the reproduction by synthetic sempervirine methochloride of the very characteristic ultraviolet absorption behavior of the salt from the natural alkaloid [$\lambda\lambda_{max.}$ (log $\epsilon$): 241 (4.56), ~250 (4.49), 292 (4.20), 330 (4.28), 395 (4.22); $\lambda\lambda_{min.}$ (log $\epsilon$): 280 (4.14) 305 (4.09), 365 (4.10)].

(3) *Cf.* Späth and Lederer, *Ber.*, **63**, 2102 (1930). Our material was made from N-methyltryptophan, which was itself prepared very smoothly by a new synthesis analogous to that used by Warner and Moe (THIS JOURNAL, **70**, 2766 (1948)) for the preparation of tryptophan. Our melting point (285°) for N-methyltryptophan agrees wth that (289°) of Wieland, Konz and Mittasch (*Ann.*, **513**, 23 (1934)) rather than that (225°) recently reported by Snyder and Eliel (THIS JOURNAL, **70**, 3855 (1948)).

CONVERSE MEMORIAL LABORATORY
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W. M. MCLAMORE

RECEIVED JANUARY 11, 1949

# NEW BOOK

**Microdiffusion Analysis and Volumetric Error.** By EDWARD J. CONWAY, M.B., D.Sc., Professor of Biochemistry, University College, Dublin, and Member of the Royal Irish Academy. Crosby Lockwood and Son, Ltd., 20 Tudor Street, London, E. C. 4, England, 1947. xix + 357 pp. Illustrated. 14 × 22.5 cm. Price 21/- net.

Although the literature shows an ever-increasing application of the microdiffusion principle, the lack of a general description of the technique in books on methodology makes this detailed and carefully written book especially valuable.

Conway was the first to develop the microdiffusion technique to a point where full advantage is taken of the simplicity, accuracy and convenience inherent in this method. By eliminating distillation or aeration in the determination of volatile substances, labor, apparatus and time are saved particularly in serial analyses. It may surprise many that the diffusion time in the micro-ammonia procedure, for example, may be less than thirty minutes and that the accuracy is equal to that of the macro procedure.

The book is divided into three sections. The first deals with the design of the diffusion cell and the factors governing the rate of diffusion. The second section describes critically and in detail most of the published applications of the microdiffusion principle. The last section discusses the factors influencing variable error in volumetric analysis and establishes a rational basis for maintaining macro accuracy in micro procedure. This discussion should be of value to all analysts who wish to maintain given standards of accuracy in volumetric analysis.

JACOB W. DUBNOFF

## BOOKS RECEIVED

November 10, 1948–December 10, 1948

A. D. BOOTH. "Fourier Technique in X-Ray Organic Structure Analysis." Cambridge at the University Press. The Macmillan Company, 60 Fifth Ave., New York 11, N. Y. 1948. 106 pp. $2.75.

LI CH'IAO-P'ING. "The Chemical Arts of Old China." Chemical Education Publications, 2030 Northampton St., Easton, Pa. 1948. 215 pp. $5.00.

ALEXANDER FINDLAY. "A Hundred Years of Chemistry." The Macmillan Company, 60 Fifth Ave., New York 11, N. Y. 1948. 318 pp. $4.50.

R. W. HARMON AND C. B. POLLARD. "Bibliography of Animal Venoms." University of Florida Press, Law Building, Gainesville, Fla. 1948. 340 pp. $8.00.

JOSEPH H. KEENAN AND JOSEPH KAYE. "Gas Tables. (Thermodynamic Properties of Air Products of Combustion and Component Gases. Compressible Flow Functions.)" John Wiley and Sons, Inc., 440 West 44th St., New York 16, N. Y. 1948. 238 pp. $5.00.

HUGH C. MULDOON. "Organic Chemistry." Third Edition. The Blakiston Company, Philadelphia 5, Pa. 1948. 648 pp.

R. T. SANDERSON. "Vacuum Manipulation of Volatile Compounds." John Wiley and Sons, Inc., 440 West 44th St., New York, N. Y. 1948. 162 pp. $3.00.

R. STOOPS, Editor. "Rapports et Discussions sur les Isotopes." 76–78 Coudenberg, Bruxelles. 411 pp.

"Reports of the Biochemical Research Foundation of the Franklin Institute." Vol. IX. 1946–47. Dr. Ellice McDonald, Director. Biochemical Research Foundation, Newark, Del.



JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

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VOLUME 71 FEBRUARY 28, 1949 NUMBER 2

# GIUSEPPE BRUNI

## 1873–1946

BY MARIO A. ROLLIER

Twenty-five years ago, in 1923, the chemists of Yale, Columbia and Ohio Universities, as well as of the Mellon Institute, had the opportunity to hear through the living voice of Giuseppe Bruni a series of lectures[1] which he delivered on "Solid Solutions."

Starting from van't Hoff's theories, Bruni in his lectures gave an extremely cogent exposition of all that was known on the solubility in the solid state at that time and which had been in large part due to his own contributions. He treated the subject from the several points of view of the diffusion in the solid state, the heat of formation of solid solutions, their constitution and the applicability of the laws of solutions to solid solutions. In these lectures and the resulting monograph Bruni condensed the results of twenty-five years of study, research and widespread scientific coöperation on the subject.

Having thus pointed out what is Bruni's chief claim to be remembered in the chemical world, it is timely to add something on his very brilliant scientific and academic career. Bruni was born on August 25, 1873, in Parma (Northern Italy). Immediately after he received his doctor's degree at Parma in 1896, he entered the best Italian School of Chemistry of that period, the Institute of Ciamician at Bologna University, the general trend of his research being already chosen (isomorphism and solid solutions) in his first paper. He remained with Ciamician for ten busy and quiet years, only interrupted by his trip to Germany and the long visit he paid to van't Hoff at Wilmersdorf in 1900–1901. During this decade he had the opportunity of applying the phase rule to the field of concentrated solid solutions, reaching the same results which Bakhuis–Roozeboom had arrived at independently, and gave proof of his clear and synthetic mind in a monograph on the general subject of his research, published in Germany in 1908 under the title "*Feste Lösungen und Isomorphismus.*" A few years before van't Hoff had occasion to pay a tribute to Bruni's contribution in this field, stating:

*Ce savant a contribué d'une partie prépondérante à l'adoption des lois sur les solutions solides et les mélanges isomorphes, qui, sans son intervention auraient été troublées par des notions confuses.*

Many years before Bragg and Laue's discoveries opened the road to modern structural chemistry, Bruni had already said that the distinctive function of the chemist, as compared with the physicist and the mineralogist, was to discover and explain chemical constitution and to use all the available data in the fields of isomorphism, crystallography, energetics, etc., to solve chemistry's central problem, namely, from physical properties of a substance to deduce and to predict the constitution and the actual position of atoms inside its molecules. What already had been van't Hoff's was also Bruni's chief concern: the position of

(1) Published with the same title in *Chem. Rev.*, I, No. 4, January, 1925, page 345.

atoms in space (*Die Lagerung der Atome im Raume*).

In 1907 Bruni was called to the University of Padua as full Professor of General and Inorganic Chemistry, and there he taught and worked for another active decade, advocating in the dispute between the "atomists" and the "energetists," the real existence of atoms and issuing accurate and valuable papers on diffusion in the solid state both in alloys and in ionic salts, and on the limits of validity of the cryoscopic method. The same year he became one of the founders of the periodical of scientific synthesis called "SCIENTIA" in which he was able to secure the active collaboration of such scientists as Russell, van't Hoff, Arrhenius, Nernst, Langevin, Poincaré, Ciamician and many others.

During World War I Bruni entered the arena of industrial chemistry, being first appointed chief consulting chemist and then chief of the Research Laboratories of "Pirelli," the rubber and tires manufacturing company. This appointment was connected with his discovery of ultra-accelerators for rubber vulcanization. Bruni's process of rapid, cold vulcanizing (1919) is based on the formation inside the rubber of N,N-diphenylthiourea (thiocarbanilide) bringing carbon disulfide to act on aniline in the presence of sulfur and zinc oxide. A few months later W. Bedford and W. Scott were obtaining the same results in the Goodyear Laboratories starting from piperidine instead of from aniline.

After the end of the war Bruni traveled extensively on behalf of the Pirelli Company, visiting Java and Malacca in 1921 and, in 1923 staying for a rather long time in the United States where he made connections which he held very dear and which he liked to recall, such as his acquaintance with Dr. Charles L. Parsons, the former Secretary of the American Chemical Society.

To the same period belongs one of the most important achievements of Bruni's scientific leadership: prepared as he was by his past works, he saw the decisive importance of X-ray investigations for the knowledge of the solid state. He sent Professor G. R. Levi, then his assistant, to Professor Debye in Zurich, and shortly thereafter the first laboratory equipped with all the necessary tools for X-ray structural research was operating in Italy at the Polytechnic School of Milan, whither in the meantime Bruni had been called as Professor of General and Inorganic Chemistry. For a little over twenty-five years Bruni was to teach chemistry at this Polytechnic School of Milan, an organization which, though on a smaller scale, comes nearest to something like the Massachusetts Institute of Technology.

Bruni is thus to be regarded as the founder of the Italian school of structural chemistry, to which scientists like G. R. Levi, G. Natta and A. Ferrari, all of them Bruni's students, belong, and which has done good and valuable work and has kept pace, under Bruni's influence and advice, with the developments of the newer techniques of structural research (electron diffraction, infrared spectra, dipole measurements, etc.).

Bruni was extremely brilliant in controversies involving industrial patents. His acute judgment was blended with humor and his advisory help was in great demand both in Italy and abroad. From his experience in this field, in his later years he turned his attention to the problems of intellectual property and in 1935–41 he published a series of papers on patent law, urging international recognition of the principle that "the inventor should have the right to patent an invention *even* if preliminary publications *by him* on the same subject were already circulating in the technical literature" and struggling for the introduction of the "provisional specification" in the Italian patent law.

Two months before Bruni died (January 3, 1946) he sent to the editors of "SCIENTIA" his last contribution, a letter on the large-scale use of nuclear energy in the atomic bomb, in which he hailed the event as the true beginning of a new era upsetting the balance of natural power at the disposal of mankind and scoffed with his customary clear-sightedness at the claims of "secrecy," all the secrecy being a question of industrial development and the theoretical basis of the large-scale transformation of nuclear in lower forms of energy being known. Though still without any connections with scientists of the western world, because of the war, he joined them in their deep concern about nuclear energy, writing:

> By far the most important problem is not that of the industrial applications of atomic energy but another one, which may be looked at with great anxiety. Will not the release of these formidable forces have a general and permanent influence on the world's economic arrangement, on its overall balance, both material and energetic, and on its evolution?

A question certainly yet unanswered.

Bruni earned many recognitions of his high scientific merit. He was awared the King's Prize for Chemistry by the *Academia dei Lincei* in 1913 and was elected a member of the same Academy in 1917. He was a member of the American Chemical Society from 1912, and in 1924 was elected (the only Italian) an Honorary Member of that body. He was a member of many other scientific societies and academies, as well as a member of the Board of Directors and Chairman of the Patent Committee of International Latex Processes Limited.

Bruni's participation in the public life of his country (he was a member of Parliament from 1929 on and was nominated Senator by the King early in 1943) was to end in sheer bitterness because, owing to his awareness and acute sense of responsibility, he foresaw the outcome of many absurdities he was witnessing but was unable to avail against them because his spirit of tolerance and moderation went unheeded in that tragic period. When the dictatorship collapsed in July,

1943, soon to be followed by the collapse of the monarchy, Bruni retired to strictly private life, but the writer received many demonstrations of his sympathy for the new birth of democracy in his country. Bruni's last concern and last working effort in the summer of 1945 were for his book, a treatise on general and inorganic chemistry for student use. In the foreword of the last edition, Bruni had written:

I give this book to the printer not without emotion because, thus enlarged and completed, it represents my scientific legacy.

INSTITUTE OF GENERAL CHEMISTRY
OF THE POLYTECHNIC SCHOOL OF MILAN

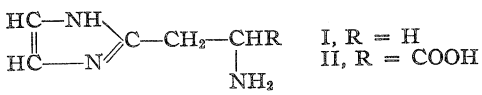
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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Studies on Imidazole Compounds. I. A Synthesis of Imidazoles with Functional Groups in the 2-Position

BY REUBEN G. JONES

In connection with a broad study of possible relationships of chemical structure to biological activity, it was of interest to prepare the isomer (I) of histamine and the isomer (II) of histidine in which the side chains were attached to the 2-position of the imidazole nucleus.




These compounds have been synthesized by a method which appears to be generally applicable to the preparation of a variety of 2-substituted imidazoles. A number of other new members of this little-known class of compounds are also reported at this time.

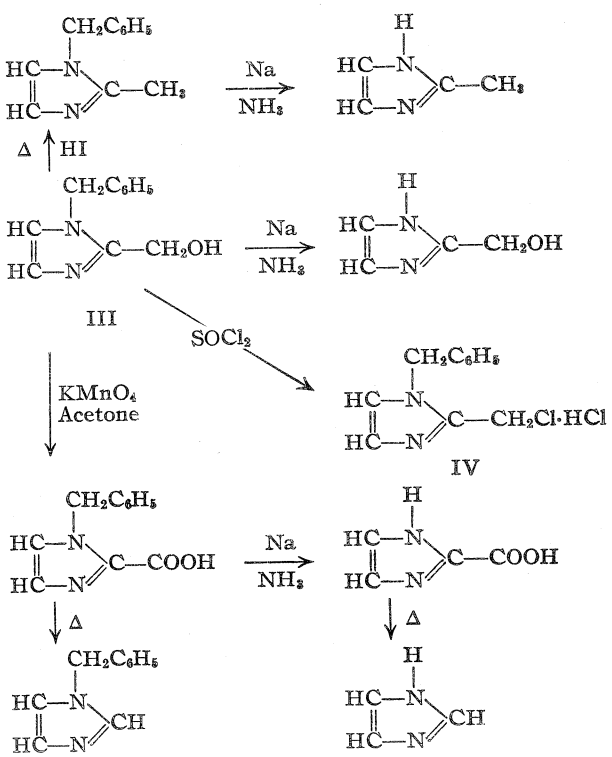
It has been shown[1a,b,c] that certain imidazoles having a methyl group in the 1-position will condense with formaldehyde to yield the corresponding 2-hydroxymethylimidazoles. These compounds can then be converted to a variety of other derivatives.[1b] In the present investigation 1-benzylimidazole has been used as the starting material. When heated with an excess of aqueous formaldehyde, 1-benzylimidazole gave an almost quantitative yield of 1-benzyl-2-hydroxymethylimidazole (III) which was isolated easily as the crystalline hydrochloride. Proof that the hydroxymethyl group entered the 2-position was provided by hydriodic acid reduction of the compound to yield 1-benzyl-2-methylimidazole. This was dissolved in liquid ammonia and treated with sodium to remove the benzyl group according to the method of du Vigneaud and Behrens.[2] The known 2-methylimidazole was thus obtained. It was found that in general these 1-benzylimidazoles are easily debenzylated by the sodium–liquid ammonia method. On the other hand one attempt to cleave the benzyl group by catalytic hydrogenolysis[3] did not meet with success.

(1) (a) Sarasin, *Helv. Chim. Acta*, **6**, 377 (1923). (b) Sonn, Hotes and Sieg, *Ber.*, **57**, 953 (1924). (c) Grindley and Pyman, *J. Chem. Soc.*, 3128 (1927).

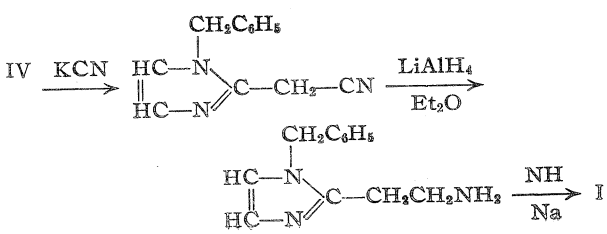
(2) du Vigneaud and Behrens, *J. Biol. Chem.*, **117**, 27 (1937).

(3) Cirkofer, *Ber.*, **75**, 429 (1942).

A number of transformations of 1-benzyl-2-hydroxymethylimidazole (III) are outlined in the reactions

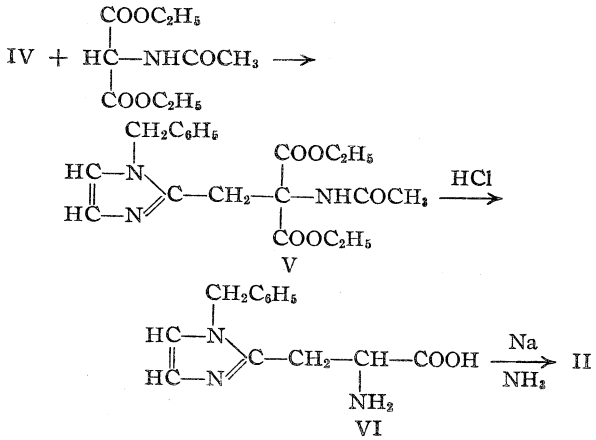



For the synthesis of 2-β-aminoethylimidazole (I), 1-benzyl-2-chloromethylimidazole (IV) was converted to 1-benzyl-2-cyanomethylimidazole. This compound underwent smooth reduction with



lithium aluminum hydride[4] to give 1-benzyl-2-β-aminoethylimidazole which was debenzylated to yield (I).

The amino acid (II) was prepared from (IV) *via* acetamidomalonic ester.[5] The substituted malonic ester (V) was obtained as a sirup which was hydrolyzed directly with hydrochloric acid to form 1-benzyl-2-imidazolealanine (VI). Debenzylation of (VI) with sodium and liquid ammonia led to the desired 2-imidazolealanine (II).




1-Benzyl-2-chloromethylimidazole (IV) underwent normal condensation with sodium malonic ester. The resulting product was converted to 1-benzyl-2-β-carbethoxyethylimidazole which was debenzylated to yield 2-β-carbethoxyethylimidazole.

## Experimental

**1-Benzyl-2-mercaptoimidazole.**—N-Benzylaminoacetal was prepared in 80–85% yield by heating benzylamine with chloroacetal according to the method of Rügheimer and Schön[6] except that a threefold excess of benzylamine was used.

To a mixture of 223 g. (1.0 mole) of N-benzylaminoacetal, 95 g. (1.17 mole) of sodium thiocyanate and 500 ml. of 50% aqueous alcohol was added with stirring 100 ml. (1.2 mole) of 12 *N* hydrochloric acid. The resulting mixture in an open beaker was heated on the steam-bath for five hours during which time most of the alcohol evaporated leaving a violet colored, water insoluble, crystalline mass. The product was dissolved in sodium hydroxide solution. The solution was treated with carbon, filtered and acidified with hydrochloric acid to yield 165 g. (87%) of 1-benzyl-2-mercaptoimidazole. A sample for analysis was recrystallized from ethyl acetate; m. p. 144–145°.

*Anal.* Calcd. for $C_{10}H_{10}N_2S$: N, 14.74. Found: N, 14.75.

**1-Benzylimidazole.**—1-Benzyl-2-mercaptoimidazole (165 g., 0.87 mole) was added in portions to a stirred solution of 200 ml. of concentrated nitric acid in 500 ml. of water maintained at 40–50° by cooling in an ice-bath. When the reaction was complete, the solution was treated with 300 ml. of 12 *N* sodium hydroxide solution. The mixture was extracted with chloroform. The brown oil which remained after evaporation of the dried chloroform solution was distilled at reduced pressure to give 120 g. (87.5% yield) of 1-benzylimidazole; b. p. 187–189° (25 mm.), 166–167° (13 mm.); m. p. 71–72° (lit.[7] 70–71°). The picrate, recrystallized from water, melted at 75–76°.

*Anal.* Calcd. for $C_{16}H_{13}N_5O_7$: N, 18.20. Found: N, 18.00.

**1-Benzyl-2-hydroxymethylimidazole** (III).—A solution of 28 g. (0.177 mole) of 1-benzylimidazole in 45 g. of 40% formalin in a sealed Carius tube was heated at 140° for six hours. The tube was opened, and the colorless liquid was washed out with methanol. The methanol solution was evaporated *in vacuo* on the steam-bath leaving a viscous, colorless sirup which did not crystallize after standing for several days. The sirup was taken up in 100 ml. of alcohol, 25 ml. of 12 *N* hydrochloric acid was added, and the solution was evaporated to dryness in vacuum. The white crystalline residue was dissolved in 100 ml. of boiling absolute alcohol. The solution was cooled somewhat, 200 ml. of anhydrous ether added, then the mixture was chilled. The resulting crystalline product weighed 34.5 g. after air drying, and by working up the filtrate an additional 3.0 g. was obtained bringing the total yield of 1-benzyl-2-hydroxymethylimidazole hydrochloride to 37.5 g. (94.5%), m. p. 159–160°. A sample of the hydrochloride obtained from the picrate (see below) melted at 161.5–162°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O\cdot HCl$: N, 12.47. Found: N, 12.55.

Equally good yields of the 2-hydroxymethyl compound were obtained by heating the 1-benzylimidazole–formalin mixture at 110–120° for fifteen hours instead of 140° for six hours.

1-Benzyl-2-hydroxymethylimidazole picrate obtained in 85% yield from the sirupy free base and hot aqueous picric acid melted at 132–133° after recrystallization from water.

*Anal.* Calcd. for $C_{17}H_{15}N_5O_8$: N, 16.78. Found: N, 16.72.

**1-Benzyl-2-methylimidazole and 2-Methylimidazole.**—A mixture of 10.0 g. (0.045 mole) of 1-benzyl-2-hydroxymethylimidazole hydrochloride, 1.3 g. of red phosphorus and 25 ml. of hydriodic acid (sp. gr. 1.7) in a sealed tube was heated at 160° for five hours. The contents of the tube were filtered, and the clear colorless filtrate was evaporated to a sirup. This was treated with excess 12 *N* sodium hydroxide solution and the mixture extracted with benzene. After drying over sodium carbonate the benzene was distilled and the residual product distilled *in vacuo* to yield 6.5 g. (85%) of 1-benzyl-2-methylimidazole as a colorless viscous liquid b. p. 125–127° (3 mm.). The picrate crystallized from water as bright yellow needles; m. p. 153–154°.

*Anal.* Calcd. for $C_{17}H_{15}N_5O_7$: N, 17.45. Found: N, 17.70.

To a solution of 6.0 g. (0.035 mole) of the above 1-benzyl-2-methylimidazole in 150 ml. of liquid ammonia was added sodium metal in small pieces until a permanent blue color was formed. This required 1.7 g. of sodium. The mixture was treated with 5 g. of ammonium chloride, and, after the ammonia had been removed by gentle warming, the residue was extracted with 200 ml. of hot benzene. Evaporation of this solution left 2.65 g. (92.5% yield) of 2-methylimidazole, m. p. 130–132°. The crude product was sublimed *in vacuo* and then recrystallized from benzene–petroleum ether to give white needles melting at 140–141°. Authentic 2-methylimidazole melted at 140.5–141.5° (lit.[8] 136–137°), and the mixed melting point was also 140.5–141.5°.

**2-Hydroxymethylimidazole.**—A solution of 19 g. (0.10 mole) of the crude sirupy 1-benzyl-2-hydroxymethylimidazole in 150 ml. of liquid ammonia was treated with small pieces of sodium metal until a permanent blue color was formed (6.8 g. of sodium). Then 25 g. of ammonium

(4) Nystrom and Brown, THIS JOURNAL, **69**, 1147 (1947). Private communication, Metal Hydrides Incorporated, Beverly, Massachusetts.

(5) Albertson and Archer, THIS JOURNAL, **67**, 308 (1945).

(6) Rügheimer and Schön, *Ber.*, **41**, 17 (1908).

(7) Wallach, *ibid.*, **16**, 539 (1883).

(8) Dedichen, *ibid.*, **39**, 1838 (1906).

chloride was added in small portions after which the mixture was allowed to evaporate to dryness. The residue was extracted with 200 ml. of boiling absolute alcohol. This solution was evaporated *in vacuo* to about 50 ml., filtered and the filtrate evaporated *in vacuo* to yield a sirup which could not be induced to crystallize. The sirup was dissolved in 25 ml. of water, and this solution was added to a hot solution of 25 g. of picric acid in one liter of boiling water. Nothing separated when the solution was cooled to room temperature, but after standing overnight 19 g. of large cubic crystals was deposited. This product, m. p. 144–145°, was recrystallized from 100 ml. of absolute alcohol to yield 15.5 g. (47.5%) of 2-hydroxymethylimidazole picrate as yellow needles, m. p. 151–152°.

*Anal.* Calcd. for $C_{10}H_9N_5O_8$: N, 21.41. Found: N, 21.42.

A mixture of 15.0 g. (0.046 mole) of the above picrate, 25 ml. of nitrobenzene and 25 ml. of 6 *N* hydrochloric acid in a small separatory funnel was shaken until all solid had dissolved. The nitrobenzene layer was drawn off, and the aqueous solution was washed with four 25-ml. portions of chloroform. The water solution was evaporated to dryness *in vacuo*. To the residue was added 50 ml. of absolute alcohol and again the mixture was evaporated to dryness *in vacuo* at 100°. The residue was dissolved in 25 ml. of hot absolute alcohol, and this solution was diluted with dry ether whereupon 6.1 g. (98% yield) of 2-hydroxymethylimidazole hydrochloride separated as white needles; m. p. 111–113°. The product was not hygroscopic.

*Anal.* Calcd. for $C_4H_6N_2O{\cdot}HCl$: N, 20.82. Found: N, 20.80.

**1-Benzyl-2-imidazolecarboxylic Acid.**—A solution of 19 g. (0.10 mole) of crude 1-benzyl-2-hydroxymethylimidazole in 200 ml. of acetone was cooled in an ice-bath and stirred while 22 g. (0.14 mole) of 100-mesh potassium permanganate was added in small portions during one-half hour. The temperature was maintained at 5–10°, and the mixture was stirred for one additional hour. The acetone was removed by evaporation at reduced pressure and the black residue was extracted with two one-liter portions of hot water. Evaporation *in vacuo* of the water solution left a white solid. The product was washed with chloroform and then recrystallized from absolute alcohol–ether to yield 13 g. of white crystalline solid which appeared to be a hydrated potassium salt; m. p. 94–96° with shrinking at 75–80°. No satisfactory analyses were obtained.

The above salt (12.0 g.) was dissolved in 20 ml. of water and the clear solution was treated with concentrated hydrochloric acid until the *p*H was about 2.0. The crystalline precipitate was collected on a filter and air dried. It weighed 9.5 (43% yield); m. p. 103–104° (dec.). A sample recrystallized from water melted at 106° (dec.). The analytical sample was dried *in vacuo* at 60° for one hour.

*Anal.* Calcd. for $C_{11}H_{10}N_2O_2.H_2O$: N, 12.72; neut. equiv., 220.2. Found: N, 12.54; neut. equiv., 213.

The acid decarboxylated very readily at the melting point, and even in hot water it slowly evolved carbon dioxide. A 1.0 g. portion was decarboxylated by melting, and the resulting product was sublimed *in vacuo* to yield 0.79 g. (99%) of 1-benzylimidazole, m. p. 72–73°; mixed with an authentic sample, m. p. 72–73°.

**2-Imidazolecarboxylic Acid.**—In 50 ml. of liquid ammonia was suspended 4.4 g. (0.02 mole) of 1-benzyl-2-imidazolecarboxylic acid monohydrate. Sodium in small pieces was added until a permanent blue color resulted (1.0 g. of sodium). The blue color was discharged with a little ammonium chloride, and the solution was evaporated to dryness, finally by gentle warming *in vacuo*. The residue was taken up in 25 ml. of water. The cloudy solution was stirred with a little carbon, filtered and acidified to *p*H 2.0 with concentrated hydrochloric acid. Soon the 2-imidazolecarboxylic acid separated as silvery platelets which, after cooling the mixture for one hour in an ice-bath, were collected on a filter and air dried. The yield was 1.95 g. (87%). A sample recrystallized from 80% alcohol melted at 163–164° (dec.).

*Anal.* Calcd. for $C_4H_4N_2O_2$: N, 25.00; neut. equiv., 112.09. Found: N, 24.53; neut. equiv., 113.5.

A 0.2 g. sample of the acid in a sublimation apparatus was heated until decarboxylation was complete, and the resulting imidazole was sublimed *in vacuo*. The yield was 0.1 g., m. p. 85–86°. A mixture with authentic imidazole melted at 87–88°.

**1-Benzyl-2-chloromethylimidazole (IV).**—To 60 ml. of thionyl chloride was added in small portions 68 g. (0.30 mole) of 1-benzyl-2-hydroxymethylimidazole hydrochloride. Reaction took place immmediately with heat evolution, and a clear solution resulted. The solution was heated on the steam-bath for fifteen minutes, and then the excess thionyl chloride was distilled under reduced pressure on the steam-bath. The residual crystalline 1-benzyl-2-chloromethylimidazole hydrochloride was washed with dry ether and air dried. It weighed 73 g. (100% yield), m. p. 181–182°.

*Anal.* Calcd. for $C_{11}H_{11}N_2Cl{\cdot}HCl$: N, 11.53; Cl, 29.17. Found: N, 11.76; Cl, 28.86.

**1-Benzyl-2-cyanomethylimidazole.**—A solution of 90 g. of potassium cyanide in 100 ml. of water was cooled to 5° and with continuous stirring a solution of 37 g. (0.15 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride in 250 ml. of absolute alcohol was added during a period of one hour. The mixture was stirred at room temperature for three hours, then filtered and the salt washed with two 200-ml. portions of alcohol. The total filtrate was evaporated *in vacuo* to small volume and extracted with three 300-ml. portions of chloroform. The chloroform solution was washed with dilute sodium hydroxide solution, dried over magnesium sulfate and evaporated to dryness *in vacuo*. A brown oil remained which quickly crystallized. This crude product which melted over the range 65–80° was dissolved in 150 ml. of hot absolute alcohol and to it was added a solution of 35 g. of picric acid in 150 ml. of hot absolute alcohol. A brown oil separated which soon crystallized. The mixture was cooled to 70°, and the 1-benzyl-2-cyanomethylimidazole picrate was collected on a filter. It was washed by suspension in 100 ml. of warm absolute alcohol and air dried. The yield was 17.5 g. (27.5%), m. p. 160–162°.

In other runs lower temperatures and longer reaction periods were employed, but the yield could not be improved.

The above picrate was soluble in acetone or chloroform, sparingly soluble in absolute alcohol, insoluble in boiling water. A sample recrystallized from absolute alcohol melted at 166–167°.

*Anal.* Calcd. for $C_{18}H_{14}N_6O_7$: N, 19.72. Found: N, 19.48.

The picrate (23 g., 0.054 mole) was rubbed to a fine powder and placed in a separatory funnel with 160 ml. of nitrobenzene and 100 ml. of cold 6 *N* hydrochloric acid. The mixture was vigorously shaken until all solid had disappeared. After the nitrobenzene layer had been separated the aqueous solution was washed with three 75-ml. portions of chloroform. The nitrobenzene and chloroform solutions were then extracted with another 50 ml. portion of cold 6 *N* hydrochloric acid. The combined hydrochloric acid solution was immediately neutralized with excess sodium carbonate. The resulting mixture was extracted with four 50-ml. portions of chloroform. This chloroform extract was dried with magnesium sulfate and evaporated to dryness *in vacuo* leaving 10.3 g. (97% yield) of 1-benzyl-2-cyanomethylimidazole as a white, hard, crystalline solid, m. p. 114–115°. It was readily soluble in benzene, moderately soluble in hot petroleum ether.

*Anal.* Calcd. for $C_{12}H_{11}N_3$: N, 21.31. Found: N, 21.04.

**1-Benzyl-2-β-aminoethylimidazole.**—Eleven grams (0.056 mole) of powdered 1-benzyl-2-cyanomethylimidazole was placed in the thimble of a Soxhlet extractor above a boiling solution of 5 g. (0.13 mole) of lithium aluminum

hydride[4,9] in 500 ml. of dry ether. After about three hours, when all of the cyano compound had been dissolved and carried down into the lithium aluminum hydride solution, the latter was treated with 10 ml. of water, added dropwise, followed by 50 ml. of 12.5 *N* sodium hydroxide solution. The mixture was vigorously stirred for about one hour and then the ether was decanted into a clean flask. The mixture was extracted twice more by vigorously stirring with 300 ml. portions of ether. The total ether solution was dried with potassium carbonate and concentrated. Distillation of the residual liquid *in vacuo* gave 9.7 g. (88% yield) of 1-benzyl-2-β-aminoethylimidazole as a viscous colorless liquid, b. p. 161–163° (0.7 mm.), which crystallized to a hard, white, hygroscopic solid, m. p. 59–60°. The dipicrate, prepared in absolute alcohol, melted at 185–186°.

*Anal.* Calcd. for $C_{24}H_{21}N_9O_{14}$: N, 19.14. Found: N, 19.26.

The dihydrochloride, m. p. 224–225°, was soluble in water, absolute alcohol, insoluble in ether, and it was not hygroscopic.

*Anal.* Calcd. for $C_{12}H_{15}N_3 \cdot 2HCl$: N, 15.33. Found: N, 14.97.

**2-β-Aminoethylimidazole (I).**—A solution of 9.2 g. (0.046 mole) of 1-benzyl-2-β-aminoethylimidazole in 100 ml. of liquid ammonia was treated with 2.15 g. of sodium metal. Then 2.7 g. (0.05 mole) of ammonium chloride was added, and the ammonia was allowed to evaporate. Sodium carbonate (3 g.) and 25 ml. of water were added. The solution was evaporated to dryness *in vacuo* on the steam-bath, and the residue was extracted with two 100-ml. portions of hot absolute alcohol. This was evaporated *in vacuo* leaving a viscous oil which was dissolved in 25 ml. of water and the resulting solution was added to a solution of 30 g. of picric acid in 800 ml. of hot water. After the mixture had cooled to room temperature, the crystalline picrate was collected on a filter and recrystallized in two portions from 500 ml. of water. There was thus obtained 21 g. (80% yield) of 2-β-aminoethylimidazole dipicrate, m. p. 213–214° (dec.).

*Anal.* Calcd. for $C_{17}H_{15}N_9O_{14}$: N, 22.14. Found: N, 22.18.

The above picrate (21 g., 0.037 mole) was decomposed with 6 *N* hydrochloric acid using nitrobenzene in the usual manner, and there was obtained 6.7 g. (98% yield) of 2-β-aminoethylimidazole dihydrochloride, m. p. 229–230°. It was very sparingly soluble in hot absolute alcohol.

*Anal.* Calcd. for $C_5H_9N_3 \cdot 2HCl$: N, 22.83. Found: N, 22.46.

**1-Benzyl-2-imidazolealanine (VI).**—A solution was prepared by adding 87 g. (0.40 mole) of acetamidomalonic ester to 250 ml. of absolute alcohol in which had been dissolved 13.8 g. (0.60 g. atom) of sodium. This solution was cooled in an ice-bath and to it was added during one-half hour 49 g. (0.20 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride dissolved in 350 ml. of absolute alcohol. The mixture was stirred for two hours at room temperature and then evaporated *in vacuo* on the steam-bath to remove most of the alcohol. The residue was dissolved in 400 ml. of ice-cold 2 *N* hydrochloric acid. This solution was extracted with four 200-ml. portions of ethyl acetate to remove the unchanged acetaminomalonic ester. The water solution was neutralized with excess sodium carbonate and extracted with three 200-ml. portions of ether. The ether solution was dried and evaporated leaving the 1-benzyl-2-imidazolemethylacetaminomalonic ester as a glass which did not crystallize.

The product was dissolved in 200 ml. of 12 *N* hydrochloric acid and the solution heated on the steam-bath for sixteen hours. Evaporation of this solution left a glass-like product which could not be induced to crystallize. It was dissolved in 200 ml. of water and the solution was brought to *p*H 8.15 with sodium hydroxide. This solution was evaporated *in vacuo* almost to dryness, and the residue was extracted with 500 ml. of hot 90% alcohol. The alcohol extract was evaporated in an open beaker to a volume of about 200 ml. After standing and cooling it deposited 24 g. of white crystalline solid; m. p. 203–204°. The solid was washed by suspension in 100 ml. of absolute alcohol and then in 25 ml. of water in which it was somewhat soluble. It was recrystallized from 140 ml. of 70% alcohol to yield 19.5 g. (38.4%) of 1-benzyl-2-imidazolealanine hemihydrate, m. p. 216–217° (dec.).

*Anal.* Calcd. for $C_{13}H_{15}N_3O_2 \cdot {}^1/_2H_2O$: C, 61.40; H, 6.34. Found: C, 61.27; H, 6.68.

**2-Imidazolealanine (II).**—A solution of 12.7 g. (0.05 mole) of 1-benzyl-2-imidazolealanine in 100 ml. of liquid ammonia was treated with sodium as described above. The residue, after evaporation of the ammonia, was dissolved in 50 ml. of water, and the solution was brought to *p*H 8.0 by the careful addition of concentrated hydrochloric acid. The white crystalline precipitate, 5.3 g. (68.5% yield crude), was recrystallized from 70 ml. of water using carbon to decolorize the solution. There was obtained 4.4 g. (57% yield) of pure 2-imidazolealanine, m. p. 254–255° (dec.).

*Anal.* Calcd. for $C_6H_9N_3O_2$: N, 27.05. Found: N, 26.81.

**1-Benzyl-2-β-carbethoxyethylimidazole.**—1-Benzyl-2-chloromethylimidazole hydrochloride was caused to condense with sodiomalonic ester in a manner similar to that described above for the condensation with sodioacetamidomalonic ester. The resulting crude 1-benzyl-2-imidazolemethylmalonic ester was heated with concentrated hydrochloric acid, and the sirupy 1-benzyl-2-β-carboxyethylimidazole hydrochloride thus obtained was esterified with absolute alcoholic hydrogen chloride to give 1-benzyl-2-β-carbethoxyethylimidazole in an over-all yield of 83%. It distilled at 164–166° (0.3 mm.) $n^{25}D$ 1.5352.

*Anal.* Calcd. for $C_{15}H_{18}N_2O_2$: N, 10.85. Found: N, 10.60.

**2-β-Carbethoxyethylimidazole.**—1-Benzyl-2-β-carbethoxyethylimidazole (20.8 g., 0.08 mole) in 300 ml. of liquid ammonia was debenzylated with sodium. After evaporation of the ammonia the product was extracted from the residue with chloroform. There was obtained 9.5 g. of crude product which was recrystallized from benzene–petroleum ether to yield 8.1 g. (60%) of 2-β-carbethoxyethylimidazole, m. p. 103–104°.

*Anal.* Calcd. for $C_8H_{12}N_2O_2$: N, 16.66. Found: N, 16.94.

An attempt to remove the benzyl group from 1-benzyl-2-β-carbethoxyethylimidazole by hydrogenolysis in glacial acetic acid using Adams catalyst was not successful. Although the theoretical quantity of hydrogen was absorbed no toluene was split off. Presumably the material underwent partial hydrogenation.

**Acknowledgment.**—The author is grateful to K. C. McLaughlin for valuable assistance and to W. L. Brown and H. L. Hunter for the microanalyses reported herein.

## Summary

A method for the preparation of 2-substituted imidazoles has been described.

The isomers of histamine and histidine and a number of other 2-substituted imidazole compounds have been prepared and characterized.

(9) Obtained from Metal Hydrides, Inc., Beverly, Massachusetts.

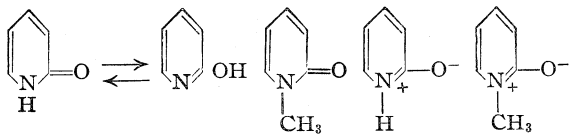
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Triarylpyridylmethanes

BY ROGER ADAMS, JACK HINE AND JOHN CAMPBELL

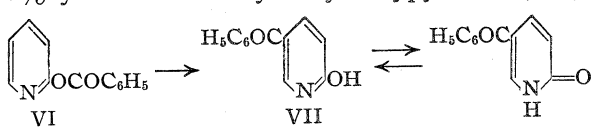
The absorption spectra of 2-pyridone (I) or its tautomer, 2-hydroxypyridine (II) and 1-methyl-2-pyridone (III) are very similar and suggest an analogous formulation. A considerable contribution of a "Zwitterion" resonance form of each (IV and V) to the total structure of the molecules is compatible with the physical properties of the compounds.[1]



I II III IV V

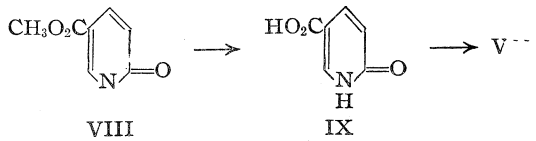
If this proposal is correct, analogous chemical reactivity of IV and V might be anticipated. Such similarity is exemplified in the halogenation,[2,3] nitration,[3,4] sulfonation[5] and arsonation[6] of 1-methyl-2-pyridone which leads to 5-mono- or 3,5-disubstituted products analogous to those obtained from 2-pyridone or 2-hydroxypyridine with the same reagents. Attempts to apply the Friedel and Crafts reaction with acyl and aroyl halides failed probably because of the complexing of the catalysts, aluminum chloride or boron trifluoride, with the pyridones. Thiocyanation and nitrosation were also unsuccessful.

The application of the Fries rearrangement to the O-benzoate of 2-hydroxypyridine (VI) under the conditions used of fusion of the benzoate with anhydrous aluminum chloride gave only a 1% yield of 5-benzoyl-2-hydroxypyridine (VII).



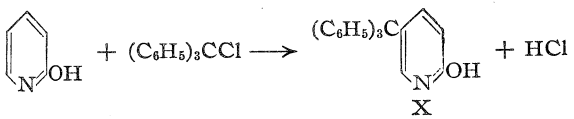
VI VII

The structure of VII was proved by an unequivocal method. Methyl coumalinate (VIII) prepared by esterification of coumalinic acid formed from maleic acid, was converted by ammonia followed with alkali to 2-hydroxypyridine-5-carboxylic acid (IX). This was transformed to VII through the acid chloride and condensation with benzene in the presence of aluminum chloride.



VIII IX

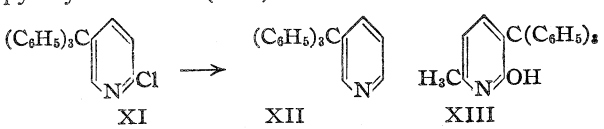
2-Hydroxypyridine or 2-pyridone and 1-methyl-2-pyridone both condensed readily with triphenylchloromethane without catalyst or with triphenylcarbinol in the presence of a little sulfuric acid merely by heating. The N-methyl group in the latter was lost and the same product resulted, 5-triphenylmethyl-2-hydroxypyridine (X). The position of the triphenylmethyl radical is assumed on the basis of that taken by other groups when substituted in 2-hydroxypyridine. Thus, the reaction resembles that which



X

occurs between triphenylchloromethane or triphenylcarbinol and phenols or aromatic amines. The carbonium ions so readily formed from triphenylmethyl derivatives may account for the ease of substitution.

5-Triphenylmethyl-2-hydroxypyridine is transformed almost quantitatively by the action of phosphorus oxychloride in a sealed tube to 5-triphenylmethyl-2-chloropyridine (XI). The latter upon catalytic reduction yields triphenylpyridylmethane (XII).



XI XII XIII

The reaction appears to be a fairly general one. Triphenylchloromethane reacts readily with 3-methyl-2-hydroxypyridine, and diphenylxenylchloromethane or the corresponding carbinol reacts with 2-hydroxypyridine and with its 3-methyl derivative. The yields were 45–60% in all cases. 6-Methyl-2-hydroxypyridine, however, condenses with triphenylchloromethane to give only a 9% yield of product although with the carbinol a 22% yield results. It is assumed that the triphenylmethyl group has probably entered the 3-position (XIII) in this case since the condensation product unlike all the others could not be converted to the chloropyridine and is insoluble in aqueous ethanolic sodium hydroxide, presumably because of the steric hindrance of the *o*-triphenylmethyl group.

5-Triphenylmethyl-2-hydroxypyridine reacts similarly to 2-hydroxypyridine with organic

(1) Specker and Gaurosch, *Ber.*, **75B**, 1338 (1942); see also Baker and Baly, *J. Chem. Soc.*, **91**, 1126 (1906); v. Auwers, *Ber.*, **63B**, 2111 (1936); Arndt and Kalischek, *ibid.*, **63B**, 587 (1930); Arndt, *ibid.*, **63B**, 2963 (1930); Hückel, *Z. Elektrochem.*, **43**, 752 (1937).

(2) Dohrn and Thiele, German Patent 500,915; *Frdl.*, **17**, 2440 (1932).

(3) Fischer and Chur, *J. prakt. Chem.*, [2] **93**, 363 (1916).

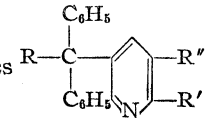
(4) Chichibabin and Konowalowa, *Ber.*, **58**, 1712 (1925).

(5) (a) v. Schickh, German Patent 601,896; *Frdl.*, **21**, 517 (1937); (b) Naegeli, Kündig and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938); Haack, German Patent 597,452; *Frdl.*, **21**, 518 (1937).

(6) Binz, Räth and Maier-Bode, *Ann.*, **478**, 22 (1930).

TABLE I

TRIARYLPYRIDYLMETHANES



| R | R′ | R″ | Yield, % | Solvent[a] for rexl. | M. p.,[b] °C. (cor.) | Formula | Percentage composition: Calcd. C | Calcd. H | Calcd. N | Calcd. Cl | Found C | Found H | Found N | Found Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$– | –OH | –H | 48 | A | 365–368 | $C_{24}H_{19}ON$ | 85.43 | 5.68 | 4.15 | | 85.18 | 6.02 | 4.15 | |
| $C_6H_5$– | –OH | $–CH_3$ | 54 | E | 260–262 | $C_{25}H_{21}ON$ | 85.43 | 6.02 | 4.00 | | 85.23 | 6.22 | 4.18 | |
| $p$-$C_6H_5C_6H_4$– | –OH | –H | 58 | B | 298–300 | $C_{30}H_{23}ON$ | 87.13 | 5.61 | 3.39 | | 87.04 | 5.86 | 3.21 | |
| $p$-$C_6H_5C_6H_4$– | –OH | $–CH_3$ | 56 | B, E | 307–310 | $C_{31}H_{25}ON$ | 87.08 | 5.89 | 3.28 | | 87.14 | 6.13 | 3.46 | |
| $C_6H_5$– | –Cl | –H | 88 | B, E | 256–257 | $C_{24}H_{18}NCl$ | 81.00 | 5.10 | 3.94 | 9.96 | 81.03 | 4.92 | 3.84 | 9.78 |
| $C_6H_5$– | –Cl | $–CH_3$ | 92 | L | 130[c] | $C_{25}H_{20}NCl$ | 81.18 | 5.45 | 3.79 | | 81.41 | 5.20 | 4.01 | |
| $p$-$C_6H_5C_6H_4$– | –Cl | –H | 95 | B, L | 182–183 | $C_{30}H_{22}NCl$ | 83.41 | 5.13 | 3.24 | 8.21 | 83.59 | 5.42 | 3.23 | 8.05 |
| $p$-$C_6H_5C_6H_4$– | –Cl | $–CH_3$ | 93 | E | 158–159 | $C_{31}H_{24}NCl$ | 83.48 | 5.42 | 3.14 | 7.95 | 83.20 | 5.62 | 2.90 | 8.00 |
| $C_6H_5$– | –H | –H | 66 | B, E | 269–270 | $C_{24}H_{19}N$ | 89.68 | 5.96 | 4.36 | | 89.45 | 6.30 | 4.51 | |
| $C_6H_5$– | –H | $–CH_3$ | 83 | E | 153–154 | $C_{25}H_{21}N$ | 89.51 | 6.31 | 4.18 | | 89.54 | 6.24 | 4.40 | |
| $p$-$C_6H_5C_6H_4$– | –H | –H | 91 | E | 195–196 | $C_{30}H_{23}N$ | 90.64 | 5.83 | 3.53 | | 90.22 | 5.93 | 3.40 | |
| $p$-$C_6H_5C_6H_4$– | –H | $–CH_3$ | 91 | E | 188–189 | $C_{31}H_{25}N$ | 90.48 | 6.12 | 3.40 | | 90.23 | 6.23 | 3.55 | |

[a] Solvents as follows: A = glacial acetic acid, B = benzene, E = absolute ethanol, L = ligroin (b. p. 80–110°). Combinations denote recrystallization from mixed solvents. [b] All melting points above 200° were taken in a melting point block. [c] Double m. p.—solidified and remelted at 151–152°.

halides in alkaline solution. It is converted with potassium hydroxide and chloroacetic acid into N-carboxymethyl-5-triphenylmethyl-2-pyridone.

Triphenylpyridylmethane, like tetraphenylmethane, has a high melting point of 269–270°. Its solubility characteristics are likewise almost identical, insoluble in ether and petroleum ether, very slightly soluble in hot ethanol and glacial acetic acid and soluble in hot benzene.

It exhibits a marked phosphorescence after irradiation with ultraviolet light at room temperature. The brilliant blue-green afterglow from tetraphenylmethane has a visible duration of twenty-three seconds[7] and the greenish-white afterglow from triphenylpyridylmethane only one second.

The infrared absorption spectra of triphenylpyridylmethane and tetraphenylmethane are similar as shown in Chart I. In the infrared absorption spectra the CH deformational frequencies (1450, 1470 cm.$^{-1}$) and phenyl frequencies (1490, 1598 cm.$^{-1}$) are almost identical. Curve II shows additional absorption characteristics of the pyridine at 1412, 1570 and 1588 cm.$^{-1}$.

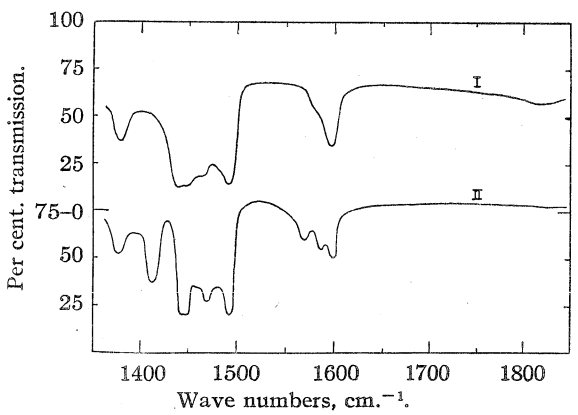



Fig. 1.—Curve I, tetraphenylmethane; Curve II, triphenyl-$\beta$-pyridylmethane. Both compounds were examined in mineral oil paste.

(7) Clapp, THIS JOURNAL, **61**, 523 (1939).

The properties of the various pyridones and pyridines are recorded in Table I.

## Experimental

**2-Pyridyl-$p$-nitrobenzenesulfonate.**—To 7.3 g. of melted $p$-nitrobenzenesulfonyl chloride was added slowly 3.86 g. of anhydrous sodium 2-hydroxypyridine. An exothermic reaction occurred. When this had subsided, the vessel was heated and the contents stirred, dissolved in benzene, filtered, and petroleum ether added to the cloud point. The solution was cooled, and the light yellow crystals which were removed by filtration weighed 7.4 g. (80%). Decolorization with Norit and two recrystallizations from benzene yielded material of m. p. 157–160° (cor.).

*Anal.* Calcd. for $C_{11}H_8O_5N_2S$: C, 47.17; H, 2.87; N, 10.00. Found: C, 47.33; H, 2.92; N, 9.83.

**2-Pyridyl Benzoate from Sodium 2-Hydroxypyridine and Benzoyl Chloride.**—This compound was prepared by a method somewhat different from any of the three used by Chichibabin and Oparina.[8] To 11.7 g. of anhydrous sodium 2-hydroxypyridine was added 15.0 g. of freshly redistilled benzoyl chloride. Heat was evolved, and a reddish color developed. The material was heated to 200° for an hour to complete the reaction and then distilled in vacuum. After a slight forerun, most of the remainder of the material was collected at 180–190° (25 mm.). The colorless liquid crystallized to a white solid which weighed 17 g. (85%) and melted at 35–40°.

**2-Pyridyl Benzoate from Benzoyl Chloride and 2-Hydroxypyridine in Pyridine.**—A solution of 14.1 g. of freshly redistilled benzoyl chloride and 4.75 g. of 2-hydroxypyridine in 39.5 (0.5 mole) of pyridine was refluxed for three hours. The solution was then distilled until the overhead temperature reached 120° in order to remove most of the pyridine. The residue was poured on ice and the mixture extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and distilled under vacuum. The material distilling between 180–195° (30

(8) Chichibabin and Oparina, *J. Russ. Phys.-Chem. Soc.*, **56**, 153 (1925).

mm. pressure) was collected and found to weigh 9.0 g. (90%). The yellow liquid began to crystallize when cooled to 30°, and was completely solid at 15°. It was identified as 2-pyridyl benzoate by its boiling point and by hydrolysis to benzoic acid. No crystals were obtained from the small amount of residue from the vacuum distillation.

**Fries Reaction with 2-Pyridyl Benzoate.**—To 11.1 g. of 2-pyridyl benzoate (m. p. 35–40°) was added 27 g. of freshly resublimed aluminum chloride. The material was stirred and heated by an oil-bath which was maintained at 180° for three hours. After the reaction mixture had cooled it was poured on ice. At this point the odor of benzoyl chloride was quite evident. The aqueous suspension was boiled and filtered. The precipitate was extracted with ether and filtered. The ether solution in turn was extracted with sodium bicarbonate in order to remove benzoic acid. The ether was evaporated, and the residue dried in a vacuum desiccator. It was then recrystallized from a mixture of chloroform and ligroin, yielding 0.09 g. (0.81%) of brown crystals melting at 152–170° (cor.). These were sublimed in vacuum at about 160° to give cream colored crystals, which were recrystallized from aqueous ethanol to give almost white crystals sintering at 188° and melting at 194–196° (cor.). The melting point of a mixture of this material with the 5-benzoyl-2-hydroxypyridine prepared from 2-hydroxypyridine-5-carboxylic acid showed no depression. The infrared spectra of the two compounds were identical.

*Anal.* Calcd. for $C_{12}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.36; H, 4.54; N, 7.07.

**5-Benzoyl-2-hydroxypyridine.**—This was prepared from 2-hydroxypyridine-5-carboxylic acid in a manner analogous to the synthesis by Kirpal[9] of 3-benzoyl-2-hydroxypyridine from 2-hydroxypyridine-3-carboxylic acid. To 1.05 g. of 2-hydroxypyridine-5-carboxylic acid[10] was added 3.5 g. of thionyl chloride. The mixture was maintained at a temperature of 80° for forty minutes; then the excess thionyl chloride was removed under vacuum. The acid chloride, after cooling, solidified. It was covered with 17.4 g. of benzene, and 8.0 g. of white, freshly resublimed aluminum chloride was added in several portions with stirring. The solution was refluxed for two hours, cooled, and poured on ice. The resulting solution was steam-distilled to remove the benzene, concentrated and filtered. The precipitate was decolorized with Norit and recrystallized from aqueous ethanol to give 1.0 g. (66%) of yellow crystals. These were sublimed in vacuum at 160°, and recrystallized from aqueous ethanol to give white crystals, m.p. 194–196° (cor.).

**2-Chloropyridine-5-sulfonyl Chloride.**—To a flask containing 13.5 g. of carefully dried 1-methyl-2-pyridone-5-sulfonic acid[5a] was added 26 g. of phosphorus pentachloride. The flask was heated in an oil-bath. When the temperature reached 110° liquid started to form, and gas was evolved so rapidly that a little material was lost. The oil-bath was kept at a temperature of 125° for two hours, at which time the evolution of gas had almost ceased. The mixture was then cooled to 0°, ground with ice, filtered, dried and found to weigh 11.35 g. (76%). Two recrystallizations from mixtures of petroleum ether (b.p. 50–80°) and benzene yielded white crystals of m.p. 50–51° (cor.). Naegeli, Kündig and Brandenburger[5b] report a melting point of 51.5°.

*Anal.* Calcd. for $C_5H_3O_3Cl_2NS$: C, 28.30; H, 1.51; N, 6.60. Found: C, 28.35; H, 1.48; N, 6.70.

**2-Chloropyridine-5-sulfonamide.**—To 11.35 g. of 2-chloropyridine-5-sulfonyl chloride was added 200 ml. of concentrated aqueous ammonia. The mixture was then heated to boiling while 200 ml. of additional concentrated aqueous ammonia was added. The solution was concentrated to 200 ml. and allowed to cool. The white crystals were removed by filtration, dried and found to weigh 6.79 g. (66%). Recrystallization from aqueous ethanol yielded crystals of m.p. 157–159° (cor.). This is the same melting point reported by Naegeli, Kündig and Brandenburger.[5b]

**2-Chloropyridine-5-(N-2-pyridyl-sulfonamide).**—To 0.140 g. of 2-chloropyridine-5-sulfonyl chloride dissolved in 5 ml. of benzene was added a solution of 0.23 g. of 2-aminopyridine in 5 ml. of benzene. The solution was evaporated and petroleum ether added until most of the benzene had been removed. It was then cooled in the ice-box, collected by filtration, dried, and washed with water to remove aminopyridine and its salts. The product weighed 0.12 g. (66%). Two recrystallizations from ethanol yielded material of m.p. 237–239° (cor.). Chichibabin and Vialatout[11] did not report a melting point.

**2-Methoxypyridine-5-sulfonamide.**—To a solution of 3 g. of sodium in 50 ml. of methanol, 6.76 g. of 2-chloropyridine-5-sulfonamide was added. The solution was refluxed for about sixty hours, most of the methanol was evaporated, water was added, the solution again concentrated, cooled overnight and filtered. The dark brown odoriferous material obtained was decolorized with Norit and recrystallized from water to yield 5.06 g. (77%). Further decolorization and recrystallization from water yielded white crystals, m.p. 149–150° (cor.).

*Anal.* Calcd. for $C_6H_9O_3N_2S$: C, 38.29; H, 4.28; N, 14.89. Found: C, 38.54; H, 4.27; N, 14.79.

**5-Triarylmethyl-2-hydroxypyridines.**—The reaction was carried out in the same fashion in all cases, by heating the 2-hydroxypyridines with the triarylchloromethane or with the triarylcarbinol and a few drops of concentrated sulfuric acid. A typical condensation is the preparation of 5-triphenylmethyl-2-hydroxypyridine.

A mixture of 3 g. of triphenylcarbinol and 3 g. of 2-hydroxypyridine was melted, two drops of concentrated sulfuric acid added and an air-cooled reflux condenser attached to the flask. It was heated in a metal-bath at 250° for twenty minutes, cooled, and 60 ml. of boiling absolute ethanol added. The precipitate was removed by filtration, washed with 30 ml. of hot absolute ethanol and dried to give a light cream-colored powder. Two recrystallizations from glacial acetic acid yielded a white powder, m.p. 365–368° (cor.). The compound is extremely insoluble in most organic solvents. The condensation of hydroxypyridines with triarylchloromethanes without addition of sulfuric acid was carried out under identical conditions. The yields were usually a few per cent. less than those from the carbinols. All the products were insoluble in aqueous 10% sodium hydroxide but readily dissolved upon the addition of an equal volume of ethanol.

In preparing 5-triphenylmethyl-3-methyl-2-hydroxypyridine, the product was soluble in hot ethanol and was recrystallized from the resulting solution with the use of Norit.

**3-Triphenylmethyl-6-methyl-2-hydroxypyridine.**—The condensation of triphenylcarbinol and 6-methyl-2-hydroxypyridine carried out as above afforded a dark brown product. After decolorizing twice with Norit and recrystallizing from benzene, a white powder was obtained in 22% yield. Only a 9% yield was obtained using triphenylchloromethane in the condensation. Three recrystallizations from benzene gave a product melting at 314–317° (cor.). It was insoluble in aqueous ethanolic sodium hydroxide and was recovered almost quantitatively on attempting to treat it with phosphorus oxychloride as described below.

*Anal.* Calcd. for $C_{25}H_{21}ON$: C, 85.43; H, 6.02; N, 4.00. Found: C, 85.38; H, 5.86; N, 3.97.

**5-Triarylmethyl-2-chloropyridines.**—The 5-triarylmethyl-2-hydroxypyridine and phosphorus oxychloride react under the following general conditions. A mixture of the hydroxypyridine and a six-fold excess of phosphorus oxychloride was sealed in a tube and placed on the steam-bath for forty-eight hours. After opening the cooled tube the resulting homogeneous solution was poured onto cracked ice and stirred. The mixture was boiled for

(9) Kirpal, *Monatsh.*, **27**, 371 (1906).

(10) v. Pechmann and Welsh, *Ber.*, **17**, 2384 (1884).

(11) Chichibabin and Vialatout, *Bull. soc. chim. France*, [5] **6**, 736 (1939).

several minutes to coagulate the gelatinous precipitate. The latter was removed by filtration, washed with water, dried, and recrystallized from the appropriate solvent. Yields were nearly quantitative. Refluxing with phosphorus oxychloride or heating with phosphorus pentachloride for forty-eight hours in an open vessel gave a product in only one case, and then in poor yield, indicating that a closed system was essential.

**5-Triarylpyridylmethanes.**—The 5-triarylmethyl-2-chloropyridines were reduced to the corresponding pyridines by the same general method, using Raney nickel catalyst in ethanolic potassium hydroxide solution. The reductions were run in very dilute solution and at 70° to effect solution of the reactants and products. A typical run is described.

One gram of 5-triphenylmethyl-2-chloropyridine and 0.50 g. of potassium hydroxide were dissolved in 200 ml. of hot absolute ethanol. One-half gram of Raney nickel was added and the mixture shaken for six hours at 70° under 45 lb. hydrogen pressure. After removing the catalyst by filtration the solution was evaporated until it became cloudy. Upon cooling, white crystals separated. Two recrystallizations from benzene–ethanol mixture (1:1) gave a product melting at 269–270° (cor.).

**N-Carboxymethyl-5-triphenylmethyl-2-pyridone.**—A suspension of 0.80 g. of 5-triphenylmethyl-2-hydroxypyridine, 0.67 g. of chloroacetic acid and 0.85 g. of potassium hydroxide in 25 ml. of absolute ethanol was refluxed for six hours. After removal of precipitated potassium chloride by filtration, the resulting solution was diluted with 25 ml. of water and acidified with hydrochloric acid. The bulky white precipitate which formed was removed by filtration, washed well on the filter with water and dried; yield, 0.84 g. (92%). Two recrystallizations from dioxane gave microscopic white crystals, m.p. 264–266° (cor.) with decomposition. The product forms an emulsion with aqueous 10% sodium hydroxide but dissolves upon the addition of an equal volume of ethanol.

*Anal.* Calcd. for $C_{26}H_{21}O_3N$: C, 78.97; H, 5.35. Found: C, 79.04; H, 5.04.


## Summary

1. The Fries rearrangement has been applied to the O-benzoate of 2-hydroxypyridine. A very small yield of 5-benzoyl-2-hydroxypyridine resulted. The structure of this latter product was determined by an unequivocal synthesis; methyl coumalinate was converted by ammonia followed by alkali to 2-hydroxypyridine-5-carboxylic acid which was transformed into the acid chloride and condensed with benzene in the presence of aluminum chloride.

2. Triphenylchloromethane and diphenylxenylchloromethane condense with 2-hydroxypyridine and 3-methyl-2-hydroxypyridine to give the corresponding 5-triarylmethyl-2-hydroxy- or 5-triarylmethyl - 2 - hydroxy - 3 - methylpyridines. Similar condensations occur with the triarylcarbinols and the 2-hydroxypyridines in presence of a few drops of sulfuric acid. With phosphorus oxychloride the triarylmethyl hydroxypyridines are converted to the chloropyridines which upon reduction yield triarylpyridylmethanes. Triphenylpyridylmethane resembles tetraphenylmethane in physical properties and in its phosphorescence after illumination with ultraviolet light.

3. 6-Methyl-2-hydroxypyridine condenses with triphenylchloromethane or the carbinol in low yields to give a product, presumably 3-triphenylmethyl-6-methyl-2-hydroxypyridine since it is alkali-insoluble and does not react with phosphorus oxychloride.


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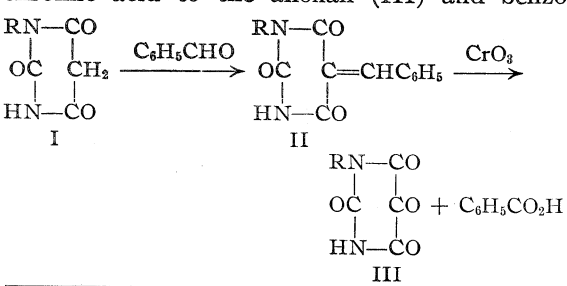
[CONTRIBUTION FROM THE SECTION OF PHARMACOLOGY, THE HEBREW UNIVERSITY AND HADASSAH]

# Preparation and Properties of New Derivatives of Alloxan

BY G. BRÜCKMANN[1] AND S. D. ISAACS

The discovery by Shaw-Dunn and co-workers[2] that alloxan causes diabetes in experimental animals by selective destruction of the insulin-producing pancreatic islet cells has evoked considerable interest. An investigation undertaken in this Laboratory of the structural specificity of the effect required the preparation of a number of new members of the series, since the only previously described N-substituted alloxans are the 1-methyl,[3] 1-ethyl,[4] 1-phenyl,[5] 1,3-dimethyl,[6] 1,3-diethyl[7] and 1-methyl-3-ethyl[8] derivatives.

For preparation of several additional derivatives of interest for pharmacological study, an N-substituted urea was first condensed with malonic acid in the presence of acetic anhydride,[9] or with malonic ester in the presence of sodium methoxide (advantageous in the preparation of 1-phenylbarbituric acid). In accordance with the method of Biilman and Berg,[10] the resulting N-substituted barbituric acid (I) was then converted into the benzal derivative (II) and this was oxidized with chromic acid to the alloxan (III) and benzoic




(1) Dr. Brückmann was killed during the War in Israel. The revised version of the paper was prepared by L. F. Fieser.—*The Editor.*

(2) Shaw-Dunn, Sheehan and McLetchie, *Lancet*, **1**, 484 (1943).

(3) Fischer and Clemm, *Ber.*, **30**, 3090 (1897).

(4) Biltz and Sedlatschek, *ibid.*, **57**, 175 (1924).

(5) Winslow, THIS JOURNAL, **61**, 2089 (1939).

(6) Biltz, *Ber.*, **45**, 3659 (1912).

(7) Sembritzki, *ibid.*, **30**, 1821 (1897).

(8) Biltz and Max, *Ann.*, **414**, 95 (1917).

(9) Biltz and Wittek, *Ber.*, **54**, 1035 (1921).

(10) Biilman and Berg, *ibid.*, **63**, 2188 (1930).

acid. The benzal derivative can be prepared from the reaction mixture containing the barbituric acid without isolation of this intermediate. The alloxans are not very soluble and can be isolated from the oxidation reaction mixture, but in most cases it is preferable to reduce the crude product with stannous chloride and to isolate the resulting alloxantin, which subsequently can be reoxidized to the alloxan with nitric acid. A number of new N-alkyl and N-aryl alloxans and alloxantins were prepared by this process. When dried *in vacuo* over sulfuric acid, the alloxans invariably retained one molecule of water, whereas the alloxantins were obtained anhydrous or as mono- or dihydrates.

Attempts to prepare 2-thioalloxan by the method of Biilman and Berg were no more successful than the attempts of Robinson and Tomlinson[11] to prepare the compound by other methods. The substance apparently is unstable, possibly because of tautomerism to the sulfhydryl derivative and subsequent oxidation.

Aqueous solutions of the new alloxans all exhibited the following typical reactions in varying degree of intensity: (a) murexide formation in contact with the skin or when heated with α-amino acids; (b) reduction by ascorbic acid to a dialuric acid, as indicated by the formation of a violet precipitate on addition of barium hydroxide; (c) transient blue color on addition of traces of ferrous sulfate and alkali; (d) reaction with hydroxylamine hydrochloride to give a violuric acid recognizable from the intense, stable blue color resulting on the addition of ferrous sulfate.

Since a reaction analogous to the known ready decomposition of alloxan by alkali to alloxanic acid may possibly play a role in the inactivation of alloxan in the body, we compared various alloxan derivatives with respect to their stability to alkali. Known amounts of the compounds were added to 5-cc. portions of Krebs–Ringer phosphate buffer (*p*H 7.3) and the alloxan content of the solution was determined at two-minute intervals by the colorimetric method recently described.[12] The decomposition curves for the various alloxans studied were of similar shape and the percentages of unaltered material remaining after two minutes were as follows: alloxan, 68%; butylalloxan, 65%; dimethylalloxan, 34%; benzylalloxan, 29%; phenylalloxan, 12%. Similar figures were obtained when sodium hydroxide was used for alkalinization instead of phosphate buffer. Comparative determinations of the rate of α-amino acid oxidation by the same compounds have indicated that the order of decreasing activity is as follows: alloxan, butyl-, propyl-, methyl-, ethyl-, benzyl-, dimethyl- and phenylalloxan.[13] It is thus evident that high stability toward alkali corresponds to high potency in amino acid oxidation.

(11) R. Robinson and Tomlinson, *J. Chem. Soc.*, 467 (1935).

(12) Brückmann, *J. Biol. Chem.*, **165**, 103 (1946).

(13) Brückmann and Wertheimer, *ibid.*, **168**, 241 (1947).

The toxicity of the N-alkylalloxans increases sharply with increasing length of the aliphatic side chain. The disubstituted alloxans are particularly toxic, whereas phenylalloxan is practically non-toxic. Methyl-, ethyl- and propylalloxan possess diabetogenic activity.[13]

## Experimental[14]

**1-*n*-Propylbarbituric Acid.**—A mixture of carefully dried malonic acid (15 g.) and N-propylurea (13 g.) in glacial acetic acid (34 cc.) was heated in an oil-bath maintained at 70–80° and acetic anhydride (34 cc.) was added in the course of ninety minutes. The temperature was then raised to 90° for three hours, the red-brown mixture was cooled, treated with a little water (6 cc.), and concentrated in vacuum at 60° to a sirup. This was dissolved in hot ethanol, and the solution on cooling deposited 7.7 g. of crude yellow crystals. Repeated crystallization from water gave white needles of product, m. p. 104° (sparingly soluble in water).

*Anal.* Calcd. for $C_7H_{10}O_3N_2$: N, 16.48. Found (Kjeldahl): N, 16.08.

Treatment of the mother liquors with benzaldehyde (5 cc.) afforded 8 g. of the benzal compound.

**1-*n*-Propyl-5-benzalbarbituric Acid.**—Benzaldehyde (1.5 cc.) was added slowly to a refluxing solution of crude propylbarbituric acid (2.1 g.) in ethanol (12 cc.) and after one-half hour the mixture was cooled and the crystalline product collected and washed with alcohol and ether. The first crop of 2.2 g. of yellow plates, m. p. 168°, was directly pure; a further 0.3 g. was obtained from the mother liquor.

*Anal.* Calcd. for $C_{14}H_{14}O_3N_2$: N, 10.85. Found (Kjeldahl): N, 10.54.

**Di-(1-*n*-propyl)-alloxantin.**—1-*n*-Propyl-5-benzalbarbituric acid (2.6 g.) was added in small portions in the course of thirty minutes to a solution of chromic anhydride (2 g.) in water (0.7 cc.)–acetic acid (7 cc.) at 50–60°. The solution was cooled, treated with water (5 cc.) and hydrochloric acid (3.5 cc.), left for one hour at 0°. The benzoic acid that separated was removed by filtration and the filtrate was treated with stannous chloride (2 g.) dissolved in hydrochloric acid (2 cc.). The alloxantin that separated when washed with warm water until colorless weighed 1.4 g. Recrystallization from water (sparingly soluble) gave hexagonal plates, m. p. 214°, dec.

*Anal.* Calcd. for $C_{14}H_{18}O_8N_4 \cdot H_2O$: N, 14.42. Found (Kjeldahl): N, 14.36.

**1-*n*-Propylalloxan.**—A suspension of the above alloxantin (1 g.) in water (5 cc.) was treated at about 50° with concentrated nitric acid, added by drops, until the solid had dissolved. The solution, filtered if necessary, was kept in a desiccator over sulfuric acid until the product crystallized. The alloxan separated in small plates, m. p. 122° dec. The first crop amounted to 0.15 g.; a further crop of 0.16 g. was obtained from the mother liquor.

*Anal.* Calcd. for $C_7H_{10}O_5N_2$: N, 13.86. Found (Kjeldahl): N, 14.22.

**1-*n*-Butylbarbituric Acid.**—N-Butylurea (4.4 g.) was condensed with malonic acid (4.4 g.) in acetic acid (10 cc.) –acetic anhydride (10 cc.) by the procedure described above. Crystallization of the reaction product from ethanol gave yellowish needles, m. p. 136–140°, very sparingly soluble in water.

(14) In the alloxan series melting points are not very characteristic and in most cases represent temperatures of decomposition that depend upon such factors as the rate of heating and the nature of the capillary tube. Kjeldahl nitrogen determinations gave satisfactory results for all compounds studied except 1-phenylalloxan, for which the figures found for nitrogen were consistently low, even when copper sulfate was replaced by mercuric oxide, as recommended for the analysis of lysine by Miller and Houghton, *ibid.*, **165**, 103 (1946). Satisfactory results were obtainable only by the micro-Dumas method.

*Anal.* Calcd. for $C_8H_{12}O_3N_2 \cdot 2H_2O$: N, 12.72. Found (Kjeldahl): N, 12.31.

**1-*n*-Butyl-5-benzalbarbituric acid** was prepared without isolation of the butylbarbituric acid by the procedure described for the propyl homolog. The total yield of satisfactory product (two crops) from 4.4 g. of N-butylurea was 3.9 g. The substance crystallized in yellow plates, m. p. 154–156°.

*Anal.* Calcd. for $C_{15}H_{16}O_3N_2$: N, 10.28. Found (Kjeldahl): N, 9.99.

**Di-(1-*n*-Butyl)-alloxantin.**—Oxidation of 3.8 g. of the benzal compound and reduction of the crude product by the procedure described above afforded 1.8 g. of crude alloxantin. Crystallization from water afforded small white plates, m. p. 204°, dec.

*Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: N, 14.13. Found (Kjeldahl): N, 13.89.

**1-*n*-Butylalloxan.**—Nitric acid oxidation of the alloxantin (1 g.) gave a first crop of 0.7 g. of product and 0.1 g. from the mother liquor. The substance crystallized in thin plates, m. p. 106–109°.

*Anal.* Calcd. for $C_8H_{12}O_5N_2$: N, 12.96. Found (Kjeldahl): N, 13.00.

**1-Isobutylbarbituric Acid.**—The sirup resulting from evaporation of the reaction mixture from isobutylurea (3 g.), malonic acid (3 g.), acetic acid (6.5 cc.) and acetic anhydride (6.5 cc.) when mixed with hot ethanol (7 cc.) afforded 1.8 g. of crystalline product. Crystallization from alcohol gave slightly pink plates, m. p. 138–140°, insoluble in water.

*Anal.* Calcd. for $C_8H_{12}O_3N_2$: N, 15.21. Found (Kjeldahl): N, 15.90.

**1-Isobutyl-5-benzalalloxan.**—Condensation of 1.5 g. of the barbituric acid with benzaldehyde (1.5 cc.) in ethanol (15 cc.) yielded 1.3 g. of yellow plates, m. p. 177–178°.

*Anal.* Calcd. for $C_{15}H_{16}O_5N_2$: N, 10.28. Found (Kjeldahl): N, 10.36.

**Di-(1-isobutyl)-alloxantin.**—The benzal compound (2.3 g.) was oxidized with chromic anhydride (1.7 g.) in acetic acid (5 cc.), and the alloxantin was obtained by addition of water (12 cc.) and stannous chloride (1 g.)–hydrochloric acid (1 cc.). The product separated as white plates (0.3 g.), m. p. 214–216°, moderately soluble in water.

*Anal.* Calcd. for $C_{16}H_{22}O_8N_4 \cdot 2H_2O$: N, 12.96. Found (Kjeldahl): N, 12.61.

**1-Isobutylalloxan** was obtained directly by cooling the above-described oxidation mixture; yield 0.5 g. (crude). Crystallization afforded white plates, m. p. 145–147°, dec.

*Anal.* Calcd. for $C_8H_{12}O_5N_2$: N, 12.96. Found (Kjeldahl): N, 12.70.

**1-Phenylbarbituric Acid.**—The method used was similar to that of Aspelund and Lindh,[15] but ethanol was replaced by methanol, as follows. To a cooled solution of sodium (4.2 g.) in absolute methanol (50 cc.), a solution of diethyl malonate (35 g.) and phenylurea (29 g.) in hot methanol (50 cc.) was added. The mixture was heated under reflux at 70–80° for six hours and poured into hydrochloric acid (25 cc.) and water (120 cc.) and cooled. The yield of the barbituric acid, washed with ethanol and ether, was 25 g.; recrystallized material melted at 262°.

**1-Phenyl-5-benzalbarbituric Acid.**—The condensation of crude phenylbarbituric acid (24 g.) with benzaldehyde (16 cc.) in boiling ethanol (180 cc.) afforded 31 g. of yellow, sharp-edged needles, m. p. 237–238°.

**1-Phenylalloxan.**[16]—The benzal compound (2.5 g.) was added in the course of twenty minutes to a mixture of chromic anhydride (3 g.), water (2.5 cc.) and acetic acid (13 cc.) at a temperature of 50–60°. The alloxan separated in a stiff paste and was collected and washed on the filter with acetic acid until the washings were nearly colorless. The product was dissolved in a little hot water and the solution treated with acetic acid and cooled, when 1.2 g. of silky white needles separated. The substance, m. p. 158°, is very soluble in water, ethanol or hot acetic acid and is sparingly soluble in chloroform.

*Anal.* Calcd. for $C_{10}H_8O_5N_2$: N, 11.87. Found (Dumas): N, 11.66.

Reduction with stannous chloride afforded the alloxantin (white needles from water, m. p. 255° dec.) described by Winslow.[16]

**1-Benzylbarbituric acid** was prepared by condensing benzylurea (2.9 g.) with malonic acid (2.2 g.) in acetic acid (5 cc.)–acetic anhydride (5 cc.). The crude product (2 g.) on crystallization from ethanol gave white prisms, m. p. 146–150°.

*Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.84. Found (Kjeldahl): N, 13.30.

**1-Benzyl-5-benzalbarbituric acid** was prepared from the barbituric acid (1.8 g.) by the usual process, yield 2.2 g. The substance formed thin yellow prisms, m. p. 200–204°.

*Anal.* Calcd. for $C_{18}H_{14}O_3N_2$: N, 9.15. Found (Kjeldahl): N, 9.08.

**Di-(1-benzyl)-alloxantin** was prepared by the general procedure described; yield 1 g. from 2 g. of benzal compound. Crystallization from hot water gave small needles, m. p. 199°.

*Anal.* Calcd. for $C_{22}H_{18}O_8N_4 \cdot H_2O$: N, 11.58. Found (Kjeldahl): N, 11.73.

**1-Benzylalloxan.**—The alloxantin (1.2 g.) was warmed with nitric acid until dissolved, and the white crystals that separated on cooling were washed with water and with chloroform; yield 0.7 g. The product, m. p. 140–143°, is soluble in acetone, ethanol, or ether, and sparingly soluble in water.

*Anal.* Calcd. for $C_{11}H_{10}O_5N_2$: N, 11.20. Found (Kjeldahl): N, 11.20.

## Summary

A number of new derivatives of alloxan and alloxantin have been synthesized. In the alloxan series, ability to oxidize α-amino acids runs parallel to the stability of the compounds to decomposition by alkali.

JERUSALEM, PALESTINE RECEIVED JULY 31, 1948

(15) Aspelund and Lindh, *Acta Acad. Aboensis Math. et Phys.*, **11**, No. 10 (1938).

(16) In preparing this paper for publication we found that this compound has been prepared by a different method by Winslow, THIS JOURNAL, **61**, 2089 (1939).

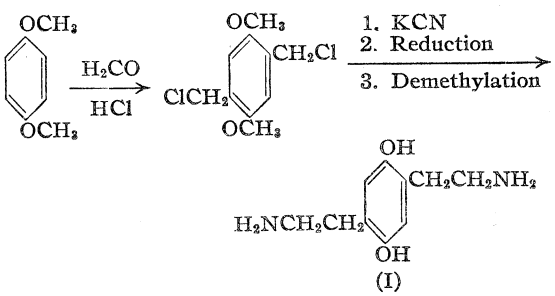
[CONTRIBUTION NO. 55 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF TENNESSEE]

# Di-($\alpha$- and $\beta$-Substituted Aminoethyl)-benzenes. I. 2,5-bis-(2-Aminoethyl)-hydroquinones[1]

BY J. H. WOOD AND ROGER E. GIBSON[1a]

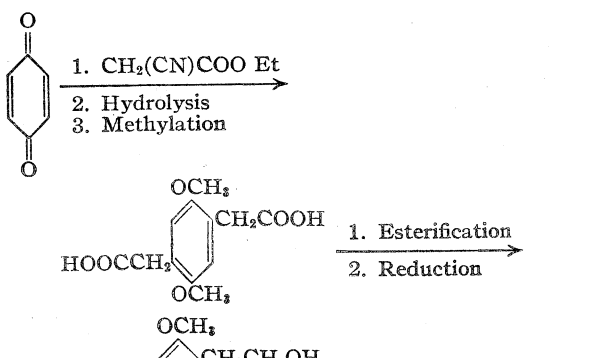
The aminoethyl function is a component common to a large number of physiologically active compounds. In the benzene nucleus, it gives rise to a series of compounds noted for their sympathomimetic activity, benzedrine and ephedrine being familiar examples. Studies so far made among these compounds relating structure with activity have been concerned with introducing substituents on the $\alpha$- and $\beta$-carbons, on the nitrogen and in the ring of the parent $\beta$-phenylethylamine. We have prepared for pharmacologic activity study a series of new compounds in which the $\beta$-aminoethyl function is repeated in a para relationship. Additional interest on our part in these compounds is occasioned by our need for them as intermediates in the preparation of certain heterocyclic types.

The parent of the series reported in this paper, 2,5-bis-(2-aminoethyl)-hydroquinone, I, was synthesized by two independent paths, as follows




(I)

The second method, important in the proof of structure, gave poor yields




I

The methods of preparation, analyses, and conversion into known compounds serve to characterize the new amines and their intermediates.

Pressor, bronchodilator and antihistamine activity tests, made by The Lilly Research Laboratories of Eli Lilly and Company on the hydrochloride salts of I and its O-methyl, N-dimethyl and O-methyl-N-dimethyl derivatives, revealed that these amines are inactive in these respects. They showed less than 10% "Egotrate" activity. Since the introduction of a second $\beta$-aminoethyl function does not significantly alter the chemical properties of the molecule the loss of activity must be ascribed to other effects. It is planned to continue this study by preparing and testing the activity of derivatives in which the positions of the aminoethyl functions are varied as well as the substituents on their $\alpha$- and $\beta$-carbon atoms.

## Experimental[2]

**2,5-bis-(Chloromethyl)-hydroquinone Dimethyl Ether.**—The following is an adaptation of Brunner's[3] general method for the chloromethylation of aromatic compounds. To a stirred solution of 103 g. (0.75 mole) of the dimethyl ether of hydroquinone, 600 ml. of dioxane and 100 ml. of concentrated hydrochloric acid was added three 50 ml. portions of 40% formalin (2 moles) at thirty-minute intervals. During the period of addition, hydrogen chloride gas was passed through. Stirring and the introduction of hydrogen chloride gas were continued for three hours longer and then 450 ml. of concentrated hydrochloric acid was added. After cooling, the solid material which had formed was removed by filtration and allowed to dry. One recrystallization from acetone gave 135 g. (77%) of white, crystalline material that melted at 163–164°. Further purification, which was unnecessary for most purposes, gave a product which melted at 167.5°. Brunner reported the melting point as about 165°.

*Anal.* Calculated for $C_{10}H_{12}O_2Cl_2$: Cl, 30.16. Found: Cl, 30.14.

**2,5-bis-(Cyanomethyl)-hydroquinone Dimethyl Ether.**—To a hot, stirred solution of 300 ml. of ethylene glycol monoethyl ether, 500 ml. of acetone and 117.5 g. (0.5 mole) of 2,5-bis-(chloromethyl)-hydroquinone dimethyl ether, in a reflux apparatus, was added slowly an aqueous solution containing 97.5 g. (1.5 moles) of potassium cyanide in 125 ml. of warm water. After refluxing four hours, the hot mixture was filtered. The residue consisted of a mixture of potassium chloride and the cyanomethyl compound. The filtrate, upon cooling in an ice-bath, deposited additional cyanomethyl compound in the form of grayish crystals. After filtering, the mother liquor was used to extract the cyanomethyl compound from potassium chloride in the residue obtained from the first filtration. This extraction was repeated (usually three times) until no solid was obtained upon cooling the filtered, hot extracting solution. The combined residues of the cyanomethyl compound, after washing with methanol, weighed 68 g., m. p. 193–195°. Recrystallization from dioxane gave 59 g. (54.5%) of white, crystalline material, m. p. 195–196.5°, which was pure enough for our work. A small portion was further purified for analysis and melted at 198°.

*Anal.* Calculated for $C_{12}H_{12}O_2N_2$: N, 12.96. Found: N, 12.99.

(1) Presented at the 114th meeting of the American Chemical Society, St. Louis, Missouri, September, 1948.

(1a) University of Tennessee Fellow, 1947–48.

(2) All melting points are corrected.

(3) Brunner, U. S. Patent 1,887,396 (1933).

**2,5-Dimethoxy-*p*-benzenediacetic Acid Diethyl Ester.**—A solution of 225 g. (0.88 mole) of 2,5-dimethoxy-*p*-benzenediacetic acid[4] (prepared from the hydroquinone[5]), 2 l. of absolute ethanol, and 750 ml. of benzene was placed in a 3-l. flask fitted with stirrer and a 75-cm. Vigreux column equipped with a variable take-off. Esterification was accomplished by keeping the solution saturated with hydrogen chloride gas over a four-hour reflux period during which time the low-boiling fraction was continuously removed. The volume of the reaction mixture was then increased to about 4 l. by the addition of 95% ethanol, heated to boiling and filtered. Upon cooling, the ester separated as grayish crystals which were removed by filtration. Evaporation of the filtrate to about one-third of its volume and cooling yielded an additional amount. Total yield of crude ester was 210 g. (76.5%). Further purification was achieved by recrystallization from alcohol and gave a colorless, crystalline material, m. p. 115.5°.

*Anal.* Calculated for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.78; H, 7.11.

**2,5-bis-(2-Hydroxyethyl)-hydroquinone Dimethyl Ether.**—To 150 g. (6.5 g. atoms) of melted sodium dispersed in hot xylene contained in a 3-liter flask fitted with stirrer and condenser was slowly added a warm solution of 250 ml. of xylene and 500 ml. of absolute butanol containing 140 g. (0.45 mole) of 2,5-dimethoxy-*p*-benzenediacetic acid diethyl ester. Xylene was added at intervals in sufficient quantities to prevent the reaction mixture from setting to a gel. The mixture was then heated with stirring until all sodium had dissolved. Water was added and the mixture was steam distilled until the xylene and butanol had been removed. Upon cooling to 0°, 40 g. (39%) of the slightly impure alcohol separated. Recrystallization from water with decolorization gave white crystals, m. p., 133.5–134°.

*Anal.* Calculated for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.39; H, 8.12.

Acidification of the mother liquor from the above reaction yielded 54 g. of the acid formed by the hydrolysis of the unreduced ester.

**2,5-bis-(2-Aminoethyl)-hydroquinone Dimethyl Ether.**—Method No. 1: Into a steel bomb of 600-ml. capacity were placed 25 g. (0.12 mole) of 2,5-bis-(cyanomethyl)-hydroquinone dimethyl ether, 250 ml. of absolute ethanol saturated with ammonia, and about 10 g. of Raney nickel catalyst. After introducing hydrogen to a pressure of 1,900 lb./sq. in., the bomb was placed in the heating jacket of a hydrogenation apparatus and shaken at 120° for forty-five minutes. The pressure fall was very rapid the first fifteen minutes. After cooling, the contents were removed, filtered, and the filtrate evaporated under reduced pressure on the steam-bath, leaving a red oil. This oil was distilled at 150–155° at a pressure of less than 1 mm., using a very short path still with a large side arm. About 20 g. (77%) of the pure amine was thus obtained as a white, crystalline solid. The amine proved to be very basic, removing carbon dioxide from air. Freshly prepared, it melted at about 90°. Upon standing in air, its melting point changed very rapidly. It, as well as its sulfonamide and hydrochloride, proved to be identical with the amine obtained by method 2.

Method No. 2: A small excess of thionyl chloride was added to a mixture of 10 g. (0.044 mole) of 2,5-bis-(2-hydroxyethyl)-hydroquinone dimethyl ether and 100 ml. of dry ethyl ether. After carefully warming for a few minutes, the mixture was slowly evaporated to dryness on the steam-bath. The chloride thus presumably formed was not purified. Potassium phthalimide, 20 g. (0.11 mole), was added, a small air condenser attached, and the mixture heated for eight hours at 160–170° with occasional stirring. After cooling, the solid product was broken up and about 175 ml. of alcohol and 15 ml. of 40% hydrazine hydrate were added. After heating one hour on the steam-bath, excess hydrochloric acid was added and the mixture filtered. The filtrate was evaporated to about 100 ml. and then refiltered. The filtrate was made alkaline with excess sodium hydroxide and then boiled a few minutes to expel any hydrazine present. After extracting with ether, the amine was precipitated as the salt by passing hydrogen chloride into the ether solution. The yield was about 10%. The amine thus obtained was identical with the one obtained in method 1.

The **dihydrochloride** salt, a white, hygroscopic solid, melted at 335° dec.

*Anal.* Calculated for $C_{12}H_{22}O_2N_2Cl_2$: Cl, 23.86. Found: Cl, 23.91.

The **benzenesulfonamide** derivative was a white, crystalline solid after recrystallization from alcohol, m. p., 195.5°.

*Anal.* Calculated for $C_{24}H_{28}O_6N_2S_2$: N, 5.55. Found: N, 5.60.

**2,5-bis-(2-Aminoethyl)-hydroquinone.**—A solution of 15 g. (0.067 mole) of 2,5-bis-(2-aminoethyl)-hydroquinone dimethyl ether in 100 ml. of 48% hydrogen bromide was refluxed eight hours. Upon cooling, the amine hydrobromide precipitated as a tan material. Evaporation of the mother liquor to about one-third of its former volume gave a small additional amount. After drying to remove excess hydrogen bromide, the salt was dissolved in 80 ml. of water. The free amine was then obtained as a gray solid upon adding excess sodium bicarbonate. This phenolic amine, while stable in acidic solutions, was unstable in alkali solutions, its solution in sodium hydroxide rapidly forming a black precipitate. The amine freshly precipitated with sodium bicarbonate from an aqueous solution of the recrystallized hydrochloride salt was a slightly colored solid, m. p. 234° dec., soluble in alcohol, ether, acids and bases.

The **dihydrochloride** was prepared by adding a small amount of water to the gray solid obtained above and then adding an excess of concentrated hydrochloric acid. Upon evaporating to 75 ml. and cooling, the salt precipitated. After washing with absolute alcohol and then ether, the salt was twice recrystallized from an alcohol–water mixture to give 7 g. (39%) of a white, crystalline solid, m. p. 313° dec.

*Anal.* Calculated for $C_{10}H_{18}O_2N_2Cl_2$: Cl, 26.35. Found: Cl, 26.25.

**N,N'-Tetramethyl-2,5-bis-(2-aminoethyl)-hydroquinone Dimethyl Ether.**—This compound was prepared by the method of Icke, Wisegarver and Alles[6]: 22.4 g. (0.1 mole) of 2,5-bis-(2-aminoethyl)-hydroquinone dimethyl ether yielded the crude tertiary amine in the form of a red oil. This was distilled at 133–135° at less than 1 mm. to give 17.5 g. (62.5%) of a white, crystalline solid, m. p. 51–52°, soluble in alcohol and ether. A Hinsberg test indicated a tertiary amine.

The **dihydrochloride** melted at 275° dec.

*Anal.* Calculated for $C_{16}H_{30}O_2N_2Cl_2$: Cl, 20.07. Found: Cl, 19.97.

**N,N'-Tetramethyl-2,5-bis-(2-aminoethyl)-hydroquinone.**—This compound was prepared in a manner analogous to that described above for 2,5-bis-(2-aminoethyl)-hydroquinone. The free amine obtained from the hydrochloride salt was a light brown solid, m. p. 178, which darkened upon standing in air, and was soluble in ether, alcohol, acids and bases. The yield of pure hydrochloride was about 38%.

The **dihydrochloride** salt, m. p. 278° dec., was a white, crystalline solid.

*Anal.* Calculated for $C_{14}H_{26}O_2N_2Cl_2$: Cl, 21.80. Found: Cl, 21.92.

## Summary

1. Procedures have been developed for synthesizing phenolic derivatives containing two

(4) Wood, Colburn, Cox and Garland, THIS JOURNAL, **66**, 1541 (1944).

(5) Wood and Cox, "Organic Syntheses," **26**, 24 (1946).

(6) Icke, Wisegarver and Alles, "Organic Syntheses," **25**, 89 (1945).

β-aminoethyl functions in a para relationship.

2. Pressor, bronchodilator and antihistamine activity tests have been made on the amines.

3. Several new compounds intermediate in the formation of the amines are reported.

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[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

# Ethers of *p*-Hydroxydiphenylamine as Alkyl Halide Identification Derivatives

BY DAVID F. HOUSTON

The preparation of several ethers of *p*-hydroxydiphenylamine as intermediates for other syntheses drew attention to their value as derivatives for the identification of alkyl halides. These ethers offer an alternative choice to previously reported[2,3,4,5] derivatives.

The hydroxydiphenylamine is commercially available and can be readily purified. The synthesis of the ethers was convenient, and the products were easily crystallized. Ether formation from primary halides was general. *s*-Butyl chloride gave unreacted amine together with oil and tarry matter. Tertiary halides were not investigated. Mixtures of two ethers with closely similar melting points showed melting-point depressions of several degrees.

Data on the ethers are collected in the accompanying table. The melting points follow the usual trend for a homologous series, and those for the even-carbon alkyl ethers above the hexyl compound follow a smooth curve.

TABLE I

*p*-HYDROXYDIPHENYLAMINE ETHERS, $ROC_6H_4NHC_6H_5$

| Halide used | M. p., °C. | Empirical formula | Analytical data, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|
| *n*-Propyl iodide | 62.2–62.9 | $C_{15}H_{17}NO$ | 79.26 | 79.4 | 7.54 | 7.55 | 6.16 | 6.06 |
| Isopropyl[a] | 86.3–87.1 | $C_{15}H_{17}NO$ | 79.26 | 79.3 | 7.54 | 7.56 | 6.16 | 6.12 |
| *n*-Butyl bromide | 46.9–47.3 | $C_{16}H_{19}NO$ | 79.63 | 79.6 | 7.94 | 7.90 | 5.80 | 5.80 |
| *n*-Amyl iodide | 40.9–41.3 | $C_{17}H_{21}NO$ | 79.96 | 80.2 | 8.29 | 8.31 | 5.49 | 5.46 |
| *n*-Hexyl bromide | 41.0–41.5 | $C_{18}H_{23}NO$ | 80.25 | 80.4 | 8.60 | 8.59 | 5.20 | 5.18 |
| *n*-Heptyl bromide | 44.9–45.3 | $C_{19}H_{25}NO$ | 80.52 | 80.5 | 8.89 | 8.92 | 4.94 | 4.89 |
| *n*-Octyl bromide | 45.5–46.3 | $C_{20}H_{27}NO$ | 80.76 | 80.9 | 9.15 | 9.03 | 4.71 | 4.69 |
| *n*-Dodecyl bromide | 61.3–61.9 | $C_{24}H_{35}NO$ | 81.53 | 81.6 | 9.98 | 9.88 | 3.96 | 3.94 |
| *n*-Hexadecyl bromide | 74.5–75.3 | $C_{28}H_{43}NO$ | 82.10 | 82.2 | 10.57 | 10.44 | 3.42 | 3.39 |
| Benzyl chloride | 95.2–95.8 | $C_{19}H_{17}NO$ | 82.88 | 82.9 | 6.22 | 6.17 | 5.09 | 5.08 |

[a] Purified from commercial product; see text.

## Experimental

**Materials.**—The *p*-hydroxydiphenylamine was a sample of commercial product with a stated 92% purity. It was further purified by distillation with superheated steam,[6] collecting the product distilling at 170–180°. The dark still residue contained some diphenyl-*p*-phenylenediamine. Final recrystallizations from benzene–hexane gave material melting at 69–70° in agreement with the reported[7] value of 70°. Less rigorous purification may be satisfactory, as indicated by the fact that the octyl ether prepared directly from the commercial *p*-hydroxydiphenylamine, though remaining somewhat dark colored, melted at 45.5–46.2° in complete agreement with the analytical sample from the purified amine.

*n*-Propyl and *n*-amyl iodides, heptyl bromide, and *s*-butyl and benzyl chlorides were obtained from Eastman Kodak Company. The hexyl, octyl, dodecyl and hexadecyl bromides were research-grade chemicals (boiling within a two degree range) obtained from a commercial supplier of halogen chemicals. *n*-Butyl bromide had been prepared and fractionally distilled in this Laboratory.

The isopropoxydiphenylamine was a commercial product. It was distilled at reduced pressure, and the portion distilling at 140–145° at 1.5 mm. was purified by decolorizing a methanol solution with charcoal and crystallizing the product from aqueous methanol (1:3).

**Procedure.**—Preparation of the ethers, essentially the same in all cases, is illustrated by synthesis of the *n*-propyl compound. Equivalent amounts (0.02 mole) of *p*-hydroxydiphenylamine (3.70 g.) and *n*-propyl iodide (2.46 g.) were added to 18 cc. of 10% alcoholic potassium hydroxide (0.03 equivalent). The solution was refluxed three hours with stirring by magnetic stirrer, cooled, diluted to 200 cc. with water, acidified slightly with hydrochloric acid, and chilled to 0°. The dark solids were filtered off, and decolorized with charcoal in 85 cc. of alcohol. The filtrate was diluted with water to clouding, cooled to 0°, and again filtered. The yield at this point was 2.78 g. (61%). Two recrystallizations from aqueous alcohol gave pearly flakes melting at 40.9–41.3° (cor.).

The halides used, and the melting points and analytical data for the ethers formed, are presented in the table.

**Acknowledgment.**—I wish to express my appreciation to E. B. Kester for his interest in this

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyright.

(2) L. L. Merritt, Jr., S. Levey and H. B. Cutter, THIS JOURNAL, **61**, 15 (1939).

(3) R. D. Drew and J. M. Sturtevant, *ibid.*, **61**, 2666 (1939).

(4) W. M. Lauer, P. A. Sanders, R. M. Leekley and H. E. Ungnade, *ibid.*, **61**, 3050 (1939).

(5) H. B. Cutter and H. R. Golden, *ibid.*, **69**, 831 (1947).

(6) A. A. Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, pp. 144–145.

(7) A. Calm, *Ber.*, **16**, 2799 (1883).

investigation, and to L. M. White and Geraldine Secor for performing the microanalyses.

## Summary

Alkyl ethers of *p*-hydroxydiphenylamine have been prepared from a variety of alkyl halides and have properties suitable for use in identification of alkyl halides. Ether formation from primary halides was general, but secondary alkyl halides did not always operate satisfactorily. Tertiary halides were not investigated.

RECEIVED JULY 20, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC COMPANY]

# Pentachlorophenyl Derivatives. III. The Effect of Temperature on the Composition of the Product in the Chlorination of Ethylpentachlorobenzene

BY SIDNEY D. ROSS, MOUSHY MARKARIAN AND MATTHEW NAZZEWSKI

In previous reports from this Laboratory[1] it was shown that the major product isolated from the chlorination of ethylpentachlorobenzene was 1-pentachlorophenyl-2-chloroethane, I. Bromination, on the other hand, resulted in an almost quantitative yield of the $\alpha$-substitution product, 1-pentachlorophenyl-1-bromoethane. This difference in the direction of substitution was attributed to a combination of two factors—the greater reactivity of the chlorine atom[2] and steric hindrance about the $\alpha$-position. Evidence indicating the presence of steric hindrance in systems of this type has been presented in a previous report.[3] We have postulated that with ethylpentachlorobenzene the energy barrier for reaction is smaller for an attack at the $\alpha$-position but that this position is so shielded sterically by the ortho chlorine substituents that many collisions occur at the $\beta$-position before a collision occurs at the $\alpha$-position. The chlorine atom is so reactive that even a collision at the $\beta$-position is sufficiently effective to result in reaction, but with the less reactive bromine atom only a collision at the $\alpha$-position is effective and no $\beta$-bromide is formed.

On the above basis it would be predicted that $\beta$-chlorination would be favored over $\alpha$-chlorination at higher temperatures but that with decreasing temperature the ratio of $\beta$- to $\alpha$-chlorination would decrease. In our previous work we studied the products of the chlorination at both 200 and 68–73°. At both temperatures the predominant product was I. At the higher temperature the only other products isolated were hexachlorobenzene and a highly chlorinated ethylpentachlorobenzene which was not fully characterized. At the lower temperature the other isolable products were hexachlorobenzene and pentachlorostyrene, II, and it was suggested that II arose from decomposition of 1-pentachlorophenyl-1-chloroethane, III, during the distillation process and constituted indirect evidence for the occurrence of some $\alpha$-chlorination at the lower temperature. In both cases the yield of $\beta$-chloride, I, actually isolated was never more than 35% so that the possibility of some $\alpha$-chlorination even at the higher temperature was not eliminated. It is our present purpose to show that some $\alpha$-chlorination takes place at both 70–75° and 180° and that the relative amounts of $\beta$- and $\alpha$-chlorination at the two temperatures support the postulated mechanism to account for the difference in the direction of substitution on bromination and chlorination.

If ethylpentachlorobenzene, is chlorinated and then reacts, without purification, with benzene in the presence of aluminum chloride the major product is a mixture of two solids, one melting from 110.5–112.5° and the other from 153–155°. Although the two compounds distil at similar temperatures and pressures they can be readily separated by crystallization and both analyze correctly for $C_{14}H_4Cl_5$. The lower melting one, IV, was synthesized from both 1-pentachlorophenyl-1-bromoethane and pentachlorostyrene by reaction with benzene in the presence of aluminum chloride and must, therefore, be 1-pentachlorophenyl-1-phenylethane. The higher melting product, V, is the isomeric 1-pentachlorophenyl-2-phenylethane and was synthesized by treating I with benzene and aluminum chloride. V can result only from the presence of I in the crude chlorination mixture. IV can result either from III or from pentachlorostyrene. However, since pentachlorostyrene itself probably results from III it is still valid to assume that the amounts of IV and V isolated from the coupling reaction are indicative of the amounts of $\alpha$- and $\beta$-chlorination in the chlorination reaction and we have applied this criterion to the products obtained by chlorination at 180 and 70–75°.

Chlorination of 1000 g. of ethylpentachlorobenzene at 180° followed by coupling with benzene at 50° gave a crude product which yielded five fractions on distillation—a forerun weighing 229 g., the main fraction weighing 546 g., an intermediate fraction of 60 g., a high boiling fraction of 123 g., and a final fraction of 36 g. collected after decomposition of the pot residue had started.

(1) Ross, Markarian and Nazzewski, THIS JOURNAL, **69**, 1914, 2468 (1947).

(2) Schumacher, *Angew. Chem.*, **53**, 501 (1940).

(3) Ross, THIS JOURNAL, **70**, 4039 (1948).

Crystallization of the forerun yielded two pure products—11 g. of hexachlorobenzene and 110 g. of unreacted ethylpentachlorobenzene. The main fraction on crystallization gave 403 g. of V and 94 g. of IV. From the intermediate fraction the only pure product isolated was 32 g. of V. No more of IV or V was isolated from the subsequent fractions. The over-all yield of monophenyl-substituted ethylpentachlorobenzene is thus 41.4%. Of this 82.1% is the β-substituted product and 17.9% the α-substituted product, and based on this evidence the ratio of β-chlorination to α-chlorination is almost 4.6:1.

The final fraction was largely the product of decomposition and only hexachlorobenzene was isolated from it. The high boiling fraction proved to be a mixture which was particularly resistant to separation. By a combination of crystallization and flotation we succeeded in isolating two pure compounds. One, VI, melted from 143–143.5°, and the other, VII, from 132–133°. Both analyzed correctly for $C_{20}H_{13}Cl_5$, and they must, therefore, be isomeric diphenylethylpentachlorobenzenes. VI was synthesized by treating 1-pentachlorophenyl-1,2-dibromoethane with benzene in the Friedel-Crafts reaction and is 1-pentachlorophenyl-1,2-diphenylethane. VII is either 1-pentachlorophenyl-1,1-diphenylethane or 1-pentachlorophenyl-2,2-diphenylethane. The preponderance of β-chlorination makes the former structure extremely unlikely and we have assigned the latter structure to VII.

The product of chlorination at 70–75° after similar treatment gave three fractions—a forerun of 208 g., the main fraction of 683 g., and a high boiling fraction of 84 g. From the forerun we isolated three compounds; 42.5 g. of unreacted ethylpentachlorobenzene, 11 g. of hexachlorobenzene, and 22 g. of V. From the main fraction we obtained 369 g. of V and 253 g. of IV and from the final fraction we isolated only 5 g. of V and 5 g. of VI. The over-all yield of monophenyl substituted ethylpentachlorobenzene isolated is thus 51%. Of this 61% is the β-substituted product and 33% the α-substituted and the ratio of β-chlorination to α-chlorination is in this case slightly below 1.6:1.

These results clearly indicate that β-chlorination is favored at higher temperatures and that with decreasing temperature the ratio of β- to α-chlorination decreases. This finding is in accord with our postulation that the activation energy for the α-chlorination is lower than for the β-chlorination and lends support to the hypothesis which we previously advanced[1] to account for the difference in the directions of chlorination and bromination of ethylpentachlorobenzene.

## Experimental[4]

**1-Pentachlorophenyl-2-phenylethane, V.**—1-Pentachlorophenyl-2-chloroethane (63 g., 0.2 mole) in 200 cc. of benzene was added dropwise at room temperature over a two-hour period to a stirred suspension of aluminum chloride (2 g.) in 50 cc. of benzene. Stirring was continued until the evolution of hydrogen chloride ceased. The reaction mixture was decomposed with ice and dilute hydrochloric acid. The benzene layer was separated, washed with water, 10% sodium hydroxide, and again with water and finally dried over calcium sulfate. The benzene was removed and the crude product obtained was crystallized from ethanol–benzene (1:1) to yield 52 g. (73.4%) of product melting from 148–153°. Two recrystallizations raised the melting point to 153–155°.

*Anal.* Calcd. for $C_{14}H_9Cl_5$: C, 47.42; H, 2.62. Found: C, 46.93, 46.99; H, 2.79, 2.86.

**1-Pentachlorophenyl-1-phenylethane, IV.**—1-Pentachlorophenyl-1-bromoethane (71.5 g., 0.2 mole) in 250 cc. of benzene was reacted with aluminum chloride (2 g.) in 50 cc. of benzene exactly as above. The yield of crude product was in this case quantitative. A sample crystallized two times from ethanol for analysis melted from 110.5–112.5°.

*Anal.* Calcd. for $C_{14}H_9Cl_5$: C, 47.42; H, 2.62. Found: C, 47.01, 47.16; H, 2.95, 2.77.

When pentachlorostyrene was coupled with benzene as above the same product was obtained in 89% yield.

**1-Pentachlorophenyl-1,2-diphenylethane, VI.**—1-Pentachlorophenyl-1,2-dibromoethane (2 g.) in 40 cc. of benzene was added dropwise to a stirred mixture of aluminum chloride (0.5 g.) in 40 cc. of benzene. The reaction mixture was warmed for three hours after which it was decomposed with water and 10% sodium hydroxide. The benzene layer was separated and dried. The crude product, obtained by removing the benzene, was crystallized from ethanol yielding 1.1 g. of melting point 140–141°. Another crystallization raised the melting point to 143–143.5°.

*Anal.* Calcd. for $C_{20}H_{13}Cl_5$: C, 55.80; H, 3.04. Found: C, 56.11, 56.30; H, 3.10, 2.94.

**Chlorination of Ethylpentachlorobenzene at 70–75°.**—Redistilled ethylpentachlorobenzene (1000 g.) was illuminated with a 500-watt bulb and chlorinated at 70–75° to a gain in weight of 136 g. This total product in 750 cc. benzene was added to a stirred suspension of aluminum chloride (62.5 g.) in 1000 cc. of benzene and worked up in the usual manner. Distillation of the total product gave the following fractions: (1) 208 g. of b. p. 100–160° at 0.06 mm.; (2) 683 g. of b. p. 160–187° at 0.06 mm.; (3) 84 g. of b. p. 190–238° at 0.3 mm. Fraction 1 was first separated in the cold into trichloroethylene soluble material and trichloroethylene insoluble material. By repeated crystallization of the insoluble material first from trichloroethylene and then from benzene we isolated pure hexachlorobenzene and V. Removal of the solvent from the trichloroethylene soluble material and repeated crystallization first from benzene-alcohol (2:1) and finally from alcohol alone gave finally additional pure V and ethylpentachlorobenzene. In all we isolated 11 g. of hexachlorobenzene, 42.5 g. of ethylpentachlorobenzene and 22 g. of V from this fraction. Fraction 2 was first redistilled at 0.2 mm. to yield 669 g. boiling from 170–202°. This total product was crystallized by dissolving it in hot trichloroethylene and then adding ethanol until the hot solution began to get cloudy. On cooling V precipitated. The mother liquors were then concentrated until half of the original trichloroethylene had been removed and alcohol was again added to incipient crystallization. Both this crop and a third crop obtained by repetition of this process proved to be 1-pentachlorophenyl-1-phenylethane, IV. In all we obtained 369 g. of V and 253 g. of IV. Fraction 3 was first extracted with 3 300-cc. portions of ethanol and then each extract and the residue were repeatedly crystallized from benzene–ethanol (5:1). In this way we succeeded in isolating 5 g. of pure V and 5 g. of a compound melting from 132–133°. To this latter compound we have assigned the structure VI.

*Anal.* Calcd. for $C_{20}H_{13}Cl_5$: C, 55.81; H, 3.05. Found: C, 55.42, 55.49; H, 3.10, 2.89.

(4) The microanalyses were performed by Dr. Carl Tiedcke.

**Chlorination of Ethylpentachlorobenzene at 180°.**—Redistilled ethylpentachlorobenzene (1000 g.) was illuminated with a 500-watt bulb and chlorinated at 180° to a gain in weight of 132 g. and then reacted with benzene as above. Distillation gave the following fractions: (1) 229 g. of b. p. 100–160° at 0.15 mm.; (2) 546 g. of b. p. 168–180° at 0.2 mm.; (3) 60 g. of b. p. 186–205° at 0.3 mm.; (4) 123 g. of b. p. 210–232° at 0.8 mm.; (5) 36 g. of b. p. 232° at 2.5 mm. Fraction 1 was separated into material soluble in trichloroethylene in the cold and material insoluble in trichloroethylene in the cold. The insoluble material was crystallized from trichloroethylene yielding 11 g. of hexachlorobenzene. The soluble material was crystallized from ethanol yielding 110 g. of ethylpentachlorobenzene. Fraction 2 was crystallized as in the previous case from trichloroethylene-alcohol yielding 403 g. of V and 94 g. of IV. Fraction 3 was also crystallized from trichloroethylene-alcohol and gave only 32 g. of V. When Fraction 4 was crystallized from trichloroethylene–alcohol (1:2) both rods and a powder deposited. The two were separated by floating off the powder with mother liquor and were then crystallized separately to yield pure VII, m. p. 132–133° and pure VI, m. p. 143–143.5°. In all we isolated only 11 g. of VII and 7 g. of VI. Crystallization of Fraction 5 from trichloroethylene–alcohol (2:1) gave only 10 g. of hexachlorobenzene.


## Summary

To determine the relative amounts of $\alpha$- and $\beta$-chlorination of ethylpentachlorobenzene at 70–75° and 180° the crude chlorination products were treated in the Friedel–Crafts reaction with benzene and the products of this reaction were then separated by standard methods. To identify the products formed 1-pentachlorophenyl-1-phenylethane, 1-pentachlorophenyl-2-phenylethane and 1-pentachlorophenyl-1,2-diphenylethane were synthesized from starting materials of known structure.

At 70–75° the ratio of $\beta$- to $\alpha$-chlorination is approximately 1.6:1 and at 180° almost 4.6:1, thus indicating a lower activation energy for the $\alpha$-chlorination. This lends support to the mechanism previously postulated to account for the difference in the direction of chlorination and bromination of ethylpentachlorobenzene.


RECEIVED AUGUST 5, 1948

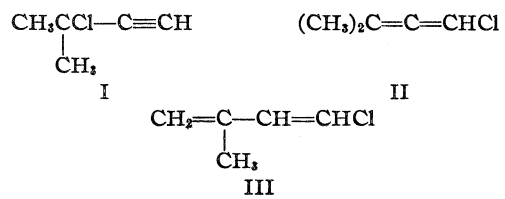
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# The Reaction of Dialkylethynylcarbinols with Acidic Reagents

BY CHARLES D. HURD AND WARREN D. MCPHEE[1]

Several branched isomers of the formula $C_5H_7Cl$ are reported in the literature. One such is 3-chloro-3-methyl-1-butyne (I) formed by reaction of dimethylethynylcarbinol with hydrochloric

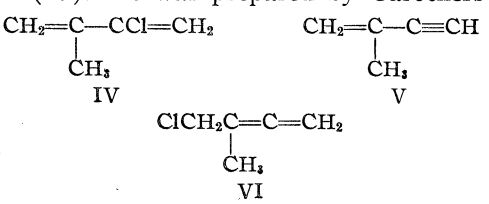


acid (at 20°) in the presence of cupric (or cuprous) chloride and ammonium chloride.[2] Apparently it was stable during distillation, b. p. 74–76°. The compound reacted with ammoniacal silver nitrate and underwent hydrolysis in the presence of calcium carbonate to the original carbinol. On standing in the presence of cuprous and ammonium chlorides, (I) gradually rearranged into isomers which were indifferent toward ammoniacal silver nitrate and which were assigned structures II (b. p. 101–104°) and III (b. p. 97.5–98°, $d^{20}_4$ 0.9543). II was indifferent, but III was reactive toward maleic anhydride, giving rise to four products of m. p. 210, 239, 298, 352°. Oxidation of II by potassium permanganate yielded acetone and $\alpha$-hydroxyisobutyric acid.

(1) Holder of Commercial Solvents Corporation Fellowship, 1938–1940. Present address: G. D. Searle and Company, Chicago, Illinois.

(2) Favorskiĭ and Favorskaya, *Compt. rend.*, **200**, 839 (1935); Favorskaya, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 386, 1237 (1939); Favorskaya and Zakharova, *ibid.*, **10**, 446 (1940).

Another isomer is 2-chloro-3-methyl-1,3-butadiene (IV). It was prepared by Carothers and



Coffman[3] by addition of hydrochloric acid to methylbutenyne (V) in the presence of ammonium chloride and cuprous chloride. It possessed constants (b. p. 93° with some polymerization, 37° (105 mm.), $d^{20}_4$ 0.9593, $n^{20}D$ 1.4689) which are remarkably close to those given for III. The substance was volatile in steam and polymerizable to a jelly on standing for five days in a tube containing a trace of air. It underwent the Diels–Alder reaction with $\alpha$-naphthoquinone, the yield of adduct not being given. Oxidation of the adduct gave the known 2-chloro-3-methylanthraquinone, which is confirmatory evidence for structure IV.

The present work also deals with a product of formula $C_5H_7Cl$ which was obtained by interaction of hydrochloric acid with dimethylethynylcarbinol. A chloride of structure IV would be expected (via V + HCl) on the basis of the behavior of other related ethynylcarbinols[4] toward acidic reagents. Certain facts agreed with this expecta-

(3) Carothers and Coffman, THIS JOURNAL, **54**, 4071 (1932); Carothers and co-workers, *ibid.*, **53**, 4203 (1931); **54**, 4066 (1932).

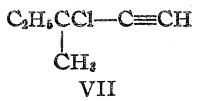
(4) Hurd and Jones, *ibid.*, **56**, 1924 (1934); Hurd and Christ, *ibid.*, **59**, 118 (1937).

tion. It was volatile in steam. It polymerized to a brown-black gum if kept for a few hours at room temperature. It underwent the Diels–Alder reaction (42% yield). The adduct with maleic anhydride melted at 124–126°. On the other hand, it was not distillable without polymerization unless quite low pressures were used. Also, the refractive index of the distilled material was low ($n^{20}$D 1.445). Any allene isomer VI that might have been present (also via V + HCl) should have caused a higher index of refraction, not a lower one. This follows from the observation that for the pair of lower homologs, 4-chloro-1,2-butadiene and chloroprene, the compound with the allene structure possesses[3] the higher refractive index (1.4775 and 1.4583, respectively).

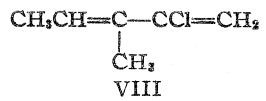
In view of the above facts, ozonolysis was undertaken to help elucidate the structure. A compound of structure I should yield acids but no aldehydes, whereas IV should yield formaldehyde and acetic (or pyruvic) acid in a 2:1 ratio. Our chloride did yield formaldehyde in this operation. It was identified by its reaction with 2-naphthol, a procedure used by Carothers[3] in the identification of formaldehyde following ozonolysis of 4-chloro-1,2-butadiene. Reaction of the formaldehyde (present work) with methone revealed a yield of 36%. The quantity of IV actually present must, therefore, have been far in excess of 36%, since this value corresponds to the isolated yields[5] of aldehydes obtained by ozonolysis of olefins. A quantitative determination of acetic acid showed that two moles of formaldehyde were obtained on ozonolysis for each mole of acetic acid obtained after further oxidation. Direct oxidation of the substance also afforded acetic acid, characterized by means of Duclaux constants and its *p*-bromophenacyl ester. Since none of the other isomers could behave in this manner, this provides strong support for structure IV.

The question arises why this material differs from the chloroisoprene obtained by Carothers and Coffman. No certain answer is at hand, but since it was prepared from dimethylethynylcarbinol, possibly it contains some I as well as IV. This would explain the lower refractive index but would not account for the instability during vacuum distillation. Furthermore, if Carothers' sample of IV contained a little VI, the latter would bring about a higher refractive index. These questions cannot be answered definitely with the present evidence.

The study was extended to methylethylethynylcarbinol. Campbell[6] used concentrated hydrochloric acid, whereas Favorskaya and Zakharova[2] used this acid in the presence of cuprous and ammonium salts. Structure VII was assigned to the product. The chlorine in this compound (b. p. 48–50° (100 mm.), 51–52° (135 mm.), $n^{20}$D 1.4331) should be reactive, and we found that a comparable sample of it ($n^{20}$D 1.4332) did readily convert silver nitrate solution into silver chloride That some isomeric VIII was present also was confirmed by ozonolysis and characterization of formaldehyde. VIII has been synthesized previously (b. p. 57–60° (96 mm.), $n^{20}$D 1.4671) from 3-methyl-3-penten-1-yne.[3]



VII



VIII

Reaction of dimethylethynylcarbinol with formic acid has been stated by Rupe[7] to yield isopropylideneacetaldehyde, $(CH_3)_2C{=}CHCHO$, but no direct proof of this structure was offered. Traces of it may have been formed,[8] but probably the bulk of any $C_5H_8O$– material was the isomeric[4] 1-methylvinyl methyl ketone, $CH_2{=}C(CH_3)–COCH_3$. In the present investigation it was found that dimethylethynylcarbinol yields only traces of a carbonyl derivative when treated with formic acid. The main product was methylbutenyne (V), indicating that the initial reaction was one of dehydration. 1-Methylvinyl methyl ketone was obtained by first hydrating the ethynylcarbinol in the presence of mercuric acetate to 3-methyl-3-hydroxy-2-butanone and then dehydration of the latter by means of *p*-toluenesulfonic acid. This unsaturated ketone had been prepared previously by Morgan[9] in poor yield by the condensation of formaldehyde with methyl ethyl ketone followed by dehydration. Synthesis by this method demonstrated the identity from the two sources. The compound was shown to possess the structure indicated rather than ethyl vinyl ketone by ozonization to formaldehyde and diacetyl. Oxidation with chromic acid[10] gave 1.2 moles of acetic acid per mole of ketone. Hydrogenation of the unsaturated ketone afforded methyl isopropyl ketone, identified by its carbonyl derivatives.

## Experimental

### Reactions of Dimethylethynylcarbinol

**Hydrochloric Acid.**—When shaken at room temperature for ten to twenty minutes with an excess of concentrated hydrochloric acid, dimethylethynylcarbinol is easily converted to an organic chloride. In a typical experiment, 10 ml. (0.1 mole) of dimethylethynylcarbinol was shaken in a separatory funnel for fifteen minutes with 30 ml. (0.3 mole) of concentrated hydrochloric acid. The solution turned from light to dark green, and a light green-yellow oil separated. This was removed and dried in the refrigerator with anhydrous potassium carbonate. The weight of dried liquid after filtration was 7.5 g. or 73%.

Sometimes the oil was removed from the reaction mixture by distillation, then separated and dried. In general, the purity of the material isolated this way was no higher than if it was simply separated from the reaction mixture, because polymerization set in during distillation. The yields (60–70%) were usually less for the same reason.

(5) Church, Whitmore and McGrew, THIS JOURNAL, **56**, 176 (1934).

(6) Campbell, Campbell and Eby, *ibid.*, **60**, 2882 (1938).

(7) Rupe and Kambli, *Helv. Chim. Acta*, **9**, 672 (1926); Rupe, U. S. Patent 1,670,825 (1928).

(8) Chanley, THIS JOURNAL, **70**, 244 (1948).

(9) Morgan and Holmes, *J. Chem. Soc.*, 2667 (1932); British Patent 404,317; Morgan and Griffith, *ibid.*, 841 (1937).

(10) Hurd and Pollack, *ibid.*, **3**, 550 (1939).

Distillation at reduced pressure from a water-bath at 30–40° did not prevent polymerization nor give a purer product. The presence of such substances as hydroquinone or picric acid were ineffectual as inhibitors and a considerable tar was formed even when they were taken. Refractive index ($n^{20}D$) of product isolated in this manner ranged from 1.431 to 1.441.

**Dry Hydrogen Chloride.**—Dry hydrogen chloride was passed into 10 ml. (0.1 mole) of dimethylethynylcarbinol at 0° for thirty hours. The mixture became deep red, but never tarry or immobile as was often the case at higher temperatures. The product was treated with anhydrous sodium carbonate. The top layer was separated and dried with fresh carbonate. The yield of product, $n^{20}D$ 1.4440, was 6 g. or 52%.

*Anal.* Calcd. for $C_5H_7Cl$: Cl, 34.7. Found: Cl, 35.0.

In another experiment, 30 ml. (0.3 mole) of dimethylethynylcarbinol was saturated with dry hydrogen chloride at 0°. In thirteen hours the reaction mixture gained 13 g. in weight, after which it gained no more. The mixture was always mobile and free from tar. The product was worked up as in the preceding experiment; $n^{20}D$ 1.4447, yield 20 g. or 67%.

**Distillation.**—A 20-g. sample of the crude reaction product was distilled through a Davis column.[11] The flask was maintained at 0° in an ice-bath and the head of the column was cooled to −35° with Dry Ice and acetone. Pressure was lowered and adjusted until reflux was established. Ten grams of colorless distillate was collected at −8 to −7° and 5–6 mm.; $n^{20}D$ 1.4453.

**Ozonization.**—Five grams of product, $n^{20}D$ 1.4435, dissolved in 40 ml. of anhydrous carbon tetrachloride, was treated at 0° with the theoretical amount of ozone. After decomposition[5] of the ozonide, the total volume of aqueous solution was 38 ml. Five ml. of this solution was decolorized with Norit and then refluxed with one drop of concentrated hydrochloric acid and 0.1 g. of 2-naphthol. The crystals of methylenedi-2-naphthol were separated from the boiling solution and were recrystallized from dilute alcohol. The m.p.[12] and mixed m.p. was 203–204°.

The 2-naphthol method is not quantitative for formaldehyde. Dimethyldihydroresorcinol (methone), however, precipitates[13] formaldehyde from very dilute solutions (0.0018 g. per 100 ml.). To 2 ml. of the solution from the ozonization, after decolorization and neutralization, was added 250 ml. of an aqueous solution containing 1.5 g. of dimethyldihydroresorcinol. After twelve hours, 0.55 g. (0.0019 mole) or 36% yield of methylenebis-dimethyldihydroresorcinol was collected. It melted[14] at 187–188° after recrystallization from alcohol.

Another 5 ml. of the ozonized solution was treated with 50 ml. of 3% hydrogen peroxide.[15] The solution was refluxed until gases were no longer evolved (ninety minutes), then distilled. Since the Duclaux constants (7.7, 8.7, 10.8) corresponded to no acid, the solutions were recombined and oxidized for fifteen minutes with refluxing chromic acid solution[16] (6 g. of potassium dichromate, 15 ml. of concd. sulfuric acid, 100 ml. of water). The volatile acid was removed completely by exhaustive distillation[10] and shown to contain 0.0028 mole of acid. That it was acetic acid was shown by Duclaux constants: 6.5, 6.9, 7.4. The neutralized solutions were evaporated and the sodium salt was placed in reaction with 0.5 g. of *p*-bromophenacyl bromide to form *p*-bromophenacyl acetate, m.p. and mixed m.p. 84°.

Chromic acid solution as prepared above will oxidize formic acid quantitatively without affecting acetic acid. Hence the total acetic acid in the total ozonization mixture was 0.0213 mole. The total formaldehyde was 0.0365 mole. The ratio of formaldehyde to acetic acid was, therefore, 1.7 to 1.

**Reaction with Maleic Anhydride.**—Five ml. of the product ($C_5H_7Cl$) was treated with 2.3 g. of maleic anhydride. The mixture was boiled gently and the anhydride dissolved to form an amber solution. The solid obtained on cooling was recrystallized twice from dry pyridine. The white needles of 1,2,3,6-tetrahydro-4-chloro-5-methylphthalic anhydride melted at 124–126°; yield, 2 g. (42%). It dissolved readily in water.

*Anal.* Calcd. for $C_9H_9ClO_5$: equiv. wt., 100.3. Found: equiv. wt., 102.3, 98.06.

**Reaction of Methylethylethynylcarbinol with Hydrochloric Acid.**—Forty grams (0.4 mole) of methylethylethynylcarbinol was shaken for fifteen minutes with 200 ml. (2 mole) of concentrated hydrochloric acid. The mixture became warm and dark on shaking. The light yellow top layer was separated, dried at 0° with potassium carbonate, filtered, and distilled through a 60-cm. column packed with nichrome helices. The material was not of uniform composition, since of the 23 g. (48% yield) collected in several fractions, between 100–103°, $n^{20}D$ values change from 1.4222 to 1.4385. Of this, 10 g. had b.p. 102.5–102.7°, $n^{20}D$ 1.4332, which corresponds to the chloride described by Campbell.[4] This material is exceptionally more stable than the lower homolog obtained from dimethylethynylcarbinol.

**Oxidation.**—A mixture of 5.5 g. of this chloride (b.p. 102.5–102.7°) and 100 ml. of water was added to a chromic acid solution (48 g. potassium dichromate, 120 ml. concd. sulfuric acid, 400 ml. distilled water). The mixture was refluxed for three hours and the volatile acid was completely removed by exhaustive distillation. Titration revealed 0.0943 mole of acid, or 2.0 moles of acid per mole of substance oxidized. The distillate gave no test for sulfate or chloride. Duclaux constants were satisfactory for acetic acid (7.1, 7.5, 7.9). One gram of the dry salt, obtained by neutralizing the acid, was converted to *p*-bromophenacyl acetate, m.p. and mixed m.p. 84–85°.

**Ozonization.**—The product (9.1 ml.), b.p. 102.5–102.7°, was dissolved in 50 ml. of dry carbon tetrachloride and treated with ozone as above outlined to yield 35 ml. of an aqueous solution of formaldehyde, from which methylenedi-2-naphthol, m.p. 203–204°, was obtained by reaction as before with hydrochloric acid and 2-naphthol.

**Reaction of Dimethylethynylcarbinol with Formic Acid.**—When this reaction was carried out in the manner outlined by Rupe,[7] a pure product was never isolated. A typical run consisted in refluxing 24 ml. (0.6 mole) of 85% formic acid with 9.8 ml. (0.1 mole) of dimethylethynylcarbinol for two and one-half hours. The solution soon became dark. It was cooled, extracted thrice with ether, and the extracts were washed with sodium carbonate solution, dried and distilled. Three grams of the carbinol was collected between 100–107° ($n^{20}D$ 1.421) and 1.1 g. of distillate was collected in three fractions between 107–130° ($n^{20}D$ 1.425, 1.429, 1.447). All fractions, even the carbinol collected, gave semicarbazones of m.p. 214°. Rupe gives the m.p. of "isopropylideneacetaldehyde" semicarbazone as 244°, but recrystallization never raised the m.p. of our semicarbazone above 214°.

To isolate methylbutenyne, 17.2 g. (20 ml.) of dimethylethynylcarbinol and 50 ml. of 85% formic acid were refluxed under a condenser maintained at 50–60°. Volatile material was conducted into a trap at 5° and another at −78°. After fourteen hours of refluxing, 10.2 g. of volatile product was condensed by the cold traps. The yield of methylbutenyne, b.p. 31–34°, $n^{20}D$ 1.4105 was 9.7 g. or 72%. Similar boiling points were reported by Carothers[3] and Scheibler and Fischer.[17] The product gave definite voluminous precipitates with potassium mercuric iodide solution[18] and with ammoniacal silver nitrate.

**Dehydration of 3-Methyl-3-hydroxy-2-butanone.**—Thirty grams of 3-methyl-3-hydroxy-2-butanone, prepared by the method of Scheibler and Fischer,[17] was added

(11) Davis, *Ind. Eng. Chem., Anal. Ed.*, **1**, 61 (1929).
(12) Hurd and Blunck, THIS JOURNAL, **60**, 2419 (1938), list 204°.
(13) Ionescu and Slusanschi, *Bull. soc. chim.*, [4] **53**, 908 (1933).
(14) Vorlander, *Ann.*, **294**, 253 (1896), lists 189°.
(15) Hurd and Williams, THIS JOURNAL, **58**, 962 (1936).
(16) Macnair, *Chem. News*, **55**, 229 (1887).
(17) Scheibler and Fischer, *Ber.*, **55**, 2903 (1922).
(18) Johnson and McEwen, THIS JOURNAL, **48**, 469 (1926).

dropwise to 5 g. of *p*-toluenesulfonic acid in a distilling flask in an oil-bath at 150°. Of the 30 g., 14.5 g. was recovered. The 1-methylvinyl methyl ketone steam distilled directly. It was dried with Drierite and distilled, b.p. 94–98°; yield, 10 g. The yield, based on the unrecovered starting product, was 74%.

The semicarbazone of this ketone was prepared from 1 g. of the ketone and recrystallized twice from water. It melted at 178°.

*Anal.* (method of Smith and Wheat[19]). Calcd. for $C_6H_{11}N_3O$: $NNHCONH_2$, 51.74. Found: $NNHCONH_2$, 51.63.

**Preparation of 1-Methylvinyl Methyl Ketone.**—A modification of Morgan's method[9] was used, taking 108 g. of methyl ethyl ketone, 225 g. of 40% formalin, and 25 ml. of 2 *N* sodium hydroxide solution. The initial reaction is vigorous and requires a long, efficient reflux condenser. There was obtained 36 g. of 3-methyl-4-hydroxy-2-butanone, b.p. 95–110° (18 mm.). This was dehydrated to 1-methylvinyl methyl ketone by distillation with a trace of iodine, instead of with potassium acid sulfate as used by Morgan. The yield was increased by this change. The product was dried (sodium sulfate) and distilled; b.p. 94–97°, $n^{20}D$ 1.4224. The yield of 14 g. is an over-all yield of 11%. Morgan reported 4%. The semicarbazone of this ketone (m.p. 178°) did not depress the m.p. of that prepared above.

**Ozonization.**—A solution of 5.2 g. of 1-methylvinyl methyl ketone in 50 ml. of carbon tetrachloride (dried with Drierite) was treated at 0° with ozone as outlined above to form an aqueous solution (35 ml.) neutral to litmus, containing aldehydes and ketones. A 5-ml. sample of the solution, treated with 0.5 g. of semicarbazide hydrochloride and 0.5 g. of anhydrous sodium acetate and kept at 0°, gave rise to 0.46 g. (31% yield) of biacetyl semicarbazone. After recrystallization from alcohol, it melted at 273–275° (d.). When mixed with an authentic specimen, the m.p. of 277–277.5° was not depressed.

Another 5-ml. portion was treated with 0.02 g. of 2,4-dinitrophenylhydrazine in 5 ml. of aqueous alcoholic sulfuric acid solution. Gradually at 0°, yellow crystals of formaldehyde 2,4-dinitrophenylhydrazone, m.p. 165–167° (d.), appeared.

**Oxidation.**—Two and one-half grams of 1-methylvinyl methyl ketone was heated with a solution of 21 g. of potassium dichromate, 52 ml. of concentrated sulfuric acid and 175 ml. of water. After the evolution of carbon dioxide ceased (thirty minutes), the mixture was refluxed for thirty minutes. It was then distilled.

Duclaux constants: 7.4, 7.5, 8.0; 7.5, 7.9, 8.6; 7.0, 7.5, 8.2, agree better for acetic acid, 6.8, 7.1, 7.4, than for propionic acid, 11.9, 11.7, 11.3. The neutral solution from the Duclaux measurements was evaporated to 2 ml. and converted into *p*-bromophenacyl acetate, m.p. 83–84°.

A sample (0.670 g. or 0.00796 mole) of 1-methylvinyl methyl ketone was oxidized as above, but with the oxidizing mixture diluted to half the previous concentration. The acetic acid was distilled slowly in an all-glass system until crystals formed. The distillate, which gave no test for sulfate, contained 0.00897 mole of acetic acid, or 1.2 moles of acid per mole of ketone oxidized.

(19) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

**Hydrogenation.**—Twenty-six grams (0.31 mole) of 1-methylvinyl methyl ketone, dissolved in 25 ml. of pure pentane, was hydrogenated at 25° and 1000 pounds pressure in the presence of 3 g. of a reduced nickel catalyst.[20] The hydrogen absorbed was 0.31 mole. From the filtered solution was obtained 19.5 g. of methyl isopropyl ketone (75% yield), collected in several fractions. Of the total yield, 13.2 g. of the ketone had b.p. 93–98°, $n^{20}D$ 1.3875–1.3890.

All fractions also gave 2,4-dinitrophenylhydrazones, m.p. 119–122° after recrystallization from alcohol, and semicarbazones of m.p. 110–113° after recrystallization from water. The 2,4-dinitrophenylhydrazone of the known sample of methyl isopropyl ketone melted at 121° after recrystallization. Allen[21] lists the m.p. as 117°. The mixed m.p.'s were not depressed.

**Reaction of Dimethylethynylcarbinol with Ketene.**—The calculated quantity of ketene was passed into a cold (0°) solution of dimethylethynylcarbinol (10 ml.) in 10 ml. of dry carbon tetrachloride containing a drop of concentrated sulfuric acid. The solution was then neutralized with a little potassium carbonate and distilled to give 9.6 g. (74%) of a clear, pungent liquid, b.p. 126–128°. Nearly all the ester boiled sharply at 128°. Scheibler and Fischer[17] reported the b.p. as 128–136°. The dimethylpropargyl acetate gave a voluminous precipitate with ammoniacal silver nitrate solution. Its saponification equivalent was 125; calculated, 126.

## Summary

The reaction of dimethylethynylcarbinol with hydrochloric acid is not one of simple metathesis but gives rise to an extensive production of 2-chloro-3-methyl-1,3-butadiene or chloroisoprene. This conclusion is based on methods involving oxidation, ozonolysis, and reactivity toward maleic anhydride.

Methylethylethynylcarbinol reacts with hydrochloric acid to yield the metathetic product, 3-methyl-3-chloro-1-pentyne, but evidence was found for 2-chloro-3-methyl-1,3-pentadiene in this material. The product was much more stable than that from dimethylethynylcarbinol.

Ketene reacts smoothly with dimethylethynylcarbinol to produce 1,1-dimethylpropargyl acetate. With formic acid, however, the carbinol undergoes dehydration into methylbutenyne which was capable of being hydrated to 3-methyl-3-hydroxy-2-butanone. Evidence for the structure of the latter was dehydration into 1-methylvinyl methyl ketone which underwent catalytic hydrogenation to methyl isopropyl ketone.

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(20) Ipatieff and Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938).

(21) Allen, THIS JOURNAL, **52**, 2955 (1930).

[CONTRIBUTION FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

# Electron Exchange-Polymers. I

BY HAROLD G. CASSIDY

## Introduction

This paper, and subsequent ones in this series, will describe experimental results and theoretical conclusions which had their inception in the author's idea that it should be possible to prepare polymeric substances capable of reversibly exchanging electrons with the molecules or ions of a contiguous phase.

Polymeric substances of this character have been prepared and this unusual exchange property has been successfully demonstrated. The behavior is thus analogous to that of the cation exchange-polymers, some of which are able to exchange protons for other cations in a contiguous phase. It can now be stated that two of the fundamental particles, the electron and the proton, can be reversibly exchanged between polymeric substances and contiguous phases in much the same manner.

The exchange of a cation may be considered, in the sense of the generalized theory of oxidation and reduction,[1] to involve an oxidation and reduction, though electrons are only displaced in the process. The exchange of electrons would be an extreme case, and would correspond to the classical oxidation and reduction.

Analogies have frequently been pointed out between the behaviors of protons and electrons. Clark[2] has referred to this. Schwarzenbach[3] has proposed that an acid–base equilibrium be described by a normal acidity potential $E_{ac}$ defined by the equation

$$E = E_{ac} + \frac{RT}{F} \ln \frac{[\text{Acid}]}{[\text{Base}]}$$

in analogy to the oxidation–reduction equilibrium for which the normal oxidation potential of the system $E_{ox}$ is defined by

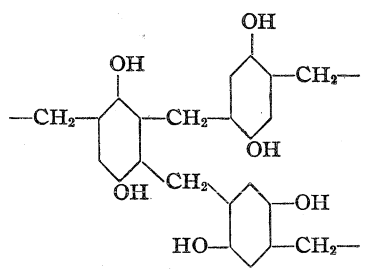
$$E = E_{ox} + \frac{RT}{F} \ln \frac{[\text{Ox.}]}{[\text{Red.}]}$$

Michaelis and Schubert[4] comment that in the field of ionization theory the acceptance of protons is the analog of the elementary reduction process. Schubert[5] has discussed the analogy between two-step ionization and two-step oxidation. There is thus ample background indicating the formal resemblance between proton exchange and electron exchange. However, the differences observed in working with the two phenomena has caused their theoretical treatments to proceed along different lines, as Schubert has pointed out.[5a]

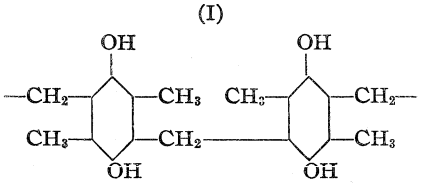
Proton exchange by cation exchange-polymers is conditioned in part by the hydrogen ion concentration of the phase contiguous to the exchanger. The electron exchange would be expected to be controlled in part by the availability of electrons to the exchanger, where availability involves potential, and the ability of the exchanger to accept them. It remained to be investigated how close the analogy would be between the two processes. The problem of constructing and establishing an electron exchanger turned out to be more difficult than had been at first anticipated. However, I am now able to report successful verification of the concept.

The electron exchange-polymer consists of given residues, capable of entering an oxidation–reduction system, which are bound together by linkages which do not necessarily interfere seriously with (though they may influence) the functional oxidizable or reducible groups. This permits building up a polymeric structure with many sites capable of accepting or donating electrons.

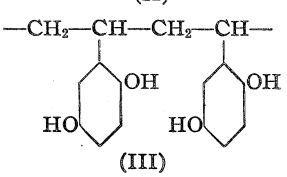
In setting up this problem, two classes of polymeric substances were considered: (1) those in which the active group forms a part of the backbone of the polymer chain, and (2) those in which the active group is a substituent on the chain. Class 1 consists of substances of the types hydroquinone–formaldehyde resins (I), substituted hy-



(I)



(II)



(III)

(1) See A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, Chapter 4.

(2) W. M. Clark, "The Determination of Hydrogen Ions," Williams and Wilkins, Baltimore, Md., 1928, 3d ed., Chapter XVIII.

(3) G. Schwarzenbach, *Helv. Chim. Acta*, **13**, 870 (1930).

(4) L. Michaelis and M. P. Schubert, *Chem. Revs.*, **22**, 437 (1938).

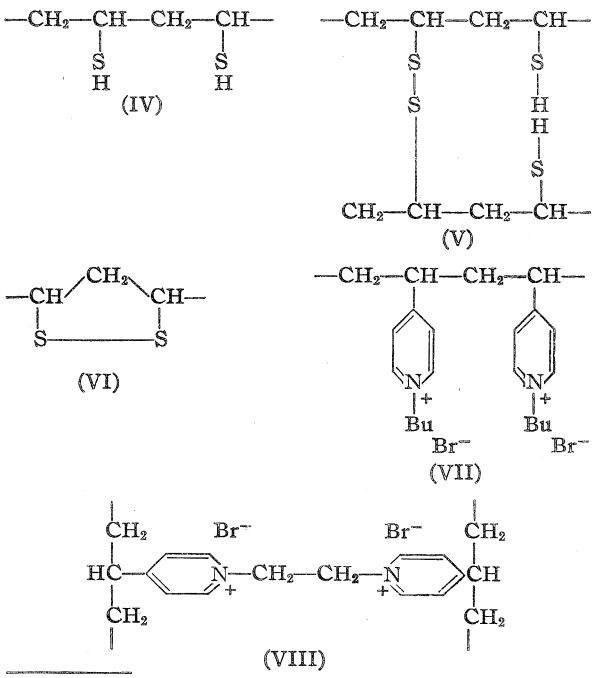
(5) M. Schubert, *Ann. New York Acad. Sci.*, **40**, 111 (1940).

(5a) Reference 4, p. 113.

droquinone-formaldehyde resins (II), and similar substances. To Class 2 belong substances like polyvinylhydroquinone (III).

The substances belonging to Class 1 would be expected to exhibit effects due to the constraints of linking and cross-linking; distortions of the ring so produced might be reflected in the observed potentials of half-reduction, or in the propensity toward semiquinone formation,[4,7] and the effects might be expected to be more marked than those exhibited for the same reason by compounds of the second class. The change from oxidized to reduced form might, in the first case (Class 1), be reflected in a marked change in polymer dimensions, since the longer diameter of the quinone ring is about 0.26 Å. longer than the diameter of the hydroquinine ring.[8] Changes in polymer dimensions and other physical properties with reduction or oxidation might also be expected in compounds of Class 2 if there were, for example, a dimerization of adjacent semiquinoid forms, or if resins of the type IV were on mild oxidation to cross-link (V) or form rings (VI).

A further classification of exchange-polymers in terms of charge-type of the oxidized form may be made: (a) the oxidized form carries no charge (*e. g.*, of III or IV), and (b) the oxidized form carries a positive charge, as would be the case with a polymer such as butyl polyvinylpyridinium halide (VII).[9] These charge-types might be found in polymers of Class 1 or Class 2. An example of a polymer belonging to Class 1b would be polyvinylpyridinium bromide cross-linked with the ethylene bridge (VIII).[10]




The idea of electron exchangers and the hypothesis based upon it have been illustrated with specific structures (I to VIII) but naturally many other chemical examples could have been chosen. These would differ in oxidizable groups, *e. g.*, indophenols might be used, or other groupings found in oxidation–reduction indicators and similar but colorless substances. They might differ in methods of linking of monomers, *e. g.*, instead of the illustrated type of linking, polyesters, ethers, polyamides, might be produced.

## Experimental

It seemed desirable to make an initial test of this hypothesis against a relatively simple polymeric substance, and for this reason polymerized vinylhydroquinone was chosen. This substance was prepared (see the following paper) from vinylhydroquinone, a new compound, prepared by decarboxylation of dihydroxycinnamic acid. This substance was prepared from *o*-hydroxycinnamic acid by the method of Neubauer and Flatow.[11] The resin was a pale yellow, polystyrene-like material, not very soluble in benzene, soluble in some organic liquids such as glacial acetic acid, and becoming tacky in water. It was extracted with benzene to remove monomer.

The oxidation titrations reported in this and the following paper were carried out in the conventional manner,[12] using a bright platinum electrode referred to a saturated calomel electrode. The potentials were read with an L. & N. Student Potentiometer. Equilibrium was taken to have been reached when the same potential was read at the end of each of three successive minutes following 30 sec. mechanical stirring and 30 sec. without stirring. The data were recorded to the nearest tenth of a millivolt and calculated to the standard of the normal hydrogen half-cell. The temperature was that of the room. In common with the observations of other workers,[13] the greatest variations in mid-point potential were found with changes in solvent systems.

The oxidation of polymerized vinylhydroquinone could be carried out in solution in 90% acetic acid according to the method of Michaelis and Hill.[14] In the experiment reported here 90 parts of glacial acetic acid was made up to 100 by adding water, and the *p*H (glass electrode) found was −0.45. Polymerized vinylhydroquinone (12.094 mg., 0.1777 me.) was dissolved in 10 ml. of acetic acid solution and titrated with 0.0359 *N* bromine solution in the same solvent. Room temperature was 23°. During the course of the titration the solution developed a pinkish-orange coloration. The system came to equilibrium slowly, but stable potentials were obtained except at the beginning and very end of the titration, when there was evident a tendency to a slow drift of the potential downwards. The course of the titration is shown in Fig. 1. The mid-point potential was −0.713 v.; the final *p*H approximately −0.6. The end-point, if all the hydroquinone residues had been available, should have come at 4.95 ml. bromine solution; found, a little over 4.90 ml. The abscissa of the curve in Fig. 1 is calculated on 4.95 ml. as 100% oxidation. Included in Fig. 1 for reference purposes are the titration data for hydroquinone and ethylhydroquinone. 10.043 mg. of recrystallized hydroquinone

(7) L. Michaelis, *Chem. Revs.*, **16**, 243 (1935); *Ann. New York Acad. Sci.*, **40**, 39 (1940).

(8) Determined graphically from data given by J. M. Robertson, *Chem. Revs.*, **16**, 417 (1935); *Proc. Roy. Soc.* (*London*), **A150**, 106 (1935).

(9) G. I. Cathers, Dissertation, Yale University, 1948; R. M. Fuoss and U. P. Strauss, *J. Polymer Sci.*, **3**, 246 (1948).

(10) G. I. Cathers, Dissertation, Yale University, 1948.

(11) O. Neubauer and L. Flatow, *Z. physiol. Chem.*, **52**, 375 (1907).

(12) L. Michaelis, "Potentiometry," in "Physical Methods of Organic Chemistry," A. Weissberger, ed., Interscience Publishers, New York, N. Y., 1946, p. 1051.

(13) H. Gilman, Editor, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 812.

(14) L. Michaelis and E. S. Hill, THIS JOURNAL, **55**, 1481 (1933).

in 10 ml. 90% acetic acid ($p$H 0.0) was titrated with bromine in the same solvent; final $p$H *ca.* −0.4; room temperature 24°. For the latter, 12.918 mg. of ethylhydroquinone in 10 ml. of acetic acid–water, $p$H −0.45, was titrated with bromine in the same solvent. The final $p$H was *ca.* −0.6. In Fig. 1, a curve is drawn through the points for the polymerized vinylhydroquinone for increased ease of visualization.

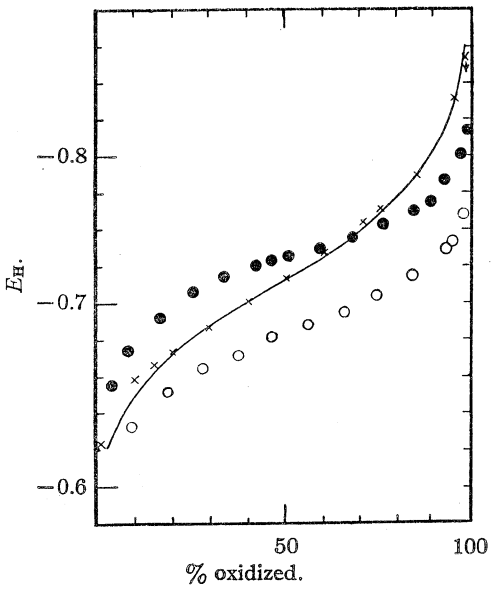



Fig. 1.—Oxidation of polymerized vinylhydroquinone, of hydroquinone and of ethylhydroquinone in solution in aqueous acetic acid with bromine in the same solvent: $E_H$ potential in volts referred to the normal hydrogen electrode: ×, polymerized vinylhydroquinone; $p$H, −0.45 to −0.6; temperature 23°. The line is drawn through the points to improve visualization of the curve. ⁑, this point showed a slight downward drift. ●, hydroquinone, $p$H 0.0 to −0.4, temperature 24°; O, ethylhydroquinone, $p$H −0.45 to −0.6, temperature 23°.

The oxidation of polymer in solution was thus shown to be possible. It was found difficult to show stoichiometric electron exchange when the polymer was in the solid form in bulk. When the polymer was dispersed by dissolving *ca.* 10 mg. in 0.1 ml. glacial acetic acid and adding 10 ml. of buffer in which the polymer was insoluble, milky-white suspensions were formed which with the first drop of oxidant became orange-opalescent, and which on further oxidation threw down a curdy, orange precipitate. The oxidized form of the resin is orange-yellow in color.

It was decided to disperse the polymer with a carrier or stabilizer. It then became possible to obtain more nearly quantitative oxidation and to obtain clear evidence of the reversible oxidation of the polymer. Polymerized vinylhydroquinone (14.871 mg., 0.2185 me.) was dissolved in 0.15 ml. of glacial acetic acid and treated with 10 ml. of buffer (sulfuric acid–potassium sulfate) containing 2.44 mg. ($3.5 \times 10^{-5}$ millimole) of bovine plasma albumin (Armour, crystalline). A milky suspension formed. This was titrated under nitrogen with ceric sulfate, $p$H 0.54, 0.0279 *N*. At the first drop of oxidant the suspension began to flocculate and a pinkish-orange color developed. The color became somewhat more intense as the titration progressed, and the precipitate, now brick-red, became dispersed. As the mid-point was passed the color of the precipitate became gradually less red until it was quite noticeably paler at the end-point. The potential changed quite suddenly, between 6.10 and 6.25 ml. cerate, from −0.466 to −0.72 v. (against the saturated calomel electrode). The calculated end-point for equivalence was 7.83 ml. assuming all hydroquinone residues available. The difference between the calculated and found volumes of ceric sulfate is ascribable to polymer inside the particles of precipitate and thus inaccessible to oxidant. At this point the titration was stopped, purified hydrogen gas led in, and 0.5 ml. palladium catalyst added[15] with stirring.

A platinized electrode came to a stable potential of −0.2730 v. against the calomel half cell ($p$H 0.46) after one and one-quarter hours. The vessel was then flushed with nitrogen for two and one-half hours, until the potential had fallen −0.13 v.[14] The suspension was now grayish (*i. e.*, polymer reduced) and there was a small amount of granular orange precipitate (unreduced polymer) present. Titration with ceric sulfate was again carried out, an orange color and flocculation of the precipitate appearing with the first drops of oxidant. The course of this titration followed closely that of the first one. The $p$H of the final solution was 0.50. The amount of cerate used at the end-point was 5.1 ml., indicating again that some polymer was unavailable. The potential data, calculated for per cent. oxidation based on the amount of oxidant actually used, are shown in Fig. 2 and indicate good agreement between the two experiments. A separate test of the albumin solution showed the amount of oxidant used to be inconsequential.

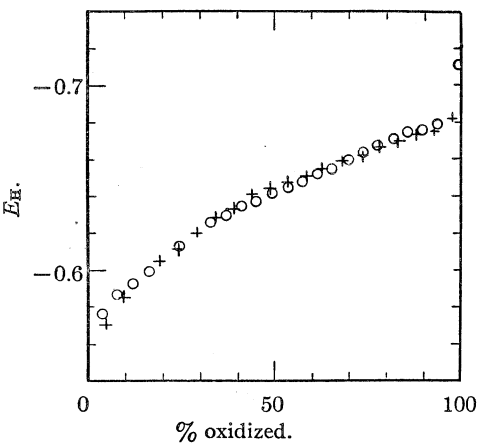



Fig. 2.—Oxidation, and reoxidation following reduction, of polymerized vinylhydroquinone suspended in the presence of albumin: $E_H$ potential in volts referred to the normal hydrogen electrode: O, oxidation with ceric sulfate, $p$H 0.54; +, repetition of above after reduction with hydrogen and removal of excess hydrogen; final $p$H 0.50.

A titration of polymerized vinylhydroquinone dispersed at another $p$H is given in the following paper, together with reference titrations of other substances and a summary of pertinent data. A large number of titrations of the polymer have been made under a variety of conditions. Some of the curves obtained have shown unusual features difficult as yet to interpret. The curves given in this and the following paper are quite reproducible on repetition of the given experiments.

## Discussion

The slopes of the curves which can be drawn for hydroquinone and ethylhydroquinone speak for a bivalent oxidation, while the slopes of the polymerized vinylhydroquinone curves are near that of a monovalent oxidation (see Figs. 1 and 2).

(15) 0.05 g. $PdCl_2 \cdot 2H_2O$ dissolved with 0.05 g. of gum arabic in 50 ml. of water. See J. Houben, "Die Methoden der organischen Chemie," 3rd ed., 2, p. 325 (method of Paal and Skita).

The interpretation of these curves is of interest, especially in connection with the use of these polymers as models of more complicated systems. Michaelis and his co-workers[16] have already formulated the theory for the slopes of the potentiometric titration curves. According to their analysis the rather flat curves are obtained when there is no appreciable semiquinone formation, and no appreciable dimerization; that is, when there is no appreciable formation of an intermediate compound during the oxidation of the reduced form of the substance or the reduction of the oxidized form.

For substances which form no intermediate the slope ($\delta$) at the mid-point of the curve is 0.026 volts per unit of $\mu$, where $\mu$ has the following meaning: at 0% oxidation $\mu = -1$; at 50% oxidation $\mu = 0$; at 100% oxidation $\mu = +1$. At the mid-point the index potential $E_i$, which is defined as the potential difference between 50% oxidation and 25% (or 75%) oxidation, is 0.0143 v. at 30°. If appreciable intermediate compound formation occurs it is recognized from the slope of the titration curve. With increase in intermediate formation $\delta$ increases and $E_i$ increases, and when the amount of intermediate formation becomes great enough points of inflection appear in the curves below and above the midpoint. The formation of semiquinone intermediate is increased if the *p*H of the medium is such that ionization of the substance is aided, for the increased number of resonance forms of the semiquinoid ion stabilize it as compared with the un-ionized semiquinone form. Thus the shapes of these curves will vary with *p*H.

Under the acid conditions employed in these experiments hydroquinone and ethylhydroquinone show no appreciable semiquinone formation. The semiquinone form of hydroquinone, and presumably of the other compound, is not stable in aqueous solution. In solution the rate of its dismutation is so great that little semiquinone can accumulate. Thus when quinhydrone is dissolved in acid a pale yellow solution is obtained rather than the highly colored solution which would be expected of this greenish-brown substance. Accordingly in the titrations (Fig. 1) hydroquinone showed $E_i$ 20, 14 mv.; $\delta$, 27 mv. per unit of $\mu$. Ethylhydroquinone showed $E_i$ 22, 22 mv.; $\delta$ *ca.* 42 mv. per unit of $\mu$.

When polymerized vinylhydroquinone is titrated in the dissolved state the initially colorless solution becomes pink-orange with the first drop of oxidant. With further addition of oxidant the pink-orange color becomes more intense, the pinkness becoming more marked. After the titration has proceeded some distance the solution begins to lose its pinkness and a yellow color supervenes. This sequence of colors could be produced if the polymer were in colloidal suspension and were to pass through a sequence of particle-size changes with its oxidation. This possibility has not been experimentally ruled out. The effective particle size might change if a thread-like molecule were to bunch up, or to become extended; or if many molecules were to clump together reversibly; and such behavior might occur under the influence of the added electrolyte or through a dimerization of semiquinoid forms within a molecule or between molecules, or through mechanisms such as discussed by Rabinowitch and Epstein.[17]

Against this interpretation of the color change are the observations that the same color sequence appears whether the oxidizing agent is bromine, cerate (or dichromate—see paper II), and whether the titration is carried out in a solution of a given concentration or in a solution one-tenth as concentrated. The same sequence of colors with these different oxidizing agents argues against a particle-size change due to the influence of added electrolyte, because the charge-type changes are so different. The lack of influence of dilution, the same shape of curve being obtained experimentally with a ten-fold difference in concentration, argues against an association of molecules. However, when the dispersed polymer is titrated with cerate the particles have been observed to flocculate, to be peptized, and to reflocculate at different stages during the titration (see above) when the stirring is stopped to enable a reading, but this behavior does not seem to influence the color of the solution and suspended matter. These present arguments are admittedly qualitative, and further pursuit of this phase of the problem is of course contemplated.

A more likely explanation of the color change seems to lie in semiquinone formation, with or without accompanying dimerization. In the polymeric molecules large numbers of oxidizable groups are held in a more or less constrained relation to each other. If some of these groups were to be oxidized to the semiquinone stage (the first step[16] in the oxidation) then even though the semiquinone were inherently easily dismutable (as judged by analogy with hydroquinone itself) yet since it requires the *conjunction* of two semiquinoid forms for dismutation to occur the constraints of the linkage might well hamper the dismutation. While this would not stabilize the semiquinone it would certainly allow it to accumulate. If optical examination of the polymer during the oxidation showed not a peak of color formation at 50% oxidation, but a plateau over a range of added oxidant, this supposition would receive support.

It seems to us, therefore, that the color change observed during the course of the titration can best be explained on the basis of the formation of some semiquinone. The formation of semiquinone would account for the appearance of the pink color, the yellow being attributable to the fully quinoid residues.

(16) L. Michaelis, *Chem. Revs.*, **16**, 243 (1935); L. Michaelis and M. P. Schubert, *ibid.*, **22**, 437 (1938); L. Michaelis, *Ann. New York Acad. Sci.*, **40**, 39 (1940).

(17) E. Rabinowitch and L. F. Epstein, THIS JOURNAL, **63**, 69 (1941).

There is in this interpretation a possible explanation of an observation by Haas[18] that the combination of the active group of yellow ferment with its specific protein in the presence of a large excess of triphosphopyridine nucleotide allows on reduction at *p*H 7 (0°) the appearance of an amount of the red free-radical form which is otherwise observed with the *free* active group only in strongly acid solution, where the increased ionization of the free substance allows increased resonance stabilization. It was inferred from this observation that the Michaelis relation of radical dismutation[16] was displaced toward the radical. The mechanism which our observations suggest is that the active group when combined with the specific protein into the ferment complex is so isolated from other active groups that accumulation of radical is favored by the hampering of dismutation, and not *necessarily* by a stabilizing of the radical form.

The formation of semiquinone would also account satisfactorily for the increased slope of the curve for polymerized vinylhydroquinone (Fig. 1). Here $E_i$ was found to be 32 and 35 mv., and $\delta$ *ca.* 70 mv. per unit of $\mu$. It has seemed to us, however, that there is another phenomenon which might and probably does contribute to the shape of the curve, and which would be adequate of itself to account for the slope were not the special color change observed during the titration. This other phenomenon is treated in the following paper.

The behaviors of all the polymers so far investigated indicate a certain instability toward very strong oxidizing agents, and tendency toward some further reactions. Thus in strong acid (hydrochloric, etc.) with ceric sulfate some oxidation of the quinones might be expected, as well as addition of the acid to the unsaturated system. Or, with the reduced polyvinylpyridinium compounds further reduction might be anticipated, or addition of reactants from the medium, as observed by, for example, Karrer, *et al.*,[19] when the dihydropyridinium products of hydrosulfite reduction were found to contain sulfur. These problems will be discussed in succeeding papers. It need only be mentioned here that strong oxidizing agents slowly destroy hydroquinone–formaldehyde resins, and a strong reducing agent seems to carry the reduction of polyvinylpyridinium polymer beyond the dihydro stage.

These results, together with those reported in the paper which follows, indicate quite conclusively that electron exchange-polymers can be and have been prepared. It will no doubt be possible by appropriate variations in structure, reaction medium and *p*H, to run the gamut of reduction potentials with these substances. Some control of *p*H is to be expected if ion exchange monomer were copolymerized with an electron exchanger.

Apart from the very interesting theoretical problems opened up by the development of these substances their production makes possible a systematic attack from a new direction on a number of important biochemical problems. Early in this work it was suggested to me by Dr. G. J. de Suto-Nagy that these polymers might serve as models for certain biological systems. It might be possible to investigate some of the problems stated by, for example, Korr,[20] for here one could work with a heterogeneous system in which structurally-known constraining arrangements (as in Class 1 polymers) might be introduced, or constraints of other kinds such as those due to copolymerization with basic or acidic monomer. The activating or deactivating effects of such constraints, reflected in the semiquinone formation constants, for example, might well find analogies in biological systems. It might be supposed,[21] for example, that the reduction–oxidation polymers might serve as catalysts in organic and other oxidations through their ability to take up electrons and pass them on to other molecules, in a function which has been laid to the coenzyme.[22]

We have in these electron exchange-polymers a new chemical instrument by means of which many interesting chemical and biochemical problems may be attacked. Emphasis should probably be laid on the value of these polymers as substances by means of which convenient, simplified models of much more complicated systems may be contrived.

**Acknowledgment.**—I would like to acknowledge the stimulating discussions of this problem held with Dr. Charles S. Cleaver, Dr. G. J. de Suto-Nagy, Dr. Joseph Fleischer, Mr. Robert A. Hardy, Mr. Harold K. Inskip, Dr. F. H. M. Nestler, Mr. Ivor H. Updegraff and Mr. Vincent Verplanck.

## Summary

The hypothesis that electron exchange-polymers could be produced has been advanced and tested by oxidation studies made on a polymerized vinylhydroquinone. Analogies to the proton exchange-resins have been pointed out. During the oxidation of the polymer, whether in solution or in a dispersed solid form, a pink color develops. This is interpreted to indicate the accumulation of semiquinoid residues the dismutation of which is hampered by the constraints of the polymer structure. An observation of E. Haas on the effect of the combination of yellow ferment with its specific protein on free-radical formation has been reinterpreted. The possible usefulness of electron exchange-polymers in attacking certain biochemical problems has been mentioned.

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(18) E. Haas, *Biochem. Z.*, **290**, 291 (1937).

(19) P. Karrer, F. W. Kahnt, R. Epstein, W. Jaffe and T. Ishii, *Helv. Chim. Acta*, **21**, 223 (1938).

(20) I. M. Korr, *Cold Spring Harbor Symposium on Quantitative Biology*, **7**, 74 (1939).

(21) See, for example, H. A. Abramson and I. R. Taylor, *J. Phys. Chem.*, **40**, 519 (1936); L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **119**, 133 (1937); and E. S. G. Barron, *Physiol. Revs.*, **19**, 184 (1939).

(22) See, for review, L. Michaelis and C. V. Smythe, *Ann. Rev. Biochem.*, **7**, 1 (1938).

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

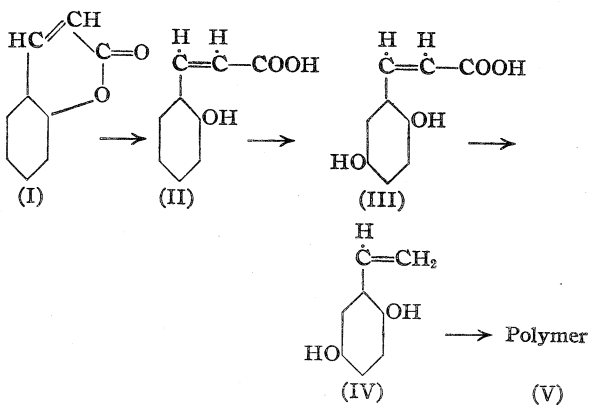
# Electron Exchange-Polymers. II. Vinylhydroquinone Monomer and Polymer

BY IVOR H. UPDEGRAFF AND HAROLD G. CASSIDY

## Introduction

A previous paper[1] set forth the requirements for an electron exchange-polymer and showed that these requirements are met by a polymerized vinylhydroquinone. This paper discusses, and describes the preparation and properties of, vinylhydroquinone and polymerized vinylhydroquinone.

The synthetic scheme is illustrated by structures I to V




Coumarin (I) was converted to *o*-coumaric acid (II) by refluxing it with sodium ethylate according to the directions of Ebert.[2] The *o*-coumaric acid was then converted to 2,5-dihydroxycinnamic acid (III) by treating it with potassium persulfate according to the method of Neubauer and Flatow.[3] The decarboxylation of 2,5-dihydroxycinnamic acid was carried out by heating the free acid under reduced pressure in a sublimation apparatus to a temperature slightly above its melting point. The vinylhydroquinone (IV) produced by the loss of carbon dioxide sublimed as it was formed together with some of the unchanged acid.

For polymerization, the vinylhydroquinone was sealed in a glass tube under reduced pressure and heated to 125° for many hours without added catalyst. Within the first minutes of heating the monomer melted to a pale amber, mobile liquid. This became very viscous within the course of an hour. After cooling, the polymer was extracted with hot benzene to remove unchanged or slightly polymerized monomer.

Vinylhydroquinone has not been previously described. It is a colorless crystalline solid which melts at 111°. Its identity was established by ultimate analysis as well as by catalytic hydrogenation to the known compound ethylhydroquinone.

(1) H. G. Cassidy, THIS JOURNAL, **71**, 402 (1949).
(2) G. Ebert, *Ann.*, **226**, 347 (1884).
(3) O. Neubauer and L. Flatow, *Z. physiol. Chem.*, **52**, 375 (1907).

Polymerized vinylhydroquinone is a pale amber, brittle solid. It is soluble in polar organic solvents and insoluble in benzene. In the presence of water it becomes soft and tacky. An attempted catalytic hydrogenation failed to reveal unsaturation. The oxidation equivalent determined by mild oxidation is that which would be expected for the conversion from the hydroquinoid to the benzoquinoid form of a polymer in which the functional hydroxyl groups are not involved in cross-linking. The polyquinone so produced is a reddish-orange solid, insoluble in water but easily soluble in most organic solvents, and attacked by strong oxidizing agents.

## Experimental

***o*-Coumaric Acid.**—Coumarin (E. K. Co.) was converted to *o*-coumaric acid by refluxing it for four hours with sodium ethylate, diluting with water, removing most of the solvent *in vacuo*, and neutralizing with concentrated hydrochloric acid. The purified acid was obtained in a yield of 82%; m. p. 207–208° with dec.; neutralization equivalent calcd. 164, found 162.5.

**2,5-Dihydroxycinnamic Acid.**—Coumaric acid (93 g., 0.57 mole) was dissolved in a solution of 160 g. of sodium hydroxide in 3 liters of water. To this solution was added 170 g. of potassium persulfate as a slurry in 1 liter of water. The solution was swirled until all the persulfate had dissolved and was then allowed to stand for twenty-four hours. Concentrated hydrochloric acid was added in small amounts until the solution was red to methyl orange. It was then extracted with ethyl ether in a continuous extractor for twenty-four hours. The extract (35 g.) consisted principally of unchanged coumaric acid. The remaining solution was treated with 600 ml. of concentrated hydrochloric acid and the extraction continued for one week. The crude extract (54 g.) which remained after the evaporation of the ether was puddled with fresh ether and the solid retained on a Büchner funnel. The solid (crude 2,5-dihydroxycinnamic acid) was further purified by treatment with activated charcoal in boiling water. It crystallized from water in the form of needles. Even after repeated crystallization the acid retained a pale green color; yield 23 g. (0.13 mole, 23%); m. p. 208° with decomposition; neutralization equivalent calcd. 180, found 178.5.

**Vinylhydroquinone.**—2,5-Dihydroxycinnamic acid (5 g., 0.028 mole) was charged to a vacuum sublimation apparatus, the pressure reduced to approximately 0.01 mm., and the bulb heated in an oil-bath to 200°. Decarboxylation began at this temperature. The temperature was then slowly raised to 220° over a period of one hour. When the apparatus had cooled the crude sublimate was scraped from the cold surface. It was mixed with about 50 ml. of benzene and the mixture heated to boiling. The warm solution was then filtered to remove unchanged 2,5-dihydroxycinnamic acid which had sublimed with the vinylhydroquinone. On cooling the solution vinylhydroquinone separated as colorless needles; yield 1.45 g. (0.01 mole, 38%), m. p. 111°, cor.

*Anal.* Calcd. for $C_8H_8O_2$: C, 70.59; H, 5.92. Found: C, 70.17, 70.61; H, 5.83, 5.99.

Vinylhydroquinone (0.0934 g., 0.000686 mole) was dissolved in 15 ml. of ethyl acetate and treated with hydrogen at atmospheric pressure in the presence of Adams catalyst. Volume of hydrogen adsorbed (S.T.P.) 16.4 ml., calcd. 15.4. The hydrogenation mixture was decanted from the

catalyst and the ethyl acetate removed under reduced pressure. The residue was dissolved in about 3 ml. of warm benzene and allowed to cool. Colorless crystals were obtained, m. p. 115°. Ethylhydroquinone[4] melts at 113–114°. This material was titrated with ceric sulfate: oxidation equivalent calcd. 69.08, found 70.5.

**Polymerized Vinylhydroquinone.**—Approximately 1 g. of vinylhydroquinone was placed in a glass tube, evacuated to approximately 1 mm. and sealed off. The sealed capsule was placed in an oven at 125° for one hundred hours. After cooling, the brittle solid which had formed was powdered and treated three times with boiling benzene, the successive portions of benzene being decanted from the insoluble residue. The product was an amber, brittle solid, insoluble in benzene, soluble in alcohol, acetic acid, ether and acetone, somewhat soluble in boiling water, becoming soft and tacky in cold water. This material was titrated with bromine in 90% acetic acid.[5] Oxidation equivalent calcd. 68.06, found 68.

Oxidations were carried out[1] on polymerized vinylhydroquinone, hydroquinone and a number of related substances.

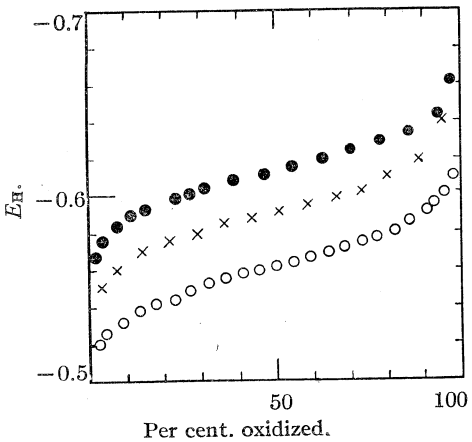



Fig. 1.—Oxidation of hydroquinone, vinylhydroquinone and ethylhydroquinone: $E_H$, potential in volts referred to the normal hydrogen electrode; ●, data for hydroquinone, *p*H 1.3, no. (1) in experimental part; ×, data for vinylhydroquinone, *p*H 1.3, (7); ○, data for ethylhydroquinone, *p*H 1.26, (4).

Figure 1 shows the data for hydroquinone, vinylhydroquinone and ethylhydroquinone oxidized in solution in 50% acetic acid; Fig. 2 shows the data for hydroquinone, ethylhydroquinone, and dispersed polymerized vinylhydroquinone; Fig. 3 shows the curve for dispersed polymerized vinylhydroquinone from Fig. 2, and the curve for a mixture of hydroquinone and ethylhydroquinone. Pertinent data from these titrations and those reported previously[1] are gathered below. $E_0$ is the mid-point potential referred to the normal hydrogen half-cell and calculated to a *p*H of 0. $E_i$ is the index potential, the potential difference between 50% oxidation and 25% (or 75%) oxidation. $\delta$ is the slope at the midpoint of the titration curve, and was determined graphically from our data. $\delta$ is given in millivolts per unit of $\mu$, where $\mu$ is −1 at 0% oxidation, 0 at 50% oxidation and +1 at 100% oxidation. The implications of these values are given in Paper I.[1] The nomenclature is that of Michaelis.[6]

**Oxidation of Hydroquinone.**—(1) (Fig. 1) 7.76 mg. in 10 ml. 50% acetic acid, oxidized with potassium dichromate in 50% acetic acid. Final *p*H 1.3; *T ca.* 28°.

(4) T. B. Johnson and W. W. Hodge, THIS JOURNAL, **35**, 1014 (1913).

(5) L. Michaelis and E. S. Hill, *ibid.*, **55**, 1481 (1933).

(6) L. Michaelis, *Chem. Revs.*, **16**, 243 (1935); L. Michaelis and M. P. Schubert, *ibid.*, **22**, 437 (1938); L. Michaelis, *Ann. New York Acad. Sci.*, **40**, 39 (1940).

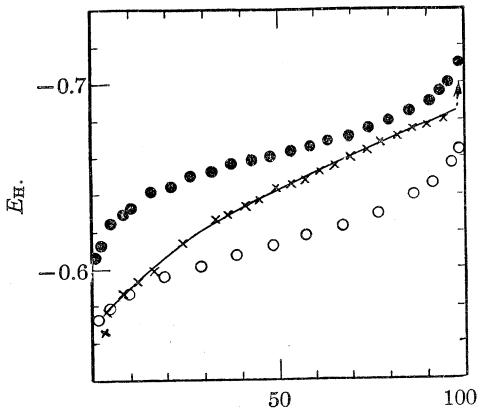



Fig. 2.—Oxidation of polymerized vinylhydroquinone compared with that of hydroquinone and ethylhydroquinone: $E_H$, potential in volts referred to the normal hydrogen electrode; ●, data for hydroquinone, *p*H 0.54, no. (2) in experimental part; ×, data for polymerized vinylhydroquinone, *p*H 0.54 to 0.50, (8); ○, data for ethylhydroquinone, *p*H 0.5, (5).

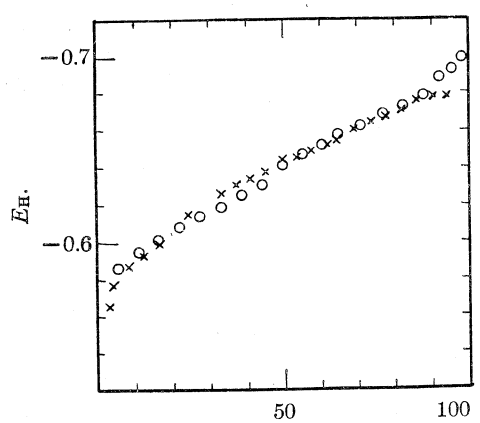



Fig. 3.—Comparison of oxidation of polymerized vinylhydroquinone with oxidation of a mixture of hydroquinone and ethylhydroquinone: $E_H$, potential in volts referred to the normal hydrogen electrode; ×, data for polymerized vinylhydroquinone, as in Fig. 2; ○, data for a mixture of hydroquinone and ethylhydroquinone, *p*H 0.54, (10). The correspondence of the two curves is probably fortuitous; the shapes are of chief interest.

$E_0$ −0.697; $E_i$ 13 and 14 mv.; $\delta$ 26 mv. per unit of $\mu$. (2) (Fig. 2) 14.777 mg. in 10 ml. sulfuric acid–potassium sulfate buffer *p*H 0.53 oxidized with ceric sulfate, *p*H 0.54. $E_0$ −0.692; $E_i$ 13, 14 mv.; $\delta$ 24 mv./$\mu$. (3) (Fig. 1, Paper I) 10.043 mg. in 10 ml. 90% acetic acid (*p*H 0.0) titrated with bromine in 90% acetic acid. Final *p*H *ca.* −0.4; *T* 24°. $E_0$ −0.697; $E_i$ 20, 14 mv.; $\delta$ 27 mv./$\mu$.

**Oxidation of Ethylhydroquinone.**—(4) (Fig. 1) 17.311 mg. in 10 ml. 50% acetic acid, with dichromate. Final *p*H 1.26; *T* 20°. $E_0$ −0.636; $E_i$ 16, 14 mv.; $\delta$ 27 mv./$\mu$. (5) (Fig. 2) 9.5 mg. in 10 ml. sulfuric acid–potassium sulfate buffer, with cerate. *p*H 0.5; *T* 26°. $E_0$ −0.644; $E_i$ 14, 15 mv.; $\delta$ 23 mv./$\mu$. (6) (Fig. 1, Paper I) 12.918 mg. in 10 ml. acetic acid–water, *p*H −0.45. Titrated with bromine in same solvent. Final *p*H *ca.* −0.6. $E_0$ *ca.* −0.65; $E_i$ 22, 22 mv.; $\delta$ *ca.* 42 mv./$\mu$.

**Oxidation of Vinylhydroquinone.**—(7) (Fig. 1) 5.13 mg. in 10 ml. 50% acetic acid, with dichromate. Final *p*H 1.3, $E_0$ −0.667; $E_i$ 13, 12 mv.; $\delta$ 23 mv./$\mu$.

**Oxidations of Polymerized Vinylhydroquinone (PVH).**—(8) (Figs. 2 and 3) 14.871 mg. in 0.15 ml. acetic acid mixed with 10 ml. sulfuric acid–potassium sulfate buffer containing 2.44 mg. of albumin.[1] *p*H 0.54 to 0.5; *T* 25°. $E_0$ −0.673; $E_i$ 28 and 22 mv.; "$\delta$" 45 mv./$\mu$. (9) (Fig. 1, Paper I). 12.094 mg. in 10 ml. acetic acid–water, *p*H −0.45, with bromine in the same solvent. Final *p*H −0.6; *T* 23°. $E_0$ −0.679; $E_i$ 32, 35 mv.; $\delta$ *ca.* 70 mv./$\mu$. A number of titrations of PVH have been carried out with and without albumin and in solution and dispersed. The mid-point potentials ($E_m$) have hardly ever been more than 10 mv. different, but the slopes have varied considerably. The curves given are typical ones. The titration behavior of this polymer needs considerable study. The amount of albumin used was from 2 to 3 mg. in these experiments. In a separate experiment this was found equivalent to 0.052 to 0.08 ml. of 0.0279 *N* cerate at *p*H 0.5, with an $E_m$ of −0.680 v. The effect of this small amount of albumin seemed to be to render a little less sharp the end-point of the titration, the $E_m$ of the albumin lying usually well above that of the other reductant.

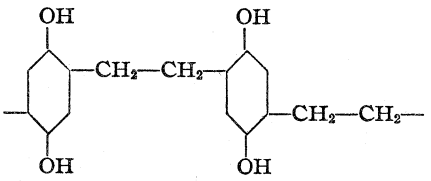
**Oxidation of Mixture.**—(10) (Fig. 3) 6.832 mg. (0.0696 me.) hydroquinone and 4.162 mg. (0.0603 me.) ethylhydroquinone in 1 ml. of acetic acid mixed with 10 ml. of sulfuric acid–potassium sulfate buffer and titrated with cerate. Final *p*H 0.54; *T* 27°; $E_0$ −0.672; $E_i$ 29, 27 mv.; "$\delta$" 55 mv./$\mu$.

## Discussion

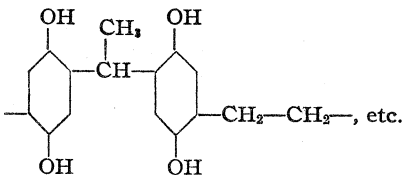
It may appear odd that vinylhydroquinone should undergo polymerization readily when hydroquinone is an inhibitor for styrene polymerization. It was in fact found that vinylhydroquinone was somewhat more effective than hydroquinone itself in delaying the polymerization of styrene. This is in accord with the proposal of Cohen[7] concerning the relative ease of oxidation of hydroquinones and their effectiveness as inhibitors of polymerization. Vinylhydroquinone is more readily oxidized than hydroquinone (see above) and hence would maintain a lower concentration of free radicals in any polymerization mixture.

Vinylhydroquinone itself, however, polymerizes quite rapidly. Perhaps the rate of chain propagation is greater than the rate at which free radicals are destroyed by oxidizing vinylhydroquinone to vinylquinone. An alternative explanation may be that the interaction of a free radical with an hydroxyl group of vinylhydroquinone does not lead to an inert product because the odd electron may migrate to the vinyl group where further chain growth may be initiated. Hence the type of chain-terminating reaction characteristic of hydroquinone merely leads to chain transfer in the case of vinylhydroquinone. On this supposition one might expect vinylhydroquinone to be a chain transfer agent in styrene polymerization rather than an inhibitor. The fact that it does inhibit styrene polymerization throws some doubt on the second of the explanations given above.

Some suppositions may be made regarding the structure of the polymer formed from vinylhydroquinone. It has been suggested[8] that the very active *o*-hydrogens may become involved in the reaction, leading to a certain amount of linking of the types VI and VII. This possibility has not been excluded. The following considerations make it seem that we may be dealing with a polyvinyl hydroquinone: (1) The substance appears to be polymeric:




(VI)




(VII)

The monomer is soluble in benzene, while even boiling benzene did not dissolve the polymer appreciably. (2) The substance has the physical appearance of polystyrene and is soluble in polar organic solvents. When this is combined with the observation that hydroquinone–formaldehyde polymers are dark in color and insoluble it would appear a reasonable conclusion that there is not much cross-linking of the types VI and VII present. The analogy is not strict, however, for phenols are known to polymerize with formaldehyde in part through –OH interactions and this may account for the differences noted. (3) The majority of the –OH groups in the polymer are free to be oxidized and reduced, as shown by the oxidation data. (4) The mid-point potential falls at a reasonable value between those of hydroquinone and ethylhydroquinone, and close to that of vinylhydroquinone. This is strong evidence that there is not much substitution on the rings such as would be suggested by the structures VI and VII and similar ones. At the suggestion of a Referee experienced in this field we have used the term polymerized vinylhydroquinone to describe the polymer rather than polyvinylhydroquinone until more concrete evidence can be brought to bear on the structure.

The increased slope and the shape of the oxidation curve of the polymer were interpreted in the previous paper[1] as possibly due to the accumulation of semiquinone during the titration. This interpretation was based on the appearance of a pink color near the beginning of the titration, its persistence during the titration, and its diminution toward the end-point, and the relation between color-formation, semiquinone formation and increased slope of the titration curve as worked out by Michaelis and his co-workers.[6] A mechanism for the accumulation of semiquinone was suggested in the hampering of dismutation un-

(7) S. G. Cohen, THIS JOURNAL, **69**, 1057 (1947).

(8) By Mr. George W. Barber.

der the constraints put on the oxidizable residues by their being fastened on a long chain. It has seemed to us, also, that another phenomenon may contribute to the slope and shape of the titration curve of the polymerized vinylhydroquinone.

It may be assumed that the spatial arrangement of an oxidizable residue relative to other residues may affect its ease of oxidation through interactions such as might arise from hydrogen-bonding, dimerization, purely geometrical (steric) effects, as well as from actual differences in linkage such as were suggested in a previous paper.[1] If this were correct then it would follow that over these polymer chains there would be a spread of residues with different oxidizabilities, and during a titration the more easily oxidizable ones would go first (with the usual equilibrium restrictions), the more difficultly oxidizable ones requiring a higher potential. The titration curve would thus be "smeared out" over a wider potential range than for a single substance. To test this in a simple way a mixture of hydroquinone and ethylhydroquinone was titrated. The data obtained are shown in Fig. 3 in relation to the data for polymerized vinylhydroquinone. The slope of this curve ("$\delta$") was about 0.055 v. per unit of $\mu$. At no point during the titration was any color observed other than the pale yellow of the quinoid forms of the substances. A "statistical" effect such as this would complicate the interpretation of these curves. While we suspect that both the semiquinone formation and the statistical effect contribute to the total result we are not yet able to apportion to each its part. The correspondence of curves in Fig. 3 is probably fortuitous.[9]

The increased slope of the titration curve and the sequence of colors reported above for titrations of polymerized vinylhydroquinone in solution were observed also for the polymer dispersed in the presence of albumin. Another not unexpected observation was also made in these cases. With the dispersed polymer it was not possible to oxidize quite a number of the groups present. It seemed as though some of the groups, known to be present from in-solution oxidations of the resin, were unavailable when the resin was dispersed in a particulate form. The usual titration curves were obtained, however, when drawn on the basis of per cent. actually oxidized. When the resin was dispersed in the presence of a little albumin it seemed that more groups became available, though not all. In an experiment reported earlier[1] 77.8% were found in the presence of albumin, and upon reduction with hydrogen and retitration, 65% were reoxidizable. Some may have become unavailable due to conglomeration of the particles, or steric factors,[1] and some may have been destroyed by the oxidant. In another experiment with about 10 times as much albumin it seemed possible to titrate a larger percentage of the polymer groups, but the oxidation of albumin complicated matters. In a titration of the polymer (0.1863 me.) with bromine at a *p*H of 0.53 in the presence of 2.24 mg. of albumin (10 ml. solution) 86% of the groups could be titrated. Inaccessibility of certain groups to certain oxidizing agents might also affect the shape of the titration curve from an oxidant of one charge type or molecular size to another.

It will be interesting to determine the behavior of the polymer dispersed with polysaccharide and other natural and synthetic polymeric carriers. The stoichiometry of these combinations is also under investigation. It is further of interest to note that due to the constraints mentioned above the curves for the dispersed polymer are to a large extent linear, thus a normally logarithmic relationship has been converted to one substantially arithmetic.

(9) A Referee called our attention to a paper by Kern (W. Kern, *Z. physik. Chem.*, **A181**, 249 (1938)) on the titration of polyacrylic acids, where a spread of dissociabilities could be expected. The titration curve showed a slope different from that of isobutyric acid.

## Summary

Potentiometric titration curves are given for hydroquinone, ethylhydroquinone, vinylhydroquinone, and compared with the curve for polymerized vinylhydroquinone. Explanations are advanced for the differences observed, and the new features which appear in the titration of the electron exchange-polymer are discussed.

NEW HAVEN, CONN. RECEIVED JUNE 26, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

# The Electric Moments of Some Organic Molecules in the Vapor State[1]

BY EUNICE M. MOORE[2] AND MARCUS E. HOBBS

The desirability of measuring the electric moments of molecules in the gas phase is well recognized although, in the case of some substances, the experimental difficulties may make such measurements impracticable. The present series of determinations were undertaken with the object of increasing the number of electric moment values established from vapor phase measurements since, with such values, a detailed inquiry may be made into the basis and extent of various intramolecular interactions such as deviations from additivity of the vector bond moments of molecules. This paper reports the results of the first of a series of such vapor phase measurements carried out in this Laboratory.

## Materials and Method

The materials were Eastman Kodak Company best grade chemicals and each was fractionated in a 60-cm. Widmer column, the middle fraction being used for the measurement. The distilling temperatures and pressures (cor.) are given. The range when not indicated was of the order of 0.01°.

| | | |
|---|---|---|
| Fluorobenzene | 84.74– 84.76° | at 760.0 |
| Chlorobenzene | 131.24–131.25° | at 745.9 |
| *o*-Dichlorobenzene | 179.7° | at 746.2 |
| *o*-Fluorotoluene | 113.1° | at 755.0 |
| *m*-Fluorotoluene | 115.1° | at 755.0 |
| *p*-Fluorotoluene | 115.5° | at 755.0 |

*m*-**Difluorobenzene.**—This compound was prepared by Mr. Irving Waltcher in this Laboratory. The details of the preparation have been reported.[3] The n. b. p. of the fraction used was 83.05° and the f. p. −59.3°.

**Diethyl Ether.**—One sample of this material was Merck "pro analysi" grade and was subjected to no purification as the results of the measurements were to be compared with some values reported in the literature. The other sample was purified by refluxing over sodium and finally distilling from fresh sodium. The distillation range of the fraction used was 34.51–34.52° at 760 mm. (cor.).

**Methyl Ethyl Ether.**—This compound was prepared from ethyl bromide and sodium methylate by the Williamson reaction. The product was repeatedly fractionated until it was free of bromides when treated with alcoholic potassium hydroxide and was inactive toward metallic sodium. The approximate distillation temperature was 10.2° at 755 mm. (cor.).

The apparatus has been described elsewhere.[4] The method employed follows. The gas system was evacuated to < 0.05 mm. and flushed twice with the vapor to be measured. The vapor was then introduced until a usable pressure for the given temperature was obtained. After thermal equilibrium was established the gas condenser capacitance was placed in parallel with a high precision air condenser by an appropriate switching device and the pressure in the gas system slowly reduced to some lower level. After thermal equilibrium was established at the lower pressure the new setting of the high precision capacitor necessary to bring the total capacitance of the measuring circuit back to its original value was determined. Slight frequency drifts that took place during the manipulations and waiting periods were compensated for by making all readings with reference to a fixed air capacitance. The above procedure was repeated until the total pressure in the gas system was of the order of 20–30 mm.

The values of capacitance measured as above were then plotted against pressure and the resulting line extrapolated to zero pressure. The total change in capacitance caused by the gas was therefore the sum of all capacitance changes from zero pressure up to the particular pressure under consideration. The capacitance change caused by the gas was generally found to be linear with the measured values of the pressure in the pressure ranges involved, the small deviations from linearity being randomly distributed. All changes were measured in terms of a capacitance calibration unit ($\Delta S$) which was equivalent to about 0.4 mmf. In view of the observed linearity the average value of $\Delta S/p$ was generally used for calculating the molar polarization, $P$, of the gas at the particular temperature. In case of a real drift of $\Delta S/p$ values with $p$ the extrapolated value of $\Delta S/p$ at $p = 0$ was used. $P$ was calculated from

$$P = \frac{\Delta SRT}{p3C_{g_e}}$$

Here $R$ is the molar gas constant $T$ the temperature in °K. and $C_{g_e}$ is the insulator free "effective"[4] vacuum capacitance of the gas condenser. The use of this effective gas capacitance obviates the necessity of applying inductance corrections to the measured $\Delta S$ values. The average value of $C_{g_e}$ for the temperature range involved was 2685 $\Delta S$ units and since the temperature coefficient was very small the average value of $C_{g_e}$ was used. The values of $A$ and $B$ in the relation $P = A + B/T$ were obtained by least squares and the value of $\mu_{D(B)}$, in debyes was obtained from the relation

$$\mu_{D(B)} = 0.01281\sqrt{B}$$

An alternative way of calculating the moment is the method used by Wenzke,[5] Smyth[6] and others in which use is made of the relation

$$\mu_{D(R)} = 0.01281\sqrt{(P - R_D)T}$$

In the present work $\mu_D$ is calculated by both methods with $R_D$, the molecular refraction for the sodium lines, taken as[7]: $C_6H_6 = 26.14$, $C_6H_5CH_3$

(1) Part of a thesis of Eunice M. Moore submitted in partial fulfillment of the requirements of the Ph.D. degree in Chemistry at Duke University, June, 1939.

(2) Present address, Massachusetts General Hospital, Boston, Massachusetts.

(3) I. Waltcher, M.A. Thesis, Duke University, Durham, N. C., 1939.

(4) Hobbs, Jacokes and Gross, *Rev. Sci. Instruments*, **11**, 126 (1940).

(5) Krieger and Wenzke, THIS JOURNAL, **60**, 2115 (1938).

(6) Hannay and Smyth, *ibid.*, **68**, 1005 (1946).

(7) W. Hückel, "Theoretische Grundlagen der organishen Chemie," Vol. II, 2nd Ed., Akademische Verlagsgesellschaft, Leipzig, 1935, pp. 86 and 134.

= 3.106, C = 2.418, H = 1.100, Cl = 5.967, O (ether) = 1.643 and F[8] = 1.00.

TABLE I

| Substance | $T$ | $1/T \times 10^3$ | $\Delta S \times 10^2$ | $P$ | $\mu_{D(R)}$ |
|---|---|---|---|---|---|
| Fluorobenzene | 350.95 | 2.849 | 2.607 | 70.62 | 1.60 |
| | 362.04 | 2.762 | 2.458 | 68.78 | 1.59 |
| | 371.93 | 2.689 | 2.377 | 68.21 | 1.60 |
| | 407.29 | 2.455 | 2.047 | 64.36 | 1.60 |
| | 423.19 | 2.363 | 1.914 | 62.47 | 1.59 |
| $R_D$ = 26.0; $A$ = 25.4; $\mu_{D(B)}$ = 1.61; $\mu_{D(R)}$ = 1.60 | | | | | |
| Chlorobenzene | 353.72 | 2.827 | 3.038 | 83.30 | 1.74 |
| | 371.78 | 2.690 | 2.849 | 81.09 | 1.75 |
| | 408.23 | 2.450 | 2.440 | 77.08 | 1.76 |
| | 427.09 | 2.341 | 2.270 | 75.05 | 1.75 |
| $R_D$ = 31.0; $A$ = 33.9; $\mu_{D(B)}$ = 1.70; $\mu_{D(R)}$ = 1.75 | | | | | |
| *m*-Difluorobenzene | 352.71 | 2.834 | 2.611 | 71.20 | 1.62 |
| | 371.91 | 2.689 | 2.397 | 68.83 | 1.62 |
| | 407.31 | 2.455 | 2.094 | 65.95 | 1.64 |
| | 423.30 | 2.363 | 1.931 | 63.10 | 1.61 |
| $R_D$ = 25.9; $A$ = 27.3; $\mu_{D(B)}$ = 1.58; $\mu_{D(R)}$ = 1.62 | | | | | |
| *o*-Dichlorobenzene | 353.72 | 2.827 | 5.165 | 141.2 | 2.48 |
| | 371.92 | 2.689 | 4.730 | 136.3 | 2.50 |
| | 408.38 | 2.449 | 4.015 | 126.9 | 2.48 |
| | 424.10 | 2.341 | 3.708 | 122.2 | 2.45 |
| $R_D$ = 35.9; $A$ = 30.7; $\mu_{D(B)}$ = 2.54; $\mu_{D(R)}$ = 2.48 | | | | | |
| *o*-Fluorotoluene | 350.71 | 2.851 | 2.341 | 63.47 | 1.37 |
| | 372.07 | 2.687 | 2.152 | 61.95 | 1.38 |
| | 407.23 | 2.456 | 1.873 | 59.00 | 1.37 |
| | 423.08 | 2.363 | 1.765 | 57.20 | 1.36 |
| $R_D$ = 31.0; $A$ = 31.4; $\mu_{D(B)}$ = 1.35; $\mu_{D(R)}$ = 1.37 | | | | | |
| *m*-Fluorotoluene | 362.58 | 2.762 | 3.196 | 89.40 | 1.87 |
| | 371.76 | 2.689 | 3.070 | 88.20 | 1.87 |
| | 407.22 | 2.456 | 2.618 | 82.47 | 1.85 |
| | 423.09 | 2.363 | 2.456 | 80.41 | 1.85 |
| $R_D$ = 31.0; $A$ = 31.6; $\mu_{D(B)}$ = 1.85; $\mu_{D(R)}$ = 1.86 | | | | | |
| *p*-Fluorotoluene | 351.06 | 2.848 | 3.703 | 100.5 | 2.00 |
| | 407.24 | 2.456 | 2.898 | 91.07 | 2.00 |
| | 423.15 | 2.363 | 2.719 | 88.78 | 2.00 |
| $R_D$ = 31.0; $A$ = 30.7; $\mu_{D(B)}$ = 2.01; $\mu_{D(R)}$ = 2.00 | | | | | |
| Diethyl ether (A) | 300.09 | 3.323 | 2.273 | 52.79 | 1.22 |
| Merck pro analysi | 341.80 | 2.926 | 1.869 | 49.39 | 1.23 |
| | 372.01 | 2.688 | 1.649 | 47.44 | 1.24 |
| $R_D$ = 22.3; $A$ = 24.7; $\mu_{D(B)}$ = 1.18; $\mu_{D(R)}$ = 1.23 | | | | | |
| same (B) | 302.8 | 3.303 | 2.255 | 51.73 | 1.21 |
| (purified) | 344.5 | 2.903 | 1.841 | 48.60 | 1.22 |
| | 351.7 | 2.843 | 1.770 | 48.10 | 1.22 |
| | 371.1 | 2.695 | 1.638 | 47.02 | 1.23 |
| $R_D$ = 22.3; $A$ = 26.0; $\mu_{D(B)}$ = 1.14; $\mu_{D(R)}$ = 1.22 | | | | | |
| Methyl ethyl ether | 302.6 | 3.305 | 2.157 | 50.23 | 1.27 |
| | 340.5 | 2.937 | 1.789 | 46.76 | 1.28 |
| | 353.3 | 2.831 | 1.695 | 45.79 | 1.28 |
| | 368.8 | 2.711 | 1.583 | 44.86 | 1.29 |
| $R_D$ = 17.7; $A$ = 20.0; $\mu_{D(B)}$ = 1.22; $\mu_{D(R)}$ = 1.28 | | | | | |

(8) Fuchs and Wolf "Dielectrische Polarisation," Akademische Verlagsgesellschaft, Leipzig, 1935, p. 258.

## Results and Discussion

The data and derived values are given in Table I. The symbols in the table have their previously indicated meaning.

In Table II the essential quantities are recapitulated so as to bring the similarities and differences clearly into focus.

TABLE II

| Substance | $A$ | $R_D$ | $(A \overset{\Delta}{-} R)$ | $\mu_{D(B)}$ | $\mu_{D(R)}$ | $\Delta\mu_{(BR)}$ |
|---|---|---|---|---|---|---|
| Fluorobenzene | 25.4 | 26.0 | −0.6 | 1.61 | 1.60 | +0.01 |
| Chlorobenzene | 33.9 | 31.0 | +2.9 | 1.70 | 1.75 | −0.05 |
| *m*-Difluorobenzene | 27.3 | 25.9 | +1.4 | 1.58 | 1.62 | −0.04 |
| *o*-Dichlorobenzene | 30.7 | 35.9 | −5.2 | 2.54 | 2.48 | +0.06 |
| *c*-Fluorotoluene | 31.4 | 31.0 | +0.4 | 1.35 | 1.37 | −0.02 |
| *m*-Fluorotoluene | 31.6 | 31.0 | +0.6 | 1.85 | 1.86 | −0.01 |
| *p*-Fluorotoluene | 30.7 | 31.0 | −0.3 | 2.01 | 2.00 | +0.01 |
| Diethyl ether (A) | 24.7 | 22.3 | +2.4 | 1.18 | 1.23 | −0.05 |
| (B) | 26.0 | 22.3 | +3.7 | 1.14 | 1.22 | −0.08 |
| Methyl ethyl ether | 20.0 | 17.7 | +2.3 | 1.22 | 1.28 | −0.06 |

Some of the above compounds have had their electric moment reported in the literature. Those results that were obtained from gas phase measurements are, for purposes of comparison, recorded in Table III.

TABLE III

ELECTRIC MOMENTS (DEBYES)

| Substance | Present | Literature |
|---|---|---|
| Fluorobenzene | 1.61 | 1.57[a] |
| Chlorobenzene | 1.70 | 1.70,[a] 1.69,[b] 1.72[c] |
| *o*-Dichlorobenzene | 2.54 | 2.51,[c] 2.16[d] |
| Diethyl ether | 1.14 | 1.14,[e] 1.14,[h] 1.15,[f] 1.17[g] |

[a] MacAlpine and Smyth, *J. Chem. Phys.*, **3**, 55 (1935). [b] Groves and Sugden, *J. Chem. Soc.*, 1094 (1934). [c] Hurdis and Smyth, THIS JOURNAL, **64**, 2212 (1942). [d] Groves and Sugden, *J. Chem. Soc.*, 1782 (1937). [e] H. A. Stuart, *Z. Physik*, **51**, 490 (1928). [f] R. Sanger, *Physik. Z.*, **31**, 306 (1930). [g] Groves and Sugden, *J. Chem. Soc.*, 1779 (1937). [h] O. Fuchs, *Z. Physik*, **63**, 824 (1930).

The agreement of our values with those of Smyth (Table III) are reasonably good and our value of 1.14 *D* for diethyl ether agrees with Sanger's value within the experimental error. A least-squares recalculation of Groves and Sugden's data (g) for ether gives = 1.14 *D*. In view of the low value of $A$, we feel that our value of 2.54 *D* for *o*-dichlorobenzene is probably too high. A simplified analysis of the random error for this case indicates that an error of 1.5% in $\mu$ and 2.5 cc. in $A$ could be expected, therefore we suggest that the correct value of $\mu$ might be 0.04–0.05 *D* less than the reported value of 2.54 *D*. It may be remarked that all values of $\mu_{D(B)}$ of Table II are considered to be in error by <2% and that the error in $\mu_{D(R)}$ may be as much or considerably greater than the error in $\mu_{D(B)}$. Some of the error in $\mu_{D(R)}$ could be eliminated by making an allowance for atomic polarization, $P_A$, but such a procedure is, at best, somewhat arbitrary. In general, as the difference $(P - R_D)$ increases the influence of $P_A$ may become less and less; however, there are certain molecules where $P_A$ is rather

large,[9] therefore moments calculated from ($P - R_D$) should always be critically examined in light of the structure of the particular molecule.

The value of 1.18 $D$ obtained for unpurified ether (A) indicates that some of the previous data (Fuchs and Stuart, Table III, *e* and *h*, respectively) may be based on a sample of ether that contained a significant amount of polar impurity and that the agreement of these authors values with the others recorded may be fortuitous.

The value 1.22 $D$ for methyl ethyl ether falls between 1.14 $D$ for diethyl and 1.30 $D$[10] for dimethyl ether.

A comparison of the observed moment with that calculated for vector addition for the *o*-, *m*- and *p*-halogen toluenes is given in Table IV. The bond moments used were: $C_{ar}$–$CH_3$ (vapor) = 0.37, $C_{ar}$–$CH_3$ (solution) = 0.39, $C_{ar}$–F(vapor) = 1.61, $C_{ar}$–Cl (solution) = 1.56, $C_{ar}$–Br (solution) = 1.53 and $C_{ar}$–I (solution) = 1.38. The bond moment values for solution are taken from Tiganik,[11] the vapor $C_{ar}$–$CH_3$ from Baker[12] and the 1.61 for $C_{ar}$–F from the present investigation.

(9) (a) Coop and Sutton, *J. Chem. Soc.*, 1269 (1938); (b) Finn, Hampson and Sutton, *ibid.*, 1254 (1938).

(10) Sanger, Steiger and Gachter, *Helv. Phys. Acta*, **5**, 200 (1932). The value 1.29 given by these authors is raised to 1.30 when the new value of $N_A$ is used.

(11) L. Tiganik, *Z. physik. Chem.*, **B13**, 425 (1931).

(12) Baker and Groves, *J. Chem. Soc.*, 1144 (1939).

TABLE IV

ELECTRIC MOMENTS (DEBYES)

| Substance | Ortho Calcd. | Ortho Obs. | Meta Calcd. | Meta Obs. | Para Calcd. | Para Obs. |
|---|---|---|---|---|---|---|
| Fluorotoluene (vap.)[a] | 1.46 | 1.35 | 1.82 | 1.85 | 1.98 | 2.01 |
| Chlorotoluene (sol.)[b] | 1.41 | 1.43 | 1.79 | 1.77 | 1.95 | 1.94 |
| Bromotoluene (sol.)[b] | 1.38 | 1.44 | 1.76 | 1.75 | 1.92 | 1.93 |
| Iodotoluene (sol.)[c] | 1.24 | 1.33 | 1.61 | 1.67 | 1.77 | 1.80 |

[a] Present investigation. [b] Reference 11. [c] H. Poltz, *Z. physik. Chem.*, **B20**, 351 (1933).

Deviation from vector addivitity $\sim$ 0.1 debye occurs only for *o*-fluoro- and *o*-iodotoluenes and these are in opposite sense to each other. Until data for the chloro-, bromo- and iodo-toluenes in the vapor phase is available it is felt that a discussion of such deviations as exist is of limited value and would necessarily be somewhat speculative.

## Summary

The electric moments of several organic molecules have been determined from gas phase measurements of the dielectric constant at several temperatures and pressures. The results in debyes are: fluorobenzene—1.61, chlorobenzene—1.70, *m*-difluorobenzene—1.58, *o*-dichlorobenzene—2.54, *o*-fluorotoluene—1.35, *m*-fluorotoluene—1.85, *p*-fluorotoluene—2.01, diethyl ether—1.14 and methyl ethyl ether—1.22.

DURHAM, N. C. RECEIVED SEPTEMBER 13, 1948

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[CONTRIBUTION NO. 61 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# The Catalytic Hydrogenation of the Benzene Nucleus. V. The Hydrogenation of Benzene, the Cyclohexadienes and Cyclohexene

BY HILTON A. SMITH AND HENRY T. MERIWETHER

## Introduction

It is a well known fact that the benzene nucleus is hydrogenated with considerably greater difficulty than a simple unsaturated system. This is presumably due to the large resonance energy of the benzene ring system. If this is the case, one would expect the conjugated 1,3-cyclohexadiene to hydrogenate less readily than either the unconjugated 1,4-cyclohexadiene or cyclohexene. In order to test this, a study of the rates of hydrogenation of cyclohexene, the cyclohexadienes, and benzene was undertaken.

## Experimental

Merck reagent thiophene-free *Benzene* was purified by fractionation in an 8-ft. Vigreux column. The fraction used for rate studies distilled at a temperature of 79.2° at 741 mm., and had a refractive index, $n^{20}D$, of 1.5003.

Eastman Kodak Co. technical *cyclohexene* was first distilled through the 8-foot column and the fraction boiling between 81.8 and 82.0° collected. This was mixed with an equal volume of methanol, and azeotropic fractionation carried out in the same column. The fraction boiling at 55.8° was washed five times with cold water in order to remove the methanol, and dried with anhydrous magnesium sulfate. Fractionation of this product gave a constant boiling cut with a head temperature of 81.8° at 738 mm. pressure; $n^{20}D$ was 1.4458.

1,3-Cyclohexadiene and 1,4-cyclohexadiene were prepared by dehydration of quinitol according to the method of Zelinskii and co-workers.[1] Quinitol was prepared by the reduction of hydroquinone over Raney nickel at 150° and 2,000 p. s. i. hydrogen pressure. The solvent, ethanol, was removed from the hydrogenated product by distillation and the quinitol recrystallized from acetone. The quinitol was then dehydrated by heating with potassium bisulfate in a stream of carbon dioxide gas. The hydrocarbon and water were condensed in a cold-finger containing a little hydroquinone, to prevent polymerization. The hydrocarbon layer was separated, washed with sodium bicarbonate, and distilled from a simple distilling flask. The fraction boiling between 75 and 125° was again washed with sodium carbonate solution, dried over potassium carbonate, mixed with an equal volume of methanol, and fractionated in an 8-ft. Vigreux column. Three fractions were collected, washed five times with cold water, dried over anhydrous potassium carbonate, and refractionated. Two constant boiling cuts were obtained. The 1,3-cyclohexadiene distilled at 79.3° at 738 mm., and had

(1) Zelinskii, Denisinka and Eventova, *Compt. Rend. Acad. Sci. U. S. S. R.*, **1**, 313 (1935).

a refractive index, $n^{20}D$, of 1.4746.[2] The 1,4-cyclohexadiene distilled at 88.3° at 738 mm.; $n^{20}D$ was 1.4720.[3]

The acetic acid solvent was prepared by fractionation in a five-foot helix-packed still. The platinum catalyst was prepared by standard methods.[4] The hydrogenations were carried out in a standard low-pressure Parr catalytic reduction apparatus. The volume of the hydrogen reservoir, reaction bottle, and connections during hydrogenation was 4.43 liters. The reaction bottle was equipped with a brass jacket through which water at any desired temperature could be circulated from a twenty-liter reservoir. At the start of each run, the solvent, hydrocarbon, and catalyst were placed in the reaction bottle which in turn was placed in the water jacket and allowed to attain the temperature of the circulating water before being fitted into the rocking cradle of the apparatus. The reaction was then started in the usual manner.[5] The temperature inside the bottle was taken at the end of the hydrogenation. Usually a slight rise was found. This was caused by the heat evolved during the course of the reaction. In all cases the amount of hydrogen absorbed corresponded to that necessary for complete hydrogenation of the ring.

## Experimental Calculations and Results

It was established that all of these hydrogenations were first order with respect to hydrogen pressure, zero order with respect to the concentration of hydrogen acceptor, and directly proportional to the amount of catalyst used. This is demonstrated by Table I. Therefore rate constants were calculated from the equation

$$\log \frac{p^{\circ}_{H_2}}{p_{H_2}} = \frac{kt}{2.303V}$$

by plotting $\log p^{\circ}_{H_2}/p_{H_2}$ against $t$, and multiplying the slope of the line thus obtained by $2.303V$.[6] These constants all referring to one gram of standard catalyst[5] are given in Table II together with the energies of activation for the hydrogenation.

TABLE I

EFFECT OF VARIABLES ON THE RATE OF HYDROGENATION

| Hydrocarbon | Ml. | Grams of catalyst | Initial pressure, (p. s. i.) | $k^{\circ} \times 10^3$ (liters/g. min.) |
|---|---|---|---|---|
| Cyclohexene | 5 | 0.02 | 64.2 | 2260 |
| Cyclohexene | 5 | .02 | 28.0 | 2395 |
| Cyclohexene | 5 | .005 | 64.3 | 2170 |
| Cyclohexene | 10 | .005 | 64.0 | 2260 |
| Cyclohexadiene-1,3 | 5 | .02 | 64.6 | 1840 |
| Cyclohexadiene-1,3 | 2.5 | .02 | 29.6 | 1983 |
| Cyclohexadiene-1,3 | 5 | .01 | 64.2 | 1640 |
| Cyclohexadiene-1,3 | 2.5 | .02 | 64.1 | 1995 |
| Cyclohexadiene-1,4 | 6 | .02 | 64.0 | 1240 |
| Cyclohexadiene-1,4 | 2.5 | .02 | 30.0 | 1330 |
| Cyclohexadiene-1,4 | 5.0 | .01 | 64.2 | 1110 |
| Cyclohexadiene-1,4 | 2.5 | .02 | 64.3 | 1165 |

TABLE II

RATE CONSTANTS AND ACTIVATION ENERGIES

| Hydrocarbon | $k^{\circ}_{30} \times 10^3$ (liters/g. min.) | Activation energy (cal./mole) |
|---|---|---|
| Cyclohexene | 2350 | 2400 |
| Cyclohexadiene-1,3 | 1900 | 4500 |
| Cyclohexadiene-1,4 | 1330 | 4000 |
| Benzene | 290 | 7400 |

Figure 1 shows typical plots for the calculation of rate constants, and Fig. 2 shows the graphs from which the activation energies were calculated. It is estimated that the error in these values is of the order of ±300 calories.

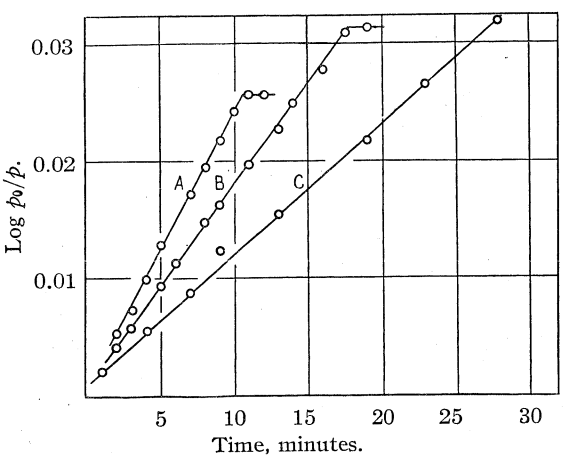



Fig. 1.—Plots for hydrogenation of the cyclohexadienes and benzene: A, 1,3-cyclohexadiene; B, 1,4-cyclohexadiene; C, benzene.

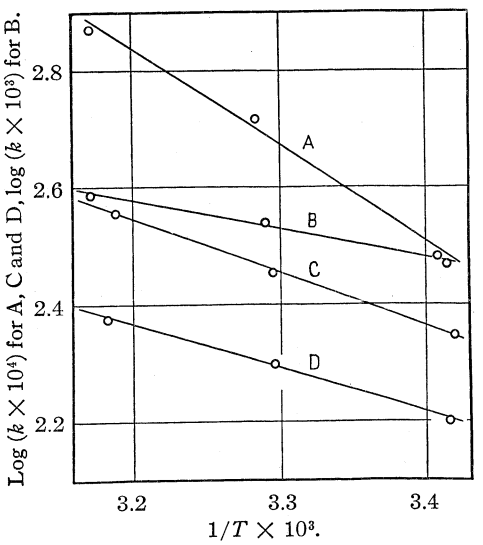



Fig. 2.—Temperature coefficients for hydrogenation reactions: A, benzene; B, cyclohexene; C, 1,3-cyclohexadiene; D, 1,4-cyclohexadiene.

## Discussion

Since these hydrogenations are all zero order with respect to the hydrogen acceptor, it follows that differences in the heats of adsorption of the cyclohexene, cyclohexadienes, and benzene on

(2) Kistiakowsky, Ruhoff, Smith and Vaughan, THIS JOURNAL, **58**, 146 (1936).

(3) M. P. Doss, "Physical Constants of the Principal Hydrocarbons," Technical and Research Division of the Texas Co., New York, N. Y., 1944, p. 159.

(4) Adams, Voorhees and Shriner, "Organic Syntheses," **8**, 92 (1928).

(5) Smith, Alderman and Nadig, THIS JOURNAL, **67**, 272 (1945).

(6) Fuzek and Smith, *ibid.*, **70**, 3743 (1948).

platinum cannot be involved in the activation energies. Since all other factors remain constant, the differences in the apparent activation energies for the catalytic reactions must represent differences in the true activation energies for the hydrogenation of these compounds on platinum.

The heats of hydrogenation of cyclohexene, 1,3-cyclohexadiene, and benzene are −28,600, −55,400, and −49,800 cal. respectively.[2,7] The corresponding value for 1,4-cyclohexadiene may be estimated as twice that of cyclohexene, or −57,200. If one assumes that the hydrogenation of benzene proceeds by the path benzene → 1,3-cyclohexadiene → cyclohexene → cyclohexane, and that the first step is rate determining, it is necessary that the energy of activation for the hydrogenation of benzene, catalytically or otherwise, be at least 5600 calories. If, by any possibility, the hydrogenation of benzene should pass through the intermediate 1,4-cyclohexadiene, the energy of activation would have to be at least 7,400 calories. The actual energy of activation, 7,400 cal., is surprisingly close to either of these requirements.

The resonance stabilization of the benzene ring as calculated from the heats of hydrogenation is 36,000 calories.[2] One would probably expect the activation energy for the hydrogenation of benzene to be at least equal to this value. If this reasoning is correct, it would appear that the benzene molecule must be adsorbed on the platinum catalyst in such a manner that its resonance is destroyed, and that the slow rate of hydrogenation of the benzene nucleus when compared to that of simple unsaturated compounds cannot be attributed to resonance.

It is also interesting to note that the conjugated 1,3-cyclohexadiene has a faster rate of hydrogenation than is found for the unconjugated 1,4-cyclohexadiene. The difference in the activation energies is probably within experimental error.

(7) Kistiakowsky, Ruhoff, Smith and Vaughan, *ibid.*, **58**, 137 (1936).

## Summary

The catalytic hydrogenations of benzene, the cyclohexadienes, and cyclohexene on platinum have been studied from a kinetic viewpoint. Rate constants and activation energies have been determined for each of these reactions. The low value for the activation energy of the hydrogenation of benzene when compared with the resonance energy of the molecule indicates the probability that such resonance is destroyed when the benzene is adsorbed on the catalyst.

KNOXVILLE, TENNESSEE RECEIVED AUGUST 20, 1948

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[CONTRIBUTION NO. 60 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# Catalytic Hydrogenation of Furan and Substituted Furans on Platinum

BY HILTON A. SMITH AND JOHN F. FUZEK

Studies of the kinetics of catalytic hydrogenation of the benzene nucleus on Adams platinum catalyst have been previously reported.[1,2] This work has now been extended to include furan and several substituted furan compounds. The aim has been to determine in a quantitative manner the effect of structure on the rate of hydrogenation of the furan nucleus with Adams platinum catalyst in acetic acid solution. Particular attention has been given the effect of varying the type of the substituent group on the rate. The results obtained have been compared with those for corresponding benzene compounds. Where necessary for such comparisons, additional work was also done in the benzene series.

## Experimental

**Preparation of Materials.—Furan** and **2-methylfuran** (E. I. du Pont de Nemours and Company) were treated with Raney nickel catalyst, dried, and fractionated in a ten-foot Vigreux column.

**Furoic acid** (Eastman Kodak Company) was purified by recrystallization and subsequent conversion to the methyl ester. This was dried, treated with Raney nickel and activated charcoal, and fractionated. The product (b. p. 181.8–182.0 (736 mm.), $n^{20}D$ 1.3880) was converted to the acid which was recrystallized and dried.

**2,5-Dimethylfuran** (Eastman Kodak Company) was azeotropically distilled with methanol (azeotrope b. p. 60.8° (743 mm.), 35–40% by volume 2,5-dimethylfuran), separated after addition of water, dried and fractionated.

**Benzyl alcohol** and **benzoic acid** were Eastman products. The alcohol was treated with Raney nickel and anhydrous magnesium sulfate, and fractionated. As in previous work, the benzoic acid was used without further purification.

**Furfural** and **furfuryl alcohol** (Quaker Oats Company) were treated with Raney nickel catalyst, anhydrous magnesium sulfate and activated charcoal for several hours. The solids were removed by filtration and the furan derivatives distilled through a fourteen-foot Vigreux column. The center fractions boiled within a 0.1° range.

**Dibenzofuran** (diphenylene oxide) (The Reilly Tar and Chemical Corporation) was treated with Raney nickel catalyst and activated charcoal in hot ethanol solution. The solution was filtered several times and the crystals recovered on cooling. They were then recrystallized from benzene. This cycle was repeated three times. The resulting crystals when dry melted within a range of 0.5°. Further purification failed to narrow this melting range.

The **Adams platinum catalyst** was prepared from 3.5-g. batches of platinum chloride in the usual manner.[3] Several of these finished batches of catalyst were mixed and then standard rates obtained as in previous work.[1] The acetic

(1) Smith, Alderman and Nadig, THIS JOURNAL, **67**, 272 (1945).
(2) Smith and Pennekamp, *ibid.*, **67**, 276 (1945).
(3) Adams, Voorhees and Shriner, "Organic Syntheses," **8**, 92 (1928).

acid used in the hydrogenations as a solvent was distilled through an eight-foot Vigreux column. The fraction boiling within the 0.1° range was retained. Tank hydrogen was used directly as in previous work.[1]

**Hydrogenation Procedure.**—The hydrogenations were carried out in a standard Parr low-pressure catalytic apparatus which was modified by substitution of a 0.790 liter hydrogen tank for the 4.02 liter tank supplied.[4] The runs were made as previously described,[1] except that due to the low boiling points of some of the materials used, the reaction bottle was not evacuated, but flushed several times with hydrogen prior to each run. It was also desirable to control the temperature of the reaction rather carefully. This was accomplished by the use of a brass jacket surrounding the reaction bottle. Water was circulated through this jacket at a rate of several gallons per minute from a constant-temperature-bath. A check of the temperature of the reaction mixture before and after the reaction indicated that the temperature of the circulating water leaving the jacket was within 0.1° of the crude temperature within the reaction bottle. The temperature during a run was maintained within ±0.2° in most cases.

**Hydrogenation Products.**—The products of hydrogenation were usually recovered from the acetic acid solution by neutralization of the acetic acid with sodium hydroxide solution with resulting separation of the layer of alcohol product. This product was dried over anhydrous magnesium sulfate and distilled through a four-foot Vigreux column or a twenty-inch Vigreux column depending on the quantity of material available. The fractions obtained were identified by their physical properties and the usual identification procedures. Difficulty was encountered in the isolation of the hydrogenation product of furfuryl alcohol since it was a dihydric alcohol and failed to separate from the neutralized acetic acid solution. Identification was affected by refluxing for several hours the filtered reaction mixture to which a small amount of concentrated sulfuric acid had been added. The diacetate thus formed proved to be easier to isolate. In the case of the product from the hydrogenation of furoic acid, the δ-hydroxyvaleric acid was converted partially to the lactone during the distillation; hence, the entire product was treated with a dehydrating agent and isolated as the lactone.

Properties of the reactants and products isolated are given in Table I.

TABLE I

PROPERTIES OF COMPOUNDS HYDROGENATED AND THEIR PRODUCTS

| Compound | $n^{20}D$ | Dist. temp., °C. B. p. | Mm. | M. p. |
|---|---|---|---|---|
| Furan | 1.4209 | 30.4 | 740 | |
| 2-Methylfuran | 1.4318 | 63.2 | 740 | |
| 2,5-Dimethylfuran | 1.4402 | 92.5 | 740 | |
| Furfuryl alcohol | 1.4845 | 170.4 | 747 | |
| Furoic acid | | | | 131.0 |
| Dibenzofuran | | | | 82.0 |
| Furfural | 1.5243 | 161.2 | 744 | |
| Benzyl alcohol | 1.5391 | 203.0 | 740 | |
| Benzoic acid | | | | 121.5 |
| Products as isolated | | | | |
| Butanol | 1.3991 | 116.1 | 740 | |
| 2-Methyltetrahydrofuran | 1.4059 | 80.1 | 743 | |
| 2-Pentanol | 1.4054 | 118.8 | 743 | |
| 2-Hexanol | 1.4125 | 137.6 | 736 | |
| 1,2-Pentanediol diacetate | 1.4210 | 114.0 | 27 | |
| Tetrahydrofuroic acid | 1.4612 | 128 | 17 | |
| δ-Hydroxyvaleric acid | 1.4630 | 130 | 17 | |
| δ-Valerolactone | 1.4575 | 124 | 24 | |
| Dicyclohexylene oxide | 1.4990 | 162 | 45 | |

(4) Fuzek and Smith, THIS JOURNAL, **70**, 3743 (1948).

## Experimental Calculations and Results

It has been established in previous work that the hydrogenation of the benzene nucleus is first order with respect to the hydrogen pressure, zero order with respect to the concentration of the hydrogen acceptor, and directly proportional to the amount of catalyst used.[1,2] Tables II, III and IV illustrate the fact that these conditions are true for the hydrogenation of the furan nucleus provided the shaking is adequate to maintain equilibrium. Table IV shows that for 2,5-dimethylfuran, the maximum amount of catalyst which can be used and still maintain shaking equilibrium is very low, namely, 0.03 g. This maximum amount of catalyst appears to be a function of the material undergoing hydrogenation.

TABLE II

EFFECT OF HYDROGEN PRESSURE ON THE RATE CONSTANT FOR THE HYDROGENATION OF THE FURAN NUCLEUS

| Furan compound | Rate constant $k$, (liters/g. min.) Pressure (p. s. i. a.) 60 | 45 | 40 | 35 | 30 | 20 |
|---|---|---|---|---|---|---|
| Furan | 0.518 | | | 0.502 | | 0.542 |
| 2-Methylfuran | .356 | | 0.390 | | | .384 |
| 2,5-Dimethylfuran | .576 | 0.560 | | | 0.574 | .599 |
| Furfuryl alcohol | .305 | | 0.328 | | | .319 |

TABLE III

EFFECT OF CONCENTRATION OF HYDROGEN ACCEPTOR ON THE RATE CONSTANT FOR THE HYDROGENATION OF THE FURAN NUCLEUS

| Furan compound | Rate constant, $k$, (liters/g. min.) Concn. (moles/l.) 0.11 | 0.22 | 0.30 | 0.66 | 1.20 |
|---|---|---|---|---|---|
| Furan | | | 0.518 | 0.542 | 0.507 |
| 2-Methylfuran | 0.328 | 0.356 | | .354 | |
| 2,5-Dimethylfuran | | .576 | | .551 | 0.552 |
| Furfuryl alcohol | .312 | .305 | | .316 | |

TABLE IV

EFFECT OF THE AMOUNT OF CATALYST ON THE RATE CONSTANT FOR THE HYDROGENATION OF THE FURAN NUCLEUS

| Furan compound | Rate constant, $k$ (liters/g. min.) g./catalyst 0.01 | 0.02 | 0.03 | 0.04 | 0.05 | 0.07 |
|---|---|---|---|---|---|---|
| Furan | | 0.475 | 0.479 | | 0.518 | 0.448 |
| 2-Methylfuran | | | .356 | | .366 | |
| 2,5-Dimethylfuran | 0.571 | .576 | .566 | 0.503 | .438 | |
| Furfuryl alcohol | | | .305 | | .321 | |

Calculations for the rate constant have been made according to the modified first order equation for heterogeneous reactions.[4] A sample hydrogenation curve is given in Fig. 1. This shows that a plot of log $p_0/p$ *versus* time results in a straight line. If the slope of this line is multiplied by 2.303 $V$, the value for the rate constant is obtained. Tabulation of such rate constants is given in Table V.

Since most of the reaction rate constants were determined at several temperatures, an apparent activation energy can be obtained from a plot of the Arrhenius equation. This equation may be represented as $k = Ae^{-E/RT}$ or $\log_e k = -E/RT + \log_e A$. Thus a plot of log $k$ *versus* $1/T$ should

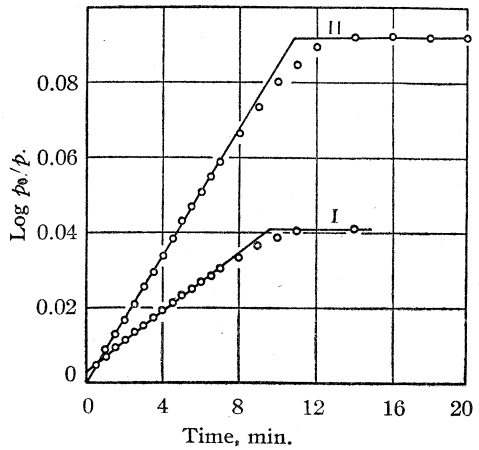



Fig. 1.—Sample hydrogenation curves: I, hydrogenation of 0.003 mole of dibenzofuran on 0.100 g. of platinum oxide in 50 ml. of acetic acid at 50°; II, hydrogenation of 0.015 mole of furan on 0.050 g. of platinum oxide in 50 ml. of acetic oxide at 26°.

TABLE V

RATE CONSTANTS FOR THE HYDROGENATION OF SOME BENZENE AND FURAN COMPOUNDS

| Derivative | $k^a$ (liters/g. min.) Furan cpd. | Benzene cpd. | Ratio F/B |
|---|---|---|---|
| Parent compound | 0.554 | 0.288 | 1.92 |
| 2-Methyl | .490 | .178[2] | 2.75 |
| 2,5-Dimethyl | .700 | .186[5](*p*) | 3.76 |
| 2-COOH | .148 | .112[a] | 1.32 |
| 2-$CH_2OH$ | .384 | .133 | 2.89 |
| 2-CHO | .269 | | |
| Dibenzofuran | .386 | | |

[a] All rate constants are corrected to a catalyst activity of 0.112 for benzoic acid. This corresponds to the value of 0.0250 in a hydrogen volume of 4.43 liters as previously reported.[1]

result in a straight line whose slope when multiplied by 2.303 $R$ is the apparent activation energy. Such plots are given in Fig. 2. A tabulation of activation energies and $A$ factors for the furans studied is given in Table VI along with comparable values for corresponding benzene compounds.

TABLE VI

APPARENT ACTIVATION ENERGIES AND $A$-FACTORS FOR SOME BENZENE AND FURAN DERIVATIVES

| Derivative | Furan compound E. | A. | Benzene compound E. | A. | Ratio |
|---|---|---|---|---|---|
| Parent compound | 8000 | $2.28 \times 10^5$ | 7400[a] | | 1.08 |
| 2-Methyl | 8600 | $5.37 \times 10^5$ | | | |
| 2,5-Dimethyl | 10200 | $1.14 \times 10^7$ | | | |
| 2-COOH | 11400 | $1.75 \times 10^7$ | 7400 | $1.75 \times 10^4$ | 1.54 |
| 2-$CH_2OH$ | 9300 | $1.45 \times 10^6$ | 6700 | $6.08 \times 10^3$ | 1.40 |
| 2-CHO[b] | 4400 | $3.21 \times 10^2$ | | | |
| Dibenzofuran | 8800 | $2.03 \times 10^6$ | | | |

[a] See ref. 6. [b] These values are for the hydrogenation of furfural to furfuryl alcohol only and do not involve hydrogenation of the ring.

(5) Smith and Pennekamp, THIS JOURNAL, **67**, 279 (1945).
(6) Smith and Meriwether, *ibid.*, **71**. 413 (1949).

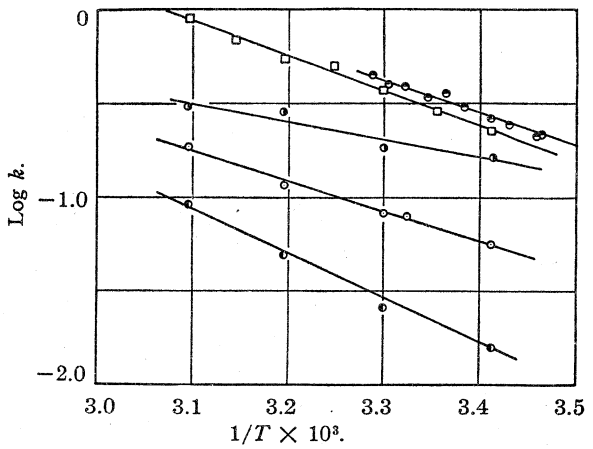



Fig. 2.—Sample Arrhenius curves: ◓, furan; □, 2-methylfuran; ◑, furfural; ⊙, benzoic acid; ◐, dibenzofuran.

## Discussion

The products of hydrogenation in the case of the furan derivatives are interesting since not only are the two double bonds in the furan ring hydrogenated, but also the ring is usually broken. A single product results from cleavage of either furan or 2,5-dimethylfuran regardless of which of the two carbon–oxygen bonds is cleaved. The former results in butanol while the latter yields hexanol-2. In both instances, the yield is almost quantitative. However, for 2-methylfuran, furfuryl alcohol and furoic acid, there are two possible products in each case, depending on which carbon–oxygen bond is broken. Ring cleavage of furoic acid occurred at the carbon–oxygen bond nearest the carboxyl group. This was shown by the fact that the principal product isolated was δ-hydroxyvaleric acid which even under mild dehydrating conditions is unstable, losing water to give δ-valerolactone. This latter compound was easier to identify due to its stability. A trace of tetrahydrofuroic acid was also obtained; the quantity was estimated at less than 10% from both the amount isolated and the deficiency in the calculated hydrogen uptake during the hydrogenation process.

The hydrogenation of 2-methylfuran and furfuryl alcohol resulted in ring cleavage at the carbon–oxygen bond removed from the functional group. For the methyl derivative, about 80 to 90% of the product was *s*-amyl alcohol. The remainder was 2-methyltetrahydrofuran. This amount was accounted for also in the amount of hydrogen absorbed in the process of hydrogenation. The furfuryl alcohol was hydrogenated almost quantitatively to 1,2-pentanediol. This product was difficult to isolate in an acetic acid solution, hence was converted to the diacetate which was more readily recovered and identified.

The formation of the tetrahydro derivative in two cases arouses interest as to the possible mechanism of the hydrogenation reactions considered. Since in all hydrogenations of 2-methylfu-

ran and furoic acid some of the tetrahydro compound was obtained, it appears questionable that the tetrahydro derivative can be an intermediate in the reaction, as it failed to hydrogenate further even when a quantity of fresh catalyst was added to the reaction mixture. Further evidence was obtained by preparing pure tetrahydrofuran by the catalytic reduction of furan on Raney nickel catalyst in absolute ethanol. This compound was purified by distillation and then subjected to hydrogenation conditions using Adams platinum catalyst and acetic acid solvent. No observable reaction occurred even after three hours. Further support for the reaction mechanism not involving the tetrahydro derivative was obtained by Bradley,[7] who hydrogenated dihydrofuran on Adams platinum catalyst in dioxane and found that only one mole of hydrogen was absorbed per mole of acceptor while furan itself rapidly absorbed three moles. From the above-cited evidence, it appears that there are two modes of reaction which the hydrogenation can follow; first, to give the cleavage product, and second, to give the tetrahydro derivative. Apparently these are two competing reactions, with the former playing the more important role in the hydrogenation of furan compounds, but the second becoming detectable for 2-methylfuran and furoic acid. Further evidence that the tetrahydro compounds are not intermediates in the reaction was obtained by analysis of partially hydrogenated samples of the various furans under study. For the other reactions studied (excepting 2-methylfuran, furoic acid and dibenzofuran), the analysis showed only the initial product and the final cleavage product.

It thus appears that, in general, the furan compounds are completely hydrogenated to the cleaved product, *i. e.*, reaction occurs with three moles of hydrogen per mole of compound before desorption from the catalytic surface.

The hydrogenation of dibenzofuran was most interesting as the reaction in this case left the furan ring intact, thus requiring six moles of hydrogen per mole of compound.[7] When a sample which had been allowed to react with only three moles of hydrogen per mole of compound was analyzed only the original dibenzofuran and the final product dicyclohexylene oxide could be isolated. Also no break in the rate curve appears when three moles of hydrogen are adsorbed (see Fig. 1). Apparently hydrogenation proceeds in such a manner that both rings are hydrogenated before the molecule is desorbed from the catalyst. Furthermore, the presence of the two benzene rings probably stabilizes the furan ring and thus prevents cleavage. This was the only furan compound studied which did not cleave to a major extent on hydrogenation.

The study of the hydrogenation of furfural was greatly hampered by the unstable nature of the compound. Even when the reactions were carried out immediately after distillation, poisoning of the catalyst was so pronounced that only the rate of hydrogenation of the aldehyde to the alcohol could be determined with the small amount of catalyst used.[8] This small amount of catalyst was necessary in order to maintain shaking equilibrium as previously discussed. Further purifications proved to be of no value. Hence the rate constant and activation energy reported are obviously subject to considerable inaccuracies. It is estimated that the probable maximum error would be about $\pm 15\%$.

A comparison of the rate constants for the furan compounds and the corresponding benzene compounds is made in Table V. The values given for the benzene derivatives previously reported have been corrected for the volume of the hydrogen void according to an equation applicable to heterogeneous reactions.[4] The ratios of the rate constants for furan to benzene derivatives is given in the last column. This ratio varies from 1.32 to 3.76; the average value is 2.5. For every derivative, the furan compound gave a rate constant considerably higher than the corresponding benzene compound.

As Table VI shows, the activation energies, as well as the rate constants for the hydrogenation of furan compounds, are greater than for the corresponding benzene derivatives. The average ratio is about 1.34. Individual values are tabulated in Table VI. The higher activation energy for furan compounds may possibly be attributed to the greater energy requirement in ring cleavage. The frequency factor for the furan compounds is also much greater than for the corresponding benzene derivatives, being of the order of $10^3$ larger. This factor may account for the slower rates for benzene derivatives. It is also possible that the frequency factor as determined includes other variables dependent upon solubility relations.

In conclusion it should be indicated that the activation energies as determined should be reasonably accurate in every case except for furfural as already discussed. In the other cases, maximum deviation from the least-squares value was less than 4% while the average deviation was 2.2%. In the case of furfural, the maximum deviation was 15% and the average was 9.4%.

**Acknowledgment.**—The authors are indebted to the Office of Naval Research for financial support which made this research possible.

## Summary

A study has been made of the kinetics of catalytic hydrogenation of some furan compounds and comparison made with corresponding benzene derivatives. The reactions were carried out at pressures up to five atmospheres absolute, in acetic acid solution, using Adams platinum catalyst. The rate constants, activation energies and frequency factors have been tabulated.

It has been shown that the rate constants,

(7) Bradley, *Iowa State Coll. J. Sci.*, **12**, 108 (1937).

(8) Kaufmann and Adams, THIS JOURNAL, **45**, 3029 (1923).

activation energies, and the frequency factors are considerably higher for the furan compounds than for corresponding benzene derivatives.

KNOXVILLE, TENNESSEE RECEIVED SEPTEMBER 15, 1948

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[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

# Ultrasonic Investigation of Molecular Properties of Liquids. IV. Cyclic Compounds[1]

BY ALFRED WEISSLER

Recent interest in the chemical applications of ultrasonics has prompted several studies[2-6] of the relation between sound velocity and molecular structure of liquids, mainly in the aliphatic field. An emerging conclusion is that the velocity of sound is a useful and important physical property, comparable to density or refractive index.

The present work was undertaken in order to extend the correlation between sound velocity and chemical structure into the classes of aromatic, alicyclic, and heterocyclic compounds. In order to simplify the interpretations, molecules containing a substituent instead of hydrogen on a ring carbon were excluded. For a few of the twenty-two liquids chosen, the velocity had been measured previously at scattered temperatures; these were included here because of the necessity for self-consistent data at a standard temperature.

## Experimental

The compounds were obtained from commercial sources, except for 1,4-thioxane, which was synthesized[7] from $\beta,\beta'$-dichlorodiethyl ether and alcoholic sodium sulfide. Each was purified before use by fractional distillation through a 40-cm. Widmer column. In order to free pyrrolidine from tenaciously-held water, it was let stand over sodium for a day, then distilled from sodium.

A three-megacycle ultrasonic interferometer, designed by Mr. Burton G. Hurdle, was used to measure sound velocities. This instrument is very similar to the one-megacycle interferometer previously described,[2] but it requires only 10 ml. of sample, because of the further scaling-down of physical dimensions permitted by the higher frequency.

If desirable, one could construct an ultrasonic interferometer which requires only a few drops of liquid sample, merely by going to a somewhat higher frequency. This illustrates the decisive advantage of ultrasonic frequencies in measuring the velocity of sound.

To minimize contamination by corrosion of the brass interferometer cell, all interior surfaces were gold plated. A 0.003-inch tantalum foil was used as the floor of the cell, directly beneath which lay the quartz crystal source of ultrasound.

Refractive indices for D light were determined with an Abbe refractometer, and densities with a 25-ml. pycnometer. Measurements of all three physical properties were made at 30°.

## Results and Discussion

The values of sound velocity, density and refractive index for the twenty-two compounds are listed in Table I. These velocities lie in the range 1100–1550 meters/second, just as is the case for the majority of unhalogenated liquids. The estimated accuracy for the velocities is about ±0.03%.

It is apparent from the table that a compound with two rings in the molecule possesses a higher sound velocity than that associated with either of the constituent rings. Other generalizations are difficult to find, however. For example, it is not true that a five-membered ring always has a lower (or a higher) velocity than its six-membered homolog; cyclopentane's is lower than cyclohexane's, but tetrahydrofuran's is higher than tetrahydropyran's.

The present data vitiate a conclusion drawn by Schaafs,[8] to the effect that in a pair of unhalogenated liquids of practically the same molecular weight, the one with the higher density also has the higher sound velocity. Both thiophene and dihydropyran have a molecular weight of 84.1, yet thiophene has the higher density but the lower sound velocity. Similarly, cyclopentene has a lower density than furan, but a higher velocity, although both have a molecular weight of 68.1.

Thus it appears that any correlations would have to take into account the specific force-interactions between molecules due to the chemical structure. For this purpose, the adiabatic compressibility is more suitable than the raw sound velocity.

**Adiabatic Compressibility.**—From the sound velocity $v$ and density $d$, the adiabatic compressibility $K_{ad}$ of a medium may be calculated readily, using the relation

$$K_{ad} = 1/v^2d \qquad (1)$$

The values so obtained, presented in Table I, support the following generalizations. Increasing the saturation of a six-membered ring, as from benzene to cyclohexane, causes the adiabatic compressibility to increase also. Even if a nitrogen or oxygen atom is substituted for one of the six carbons, as in the pyridine or pyran systems, the rate of increase of compressibility with saturation remains about the same (Fig. 1). In the five-membered rings, however, no such uniformity exists: furan has a greater compressibility than tetrahydrofuran, yet pyrrole's is smaller than that of pyrrolidine.

(1) The opinions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Navy Service at large. Article not copyrighted.

(2) Weissler, THIS JOURNAL, **70**, 1634 (1948); **71**, 93 (1949).

(3) Lagemann, McMillan and Woolsey, *J. Chem. Phys.*, **16**, 247 (1948).

(4) Lagemann, Woolf, Evans and Underwood, THIS JOURNAL, **70**, 2994 (1948).

(5) Burton, *J. Acoust. Soc. Am.*, **20**, 186 (1948).

(6) Schaafs, *Z. physik. Chem.*, **A194**, 28-50, 66-85, 170-178 (1944).

(7) Clarke, *J. Chem. Soc.*, **101**, 1806 (1912).

(8) Schaafs, *Ann. Physik*, **40**, 401 (1941).

TABLE I

PHYSICAL PROPERTIES OF CYCLIC COMPOUNDS AT 30°

| Compound | Veloc. sound m./sec. | d, g./ml. | $n_D$ | Molar sound velocity Obs. | Calcd. | Dev., % | Molar refraction Obs. | Calcd. | Dev., % | Compressibility[a] $10^{-12}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Benzene | 1276.4 | 0.8685 | 1.4949 | 975.6 | 971.0 | +0.47 | 26.22 | 26.37 | −0.57 | 70.67 |
| Cyclohexene | 1254.5 | .8023 | 1.4411 | 1113.8 | 1102.3 | +1.03 | 27.04 | 27.31 | −1.00 | 79.20 |
| Cyclohexane | 1229.1 | .7692 | 1.4206 | 1172.0 | 1167.9 | +0.35 | 27.72 | 27.78 | −0.22 | 86.06 |
| Dicyclohexyl | 1422.3 | .8790 | 1.4754 | 2127.6 | 2149.7 | −1.04 | 53.30 | 53.43 | −0.24 | 56.24 |
| Cyclopentene | 1160.3 | .7606 | 1.4168 | 941.0 | 907.6 | +3.55 | 22.51 | 22.68 | −0.76 | 97.65 |
| Cyclopentane | 1182.3 | .7350 | 1.4008 | 1008.9 | 973.3 | +3.52 | 23.17 | 23.15 | +0.09 | 97.33 |
| Dicyclopentyl | 1361.4 | .8664 | 1.4634 | 1768.4 | 1760.4 | +0.45 | 43.98 | 44.17 | −0.43 | 62.27 |
| Furan | 1104.6 | .926 | 1.4151 | 759.9 | 732.1 | +3.66 | 18.41 | 19.35 | −5.10 | 88.5 |
| Tetrahydrofuran | 1255.4 | .8785 | 1.4020 | 885.4 | 863.4 | +2.48 | 19.99 | 20.29 | −1.50 | 72.23 |
| Dihydropyran | 1263.5 | .9168 | 1.4362 | 991.9 | 992.4 | −0.05 | 24.00 | 24.45 | −1.87 | 68.32 |
| Tetrahydropyran | 1245.5 | .8744 | 1.4157 | 1059.8 | 1058.0 | +0.17 | 24.70 | 24.92 | −0.89 | 73.72 |
| Pyridine | 1396.3 | .9728 | 1.5045 | 908.6 | 908.2 | +0.04 | 24.09 | 24.71 | −2.57 | 52.73 |
| Piperidine | 1338.0 | .8524 | 1.4474 | 1100.7 | 1101.1 | −0.04 | 26.71 | 26.79 | −0.30 | 65.53 |
| Pyrrole | 1438.3 | .9578 | 1.5055 | 790.7 | 775.2 | +1.96 | 20.79 | 21.22 | −2.07 | 50.47 |
| Pyrrolidine | 1346.6 | .8573 | 1.4360 | 916.1 | 906.5 | +1.05 | 21.69 | 22.16 | −2.17 | 64.33 |
| Thiophene | 1258.2 | 1.0523 | 1.5222 | 863.2 | 842.1 | +2.45 | 24.39 | 25.03 | −2.62 | 60.03 |
| Thiazole | 1372.3 | 1.1874 | 1.5339 | 796.7 | 779.3 | +2.18 | 22.28 | 23.37 | −4.89 | 44.72 |
| 1,4-Dioxane | 1322.0 | 1.0215 | 1.4171 | 946.6 | 948.1 | −0.16 | 21.69 | 22.06 | −1.71 | 56.01 |
| Morpholine | 1423.4 | 0.9908 | 1.4501 | 989.1 | 991.2 | −0.21 | 23.64 | 23.93 | −1.27 | 49.81 |
| 1,4-Thioxane | 1419.8 | 1.1070 | 1.5025 | 1057.6 | 1058.1 | −0.05 | 27.79 | 27.74 | +0.05 | 44.81 |
| Tetralin | 1447.8 | 0.9617 | 1.5379 | 1555.1 | 1563.4 | −0.53 | 42.99 | 42.76 | +0.53 | 49.61 |
| Quinoline | 1547.7 | 1.0851 | 1.6207 | 1376.8 | 1369.4 | +0.54 | 41.85 | 40.16 | +4.03 | 38.47 |

[a] Adiabatic compressibility $10^{-12}$ cm.²/dyne.

Replacing a ring carbon by a nitrogen, oxygen, or sulfur always causes a decrease in compressibility, no matter whether the ring is five- or six-membered, saturated or unsaturated. Substitution of a second hetero atom gives a still further decrease as in dioxane, morpholine and thioxane; nitrogen and sulfur have a greater effect than oxygen. This behavior is related to the electrical forces between molecules due to the hetero atom.

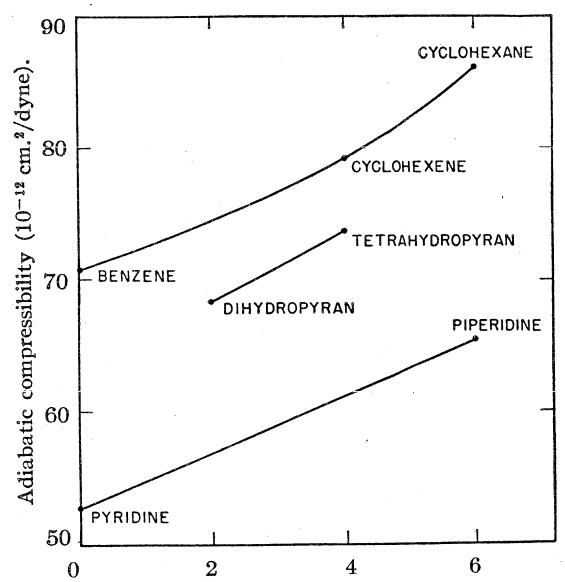



Fig. 1.—Compressibility of six-membered rings.

A compound which contains two rings has a lower compressibility than is associated with either of the individual rings.

**Molar Sound Velocity.**—Another useful quantity for studying the relation between molecular structure and sound velocity in liquids is the molar sound velocity $R$. This is defined[9] as the molar volume times the cube root of sound velocity

$$R = v^{1/3}M/d \qquad (2)$$

For most pure liquids, $R$ is independent of temperature.

Like the molar refraction, $R$ is an additive and constitutive property, which can be computed by summing the appropriate increments for all the bonds in the molecule. Some of the bond increments for molar sound velocity have been worked out by Lagemann.[10] These are listed in Table II,

TABLE II

BOND INCREMENTS FOR MOLAR CONSTANTS

| Bond | Molar sound velocity | Molar refraction |
|---|---|---|
| C—H | 95.2 | 1.69 |
| C—C | 4.25 | 1.25 |
| C=C | 129 | 4.16 |
| C—O (in ethers) | 44.5[a] | 1.51 |
| N—H | 90.7[a] | 1.81 |
| C—N | 20.7[a] | 1.54 |
| C=N | 145[a] | 3.90 |
| C—S | 99.5[a] | 4.35[a] |

[a] Previously unreported values, based on the present data and additional information from the literature.

(9) Rao, *J. Chem. Phys.*, **9**, 688 (1941).

(10) Lagemann and Dunbar, *J. Phys. Chem.*, **49**, 434 (1945).

together with previously unreported values for the N–H, C–N, C=N, C–O (in ethers) and C–S bonds, which are derived from the present work and additional data from the literature. The last column of Table II gives the corresponding increments for molar refraction, as determined by Denbigh[11] and Warrick.[12]

The values for molar sound velocity and molar refraction calculated from these bond increments are compared in Table I with the values from the observed physical properties of the liquids. It is notable that five-membered rings show the larger deviations, especially in the molar velocity. The molar refractions show an average deviation of 1.6% between observed and calculated values, while the molar sound velocities show an average deviation of only 1.2%. In the present case, therefore, the molar sound velocity appears to be more useful than the molar refraction for structure investigations, by being less subject to such anomalies as are due to ring structure and conjugation of double bonds. This conclusion is to be employed with caution, particularly in view of the relatively small number of compounds studied here.

(11) Denbigh, *Trans. Faraday Soc.*, **36**, 936 (1940).

(12) Warrick, THIS JOURNAL, **68**, 2455 (1946).

**Acknowledgment.**—The author is grateful to Dr. G. R. Ringo for stimulating discussions, and to the du Pont Company for samples of the furans and pyrans.

## Summary

Through the use of a three-megacycle ultrasonic interferometer, the velocity of sound at 30° in twenty-two cyclic compounds has been determined. Densities and refractive indices at 30° are reported also.

Correlations have been found between molecular structure and sound velocity. For example, substituting nitrogen, oxygen or sulfur for a ring carbon causes a decrease in adiabatic compressibility.

For these liquids, the molar sound velocity is more nearly an additive property than the commonly-used molar refraction. It is possible, therefore, to predict the velocity of sound in pure liquids with an average accuracy of a few per cent., simply from the molecular structure and the density.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF POLAROID CORPORATION]

# Polarographic Studies of Some Hindered and Unhindered Aromatic Nitro Compounds

BY MELVIN FIELDS,[1] CLAUDE VALLE, JR., AND MARSHALL KANE

Steric inhibition of resonance results in marked alterations of physical and chemical properties of organic molecules. Familiar examples of this phenomenon are the reduction of the dipole moments of nitromesitylene and nitrodurene from the values characteristic of aromatic nitro derivatives to approximately those of the aliphatic nitro compounds,[2] the striking alterations in the ultraviolet absorption of diphenyl derivatives[3] and of aromatic amines bearing bulky ortho substituents,[4] and the anomalous acid and base strengths of certain phenols, hydrocarbons and aromatic amines.[5] That the rates of chemical reactions may also be modified by the steric inhibition of resonance in a reacting molecule is illustrated by the numerous examples cited by Wheland.[6]

In this communication we wish to report on the results of a study of the effects of the steric inhibition of resonance on the polarographic characteristics of certain aromatic nitro compounds. Although the polarograph has been employed in the investigation of such varied phenomena as hydrogen bonding in nitrophenols[7] and in amidines,[8] semiquinone formation[9] and keto–enol tautomerism,[10] this instrument does not appear to have been utilized for the study of the effects of damped resonance on the properties of organic molecules. Suppression of the normal resonance of a reducible group with an aromatic nucleus might be expected to affect not only the ease of reduction but also the nature of the products of the reaction. In terms of the polarographic characteristics of a substance there might be observed a shift in the half-wave potential of a given stage of reduction, a change in the total number of electrons involved per molecule of electrode reaction or perhaps an alteration in the number of polarographic waves or distinct steps in which the over-all reaction occurs.

The substances which we studied were nitro-

(1) Present address: Chemical Division, Tracerlab, Inc., Boston, Mass.

(2) Birtles and Hampson, *J. Chem. Soc.*, 10 (1937); Ingham and Hampson, *ibid.*, 981 (1939).

(3) Pickett, Walter and France, THIS JOURNAL, **58**, 2296 (1936); O'Shaughnessy and Rodebush, *ibid.*, **62**, 2906 (1940); and Williamson and Rodebush, *ibid.*, **63**, 3018 (1941).

(4) Remington, *ibid.*, **67**, 1838 (1945).

(5) Wheland, "The Theory of Resonance and its Application to Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 185.

(6) Reference 5, p. 272.

(7) Astle and McConnell, THIS JOURNAL, **65**, 35 (1943); Astle and Cooper, *ibid.*, **65**, 2395 (1943); Astle and Stephenson, *ibid.*, **65**, 2399 (1943).

(8) Runner, Kilpatrick and Wagner, *ibid.*, **69**, 1406 (1947).

(9) Müller, *Ann. N. Y. Acad. Sci.*, **40**, 91 (1940).

(10) Semerano and Chisini, *Gazz. chim. ital.*, **66**, 504 (1936); Müller and Baumberger, THIS JOURNAL, **61**, 590 (1939); Zambatti and Ferrante, *Arch. Sci. biol. (Italy)*, **26**, 51 (1940).

benzene, *o*-, *m*- and *p*-nitrotoluene, 2-nitro-1,4-dimethylbenzene, 3-nitro-1,2-dimethylbenzene, nitromesitylene and nitrodurene. Of these compounds only nitromesitylene and nitrodurene would be expected to exhibit the effects of inhibition of the resonance of a nitro group with a benzene ring. The other members of the group were investigated in order to determine how the polarographic behavior of the unhindered aromatic nitro compounds is affected by the introduction of one and of two methyl groups into the nucleus and to provide reliable data obtained under identical conditions for comparison of the characteristics of the hindered and unhindered compounds. Although nitrobenzene and other aromatic nitro compounds were studied polarographically by Shikata and co-workers,[11] the nitrotoluenes and nitroxylenes were not included in these investigations. Furthermore, since much of Shikata's work appeared before significance of the half-wave potential was understood, much of his data on "reduction potentials" are now of qualitative value only.

## Experimental

**Preparation and Purification of Materials.**—The samples of nitrobenzene, *o*-, *m*- and *p*-nitrotoluene, 2-nitro-1,4-dimethylbenzene, 3-nitro-1,2-dimethylbenzene and nitromesitylene used were Eastman Kodak Co. white label grade chemicals. The liquids were purified by distillation at reduced pressure through a 30″ Podbielniak column. The sample of *p*-nitrotoluene used melted at 52–53° after several crystallizations from methanol. Nitromesitylene, crystallized several times from methanol, melted sharply at 43–44°. The physical properties of the liquid nitro compounds used are listed in Table I.

TABLE I

PHYSICAL CONSTANTS OF LIQUIDS

| Compound | B. p., °C. | Mm. | $n^{20}D$ |
|---|---|---|---|
| Nitrobenzene | 72.8 | 10.0 | 1.5522 |
| *o*-Nitrotoluene | 95.0 | 10.0 | 1.5468 |
| *m*-Nitrotoluene | 95.4 | 10.5 | 1.5460 |
| 2-Nitro-1,4-dimethylbenzene | 105.8 | 10.5 | 1.5415 |
| 3-Nitro-1,2-dimethylbenzene | 110.0 | 10.0 | 1.5432 |

Nitrodurene was prepared by nitric acid oxidation of acetoxymercuridurene according to the procedure of Smith and Taylor[12]; the sample used melted at 113–114°.

**Instruments and Cells.**—Polarographic measurements were made using a manual apparatus similar to the one described by Lingane and Kolthoff.[13] The usual H-type polarographic cell with a saturated calomel reference electrode was employed. At a pressure of 60 cm. of mercury the capillary had a drop time of 4.6 seconds and an *m*-value of 1.530 mg. of mercury per second measured on open circuit in 80% aqueous dioxane solution 0.30 *M* in sodium hydroxide.

**Supporting Electrolytes.**—The polarograms of the nitro compounds were run in buffered 80% aqueous dioxane solutions in which the concentration of supporting electrolyte in the final solutions was 0.38 *M* for the *p*H 1.0 and *p*H 7.2 solutions and 0.30 *M* for the *p*H 12.0 solutions. The dioxane was purified by prolonged refluxing over sodium. Elimination of maxima was achieved by the addition of 0.01% gelatin.

The following supporting electrolytes were used: *p*H 1.0, sodium acetate–hydrochloric acid; *p*H 7.2, sodium dihydrogen phosphate–disodium hydrogen phosphate; *p*H 12.0, sodium hydroxide. The *p*H values mentioned refer to those determined by measurement with a glass electrode[14] and are uncorrected for the non-aqueous solution error.[15]

**Procedure.**—In order to decrease the time required for deaeration of the polarographic solutions and thus to reduce the loss of the nitro compound during the deaeration process, the distilled water, the dioxane and the stock buffer solutions were freed from dissolved oxygen by bubbling purified nitrogen through the refluxing liquids for a period of about one to two hours. The oxygen-free solutions were then stored under nitrogen. The volumetric flasks were flushed with nitrogen before use, and the polarographic solutions were made up and mixed so as to minimize contact with air. When prepared by this technique, the solutions in the polarographic cell required only ten minutes sweeping prior to measurement. The nitrogen used was purified by passage through a tube filled with freshly-reduced copper filings maintained at 400 to 450°. Most of the measurements were made at a concentration of nitro compound of about $1.0 \times 10^{-4}$ *M*; where it was desired to check the effect of concentration of reducible material on the half-wave potential and on the wave height, measurements were also made at a concentration of $5.0 \times 10^{-4}$ *M*. All potentials were measured against a saturated calomel reference electrode (S. C. E.); the half-wave potentials referred to in this paper have been corrected for the *iR* drops of the solutions. Diffusion currents were corrected for the residual current of the supporting electrolyte. All measurements were made at 25 ± 0.5°.

## Results and Discussion

The marked differences in the polarographic behavior of nitrobenzene and several other aromatic nitro compounds with an unhindered nitro group and that of nitromesitylene and nitrodurene are illustrated by the representative current–voltage curves shown in Figs. 1–6 for some of these compounds. Substances of the first group all yield two fairly well defined waves in buffered 80% aqueous dioxane solution at *p*H 1.0 and only a single distinct wave at *p*H 12.0. In alkaline solution the derivatives with a methyl substituent ortho to the nitro group reveal a tendency for the polarographic wave to break up near the diffusion current region into two separate steps. The polarogram of *p*-nitrotoluene also shows a barely perceptible indication of separating into two waves, but in this case the inflection occurs in the first third of the wave. Complete separation of the two waves is not achieved for any of the unhindered compounds under these conditions. On the other hand, nitromesitylene and nitrodurene each produce a single wave in strongly acid solution and two distinct waves in sodium hydroxide solution. At *p*H 7.2 a single wave is observed for compounds of both classes although with nitrodurene there is a slight indication of a second wave following the main one. In buffered 80% aqueous dioxane solution of *p*H 7.2 the half-wave potentials are

(11) Shikata, *Trans. Faraday Soc.*, **21**, 42 (1925); Shikata and co-workers, *J. Agr. Chem. Soc. Japan*, **1**, 533 (1925); **4**, 924 (1928).

(12) Smith and Taylor, THIS JOURNAL, **57**, 2460 (1935).

(13) Lingane and Kolthoff, *ibid.*, **61**, 825 (1939).

(14) Coleman Electric Company, Model 3A *p*H Electrometer.

(15) Dole, "Principles of Experimental and Theoretical Electrochemistry," McGraw-Hill Book Co., New York, N. Y., 1935, p. 240.

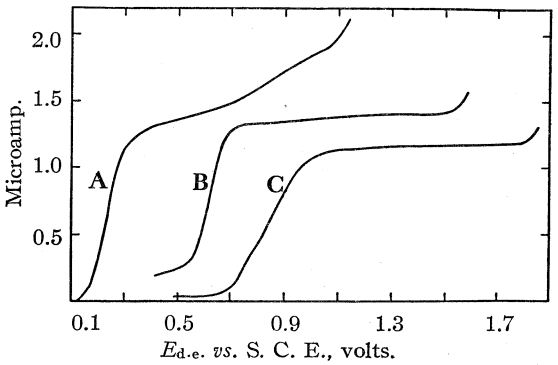



Fig. 1.—Polarograms of nitrobenzene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 1.06 × $10^{-4}$ *M*; B, *p*H 7.2, 1.06 × $10^{-4}$ *M*; C, *p*H 12, 1.01 × $10^{-4}$ *M*.

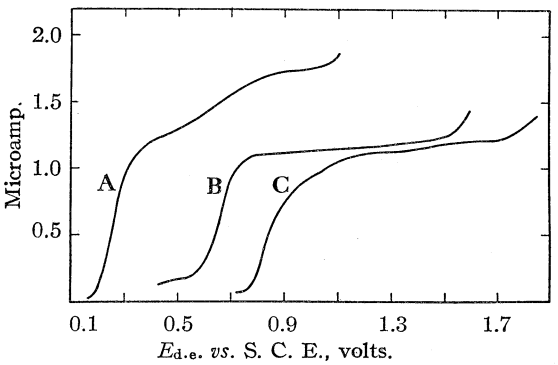



Fig. 2.—Polarograms of *o*-nitrotoluene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 0.99 × $10^{-4}$ *M*; B, *p*H 7.2, 0.99 × $10^{-4}$ *M*; C, *p*H 12, 0.99 × $10^{-4}$ *M*.

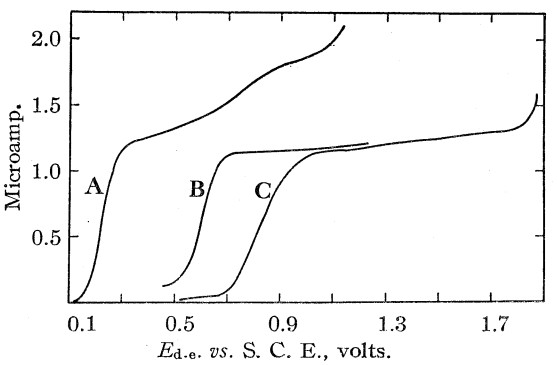



Fig. 3.—Polarograms of *m*-nitrotoluene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 0.99 × $10^{-4}$ *M*; B, *p*H 7.2, 0.99 × $10^{-4}$ *M*; C, *p*H 12, 0.99 × $10^{-4}$ *M*.

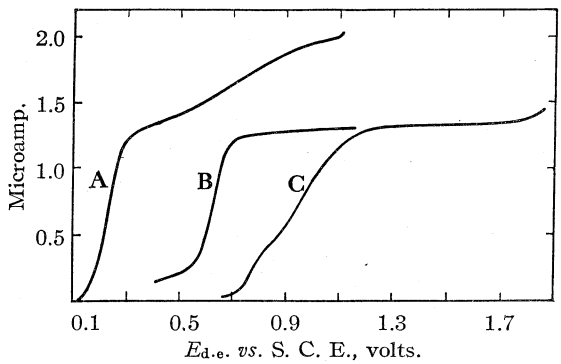



Fig. 4.—Polarograms of *p*-nitrotoluene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 1.14 × $10^{-4}$ *M*; B, *p*H 7.2, 1.02 × $10^{-4}$ *M*; C, *p*H 12, 1.14 × $10^{-4}$ *M*.

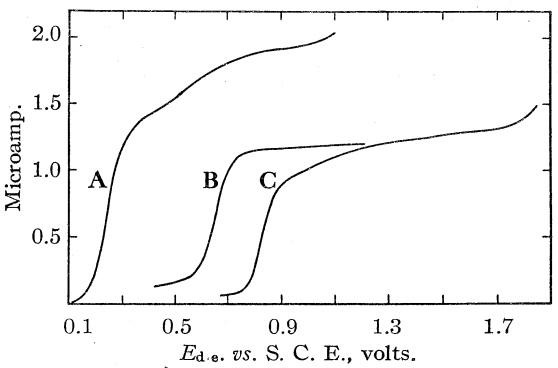



Fig. 5.—Polarograms of 3-nitro-1,2-dimethylbenzene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 1.02 × $10^{-4}$ *M*; B, *p*H 7.2, 1.02 × $10^{-4}$ *M*; C, *p*H 12, 1.02 × $10^{-4}$ *M*.

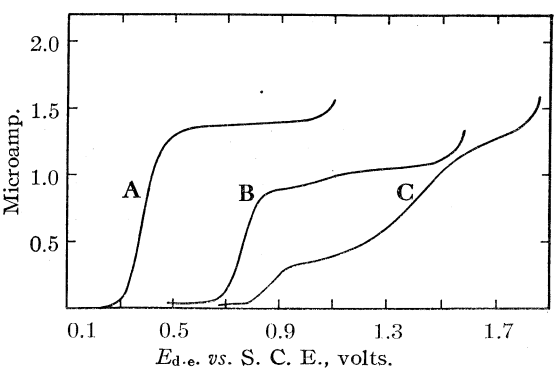



Fig. 6.—Polarograms of nitrodurene in buffered 80% aqueous dioxane solutions: A, *p*H 1.0, concn., 0.98 × $10^{-4}$ *M*; B, *p*H 7.2, 0.98 × $10^{-4}$ *M*; C, *p*H 12, 0.99 × $10^{-4}$ *M*.

independent of and the wave heights proportional to concentration over the range of 1 × $10^{-4}$ to 5 × $10^{-4}$ *M* for all the compounds except nitrodurene whose low solubility prohibited extension of the measurements beyond 2 × $10^{-4}$ *M*. Nitrobenzene showed similar behavior at *p*H 1.0 and 12.0. The data in Table II indicate that the presence of one methyl group and, in the cases of the two nitroxylenes studied, of two methyl substituents has only a small effect on the half-wave potential of the first polarographic wave, $(E_{1/2})_1$. For these substances and for nitrobenzene itself the values of $(E_{1/2})_1$ fall within the narrow ranges of −0.22 to −0.26 v. at *p*H

1.0, − 0.60 to −0.66 v. at *p*H 7.2 and −0.82 to −0.84 v. at *p*H 12.0. The polarogram of *p*-nitrotoluene which at *p*H 12 shows a slight indication of separating into two waves has a half-wave potential, calculated from the total wave height, of −0.91 v. *vs.* S.C.E. The replacement of hydrogen by methyl groups, however, has a much more striking effect on $(E_{1/2})_2$, the half-wave potential of the second wave observed at *p*H 1.0. Although in some cases this step is poorly defined, estimates of $(E_{1/2})_2$ are sufficiently accurate to show that the effect of the methyl substituents is to shift toward more positive values the potential at which this stage of reduction occurs.

TABLE II

HALF-WAVE POTENTIALS VOLTS *vs.* S.C.E.

| Compound | *p*H 1.0 $(E_{1/2})_1$ | *p*H 1.0 $(E_{1/2})_2$ | *p*H 7.2 $(E_{1/2})_1$ | *p*H 12.0 $(E_{1/2})_1$ |
|---|---|---|---|---|
| Nitrobenzene | −0.24 | −0.84 | −0.62 | −0.83 |
| *o*-Nitrotoluene | − .26 | − .64 | − .66 | − .84 |
| *m*-Nitrotoluene | − .22 | − .71 | − .60 | − .82 |
| *p*-Nitrotoluene | − .24 | − .71 | − .62 | − .91[a] |
| 2-Nitro-1,4-dimethylbenzene | − .25 | − .58 | − .64 | − .82 |
| 3-Nitro-1,2-dimethylbenzene | − .25 | − .59 | − .65 | − .82 |
| Nitromesitylene | − .38 | .... | − .75 | − .88,[b] − 1.36[c] |
| Nitrodurene | − .38 | .... | − .75 | − .87,[b] − 1.42[c] |

[a] A slight inflection was observed in this case; since the "break" between the two steps is only barely perceptible, the value above refers to the total wave. [b] First wave. [c] Second wave.

One effect of the steric inhibition of resonance of a nitro group with a benzene ring is to render more difficult the reduction of the nitro group. At *p*H 1.0 the $(E_{1/2})_1$ values of nitromesitylene and nitrodurene are −0.38 v. *vs.* S.C.E., approximately 0.12 to 0.16 v. more negative than those for the other compounds studied; at *p*H 7.2 a similar shift in $(E_{1/2})_1$ is observed with the values for the hindered compounds approximately 0.09 to 0.15 v. more negative than those of the unhindered. Values of the half-wave potentials for nitromesitylene and nitrodurene at *p*H 12.0 are respectively −0.88 and −0.87 v. *vs.* S.C.E. for the first stage of reduction and −1.36 and −1.42 v. *vs.* S.C.E. for the second. These values are only approximate because of the poorly defined limiting heights of the waves.

The diffusion current constants of the nitro compounds listed in Table III were calculated from the Ilkovic equation using drop-times measured at the same potentials as the diffusion currents. For each of the compounds with an unhindered nitro group the ratio of the diffusion current constant of the first wave to that of the total wave at *p*H 1.0 is about 0.75. Since a value only slightly higher than this is obtained for the ratio of the diffusion current constant of the single wave of nitromesitylene or nitrodurene to the average value of the constant for the total wave of the unhindered compounds, the *n*-values of the over-all reactions in acid solution

TABLE III

DIFFUSION CURRENT CONSTANTS[a]

| Compound | *p*H 1.0 $(i_d)_1$ $Cm^{2/3}t^{1/6}$ | *p*H 1.0 $(i_d)_t$[b] $Cm^{2/3}t^{1/6}$ | *p*H 7.2 $i_d$ $Cm^{2/3}t^{1/6}$ | *p*H 12.0 $i_d$ $Cm^{2/3}t^{1/6}$ |
|---|---|---|---|---|
| Nitrobenzene | 6.7 | 9.0 | 5.7 | 5.5 |
| *o*-Nitrotoluene | 6.8 | 9.1 | 5.2 | 5.4[c] |
| *m*-Nitrotoluene | 6.6 | 9.2 | 5.4 | 5.9 |
| *p*-Nitrotoluene | 7.0 | 9.7 | 5.5 | 5.6[d] |
| 2-Nitro-1,4-dimethylbenzene | 7.3 | 9.3 | 4.9 | 5.3 |
| 3-Nitro-1,2-dimethylbenzene | 7.5 | 9.4 | 5.1 | 5.6 |
| Nitromesitylene | ... | 7.7 | 4.6 | 1.2[e]; 2.8[f] |
| Nitrodurene | ... | 7.6 | 5.1 | 1.9[e]; 5.2[f] |

[a] Microamp./millimole/mg.$^{2/3}$sec.$^{1/2}$. [b] Calculated from the total wave height. [c] The single well-defined wave showed a slight tendency to break up into two waves; the diffusion current constant was calculated from the total wave height. [d] A slight inflection was observed in this case; since the "break" between the two steps is barely perceptible, the value above refers to the total wave height. [e] First wave. [f] Second wave.

are probably different for the two classes of aromatic nitro compounds. The marked decrease in the values of the diffusion current constants on going from acid to neutral and alkaline solutions suggests a change in the nature of the products of the electrode reactions. At *p*H 7.2 and *p*H 12.0 these constants for a compound with an unhindered nitro group are approximately six-tenths as large as that for the total wave of the compound at *p*H 1.0. Furthermore, the diffusion current constants of nitromesitylene and nitrodurene at *p*H 7.2 are only slightly lower than the average value for the unhindered compounds under these conditions, suggesting that the *n*-values of the electrode reactions may not be too dissimilar. Although at *p*H 12 the polarograms of nitromesitylene and nitrodurene consist of two distinct waves with the second two or three times the height of the first, the poor definition of the total wave heights in these cases makes it difficult to estimate reliable values for the diffusion current constants.

Although it is clear from the data already presented that there are pronounced differences in the polarographic characteristics of normal aromatic nitro compounds and those in which resonance of the nitro group with the benzene ring is inhibited by bulky ortho substituents, it would be interesting to compare the electron requirements of the electrode reactions. Unfortunately the lack of reliable data for the diffusion coefficients of these compounds in the supporting electrolytes used prevents calculation of the *n*-values from the Ilkovic equation, but coulometric measurements[16] should provide an unequivocal answer to the problem.

Comparison of the polarographic behavior of the substances studied here with that of aliphatic nitro compounds is of interest because it would be

(16) Lingane, THIS JOURNAL, **67**, 1916 (1945).

anticipated that the characteristics of the hindered aromatic nitro compounds would show certain similarities to those of the aliphatic nitro derivatives. Unfortunately, however, the only data reported for the aliphatic compounds were determined in solutions in which nitromesitylene and nitrodurene are not sufficiently soluble to permit measurements to be made. The straight-chain primary and secondary aliphatic nitro compounds. with one to four carbon atoms resemble the hindered aromatic compounds in that they have been reported to yield only a single polarographic wave in acid solution; on the other hand, the aliphatic compounds are apparently non-reducible in 0.1 *M* aqueous sodium hydroxide or tetramethylammonium hydroxide solution.[17] In 0.05 *M* aqueous sulfuric acid solutions the aliphatic compounds have half-wave potentials in the range −0.57 to −0.69 v. *vs.* S.C.E. and would appear to be somewhat more difficultly reducible in acid solution than any of the substances investigated in the present work. Although the shift in half-wave potentials toward more negative values on going fro 1 the unhindered to the hindered aromatic derivatives is in the direction anticipated from the values reported for the aliphatic nitro compounds, closer comparison of the polarographic behavior of nitromesitylene and nitrodurene with that of aliphatic nitro derivatives must await re-examination of the characteristics of the latter and determination of the *n*-values of the polarographic waves for members of both series.

(17) DeVries and Ivett, *Ind. Eng. Chem., Anal. Ed.*, **13**, 339 (1941).

## Summary

The polarographic characteristics of nitrobenzene, *o*-, *m*- and *p*-nitrotoluene, 2-nitro-1,4-dimethylbenzene, 3-nitro-1,2-dimethylbenzene, nitromesitylene and nitrodurene have been examined in buffered 80% aqueous dioxane solutions at *p*H 1.0, 7.2 and 12. The behavior of nitromesitylene and nitrodurene is distinctly different from that of the aromatic nitro compounds examined in which steric inhibition of resonance does not exist.

CAMBRIDGE, MASSACHUSETTS RECEIVED[18] OCTOBER 11, 1948

(18) Original manuscript received June 2, 1948.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

# Quantitative Interpretation of the Polarographic Hydrolysis Current of Chromic Ion

BY JAMES J. LINGANE AND ROBERT L. PECSOK[1]

Chromic ion undergoes stepwise reduction at the dropping electrode, the first wave corresponding to reduction to chromous ion and the second to complete reduction to the metal.[2,3] Kolthoff and Lingane[4] called attention to the fact that the height of the second wave is significantly larger than twice the height of the first when the supporting electrolyte is unbuffered, and they attributed the discrepancy to the simultaneous discharge of hydrogen ion from the hydrolysis of the chromic ion. This has also been noted by Willis.[5]

In the present study this phenomenon has been investigated systematically, and interpreted quantitatively on the basis of diffusion current theory. Relations have been derived which are of general applicability in polarographic studies of hydrolytic equilibria in metal salt solutions.

## Experimental

Polarographic measurements were made in an H-type cell provided with a saturated calomel electrode as previously described.[6] Atmospheric oxygen was removed by purified hydrogen or nitrogen. All measurements were made with the cell in a water thermostat at 25.0 ± 0.1°. The drop time of the capillary varied from three seconds with an open circuit to about two seconds at an applied potential of two volts, and was timed as necessary at each potential. An automatic *m*-measuring device[7] was employed.

Polarograms were either recorded with a Sargent Model XI Polarograph, or obtained with a manual apparatus based on a circuit previously described.[8]

Residual currents were obtained in all cases and the proper correction applied.

The *p*H of the solutions was measured with a glass electrode.

**Chromic Solutions.**—Stock solutions of 0.1000 *M* chromic chloride and chromic sulfate were prepared determinately by reduction of a known quantity of pure potassium dichromate with sulfur dioxide or hydrogen peroxide in the appropriate acid, and the excess reducing agent was removed by boiling. A neutral solution of chromic chloride was made up from the reagent grade hexahydrate and standardized by determination of the chromium content. The stock solutions were diluted to 0.01 *M* before use in order to increase the accuracy of measurement. The ionic state of the chromium in these solutions was believed to be an equilibrium mixture of the hexaaquo- and the dichlorotetraaquochromic ions.

A stock solution of 0.1 *M* chromic perchlorate was prepared by reduction of a known quantity of reagent grade sodium chromate with hydrogen peroxide in perchloric acid,

(1) Present address: Department of Chemistry, University of California, Los Angeles 24, Calif.

(2) J. Prazler, *Collection Czechoslov. Chem. Commun.*, **3**, 406 (1931).

(3) N. Demassieux and J. Heyrovsky, *J. chim. phys.*, **26**, 219 (1929).

(4) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1946, p. 291.

(5) J. B. Willis, *J. Proc. Roy. Soc. N. S. Wales*, **78**, 239 (1944).

(6) J. J. Lingane and H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

(7) J. J. Lingane, *ibid.*, **16**, 329 (1944).

(8) J. J. Lingane and I. M. Kolthoff, THIS JOURNAL, **61**, 825 (1939).

thus eliminating the presence of chloride ion. Solutions of chromic perchlorate were polarographed in a cell with an internal mercury anode, in order to exclude chloride ion.

Supporting electrolytes were prepared from reagent grade chemicals. Commercial "Chemically pure" sodium perchlorate was found to contain a large amount (*ca.* 6%) of a basic impurity, which, from the shape of the titration curve with standard hydrochloric acid, appeared to be a mixture of sodium bicarbonate and sodium carbonate. Therefore, sodium perchlorate supporting electrolytes were prepared by careful neutralization of pure perchloric acid solutions with carbonate-free sodium hydroxide solutions to a *p*H of 6.5 to 7.0.

## Results and Discussion

Figure 1 shows polarograms of various concentrations of chromic chloride in 0.1 *M* potassium chloride with 0.01% gelatin present as a maximum suppressor. The half-wave potential of the first wave, corresponding to

$$Cr(III) + e = Cr(II) \qquad (1)$$

is −0.91 v. *vs.* S.C.E., and that of the second wave, corresponding to

$$Cr(II) + e = Cr \qquad (2)$$

is −1.47 v. *vs.* S.C.E. These values are in good agreement with previous determinations.[4]

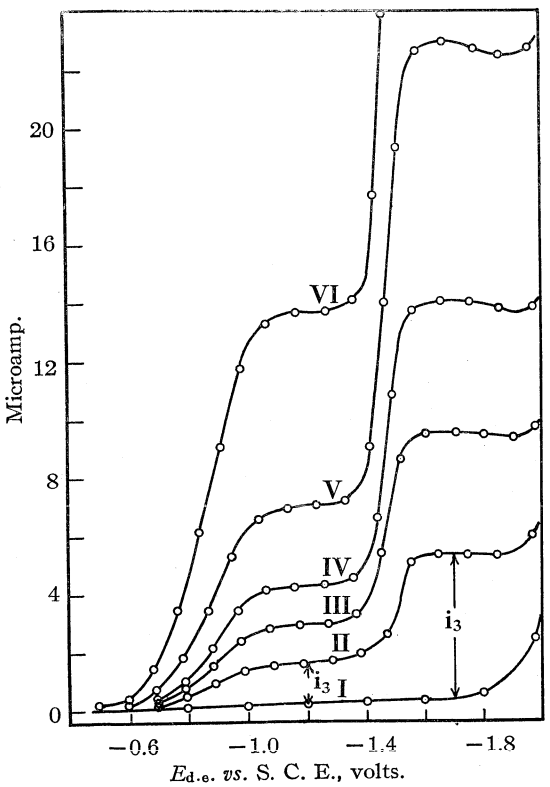



Fig. 1.—Polarograms of (I) 0, (II) 0.5, (III) 1.0, (IV) 1.5, (V) 2.5 and (VI) 5.0 millimolar chromic chloride in 0.1 *M* potassium chloride containing 0.01% gelatin.

Polarograms of chromous ion in 0.1 *M* potassium chloride, which will be described in a later paper, show a well-developed anodic wave. However, the half-wave potential of this wave is several tenths of a volt more positive than the cathodic wave of chromic ion, showing that reaction 1 does not proceed reversibly at the dropping electrode.

The influence of *p*H on the polarograms of chromic ion in 0.1 *M* potassium chloride containing 0.01% gelatin is demonstrated in Fig. 2. The natural *p*H of 1 millimolar chromic chloride in 0.1 *M* potassium chloride resulting from hydrolysis is approximately 3.8. From Fig. 2 it is seen that when the *p*H is made smaller than this value the magnitude of the second wave increases greatly because of the simultaneous discharge of hydrogen ion with the chromous ion. When the *p*H is made larger than about 3.8 the first wave becomes poorly developed and a third wave appears at −1.7 v. This latter wave doubtless results from the reduction of a more highly hydrolyzed species in sluggish equilibrium with chromic ion.

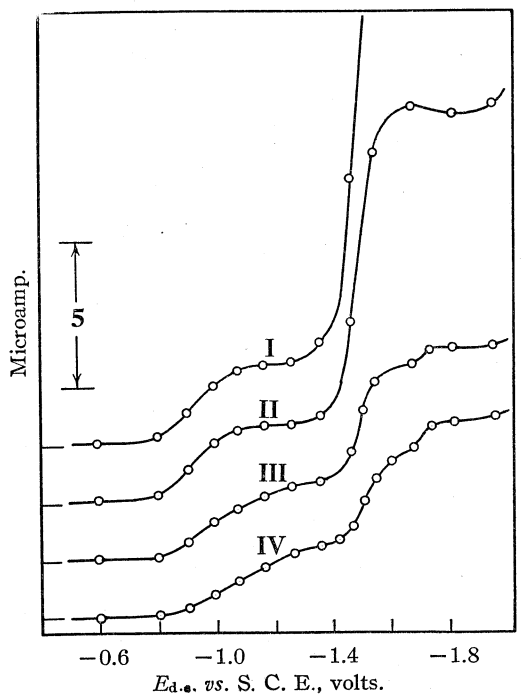



Fig. 2.—Effect of *p*H on the polarograms of 1 millimolar chromic chloride in unbuffered 0.1 *M* potassium chloride containing 0.01% gelatin. The *p*H values were (I) 2.80, (II) 3.38, (III) 4.63 and (IV) 5.00.

The effect of the concentration of potassium chloride in the supporting electrolyte was determined and a concentration of 0.1 *M* or less found to be optimum. With increasing chloride ion concentration, the magnitude of the diffusion current is decreased and the half-wave potentials shift to more negative values. This does not support the claim of Kalousek[9] that the reduction proceeds reversibly in solutions containing a very large concentration of chloride ion.

(9) M. Kalousek, *Collection Czech. Chem. Commun.*, **11**, 592 (1939).

The polarographic characteristics of chromic chloride in ammonium, lithium, barium and calcium chloride solutions, and in sodium perchlorate solutions were found to be essentially the same as in a supporting electrolyte of potassium chloride.

Diffusion current data obtained with various concentrations of chromic chloride in 0.5 *M* sodium perchlorate and 0.25 *M* potassium chloride are given in Tables I and II. The solutions contained 0.005% gelatin. The chromic chloride stock solution used was prepared from pure chromic chloride hexahydrate without added acid, and it had aged for fifteen months prior to to these experiments. The *p*H values listed are the "natural" values due to the hydrolysis of chromic ion, and they were measured for each solution with the glass electrode.

TABLE I

DIFFUSION CURRENTS IN 0.5 *M* SODIUM PERCHLORATE AT 25°

| $C_{Cr}$ millimolar | *p*H | $C_{H^+}$ millimolar | $i_1$, μa | $i_3$, μa | $I_3/I_1$ | $i_H$ (obs.), μa | $i_H$ (theor.), μa |
|---|---|---|---|---|---|---|---|
| 0.495 | 3.84 | 0.193 | 1.24 | 4.82 | 4.12 | 1.31 | 1.35 |
| 0.980 | 3.60 | .334 | 2.54 | 9.36 | 3.97 | 2.18 | 2.33 |
| 1.460 | 3.47 | .452 | 3.76 | 13.82 | 3.91 | 3.29 | 3.16 |
| 1.925 | 3.37 | .570 | 4.98 | 18.08 | 3.87 | 4.15 | 3.98 |
| 2.83 | 3.21 | .823 | 7.36 | 26.22 | 3.82 | 5.67 | 5.73 |
| 3.70 | 3.12 | 1.010 | 9.58 | 34.04 | 3.79 | 7.24 | 7.05 |
| 4.54 | 3.03 | 1.245 | 11.78 | 41.94 | 3.76 | 8.94 | 8.69 |
| 6.52 | 2.89 | 1.720 | 16.76 | 59.84 | 3.76 | 12.74 | 12.00 |
| 8.33 | 2.77 | 2.27 | 21.44 | 77.28 | 3.76 | 16.18 | 15.85 |

TABLE II

DIFFUSION CURRENTS IN 0.25 *M* POTASSIUM CHLORIDE AT 25°

| $C_{Cr}$ millimolar | *p*H | $C_{H^+}$ millimolar | $i_1$, μa | $i_3$ μa | $I_3/I_1$ | $i_H$ (obs.), μa | $i_H$ (theor.), μa |
|---|---|---|---|---|---|---|---|
| 0.465 | 4.05 | 0.114 | 1.28 | 4.78 | 3.97 | 1.15 | 0.78 |
| 0.922 | 3.80 | .202 | 2.52 | 9.18 | 3.86 | 2.07 | 1.37 |
| 1.37 | 3.67 | .274 | 3.75 | 13.28 | 3.76 | 2.68 | 1.88 |
| 1.81 | 3.58 | .337 | 4.88 | 17.24 | 3.75 | 3.41 | 2.31 |
| 2.66 | 3.46 | .445 | 7.18 | 24.70 | 3.64 | 4.35 | 3.05 |
| 3.49 | 3.39 | .521 | 9.38 | 32.02 | 3.62 | 5.47 | 3.57 |
| 4.28 | 3.32 | .614 | 11.40 | 38.48 | 3.57 | 6.23 | 4.20 |
| 6.14 | 3.20 | .809 | 16.16 | 53.9 | 3.53 | 8.0 | 5.57 |
| 7.85 | 3.13 | .905 | 21.26 | 71.3 | 3.54 | 10.7 | 6.50 |

In these tables $i_1$ is the diffusion current of the first wave, measured at −1.2 v., and $i_3$ is the total diffusion current of the doublet wave measured at −1.7 v.

The sixth column shows the corresponding ratio of the diffusion current constants, where $I = i_d/(Cm^{2/3}t^{1/6})$. The theoretical value of $I_3/I_1$ is 3, corresponding to the successive 1- and 3-electron reductions. The observed values of this ratio in Tables I and II are much larger than the theoretical value and the discrepancy increases with decreasing concentration of chromic ion. The abnormally large observed values of $I_3/I_1$ reflect the simultaneous reduction of the hydrogen ion formed by the hydrolysis of chromic ion

$$Cr(H_2O)_6^{+++} = Cr(H_2O)_5OH^{++} + H^+ \quad (3)$$

The *relative* concentration of hydrogen ion in this equilibrium increases with decreasing total concentration of the chromic salt.

The diffusion current of the first wave is directly proportional to the total chromic salt concentration. In 0.5 *M* sodium perchlorate at 25° the diffusion current constant $I_1 = i_1/(Cm^{2/3}t^{1/6})$ was found to be 1.46 ± 0.01, and in 0.25 *M* potassium chloride it is 1.50 ± 0.015, when 0.005% gelatin is present.

The *p*H values observed are consistent with the values for the hydrolysis constants of $Cr(H_2O)_6^{+++}$ ($1.58 \times 10^{-4}$) and $CrCl_2(H_2O)_4^+$ ($1.9 \times 10^{-6}$) reported by Bjerrum,[10] Lamb and Fonda,[11] and Brönsted and King.[12] The predominant ion in perchlorate medium is $Cr(H_2O)_6^{+++}$, and in the chloride solutions the less-hydrolyzed $CrCl_2(H_2O)_4^+$ ion predominates.

The "hydrolysis current" resulting from the reduction of hydrogen ion is represented by $i_H$. The observed values of $i_H$ listed in Tables I and II were computed from the relation

$$i_H = i_3 - 3i_1(t_2/t_1)^{1/6} \quad (4)$$

The values of $t_2$ and $t_1$ were measured with each concentration of chromic ion at the same time that the diffusion currents were measured.

At potentials corresponding to the second diffusion current plateau both unhydrolyzed and hydrolyzed chromic ions are reduced, and the reduction of the latter liberates hydroxyl ion at the electrode surface

$$Cr(H_2O)_5OH^{++} + 3e = Cr + 5H_2O + OH^- \quad (5)$$

The hydroxyl ions thus produced neutralize in the diffusion layer an equal number of the hydrogen ions that are diffusing up to the electrode surface. In the body of the solution the number of hydrogen ions is equal to the number of hydrolyzed chromic ions, and if the diffusion coefficients of the two were equal all of the hydrogen ions in the diffusion layer would be neutralized and there would be no contribution by hydrogen ion reduction to the second diffusion current. Acutually, however, the diffusion coefficient of hydrogen ion is several times larger than that of the hydrolyzed chromic ion. Consequently the flux of hydrogen ion at the electrode surface is greater than that required to neutralize the hydroxyl ions produced by reaction 5, and it is the reduction of these additional hydrogen ions which produce the hydrolysis current $i_H$.

There is a larger proportion of hydrogen ion to chromic ion in the diffusion layer than in the body of the solution, and the proportion increases as the electrode surface is approached. As a con-

(10) H. Bjerrum, *Z. physik. Chem.*, **59**, 336, 581 (1907).

(11) A. B. Lamb and G. R. Fonda, THIS JOURNAL, **43**, 1154 (1921).

(12) J. N. Brönsted and C. V. King, *Z. physik. Chem.*, **130**, 699 (1927).

sequence, the hydrolytic equilibrium represented by eqn. 3 tends to shift to the left. Whether or not hydrolytic equilibrium is maintained in the diffusion layer during the life of each mercury drop obviously does not alter the net amount of hydrogen ion available for reduction, because it is immaterial whether hydrogen ion is neutralized by the hydrolyzed chromic ion (reversal of reaction 3) or by the liberated hydroxyl ion.

From well known diffusion relations at the dropping electrode,[13] the flux of hydrogen ion at the electrode surface would be $(7/3\pi)^{1/2}\,(C_H D_H^{1/2}/t^{1/2})$ if there were no neutralization, where $C_H$ and $D_H$ are the concentration and diffusion coefficient of hydrogen ion in the body of the solution, and $t$ is time during the life of each mercury drop. The flux of hydrolyzed chromic ion is expressable by an exactly similar relation, and, because of the neutralization, the net flux of hydrogen ion at any instant is the difference between the two, $(7/3\pi)^{1/2}(C_H D_H^{1/2} - C_{Cr}. D_{Cr}^{1/2})/t^{1/2}$, where $C_{Cr}$ and $D_{Cr}$ refer to the hydrolyzed chromic ion in the body of the solution. Since $C_{Cr} = C_H$, and expressing the several quantities in the customary units[13] and combining the numerical constants, the hydrolysis current at 25° should obey the equation

$$i_H = 605(D_H^{1/2} - D_{Cr}^{1/2})\,C_H m^{2/3} t^{1/6} \qquad (6)$$

It is more convenient to express $i_H$ in terms of the diffusion current constants $I$, which for the 1-electron reductions involved are defined by $605\,D^{1/2}$, and eqn. 6 then becomes

$$i_H = (I_H - I_{Cr})\,C_H m^{2/3} t^{1/6} \qquad (7)$$

This equation was used to compute the theoretical values of $i_H$ in Tables I and II.

Since the diffusion coefficients of the hydrolyzed and unhydrolyzed chromic ions must be nearly identical, $I_{Cr}$ was assumed equal to the measured diffusion current constant of the first wave (1.46 in 0.5 $M$ sodium perchlorate and 1.50 in 0.25 $M$ potassium chloride).

The diffusion current constant $I_H$ of hydrogen ion was determined from measurements of the diffusion current of known concentrations (0.1 to 1 millimolar) of hydrogen ion in the same supporting electrolytes used to obtain the data in Tables I and II, and the same value, 5.64 ± 0.02, was obtained in both cases. This value agrees well with the theoretical infinite dilution value 5.84 calculated from the equivalent conductance of hydrogen ion by means of the relation[4] $D^0 = 2.67 \times 10^{-7}\lambda^0$. Special experiments showed that $I_H$ was not altered by the simultaneous reduction of chromic ion.

Since $p$H numbers as ordinarily measured do not strictly correspond to either the concentration or activity of hydrogen ion, the glass electrode $p$H meter was calibrated empirically in each of the supporting electrolytes with known small concentrations of hydrochloric acid. The data thus obtained were used to compute the concentrations of hydrogen ion in each solution of Tables I and II from the measured $p$H numbers, and these concentrations were then employed in eqn. 7 to compute $i_H$.

From Table I the agreement between the observed and theoretical values of $i_H$ in 0.5 $M$ sodium perchlorate is seen to be very good over the entire concentration range. The average difference between the two is only ± 3%, which is well within the limits of error of the measurements.

In 0.25 $M$ potassium chloride the observed values of $i_H$ average 45% larger than the theoretical values. This discrepancy can be accounted for by two factors which both operate to increase the observed value of $i_H$. First, the smaller ionic strength of the potassium chloride solutions leads to a greater possibility of some contribution by electrical migration[4] to the total limiting current. Secondly, the predominant molecular state of the + 3 chromium in 0.25 $M$ potassium chloride is probably the $CrCl_2(H_2O)_4^+$ ion, rather than the $Cr(H_2O)_6^{+++}$ ion which predominates in the perchlorate medium.[10,11,12] The reduction of each chloro complex ion frees two chloride ions at the surface of the dropping electrode, which alters the potential gradient in the diffusion layer and produces a relatively larger negative charge at the electrode surface. This tends to accelerate the passage of hydrogen ion through the diffusion layer.

## Summary

1. The polarographic behavior of chromic ion in potassium chloride and sodium perchlorate solutions has been investigated systematically. The optimum conditions for a well developed doublet wave are: (1) a concentration of supporting electrolyte of 0.1 $M$ or less, (2) the natural $p$H (about 4) resulting from the hydrolysis of chromic ion, and (3) the presence of 0.005-0.01% gelatin as a maximum suppressor.

2. The first chromic wave is directly proportional to concentration. The second wave is relatively too large and becomes more so with decreasing concentration. The excess current results from the simultaneous reduction of hydrogen ion. The diffusion and reduction of the hydrolyzed chromic ion and hydrogen ion were analyzed with the aid of diffusion current theory, and equations were developed from which the magnitude of the "hydrolysis current" can be calculated. The latter was compared with the measured excess current, and the good agreement obtained verifies the interpretation.

CAMBRIDGE 38, MASS. RECEIVED AUGUST 3, 1948

(13) Ref. 4, p. 36.

[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, MICHIGAN COLLEGE OF MINING AND TECHNOLOGY]

# Equilibrium between Ammonia and Hydrogen Selenide

BY F. F. MIKUS AND F. J. POSS[1]

The equilibrium between ammonia and hydrogen sulfide was thoroughly investigated by Isambert[2] and Magnusson.[3] A careful survey of the literature revealed no quantitative data on the equilibrium between ammonia and the analog of hydrogen sulfide, hydrogen selenide, but merely a statement that the decomposition pressure of ammonium hydroselenide is small. In this work the equilibrium constants for the dissociation of ammonium hydroselenide according to the reaction, $NH_4HSe(s) \rightleftarrows NH_3(g) + H_2Se(g)$, have been determined in the temperature range of 15 to 30.1°.

## Experimental

**Hydrogen Selenide.**—Hydrogen selenide was prepared in an evacuated flask by dropping freshly boiled water upon a large excess of aluminum selenide which had been prepared by the ignition of an intimate mixture of one part powdered aluminum and two parts selenium. Drying of the gas was effected by the excess aluminum selenide. The hydrogen selenide was used immediately upon preparation, and the purity was determined at the time the sample was withdrawn for use.

**Ammonia.**—Ammonia was prepared by warming C. P. ammonium hydroxide and by passing the resultant gas through four drying towers containing soda lime, potassium hydroxide pellets, soda lime, and potassium hydroxide pellets plus metallic sodium, respectively. The effluent gas, when absorbed in sulfuric acid, always contained less than 0.4% unabsorbable gas.

**Determination of the Equilibrium Pressure.**—The apparatus (Fig. 1) used for the determination of the equilibrium pressure, when the excess hydrogen selenide or ammonia was expelled, consisted of two Hempel burets set parallel to each other and connected with glass tubing. These were surrounded by water jackets. The temperature was maintained constant to within 0.05° by circulating water from a constant temperature bath by means of a centrifugal pump. The temperature of the room was kept slightly higher than that of the water-bath. The mercury levels were read by means of a cathetometer placed at a distance of eight feet from the apparatus.

Ammonia and hydrogen selenide were brought together in buret B with the formation of a white crystalline solid on the inner surface. The excess gas was expelled by pushing the gas into the evacuated portion E F and pumping out through G. Buret C was evacuated with a Hyvac pump, and the leveling bulb D was adjusted to leave from 10 to 40 ml. of evacuated space above the mercury. The stopcocks, E and F, were turned to allow the gas formed from the dissociation of the ammonium hydroselenide to expand into buret C. The difference in the height of the mercury in this buret before and after expansion gave the equilibrium pressure. The second reading was corrected for the change in the level of the mercury in the leveling bulb. Equilibrium was attained rapidly; no change in pressure was noted after two minutes.

An advantage of the system employed lay in the fact that it was not necessary to consider barometric pressure in the measurements. Furthermore, since the second buret was not coated with ammonium hydroselenide the adsorption of ammonia was minimized. As a result, pressure readings were more easily reproduced than in the system using one buret. When excesses of either of the gases were used, the two buret system was not used. Here it was necessary to measure the total volumes of the gases, which was done more conveniently when one buret was used. All measurements were made according to the method of Magnusson.[3]

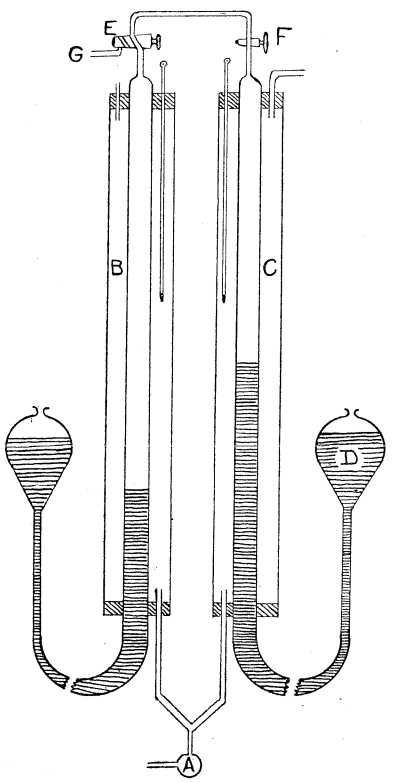



Fig. 1.

**Analysis of $NH_4HSe$.**—Considerable difficulty was encountered in attempting to analyze the white crystalline solid formed upon treating hydrogen selenide with ammonia. Traces of air coming in contact with the solid caused decomposition. A stoichiometric relationship between the two gases forming the solid was obtained by slowly introducing hydrogen selenide into a measured amount of ammonia in a buret until no decrease in volume of the gas in the buret was observed. Further addition of hydrogen selenide caused an increase. The hydrogen selenide was 93.4% pure.

## Data and Discussion

Table I shows the results of a series of determinations taken over a temperature range 15 to 30.1°. In this case, where the excess gases were expelled, $P_{NH_3} = P_{H_2Se} = P/2$, where $P$ is the observed pressure at equilibrium. The equilibrium constant then becomes, $K_p = (P/2)^2$. The dissociation pressures were found

(1) Presented as a thesis in partial fulfillment of the requirements for the Master of Science degree in chemistry.

(2) Isambert, *Compt. rend.*, **92**, 919 (1881).

(3) Magnusson, *J. Phys. Chem.*, **11**, 21 (1907).

TABLE I

DISSOCIATION OF AMMONIUM HYDROSULFIDE (15 TO 30.1°)

| Initial buret reading, mm. | Final buret reading, mm. | Temperature, °C. | Pressure, mm. of Hg | $K_p \times 10^4$ (p in atm.) Average |
|---|---|---|---|---|
| 456.8 | 463.6 | 15.0 | 6.8 | 0.20 |
| 510.2 | 517.0 | | 6.8 | |
| 433.5 | 540.2 | | 6.7 | |
| 486.7 | 494.4 | 17.0 | 7.7 | .25 |
| 434.4 | 442.0 | | 7.6 | |
| 502.9 | 510.6 | | 7.7 | |
| 510.3 | 518.9 | 18.0 | 8.5 | .31 |
| 472.3 | 480.9 | | 8.6 | |
| 447.7 | 456.0 | | 8.3 | |
| 436.3 | 445.4 | 19.0 | 9.1 | .36 |
| 481.6 | 490.6 | | 9.0 | |
| 510.5 | 519.6 | | 9.1 | |
| 437.5 | 447.8 | 21.0 | 10.3 | .45 |
| 475.9 | 486.1 | | 10.2 | |
| 510.9 | 521.1 | | 10.2 | |
| 429.4 | 441.3 | 23.0 | 11.9 | 0.62 |
| 477.8 | 489.9 | | 12.1 | |
| 510.9 | 522.9 | | 12.0 | |
| 405.7 | 419.8 | 24.8 | 14.1 | 0.85 |
| 463.5 | 477.7 | | 14.1 | |
| 514.0 | 527.9 | | 13.9 | |
| 416.1 | 434.0 | 27.7 | 17.9 | 1.4 |
| 470.3 | 488.5 | | 18.2 | |
| 509.1 | 527.1 | | 18.0 | |
| 423.8 | 444.6 | 29.3 | 20.8 | 1.9 |
| 468.3 | 489.2 | | 20.9 | |
| 512.7 | 533.6 | | 20.9 | |
| 441.1 | 441.1 | 30.1 | 23.2 | 2.3 |
| 472.6 | 495.6 | | 23.0 | |
| 510.0 | 533.0 | | 23.0 | |

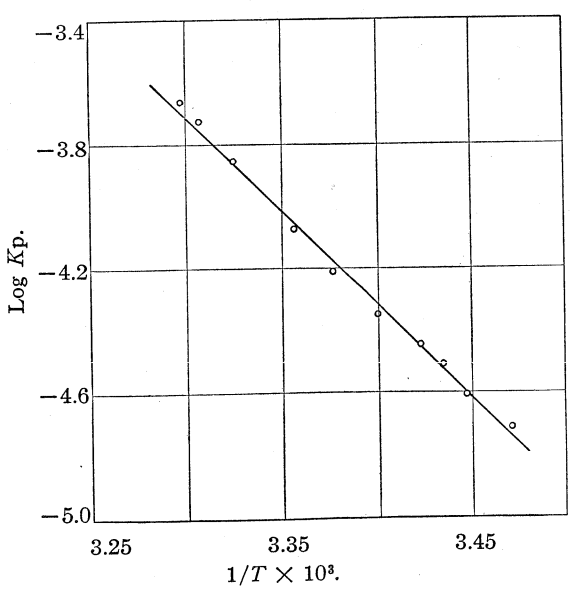



Fig. 2.

to be independent of the volume when the volume was varied between 10 and 40 ml.

TABLE II

EQUILIBRIUM WITH EXCESS AMMONIA

Excess $NH_3 = 0.301 \times 10^{-4}$ mole; temp. = 30.0°; bar. P. = 748.1 mm.

| Height of mercury, mm. Leveling bulb | Buret | Observed pressure, mm. | Volume, ml. | $K_p \times 10^4$ |
|---|---|---|---|---|
| 72.0 | 778.3 | 41.8 | 15.50 | 1.7 |
| 250.0 | 967.0 | 31.1 | 30.10 | 2.6 |
| 257.8 | 980.0 | 25.9 | 50.35 | 2.4 |
| 263.7 | 987.2 | 24.6 | 64.85 | 2.3 |
| 267.1 | 992.0 | 23.2 | 83.10 | 2.1 |
| 268.5 | 994.0 | 22.6 | 92.60 | 2.1 |

TABLE III

EQUILIBRIUM WITH EXCESS HYDROGEN SELENIDE

Excess $H_2Se + H_2 = 1.013 \times 10^{-4}$ mole; temp. = 31.5°; bar. P. = 740.0 mm.

| Height of mercury, mm. Leveling bulb | Buret | Observed pressure, mm. | Volume, ml. | $K_p \times 10^4$ |
|---|---|---|---|---|
| 714.8 | 37.7 | 62.9 | 32.95 | 2.2 |
| 710.1 | 16.1 | 46.0 | 47.30 | 1.9 |
| 705.0 | 0.8 | 35.8 | 68.40 | 2.0 |
| 755.0 | 46.6 | 31.6 | 85.00 | 2.0 |
| 751.8 | 42.1 | 30.3 | 98.07 | 2.4 |

Tables II and III show the results obtained using excesses of ammonia and hydrogen selenide, respectively. In the former case the total pressure, $P$ is equal to $P_{H_2Se} + p'_{NH_3} + p''_{NH_3}$, where $p'_{NH_3}$ is the pressure due to the dissociation of the solid ammonium hydroselenide and $p''_{NH_3}$ is the pressure due to the excess ammonia. Hence the partial pressure of hydrogen selenide, $P_{H_2Se}$ is equal to $P - p''_{NH_3}/2$, and that of ammonia, $P_{NH_3}$ is equal to $p'_{NH_3} + p''_{NH_3}$.

The calculations in the case of the excess hydrogen selenide were further complicated by the presence of hydrogen, as a result of the decomposition of the hydrogen selenide into hydrogen and selenium. Here $p_{NH_3}$ is equal to $P - p_{H_2} - p'_{H_2Se}/2$ where $p'_{H_2Se}$ is the pressure due to the excess hydrogen selenide. The sample of hydrogen selenide used in obtaining the above data contained 6.6% hydrogen.

The small value of the equilibrium constants and the presence of an excess of one of the gases makes the partial pressure of the second gas very small. A small error in the measurements would cause a large error in calculating this pressure and also in the value of $K_p$. However, the values of the $K_p$ obtained when excesses were used were of the same order of magnitude as those obtained when the excess gases were expelled.

A plot of log $K_p$ *vs.* $1/T$, shown in Fig. 2, gives a straight line, indicating that the data herein presented satisfy the requirements of van't Hoff's equation, $\log K_p = -\Delta H/2.303\,RT + \Delta S/2.303\,R$. The slope of the line is −6,020,

hence $\Delta H$ for the dissociation is 27,600 calories within the indicated temperature range.

Results of the addition of hydrogen selenide to ammonia at 21°, Table IV, show that the two gases react mole for mole in the formation of the white crystalline solid. Therefore, the product must be $NH_4HSe$.

TABLE IV

| Ml. of $H_2Se + H_2$ | Ml. of $H_2Se$ | Ml. of $NH_3$ required |
|---|---|---|
| 26.6 | 25.0 | 25.0 |
| 23.4 | 21.9 | 22.2 |
| 27.7 | 25.9 | 25.8 |
| 22.4 | 20.9 | 21.1 |

## Summary

1. The equilibrium for the dissociation of ammonia hydroselenide, $NH_4HSe(s) \rightleftarrows NH_3(g) + H_2Se(g)$, was determined in the temperature range 15° to 30.1°.

2. $\Delta H$ for this reaction was found to be 27,600 calories in the indicated temperature range.

HOUGHTON, MICHIGAN RECEIVED SEPTEMBER 28, 1948

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# Molecular Rotation in the Solid Forms of Some Long-Chain Alcohols[1]

BY JOHN D. HOFFMAN AND CHARLES P. SMYTH

X-Ray investigations on *n*-dodecyl alcohol conducted by Bernal[1a] resulted in the conclusion that the molecules rotate about their long axes several degrees below the freezing point. This result is not in accord with the more recent X-ray measurements of Ott[2] who found no evidence for rotation. Dielectric data on this substance obtained by Frosch[3] at audio frequencies disclosed strong frequency dispersion below the freezing point which would require molecular rotation in the solid if interpreted in the usual way, but the results showed great complexity and were not reproducible.

Dielectric measurements[4] on *n*-hexadecyl alcohol carried out at 0.5, 5.0 and 50 kc. indicated molecular rotation in a definite temperature range below the freezing point. It is noted that the dielectric loss factor, $\epsilon''$, in this range, which we term the "waxy" range to avoid the term "glassy," greatly exceeded the theoretical limit for orientation loss imposed on it by the relation $\epsilon''_{max} = (\epsilon_0 - \epsilon_\infty)/2$. Furthermore, the dielectric constant $\epsilon'$ rose sharply on freezing and was frequency dependent. The rise in dielectric constant would seem to demand greater molecular freedom in the solid than in the liquid, which is contrary to the fact that entropy must decrease on freezing. It must be pointed out, however, that X-ray observations[2] on *n*-hexadecyl alcohol showed that hexagonal close-packing of the molecular chains persisted for some degrees below the freezing point, which strongly suggests molecular rotation in the solid. Frosch explained the high value of the dielectric constant mentioned above as due to the co-existence of liquid and solid phases between the condenser plates, which resulted in Maxwell–Wagner polarization. The persistence of the liquid phase in contact with the solid for a long period of time at a temperature several degrees below the freezing point appears highly improbable, although a treatment based on this model accounted quantitatively for the observed dielectric constants.

The present work undertakes the study of the reported transition in *n*-dodecyl alcohol, and the investigation of the dielectric and thermal behavior of *n*-tetradecyl, *n*-octadecyl and *n*-docosyl alcohols with emphasis on the status of molecular rotation about the long axis and the isolation of the factors leading to time and frequency dependence of the abnormally high dielectric constants.

## Experimental Method

The bridge employed for the measurements was essentially that described in previous papers.[5] The frequency range and stability of the equipment were improved by using a Hewlett–Packard 200 oscillator as a signal generator and a TS12/AP amplifier (Presto Recording Corp.) as a null detector. Teflon spacers were inserted between the gold cylinders of the dielectric cell ($C_0$ = 38.6 $\mu\mu$f.; liquid capacity, 8 cc.) instead of the customary mica tabs with the result that loss across the tabs was eliminated. All temperature measurements were made with a calibrated platinum resistance thermometer.

The dielectric constants were determined by calculating the ratio, $\epsilon' = C/C_0$, where $C$ is the capacitance of the cell containing the material, exclusive of lead and insulator capacitance, and $C_0$ is the corresponding vacuum capacitance. The specific conductivity in ohms$^{-1}$ cm.$^{-1}$ was calculated from the relation $k = 0.0885/RC_0$ where $R$ is the resistance of the cell in ohms as measured in the bridge, $C_0$ being expressed in $\mu\mu$f. $\epsilon''$ was calculated from $k$ by using the relation $\epsilon'' = 1.8 \times 10^{12}\, k/f$, where $f$ is the frequency of the measurements in cycles/sec. The error in $\epsilon'$ never exceeds ±1%, and the reproducibility in the $\epsilon''$ measurements is better than ±3% except for very low values where the error becomes greater.

### Purification of Materials

*n*-Dodecyl alcohol ($C_{12}H_{25}OH$) was purified by crystallization from dry ether followed by five fractional distillations at 1 mm., f.p. 23.5°. Beilstein (I-432) gives the f.p. as 24°.

(1) This research was carried out with the support of the Office of Naval Research.

(1a) Bernal, *Nature*, **129**, 870 (1932).

(2) Ott, *Z. physik. Chem.*, **193**, 218 (1944).

(3) Frosch, *Ann. Physik*, **42**, 254 (1942).

(4) Baker and Smyth, THIS JOURNAL, **60**, 122 (1938).

(5) Smyth and Hitchcock, *ibid.*, **54**, 4631 (1932); *ibid.*, **55**, 1830 (1935).

$n$-Tetradecyl alcohol ($C_{14}H_{29}OH$) was dried over calcium oxide and fractionally distilled twice at 1 mm. pressure; f.p. 36.4°, transition point 34.4°. Phillips and Mumford[6] list 37.7° and 35° for these points, respectively. Trapeznikov[7] gives the m.p. of the anhydrous crystals as 36.7° and of the hydrate as 40°.

$n$-Octadecyl alcohol ($C_{18}H_{37}OH$) was purified by crystallization from dry ether twice and benzine twice, and was distilled three times at 1 mm. pressure; f.p. 57.7°, transition point 53.4°. Phillips and Mumford[6] list 57.95° and 53.8° for these points, respectively. According to Trapeznikov[7] the melting point of the anhydrous crystals is 58.4°, and that of the hydrate 61.5°.

$n$-Docosyl alcohol ($C_{22}H_{45}OH$) synthesized by Mr. E. N. Stirewalt was kindly given us by Dr. Nathan L. Drake of the University of Maryland. This sample was subjected to a single high vacuum distillation (about $10^{-2}$ mm.) after drying for two weeks in a vacuum desiccator, f.p. 69.6°, transition point 64.5°. Francis, Collins and Piper[8] list the f.p. as 70.8°. The transition point has not been reported previously.

In all cases, the transfer of alcohols was performed under dry conditions and every effort was made to avoid contamination with water or ionic impurities. The cooling curves and low specific conductivities of the liquids indicate the purity of these compounds.

## Experimental Results

The dielectric constants, $\epsilon'$, the specific conductivities, $k$, and the loss factors, $\epsilon''$, obtained on cooling and on subsequent re-heating of each of the compounds are given in Table I. Many values of a confirmatory nature have been omitted, and only portions of the data near transitions are included. The data in Table I are plotted in Figs. 1, 2, 3 and 4. $n$-Octadecyl alcohol was also measured on a heterodyne beat apparatus[9] at a frequency of 525 kc. in the same dielectric cell used in the impedance bridge. The data are plotted in Fig. 3 (filled squares) but are not reproduced in Table I because of their closeness to the values at 50 kc. Arrows in the diagrams indicate the direction in which the temperature is changing. Figures 5 and 6 show the behavior of the dielectric constant at 0.25 kc. for $n$-tetradecyl and $n$-octadecyl alcohols, where the normal cooling process was intentionally halted for several hours in the waxy state by holding the temperature of the

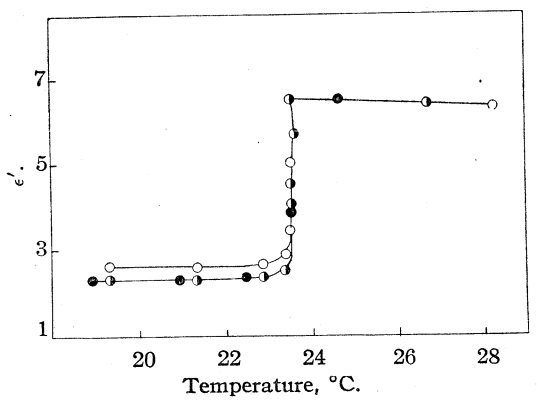



Fig. 1.—Temperature dependence of the dielectric constant of $n$-dodecyl alcohol. Hollow circles represent values at 0.5 kc., half filled circles values at 5.0 kc., and filled circles values at 50 kc.

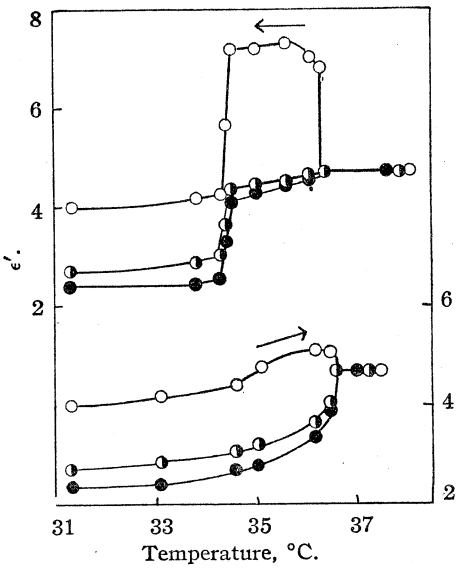



Fig. 2.—Temperature dependence of the dielectric constant of $n$-tetradecyl alcohol. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc. Upper curve scale on left, lower curve scale on right. Arrows indicate direction in which temperature is changing.

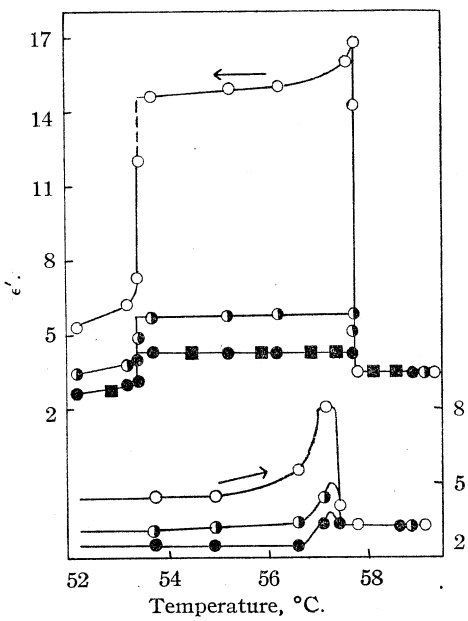



Fig. 3.—Temperature dependence of the dielectric constant of $n$-octadecyl alcohol. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., filled circles values at 50 kc., and filled squares values at 525 kc. Upper curve has scale on left, lower curve scale on right. Arrows indicate direction in which temperature is changing.

(6) Phillips and Mumford, *J. Chem. Soc.*, 235 (1933).
(7) Trapeznikov, *Acta Physicochem., U. R. S. S.*, **XX**, 589 (1945).
(8) Francis, Collins and Piper, *Proc. Roy. Soc.* (*London*), **A158**, 691 (1937).
(9) Lewis and Smyth, *J. Chem. Phys.*, **7**, 1085 (1939).

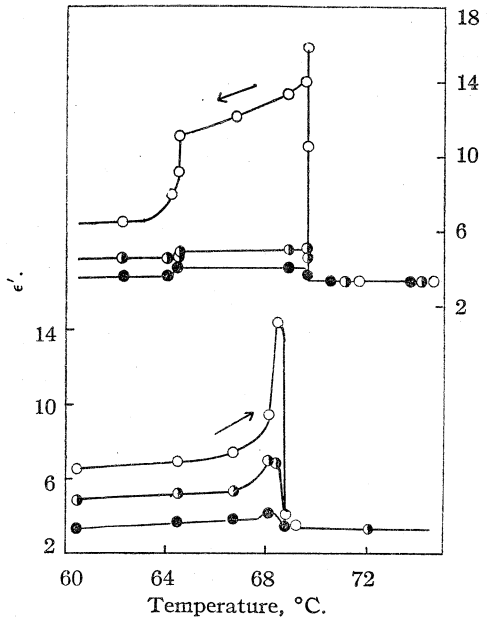



Fig. 4.—Temperature dependence of the dielectric constant of *n*-docosyl alcohol. Hollow circles represent values at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles values at 50 kc. Upper curve has scale on right, lower curve scale on left. Arrows indicate direction in which temperature is changing.

surroundings constant. After a suitable interval, the normal cooling process was allowed to proceed. Only the upper parts of the curves are shown since the other portions are repetitions of Figs. 2 and 3. In *n*-octadecyl alcohol the points ABCD were measured consecutively in order to check the reversibility of the changes taking place. A typical example of the dependence upon frequency of the

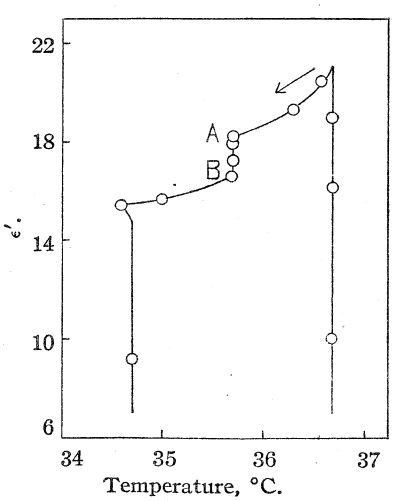



Fig. 5.—Temperature dependence of dielectric constant of *n*-tetradecyl alcohol at 0.25 kc. The sample was cooled in the usual way to 35.7° where it was held for one hour. The dielectric constant dropped from A to B. Normal cooling was then allowed to resume.

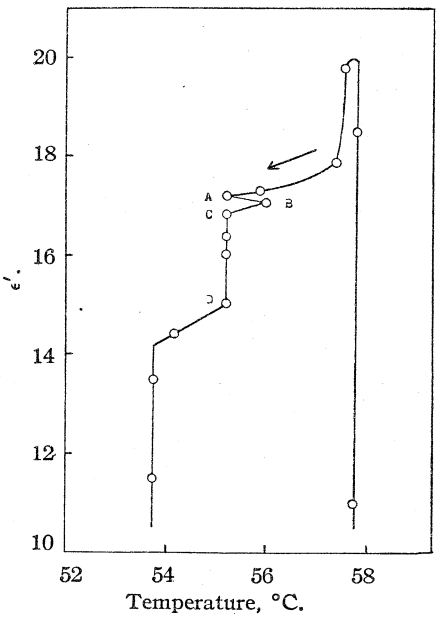



Fig. 6.—Temperature dependence of dielectric constant of *n*-octadecyl alcohol at 0.25 kc. The sample was cooled in the usual way to 55.2° (A), warmed to 56.0° (B), cooled to 55.2° (C) and held at constant temperature for six and one-half hours. The dielectric constant fell to (D). Normal cooling was then allowed to resume.

dielectric constant of *n*-octadecyl alcohol in the waxy state is shown in Fig. 7. The decrease of $\epsilon'$

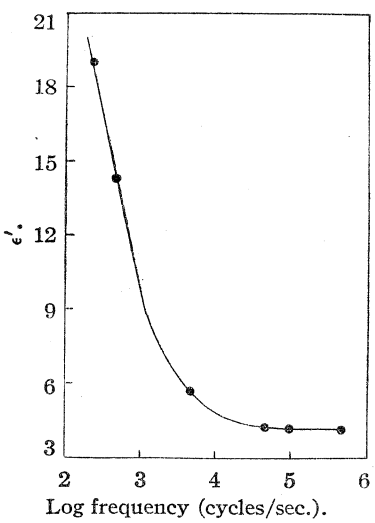



Fig. 7.—Dependence of dielectric constant on frequency for *n*-octadecyl alcohol in waxy state. Data are average values obtained from several runs at 57°.

at 0.25 kc. with time for solid *n*-octadecyl alcohol which had been rapidly cooled from 100 to 15° and held at that temperature for one hundred and fifteen hours is shown in Fig. 8. Figure 9 gives the maximum value of $\epsilon'$ at 0.5 kc. attained by this alcohol on freezing as a function of the logarithm of the

TABLE I

DIELECTRIC CONSTANTS AND SPECIFIC CONDUCTIVITIES

*n*-Dodecyl Alcohol

| $T$, °C. | $\epsilon'$ 0.5 | $\epsilon'$ 5.0 | $\epsilon'$ 50 kc. | $\epsilon''$ 0.5 | $\epsilon''$ 5 | $\epsilon''$ 50 kc. | $k \times 10^{10}$ 0.5 | $k \times 10^{10}$ 5 | $k \times 10^{10}$ 50 kc. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | (Cooling) | | | | |
| 32.1 | .. | 6.07 | .. | ... | 0.58 | .. | | 16 | .. |
| 28.2 | 6.32 | .. | .. | | | 0.06 | | .. | 15 |
| 26.7 | .. | 6.36 | .. | | .61 | | | 17 | |
| 24.6 | .. | .. | 6.52 | | | | | .. | |
| 23.5 | .. | 6.55 | | | .61 | | | 17 | |
| 23.6 | 6.02 | 5.68 | 5.60 | | .50 | | | 14 | |
| 23.5 | 5.02 | 4.57 | 4.48 | | .32 | .03 | | 8.9 | 9 |
| 23.5 | 4.03 | 4.00 | 3.90 | | .25 | | | 6.9 | |
| 23.4 | 3.42 | 3.00 | 2.92 | | .13 | | | 3.7 | |
| 23.3 | 2.80 | 2.52 | 2.55 | | .09 | .00 | | 2.5 | 0 |
| 23.2 | 2.72 | 2.42 | 2.42 | | .09 | | | 2.5 | 0 |
| 22.8 | 2.62 | 2.40 | 2.40 | | .09 | | | 2.5 | 0 |
| 21.3 | 2.55 | 2.33 | 2.33 | | .07 | | | 2.0 | 0 |
| 19.3 | 2.52 | 2.31 | 2.31 | | .. | | | .. | 0 |
| 15.3 | 2.43 | 2.28 | 2.28 | | .03 | | | 0.7 | 0 |
| − 1.6 | .. | 2.27 | .. | | | | | | |
| −128 | .. | 2.20 | .. | | | | | | |
| −170 | | 2.18 | | | | | | | |
| | | | | | (Warming) | | | | |
| 20.8 | 2.60 | 2.32 | 2.32 | | .03 | | | .7 | |
| 21.3 | 2.75 | 2.48 | 2.48 | | .09 | | | 2.5 | |
| 23.2 | 3.40 | 2.90 | 3.02 | | .. | | | .. | |
| 23.5 | 4.00 | 3.40 | 3.28 | | .26 | | | 7.3 | |
| 23.6 | 5.12 | 4.92 | 5.10 | | .40 | | | 11 | |
| 23.7 | 6.40 | 6.40 | 6.40 | | .65 | | | 18 | |
| 24.0 | 6.38 | 6.38 | 6.38 | | .65 | | | 18 | |
| 25.2 | .. | .. | 6.30 | | .. | | | .. | |
| | | | | | *n*-Tetradecyl Alcohol (Cooling) | | | | |
| 48.2 | 4.42 | 4.41 | 4.40 | 2.5 | 0.25 | 0.03 | 6.9 | 6.4 | 6.9 |
| 38.1 | 4.72 | 4.72 | 4.72 | 2.6 | .25 | .03 | 7.2 | 6.9 | 6.9 |
| 36.4 | 4.82 | 4.81 | 4.72[b] | 3.4 | .. | .. | 9.6 | .. | .. |
| 36.3 | 6.80 | 4.70 | 4.60 | 7.9 | .79 | 1.4 | 22[b] | 22[b] | 40 |
| 36.1 | 7.02 | 4.65 | 4.55 | 7.9 | 1.0 | .. | 22 | 28 | .. |
| 35.6 | 7.30 | 4.52 | 4.48 | 7.2 | 1.0 | .. | 20 | 28 | .. |
| 35.0 | 7.20 | 4.45 | 4.25 | 6.1 | 1.1 | .. | 17 | 29 | .. |
| 34.5 | 7.18 | 4.35 | 4.12 | 6.1 | .. | .. | 17 | .. | .. |
| 34.4 | 5.65 | 3.60 | 3.28 | 2.7 | .. | .. | 7.6 | .. | .. |
| 34.3 | 4.28 | 3.03 | 2.56 | 1.4 | .60 | .. | 4.0 | 18 | .. |
| 33.8 | 4.20 | 2.85 | 2.45 | 1.4 | .61 | .. | 4.0[b] | 17[b] | .. |
| 31.1 | 4.00 | 2.73 | 2.40 | 1.3 | .54 | .. | 3.4 | 15 | .. |
| 24.7 | 3.40 | 2.48 | 2.25 | 1.2 | .40 | 0.0 | 3.3 | 11 | 22 |
| | | | | | (Warming, after remaining at 20° one hour) | | | | |
| 33.1 | 4.18 | 2.85 | 2.40 | 1.1 | .36 | .09 | 3.3 | 10 | 26 |
| 34.6 | 4.40 | 3.05 | 2.70 | 1.8 | .65 | .. | 5.0 | 18 | .. |
| 35.1 | 4.78 | 3.20 | 2.80 | 2.4 | .68 | .. | 6.8 | 19 | .. |
| 36.2 | 5.10 | 3.65 | 3.35 | 3.1 | .72 | .14 | 8.5 | 20 | 40 |
| 36.5 | 5.05 | 4.05 | 3.88 | 3.1 | .58 | .. | 8.5 | 16 | .. |
| 36.6 | 4.80 | 4.38 | 4.36 | 2.7 | .58 | .. | 7.5 | 16 | .. |
| 36.6 | 4.72 | 4.58 | 4.58 | 2.7 | .40 | .. | 7.5 | 11 | .. |
| 37.0 | 4.68 | 4.68 | 4.67 | 2.5 | .23 | .. | 7.0 | 6.5 | .. |
| 37.7 | 4.62 | 4.62 | 4.62 | 2.5 | .23 | .03 | 7.0 | 6.5 | 6.5 |
| | | | | | (Separate run, cooling) | | | | |
| 13 | | 2.23 | | | | | | | |
| − 40 | | 2.19 | | | | | | | |
| −105 | | 2.17 | | | | | | | |

TABLE I (*Concluded*)

| T, °C. | $\epsilon'$ 0.5 | $\epsilon'$ 5.0 | $\epsilon'$ 50 kc. | $\epsilon''$ 0.5 | $\epsilon''$ 5 | $\epsilon''$ 50 kc. | $k \times 10^{10}$ 0.5 | $k \times 10^{10}$ 5 | $k \times 10^{10}$ 50 kc. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *n*-Octadecyl Alcohol (Cooling) | | | | | |
| 63.3 | 3.35 | 3.35 | 3.35 | 0.00 | 0.00 | 0.00 | 0.04 | 0.04 | 0.04 |
| 58.8 | 3.41 | 3.41 | 3.41 | | | | | | |
| 57.8 | 3.42 | 3.42 | 3.42[b] | | | | | | |
| 57.7 | 3.62 | 3.65 | 3.50 | 7.2 | .79 | .12 | 20 | 22 | 32 |
| 57.7 | 14.3 | 5.08 | 4.05 | 23 | 4.7 | .54 | 65 | 130 | 150 |
| 57.7 | 16.8 | 5.78 | 4.25 | 27 | 5.2 | .68 | 75[b] | 145[b] | 190[b] |
| 57.6 | 16.0 | 5.80 | 4.24 | 21 | 5.2 | .57 | 62 | 145 | 160 |
| 56.2 | 15.0 | 5.76 | 4.22 | 19 | 4.3 | .57 | 53 | 120 | 160 |
| 55.2 | 14.9 | 5.72 | 4.21 | 19 | 4.2 | .54 | 52 | 117 | 150 |
| 53.7 | 14.6 | 5.65 | 4.21 | 16 | 3.9 | .52 | 45 | 108 | 145 |
| 52.9 | 13.3 | 4.88 | 4.11 | 13 | .. | .. | 36 | .. | .. |
| 53.4 | 11.9 | 4.35 | 3.80 | 10 | 2.6 | .30 | 28 | 73 | 84 |
| 53.4 | 7.35 | 3.90 | 3.10 | 3.6 | 1.0 | .30 | 10 | 28 | 85 |
| 53.2 | 6.08 | 3.70 | 2.85 | 1.9 | .8 | .29 | 5.2 | 23 | 81 |
| 52.2 | 5.25 | 3.38 | 2.58 | 1.2 | .8 | .29 | 3.2[b] | 23[b] | 80[b] |
| 48.5 | 4.66 | 3.10 | 2.45 | 1.1 | .7 | .22 | 3.0 | 21 | 60 |
| | | | | (Warming after standing at 30° twenty hours) | | | | | |
| 45.1 | 3.75 | 2.78 | 2.38 | .75 | .47 | .14 | 2.1 | 13 | 40 |
| 49.8 | 4.05 | 2.95 | 2.42 | .97 | .54 | .25 | 2.7 | 15 | 69 |
| 53.7 | 4.40 | 3.10 | 2.45 | 1.3 | .65 | .27 | 3.7 | 18 | 76 |
| 54.9 | 4.50 | 3.18 | 2.48 | 1.3 | .69 | .. | 3.7 | 19 | .. |
| 56.6 | 5.60 | 3.40 | 2.58 | 1.8 | .72 | .. | 5.0 | 20 | . |
| 57.1 | 8.12[a] | 4.49 | 3.46 | 3.6 | 1.8 | .33 | 10 | 50 | 92 |
| 57.4 | 3.45 | 3.42 | 3.42 | 0.02 | 0.00 | .00 | 0.07 | 0.04 | 0.04 |
| 57.5 | 3.42 | 3.42 | 3.42 | | 0 | | .04 | .04 | .04 |
| 58.5 | 3.35 | 3.35 | 3.35 | | | | .04 | .04 | .04 |
| | | | | (Separate run, cooling) | | | | | |
| − 19.4 | | 2.20 | | | | | | | |
| − 34 | | 2.16 | | | | | | | |
| −149 | | 2.12 | | | | | | | |
| −180 | | 2.12 | | | | | | | |
| | | | | *n*-Docosyl Alcohol (Cooling) | | | | | |
| 75.4 | 2.95 | 2.95 | 2.95 | .18 | .02 | 0.00 | 0.5 | 0.5 | 0.5 |
| 70.8 | 2.97 | 2.97 | 2.96[b] | | | | | | |
| 69.6 | 10.8 | 4.10 | 3.50 | 15 | 3.2 | .40 | 43 | 90 | 110 |
| 69.6 | 15.9 | 4.81 | 3.76 | 21 | 4.2 | .65 | 57[b] | 115[b] | 180[b] |
| 69.5 | 14.2 | 5.10 | 3.88 | 14 | 4.0 | .. | 40 | 110 | .. |
| 68.8 | 13.0 | 5.10 | 3.84 | 12 | 3.2 | .43 | 34 | 90 | 120 |
| 66.7 | 12.1 | .. | .. | ... | .. | .. | ... | .. | .. |
| 64.5 | 11.0 | 4.82 | 3.75 | 6.1 | 2.1 | .41 | 17 | 60 | 115 |
| 64.5 | 9.20 | 4.65 | 3.50 | 3.1 | 1.8 | .. | 8.5 | 50 | .. |
| 64.1 | 7.76 | 4.48 | 3.38 | 3.1 | 1.6 | .. | 8.5 | 45 | .. |
| 62.2 | 6.65 | 4.40 | 3.18 | 0.50 | .. | .. | ... | .. | .. |
| 58.4 | 6.60 | .. | 3.12 | .54 | 0.18 | 0.40 | 3.5[b] | 14[b] | 116[b] |
| 56.8 | 6.40 | .. | 3.08 | .54 | .50 | .38 | 3.5 | 12 | 105 |
| 51.9 | 5.78 | 4.18 | 2.85 | ... | .40 | .32 | ... | 11 | 95 |
| | | | | (Warming, after standing at 20° twenty hours) | | | | | |
| 45.1 | 6.82 | 3.72 | 2.60 | .68 | .21 | .02 | 1.9 | 6 | 60 |
| 55.2 | 5.98 | 4.36 | 3.00 | .68 | .47 | .34 | 1.9 | 13 | 95 |
| 60.2 | 6.40 | 4.70 | 3.22 | .68 | .50 | .38 | 1.9 | 14 | 105 |
| 64.5 | 6.88 | 5.08 | 3.48 | .68 | .54 | .43 | 1.9 | 15 | 120 |
| 66.7 | 7.42 | 5.20 | 3.56 | .68 | .61 | .43 | 1.9 | 17 | 120 |
| 68.1 | 9.56 | 7.00 | 3.68 | 1.7 | 1.0 | .45 | 4.7 | 28 | 125 |
| 68.4 | 14.3 | 6.80 | 3.95 | 4.0 | 2.0 | .47 | 11 | 57 | 130 |
| 68.9 | 4.07 | 3.40 | 3.08 | 0.68 | 0.39 | .14 | 1.9 | 11 | 40 |
| 69.2 | 2.96 | 2.95 | 2.95 | .2 | 0.00 | .00 | 0.5 | 0.5 | 0.5 |
| 70.4 | 2.95 | 2.96 | 2.96 | .2 | | | .5 | .5 | .5 |

[a] When the same sample was rewarmed *immediately* a value of 19.5 was reached. [b] These data are used in Table II to calculate $\epsilon'$.

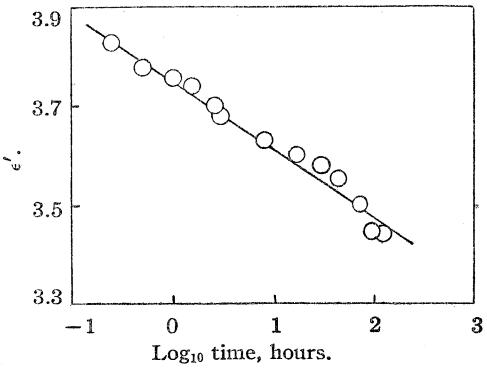



Fig. 8.—Dependence of dielectric constant of *n*-octadecyl alcohol on time at 0.25 kc. and 15.0°. The sample was rapidly cooled from 100 to 15° and held at this temperature.

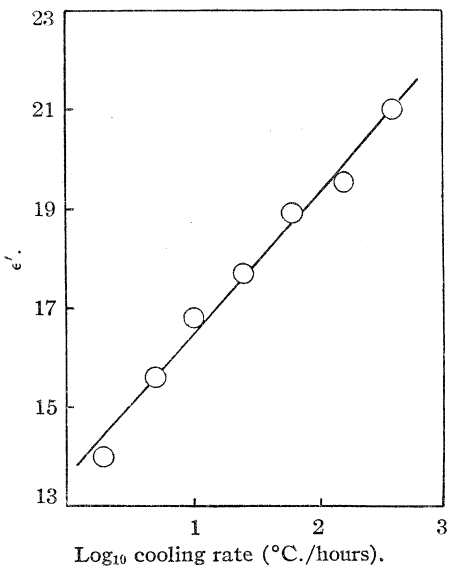



Fig. 9.—Dependence of maximum value of dielectric constant in waxy state on cooling rate of *n*-octadecyl alcohol. Data are for cooling rates as measured 1° above the freezing point and were obtained at 0.5 kc.

cooling rate measured 1° above the freezing point. The cooling and warming curves which were obtained concurrently with the dielectric runs are illustrated in Fig. 10. The dielectric data on impure *n*-dodecyl and *n*-octadecyl alcohols as received from the manufacturers are given in Fig. 11 to permit comparison of the properties of pure and impure materials.

## Discussion of Results

*n*-Dodecyl alcohol (Fig. 1) shows no transitions in the solid, either in the cooling curve or in the dielectric data, and exhibits typical rotational freezing of dipoles on solidification. The conductivity of the liquid alcohol is less than that found by Frosch[3] ($17 \times 10^{-10}$ compared to $42 \times 10^{-10}$). Inasmuch as water was difficult to remove and in view of the appearance of the curve for the impure sample (Fig. 11) it is suggested that water, which forms a higher melting hydrate,[7] or other impurities may have caused previous investigators to obtain results which might be interpreted as indicating molecular rotation.

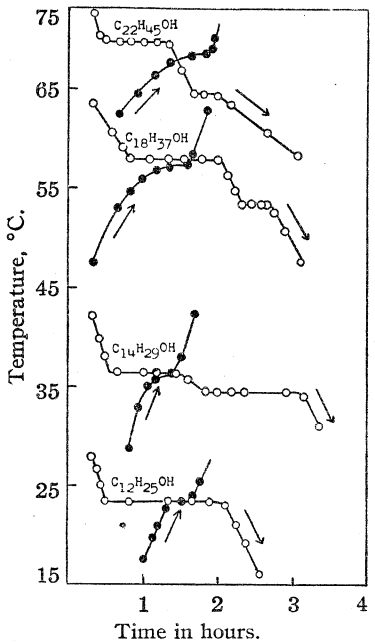



Fig. 10.—Temperature–time curves for *n*-dodecyl, *n*-tetradecyl, *n*-octadecyl and *n*-docosyl alcohols. Arrows indicate warming and cooling curves.

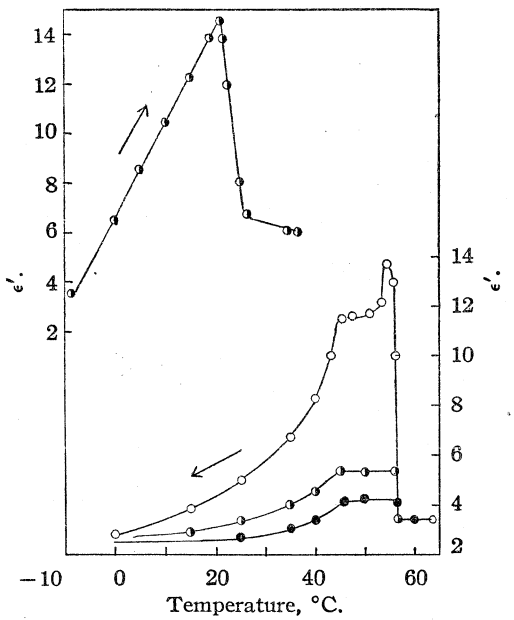



Fig. 11.—Temperature dependence of dielectric constant for impure alcohols. Upper curve, *n*-dodecyl alcohol, scale on left. Lower curve, *n*-octadecyl alcohol, scale on right. Hollow circles represent data at 0.5 kc., half-filled circles values at 5.0 kc., and filled circles data at 50 kc. Arrows indicate direction of temperature change.

*n*-Tetradecyl, *n*-octadecyl and *n*-docosyl alcohols show dielectric and thermal behavior similar to that of *n*-hexadecyl alcohol,[4] except that the waxy ranges are shorter, and that the transitions are not enantiotropic as previously reported.[10] The change of $\epsilon'$ with time at constant temperature (see Fig. 5, AB; Fig. 6, ABCD) indicates that the waxy state consists of a mixture of two solid phases, one of which is unstable. The alcohols change from clear-translucent to opaque-white on standing at constant temperature in the waxy state. The white regions appear first as small nuclei which slowly permeate the whole mass. This coexistence of two phases has been indicated by the X-ray measurements of Malkin[11] on *n*-hexadecyl alcohol, which simultaneously show the crystal spacings of the vertical and tilted forms.

The dielectric dispersion found in the waxy state of these alcohols may be quantitatively accounted for by Maxwell–Wagner polarization between two solid phases which we denote as $\alpha$ (unstable, clear) and $\beta_2$ (stable, white). The $\alpha$ form which crystallizes first from the liquid shows a much higher conductivity than the liquid or crystalline solid at low temperature. Frosch[3] arbitrarily pictured the two phase dielectric as two layers with interfaces parallel to the condenser plates, and, by the use of circuit analysis of the impedances, derived an equation for the observed capacitance as a function of the conductivities of the two phases. Using a similar method, we have obtained the following expression for the maximum observed dielectric constant

$$\epsilon'_m = \epsilon + \epsilon(k_1 - k_2)^2/4k_1k_2$$

where $k_1$ and $k_2$ are the specific conductivities of the two phases, and $\epsilon$ is the dielectric constant arbitrarily taken as the same for each phase. The observed maximum in $\epsilon'_m$ appears for an optimum thickness of a given layer. In the derivation of the above expression it was assumed that $\epsilon'' > \epsilon'$, which is true only for a dielectric possessing conductivity other than that due to orientation loss. The alcohols show sufficient conductivity in the waxy state to cause $\epsilon''$ to exceed $\epsilon'$ at moderately high frequencies, as may be seen in Table I. The supposition by Frosch that the liquid and solid alcohol coexist over long periods of time below the freezing temperature with the interface parallel to the cell plates is contrary to our observations, since the two solid phases are seen to coexist as a mixture over a range of temperature. Despite the fact that the material is not distributed in parallel slabs, there is enough similarity in the equivalent circuits to warrant application of the equation to the case where one phase is distributed as small platelets throughout the other. According to the equipotential surface theorem, the two-layer dielectric treated by Frosch is equivalent to a dielectric where the vertical slabs are split into any number of sheets, and arranged parallel to the condenser plates in any order. To a fair approximation these thin sheets may be subdivided into platelets of smaller area and distributed throughout the other material, thus approximating the two-slab model electrically as well as representing the mixture of solid phases observed experimentally. Hence, our equation should predict the behavior of the alcohols in the waxy state.

In order to apply the equation we take the dielectric constant of the liquid at the freezing point as $\epsilon$ and the specific conductivity of the $\alpha$ phase as that observed for the waxy state as a whole. Since the $\alpha$ phase conducts so much more than the $\beta_2$ and is much more abundant, this approximation is valid. The specific conductivity of the $\beta_2$ phase is assumed to be the same as that of the solid found a few degrees below the transition point after standing for a short time. These approximations are necessary because the phases cannot be physically separated. The data employed are marked with a "b" in Table I. In Table II $\epsilon'_m$ is compared with the value calculated by means of the equation.

TABLE II

COMPARISON OF THE CALCULATED AND THE OBSERVED VALUES OF $\epsilon'_m$

| | Calculated | | | Observed | | | |
|---|---|---|---|---|---|---|---|
| Alcohol | 0.5 | 5 | 50 kc. | 0.5 | 5 | 50 | 525 kc. |
| *n*-Tetradecyl | 9.0 | 4.8 | | 7.30 | 4.81 | | |
| *n*-Octadecyl | 22 | 7.3 | 4.0 | 16.8 | 5.80 | 4.25 | 4.15 |
| *n*-Docosyl | 24 | 7.5 | 3.2 | 15.9 | 5.10 | 3.88 | |

In general, the calculated values tend to be somewhat high, but it is clear that the equation holds fairly well and that the Maxwell–Wagner polarization drops off sharply with increase in frequency. Considering the fact that no precise knowledge of the actual specific conductivities of each pure phase may be had, and that a rough model has been used, the agreement between observed and calculated values is satisfactory.

Now that analysis has shown the large increase in $\epsilon'$ to be due to Maxwell–Wagner effect, it is possible to interpret the data free of this phenomenon in terms of dipole rotation. Table II and Figs. 2, 3, 4 and 7 indicate that the Maxwell–Wagner effect is not important at 50 kc. for *n*-tetradecyl, *n*-octadecyl and *n*-docosyl alcohols. The persistence of a near-liquid value of the dielectric constant in the waxy state at this frequency clearly indicates that a state of dipole rotation exists. *n*-Octadecyl alcohol shows an increase of dielectric constant on freezing of roughly 20% even at 525 kc., and *n*-docosyl alcohol shows an increase of about 30% at 50 kc., but these increases may be accounted for largely by the increase in density of these compounds on solidification. It is possible that the values for *n*-docosyl alcohol are still slightly high at 50 kc. because of some persistence of the Maxwell–Wagner effect. *n*-Tetradecyl alcohol shows no increase in $\epsilon'$ on freezing, but, instead, falls off with decreasing temperature. This is probably due to the rather rapid transformation of the $\alpha$-phase to

(10) Meyer and Reid, THIS JOURNAL, **55**, 1574 (1933).
(11) Malkin, *ibid.*, **52**, 3739 (1930).

the more stable form during the cooling process. The true anomalous dispersion region is doubtless at a much higher frequency than any employed here, and should not be confused with the Maxwell–Wagner dispersion.

X-Ray studies show[2,11] that the oxygen atoms are arranged in a plane in the crystal, so that a sheet of rotating dipoles may be said to exist. Dipole rotation appears to be synonymous with rotation of the hydrocarbon chain. This is indicated by the cooling curves which show sharp transitions in the solid concurrent with the freezing out of dipoles, and by the X-ray data of Ott,[2] which show that the transition involves a change from rotation to non-rotation of the molecular chain. Molecular rotation about the long axis appears for shorter chain lengths in the alcohols (14 carbons) than in the corresponding hydrocarbons where 22 carbon atoms are required before rotation appears in the solid.[12]

The origin of the high conductivity attributed to the $\alpha$ phase, which is necessary to the elucidation of the dielectric behavior remains to be explained. The planes of hydroxyls in this phase, possessing rotational freedom through rotation of the entire molecules, seem to provide a possible site for the proton transfer mechanism of conduction treated by Stearn and Eyring.[13] Two important requirements are proximity of the hydroxyl groups to one another, and rotation of these groups such that an optimum configuration conducive to the transfer of a proton from a positive ion (*e. g.*, a hydronium ion) to a neutral molecule may occur with reasonable frequency in an applied field. Both requirements seem to be met in the $\alpha$ phase of the waxy state in the long-chain alcohols. No extensive sheets of hydroxyls possessing rotational freedom occur in either the liquid[14] or the low-temperature crystalline solid, and the relatively lower conductivity of these media should be due to the absence of the rotation required in the proton-transfer mechanism. Baker and Yager[15] have invoked a mechanism of proton transfer to explain the high d. c. conductivity of linear polyamides. Despite precautions, contamination of our samples with a very small amount of water is possible, but this could not account for the appearance of appreciable conductance solely in the waxy state, and not in the liquid or low temperature crystalline solid.

It is possible to correlate the properties of the vertical and tilted forms of long chain compounds with the dielectric changes and cooling curve data of the alcohols. The vertical forms found in long-chain compounds are those in which the carbon chains are perpendicular to the plane of the end groups, and the tilted forms are those in which the carbon chains are inclined at an angle to the plane of the end groups. The latter show shorter crystal spacings between the end groups than the former. For a number of long-chain compounds, including hydrocarbons, esters and acids, the vertical form tends to be clear, have a lower entropy of fusion per methylene group, and greater inter-chain mobility than the tilted form.[16] Thus it seems reasonable to assign to the clear, rotating $\alpha$ phase the vertical configuration. Ott[2] has found that the rotating molecules in *n*-tetradecyl and *n*-hexadecyl alcohols show the long crystal spacing, which proves that the $\alpha$ phases of these two substances are the vertical form. The irreversible conversion of $\alpha$ to $\beta_2$ in the waxy state, which is accompanied by a drop in $\epsilon'$ (Figs. 5 and 6) with simultaneous increase in opacity, is probably due to the slow conversion of the vertical (rotator) into the tilted (non-rotator) form; the slowness of the process is likely due to the high viscosity of the medium in which the molecules must move to achieve the configuration of lowest energy.

The transformation of the $\alpha$ phase proceeds during the freezing process in which $\alpha$ is formed from the liquid, and thus we may expect the maximum value attained by $\epsilon'$ at a given frequency to depend on the cooling rate. Figure 9 illustrates this effect for cooling rates between 2 and 400° per hour. The transformation of the $\alpha$ phase lowers the $\epsilon'_m$. Differences in cooling rate as well as impurities may evidently be an important cause of discrepancies among the results on *n*-hexadecyl alcohol as reported by other workers.[3,4,17]

It is believed that a transition point is found in the solid because that portion of the $\alpha$ phase not yet converted into $\beta_2$ in the cooling process and retaining hexagonal close-packing of the chains collapses into what Ott terms a "monoclinic" lattice, with a considerable heat of transition. Since it has been shown[2] that the $\alpha$ form has the vertical configuration, it is plausible to suggest that the change to the "monoclinic" lattice at the transition point occurs while the chains are vertical. This would produce a form which we call $\beta_1$. It has been observed that the tilted form with the "monoclinic" carbon chain lattice is the stable form in the crystalline solid,[2,3] so that we might expect a slow rearrangement of $\beta_1$ into $\beta_2$ in the solid. Changes from vertical to tilted have been observed in the solid long chain iodides by X-ray techniques,[3] and an irreversible $\beta_1$ to $\beta_2$ transition in the solid similar to the present case has been found by polarization and coefficient of expansion measurements in ethyl docosanoate.[18] The data plotted in Fig. 8 for solid *n*-octadecyl alcohol at 15° at 0.25 kc. show that the dielectric constant drops slowly with time over a period of five days, and afford a strong indication of the expected $\beta_1$ to $\beta_2$ transition. Further evidence that a change is taking place in the crystalline solid below the transition point is afforded by the fact that the

(12) Müller, *Proc. Roy. Soc.* (*London*), **A138**, 514 (1932).
(13) Stearn and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).
(14) Pierce and Macmillan, THIS JOURNAL, **60**, 779 (1938).
(15) Baker and Yager, *ibid.*, **64**, 2171 (1942).
(16) King and Garner, *J. Chem. Soc.*, 1368 (1936).
(17) Higasi and Kubo, *Bull. Chem. Soc. Japan*, **12**, 326 (1937).
(18) Buckingham, *Trans. Faraday Soc.*, **30**, 377 (1934).

dielectric data obtained on warming differed greatly in the maximum value of $\epsilon'$ attained, the difference depending on the time the solid had been allowed to stand. Thus, the highest value at 0.5 kc. reached on re-warming *n*-octadecyl alcohol which had been allowed to stand twenty hours at about 25° was 8.12 (Fig. 3), but immediate re-warming yielded a value of 19.5. A similar effect was found for *n*-docosyl alcohol. Finally, changes in melting and freezing point values give evidence for the $\beta_1$ to $\beta_2$ transition in the solid. For example, *n*-octadecyl alcohol which had stood overnight at room temperature remelted at 57.4° (Fig. 10) while that which was rewarmed immediately melted at 57.7°. An even more pronounced effect involving a temperature difference of 0.9° was observed for *n*-docosyl alcohol. These facts are in accord with the principle that those molecules which rotate in the solid tend to melt at a somewhat higher temperature than their non-rotating counterparts.[19] The thermal (Fig. 10) data illustrate the difference between freezing and melting point nicely.

The general picture proposed for the phase changes in these alcohols is the following: *n*-Dodecyl alcohol crystallizes directly into a stable form, but the higher alcohols crystallize from the liquid to a more or less transparent $\alpha$ form, which shows rotation about the long molecular axis. The $\alpha$ modification is unstable and begins to change to a more stable non-rotating form, $\beta_2$. This system, a non-equilibrium of two allotropic modifications, has the ability to exhibit Maxwell–Wagner polarization since the $\alpha$ phase is a conductor. At a transition point below the freezing point the $\alpha$ form which has not been converted to $\beta_2$ transforms into $\beta_1$. $\beta_1$ is not stable but slowly changes to the stable $\beta_2$ form. The $\beta_2$ forms melt below the original freezing point, as would be expected, since they do not possess molecular rotation.[19]

The chain length of fourteen carbon atoms at which molecular rotation is possible in the alcohols is shorter than for which it has been observed in other types of long molecules, which will be discussed in a later paper. In conformity with previous work, there is no indication that the rotation is that of the hydroxyl around the C—O bond.

(19) Baker and Smyth, *Ann. New York Acad. Sci.*, **XL**, 447 (1940).

## Summary

The dielectric constants and loss factors of *n*-dodecyl, *n*-tetradecyl, *n*-octadecyl and *n*-docosyl alcohols have been measured over a wide range of temperature and frequency in order to investigate the possibility of molecular rotation in the solid forms. When carefully purified, *n*-dodecyl alcohol gave no evidence of molecular rotation in the solid state. The other three alcohols, on cooling of the liquid, froze to waxy solids possessing dielectric constant values so high as to show the presence of strong Maxwell–Wagner polarization. The values were dependent on the cooling rate. An equation approximately representing the observed dielectric behavior of the waxy solid has been developed on the assumption of the coexistence of two solid phases of very different electrical conductivities. The two phases formed on freezing consisted of an unstable $\alpha$ phase observed to be translucent together with a small amount of a stable, opaque $\beta_2$ phase, which increased in amount with the passage of time. The $\alpha$ phase was found to show rotation of the molecules around their long axes, and its high electrical conductivity was attributed to proton transfer facilitated by the molecular rotation. On cooling, the $\alpha$ phase showed a transition to an unstable $\beta_1$ phase, in which the molecules did not possess rotational freedom. The $\alpha$ phase in *n*-tetradecyl alcohol appears to be less stable than that in *n*-octadecyl alcohol. The $\beta_1$ phase gradually changed to the $\beta_2$, which, possessing no rotational freedom, melted slightly below the freezing point. The setting-in of some dielectric dispersion just below the transition point was attributed to incompleteness of the conversion from $\beta_1$ to $\beta_2$. Differences in results obtained on warming and on cooling were related to phase changes in the solid.

PRINCETON, NEW JERSEY RECEIVED JUNE 19, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE STANDARD OIL CO. (IND.)]

# Experimental Equilibrium Constants for the Isomeric Hexanes

BY B. L. EVERING AND E. L. D'OUVILLE

In the course of the development of the naphtha isomerization process[1,2] the equilibrium constants for the isomeric hexanes were determined. Although the equilibrium constants for butanes and pentanes[3,4] have been repeatedly investigated, few experimental data have appeared for the hexanes. Two papers[5,6] have appeared on the direct experimental determination of the equilibrium constants for the hexanes but they were limited to 25 and 80°, respectively. The hexane equilibria were calculated over a wide range of temperatures from the precise measurements of the heats of combustion and best available entropy data.[7] In the present investigation the hexane equilibria were studied directly over the temperature range 21 to 204° and side reactions were reduced to a minimum by the use of hydrogen and cyclic decomposition inhibitors. The experiments were carried out on a fraction of Mid-Continent light naphtha containing both $C_5$ and $C_6$ hydrocarbons.

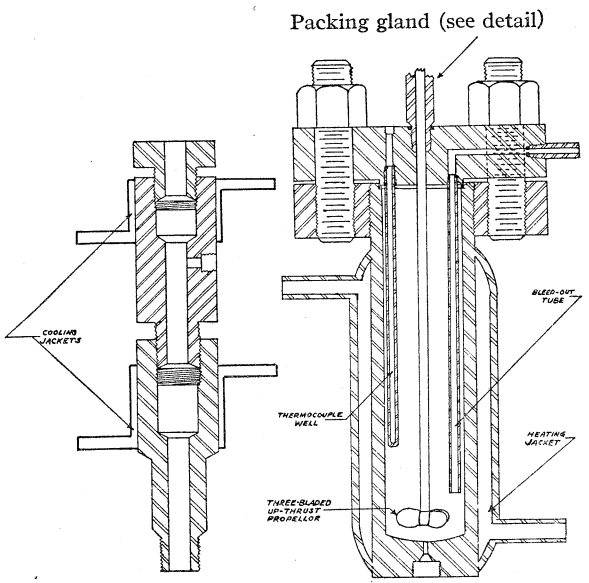



Fig. 1.

All experiments were made in a stirring reactor wherein efficient contact was obtained between the catalyst and the reactants.

## Experimental Method

A batch type stirring apparatus consisting of a 1490-cc. capacity carbon steel reactor (Fig. 1) was employed throughout this investigation. The reactor was heated with steam or hot oil by circulating these materials through a jacket surrounding the reactor. The reactor could be brought to reaction temperature in five minutes with steam and in half an hour with the hot circulating oil. In the case of steam the reactor could be quenched in five minutes by circulating cold tap water through the surrounding jacket. Cooling was somewhat slower with the hot oil since cold water could not be circulated through the jacket to cool the reactor.

The reactor was mechanically stirred at 1725 r. p. m. by a one-half horsepower electric motor driving a $^3/_8$ inch steel shaft operating through a double packing gland, the details of which are shown in Fig. 1. The lower packing holds the reactor pressure and any leakage past the main packing gland is measured by a gas meter attached to the vent between the lower and upper packing glands. In actual service, no difficulty has been experienced with leakage up to pressures of 5000 lb./sq. in. Successful operation depends primarily on the use of a drill rod shaft in conjunction with an asbestos type packing impregnated with a heavy oil and water cooling of the packing glands. The reactants were agitated with a 2.5 inch three bladed upthrust propeller placed near the bottom of the reactor. A bleedout tube dipped to near the bottom of the reactor so that liquid product could be withdrawn. The reactor system was equipped with the necessary accessory equipment to measure in known amounts of anhydrous hydrogen chloride from a calibrated pressure vessel by pressure drop and was also equipped for the addition of hydrogen.

An experiment was made as follows. Seventy-two grams of anhydrous aluminum chloride or its equivalent as aluminum chloride–hydrocarbon complex was placed in the reactor usually with one liter of light naphtha and promptly sealed. Twenty-two grams of hydrogen chloride was measured into the reactor as an activator. Hydrogen was added in the higher temperature runs until the total reactor pressure was 600 lb./sq. in. at room temperature. In the case of the experiments at 21°, anhydrous aluminum bromide, which is soluble in paraffins, was used as the catalyst in an effort to establish equilibrium more rapidly.

The reactor was heated to reaction temperature with stirring and sufficient time allowed for equilibrium to be established. At the end of this time the stirrer was stopped, the reactor was rapidly cooled and one-half hour allowed for settling the catalyst from the products. (It was experimentally established that no isomerization occurred during this cooling and settling period.) The liquid product was withdrawn from the reactor into a flask, the volatile products passed overhead through a soda lime tube to remove hydrogen chloride, then to a Dry Ice–acetone "knock back" to condense light hydrocarbons and finally to a wet test meter to measure the effluent hydrogen and any other non-condensable gases.

The products were distilled in a low-temperature column packed with glass helices equivalent to 20 theoretical plates to separate between butanes and lighter and the liquid product. Motor method octane numbers (CFR-ASTM D-357) were obtained on the liquid product for rapid estimation of the establishment of equilibrium. Those samples which had attained equilibrium were carefully fractionated in a wire gauze packed column testing 60—80

(1) B. L. Evering, N. Fragen and G. S. Weems, *Chem. Eng. News*, **22**, 1898 (1944).

(2) J. E. Swearingen, R. D. Geckler and C. W. Nysewander, *Trans. A. I. Ch. E.*, **42**, 573 (1946).

(3) Egloff, Hulla and Komarewsky, "Isomerization of Pure Hydrocarbons," Chapter I, Reinhold Publishing Co., New York, N. Y., 1942.

(4) H. Pines, B. Kvetinskas, L. S. Kassel and V. N. Ipatieff, THIS JOURNAL, **67**, 631 (1945).

(5) H. Koch and H. Richter, *Ber.*, **77**, 127 (1944).

(6) G. C. A. Schuit, H. Hoog and J. Verheus, *Rec. trav. chim.*, **59**, 793 (1940).

(7) F. D. Rossini and co-authors, API Research Project 44, "Selected Values of Properties of Hydrocarbons," Circular of the National Bureau of Standards C461, November, 1947.

theoretical plates. The accuracy of the analyses attainable with this column is shown in Table I by the fractional analysis of a known synthetic sample. The largest discrepancy from the true composition of the hexanes is in the determination of 2,3-dimethylbutane as it must be determined primarily from the refractive index and this is partially obscured by the high index of cyclopentane. Mass spectrometer analyses (not available when the analyses were made) have invariably shown the concentration of 2,3-dimethylbutane determined by fractional analysis to be approximately 20% low; therefore the values reported for 2,3-dimethylbutane in this investigation have been corrected upward by this amount with an accompanying decrease in the value of 2-methylpentane.

TABLE I

ACCURACY OF FRACTIONAL ANALYSES OF HEXANE ISOMERS

| | Volume, % | |
|---|---|---|
| | Actual composition | Fractionation |
| Cyclopentane | 3.8 | 4.0 |
| 2,2-Dimethylbutane | 20.8 | 19.7 |
| 2,3-Dimethylbutane | 7.9 | 6.2 |
| 2-Methylpentane | 30.6 | 34.3 |
| 3-Methylpentane | 15.8 | 15.7 |
| *n*-Hexane | 14.2 | 12.2 |
| Methylcyclopentane | 5.4 | 7.0 |
| Benzene | 1.5 | 0.9 |

Materials.—The aluminum chloride was a product of the Hooker Electrochemical Company. The anhydrous hydrogen chloride was from the Harshaw Chemical Company and was guaranteed 96% pure. Hydrogen was Linde commercial grade and was used from cylinders without further purification.

The hydrocarbon used in this investigation was a 67° end-point cut of Mid-Continent naphtha containing 0.009 weight per cent. sulfur and having the composition shown in Table II. Although the hydrocarbon feed contained considerable amounts of material other than hexanes in the form of pentanes, naphthenes and a small amount of aromatics, they are not believed to have any detrimental effect on the equilibrium of the hexanes. In fact, the naphthenes and benzene serve the useful function of being decomposition inhibitors, thus reducing side reactions.

TABLE II

COMPOSITION OF MID-CONTINENT LIGHT NAPHTHA (67° End-point)

| | Volume, % |
|---|---|
| Isopentane | 1.5 |
| *n*-Pentane | 35.9 |
| Cyclopentane | 3.0 |
| 2,2-Dimethylbutane | 1.0 |
| 2,3-Dimethylbutane | 1.0 |
| 2-Methylpentane | 23.3 |
| 3-Methylpentane | 13.4 |
| *n*-Hexane | 17.4 |
| $C_6$ Naphthenes | 3.0 |
| Benzene | 0.5 |

## Experimental Results

For accurate equilibrium data the first problem is assurance of the establishment of complete chemical equilibrium and the second is the reduction to a minimum of all side reactions that might affect this equilibrium.

In order to avoid the time-consuming fractional analysis of the products from all the experiments, a rapid method of determining the approach to and establishment of equilibrium was used. Since the octane numbers[8] of hydrocarbons increase with increase in the branching, determination of the octane number of the product gave a rapid estimate of the extent to which the isomerization had progressed. Series of experiments made at increasing reaction time are plotted against octane number and the leveling off of the octane number curve indicated the establishment of chemical equilibrium. Only those experiments for which chemical equilibrium was established, were analyzed by fractional distillation. Figure 2 shows that equilibrium is established quite rapidly at 161° and very slowly at the lower temperatures and especially at 21°.

The side reactions accompanying isomerization at 21 and 161° are shown in Fig. 2 where the percentage of butane and lighter (condensables) formed are taken as a measure of decomposition and plotted against time. Side reactions increase rapidly with increase in temperature so that at 161° and above hydrogen pressure was used to inhibit decomposition. Since hydrogen pressure has a slight suppression effect on the rate of isomerization it was not used at 102° and lower where the isomerization rate is very slow; instead, advantage was taken of the decomposition-inhibiting action of the naphthenes and benzene contained in the light naphtha. The inhibiting of side reactions accompanying isomerization will be reported in more detail in a subsequent paper.

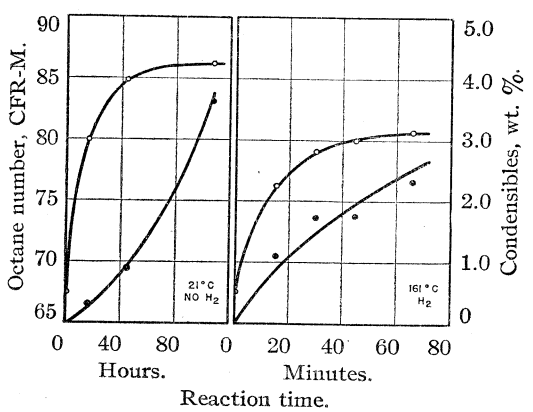



Fig. 2.— -O-, CFR-M; -●-, decomposition.

Side reactions can have a pronounced effect on chemical equilibrium and lead to erroneous results[9] due to the relative instability of one isomer compared to another and an unfavorable isomerization rate for the formation of the unstable isomer as it is depleted. For the equilibrium experiments at 21 and 161° the decomposition is sufficiently low that no appreciable error can be produced. Furthermore, although the decomposition curves in Fig. 2 are not linear, they do not indicate any

(8) J. Smittenberg, H. Hoog, B. H. Moerbeek and M. J. v. d. Zijden, *J. Inst. Petroleum*, **26**, 294 (1940).

(9) J. R. Bates, THIS JOURNAL, **68**, 511 (1946).

appreciable preferential decomposition of the more highly branched isomers as they are formed. At 102 and 204° the decomposition is considerably higher (Table IV) but does not lead to displacement of equilibrium. This was confirmed by isomerizing 2,3-dimethylbutane under insufficient hydrogen pressure so that a large amount of decomposition was produced and comparing with the results from an experiment in which the decomposition was substantially inhibited. The results reported in Table III indicate no significant difference for the two extreme cases.

TABLE III

EFFECT OF DECOMPOSITION ON HEXANE EQUILIBRIUM

| Hydrocarbon | 2,3-Dimethylbutane | 2,3-Dimethylbutane |
|---|---|---|
| Cyclopentane, vol., % | 8.3 | 0.0 |
| $AlCl_3$, g. | 69.0 | 73.6 |
| HCl, g. | 20.5 | 20.5 |
| Contact time, min. | 10 | 10 |
| Temperature, °F. | 320 | 313 |
| $H_2$ pressure, p. s. i. | 550 | 550 |
| Vol. % decomposition to lighter than $C_6$ | 7.4 | 62.9 |
| Analyses of hexanes, vol., % | | |
| 2,2-Dimethylbutane | 22.6 | 21.8 |
| 2,3-Dimethylbutane | 8.8 | 11.0 |
| 2-Methylpentane | 37.3 | 35.2 |
| 3-Methylpentane | 18.3 | 17.8 |
| *n*-Hexane | 13.0 | 14.2 |

TABLE IV

COMPOSITION OF REACTOR CONTENTS AT EQUILIBRIUM

| Temperature, °C. | 21 | 102 | 161 | 204 |
|---|---|---|---|---|
| Moles | | | | |
| Hydrogen | ..... | ..... | 0.785 | 0.900 |
| Hydrogen chloride | 0.310[a] | 0.356 | .493 | .246 |
| Propane | .010 | .055 | .020 | .121 |
| Isobutane | .360 | .920 | .382 | .714 |
| *n*-Butane | .044 | .324 | .232 | .223 |
| Isopentane | 2.600 | 2.325 | 2.515 | 1.841 |
| *n*-Pentane | 0.463 | 0.414 | 0.815 | 0.768 |
| Cyclopentane | 0.209 | 0.300 | .271 | .131 |
| 2,2-Dimethylbutane | 2.295 | 1.400 | .936 | .538 |
| 2,3-Dimethylbutane | 0.386 | 0.367 | .346 | .220 |
| 2-Methylpentane | .879 | 1.005 | 1.341 | .928 |
| 3-Methylpentane | .342 | 0.477 | 0.671 | .440 |
| *n*-Hexane | .167 | .336 | .419 | .349 |
| Methylcyclopentane | .035 | .173 | .278 | .200 |
| Cyclohexane | .573 | .352 | .272 | .120 |
| Vapor/liquid ratio (at reactor temp.) | Liquid | .006 | .75 | Vapor |
| Mole % decompn. | 5.0 | 15.3 | 7.4 | 15.9 |

[a] Anhydrous hydrogen bromide.

**Hexane Equilibria.**—Table IV shows the results of experiments at 21, 102, 161 and 204° in which equilibrium had been established. Since the contents of the reactor were cooled to room temperature before removal, the analyses reported in Table IV are for the combination of vapor and liquid phases which existed at reaction conditions. The true equilibrium values for the hexanes in the vapor and liquid phases were calculated from these data by finding the vapor and liquid composition that existed in the reactor at the experimental temperature and pressure. This was solved by trial and error knowing the fugacities of the various components in the system. The fugacities of the components in the reactor at experimental conditions were obtained from compressibility charts[10] using the best published vapor pressures and critical constants appearing in the literature. The physical properties of the isomeric hexanes were taken from the work of Willingham, Taylor, Pignocco and Rossini[11] for temperatures below the boiling point and from the work of Kay[12] at higher temperatures. The fugacities for hydrogen and hydrogen chloride are based on unpublished data from this Laboratory. The vapor and liquid phase equilibrium values for the isomeric hexanes are given in Table V together with the phase or vapor–liquid ratio calculated as existing at experimental conditions.

At 21° the phase is known to be entirely liquid and at 102° the vapor–liquid ratio can be calculated quite accurately. However, at 161°, which is relatively close to the critical and 204° which is just above the critical, the exact phase or vapor–liquid ratio cannot be known with great certainty. This uncertainty in the vapor–liquid ratio at the two higher temperatures cannot lead to any substantial errors as calculations assuming the found analyses to be either entirely vapor or entirely liquid are quite close at 161° and are equal at the critical. The composition limits for the several temperatures investigated are shown in Table V.

The vapor phase equilibrium values for the isomeric hexanes from the last column of Table V are plotted in Fig. 3. These values are compared with those obtained from the entropies and heats of combustion[7] and the experimental values of Koch and Richter[5] at 25° and Schuit, Hoog and Verheus[6] at 80°.

The agreement between the present values and those from the entropies and heats of combustion are good for *n*-hexane and 2,3-dimethylbutane but are in disagreement on 2,2-dimethylbutane and the methylpentanes. The temperature coefficient for all the isomers is in good agreement but the entropies and heats of combustion predict substantially more 2,2-dimethylbutane than has been found experimentally. Assuming that the difference lies entirely in the 2,2-dimethylbutane, then the discrepancy in the methylpentanes vanishes. Aside from the absolute values there is good agreement in the ratio of 2-methylpentane to 3-methylpentane.

The experimental equilibria determined for the hexanes by Koch and Richter[5] at 25° are in ex-

(10) Weber, "Thermodynamics for Chemical Engineers," John Wiley and Sons, New York, N. Y., 1939, p. 198.

(11) C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Natl. Bur. Standards*, **35**, 219 (1945).

(12) W. B. Kay, THIS JOURNAL, **68**, 1336 (1946).

TABLE V

EQUILIBRIUM COMPOSITION OF THE ISOMERIC HEXANES

| Run | Composition | Temp., °C. | Reactor pressure, lb./sq. in. (gage) | Vapor–liquid ratio | Observed analysis, mole % | Composition limits Vapor,[a] mole % | Composition limits Liquid,[b] mole % | Equilibrium Liquid, mole % | Equilibrium Vapor, mole % |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2,2-Dimethylbutane | 21 | 50 | Liquid | 56.4 | 66.4 | 45.6 | 56.4 | 66.4 |
| | 2,3-Dimethylbutane | | | | 9.5 | 8.2 | 10.5 | 9.5 | 8.2 |
| | 2-Methylpentane | | | | 21.6 | 16.9 | 26.3 | 21.6 | 16.9 |
| | 3-Methylpentane | | | | 8.4 | 6.0 | 11.2 | 8.4 | 6.0 |
| | *n*-Hexane | | | | 4.1 | 2.5 | 6.4 | 4.1 | 2.5 |
| 2 | 2,2-Dimethylbutane | 102 | 220 | 0.006 | 39.1 | 45.0 | 33.3 | 39.1 | 45.0 |
| | 2,3-Dimethylbutane | | | | 10.2 | 9.8 | 10.5 | 10.2 | 9.8 |
| | 2-Methylpentane | | | | 28.0 | 26.3 | 29.4 | 28.0 | 26.3 |
| | 3-Methylpentane | | | | 13.3 | 11.7 | 14.9 | 13.3 | 11.7 |
| | *n*-Hexane | | | | 9.4 | 7.2 | 11.9 | 9.4 | 7.2 |
| 3 | 2,2-Dimethylbutane | 161 | 875 | 0.75 | 25.2 | 26.2 | 24.1 | 24.9 | 25.9 |
| | 2,3-Dimethylbutane | | | | 9.3 | 9.9 | 8.8 | 9.1 | 9.7 |
| | 2-Methylpentane | | | | 36.1 | 35.2 | 37.0 | 36.4 | 35.5 |
| | 3-Methylpentane | | | | 18.1 | 17.6 | 18.6 | 18.2 | 17.8 |
| | *n*-Hexane | | | | 11.3 | 11.1 | 11.5 | 11.4 | 11.1 |
| 4 | 2,2-Dimethylbutane | 204 | 1080 | Vapor | 21.7 | 20.9 | 22.5 | | 21.7 |
| | 2,3-Dimethylbutane | | | | 8.9 | 9.1 | 8.7 | | 8.9 |
| | 2-Methylpentane | | | | 37.5 | 37.4 | 37.6 | | 37.5 |
| | 3-Methylpentane | | | | 17.8 | 18.2 | 17.3 | | 17.8 |
| | *n*-Hexane | | | | 14.1 | 14.4 | 13.9 | | 14.1 |

[a] If observed analysis is all liquid. [b] If observed analysis is all vapor.

TABLE VI

COMPARISON OF $\Delta F/T$ FROM EXPERIMENTAL DATA WITH THE VALUES OF ROSSINI AND CO-AUTHORS

| | $\Delta F/T$ cal./deg. mole, 25°C. This work | 25°C. Rossini and co-authors | 127°C. This work | 127°C. Rossini and co-authors | 200°C. This work | 200°C. Rossini and co-authors |
|---|---|---|---|---|---|---|
| *n*-Hexane | 0 | 0 | 0 | 0 | 0 | 0 |
| 2-Methylpentane | −3.68 | −3.89 | −2.39 | −2.48 | −2.06 | −1.78 |
| 3-Methylpentane | −1.68 | −1.88 | −0.85 | −1.00 | −0.67 | −0.60 |
| 2,3-Dimethylbutane | −2.23 | −3.35 | −0.22 | −1.18 | +0.79 | −0.26 |
| 2,2-Dimethylbutane | −6.33 | −7.98 | −2.94 | −4.30 | −0.61 | −2.60 |

cellent agreement with the present experimental values and lend support to the lower experimental values for 2,2-dimethylbutane over the higher values calculated by Rossini and co-authors.[7] The values of Schuit, Hoog and Verheus,[6] at 80° cannot be compared to the present values since no distinction was made between 2,2-dimethylbutane and 2,3-dimethylbutane and the total of the dimethylbutanes is obviously far from equilibrium. Their values agree well with the present values in the case of *n*-hexane and in the ratio of 2-methylpentane to 3-methylpentane.

The values of $\Delta F/T$ for the isomerization of *n*-hexane to the various isomers were calculated from the experimental equilibrium constants using the relationship

$$\Delta F/T = -R \ln K \qquad (1)$$

The smoothed values are compared in Table VI with those reported by Rossini and co-authors[7] from the entropies and heats of combustion. The largest discrepancy appears in the values for 2,2-dimethylbutane.

Since $\Delta F/T$ is related to both $\Delta H$ and $\Delta S$ through the standard free energy equation and is also related by equation (1) to the equilibrium constant, it is possible to separate the discrepancies in Table VI and assign them to either errors in the entropy or heat of isomerization or both. From the relation

$$-R \ln K = \Delta H/T - \Delta S \qquad (2)$$

the heat of isomerization and entropy of isomerization were evaluated for the conversion of *n*-hexane to its isomers by plotting log $K$ against $1/T$. The values calculated for the entropy and heat of

TABLE VII

COMPARISON OF HEAT OF ISOMERIZATION AND ENTROPY OF ISOMERIZATION DATA FOR THE HEXANES

| | $\Delta H$ cal./mole[a] This work | $\Delta H$ cal./mole[a] Rossini and co-authors | $\Delta S$ e. u.[a] This work | $\Delta S$ e. u.[a] Rossini and co-authors |
|---|---|---|---|---|
| *n*-Hexane | 0 | 0 | 0 | 0 |
| 2-Methylpentane | −1310 | −1710 | −0.78 | −1.86 |
| 3-Methylpentane | − 820 | −1020 | −1.12 | −1.59 |
| 2,3-Dimethylbutane | −2500 | −2530 | −6.07 | −5.13 |
| 2,2-Dimethylbutane | −4620 | −4390 | −8.93 | −6.74 |

[a] Average over the temperature range 25–200°.

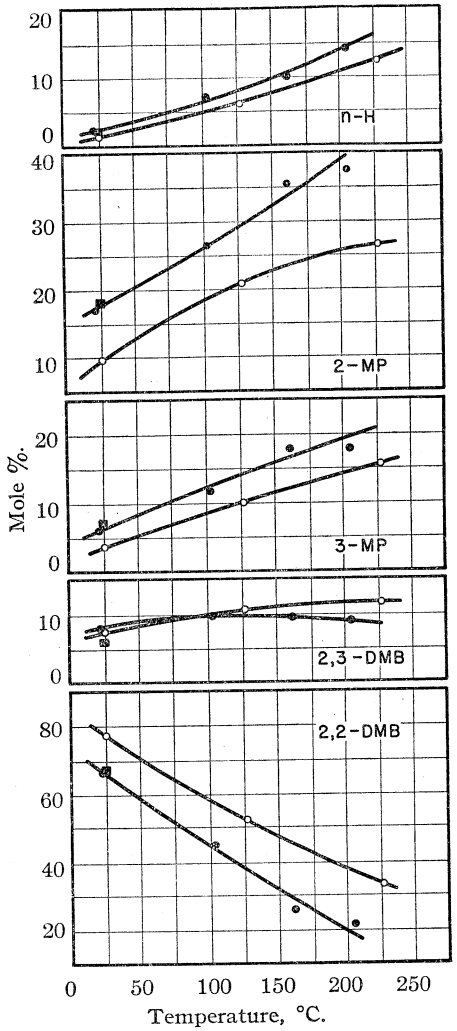



Fig. 3.— -●-, Experimental; -O-, calculated from $\Delta H$; ■, Koch and Richter.

isomerization from the present experimental work and from the calorimetric data of Rossini and co-authors are compared in Table VII. These are the values over the temperature range 25–200° and are directly comparable.

The agreement between the heats of isomerization obtained from the heats of combustion and the present experimental work are quite good. The disagreement in the equilibrium values may be traced largely to discrepancies in the entropies of isomerization. Further work will be necessary to resolve this discrepancy.

**Pentanes.**—Although this paper deals primarily with hexane equilibria, similar data were obtained simultaneously for the pentanes since the feed contained 37% pentanes. The pentanes were handled in the same fashion as described for the hexanes. The equilibrium values are shown in Table VIII for all temperatures except 21° which was obviously in error. This was due to the loss of a small amount of isopentane when

TABLE VIII

EQUILIBRIUM VALUES FOR THE PENTANES

| | | Mole % | | |
|---|---|---|---|---|
| Temperature, °C. | | 102 | 161 | 204 |
| Liquid phase | Isopentane | 84.9 | 74.8 | |
| | *n*-Pentane | 15.1 | 25.2 | |
| Gas phase | Isopentane | 87.2 | 76.7 | 71.0 |
| | *n*-Pentane | 12.8 | 23.3 | 29.0 |

washing out the very soluble aluminum bromide used in this experiment before fractionation. These values are compared with the values of Pines, Kvetinskas, Kassel and Ipatieff[4] for the gas phase in Fig. 4. The temperature coefficients are widely different and the only agreement is in the neighborhood of 100°.

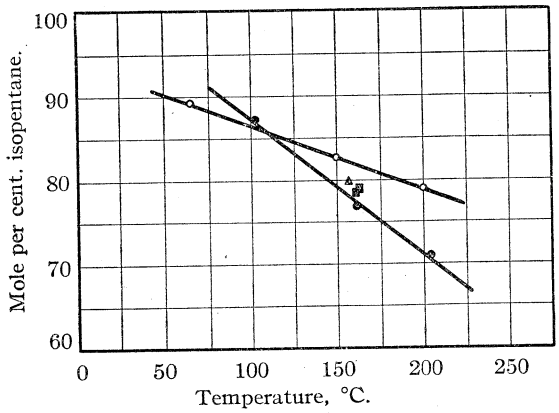



Fig. 4.— -●-, Experimental; -O-, Pines *et al.*; ■, check experiments; ▲, no hydrogen.

Since this discrepancy in the pentane equilibria at the higher temperatures might lead one to question the complete establishment of equilibria in the present work, three special experiments were made starting with compositions of pentanes corresponding to the values found by Pines and co-authors and that found in the present work. The results are shown in Table IX. The compositions of the pentane products were accurately determined by mass spectrometer analyses and further checked with infrared analysis. Neopentane was never found as a product of isomerization and is never produced except possibly in minute amounts. Due to the high pressure employed, Experiments 1 and 2, Table IX, were in the liquid phase. These values were converted to the gas phase using the Pines, Kvetinskas, Kassel and Ipatieff[4] ratio of $K_G°/K_L$ after slight extrapolation to 160° for more direct comparison. These experiments establish the equilibrium at 78.5% which is in substantial agreement with the value of 77.5% taken from the curve drawn for the values obtained from the present light naphtha work. This agreement establishes that chemical equilibrium had been obtained in the light naphtha reaction system. However, the heat of isomerization and entropy of isomerization calculated from the present experimental values for pentane are

completely in disagreement with those obtained by Rossini and co-authors[7] as shown in Table X; while the experimental values of Pines, Kvetinskas, Kassel and Ipatieff are in excellent agreement. The reason for this difference is unknown and further work will be necessary to resolve this discrepancy.

TABLE IX

EQUILIBRIUM OF PENTANES AT 160°

| Experiment | 1 | 2 | 3 |
|---|---|---|---|
| Charge | | | |
| Mole % isopentane | 77.3 | 82.5 | 80.6 |
| Mole % *n*-pentane | 22.7 | 17.5 | 19.4 |
| $H_2$ pressure at room temp. | 750 | 750 | 0 |
| Benzene inhibitor, % | 1.0 | 1.0 | 3.0 |
| Reaction time, minutes | 65 | 65 | 65 |
| Temperature, °C. | 161 | 163 | 157 |
| Reactor pressure, p. s. i. | 1455 | 1485 | 495 |
| V/L Ratio at reaction conditions | Liquid | Liquid | 0.1 |
| Products | | | |
| Mole % decomposition | 1.1 | 2.3 | 44.6 |
| Mole % based on pentanes | | | |
| Liquid phase: Isopentane | 76.9 | 77.4 | 78.4 |
| Liquid phase: *n*-Pentane | 23.1 | 22.6 | 21.5 |
| Vapor phase: Isopentane | 78.3 | 78.8 | 79.9 |
| Vapor phase: *n*-Pentane | 21.7 | 21.2 | 20.1 |

TABLE X

COMPARISON OF HEAT OF ISOMERIZATION AND ENTROPY OF ISOMERIZATION DATA FOR PENTANES

| | $\Delta H$ cal./mole | $\Delta S$ e. u. |
|---|---|---|
| Rossini and co-authors | −1930 | −1.32 |
| This paper | −3600 | −5.87 |
| Pines and co-authors | −1861 | −1.30 |

Experiment 3, Table IX, was made in the absence of hydrogen pressure to determine its effect on the pentane equilibrium. There was approximately a 1% increase in isopentane composition indicating no significant effect due to hydrogen pressure. Likewise side reactions to the extent of 44.6% had no important effect on the chemical equilibrium.

**Acknowledgment.**—The authors are indebted to the numerous members of the Standard Oil Company (Indiana) Research Laboratories who contributed their advice and services and especially to Dr. W. E. Kuentzel for design of the reactor and Mr. J. E. Swearingen for help in calculation of the fugacities.

## Summary

1. The experimental equilibria among the isomeric hexanes were determined in the range 21 to 204° using activated aluminum halide catalysts on a 67° end-point light naphtha stock containing both pentanes and hexanes.

2. The results for hexanes agree with the equilibrium values calculated from the heat of combustion and entropy for *n*-hexane and 2,3-dimethylbutane but there is considerable discrepancy for 2,2-dimethylbutane and the methylpentanes. However, there is substantial agreement in the ratio of 2-methylpentane to 3-methylpentane.

3. The experimental equilibria for the pentanes were also determined and show a higher temperature coefficient than that obtained by Pines, Kvetinskas, Kassel and Ipatieff.

4. Hydrogen and extensive side reactions were found not to have any appreciable effect on the equilibria.

WHITING, INDIANA RECEIVED[13] SEPTEMBER 27, 1948

(13) Original manuscript received July 8, 1946.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

# Studies in Stereochemistry. XIV. Reaction of Triethylamine and Quinuclidine with Alkyl Halides; Steric Effects in Displacement Reactions[1]

BY HERBERT C. BROWN[2] AND NELSON R. ELDRED[3]

In previous papers of this series, it has been demonstrated that the stability of addition compounds of the type $R_3N:BR'_3$ invariably decreases as the steric requirements of either R or R′ increase. Information gained regarding the effect of structure on the stability of addition compounds should aid in understanding the factors involved in typical displacement reactions.[4]

(1) This paper is based upon a dissertation submitted by Nelson R. Eldred in August, 1946, to the Graduate School of Wayne University in partial fulfillment of the requirements for the degree of Master of Science.

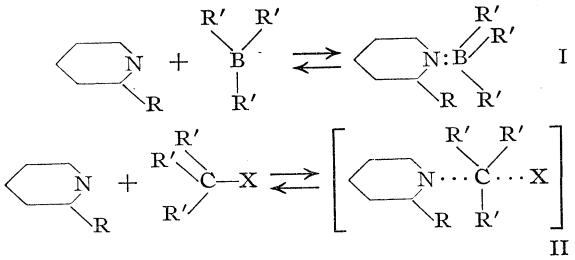
(2) Present address: Department of Chemistry, Purdue University.

(3) Present address: Department of Chemistry, Pennsylvania State College.

(4) Brown and Barbaras, THIS JOURNAL, 69, 1137 (1947).

Consider the reaction of amines with alkyl halides. It is well established that an increase in the steric requirements of the amine increases the steric strain in the addition compound (I) and results in a marked decrease in stability. Similarly, an increase in the steric requirements of the amine should result in a marked increase in steric strain in the activated complex (II) formed from the amine and alkyl halide. In the first instance, a decrease in the heat of dissociation is observed, corresponding in magnitude to the increase in steric strain; in the second, an increase in the energy of activation should be noted, corresponding to the increased strain in the activated complex.

Increase in the steric requirements of the groups



I



II

R′ attached to either boron in the addition compound or to carbon in the activated complex should also bring about increase in steric strain with similar results.[5]

Considerations of this kind lead to the following generalizations for the effects of changing steric requirements on the reactions of amines with alkyl halides. 1. Of two amines of equal base strengths but different steric requirements, the base with the lower steric requirements will react more rapidly with a given alkyl halide. Moreover, the reactions of the base with the greater steric requirements will involve higher activation energies, corresponding to the increase in steric strain. 2. The greater the steric requirements of the alkyl halide, the slower should be the reaction with a given amine. Thus the rate should decrease in the order MeX > EtX > *i*-PrX > *t*-BuX, and the energies of activation should increase in the opposite order. 3. The lower the steric requirements of the alkyl halide, the smaller should be the effect of differences in the steric requirements of the bases. Conversely, the greater the steric requirements of the alkyl halide, the larger should be the effect of differences in the steric requirements of the bases.

To test the validity of these generalizations, as well as the validity of the proposed similarity between the formation of addition compounds and the formation of activated complex, it was decided to measure and compare the rates of reactions of a series of alkyl halides with two amines of similar base strength but with markedly different steric requirements.

In the preceding paper of this series evidence was advanced to support the conclusion that the steric requirements of triethylamine (Fig. 1) are markedly greater than those of quinuclidine (Fig. 2).[6] Although the strengths of the two bases in aqueous solution are not markedly different, their addition compounds with trimethylboron show an amazing difference in stability. Quinuclidine forms an exceedingly stable addition compound, with heat of dissociation of 19.94 kcal., whereas the corresponding addition compound of triethylamine exists only at low temperatures and its heat of dissociation has been estimated to be as low as 10 kcal.[7]

Quinuclidine and triethylamine appeared to fill all the requirements for the two test amines. Accordingly, a study was made of the rate of reaction of quinuclidine with methyl, ethyl and isopropyl iodides and of triethylamine with ethyl iodide. The results, together with other rate data available in the literature, permit a thorough test of the proposed generalizations.

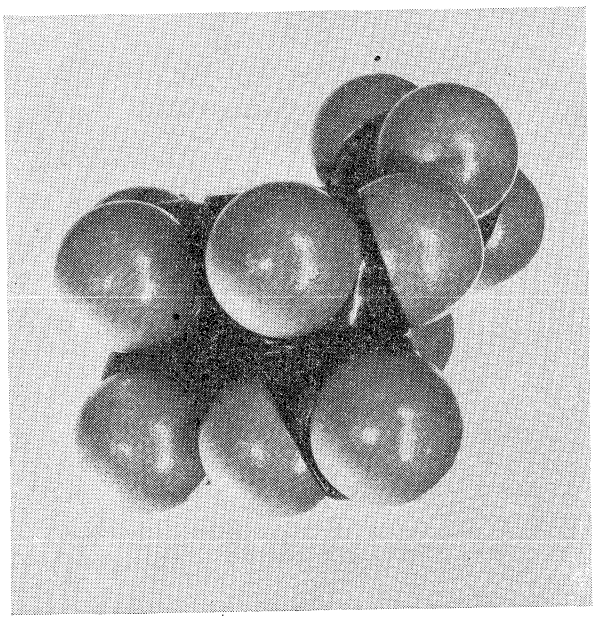


Fig. 1.—Molecular model of triethylamine (note hindered approach to nitrogen atom).

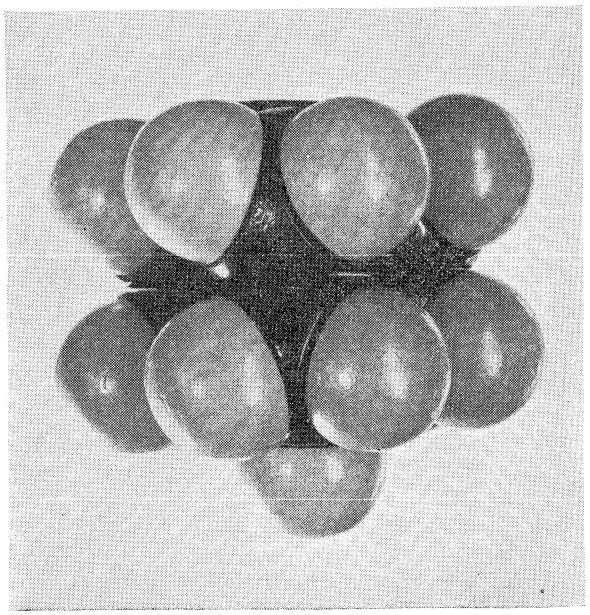


Fig. 2.—Molecular model of quinuclidine (note free approach to nitrogen atom).

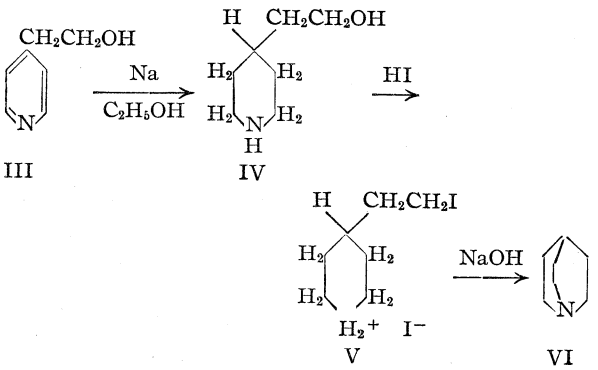
(5) In this discussion it has been assumed that the changes in the groups R and R′ would be of such a nature as not to alter significantly the inherent donor and acceptor properties of the base and acid, respectively.

(6) Brown and Sujishi, THIS JOURNAL, **70**, 2878 (1948).

(7) Brown and Taylor, *ibid.*, **69**, 1332 (1947).

## Results

Quinuclidine (VI) was conveniently synthesized by the following series of reactions,[8] starting with the commercially available 4-pyridineëthanol (III).




The rates of reaction with the alkyl iodides were determined in nitrobenzene solution. The reaction was followed by estimation of the free amine by titration.

The results, together with earlier data from the literature for triethylamine and pyridine are listed in Table I.

TABLE I

RATE DATA FOR THE REACTION OF TERTIARY AMINES WITH ALKYL IODIDES IN NITROBENZENE SOLUTION

| Amine | Alkyl iodide | $k_{25°}$ (liters mole$^{-1}$ sec.$^{-1}$) | $E_{exp.}$, kcal. | log $PZ$ |
|---|---|---|---|---|
| Triethylamine | Methyl[a] | $3.29 \times 10^{-2}$ | 9.7 | 5.65 |
| | Ethyl[b] | $1.92 \times 10^{-4}$ | 12.5 | 5.44 |
| | Isopropyl[a] | $1.13 \times 10^{-6}$ | 16.0 | 5.86 |
| Quinuclidine | Methyl[b] | 1.88 | 9.5 | (7.2)[c] |
| | Ethyl[b] | $4.87 \times 10^{-2}$ | 10.9 | 6.68 |
| | Isopropyl[b] | $7.97 \times 10^{-4}$ | 13.6 | 6.86 |
| Pyridine | Methyl[a] | $3.43 \times 10^{-4}$ | 13.6 | 6.50 |
| | Isopropyl[a] | $1.55 \times 10^{-6}$ | 16.7 | 6.43 |

[a] Laidler and Hinshelwood, *J. Chem. Soc.*, 852 (1938). [b] Present investigation. [c] Reaction was so very rapid that the possibility of considerable error exists, in spite of the satisfactory precision of the experimental data.

Examination of the data from the point of view of the proposed generalizations on the effects of steric requirements is quite interesting.[9] 1. Comparing quinuclidine and triethylamine, two bases of approximately equal base strength but with markedly different steric requirements, it is noted that quinuclidine, the amine of lower steric requirements, reacts considerably faster than triethylamine with each of the three alkyl iodides investigated. At 25°, $k_Q/k_T = 57$, 254 and 705 for methyl, ethyl, and isopropyl iodides, respectively.[10] Again, the reaction of quinuclidine with a given alkyl halide involves the lower energy of activation in each case. 2. The rates show a marked decrease from methyl to ethyl to isopropyl iodide and the energies of activation show a corresponding increase. This accords with the predicted behavior based on the effect of increasing steric requirements of the alkyl groups. 3. Finally, it is observed that the greater the steric requirements of the alkyl halide, the greater are the effects of differences in the steric requirements of the bases. Thus, in the case of methyl iodide, where the steric requirements of the methyl group are relatively small, the differences in the rate constant and activation energy with the two bases, quinuclidine and triethylamine, are relatively small: at 25°, $k_Q/k_T = 57$; $E_T - E_Q = 0.2$ kcal. However, as the steric requirements of the alkyl group become larger, these differences become greater. For ethyl iodide at 25° $k_Q/k_T = 254$ and $E_T - E_Q = 1.6$ kcal., and for isopropyl iodide $k_Q/k_T = 705$ and $E_T - E_Q = 2.4$ kcal.

The results clearly support the proposed generalizations on the effect of steric requirements on the rate of a typical displacement reaction of the type under consideration.

These generalizations were primarily based upon a postulated similarity between the formation of addition compounds and the formation of activated complexes in displacement reactions. Experimental verification for the proposed generalizations also lends credence to the proposed relationship, and indicates that the study of addition compounds may contribute considerably to a better understanding of the effect of structure on the rates of displacement reactions.

One further point of interest should be mentioned. Hammett[11] has pointed out that reactions involving meta and para derivatives of benzene involve constant entropies of activation and lend themselves particularly well to quantitative treatment. Apparently, the rigidity of the benzene ring and the location of the substituent far from the reaction center causes the substituent to have little effect upon the entropy of activation. On the other hand, structural changes in aliphatic compounds produce marked changes in the entropy of activation and the effect of substituents in such compounds cannot be simply treated.

It is, therefore, of interest that the data in Table I indicate that with the exception of methyl iodide (see note [c] in Table I), the entropies of activation

(8) Meisenheimer, Neresheimer and Schneider, *Ann.*, **420**, 190 (1920).

(9) It has long been recognized that in the absence of important steric effects, the stronger of two amine bases should react faster with a given alkyl halide. This generalization results from the Polanyi picture of the displacement reaction [Evans and Polanyi, *Trans. Faraday Soc.*, **34**, 11 (1938)]. Although this generalization is well established and accepted, it is of interest that the experimental results are in complete agreement. Thus, quinuclidine and pyridine are two bases of similar (low) steric requirements, but of markedly different base strength. In accordance with prediction, quinuclidine, the stronger of the two bases, reacts much more rapidly with either methyl iodide or isopropyl iodide. Moreover, the reactions with quinuclidine involve lower energies of activation.

(10) In the ensuing discussion the symbols, $k_Q$, $k_P$, and $k_T$ will be used to refer to the specific rate constants for quinuclidine, pyridine and triethylamine, respectively, and the symbols $E_Q$, $E_P$, $E_T$ to the energy of activation for the amine indicated.

(11) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, pp. 121–124

for the reactions of quinuclidine and alkyl iodides are in close agreement with the corresponding quantities for the pyridine reactions. This suggests that the cage system of quinuclidine gives the molecule sufficient rigidity that in its effect upon the entropy factor quinuclidine resembles more closely the rigid aromatic ring systems than it does the flexible, open-chain aliphatic compounds.

More detailed studies of the reactions of quinuclidine and pyridine (and their derivatives) with alkyl halides are underway. It is hoped that more extensive and more accurate data from these investigations will permit a detailed analysis of this interesting problem.

## Discussion

It has long been recognized that the rates of reactions involving nucleophilic displacements on carbon vary with the alkyl group in the order, methyl > ethyl > isopropyl > *t*-butyl.[12] Two different interpretations of the observed order have been advanced. Meer and Polanyi[13] attributed the observed order to steric hindrance effects. However, this interpretation was not widely adopted by workers in the field. Prevailing opinion has appeared to favor the idea that the decrease in rate in these reactions with increasing branching was primarily a polar effect. The increasing number of alkyl groups attached to the reaction center was considered to increase the electron density at that center (+I effect of alkyl groups) and thereby hinder the approach of the nucleophilic reagent.

Typical of the viewpoint is the discussion by Hinshelwood, Laidler and Timm.[14] These workers attribute the pronounced rise in activation energy observed in the reactions of amines with methyl and isopropyl iodides to "the diminished positive charge on the carbon atom which attracts the approaching base." The increase in activation energy in passing from methyl iodide to isopropyl iodide is considerably larger for the stronger base, triethylamine, than for the weaker base, pyridine ($E_{\text{T-}i\text{-PrI}} - E_{\text{T-MeI}} = 6.3$ kcal.; $E_{\text{P-}i\text{-PrI}} - E_{\text{P-MeI}} = 3.1$ kcal.). The authors consider these differences in the energies of activation to be especially significant and to offer strong support for the polar interpretation they favor.

The argument follows. It is considered that the nitrogen atom of the stronger base, triethylamine, will carry a considerably higher negative charge than the nitrogen atom of the weaker base, pyridine. With the increased number of methyl groups attached to the reaction center of the alkyl halide, the increased negative charge at that center (or decreased positive charge) will hinder the approach of the amine, but the hindrance should be particularly effective for the amine with the higher negative charge, namely, triethylamine. The reaction will, therefore, require a considerable increase in the energy of activation to overcome the large electrostatic repulsion forces.

This interpretation satisfactorily accounts for the observed differences in the behavior of triethylamine and pyridine in terms of their marked difference in base strength. However, it cannot be extended to cover the behavior of quinuclidine. The present study reveals that, in these displacement reactions, this base, one comparable in strength to triethylamine and much stronger than pyridine, is much more like pyridine in its behavior than like triethylamine. For example, the difference in the energies of activation for the reactions of quinuclidine with isopropyl and methyl iodides ($E_{\text{Q-}i\text{-PrI}} - E_{\text{Q-MeI}}$) is 4.1 kcal., whereas the corresponding quantities for reactions involving pyridine and triethylamine are 3.1 and 6.3 kcal., respectively.

The electrostatic hypothesis favored by Hinshelwood, Laidler and Timm does not appear capable of accounting for the behavior of quinuclidine. Moreover, the data offer no support for the widely-held view that the decreased susceptibility of isopropyl and *t*-butyl halides to attack by nucleophilic reagents is primarily a result of increased electron accession at the reaction center. Until definite evidence of the importance of such electron accession on the rate of nucleophilic displacements is available, it appears preferable to interpret the results of displacement reactions of alkyl halides primarily in terms of the nucleophilic characteristics of the displacing agent and the steric requirements of the reagents, as outlined in the generalizations presented in this paper.

It is hoped that an extensive investigation of the problem, now underway at Purdue University and supported by the Office of Naval Research, will aid in clarifying the situation.

## Experimental Part

**Materials.**—With the exception of quinuclidine, the chemicals were commercially available products, which were purified by standard procedures. The nitrobenzene was purified by partially freezing the material which melted in the range from 5.1 to 5.7°, with most of the material melting from 5.5 to 5.7°. A total of 4 l. was prepared and used to make up all solutions.

**Quinuclidine.**—Quinuclidine was originally prepared by Löffler and Stietzel[15] in impure form and later prepared in pure form by Meisenheimer and his co-workers.[8] These authors isolated 4-picoline from commercial picoline in poor yield. By treatment with formaldehyde the 4-picoline was converted to 4-pyridineëthanol in yield of but 1.5%. Although the yields in subsequent stages of the synthesis (III–VI) were satisfactory, this minute yield in the initial stages deterred other investigators from following the Löffler–Meisenheimer synthesis. Other syntheses were, therefore, developed and utilized.[16]

The commercial availability of 4-pyridineëthanol from the Reilly Tar and Chemical Corporation led to the selection of the Löffler–Meisenheimer synthesis as most convenient.

(12) Evans, "The Reactions of Alkyl Halides in Solution," The Manchester University Press, Manchester, 1946, pp. 1–2.

(13) Meer and Polanyi, *Z. physik. Chem.*, **B19**, 164 (1932).

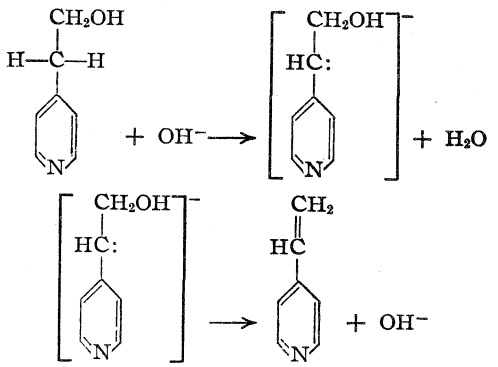
(14) Hinshelwood, Laidler and Timm, *J. Chem. Soc.*, 848 (1938).

(15) Löffler and Stietzel, *Ber.*, **42**, 124 (1909).

(16) Clemo and Metcalfe, *J. Chem. Soc.*, 1989 (1937); Prelog, *et al.*, *Ann.*, **525**, 292 (1936); **532**, 69 (1937); **535**, 37 (1938); **545**, 229 (1940).

The commercial product was purified by distillation through a Vigreux column. The fraction which distilled at 146–147° at 8 mm. was utilized. Various fractions gave values for the refractive index of $n^{25}D$ 1.5388 ± 0.0003. The product was very viscous and exceedingly hygroscopic—considerable difficulty was encountered in obtaining satisfactory melting or freezing points. However, a number of fractions, previously frozen, melted in the range from 13.1 to 13.3°.

Attempts to dry the compound by contacting the material with solid potassium hydroxide led to the conversion of the 4-pyridineëthanol to 4-vinylpyridine (b. p. 54° at 7 mm.; $n^{25}D$ 1.5490–1.5495). The 4-pyridineëthanol apparently undergoes a base-catalyzed elimination reaction with remarkable ease. It is probable that the attack is on the active hydrogen atoms, alpha to the pyridine ring.




Several attempts were made to hydrogenate the 4-pyridineëthanol in an Aminco hydrogenator over Raney nickel or U. O. P. nickel catalyst. However, no evidence of hydrogen absorption was observed at 2000 lb. pressure and temperatures as high as 200°. Instability of the compound prevented investigation of higher temperatures. The compound was successfully hydrogenated with sodium and alcohol. The piperidine derivative (IV) was isolated in 75% yield, b. p. 148–153° at 18 mm., $n^{25}D$ 1.4980.

The piperidine derivative was converted into 4-(β-iodoethyl)-piperidine hydroiodide (V) by treatment with concentrated hydriodic acid and red phosphorus. The product, after purification by recrystallization, was obtained in 50% yield. Further recrystallized from a mixture of 60 parts ethyl acetate to 20 parts ethanol it was obtained as nearly colorless crystals which melted at 198–199° as compared to the 190–191° value reported by Meisenheimer.

Previous workers[8] had cyclized the hydroiodide by addition of sodium hydroxide to a dilute solution of the salt in water. The free quinuclidine was distilled from the reaction with water and recovered as the picrate. The picrate was then transformed into the free base. This procedure for isolating the quinuclidine was found to be tedious and the yields unsatisfactory. It was, therefore, discarded in favor of isolation of the base as the hydrochloride. The procedure follows.

The aqueous distillate containing quinuclidine was collected in a flask containing 15 ml. of 15% hydrochloric acid (excess). The distillation was stopped as soon as the distillate was no longer basic to litmus, and the distillate evaporated to dryness. The yield of crude salt was 5.1 g., 75% of the theoretical from the 4-(β-iodoethyl)-piperidine hydroiodide. The hydrochloride was recrystallized from 50 ml. of *n*-butyl alcohol. It was obtained in the form of brilliant white crystals, which melted with decomposition and sublimation at 369–374° in a sealed tube. The salt was analyzed for chloride ion: Calcd. for $C_7H_{14}NCl$: Cl, 24.01. Found: Cl, 24.04.

The free base was prepared by running a concentrated aqueous solution of the hydrochloride into an evacuated flask containing a large excess of potassium hydroxide pellets. The free base was distilled under high vacuum at room temperature from the flask into a U-tube fitted with stopcocks at the entrance and exit. Traces of water which co-distilled could be removed by treatment with sodium or by fractional distillation through a series of such U-tubes, the water being removed as the more volatile component. The yields were practically quantitative. The quinuclidine was obtained as a transparent, glassy solid, which, when dry, crumbled easily.

Vapor pressure data for quinuclidine are reported in an earlier paper.[6]

**Kinetic Studies.**—Equimolar solutions of amine and alkyl iodides in nitrobenzene were prepared. Usually the concentration of the stock solutions was 0.200 *N*, so that on mixing equal volumes of the two stock solutions the concentration would be 0.100 *N*. For the faster reactions, where it was desirable to have less concentrated solutions, the stock solutions were diluted with the solvent before they were mixed. For temperatures other than 25°, the concentrations of the reactants were corrected for expansion or contraction of the solvent.

The reactants, brought to constant temperature, were placed in a Kjeldahl flask closed with a tightly fitting stopper. After suitable intervals, 5-ml. samples were withdrawn and run into standard *N*/50 hydrochloric acid and the excess acid was back-titrated with *N*/50 barium hydroxide, using methyl red as the indicator.

The rate constants were then calculated using the expression for a second-order reaction in which the two components are present in equal concentrations

$$k = \frac{1}{t} \times \frac{x}{a(a - x)}$$

where $t$ is the time in seconds, $x$ is the moles per liter of amine or alkyl iodide reacted at time $t$, and $a$ is the initial concentration of amine and alkyl iodide in moles per liter.

The energy of activation for each reaction and the $PZ$ term of the equation

$$k = PZe^{-E/RT}$$

were calculated from the rate constants determined at three to four temperatures, using the method of least squares.

In order to test the procedure, a study was made of the reaction of triethylamine and methyl iodide at 25°. The results are reported in Table II. The value of the rate constant, 0.0329 at 25°, is in satisfactory agreement with the value 0.03085 at 24.8° reported by Laidler and Hinshelwood.[17]

TABLE II

REACTION RATE DATA FOR TRIETHYLAMINE AND METHYI IODIDE IN NITROBENZENE AT 25°

| Time, sec. | $x$($a$ = 0.0198) | $k$(liters mole$^{-1}$ sec.$^{-1}$) |
|---|---|---|
| 1200 | 0.00876 | 0.0334 |
| 1800 | .01066 | .0327 |
| 2400 | .01208 | .0329 |
| 3600 | .01392 | .0332 |
| 4500 | .01476 | .0328 |
| 5400 | .01538 | .0325 |
| | Average $k$ = | 0.0329 |
| Duplicate determination, average $k$ = | | 0.0329 |

The small quantity of quinuclidine available for these studies made it necessary to limit the number of individual samples taken in the course of a determination to 3 or 4. The precision of the data for quinuclidine are, therefore, somewhat

(17) Laidler and Hinshelwood, *J. Chem. Soc.*, 852 (1938).

lower than those reported in Table II for triethylamine and methyl iodide and similar data obtained for triethylamine and ethyl iodide. Moreover, the reaction of quinuclidine with methyl iodide is so rapid (it is essentially complete in four minutes at room temperature with reagents present in as low concentrations as 0.0132 mole per liter), that in this reaction especially the results are subject to considerable uncertainty. It is estimated that the errors in the energies of activation may be as large as 500 cal.

The rate constants obtained are listed in Table III.

TABLE III

RATE CONSTANTS FOR THE REACTION OF TRIETHYLAMINE AND QUINUCLIDINE WITH ALKYL IODIDES

| Amine | Alkyl iodide | $T$, °C. | $k$ (liters mole$^{-1}$ sec.$^{-1}$) |
|---|---|---|---|
| Triethylamine | Methyl | 25.0 | $3.29 \times 10^{-2}$ |
| Triethylamine | Ethyl | 25.0 | $1.92 \times 10^{-4}$ |
| | | 35.0 | $3.81 \times 10^{-4}$ |
| | | 45.0 | $7.24 \times 10^{-4}$ |
| Quinuclidine | Methyl | 5.5 | 0.610 |
| | | 15.0 | 1.06 |
| | | 25.0 | 1.88 |
| Quinuclidine | Ethyl | 5.5 | $1.27 \times 10^{-2}$ |
| | | 15.0 | $2.55 \times 10^{-2}$ |
| | | 25.0 | $4.87 \times 10^{-2}$ |
| | | 35.0 | $8.34 \times 10^{-2}$ |
| Quinuclidine | Isopropyl | 25.0 | $7.97 \times 10^{-4}$ |
| | | 35.0 | $17.2 \times 10^{-4}$ |
| | | 45.0 | $31.6 \times 10^{-4}$ |

Values for the energies of activation and log $PZ$ calculated from these values for the specific rate constants are listed in Table I.

**Acknowledgment.**—The authors wish to acknowledge their debt to Mr. Arno Cahn of the Department of Chemistry of Purdue University for his valuable assistance in checking the calculations of the rate constants and in applying the least squares procedure to the estimation of the energies of activation.

## Summary

1. Quinuclidine has been prepared in good yield starting with the commercially available 4-pyridineëthanol. Quinuclidine hydrochloride has been prepared and characterized.

2. Kinetic studies have been made of the reaction of triethylamine with ethyl iodide and of quinuclidine with methyl, ethyl and isopropyl iodide in nitrobenzene solution at several temperatures.

3. A number of generalizations are proposed for the effects of changing steric requirements on displacement reactions. These generalizations, based largely on analogy with the effect of steric requirements on the stability of addition compounds, permit a simple interpretation of the experimental data. The results do not support previous interpretations based primarily on postulated polar effects of structural changes in alkyl groups.

LAFAYETTE, IND. RECEIVED JULY 8, 1948

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[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL]

# Monolayers of Pepsin and of Insulin

BY HECTOR A. DIEU[1] AND HENRY B. BULL

Monolayers of egg albumin and of β-lactoglobulin have been investigated at surface pressures below one dyne per centimeter.[2] The equation represents the relation between the area $A$ and the film pressure $F$ for monolayers of these proteins in the low pressure region. When $FA$ is plotted against $F$, the slope of the line ($\alpha$) yields the gaseous area of the film and at 25° the intercept $\beta$ is equal to $24.6 \times 10^2$/mol. wt. where mol. wt. is the number average molecular weight of the film molecules.

$$FA = \alpha F + \beta \qquad (1)$$

It has been found that spread films of pepsin and of insulin obey eqn. 1, and it has thus been possible to calculate the film molecular weights as well as the gaseous area of these proteins.

## Experimental

The pepsin was prepared according to Northrop,[3] and its activity was found to be 0.19 Hb. U. per mg. of nitrogen. The pepsin solutions were dialyzed against 0.2 $M$ acetate buffer at $p$H 5.2 before use. The pepsin concentration was determined by micro-Kjeldahl using the factor indicated by Northrop.[3]

We are grateful to Armour and Company for a supply of crystallin insulin. Before use the insulin was dialyzed against a buffer at $p$H 3.5 for seventy-two hours at 0°. The concentration of insulin was determined by micro-Kjeldahl.

A Wilhelmy balance has been used to register the film pressures. The wettability of the slides has been improved by the addition of glycerol to the 5% ammonium sulfate solution to the extent of 2% by volume. It is necessary to exercise care in the preparation of the substrate solutions, and the glycerol was exhaustively extracted with petroleum ether and the ether removed completely before addition to the ammonium sulfate solution. The ammonium sulfate solutions were treated with activated charcoal and the charcoal removed by filtering before the addition of the glycerol. The protein solutions were added to the surface with a Blodgett pipet which delivered 0.085 cc. of solution.

## Results

The molecular weights and the gaseous areas of spread films of pepsin and of insulin have been calculated with the aid of eqn. 1. Tables I and II

(1) Research Fellow of the Belgian American Foundation.
(2) Bull, THIS JOURNAL, **67**, 4 (1945); **68**, 745 (1946).
(3) Northrop, *J. Gen. Physiol.*, **30**, 177 (1946).

show the gaseous areas and molecular weights of pepsin as a function of the elapsed time between spreading and compression. The results in Table I were obtained using a spreading concentration of 0.38 mg. of pepsin per square meter, while Table II shows results obtained using 0.74 milligram per square meter as the spreading concentration of pepsin.

TABLE I

FILM MOLECULAR WEIGHTS AND GASEOUS AREAS OF PEPSIN WHOSE SPREADING CONCENTRATION WAS 0.38 MG./SQ. M.

| Time, minutes | Gaseous area, sq. m./mg. | Molecular weights |
|---|---|---|
| 0.5 | 0.60 | 32,000 |
| 1 | .74 | 32,500 |
| 2 | .86 | 35,000 |
| 5 | .92 | 35,400 |
| 10 | 1.08 | 36,200 |
| 60 | 1.24 | 33,000 |
| 360 | 1.35 | 37,000 |

TABLE II

FILM MOLECULAR WEIGHTS AND GASEOUS AREAS OF PEPSIN WHOSE SPREADING CONCENTRATION WAS 0.74 MG./SQ. M. ON 5% AMMONIUM SULFATE

| Time, minutes | Gaseous area, sq. m./mg. | Molecular weights |
|---|---|---|
| 0.5 | 0.4–0.50 | 35,200 |
| 2 | .61 | 34,600 |
| 6 | .73 | 34,000 |

Table III shows the influence of elapsed time between spreading and compression on the properties of pepsin films spread on hydrochloric acid at *p*H 1.2 instead of on ammonium sulfate.

TABLE III

FILM MOLECULAR WEIGHTS AND GASEOUS AREAS OF PEPSIN WHOSE SPREADING CONCENTRATION WAS 0.38 MG./SQ. M. ON HYDROCHLORIC ACID AT *p*H 1.2

| Time, minutes | Gaseous areas, sq. m./mg. | Molecular weights |
|---|---|---|
| 1 | 1.25 | 33,400 |
| 15 | 1.40 | 34,500 |
| 16 | 1.48 | 37,000 |
| 100 | 1.48 | 37,000 |

Table IV shows the influence of cupric ions on the pepsin films.

TABLE IV

FILM MOLECULAR WEIGHT AND GASEOUS AREA OF PEPSIN WHOSE SPREADING CONCENTRATION WAS 0.38 MG./SQ. M. ON 5% AMMONIUM SULFATE CONTAINING 0.08 MOLAR COPPER SULFATE

| Time, minutes | Gaseous area sq. m./mg. | Molecular weights |
|---|---|---|
| 1 | 1.40 | 34,000 |
| 20 | 1.44 | 32,500 |
| 45 | 1.49 | 35,000 |

Table V shows the influence of time on an insulin film whose spreading concentration was 0.417 mg./sq. m. on 5% ammonium sulfate.

TABLE V

FILM MOLECULAR WEIGHTS AND GASEOUS AREAS OF INSULIN WHOSE SPREADING CONCENTRATION WAS 0.417 MG./SQ. M. ON 5% AMMONIUM SULFATE

| Time, minutes | Gaseous areas, sq. m./mg. | Molecular weights |
|---|---|---|
| 0.5 | 0.70 | 19,700 |
| 2 | 1.07 | 18,000 |
| 30 | 1.13 | 19,000 |
| 270 | 1.26 | 20,100 |
| 1200 | 1.74 | 18,700 |

Table VI shows the influence of cupric ions on the film molecular weight and on the gaseous area of insulin films whose spreading concentration was 0.417 mg./sq. m. The films were compressed two minutes after spreading.

TABLE VI

FILM MOLECULAR WEIGHTS AND GASEOUS AREAS OF INSULIN FILMS SPREAD ON 5% AMMONIUM SULFATE CONTAINING VARYING AMOUNTS OF COPPER SULFATE

| $CuSO_4$, moles/liter | Gaseous areas, sq. m./mg. | Molecular weights |
|---|---|---|
| 0 | 1.07 | 18,000 |
| $2 \times 10^{-4}$ | 0.98 | 35,100 |
| $4 \times 10^{-4}$ | .97 | 38,200 |
| $100 \times 10^{-4}$ | .89 | 37,900 |

Table VII shows the influence of time on the properties of an insulin film spread on a 5% ammonium sulfate solution containing $1 \times 10^{-2}$ molar copper sulfate.

TABLE VII

MOLECULAR WEIGHTS AND GASEOUS AREAS OF INSULIN WHOSE SPREADING CONCENTRATION WAS 0.417 MG./SQ. M. ON A 5% AMMONIUM SULFATE CONTAINING $1 \times 10^{-2}$ MOLAR COPPER SULFATE

| Time, minutes | Gaseous area, sq. m./mg. | Molecular weights |
|---|---|---|
| 2 | 0.89 | 37,900 |
| 30 | 1.05 | 35,800 |
| 120 | 1.13 | 37,200 |

## Discussion

Apparently, the film molecular weight of pepsin is influenced neither by the spreading process nor by the composition of the substrate solution. The average value of the film molecular weight of pepsin is 34,400 which compares favorably with that reported for the molecular weight of pepsin in solution.[4] We did find a film molecular weight of about 18,000 for a pepsin solution which had been incompletely dialyzed and no doubt contained split products of pepsin. Curiously, the addition of copper sulfate to the substrate solution in this case restored the molecular weight to 35,000.

The gaseous area of pepsin films is greatly dependent both on the spreading concentration and on the elapsed time between spreading and compression. It appears from Table I and particularly from Table II that at short time intervals and

(4) Northrop, Kunitz and Herriott, "Crystalline Enzymes," Columbia University Press, New York, N. Y., 1948.

at higher spreading concentrations that the gaseous area is considerably smaller than 0.80 sq. meters per milligram which is the area occupied by a fully compressed monolayer of peptide chains.[5] The fact that the correct value for the molecular weight of pepsin was obtained indicates that all the pepsin applied to the surface remained on the surface. The expansion of the film with time arises, therefore, from the expansion of individual pepsin molecules and not from the appearance of additional pepsin molecules on the surface. The initial step in the spreading of pepsin appears to be the formation of a duplex film. A monomolecular film is quickly formed from the duplex film and this transformation is followed by a slow expansion of the individual gaseous molecules. Twenty hours after spreading, the gaseous area of pepsin is about 1.60 sq. meters per milligram. It can be estimated that the area of a β-keratin chain lying flat on the surface would be about 1.70 sq. meters per milligram.[5] Evidently, after a time the pepsin approaches the condition of a β-keratin film on the surface. This slow expansion of the gaseous area may be regarded as a type of surface denaturation.

Insulin molecules tend to dissociate on the surface as shown in Table V. It will be recalled that insulin in solution likewise tends to dissociate.[6] The gaseous area of the insulin film expands with time and after twenty-four hours reaches the area of a β-keratin chain lying flat on the surface. The results given in Table VI demonstrate that a small amount of copper sulfate in the substrate solution prevents the dissociation of the insulin molecules. This parallels the behavior of films of β-lactoglobulin.[2]

We have investigated the coefficient of compressibility of pepsin and of insulin films at higher film pressures spread on 5% ammonium sulfate solutions. The minimum coefficient of compressibility of a pepsin film compressed fifteen minutes after spreading was 0.0275 centimeter per dyne which corresponded to a film pressure of 5 dynes per centimeter and to an area of 0.82 sq. meter per milligram. A pepsin film compressed six hours after spreading yielded a minimum compressibility coefficient of 0.025 centimeter per dyne corresponding to a film pressure of 10 dynes per centimeter and to an area of 1.08 sq. meters per milligram. Evidently, the area of a film at higher pressures depends significantly on the time between spreading and compression. The results shown in Tables I and II indicate that the amount of protein on the surface is independent of time and, accordingly, the variation of area with time is simply a reflection of the expansion of the individual protein molecules. This consideration means that some of the variable protein film areas reported in the literature may not be due to loss of protein in the substrate solution but unequal expansion of the surface protein molecules.

The insulin film was compressed within two minutes of spreading and the coefficient of minimum compressibility was 0.025 centimeter per dyne which corresponded to an area of 0.90 sq. meter per milligram and to a surface pressure of 7.6 dynes per centimeter. In accord with the discussion elsewhere,[5] it is believed that the point of minimum compressibility represents the smallest area to which a film can be compressed without partial collapse of the film occurring.

(5) Bull, "Advances in Protein Chemistry," Vol. III, 1947.
(6) Gutfreund, *Biochem. J.*, **42**, 156 (1948).

## Summary

1. The film molecular weights and the gaseous areas of films of pepsin and of insulin have been determined as a function of several variables.

2. The film molecular weight of pepsin is about 34,400 and pepsin molecules do not dissociate on the surface.

3. The gaseous area of the pepsin film increases with time and is smaller the greater the spreading concentration. It appears that the initial step in the spreading of pepsin is the formation of a duplex film which quickly changes into a monolayer. Following the transformation, the gaseous pepsin molecules slowly expand to an area which would be occupied by a β-keratin chain lying flat on the surface.

4. Insulin molecules dissociate on the surface but a small amount of copper ions in the substrate solution prevents this dissociation.

5. The pepsin and insulin films have also been examined in the high pressure region and the coefficients of compressibility of these films calculated and reported.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 11, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE RICE INSTITUTE]

# Sulfonation of 2-Pentene by Chlorosulfonic Acid[1]

BY SIMON MIRON[2] AND GEORGE HOLMES RICHTER

The reaction of chlorosulfonic acid with 2-pentene in chloroform solution at 0–5° gave a mixture of isomeric pentenesulfonic acids. It was shown, by reducing the double bond of the isomers and comparing the reduced mixture with pentane-2-sulfonic acid and pentane-3-sulfonic acid, that sulfonation had occurred on the carbon atoms comprising the original position of the double bond, approximately 80% having taken place on carbon atom 2 and 20% on carbon atom 3. The exact position of the double bond in the resulting products was not demonstrated; it would be in the 2 position if no isomerization occurred during the reaction or isolation of the products.

## Experimental

**Raw Materials.**—The 2-pentene was prepared by dehydration of 2-pentanol[3] and was purified by distillation through a laboratory bubble column consisting of eight bubbler units.[4] The fraction collected for use had a boiling range 35.8–36.3° at 763 mm. It probably consisted of approximately 75% *trans*-2-pentene and 25% *cis*-2-pentene[5] and may also have contained a small amount of 1-pentene.[6]

The chlorosulfonic acid (Eastman Kodak Co. "practical" grade) was dark brown in color, and was used without further purification.[7]

**Sulfonation of 2-Pentene.**—The sulfonation was carried out in a 500-ml. flask surrounded by cracked ice and equipped with agitator (mercury sealed), dropping funnel, thermometer and ice-water condenser. A solution of 35.0 g. (0.50 mole) of 2-pentene in 50 ml. of dry chloroform was introduced in the flask and treated over three hours time, under good agitation, with a solution of 53.6 g. (0.46 mole) of chlorosulfonic acid in 70 ml. of dry chloroform, after which the chloroform solution was extracted with water until neutral. Sulfuric acid was removed from the extract by treatment with barium carbonate and filtration, and most of the chloride ion was removed from the evaporated filtrate by mixing the salt with 85% phosphoric acid[8] and keeping the paste at low pressure over solid potassium hydroxide for several days, with occasional warming. Neutralization of the mixture with barium carbonate resulted in a crude barium salt whose chloride ion content was appreciably diminished; yield, 37 g. (0.085 mole) of crude barium salt (37%).

*Anal.*[9] Calcd. for $C_{10}H_{18}O_6S_2Ba$: Ba, 31.54. Found: Ba, 31.66.

**Properties of the Barium Pentenesulfonate Mixture.**—A solution of the barium salt reduced both potassium permanganate solution and bromine water. The salt was slightly soluble in absolute ethanol and quite soluble in warm *i*-amyl alcohol and in 1,4-dioxane, but warm solutions in the latter two solvents tended to gel upon cooling.

**Sodium Pentenesulfonates.**—A portion of the barium pentenesulfonate mixture was converted to the corresponding sodium salt by treatment of an aqueous solution with sodium sulfate solution until no more barium sulfate precipitated. The suspension was filtered and the filtrate evaporated to dryness. The sodium salt was soluble in hot ethanol and could be freed of most of the contaminating sodium chloride by recrystallization from this medium.

*Anal.* Calcd. for $C_5H_9O_3SNa$: Na, 13.37. Found: Na, 13.02.

**Free Pentenesulfonic Acid Mixture.**—The purified barium salt was dissolved in water and treated with excess sulfuric acid followed by excess basic lead carbonate. The supension was filtered and the hot filtrate saturated with hydrogen sulfide. After removal of the excess hydrogen sulfide and treatment with "Norite" carbon, the resulting solution was evaporated to complete dryness over phosphoric anhydride at reduced pressure. The acid was highly viscous, having almost a glassy consistency at room temperature; $d^{20}_4$ 1.277,[10] $n^{20}D$ 1.4735, $MR_D$ (molecular refraction) 33.03. It was soluble in absolute ethanol, chloroform, *i*-amyl alcohol and acetic acid and insoluble in carbon tetrachloride and carbon disulfide. In water it dissolved with considerable evolution of heat. It decolorized bromine water and a carbon tetrachloride solution of bromine, forming an insoluble liquid product without evolution of hydrogen bromide.

**Reduction of the Double Bond.**—The unsaturated barium sulfonate (8.4 g.) was dissolved in 100 ml. of water and reduced in the conventional manner over 0.25 g. of finely powdered platinum oxide catalyst at 30 p.s.i. gage pressure of hydrogen, reduction being complete in one-half hour. The resulting solution, filtered free of platinum, was completely inert to potassium permanganate, and was evaporated to crystallization. Unlike the unsaturated barium salt, the saturated compound crystallized readily from hot water. The dry salt was white; it burned upon ignition and gave a slight test for chlorides. This saturated barium salt was reserved for proof of structure as described below.

**Pentane-2-thiol.**—This was prepared from 2-bromopentane[11] by the method of Noller and Gordon.[12] The crude product was oxidized directly to the sulfonic acid.[13]

**Barium Pentane-2-sulfonate.**—The mixture of pentane-2-thiol and water obtained by reduction of the disulfide

(1) Presented at the Southwest Regional Meeting of the American Chemical Society in Houston, Texas, Dec. 12–13, 1947.

(2) Present address: Pan American Refining Corporation, Texas City, Texas.

(3) James F. Norris, "Organic Syntheses," Coll. Vol. I, ed. Henry Gilman, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 430.

(4) H. T. Clarke and E. J. Rahrs, *Ind. Eng. Chem.*, **18**, 1092 (1926).

(5) H. J. Lucas, M. J. Schlatter and R. C. Jones, THIS JOURNAL, **63**, 23 (1941).

(6) H. J. Lucas and A. N. Prater, *ibid.*, **59**, 1683 (1937).

(7) A run made with freshly distilled, colorless chlorosulfonic acid gave no substantial improvement in yield.

(8) Phosphoric acid appeared to have less tendency to cause charring of the product than did concentrated sulfuric acid.

(9) The analysis was carried out on a sample of the barium salt which had been treated exhaustively to remove chloride ion.

(10) By capillary pycnometer; measurements made only to the third decimal place because of the viscous and hygroscopic nature of the liquid.

(11) Produced by reaction of 2-pentanol and phosphorus bromide at room temperature. Since the tendency of secondary alkyl bromides to isomerize is quite common, the structure of the bromide was confirmed by converting a small portion to the Grignard reagent and reacting with phenyl isocyanate, according to the method of Schwartz and Johnson (A. M. Schwartz and John R. Johnson, THIS JOURNAL, **53**, 1063–1068 (1931)), resulting in N-phenyl-2-methylvaleramide, m. p. 84.5–88.5°.

(12) C. R. Noller and J. J. Gordon, *ibid.*, **55**, 1090–1094 (1933).

(13) A small portion of the crude mercaptan was purified by distillation in order to record its properties, the main fraction boiling in the range 112.9–114.0° at 772 mm.; $d^{20}_4$ 0.828; $n^{20}D$ 1.4395. The lead mercaptide, prepared from an ethanolic solution of the thiol and aqueous lead acetate, came down as a canary-yellow oil which failed to crystallize.

*Anal.* Calcd. for $C_{10}H_{22}S_2Pb$: Pb, 50.12. Found: Pb, 49.86.

was added slowly to excess 10 *M* nitric acid on the steam-bath, and the mixture was heated until a test sample showed the absence of nitric acid by failing to color a droplet of diphenylamine–sulfuric acid reagent. After dilution with water and treatment with excess barium carbonate, the mixture was filtered and the filtrate purified by extraction with ether and treatment with activated carbon. On evaporation of the ensuing filtrate the barium salt separated in characteristic, lustrous white crystals.

*Anal.* When dried at 110–120° for 80 min. the salt apparently retained a molecule of water. Calcd. for $C_{10}H_{22}O_6S_2Ba\cdot H_2O$: Ba, 30.01. Found: Ba, 30.07.

**Pentane-2-sulfonic Acid.**—This acid has been only incompletely described in the literature.[14,15] A solution of barium pentane-2-sulfonate was converted to the lead salt and treated with hydrogen sulfide as described previously. The aqueous solution was concentrated *in vacuo* over phosphoric anhydride. White crystals separated when the water was almost entirely removed, but further drying resulted in complete liquefaction, suggesting that the acid may form a crystalline hydrate. The resulting acid had the following properties: $d^{20}_4$ 1.173, $n^{20}D$ 1.4502, $MR_D$ 34.89.

**Phenylhydrazine Pentane-2-sulfonate.**—The phenylhydrazine salt was selected as a characterizing derivative and was prepared according to Latimer and Bost,[16] using 0.55 g. (0.0013 mole) of recrystallized barium pentane-2-sulfonate and 0.24 ml. (0.0026 mole) of phenylhydrazine. The phenylhydrazine salt separated from the ethanol–ether solution as small white flakes, which were washed with ether and dried in a desiccator, m.p. 121.6–123.6°.

*Anal.* Calcd. for $C_{11}H_{20}O_3N_2S$: C, 50.74; H, 7.74. Found: C, 50.75; H, 7.55.

**Barium Pentane-3-sulfonate.**—This was prepared by oxidation of the disulfide of 3-bromopentane.[17] A solution of 46.5 g. (0.194 mole) of sodium sulfide nonahydrate and 8.8 g. (0.271 mole) of powdered sulfur in aqueous methanol was heated to boiling and 41.0 g. (0.271 mole) of 3-bromopentane was added. After seventy minutes of refluxing the mixture was poured into water and the disulfide layer separated and washed with water; yield of wet disulfide, 26 g.

Six grams of the disulfide was oxidized by 40 ml. of hot 10 *M* nitric acid, in the manner described for pentane-2-thiol. The barium salt crystallized in lustrous white platelets; yield, 8.6 g. (62.4% theoretical yield).

*Anal.* Calcd. for $C_{10}H_{22}O_6S_2Ba\cdot H_2O$: Ba, 30.01. Found: Ba, 30.29.

**Pentane-3-sulfonic Acid.**—No reference to this acid is found in the literature through 1947.

The free acid was obtained from the barium salt by the procedure described for pentane-2-sulfonic acid, and as in that instance, white crystals were observed when the acid was almost dry but disappeared on further removal of water; $d^{20}_4$ 1.186, $n^{20}D$ 1.4525, $MR_D$ 34.66. The similarity in molecular refractions for pentane-2 and -3 sulfonic acids is as expected for isomers.

**Phenylhydrazine Pentane-3-sulfonate.**—This product was prepared as described for the isomeric salt. The crystals were deposited as feathery white needles. The m.p. was 97.4–99.2° after ordinary drying, but after fusion to removal all traces of water was 104.7–106.8°.

*Anal.* Calcd. for $C_{11}H_{20}O_3N_2S$: C, 50.74; H, 7.74. Found: C, 50.91; H, 7.48.

**Phenylhydrazine Salt of the Reduced Pentenesulfonic Acid Mixture.**—A portion of the semi-pure barium pentanesulfonate mixture from the catalytic reduction of the unsaturated salt was carefully freed of contaminating chloride ion and converted to the phenylhydrazine salt, m.p. 111–117.4°.

In order to determine the relative ratio of the two isomers in the above salt, mixtures of the two pure derivatives in stepwise concentrations varying by 10% were prepared, fused, resolidified and powdered finely. The capillary melting points (cor.) were taken, the bath temperature being allowed to rise very slowly, and the point of complete disappearance of the crystals observed with a lens and recorded as the melting point. A melting point diagram was then prepared, shown in Fig. 1.

According to Fig. 1, the reduced mixture appeared to consist of approximately 80% of the "2" isomer. As a further check, mixed melting points were taken using equal parts of the reduced mixture and the known 80% "2"–20% "3" mixture, as well as with samples of the known 90–10 and 70–30 mixtures. Results are shown in Table I.

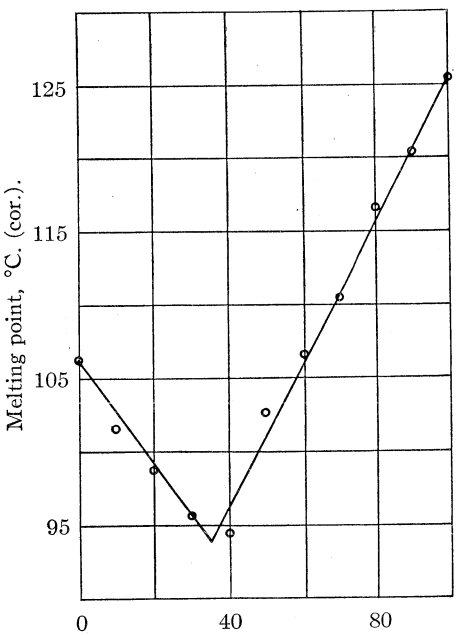



Fig. 1.—Melting points of phenylhydrazine pentane-2-sulfonate and phenylhydrazine pentane-3-sulfonate mixtures.

TABLE I

| Mixture | M. p., °C. (cor.) |
|---|---|
| 90% "2"–10% "3" | 120.3 |
| 80% "2"–20% "3" | 116.6 |
| 70% "2"–30% "3" | 110.4 |
| Reduced derivative (average) | 117.4 |
| Equal parts reduced + (90-10 mixture) | 121.5 |
| Equal parts reduced + (80-20 mixture) | 117.2 |
| Equal parts reduced + (70-30 mixture) | 114.8 |

The fact that the melting point of the reduced mixture was unchanged upon incorporation with the 80–20 mixture, and that incorporation with the 70–30 mixture served to *raise* the melting point of the latter would indicate the relative non-interference of incidental impurities. It was, therefore, concluded that the reduced derivative consisted of approximately 80% of phenylhydrazine-pentane-2-sulfonate and 20% of phenylhydrazine-pentane-3-sulfonate, and that, consequently, the sulfonation of 2-

(14) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 587–605 (1927).

(15) F. C. Wagner and E. E. Reid, THIS JOURNAL, **53**, 3407–3413 (1931).

(16) P. H. Latimer and R. W. Bost, *ibid.*, **59**, 2500–2501 (1937).

(17) Prepared from 3-pentanol and phosphorus tribromide at room temperature. Reaction of the corresponding Grignard reagent with phenyl isocyanate gave N-phenyl-2-ethylbutyramide, m. p. 121–124.5°, thus confirming the structure of the bromide.

pentene by chlorosulfonic acid had taken place largely on carbon atom 2, with about 20% on carbon atom 3.[18]

## Summary

1. Sulfonation of 2-pentene by chlorosulfonic acid in chloroform solution at 0–5° gave a mixture of isomeric pentenesulfonic acids.

2. By comparison of the catalytically-reduced mixture with pentane-2 and -3-sulfonic acids, the sulfonation was shown to have occurred to the extent of approximately 80% on carbon atom number 2 and 20% on carbon atom number 3.

HOUSTON, TEXAS RECEIVED APRIL 12, 1948

(18) Inasmuch as Lucas, Schlatter and Jones[5] claim that 2-pentene derived from 2-pentanol consists of approximately 75% *trans*- and 25% *cis*-isomer, it is possible that the *trans*-isomer may have sulfonated in the 2-position and the *cis*- isomer in the 3-position. However, proof of this possibility would rest upon sulfonation experiments with the pure isomers.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

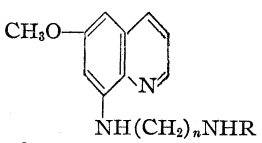
# Synthetic Antimalarials. Some Derivatives of 8-Aminoquinoline. II[1]

BY NATHAN L. DRAKE, ROBERT A. HAYES, JOHN A. GARMAN, ROBERT B. JOHNSON, GORDON W. KELLEY, SIDNEY MELAMED AND RICHARD M. PECK

Continuing the research that led to the synthesis of pentaquine (SN 13,276),[2,3] a number of new 8-aminoquinolines have been synthesized. In eleven of these, only the terminal amino group of SN 13,276 has been varied; in seven more, the length of the side chain has been changed. One compound containing an additional nuclear substituent has also been made.

Two general methods were used for the synthesis of all but one of the drugs. Method I consisted of heating 8-amino-6-methoxyquinoline in the presence of water with the appropriate side chain chloride hydrochloride in much the same manner as was reported for the synthesis of SN 13,276.[3] Method II consisted of the reductive alkylation of the appropriate 6-methoxy-8-aminoalkylaminoquinoline with the requisite aldehyde or ketone in ethanol solution in the presence of Adams catalyst at room temperature.[4] The condensation of isopropyla-

TABLE I




| UM No. | R | n | Method of synthesis | Salt[a] prepared | Overall yield[b] of salt, % | M. p.[c] of salt, °C. | Analyses,[d] % Calculated Carbon | Calculated Hydrogen | Found Carbon | Found Hydrogen | Homogeneity %[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 137 Q | $CH(CH_3)CH_2CH_2CH_3$ | 5 | I | A | 15 | 167.1–168.2 | 65.75 | 8.67 | 65.48, 65.41 | 8.66, 8.84 | |
| 135 Q | $CH(C_2H_5)_2$ | 5 | I | B | 41 | 103–105 | 45.71 | 7.10 | 45.80, 45.75 | 7.33, 7.18 | |
| 136 Q | $CH(CH_3)C_2H_5$ | 5 | I | C | 54 | 164.3–165.1 | 57.57 | 7.57 | 57.67, 57.50 | 7.62, 7.56 | |
| 139 Q | $CH(CH_2)_4CH_3$ | 5 | I | A | 12 | 168–169 | 66.8 | 8.48 | 66.64 | 8.44 | |
| 170 Q | $CH_2C(CH_3)_3$ | 5 | I | A | 22 | 188.9–189.5 | 65.75 | 8.76 | 66.00, 65.85 | 8.75, 8.65 | 98 ± 2 |
| 177 Q | $CH_2CH(CH_3)_2$ | 5 | II | C | 20 | 175.7–176.9 | 57.57 | 7.57 | 57.79, 57.70 | 7.61, 7.81 | 98 ± 2 |
| 178 Q | $CH_2CH(CH_3)C_2H_5$ | 5 | II | C | 26 | 149.5–150.5 | 65.75 | 8.73 | 65.52, 65.81 | 9.02, 9.04 | 98 ± 2 |
| 179 Q | $(CH_2)_2CH_3$ | 5 | I | C | 14 | 135.6–136.8 | 57.57 | 7.57 | 57.90, 57.62 | 7.17, 7.28 | 94 ± 3 |
| 180 Q | $(CH_2)_4CH_3$ | 5 | I | C | 27 | 123.5–124.9 | 58.54 | 7.80 | 58.73, 58.89 | 7.90, 7.94 | 94 ± 3 |
| 181 Q | $CH_2CH_2CH(CH_3)_2$ | 5 | I | C | 5 | 143.3–144.6 | 58.54 | 7.80 | 58.74, 58.88 | 7.92, 7.93 | 98 ± 2 |
| 182 Q | $CH(CH_3)CH(CH_3)_2$ | 5 | I | C | 7 | 164.2–165.1 | 58.54 | 7.80 | 58.54, 58.81 | 7.68, 7.94 | 97 ± 2 |
| 183 Q | $CH(CH_3)CH(CH_3)_2$ | 4 | II | C | 7 | 173.4–175.0 | 57.57 | 7.57 | 57.55, 57.78 | 7.65, 7.67 | 98 ± 2 |
| 171 Q | $CH_2C(CH_3)_3$ | 4 | II | A | 41 | 197.2–198.6 | 64.96 | 8.55 | 65.10, 65.02 | 8.45, 8.55 | 91 ± 5 |
| 165 Q | $CH_2C(CH_3)_3$ | 3 | I | C | 10 | 200.1–201.1 | 56.54 | 7.33 | 56.57, 56.48 | 7.30, 7.28 | 98 ± 2 |
| 168 Q | $CH(C_2H_5)_2$ | 3 | I | D | 41 | 133–135 | 46.67 | 6.31 | 46.89, 46.75 | 6.45, 6.39 | |
| 172 Q | $CH(C_2H_5)_2$ | 2 | I | D | 40 | 237.0–237.4 | 45.43 | 6.01 | 45.67, 45.64 | 6.21, 6.19 | |
| 176 Q | $CH(CH_3)CH_2CH_2CH_3$ | 2 | I | D | 17 | 233.1–233.9 | 45.43 | 6.01 | 45.83, 45.62 | 6.37, 6.26 | |
| 166 Q | $CH_2C(CH_3)_3$ | 2 | I | D | 6 | 235.6–236.8 | 45.43 | 6.01 | 45.76, 45.85 | 6.22, 6.17 | 96 ± 3 |

[a] A represents the monohydrochloride; B, a diphosphate; C, a monohydrobromide; and D, a dihydrobromide. [b] The yields for those compounds prepared by Method I were calculated from the amino alcohol. Those prepared by method II were calculated from the aminoalkylaminoquinoline. [c] Melting points in this table and in following tables are corrected. [d] Analyses by Miss Eleanor Werble, Mrs. Mary Aldridge and Byron Baer. [e] Homogeneities were determined by the countercurrent extraction technique. See Williamson and Craig, *J. Biol. Chem.*, 168, 687 (1947). For simplified method of calculation see Lieberman, *ibid.*, **173**, 63 (1948).

(1) This work was entirely supported by a grant-in-aid from the United States Public Health Service (RG-191).

(2) N. L. Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).

(3) N. L. Drake, *et al.*, *ibid.*, **68**, 1529 (1946).

(4) A. C. Cope, private communication. This general method was used by Cope to make 8-(4-isopropylamino-*n*-butylamino)-6-methoxyquinoline (SN-13,275).

TABLE II

| Compound | Melting point, °C. | Calculated Carbon | Calculated Hydrogen | Analyses, % Found Carbon | | Found Hydrogen | |
|---|---|---|---|---|---|---|---|
| 5-Chloro-N-(2-amyl)-1-amylamine hydrochloride | 128–129 | 52.62 | 10.16 | 52.37 | 52.50 | 9.87 | 10.03 |
| 5-Chloro-N-(3-amyl)-1-amylamine hydrochloride | 85.2–88.0 | 52.62 | 10.16 | 52.99 | | 10.09 | |
| 5-Chloro-N-(2-butyl)-1-amylamine hydrochloride | 145.5–147.0 | 50.50 | 9.89 | 50.28 | 50.54 | 9.82 | 9.82 |
| 5-Chloro-N-cyclohexyl-1-amylamine hydrochloride | 221–223 | 55.00 | 9.59 | 54.77 | 54.88 | 9.50 | 9.55 |
| 5-Chloro-N-neopentyl-1-amylamine hydrochloride | 180.7–183.7 | Ionic Cl, 15.6 | | Ionic Cl, 15.5, 15.7 | | | |
| 5-Chloro-N-(1-butyl)-1-amylamine hydrochloride | 222.3–225.2 | Ionic Cl, 16.6 | | Ionic Cl, 16.6, 16.6 | | | |
| 5-Chloro-N-(1-amyl)-1-amylamine hydrochloride | 229.0–231.6 | Ionic Cl, 15.6 | | Ionic Cl, 15.7, 15.9 | | | |
| 5-Chloro-N-(isoamyl)-1-amylamine hydrochloride | 221.7–224.1 | Ionic Cl, 15.6 | | Ionic Cl, 15.7, 15.8 | | | |
| 5-Chloro-N-(2-methyl-3-butyl)-1-amylamine hydrochloride | 137.4–138.9 | Ionic Cl, 15.6 | | Ionic Cl, 15.5, 15.6 | | | |
| 3-Bromo-N-neopentyl-1-propylamine hydrobromide | 253–254 | 33.33 | 6.57 | 33.42 | 33.27 | 6.61 | 6.89 |
| 3-Chloro-N-(3-amyl)-1-ethylamine hydrochloride | 134–136 | 48.00 | 9.57 | 47.48 | 47.41 | 9.69 | 9.16 |
| 2-Chloro-N-(3-amyl)-1-ethylamine hydrochloride | 135.6–136.2 | 45.16 | 9.14 | 44.52 | 44.47 | 8.94 | 9.31 |
| 2-Chloro-N-(2-amyl)-1-ethylamine hydrochloride | 137.4–138.2 | 45.16 | 9.14 | 43.77 | 43.91 | 9.29 | 9.13 |
| 2-Chloro-N-neopentyl-1-ethylamine hydrochloride | 246–247 | 45.16 | 9.14 | 45.30 | 45.20 | 9.18 | 9.08 |

TABLE III

| Compound | Method of synthesis | Yield, % | Boiling point °C. | Boiling point Mm. | Analyses, % Calculated | Found |
|---|---|---|---|---|---|---|
| 5-(2-Amylamino)-1-pentanol | B | 76 | 119–121 | 7.5 | N. E. 173 | 175 |
| 5-(3-Amylamino)-1-pentanol | B | 62 | 110–112 | 4 | N. E. 173 | 175, 175 |
| 5-(2-Butylamino)-1-pentanol | B | 74 | 107–109 | 3.5 | N. E. 159 | 162 |
| 5-(Cyclohexylamino)-1-pentanol | B | 84 | [b] | | C, 71.4 | 71.04, 71.25 |
| | | | | | H, 12.45 | 12.73, 12.65 |
| 5-(Neopentylamino)-1-pentanol | A | 76 | 126–131 | 17 | N. E. 173 | 174 |
| 5-(*n*-Butylamino)-1-pentanol | B | 62 | 155–156 | 28 | N. E. 159 | 163 |
| 5-(*n*-Amylamino)-1-pentanol | B | 61 | 164–165 | 30 | N. E. 173 | 174 |
| 5-(Isoamylamino)-1-pentanol | A | 70 | 136–138 | 10 | N. E. 173 | 175 |
| 5-(2-Methyl-3-butylamino)-1-pentanol | A | 58 | 130–132 | 13 | N. E. 173 | 174 |
| N-(3-Methoxypropyl)-neopentylamine | A | 69 | 73–75 | 20 | N. E. 158 | 159 |
| 3-(3-Amylamino)-1-propanol | [a] | 51 | 102–105 | 12 | N. E. 145 | 148 |
| 2-(3-Amylamino)-1-ethanol | A | 70 | 96–98 | 7 | N. E. 131 | 131 |
| 2-(2-Amylamino)-1-ethanol | A | 83 | 81–83 | 6.4 | N. E. 131 | 132 |
| 2-Neopentylamino-1-ethanol | A | 74 | 75–80 | 10 | N. E. 131 | 132 |

[a] This compound was prepared from trimethylene chlorohydrin and 3-aminopentane. [b] This compound was not distilled. It was isolated by crystallization from petroleum ether and melted at 79.0–80.5°.

minoamylbromide hydrobromide with 8-amino-6-methoxy-5-(4-methoxyphenoxy)-quinoline gave only starting material when Method I was attempted but proceeded satisfactorily when the reactants were refluxed in alcohol.[5] Most of the drugs were finally purified as monohydrochlorides, hydrobromides or hydriodides; four of them were purified as dihydrobromides, and one as a diphosphate. All but one of the drugs prepared are listed in Table I.

The synthesis of all but one of the side chains for the compounds prepared by Method I was carried out by the action of thionyl chloride on the appropriate aminoalcohol. 3-Methoxy-N-neopentyl-1-propylamine was heated with an excess of constant-boiling hydrobromic acid. In most cases the side chain was used for the condensation without purification. The side chains prepared are listed in Table II.

The desired alkylaminoalcohols were prepared by (A), reductive alkylation of the appropriate aminoalcohol with the appropriate aldehyde or ketone, or (B), in the case of several of the alkylaminoamyl alcohols, from dihydropyran according to the procedure used in the preparation of isopropylaminopentanol.[3] All of the aminoalcohols prepared are listed in Table III.

Short-term chronic toxicities of the compounds are listed in Table IV.

(5) E. Rohrman and H. A. Shonle, THIS JOURNAL, **66**, 1640 (1944).

## Experimental

**2-Aminopentane.**[6]—A mixture of 258 g. of 2-pentanone and 250 ml. of anhydrous ammonia was heated at 140° with hydrogen and Raney nickel at 4000 p. s. i. After the reduction mixture was filtered, it was made acidic with hydrochloric acid and steam distilled to remove non-basic impurities. The aqueous residue was then made strongly basic, extracted with ether and the dried extracts were carefully distilled; 170 g. of product which boiled at 89° was obtained (66%).

**3-Aminopentane.**[7]—This compound was synthesized from diethyl ketone by the reductive amination method used in the preparation of 2-aminopentane; the reduction

(6) I. Tafel, *Ber.*, **22**, 1854 (1889).

(7) W. A. Noyes, THIS JOURNAL, **15**, 539 (1893).

TABLE IV

THE TOXICITY OF SOME 8-AMINOQUINOLINES[a]

| Drug | Pamaquine equivalent | Qualitative aspects of toxicity resemble those observed with: |
|---|---|---|
| SN 13,276 | 0.25 | |
| UM 135Q | .5 | Pamaquine |
| UM 136Q | .5 | Pentaquine |
| UM 137Q | .5 | Pentaquine |
| UM 139Q | 1.0 | Pamaquine |
| UM 165Q | 0.5 | Plasmocid |
| UM 166Q | 2 | Plasmocid |
| UM 168Q | 4 | Plasmocid |
| UM 170Q | 0.5 | Pamaquine or pentaquine |
| UM 171Q | 0.5 | Pamaquine |
| UM 172Q | 2 | Plasmocid |
| UM 176Q | 2 | Plasmocid |
| UM 177Q | 0.5 | Pamaquine |
| UM 178Q | .5 | Pamaquine |
| UM 179Q | .5 | Pamaquine |
| UM 180Q | .5 | Pentaquine closely |
| UM 181Q | .5 | Pamaquine |
| UM 182Q | .5 | Pamaquine |
| UM 183Q | .5 | Pamaquine |

[a] We are indebted to Dr. L. H. Schmidt, Christ Hospital, Mount Auburn, Cincinnati, Ohio, for the data from which this table was compiled. The test, which is for short term chronic toxicity in Rhesus monkeys, has been described (see "Survey of Antimalarial Drugs 1941–1945," Wiselogle ed., Vol. I, Edwards Bros., Ann Arbor, Michigan, 1946, p. 508).

was carried out at 150°. The yield was 59.7%,[8] and the boiling point of the amine was 91–92°.

**Alkylaminoalcohols, Method (A).**—A mixture of 1 mole of the primary amine and 1.25 moles of the desired aldehyde or ketone was heated with hydrogen in the presence of Adams catalyst at 100° and 2000 p. s. i.; the reduction was complete in about four hours. The catalyst was removed by filtration and the filtrate was distilled under diminished pressure. The yield varied from 56–83%.

**Alkylaminopentanols, Method (B).**—A solution of 20.4 ml. of concentrated hydrochloric acid in 250 ml.of distilled water was cooled to 0–5° in an ice-bath. The ice-bath was removed and 84 g. (1.0 mole) of dihydropyran was added all at once. The resulting mixture was stirred until it became homogeneous, allowed to stand for ten minutes, and then cooled in an ice-bath to 10–15°. To this solution was added slowly with cooling 1.25 moles of the desired amine while the temperature was kept below 25°. The resulting mixture was shaken with hydrogen and Adams catalyst at 25° and an initial pressure of 2000 p. s. i. The process was complete in about two hours. The catalyst was removed by filtration, and the solution was saturated with solid sodium hydroxide. The upper layer was separated and distilled under diminished pressure. The yield varied from 61–76%.

**3-(3-Amylamino)-1-propanol.**—A mixture of 38.8 g. of trimethylene chlorohydrin and 72 g. of 3-aminopentane was allowed to stand at room temperature for eighty hours, according to the method of Elderfield.[9] The precipitate was removed by filtration and the filtrate was heated at 115° to remove excess amine. After acidification with hydrochloric acid and re-addition of the original precipitate, the solution was extracted with ether, and the extracts were discarded. The aqueous portion was saturated with potassium hydroxide and extracted with ether. The extracts were dried and concentrated, and the residue was distilled under diminished pressure; 30.5 g. (51%) of product which boiled at 102–105° (12.5 mm.) was obtained. The neutral equivalent was 148 (calcd. 145) and the refractive index was $n^{25}D$ 1.4466.

**ω-Chloro-N-alkyl-1-alkylamine Hydrochlorides.**—To a stirred solution of 1 mole of the appropriate aminoalcohol in 600 ml. of petroleum ether (90–100°) was added slowly 138 g. (1.1 moles) of thionyl chloride. The mixture was stirred and refluxed for three hours and then allowed to stand overnight. The crude product was removed by filtration and washed well with petroleum ether. In most cases the product was used without further purification. The product can be purified by recrystallization from absolute ethanol and ether.

**3-Bromo-N-neopentyl-1-propylamine Hydrobromide.**—A solution of 63 g. of 3-methoxy-N-neopentyl-1-propylamine in 420 g. of 48% hydrobromic acid was warmed overnight on a steam-bath, and the solution was then evaporated to dryness under reduced pressure. The crude semisolid residue was used directly in the next step. Recrystallization of a small portion from acetone yielded a white crystalline material which melted at 252–253°.

*Anal.* Calcd. for $C_8H_{19}NBr_2$: C, 33.22; H, 6.57. Found: C, 33.42, 33.27; H, 6.61, 6.69.

**5-Bromo-N-isopropyl-1-amylamine Hydrobromide.**—This compound was prepared by the reaction of 5-isopropylamino-1-pentanol[3] and 48% hydrobromic acid at reflux temperature for four hours.The product was isolated by removal of the excess hydrobromic acid under diminished pressure, and the crude material was used directly in the next step.

**8-(ω-Alkylaminoalkylamino)-6-methoxyquinoline, Method I.**—A mixture of 1 mole of the side chain, 2 moles of 8-amino-6-methoxyquinoline, and 100 ml. of water was heated and stirred at 80° for twenty hours, and then at 100° for four hours. The melt was poured into an equal volume of water, and alkali and sodium acetate were added successively until the *p*H rose to 5.0. The mixture was then heated to 60° and extracted with several portions of benzene.[10] The aqueous portion was cooled to 20°,[11] treated with aqueous alkali, and extracted with ether. The product was obtained from the dried, concentrated ether solution by distillation under diminished pressure.

**8-(ω-Alkylaminoalkylamino)-6-methoxyquinoline, Method II.**—An aqueous solution of 28.5 g. (0.07 mole) of 8-(4-aminobutylamino)-6-methoxyquinoline dihydrochloride hemihydrate[4] was treated with aqueous alkali and extracted with chloroform. The concentrated extracts were dissolved in 75 ml. of albsolute ethanol, 0.20 mole of the desired aldehyde or ketone was added and the solution was hydrogenated over Adams catalyst at 2000 p. s. i. The reduction required about one hour. After removal of the catalyst by filtration, the solution was evaporated to dryness, and the residue was distilled in a molecular still.

The substitution of 26.9 g. (0.07 mole) of 8-(5-aminoamylamino)-6-methoxyquinoline dihydrochloride trihydrate[12] in the above procedure yields the desired alkylaminoamylaminoquinoline.

**8-(5-Isopropylaminoamylamino)-6-methoxy-5-(4-methoxyphenoxy)-quinoline Monohydriodide.**—A mixture of 30.9 g. of 8-amino-6-methoxy-5-(4-methoxyphenoxy)-quinoline, 35 g. of 5-bromo-N-isopropyl-1-amylamine hydrobromide, 100 ml. of absolute ethanol, and 75 ml. of ethylene glycol was refluxed for seventy-two hours, cooled,

(8) This compound was also prepared in 29% yield by the catalytic reduction of 3-pentanone oxime. The oxime was prepared by the method of "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p. 313. See also R. Scholl, *Ber.*, **21**, 506 (1888).

(9) R. C. Elderfield, THIS JOURNAL, **68**, 1579 (1946).

(10) The small amount of crystalline material that usually separated from the cooled benzene extracts was returned to the aqueous mixture, as was a 200-ml. aqueous extract of the combined benzene extracts. About 1 mole of 8-amino-6-methoxyquinoline was recovered from the benzene solution by concentration and distillation under diminished pressure.

(11) In some cases the product crystallized at this point in the procedure. If so, it was removed by filtration and then treated with alkali.

(12) Baldwin, *J. Chem. Soc.*, 2959 (1929).

and poured into an aqueous solution of 13.6 g. of sodium acetate trihydrate. The *p*H of the solution was adjusted to 4.5 and the mixture was extracted with chloroform. The chloroform solution was shaken first with 10% sodium hydroxide solution and then with salt water. It was dried, concentrated to 500 ml., and 250 ml. of petroleum ether (60–80) was added. The product was adsorbed by passing the solution through a column of activated alumina and was eluted with a mixture of chloroform and petroleum ether. The eluate, when concentrated under diminished pressure yielded 15 g. of a viscous oil. The oil was dissolved in aqueous hydrochloric acid and, after the *p*H had been adjusted to 5.0 with sodium acetate, a 10% excess of potassium iodide was added. An oil precipitated which, after decantation of the solution, was taken up in hot methanol. Addition of ether precipitated an impure salt which was recrystallized from methanol–ether; 5 g. (11.4%) of monohydriodide which melted at 159.0–160.5° was obtained.

*Anal.* Calcd. for $C_{25}H_{33}N_3O_3$.HI: C, 54.5; H, 6.17. Found: C, 54.26, 54.11; H, 6.42, 6.12.

**Monohydrochlorides and Hydrobromides of 8-Alkylaminoalkylaminoquinolines.**—Two general methods for the preparation of these salts were used. The first consisted of dissolving the base in dilute acetic acid and adding and excess of a concentrated aqueous solution of sodium bromide or sodium chloride. The other method consisted of dissolving the base in a slight excess of dilute hydrochloric or hydrobromic acid and adding a concentrated aqueous solution of sodium acetate until the *p*H of the mixture was 5.0. The salts were recrystallized from water, ethanol, or ethanol and ether.

**Dihydrobromides and Diphosphates of 8-Alkylaminoalkylaminoquinolines.**—These salts were prepared by adding a slight excess of 48% hydrobromic acid or 85% phosphoric acid to a refluxing ethanol solution of the base. The solution was cooled and the crystals removed by filtration. The product was recrystallized from ethanol or ethanol and ether.

## Summary

1. Eighteen new relatives, and one nuclear substitution product of pentaquine (SN-13,276), together with the intermediates necessary for their preparation, are described.

2. Short-term chronic toxicities, determined in Rhesus monkeys, are given.

3. None of the drugs is less toxic than pentaquine.

COLLEGE PARK, MD. RECEIVED AUGUST 23, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Alkane-choleic Acids: Compounds of Paraffin Hydrocarbons with Desoxycholic Acid[1]

BY ERNEST H. HUNTRESS AND RALPH F. PHILLIPS[2,3,4]

The number of addition products of desoxycholic acid with organic compounds of widely diverse types is legion, but the only choleic acids from alkanes reported at the time of our work was carried out (February, 1938–June, 1939) were two products incidentally mentioned[5] without details in a report on polycyclic carcinogenic hydrocarbons. Furthermore, Rheinboldt had long been concerned with studies on desoxycholic acid addition products, but none of his work involved alkanes until a paper published[6] after our experiments had been completed. This included certain data on desoxycholic acid compounds of the normal alkanes with 11, 12, 13, 14, 15, 16, 35 and 43 carbon atoms.

Under suitable conditions every one of the thirty-four alkanes which were studied in our work combined with desoxycholic acid in methanol solution to give in good yield a definite compound containing from two to eight moles of desoxycholic acid per mole of hydrocarbon. The composition of this resultant alkane-choleic acid was established by determination of the neutralization equivalent of the complex by titration with standard alkali. In the consolidation of our many experiments to the simple form of Table II, we have taken the mean neutralization equivalent of several runs rarely differing among themselves by more than 3–4 units out of 400–440. Comparison of the values of Table II with the various Kz values for a given composition (Table I) shows that the nearest correspondence is rarely in doubt. Our results show that in general the number of coördinated molecules of desoxycholic acid diminishes with increased forking of the hydrocarbon chain, but that this effect is not sufficiently critical to serve as an infallible means of distinction.

TABLE I

CALCULATED NEUTRALIZATION EQUIVALENTS OF ALKANE-CHOLEIC ACIDS

N = number of molecules of desoxycholic acid (mol. wt., 392) per mole of alkane = Kz (coördination number)

Neutralization Equivalent = (392 N + M.W.)/N = 392 + (M.W./N)

| N | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| $C_6H_{12}$ | 464 | 428 | 416 | 410 | 406.4 | 404 | 402.3 | 401 |
| $C_8H_{14}$ | 478 | 435 | 420.7 | 413.5 | 409.2 | 406.3 | 404.3 | 402.7 |
| $C_7H_{16}$ | 492 | 442 | 425.3 | 417 | 412 | 408.6 | 406.3 | 404.5 |
| $C_8H_{18}$ | 506 | 449 | 430 | 420.5 | 414.8 | 411 | 408.3 | 406.3 |
| $C_9H_{20}$ | 520 | 456 | 434.7 | 424 | 417.6 | 413.3 | 410.3 | 408 |
| $C_{10}H_{22}$ | 534 | 463 | 439.3 | 427.5 | 420.4 | 415.7 | 412.3 | 409.8 |

## Experimental Part

**Materials Used.**—For many of the samples of highly purified alkanes used in this work the authors are indebted to Messrs. H. Beatty, J. H. Bruun, G. Calingaert, P. L. Cramer, N. L. Drake, G. Egloff, A. V. Grosse, F. D. Rossini and the late F. C. Whitmore as individuals, and

(1) Presented April 23, 1942, at the Memphis Meeting of the American Chemical Society.

(2) This paper has been constructed from a thesis submitted in May, 1939, by Ralph F. Phillips in partial fulfillment of the requirements for the degree of Ph.D. in Organic Chemistry.

(3) A. D. Little Fellow in Chemistry, M. I. T., 1938–1939.

(4) Present address: Sugar Research Foundation, 52 Wall Street, New York 5, N. Y.

(5) Fieser and Newman, THIS JOURNAL, **57**, 1603 (1935).

(6) Rheinboldt, *J. prakt. Chem.*, [2] **153**, 313–326 (1939).

TABLE II

OBSERVED NEUTRALIZATION EQUIVALENTS AND COÖRDINATION NUMBERS FOR DESOXYCHOLIC ACID COMPOUNDS WITH VARIOUS ALKANES

For calculated values see Table I

| Hydrocarbon | Dried at 20° Neut. equiv. | Kz | *DT* in °C. uncor. | Dried at 110°[a] Neut. equiv. | Kz |
|---|---|---|---|---|---|
| $C_5H_{12}$[e] | | | | | |
| *n*-Pentane | 409 | 4 | 148–150 | 398 | 8 |
| 2-Methylbutane | 415 | 3 | 148–149 | 403 | 6 |
| 2,2-Dimethylpropane | 434 | 2 | 147–152 | ... | |
| $C_6H_{14}$ | | | | | |
| *n*-Hexane | 421 | 3 | 148–150 | 408 | 6 |
| 2-Methylpentane | 415[f] | 4[f] | 147–150 | 406 | 6 |
| 3-Methylpentane | 422 | 3 | 149–150 | ... | |
| 2,2-Dimethylbutane | 421 | 3 | 149–152 | 407 | 6 |
| 2,3-Dimethylbutane | 421 | 3 | 152–154 | 410 | 6 |
| $C_7H_{16}$ | | | | | |
| *n*-Heptane | 416 | 4 | 147–148 | 407 | 6 |
| 2-Methylhexane | 417 | 4 | 148–150 | ... | |
| 3-Methylhexane | 418 | 4 | 146–149 | 406 | 8 |
| 2,2-Dimethylpentane[g] | 418 | 4 | 147–148 | 401 | 8 |
| | | | | 409 | 6 |
| 2,4-Dimethylpentane[g] | 417 | 4 | 147–149 | 402 | 8 |
| | | | | 408 | 6 |
| 3,3-Dimethylpentane | 439 | 2 | 148–154 | 424 | 3 |
| 2,2,3-Trimethylbutane[h] | 442 | 2 | 166–172 | 428 | 3 |
| $C_8H_{18}$[i] | | | | | |
| *n*-Octane | 423 | 4 | 157–160 | 403 | 8[b] |
| 2-Methylheptane | ... | | ..... | 411 | 6[c] |
| 2,3-Dimethylhexane | 430 | 3 | 147–149 | ... | |
| 2,5-Dimethylhexane | 430 | 3 | 152–154 | ... | |
| 3,4-Dimethylhexane | 430 | 3 | 147–149 | ... | |
| 2,2,3-Trimethylpentane | 430 | 3 | 148–151 | ... | |
| 2,2,4-Trimethylpentane[i] | 433 | 3 | 149–151 | 421 | 4 |
| 2,2,3,3-Tetramethylbutane[j] | 447 | 2 | 169–171 | 431 | 3[c] |
| $C_9H_{20}$ | | | | | |
| 2-Methyloctane | 434 | 3 | 165–166 | 410 | 6[c] (or 8) |
| 4-Methyloctane | 436 | 3 | 161–163 | 411 | 6[c] (or 8) |
| 2,6-Dimethylheptane | 434 | 3 | 159–160 | 413 | 6[c] |
| $C_{10}H_{22}$ | | | | | |
| *n*-Decane | 427 | 4 | 168–170 | 407 | 8[d] |
| 2-Methylnonane | 429 | 4 | 168–170 | 413 | 6[c] |
| 3-Methylnonane | 437 | 3 | 163–165 | 416 | 6[c] |
| 4-Methylnonane | 439 | 3 | 165 | 416 | 6[c] |
| 5-Methylnonane | 436 | 3 | 169–170 | 414 | 6[c] |
| 2,7-Dimethyloctane[l] | 430 | 4 | 161–163 | 430 | 4[d] |
| 3,3,5-Trimethylheptane[k] | 440 | 3 | None | 430 | 4 |
| 2,2,3,4-Tetramethylhexane[k] | 441 | 3 | None | 433 | 4[c] |

[a] Heated two hours unless otherwise specified. [b] Heated thirteen hours. [c] Heated three hours. [d] Heated four hours. [e] With these especially volatile alkanes a large excess of hydrocarbon (2 or 3 ml.) gave better yields than the usual 1 ml. [f] Three runs on one sample and two on a different sample all agreed closely. [g] Unlike any of the other heptanes, these isomers required chilling to start precipitation of the alkane-choleic acid. They appear to represent transitional cases from Kz = 4 to Kz = 2 at 20°. [h] The product from this hydrocarbon was the only alkane-choleic acid below $C_{14}H_{30}$ which was not completely soluble in the original boiling methanol solution. [i] Of the isomeric octanes the choleic acid from this isomer ("isoöctane") was slowest in forming and required 1 ml. of alkane instead of usual 0.5 ml. [j] Fieser and Newman[5] were unable to obtain a choleic acid of this isomer. [k] The choleic acids of these isomers were the most difficult to prepare and were the only ones for whose formation heating was essential. [l] This was the only branched chain case observed where the coördination number of the choleic was unchanged by heating.

to the Ethyl Gasoline Corporation, General Motors Corporation, Sun Oil Company and Universal Oil Products Company as companies. The desoxycholic acid (Riedel-de-Haen, Inc.) proved of high purity[7] and was therefore used directly.

**Standard Procedure for the Preparation of Alkane-choleic Acids.**—Each choleic acid was prepared simply by adding the hydrocarbon (0.5 ml. for those with $C_8$ or above; 1.0 ml. for those below $C_8$) to 5 ml. of a filtered solution of desoxycholic acid (10 g.) in acetone-free methanol (50 ml.). The clear solution was then allowed to stand at room temperature for fifteen minutes. If no precipitation had then occurred the solution was chilled in ice water for half an hour, and filtered cold. Blank experiments demonstrated that under these circumstances the original bile acid itself remained completely in solution. If the solid jell produced by chilling was gently warmed in the mother liquor it generally redissolved completely and on cooling would reprecipitate as before. With some hydrocarbons this resolution appeared to effect a slight improvement in yields, which varied from 50–90%. With certain of the higher, less soluble highly branched paraffins the rewarming cycle was essential to choleic acid formation.

The alkane-choleic acid thus precipitated was dried at the pump for half an hour or more to remove excess solvent and/or hydrocarbon. The product may not be dried in the oven since such treatment results in removing sufficient hydrocarbon to mask observation of the decomposition temperature. Although methyl alcohol (contrary to the literature) was found to form a choleic acid itself, the resultant compound is quite soluble in excess methanol as compared to the alkane-choleic acids and does not precipitate under the conditions of our experiments. Other organic solvents may not be employed because of interference from their respective choleic acids, nor may the alkane-choleic acids be recrystallized even from methanol because of their tendency toward dissociation. Attempts to dispense with any solvent and use only the alkane itself with desoxycholic acid were unsuccessful.

**Method of Analysis of Alkane-choleic Acids.**—Since because of the molecular magnitudes carbon-hydrogen analyses of these products can have no determinative significance, the various alkane-choleic acids were characterized by their individual neutralization equivalents. Although special manipulative care in weighing and titration were required, experience soon convinced us that consistent values could be reproducibly obtained. Subsequent experiments by entirely different workers on analogous types of compounds have confirmed our procedure. Weighings were made on a long beam balance set to a sensitivity of two divisions per milligram and were by difference to four places. Titrations were made on samples of 50–80 mg. dissolved in neutral methanol (or ethanol) using aqueous 0.01 *N* sodium hydroxide with phenolphthalein as indicator. Frequently better results were obtained by dissolving the sample in excess standard alkali and titrating back with 0.01 *N* hydrochloric acid. The acid and alkali were frequently restandardized to eliminate errors attributable to slight changes of titer. Recognition of the end-point required some experience but was then readily determined. The end-point was delicate but achievable by working in daylight over a white surface particularly by comparison of the titration solution with a water-white blank placed beside it.

**Decomposition Temperature of Alkane-choleic Acids.**—Although the literature contains many records of melting points observed on other types of choleic acids, it is our observation that alkane-choleic acids do not melt AS SUCH at all. On heating they begin to dissociate at some fairly definite temperature, some of the component hydrocarbon is given off, and the corresponding desoxycholic acid remains, eventually to liquefy at its usual melting point (if pure) or somewhat below it if any hydrocarbon remains. At the temperature of decomposition (*DT*) the initial alkane-choleic acid shrinks sharply with marked softening and coalescence into a small worm-like shape, or some-

(7) Sobotka and Goldberg, *Biochem. J.*, **26**, 555–568 (1932).

times even globules. These always display a *convex* surface, do not form liquids (with concave upper surfaces) in the capillary melting point tube, and hence are not true melting phenomena. Frequently the solid becomes momentarily translucent changing with continued heating to an opaque condition, and finally melting (often quite sharply) at the melting point of the residual desoxycholic acid.

The loss of alkane probably is incomplete at the decomposition temperature, but slowly continues up to and perhaps beyond the melting point of the residual desoxycholic acid. When the temperature is raised at the rate of 4–8° per minute the decomposition temperature is readily reproducible within a degree or two. More rapid rates of heating lead to erratic and erroneous results; slower heating fails to produce deacholation at a rate sufficient to display in the sample the characteristic change of appearance required for easy recognition of the temperature.

Although the decomposition temperatures for the alkane-choleic acids are not in general sufficiently distinctive to warrant their use as a diagnostic tool, they are, at the request of the referees, reported in this paper. While by proper technique the loss of alkane can occur in such fashion as to give easily reproducible DT's, it is also true that the coördination number varies with temperature. Although a given alkane-choleic acid is perfectly stable at a given temperature, if it is maintained at a higher temperature, hydrocarbon is slowly lost without any corresponding change in appearance, DT, or final melting point. The change is evident only from the marked increase in coördination number as detected by diminution of neutralization equivalent. Of the thirty-four alkane-choleic acids here reported, only that from 2,7-dimethyloctane failed to lose achole on heating. This general change of coördination number with temperature emphasizes the necessity for its determination prior to any heating whatever.

**The Deacholation of *n*-Heptane-choleic Acid by Heat.**—In order to convince ourselves that our products really did obtain hydrocarbon some relatively large-scale experiments were carried out on the choleic acid from *n*-heptane. For example, a 19.3-g. sample of heptane-choleic acid (neut. equiv. 407) prepared from 10 g. of *n*-heptane and 25 g. of desoxycholic acid was placed in a 125-ml. distilling flask with a thermometer dipping into the powdered solid and the whole heated in an oil-bath. No observable effect was noted until after three hours (by which time the inside thermometer had attained 150°) when a visible crack appeared in the powdered solid and the latter began to shrink. During a final hour of heating the inside thermometer rose from 150° to 171°, the flask contents melted to a clear viscous liquid, and about 0.5 ml. of clear distillate weighing 0.2852 g. was collected. This product had a b. p. of 98–99° (recorded for *n*-heptane 98.4°) and had refractive index $n^{23}D$ 1.3842 (original *n*-heptane used 1.3845, recorded $n^{20}D$ 1.3877). This was taken as evidence that it was in fact *n*-heptane. The recovery was 36.5% theoretical.

In a second experiment entirely similar except that the *n*-heptane-choleic acid had previously been washed with ether (to see if exchange of ether for hydrocarbon would occur) 16.05 g. gave 0.4431 (67.6%) of *n*-heptane, b. p. 97–98.5°, $n^{23}D$ 1.3848. (Note the value for ether is much lower, *viz.*, 1.3526.) Furthermore, the loss in weight of the charge was 0.653 g. representing 4.07%; the per cent. of *n*-heptane in *n*-heptane-hexacholeic acid is 4.08%. During neither of these two distillations was any trace of carbon dioxide detectable in an attached barium hydroxide bubbler.

**The Action of Aqueous Alkali on Alkane-choleic Acids.**—Two samples of *n*-heptane-hexacholeic acid were dissolved, one in excess aqueous sodium hydroxide, the other in excess aqueous ammonium hydroxide. Both solutions were completely clear and showed no sign of any hydrocarbon. Upon acidification of these solutions and vacuum drying of the products, the latter shrank around 100–120°, gave a *DT* of 148° and finally melted at 168–169°. Further drying of the product from ammonium hydroxide in the oven at 85° for eighteen hours, then at 110° for seven hours gave material which still showed a *DT* of 147–150° with no sign of softening or shrinking. This is definite evidence for the survival of the original *n*-heptane-choleic acid.

## Summary

1. Thirty-four paraffin hydrocarbons have been shown to form with desoxycholic acid (in methyl alcohol) easily reproducible definite molecular compounds in which one mole of hydrocarbon is combined with from two to eight molecules of the bile acid.

2. Although the characteristics of these alkane-choleic acids proved inadequate to constitute a general means of identification, their ability to retain the hydrocarbon in alkaline solutions may be found useful in other fields of interest.

CAMBRIDGE, MASS. RECEIVED AUGUST 11, 1948

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Optically Active Compounds Related to Methadon

BY ALBERT POHLAND, FREDERICK J. MARSHALL AND THOMAS P. CARNEY

*l*-Methadon,[1] *l*-6-dimethylamino-4,4-diphenyl-3-heptanone, has been reported to have twice the analgesic activity of *dl*-Methadon.[2,3] The greatly increased activity of the levo isomer as compared with the racemic mixture led to the preparation of the optical isomers of compounds related to Methadon for pharmacological examination.

*dl*-4-Dimethylamino-2,2-diphenylvaleronitrile was resolved through the *d*-bitartrate salt by essentially the procedure of Thorpe, Walton, and Ofner.[3] The yield of both isomers was over 70% of the theoretical amount. The *d*- and *l*-nitriles were readily converted to the ketones by means of ethylmagnesium bromide. The observed rotations for *d*- and *l*-Methadon hydrochlorides were $[\alpha]^{25}D$ +126° and −127° ($c$ = 1.0 in water). The calculated specific rotations for the cations in water are +141° and −142°. Thorpe, Walton, and Ofner[3] reported $[\alpha]D$ +143° and −145° for the cations of *d*- and *l*-Methadon in water. Brode and Hill[4] resolved Methadon through the *d*-bitartrate and obtained $[\alpha]^{28}D$ +127.5° and −127.8° ($c$ = 2.96 in water) for *d*- and *l*-Methadon hydrochlorides.

(1) Council on Pharmacy and Chemistry, *J. Am. Med. Assoc.*, **134**, 1483 (1947). The Council recognized the term Methadon in place of the term Amidone.

(2) R. H. Thorpe, E. Walton and P. Ofner, *Nature*, **159**, 679 (1947).

(3) R. H. Thorpe, E. Walton and P. Ofner, *ibid.*, **160**, 605 (1947).

(4) W. R. Brode and M. W. Hill, *J. Org. Chem.*, **13**, 191 (1948).

TABLE I

| Isomer | $(CH_3)_2NCH(CH_3)$-$CH_2C(C_6H_5)_2R$ R | M. p.,[a] °C. | Yield, % | $[\alpha]^{25}D$ in water | c | Molecular formula | Analyses, % Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found | Rat tail burn test Threshold dose, mg./kg.[b] | Rat tail burn test Activity, methadon,[c] % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *d* | $-COC_2H_5$ | 239–241 dec. | 75 | +126° | 1.0 | $C_{21}H_{27}NO\cdot HCl$ | 4.05 | 4.30 | 10.25 | 10.03 | 24 | 8 |
| *l* | $-COC_2H_5$ | 239–241 dec. | 71 | −127° | 1.0 | $C_{21}H_{27}NO\cdot HCl$ | 4.05 | 3.96 | 10.25 | 10.23 | 1.25 | 160 |
| *α-dl* | $-CH(OH)C_2H_5$ | 192–193 | 86 | | | $C_{21}H_{29}NO\cdot HCl$ | 4.03 | 3.98 | 10.19 | 10.13 | 10 | 20 |
| *α-d* | $-CH(OH)C_2H_5$ | 169–171 | 93 | + 34° | 0.26 | $C_{21}H_{29}NO\cdot HCl$ | 4.03 | 3.81 | 10.19 | 10.10 | 80 | 3 |
| *α-l* | $-CH(OH)C_2H_5$ | 169–171 | 90 | − 34° | .30 | $C_{21}H_{29}NO\cdot HCl$ | 4.03 | 3.95 | 10.19 | 10.11 | 5 | 40 |
| *α-dl* | $-CH(O_2CCH_3)C_2H_5$ | 211–213 | 80 | | | $C_{23}H_{31}NO_2\cdot HCl$ | 3.59 | 3.60 | 9.09 | 9.22 | 1.5 | 133 |
| *α-d* | $-CH(O_2CCH_3)C_2H_5$ | 200–203 | 84 | + 57° | .26 | $C_{23}H_{31}NO_2\cdot HCl$ | 3.59 | 3.58 | 9.09 | 9.05 | 1 | 200 |
| *α-l* | $-CH(O_2CCH_3)C_2H_5$ | 201–202.5 | 89 | − 59° | .23 | $C_{23}H_{31}NO_2\cdot HCl$ | 3.59 | 3.58 | 9.09 | 8.92 | 5.5 | 37 |
| *dl* | $-CO_2C_2H_5$ | 178.5–180 dec. | 32 | | | $C_{21}H_{27}NO_2\cdot HCl$ | 3.87 | 3.85 | 9.80 | 9.82 | 10 | 20 |
| *d* | $-CO_2C_2H_5$ | 171–173 dec. | | + 39° | .26 | $C_{21}H_{27}NO_2\cdot HCl$ | 3.87 | 3.84 | 9.80 | 9.62 | 10 | 20 |
| *l* | $-CO_2C_2H_5$ | 172–173 dec. | | − 38° | .20 | $C_{21}H_{27}NO_2\cdot HCl$ | 3.87 | 3.78 | 9.80 | 9.73 | 60 | 3 |

[a] Melting points are uncorrected. [b] Subcutaneous. [c] Compared with *dl*-Methadon at 2 mg./kg.

Catalytic reduction of *dl*-Methadon has been reported to give only one of the two possible pairs of diastereoisomeric carbinols.[5,6] *d*- and *l*-Methadon were reduced catalytically to yield only two of the four possible optical isomers. These are designated as the *α*-isomers. The direction of optical rotation changed. *d*-Methadon hydrochloride was reduced to *α-l*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride, $[\alpha]^{25}D$ −34° (*c* = 0.30 in water). *l*-Methadon hydrochloride was reduced to *α-d*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride, $[\alpha]^{25}D$ +34° (*c* = 0.26 in water).

The *α-d*- and *α-l*-carbinol hydrochlorides were acetylated in pyridine solution by means of acetic anhydride. The observed rotations for *α-d*- and *α-l*-5-acetoxy-2-dimethylamino-4,4-diphenylheptane hydrochlorides were $[\alpha]^{25}D$ +57° and −59° (*c* = 0.2 in water).

The *d*- and *l*-nitriles were hydrolyzed by means of 70% sulfuric acid to the acids and, without isolation, converted to the ethyl esters. The observed rotations of the *d*- and *l*-ethyl 4-dimethylamino-2,2-diphenylvalerate hydrochlorides were $[\alpha]^{25}D$ +39° and −38° (*c* = 0.2 in water).

A preliminary evaluation of the analgesic activity of these compounds was made by means of the rat tail burn method. The subcutaneous threshold dosages and activities as compared with *dl*-Methadon are shown in Table I. Detailed results will be reported elsewhere.

We are indebted to Dr. K. K. Chen, Dr. C. C. Scott and Mr. E. B. Robbins for the pharmacological data reported.

## Experimental

**Resolution of *dl*-4-Dimethylamino-2,2-diphenylvaleronitrile.**—A warm solution containing 83 g. (0.3 mole) of *dl*-nitrile[7] and 45 g. (0.3 mole) of *d*-tartaric acid in 500 cc. of acetone and 50 cc. of water was cooled to yield 62 g. of *l*-nitrile *d*-bitartrate, m. p. 110–115°. After one recrystallization from aqueous acetone solution, the *l*-nitrile *d*-bitartrate melted at 114–117°, $[\alpha]^{23}D$ + 14° (*c* = 1.0 in water). The *l*-nitrile was regenerated with dilute sodium hydroxide and recrystallized from aqueous ethanol, m. p. 99–101°, wt. 31 g. (75%), $[\alpha]^{23}D$ −50° (*c* = 1.0 in ethanol).

The acetone mother liquor was concentrated to dryness *in vacuo*, treated with dilute sodium hydroxide, and the *d*-nitrile recrystallized three times from aqueous ethanol solution, m. p. 97–100°, wt. 30 g. (72%), $[\alpha]^{25}D$ + 47° (*c* = 1.0 in ethanol).

***α-dl*-, *α-d*- and *α-l*-6-Dimethylamino-4,4-diphenyl-3-heptanol Hydrochlorides.**—The nitriles were readily converted to the ketones by means of excess ethylmagnesium bromide.[3]

The ketone hydrochlorides in water solution were readily converted to the carbinol hydrochlorides at 3 atmospheres pressure of hydrogen using Adams platinum oxide catalyst. The water was removed *in vacuo* and the product crystallized from ethanol–ether solution. *d*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride was reduced to *α-l*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride. *l*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride was reduced to *α-d*-6-dimethylamino-4,4-diphenyl-3-heptanol hydrochloride.

***α-dl*-, *α-d*- and *α-l*-5-Acetoxy-2-dimethylamino-4,4-diphenylheptane Hydrochloride.**—A reaction mixture containing one part of the alcohol hydrochloride, one part of acetic anhydride, and two parts of pyridine was heated overnight at 50°. The resulting solution was diluted with ether until cloudy and chilled. The product was recrystallized from ethanol–ether solution.

***dl*-, *d*-, and *l*-Ethyl 4-Dimethylamino-2,2-diphenylvalerate Hydrochloride.**—A solution of 100 g. (0.36 mole) of *dl*-2,2-diphenyl-4-dimethylaminovaleronitrile in 300 g. of 70% sulfuric acid was stirred and heated in an oil-bath at 150° for eighteen hours.

The oil-bath was cooled to 120° and the flask fitted with a dropping funnel and distilling condenser. One liter of absolute ethanol was added during ten hours, allowing the alcohol to distill. The reaction mixture was poured onto ice and made basic with 50% sodium hydroxide solution. The oil was extracted with ether, dried over magnesium sulfate, and then distilled *in vacuo*. The fraction boiling at 158–168° (0.70 mm.), wt. 62 g., was collected. The hydrochloride was prepared in ether and recrystallized from ethanol–ether solution, m. p. 178.5–180°,[8] wt. 42 g. (32%).

The *d*- and *l*-isomers were prepared by the same procedure using the resolved nitriles.

## Summary

The optical isomers of *α-dl*-6-dimethylamino-4,4-diphenyl-3-heptanol, *α-dl*-5-acetoxy-2-dimeth-

(5) M. E. Speeter, W. M. Byrd and L. C. Cheney, THIS JOURNAL, **71**, 57 (1949).

(6) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(7) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188 (1947); E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

(8) Subsequent to submission of this paper for publication, this compound has been reported by J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2906 (1948), to melt at 151–152°. Following their procedure we have been able to obtain only the crystalline modification melting at 178.5–180°.

ylamino-4,4-diphenylheptane, and *dl*-ethyl 4-dimethylamino-2,2-diphenylvalerate hydrochlorides have been prepared using *d*- and *l*-4-dimethylamino-2,2-diphenylvaleronitrile as the starting materials.

INDIANAPOLIS, INDIANA RECEIVED JULY 21, 1948

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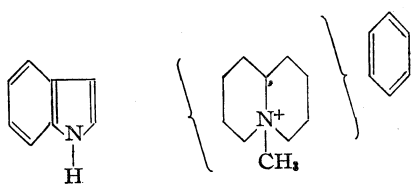
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# Curariform Activity and Chemical Structure. III. Syntheses in the 3-Indolylmethylamine Series[1]

BY L. E. CRAIG[2] AND D. S. TARBELL

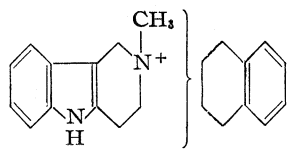
The most physiologically effective of the curare alkaloids belong to the calabash curare group. Of the eighteen alkaloids which have been isolated from calabash curare, the most active is C-toxiferine-I, which paralyzes frogs in doses of 0.005–0.009 mg./kg.[3]

Karrer and Schmid[4] showed that C-curarine-I chloride ($C_{20}H_{21}ClN_2$) contains a secondary, non-basic nitrogen, which is the nitrogen of an indole ring-system, and a quaternary nitrogen present in a tetrahydroisoquinoline ring system, common to two rings, and containing a methyl group. On the basis of this, the following structure can be drawn



Since the benzene ring must be attached in a position to give a tetrahydroisoquinoline, fourteen isomeric hexahydrobenzoindoloquinolizines are possible.

The most probable structures are those in which the quaternary nitrogen is separated from the indole ring by one carbon. On the basis of similarity of color reactions, Schmid and Karrer[3] postulated that C-toxiferine-I might be related to tetrahydro-9-pyrido(3,4-b)indoles, which would mean that the above proposed structure would have the β-carboline arrangement of the nitrogen atoms. Wieland, Witkop and Bähr[5] isolated isoquinoline, skatole and impure 3-ethylindole from a zinc dust distillation of another of the calabash curare alkaloids, C-dihydrotoxiferine-I chloride ($C_{20}H_{23}ClN_2$). The isolation of the 3-ethylindole supports the β-carboline structure proposed by Schmid and Karrer; however, the isolation of skatole suggests the γ-carboline structure, as follows:



(Four possible isomers)

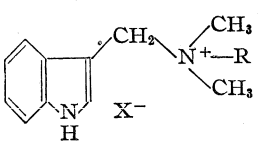
The present papers reports the synthesis of, and the preliminary pharmacological tests on, compounds containing a quaternary nitrogen in the γ-carboline structure, that is, 3-indolylmethylammonium salts.

The 3-indolylmethylamines were prepared conveniently by the Mannich reaction, essentially by the method of Kühn and Stein.[6]

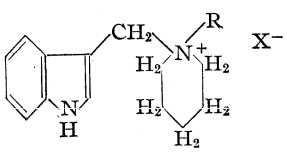
When the Mannich reaction was attempted with indole, formaldehyde and 1,2,3,4-tetrahydroisoquinoline hydrochloride, methylene-bis-(N,N'-1,2,3,4-tetrahydroisoquinoline) and a polymeric material[7] were obtained. The methylene-bis-compound was obtained in good yield when the amine hydrochloride and aqueous formaldehyde were heated together. Attempts to prepare derivatives of this previously unreported compound led to some anomalous results.

On treatment of the methylene-bis-compound with ethanolic picric acid, the picrate of 1,2,3,4-tetrahydroisoquinoline was obtained. Treatment of the bis-compound with methyl iodide yielded N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide. The cleavage of the methylenediamine linkage with ethanolic picric acid is not without precedent, as Elderfield and Kreysa[8] reported a similar reaction.

The tertiary 3-indolylmethylamines were converted by conventional methods into various quaternary salts.



I, R = $-CH_3$
II, R = $-CH_2C_6H_5$
III, R = $-CH_2CH_2C_6H_5$



IV, R = $-CH_3$
V, R = $-CH_2C_6H_5$

(1) For the second paper of this series, see Craig and Tarbell, THIS JOURNAL, **70**, 2783 (1948).

(2) Aided by a Grant from the National Foundation for Infantile Paralysis. Present address, General Aniline and Film Corporation, Easton, Pennsylvania.

(3) Schmid and Karrer, *Helv. chim. acta*, **30**, 1162 (1947).

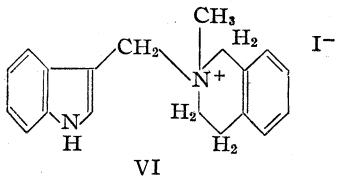
(4) Karrer and Schmid, *ibid.*, **29**, 1853 (1946).

(5) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

(6) Kühn and Stein, *Ber.*, **70**, 567 (1937).

(7) Indole has been reported to polymerize in the presence of acids; see Schmitz-Dumont, Hamann and Diebold, *ibid.*, **71**, 205 (1938).

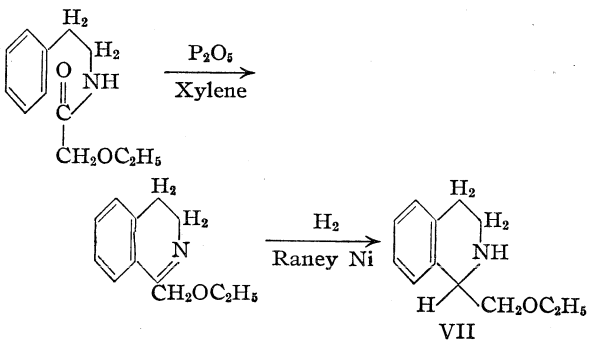
(8) Elderfield and Kreysa, THIS JOURNAL, **70**, 44 (1948).



VI

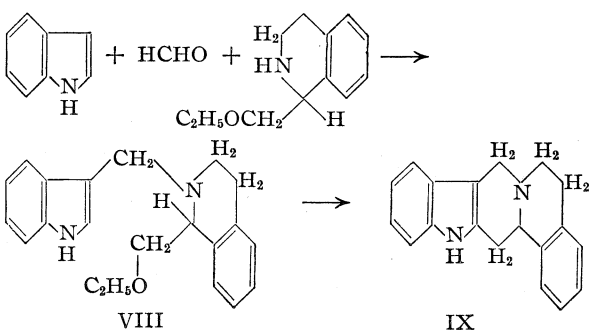
Compound VI is an open-chain analog of the γ-carboline ring system which was suggested for the calabash curare alkaloids.

Unsuccessful attempts were made to synthesize the complete hexahydrobenzoindoloquinolizine ring system (IX) by ring closure of 1-ethoxymethyl-2-(3-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline (VIII). 1-Ethoxymethyl-1,2,3,4-tetrahydroisoquinoline (VII) was obtained by hydrogenation of the 1-ethoxymethyl-3,4-dihydroisoquinoline prepared by the Bischler–Napieralski reaction from N-(β-phenylethyl)-ethoxyacetamide; by condensation of VII with indole by the Mannich



VII

reaction, 1-ethoxymethyl-2-(3-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline (VIII) was obtained in good yield.



VIII IX

Conventional methods for ether cleavage were applied to compound VIII with the hope that ring-closure to the indole ring might occur simultaneously with the cleavage of the ethoxyl group, thus forming the hexahydrobenzoindoloquinolizine (IX). The Mannich base (VIII) was treated with anhydrous aluminum bromide in refluxing benzene, concentrated hydriodic acid at reflux, boron tribromide[9,10] in refluxing benzene, zinc chloride in refluxing acetic acid, and phosphorus trichloride in refluxing benzene. Very dark tars were obtained which did not yield any desired product on attempted purifications by crystallizations and chromatography.

Compounds I, II, V and VI exhibited typical curare-like activity in mice. Compound VI was effective when injected intraperitoneally in doses of less than 16 mg./kg. and when given orally in doses of approximately 80 mg./kg. Compounds I, II and V were effective when injected intraperitoneally in doses of 40, 60 and 80 mg./kg., respectively. Compound III was ineffective in doses of 60 mg./kg. and Compound IV was a convulsant poison. While the most effective of these compounds, compound VI, has only a very small fraction of the activity of C-toxiferine-I, it is significant to note that the 3-indolylmethyl group greatly enhances curariform activity, because N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide was found to be ineffective in doses of 200 mg./kg.[11]

## Experimental[12]

**3-Indolylmethyltrimethylammonium Iodide (Gramine Methiodide)[6,13] (I).**—A solution of 25 g. (0.144 mole) of gramine and 21 g. (0.148 mole) of methyl iodide in 200 cc. of absolute ethanol was allowed to stand in the dark for twenty hours. The precipitate was collected, slurried with cold ethanol, and again collected by filtration to give 30.8 g. (97.5%) of colorless leaflets which darken at 150–200° but do not melt under 300°.[14]

**Benzyldimethyl-3-indolylmethylammonium Bromide (II).**—A solution of 1.74 g. (0.01 mole) of gramine and 1.71 g. (0.01 mole) of benzyl bromide in 25 cc. of absolute ethanol was allowed to stand at room temperature for sixteen hours. Upon adding ether to the orange solution, 1.2 g. (35%) of tan powder was obtained, which gave 1.0 g. (29%) of colorless crystals on recrystallization from methanol–ether. The product darkens at 130–135° and melts with decomposition over a temperature range between 145–155°. It is soluble in ethanol and methanol, only very slightly soluble in water and insoluble in ether.

*Anal.* Calcd. for $C_{18}H_{21}BrN_2$: C, 62.61; H, 6.13. Found: C, 62.22; H, 5.80.[15]

**Dimethyl-3-indolylmethyl-β-phenylethylammonium Bromide (III).**—A solution of 2.5 g. (0.014 mole) of gramine and 2.6 g. (0.014 mole) of β-phenylethyl bromide in 50 cc. of absolute ethanol was allowed to stand for six days at room temperature. The light pink precipitate (1.9 g., 37%) was collected and recrystallized from methanol–ether to give 1.6 g. (31%) of colorless needles, m. p. 171°. The product is soluble in methanol, only very slightly soluble in water and insoluble in ether and benzene.

*Anal.* Calcd. for $C_{19}H_{23}BrN_2 \cdot {}^1/_2H_2O$: C, 61.96; H, 6.57. Found: C, 61.76, 61.86; H, 6.30, 6.23.

**N-(3-Indolylmethyl)-piperidine.**—To a cooled solution of 8.5 g. (0.1 mole) of piperidine and 8.6 g. (0.1 mole of formaldehyde) of 35% formaldehyde in 100 cc. of 50%

(9) Gamble, Gilmont and Stiff, THIS JOURNAL, **62**, 1257 (1940).

(10) Benton and Dillon, *ibid.*, **64**, 1128 (1942).

(11) The authors are indebted to F. M. Berger, M.D., the University of Rochester School of Medicine and Dentistry, for the pharmacological tests on these compounds.

(12) All melting points are uncorrected; analyses by Mrs. G. L. Sauvage.

(13) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

(14) Kühn and Stein[6] reported that the compound darkens at 175° but does not melt under 350°.

(15) High hydrogen and low carbon values were obtained until the product was dried at elevated temperatures under reduced pressure. In subsequent experiments, the quaternary salts of the Mannich bases discolored and decomposed on heating, and the high hydrogen and low carbon values were assumed to be due to fractional molecules of water of crystallization.

acetic acid was added 11.7 g. (0.1 mole) of indole. A slight exothermic reaction occurred as the indole went into solution. After the light yellow solution had stood at room temperature for twelve hours, it was made strongly basic with sodium hydroxide and the precipitate collected by filtration. After recrystallization from dilute ethanol, 15.5 g. (74%) of colorless needles were obtained, m. p. 159–159.5°.[16]

**N-(3-Indolylmethyl)-N-methylpiperidinium Iodide (IV).**—A solution of 2 g. (0.0094 mole) of N-(3-indolylmethyl)-piperidine and 2 cc. (0.032 mole) of methyl iodide in 20 cc. of absolute ethanol was allowed to stand at room temperature for twenty-four hours. The oil which separated when ether was added crystallized slowly on standing in the refrigerator. Recrystallization of the product from methanol–ether gave 1.8 g. (55%) of colorless prisms, m. p. 142–143°. The product is soluble in methanol, ethanol and warm water, and insoluble in ether and petroleum ether.

*Anal.* Calcd. for $C_{15}H_{21}IN_2 \cdot {}^1/_4H_2O$: C, 49.94; H, 6.01. Found: C, 49.77; H, 5.98.

**N-Benzyl-N-(3-indolylmethyl)-piperidinium Bromide (V).**—A solution of 1 g. (0.0047 mole) of N-(3-indolylmethyl)-piperidine and 0.8 g. (0.0047 mole) of benzyl bromide was allowed to stand at room temperature for six days. The fine white powder that precipitated was recrystallized from ethanol–ether to give 1.1 g. (61%) of product, m. p. 147–151° with decomposition after darkening at 132–134°. The product is soluble in ethanol and warm water and insoluble in ether.

*Anal.* Calcd. for $C_{21}H_{25}BrN \cdot {}^1/_4H_2O$: C, 64.68; H, 6.59. Found: C, 64.92; H, 6.94.

**Methylene-bis-(N,N′-1,2,3,4-tetrahydroisoquinoline).**—A solution of 3.4 g. (0.02 mole) of 1,2,3,4-tetrahydroisoquinoline hydrochloride and 1 g. (0.02 mole) of 35% formaldehyde in 30 cc. of 20% acetic acid was heated on a steam-bath for one hour. The oil which separated when the solution was made basic was extracted from the mixture with two 50-cc. portions of ether. The light yellow oil left on evaporation of the ether was taken up in ethanol and crystallization induced by adding a few drops of water to give 2.1 g. (75%) of light tan powder, m. p. 88–88.5°.

*Anal.* Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97. Found: C, 82.30; H, 7.95.

A small amount of the above product was heated for a few minutes in saturated ethanolic picric acid. On cooling a picrate separated in long needles, m. p. 200–201° after softening and darkening at 185–190°.

*Anal.* Calcd. for the picrate of 1,2,3,4-tetrahydroisoquinoline, $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.89. Found: C, 50.00; H, 4.14.

As this analysis checked for the picrate of 1,2,3,4-tetrahydroisoquinoline, a mixed melting point of this picrate with that of an authentic sample of 1,2,3,4-tetrahydroisoquinoline (m. p. 201–202°) was taken. There was no depression.

A solution of 1 g. (0.0036 mole) of the bis-compound and 2.8 g. (0.02 mole) of methyl iodide in 25 cc. of dry ether was allowed to stand at room temperature for twenty-four hours. The light yellow needles which formed amounted to 0.4 g., m. p., after recrystallization from methanol–ether, 187–188°.[17] Evaporation of the filtrate to dryness left 0.5 g. of the unreacted bis-compound. The 0.4 g. of product, which was shown by analysis to be N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide, represents a yield of 40% based on the unrecovered starting material.

*Anal.* Calcd. for N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide, $C_{11}H_{16}IN$: C, 45.69; H, 5.59. Found: C, 45.97; H, 5.68.

(16) Kühn and Stein[6] reported a m. p. of 161°.

(17) Gulland and Virden, *J. Chem. Soc.*, 1791 (1929), reported a melting point of 192° for N,N-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide. They obtained the product as yellow leaflets from which it was very difficult to remove the color.

**N-(3-Indolylmethyl)-1,2,3,4-tetrahydroisoquinoline.**—A water solution of 5 g. (0.03 mole) of 1,2,3,4-tetrahydroisoquinoline hydrochloride was made strongly basic with alkali and the free base taken up in ether. After removing the ether by distillation, the residue was taken up in 20 cc. of 50% acetic acid. To this solution was added 3.4 g. (0.04 mole) of 35% formaldehyde and 3.5 g. (0.03 mole) of indole. After the light yellow solution had stood at room temperature for twelve hours, it was made strongly basic and the mixture extracted with three 50-cc. portions of ether. The residue left from the evaporation of the ether solution was recrystallized from dilute ethanol to give 4.7 g. (60%) of essentially colorless product, m. p. 139–140°. It was necessary to purify the product by chromatography, using chloroform–petroleum ether as the solvent and alumina as the adsorbent, before a satisfactory carbon–hydrogen analysis could be obtained. The melting point was not raised by this purification, but consistently high carbon values were obtained until the product was chromatographed.

*Anal.* Calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.91. Found: C, 82.10; H, 7.05.

The hydrochloride of the Mannich base was prepared by passing dry hydrogen chloride gas through a dry ether solution. Upon recrystallization from ethanol–ether, pink prisms were obtained, m. p. 179.5–180°.

*Anal.* Calcd. for $C_{18}H_{19}ClN_2$: C, 72.34; H, 6.41. Found: C, 71.92; H, 6.45.

**N-(3-Indolylmethyl)-N-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (VI).**—A solution of 1 g. (0.0038 mole) of N-(3-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline and 2 cc. (0.032 mole) of methyl iodide was allowed to stand for two hours at room temperature. The light tan, flaky precipitate amounted to 1.6 g. (quantitative), m. p. 75–80° with darkening. When the product was dissolved in methanol and a large amount of ether added, a gummy solid invariably formed, which became completely solid on washing with large amounts of ether. Several repetitions of this procedure gave an essentially colorless powder that melted at 110–112° with darkening and decomposition. The product is soluble in ethanol and methanol, rather insoluble in water and insoluble in ether.

*Anal.* Calcd. for $C_{19}H_{21}IN_2 \cdot {}^1/_4H_2O$: C, 55.82; H, 5.29. Found: C, 56.02; H, 5.32.

**Ethoxyacetyl Chloride.**—The preparation of ethoxyacetyl chloride by treatment of ethoxyacetic acid[18] with thionyl chloride according to the usual procedures was found to be unsatisfactory (13% yield), considerable cleavage of the ethoxyl group apparently taking place. The procedure used by Brown[19] for preparing various volatile acid chlorides was found to be the most satisfactory. In a 100-cc. flask, fitted with a short Vigreux column, were placed 56 g. (0.4 mole) of benzoyl chloride and 21 g. (0.2 mole) of ethoxyacetic acid. The flask was heated in an oil-bath so that a slow distillation was maintained. In one experiment, 19.8 g. (crude yield, 80%) of colorless liquid was obtained at 95–130°, the major portion coming over between 120–125°.[20] The best results were obtained when this product was used without refractionation in the subsequent experiment.

**N-(β-Phenylethyl)-ethoxyacetamide.**—The 19.8 g. (0.16 mole) of crude ethoxyacetyl chloride from the above experiment was added slowly with cooling to a solution of 48 g. (0.4 mole) of β-phenylethylamine in 100 cc. of benzene. After standing several hours, the precipitated β-phenylethylamine hydrochloride was removed by filtration. After drying the benzene solution over anhydrous magnesium sulfate, the benzene was removed by distillation and the residue distilled to give 15.3 g. (46%) of colorless liquid, b. p. 144–150° (0.6–0.9 mm.), $n^{23}D$ 1.5172.

(18) Fuson and Wojcik, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 260.

(19) Brown, THIS JOURNAL, **60**, 1325 (1938).

(20) Rothstein, *Bull. soc. chim.*, **51**, 838 (1932), reported a b. p. of 123–124°.

*Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.36; H, 8.01.

**1-Ethoxymethyl-3,4-dihydroisoquinoline.**—To a solution of 12 g. (0.06 mole) of N-(β-phenylethyl)-ethoxyacetamide in 150 cc. of refluxing xylene was added portionwise, over a period of fifteen minutes, 14 g. (0.1 mole) of phosphorus pentoxide. Reflux was maintained for another fifteen minutes. After decanting the xylene from the dark brown solid, 150 cc. of water was added and the mixture shaken until all had gone into solution. The water solution was extracted with two 50-cc. portions of ether to remove the xylene and any other ether-soluble material. The mixture which formed when the water solution was made strongly basic with alkali was extracted with four 50-cc. portions of ether. After drying the ether solution and removing the ether by distillation, the dark red-brown residue was distilled to give 4.9 g. (45%) of colorless liquid, b. p. 106–115° (1–1.5 mm.), $n^{22}D$ 1.5495. The liquid rapidly turned yellow on exposure to air.

*Anal.* Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99. Found: C, 75.48; H, 7.55. The sample had turned yellow before the analysis was made; oxidation could account for the low carbon–hydrogen values.

The picrate was obtained as yellow needles from ethanol, m. p. 138–139° with decomposition.

*Anal.* Calcd. for $C_{18}H_{18}N_4O_8$: C, 51.68; H, 4.34. Found: C, 51.94; H, 4.38.

The hydrochloride precipitated when dry hydrogen chloride gas was bubbled through a dry ether solution of the distilled free base. It was very hygroscopic and difficult to handle, recrystallization from ethanol–ether giving colorless needles, m. p. 85–86° with darkening and decomposition.

*Anal.* Calcd. for $C_{12}H_{16}ClNO \cdot 1/4H_2O$: C, 62.60; H, 7.22. Found: C, 62.84; H, 7.28.

**1-Ethoxymethyl-1,2,3,4-tetrahydroisoquinoline (VII).**—A solution of 3.6 g. (0.019 mole) of the distilled 1-ethoxymethyl-3,4-dihydroisoquinoline in 50 cc. of absolute ethanol, in the presence of about 1.0 g. of Raney nickel, was shaken for five hours at room temperature under hydrogen at 3.8 atmospheres. After removing the catalyst by filtration and the ethanol by distillation, the residue was distilled under reduced pressure to give 3.4 g. (94%) of colorless liquid, b. p. 90–103° (0.5–0.6 mm.), $n^{21}D$ 1.5360. The liquid turned light yellow on standing.

*Anal.* Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.97. Found: C, 74.66; H, 8.83. The colorless sample had turned light yellow before the analysis was run.

The picrate formed very slowly as tiny yellow needles from ethanol, m. p. 164–165°.

*Anal.* Calcd. for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.80. Found: C, 51.32; H, 4.50.

The hydrochloride was prepared by bubbling dry hydrogen chloride gas through an ethanol solution of the free base and adding ether to induce crystallization. Recrystallization from ethanol–ether gave colorless prisms, m. p. 155–156°.

*Anal.* Calcd. for $C_{12}H_{18}ClNO$: C, 63.28; H, 7.97. Found: C, 63.39; H, 7.80.

**1-Ethoxymethyl-2-(3-indolylmethyl)-1,2,3,4-tetrahydroisoquinoline (VIII).**—To a solution of 1.9 g. (0.01 mole) of 1-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline in 30 cc. of 50% acetic acid was added 0.4 g. (0.05 mole) of 35% formaldehyde and 1.1 g. (0.01 mole) of indole. After the light yellow solution had stood at room temperature for seven hours, it was made basic with dilute sodium hydroxide, a light yellow oil separating. The mixture was extracted exhaustively with ether, and the ether removed from the combined extracts by distillation. The residue was taken up in 25 cc. of ethanol and a few cc. of water added dropwise until precipitation was complete. Recrystallization of the product from dilute ethanol gave 2.2 g. (69%) of tiny colorless needles, m. p. 100–102°. A small sample recrystallized again from dilute ethanol melted at 102–103°. Although the melting point was not changed, it was necessary to purify the product by chromatography (using chloroform–petroleum ether and a column of alumina) before a satisfactory analysis was obtained. Consistently high carbon values were obtained until this was done.

*Anal.* Calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.75. Found: C, 78.80; H, 7.50; N, 8.60.

## Summary

A number of previously unreported 3-indolylmethylammonium salts, compounds which are analogous to the structures postulated for the calabash curare alkaloids, have been prepared. Some of these quaternary salts exhibit marked curariform activity, the most effective, N-(3-indolylmethyl)-N-methyl-1,2,3,4-tetrahydroisoquinolinium iodide, causing paralysis in mice in doses of 16 mg./kg.

ROCHESTER, N. Y. RECEIVED JULY 22, 1948

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[CONTRIBUTION FROM THE DEPARTMENT CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

# Curariform Activity and Chemical Structure. IV. Syntheses in the Piperidine Series[1]

BY L. E. CRAIG[2] AND D. S. TARBELL

Substituted 4-piperidones, 4-hydroxypiperidines and various piperidinium salts have been reported to exhibit rather intense curariform activity.[3,4] The present paper reports the syntheses of and the results of preliminary pharmacological tests on 4-piperidonium and 4-hydroxypiperidinium salts.

Di-β-carbomethoxyethylmethylamine (I), obtained by the addition of methylamine to methyl acrylate by the method of Mozingo and McCracken,[5] was treated with powdered sodium in xylene by the procedure of McElvain[6] to give 1-methyl-3-carbomethoxy-4-piperidone (III). Compound III, on acid hydrolysis, gave 1-methyl-4-piperidone (V), which was readily converted to 1-

(1) For the third paper of this series see Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).

(2) Aided by a Grant from the National Foundation for Infantile Paralysis. Present address: General Aniline and Film Corporation, Easton, Pennsylvania.

(3) Craig, *Chem. Revs.*, **42**, 360, 390 (1948).

(4) von Oettingen, "The Therapeutic Agents of the Pyrrole and Pyridine Group," Edwards Brothers, Inc., Ann Arbor, Michigan, 1936, p. 116.

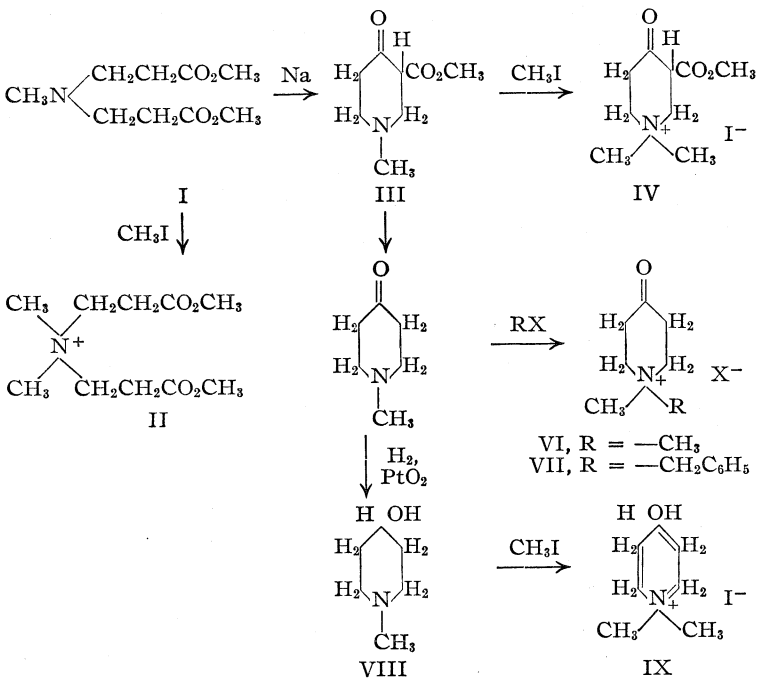
(5) Mozingo and McCracken, *Org. Syn.*, **20**, 35 (1940).

(6) McElvain, THIS JOURNAL, **46**, 1721 (1924).

methyl-4-hydroxypiperidine (VIII) by catalytic hydrogenation.

Previous workers[7,8,9] obtained a hydrochloride of 1-methyl-4-piperidone which melted at 94–95°. When dry hydrogen chloride gas was bubbled through a dry ether solution of distilled 1-methyl-4-piperidone, a hydrochloride was obtained which melted at 164–167°. It is probable that the hydrochloride melting at 94–95° contains water of crystallization (no analyses were reported). On distillation of the 1-methyl-4-piperidone, a considerable amount was left as a viscous residue in the distilling flask. As the distilled product also increased noticeably in viscosity on standing, it seems probable that it undergoes an aldol-type condensation.

The piperidone, hydroxypiperidine and the tertiary amine intermediates were converted into quaternary salts by conventional methods. The reactions carried out are summarized as




All of the quaternary salts, with the exception of compound II which produces a marked muscarinic action, cause curariform paralysis in mice. Compounds IV, VI, VII and IX are effective in doses of 180–280 mg./kg. when injected intraperitoneally. Compound IX is effective when given orally in doses of 1000 mg./kg.[10]

## Experimental

**Di-β-carbomethoxyethylmethylamine (I).**—This compound was prepared by the procedure used by Mozingo and McCracken[5] for the preparation of the corresponding carbethoxy compound. In a typical experiment, 172 g. (2.0 moles) of methyl acrylate and 31 g. (1.0 mole) of methylamine gave 183 g. (90%) of colorless liquid, b. p. 108–112° (3–4 mm.).[11]

**3-Carbomethoxy-1-methyl-4-piperidone (III).**—This compound was prepared by the procedure used by McElvain[6] for the corresponding carbethoxy compound. In one experiment, 41 g. (0.2 mole) of di-β-carbomethoxyethylmethylamine in 100 cc. of xylene was treated with 4.6 g. (0.2 mole) of powdered sodium to give 20.4 g. (60% crude yield) of light yellow oil. Attempts to distil this product resulted in considerable loss. The light yellow liquid rapidly became dark and viscous on heating and only 40–50% of the material distilled, b. p. 85–90° (1 mm.). It was found advisable to convert the entire crude product to the hydrochloride by bubbling dry hydrogen chloride gas through an ether solution (the conversion was essentially quantitative), m. p., after recrystallization from ethanol–ether, 164–165°.[12]

**1-Methyl-4-piperidone (V).**—This product was obtained by hydrolysis of 3-carbomethoxy-1-methyl-4-piperidone according to the procedure of Bolyard and McElvain.[7] The product was obtained by this procedure as the hydrochloride, m. p. 94–95°.[13] In one experiment, this crude hydrochloride was converted to the free base and the free base distilled, b. p. 54–56° (9 mm.), $n^{25}D$ 1.4588.[14] Much of the free base was not recovered on distillation and a viscous, dark residue was left in the distilling flask. The distilled product also increased noticeably in viscosity on standing. For this reason, the product was used immediately after distillation in subsequent reactions.

A stream of dry hydrogen chloride gas was bubbled through a benzene solution of the distilled free base. The hydrochloride so obtained was recrystallized from anhydrous chloroform–ether to give colorless crystals melting at 164–167°.

*Anal.* Calcd. for $C_6H_{12}ClNO$: C, 48.16; H, 8.09. Found: C, 48.11; H, 8.10.

A small amount of this hydrochloride was dissolved in water and the solution evaporated to dryness. The product so obtained melted at 94–95°. It is apparent that the hydrochloride previously reported contains water of crystallization.[15,15a]

**4-Hydroxy-1-methylpiperidine (VIII).**—The hydrochloride from 4.6 g. (0.004 mole) of freshly distilled 1-methyl-4-piperidone was dissolved in 75 cc. of ethanol and the solution shaken, in the presence of 0.3 g. of Adams platinum oxide catalyst, under hydrogen at 3.3 atm. at room temperature for eight hours. After removing the catalyst by filtration and the solvent by distillation, the residue was treated with a few cc. of concentrated alkali and the mixture exhaustively extracted with ether. The ether solution was dried over magnesium sulfate, the ether removed, and the residue distilled to give 3.1 g. (64%) of colorless

(7) Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929).

(8) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(9) Howton, *J. Org. Chem.*, **10**, 277 (1945).

(10) The authors are indebted to F. M. Berger, M.D., the University of Rochester School of Medicine and Dentistry, for the pharmacological tests on these compounds.

(11) Howton[9] reported a b. p. of 102–105° (4 mm.), and Cook and Reed, *J. Chem. Soc.*, 399 (1945), a b. p. of 137–140° (14 mm.).

(12) Howton[9] reported a m. p. of 163.7–164.5°.

(13) This m. p. agrees with that reported by other workers.[7,8,9]

(14) Prill and McElvain[8] reported a b. p. of 56–58° (11 mm.), $n^{25}D$ 1.4580.

(15) Keutel and McElvain, THIS JOURNAL, **53**, 2692 (1931), reported a m. p. of 92–94° for 4-piperidone hydrochloride containing one molecule of water of crystallization.

(15a) (Added in proof) modified procedures for the preparation of compounds V and VIII have been published recently by McElvain and Rorig, *ibid.*, **70**, 1820, 1826 (1948).

TABLE I

QUATERNARY SALTS

| Compound | M. p.,[a] °C. | Yield, % | Formula | Analyses,[b] % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| II[c] | 146 dec. | 65 | $C_{10}H_{20}INO_4$ | 34.79 | 5.84 | 34.71 | 5.96 |
| IV[d] | 127–128 dec. | 60 | $C_9H_{16}INO_3 \cdot 0.5H_2O$ | 33.60 | 5.27 | 33.81 | 5.17 |
| VI[e,f] | 174–179 dec. | 82 | $C_7H_{14}INO$ | 32.95 | 5.53 | 32.60 | 5.41 |
| VII[e] | 182 dec. | 67 | $C_{13}H_{18}BrNO$ | 54.94 | 6.38 | 54.86 | 6.20 |
| IX[d] | 309–311 dec. | 82 | $C_7H_{16}INO$ | 32.70 | 6.27 | 32.74 | 6.15 |

[a] All melting points are corrected. [b] Analyses by Mrs. G. L. Sauvage. [c] Recrystallized from ethanol. [d] Recrystallized from methanol–ether. [e] Not recrystallized. [f] Howton[9] obtained a quaternary salt which analyzed for one molecule of methanol of crystallization, m. p. 187.6–188°.

liquid, b. p. 80–87° (5–6 mm.), $n^{21}D$ 1.4718.[16] The hydrochloride melted at 155–156°.[16]

**Preparation of Quaternary Salts.**—The tertiary amines prepared in the above experiments were converted into quaternary salts by allowing benzene solutions of the distilled amine and excesses of the alkyl halide to stand at room temperature for twenty-four hours, the quaternary salts precipitating as they formed. The salts prepared are listed in Table I.

(16) Mills, Parkin and Ward, *J. Chem. Soc.*, 2613 (1927), reported a b. p. of 105° (18 mm.) and a m. p. for the hydrochloride of 157–158°. Riegel and Reinhard, THIS JOURNAL, **48**, 1334 (1926), reported a b. p. of 116–118° (36 mm.).

## Summary

A number of previously unreported 4-piperidonium and 4-hydroxypiperidinium salts have been prepared. They were found to exhibit mild curariform activity, and one was found to be effective when administered orally.

ROCHESTER 3, NEW YORK RECEIVED JULY 22, 1948

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# Isomeric Dihydroxanthopterins[1]

BY GEORGE H. HITCHINGS AND GERTRUDE B. ELION

Dihydroxanthopterin (2-amino-4,6-dihydroxydihydropteridine) has been prepared by three routes[2,3,4] involving the reduction of a pteridine. Purrmann[2] reduced xanthopterincarboxylic acid catalytically and found the resultant dihydro-acid to be readily decarboxylated to dihydroxanthopterin. Totter[3] was able to isolate the same compound from the reduction of leucopterin (2-amino-4,6,7-trihydroxypteridine) by sodium amalgam, and O'Dell, *et al.*,[4] obtained it directly by the catalytic reduction of xanthopterin (III). The latter were the first to assign a structure to the compound. They made the logical suggestion that the two hydrogen atoms might add across the 7,8 double bond to give 7,8-dihydroxanthopterin (V). The synthesis of (V) by an apparently definitive method, however, has led to a dihydroxanthopterin distinct from that formed by reductive methods. For convenience the compound produced by reductive methods will be called α-dihydroxanthopterin and the synthetic compound, β-dihydroxanthopterin.

The existence of two dihydroxanthopterins where a single substance would have been expected recalls the suggestion (not clearly established) that stable tautomers of certain dihydropyrazines may exist.[5] The establishment of this instance of isomerism has important implications in the field of pteridine chemistry; the resistance of the β-dihydroxanthopterin structure to oxidation may have some bearing on the role of oxidative reactions in the synthesis of folic acid.

β-Dihydroxanthopterin was prepared in these laboratories several years ago as a possible intermediate in the synthesis of xanthopterin, which at that time was believed to have a number of important biological functions.[6,7,8] This compound is, indeed, convertible to xanthopterin but in poor yield (20%) and only under relatively drastic conditions (concentrated sulfuric acid at 210° for fifteen minutes). The α-isomer, on the other hand, can be converted to xanthopterin by a wide range of oxidative procedures, quantitatively by exposure to oxygen in alkaline solution with[2] or without platinum catalyst or by alkaline permanganate oxidation at room temperature.[9] Other properties of the two are compared in Table I. In addition to the observed differences in oxidizability the difference in stability to acid and alkali is noteworthy. The α-isomer is gradually decomposed by acid, giving unidentified colored

(1) Presented before the Division of Organic Chemistry at the New York meeting of the American Chemical Society, September 16, 1947.

(2) Purrmann, *Ann.*, **548**, 284 (1941).

(3) Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(4) O'Dell, Vandenbelt, Bloom and Pfiffner, THIS JOURNAL, **69**, 250 (1947).

(5) D'Albe, translator, "Richter's Organic Chemistry," Vol. III, P. Blakiston's Son and Co., Philadelphia, 1923, p. 284.

(6) Tschesche and Wolf, *Z. physiol. Chem.*, **248**, 34 (1937).

(7) Totter and Day, *J. Biol. Chem.*, **147**, 257 (1943).

(8) Simmons and Norris, *J. Biol. Chem.*, **140**, 679 (1941).

(9) Elion, Light and Hitchings, forthcoming publication.

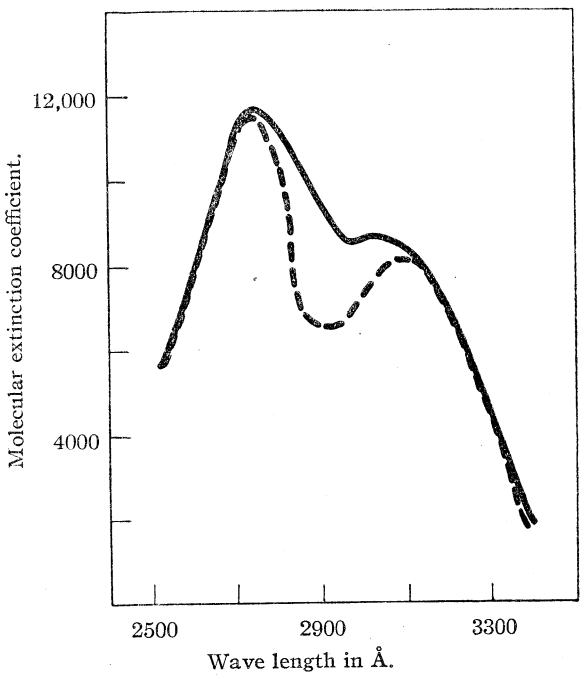



Fig. 1.—Ultraviolet absorption spectra of α-dihydroxanthopterin: —, at *p*H 1.0; ---, at *p*H 3.0.

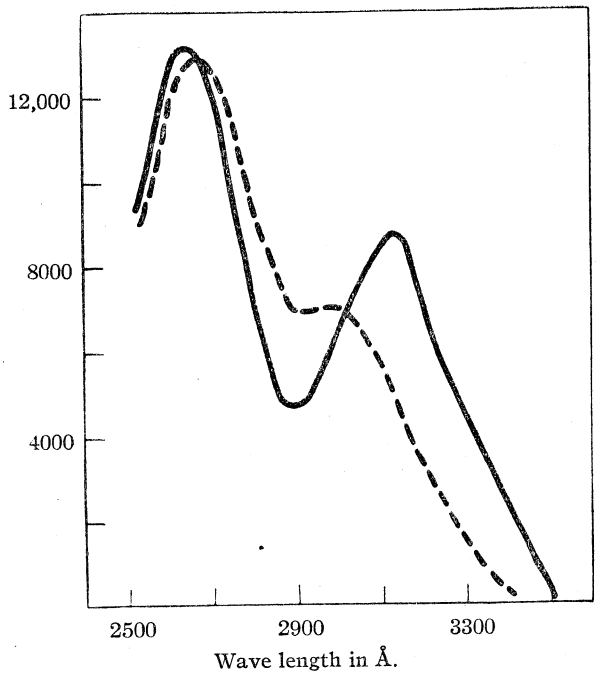



Fig. 2.—Ultraviolet absorption spectra of β-dihydroxanthopterin: —, at *p*H 1.0; ---, at *p*H 3.0.

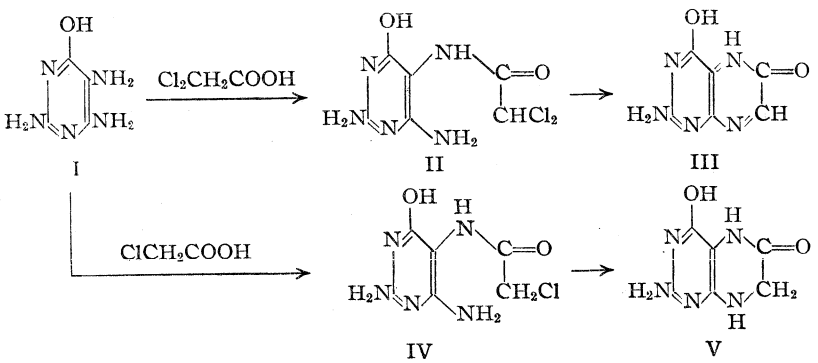
products, but is stable to alkalies. The β-isomer is stable to strong acid, but, as will be shown, the pyrazine ring is cleaved when the compound is warmed with aqueous barium hydroxide. The ultraviolet absorption spectra of the two isomers are similar but distinct (Figs. 1–4). The spectrum of the α-form at *p*H 3 resembles closely that of the β-isomer at *p*H 1, and that of the former at *p*H 1 is similar to that of the latter at *p*H 3 (Figs. 1 and 2). At *p*H 7 the two spectra are dissimilar but at *p*H 11 they are almost indistinguishable (Figs. 3 and 4). The spectra leave little doubt that the two are very closely related.

TABLE I

COMPARISON OF PROPERTIES OF DIHYDROXANTHOPTERINS

| Reagent | α | β |
|---|---|---|
| Hot acetic acid | Decomposition | Recrystallization |
| $O_2$ (Pt catalyst) | To xanthopterin | Not oxidized |
| $O_2$ (air-alkali) | To xanthopterin | Not oxidized |
| Permanganate | 2/5 mole → xanthopterin<br>4/5 mole → glycol (?) | 2/5 mole → glycol(?) |
| Barium hydroxide | Barium salt | Ring fission |
| Ferric chloride | Red color | No color |

The first synthesis of xanthopterin by Purrmann[10] was carried out by treatment of 2,4,5-triamino-6-hydroxypyrimidine (I) with dichloroacetic acid, followed by heating the silver salt of the dichloroacetamide (II) in the presence of silver carbonate to effect ring closure to xanthopterin (III). The synthesis of 7,8-dihydroxanthopterin, which is reported here, follows a similar route. The pyrimidine (I) is heated with monochloroacetic acid to give the chloroacetamide (IV) and ring closure follows a relatively mild treatment (aqueous bicarbonate at 95°) to give the dihydroxanthopterin (V). This synthesis is straightforward and the validity of the structures assigned to the intermediate (IV) and product (V) must be regarded as highly probable on *a priori* grounds. However, it is worth while to consider other possible reaction mechanisms and products. Such considerations have led to additional evidence confirming the structure of β-dihydroxanthopterin and incidentally to the discovery of a new heterocyclic, the oxazinopyrimidine, system.




(10) Purrmann, *Ann.*, **546**, 98 (1941).

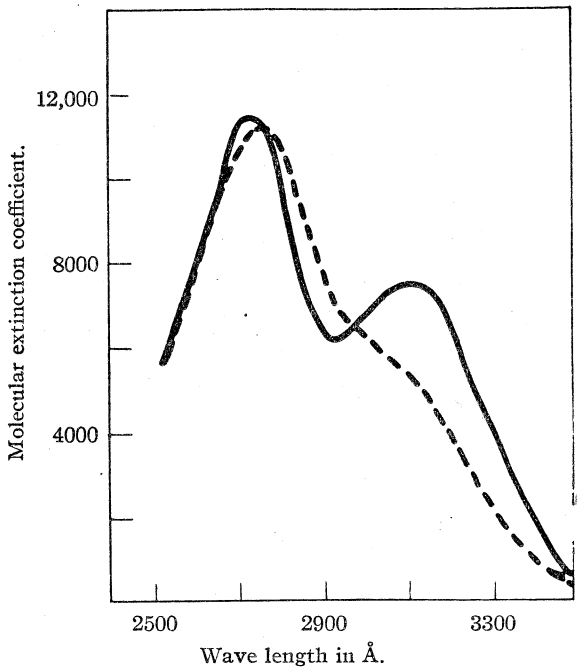



Fig. 3.—Ultraviolet absorption spectra of α-dihydroxanthopterin: —, at *p*H 7.0; ---, at *p*H 11.0.

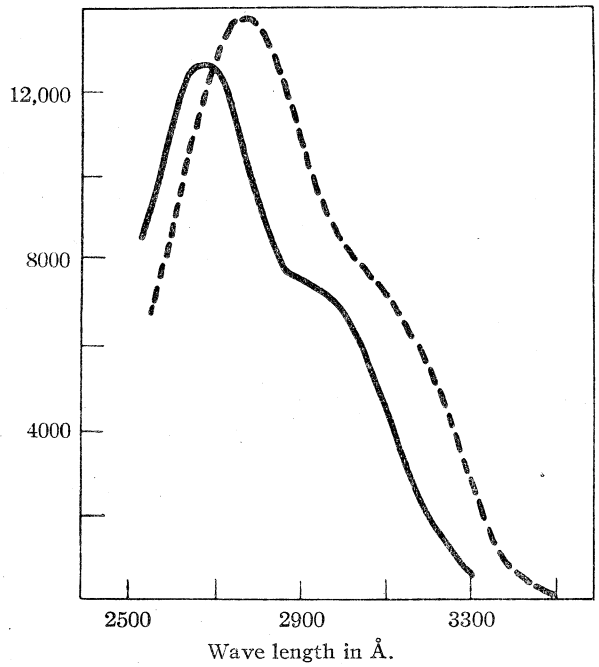



Fig. 4.—Ultraviolet absorption spectra of β-dihydroxanthopterin: —, at *p*H 7.0; ---, at *p*H 11.0.

The allocation of the chloroacetyl group of the intermediate (IV) to the 5′ position rests ultimately on the purine syntheses of Traube[11,12,13] who found 4,5-diaminopyrimidines to be acylated to monoacyl derivatives which could be converted to purines. By methylation of 1,3-dimethyl-2,6-dihydroxy-4 (or 5)-amino-5 (or 4)-formamidopyrimidine, Traube[12] obtained a trimethyl derivative from which caffeine was obtained on ring closure. On the basis of this evidence the formyl group was assigned to the 5′ position, since only the formamido group could provide the acidic hydrogen necessary for methylation. By analogy the other acylamino groups were believed to occupy the 5-position and the greater reactivity of the 5-amino group, in acylations, as compared with the 4 is a generally accepted principle of pyrimidine chemistry,[11,14] to which no exceptions have been published. To this evidence may now be added that afforded by spectrography. Using 2,4-diamino-5-formamido-6-hydroxypyrimidine and the parent triaminohydroxypyrimidine (I) as reference compounds, it is seen that acylation of the 5-amino group results in little change in the absorption spectrum at *p*H 1, but prevents the shift of absorption bands which characterizes the alkaline (*p*H 11) spectrum (Figs. 5 and 6). The chloroacetyl derivative (IV) resembles the formyl derivative so closely as to leave little doubt as to their similarity in structure (Fig. 7). Moreover, the relation of these spectra to those of the parent compounds shows a marked resemblance to that between 5-chloroacetamido-2-amino-4,6-dihydroxypyrimidine (Fig. 8) and 2,5-diamino-4,6-dihydroxypyrimidine (Fig. 9).

If the structure (IV) for the chloroacetamido derivative be granted, there remain to be considered the purine (VI) and the oxazine (VII) as possible products of the ring closure. The more remote possibility that one molecule of (IV) might alkylate another with subsequent hydrolysis and the formation of an hydantoin derivative[15] can be eliminated since such reactions could yield at most 50% of the theoretical amount of product whereas in practice a yield of 70% was obtained. The closure of the imidazole ring to give 8-hydroxymethylguanine (VI) would be expected to require much more drastic conditions than those employed.[13] Actually, attempts to form this compound by heating the sodium salt of either (IV) or the corresponding hydroxyacetyl derivative failed to give isolable amounts of this compound. However, (VI) would be expected to have an ultraviolet absorption spectrum nearly identical with that of 8-methylguanine. The dissimilarity of the spectra of the latter (Fig. 10) and β-dihydroxanthopterin (Figs. 2 and 4) is at once apparent.

The oxazine derivative (VII) can be eliminated from consideration in this connection by comparison of β-dihydroxanthopterin with derivatives of the oxazinopyrimidine structure. Compounds related to (VII) but lacking the 4-amino group (thereby excluding the pteridine structure) have been prepared from 4-methyl-5-chloroacetamido-

(11) Traube, *Ber.*, **33**, 1371 (1900).
(12) Traube, *ibid.*, **33**, 3035 (1900).
(13) Traube, *Ann.*, **432**, 266 (1923).
(14) Purrmann, *ibid.*, **548**, 284 (1941).
(15) Russell, Elion and Hitchings, forthcoming publication, p. 474.

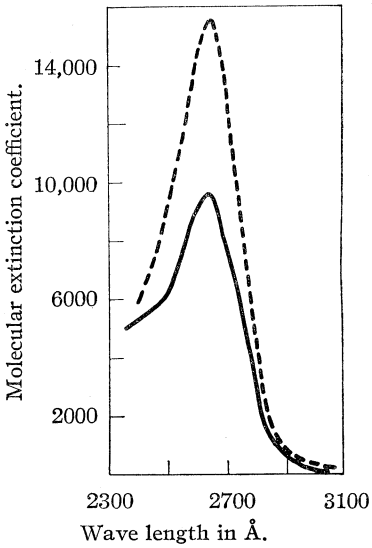



Fig. 5.—Ultraviolet absorption spectra of 2,4-diamino-5-formamido-6-hydroxypyrimidine: —, at *p*H 1.0; ---, at *p*H 11.0.

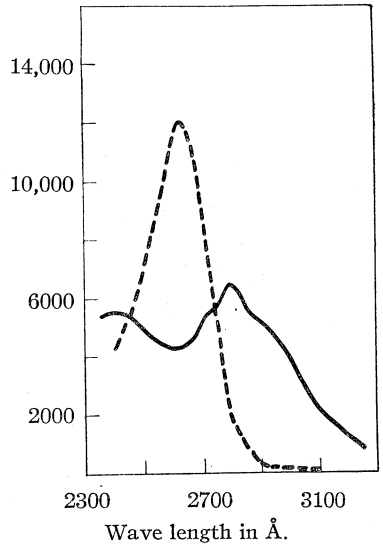



Fig. 6.—Ultraviolet absorption spectra of 2,4,5-triamino-6-hydroxypyrimidine: —, at *p*H 1.0; ---, at *p*H 11.0.

6-hydroxypyrimidines by heating with aqueous barium hydroxide.[15] There is, indeed, spectrographic evidence that the diamino derivative (VII) is formed under these conditions, though it has not yet been obtained in a pure state. Moreover, β-dihydroxanthopterin is unstable under the conditions of formation of the oxazine derivatives. The α-isomer gives only a barium salt, but the β-isomer adds the elements of water to give an acid (VIII) which can be esterified (IX). Both acid and ester revert to β-dihydroxanthopterin, the ester spontaneously in aqueous solution, the acid on warming with mineral acid. The ultraviolet absorption spectrum of the acid (VIII) is given in Fig. 11. It is consistent with that of a pyrimidine with a free amino group in the 5-position (*cf.* Compound 1 in Fig. 5). Moreover, the grouping —$NHCH_2CO_2H$ is indicated by the positive ninhydrin reaction obtained with the product of permanganate oxidation. The spectrum of (IX) is similar to that of the acid (VIII) at *p*H 1 but at *p*H 11 it is that of the β-dihydroxanthopterin indicating rapid and nearly quantitative ring closure.

The structure of β-dihydroxanthopterin appears to be established. No definitive evidence to decide the structure of the α-isomer is available. It is obviously possible to formulate the structure in a great many ways, but most of the formulations, such as (X), would be expected to be tautomeric with (V). Structures (XI) and (XII) represent types which are not necessarily obvious equivalents of (V) and for which some precedents exist. Each would be derived by hydrogenation of a C—N double bond of a xanthopterin of type (XIII) or (XIV). Biltz[16] has shown the existence among substituted uric acids of bond arrangements similar to those of (XI), (XII) and (XIII) while van Veen and Baars[17] have proposed a structure for toxoflavin with a bond arrangement simi-

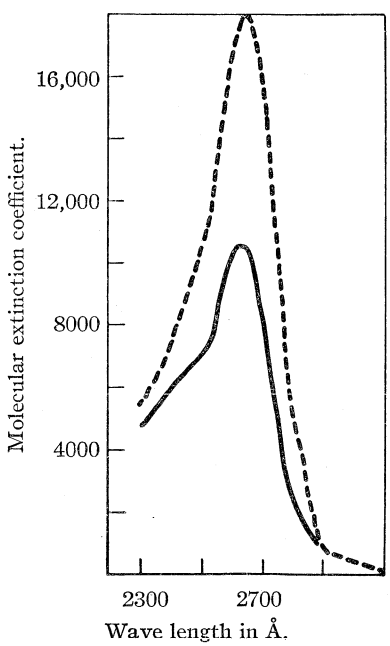



Fig. 7.—Ultraviolet absorption spectra of 2,4-diamino-5-chloroacetamido-6-hydroxypyrimidine: —, at *p*H 1.0; ---, at *p*H 11.0.

lar to that of (XIV). Obviously a considerable body of facts may be required to establish the fine structure of α-dihydroxanthopterin.

(16) Biltz, *J. prakt. Chem.*, **145**, 65 (1936).

(17) van Veen and Baars, *Rec. trav. chim.* **57**, 248 (1938).

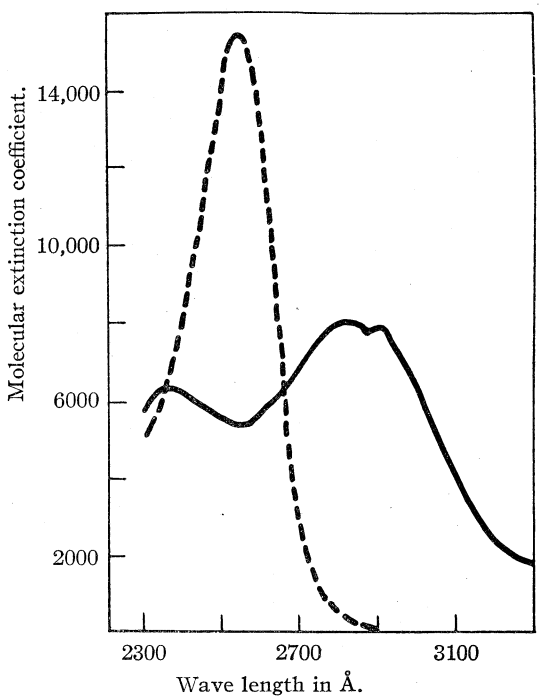



Fig. 8.—Ultraviolet absorption spectra of 2,5-diamino-4,6-dihydroxypyrimidine: —, at *p*H 1.0; ---, at *p*H 11.0.

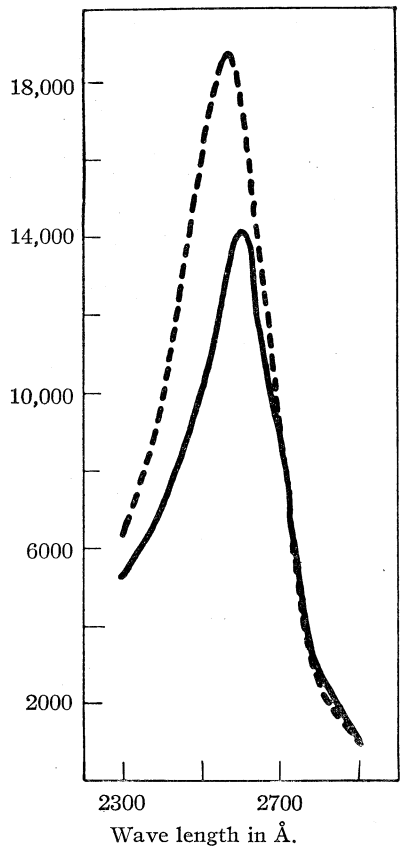
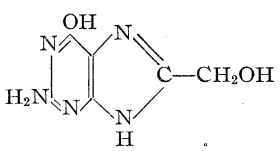
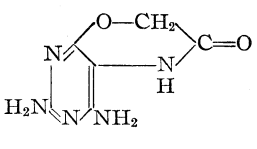
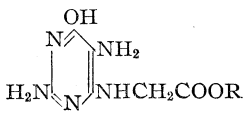
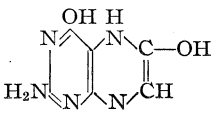


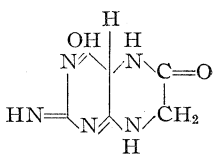

Fig. 9.—Ultraviolet absorption spectra of 5-chloroacetamido-2-amino-4,6-dihydroxypyrimidine: —, at *p*H 1.0; ---, at *p*H 11.0.

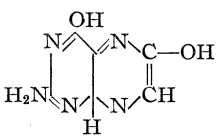

(VI)

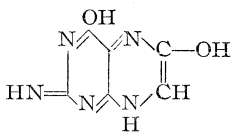

(VII)

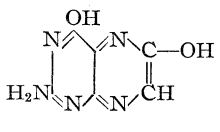

(VIII), R = H
(IX), R = $CH_3$


(X)


(XI)


(XII)


(XIII)


(XIV)

## Experimental

**2,4-Diamino-5-chloroacetamido-6-hydroxypyrimidine (IV).**—A well-ground mixture of 8 g. of 2,4,5-triamino-6-hydroxypyrimidine[11] and 24 g. of monochloroacetic acid was heated in a boiling water-bath for one hour, with intermittent evacuation of the reaction flask. After cooling, the reaction mixture was leached several times with ether to remove the excess chloroacetic acid and then recrystallized from 300 ml. of 0.2 *M* sodium acetate–acetic acid buffer of *p*H 5. The precipitate after standing overnight at 5° consisted partly of pale yellow platelets and partly of amorphous material. It was washed with water and acetone and air dried. Yield was 12.7 g. (95%). A sample was recrystallized twice from dilute acetate buffer for analysis. The crystalline monohydrate loses its water of crystallization at 130° *in vacuo*, but regains it completely on exposure to air for twenty minutes. This rapid absorption of water from the air probably accounts for the low analytical value obtained for water of crystallization.

*Anal.* Calcd. for $C_6H_8O_2N_5Cl \cdot H_2O$: C, 30.42; H, 4.23; N, 29.6; $H_2O$, 7.6. Found: C, 30.64; H, 4.10; N, 29.5; $H_2O$, 5.7.

**β-Dihydroxanthopterin (V).**—A solution of 11.9 g. (0.05 mole) of 2,4-diamino-5-chloroacetamido-6-hydroxypyrimidine and 8.4 g. (0.1 mole) of sodium bicarbonate in 350 ml. of water was kept at 95° for two hours. A yellow precipitate formed gradually. After cooling, the product was filtered, washed with water, and dried at 100°. The yield was 6.2 g. (68.5%). It loses no water on drying at 150°. For analysis, a sample was recrystallized from glacial acetic acid.

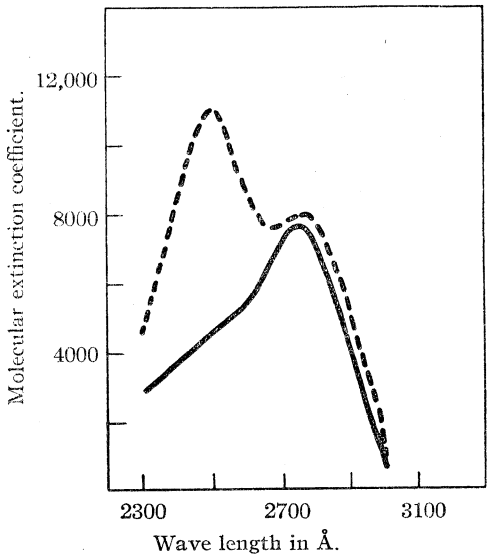



Fig. 10.—Ultraviolet absorption spectra of 8-methylguanine: —, at *p*H 1.0; --- at *p*H 11.0.

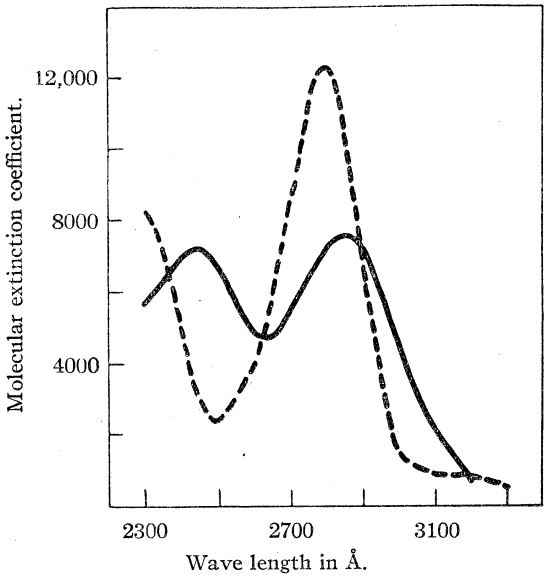



Fig. 11.—Ultraviolet absorption spectra of acid VIII (2,5 - diamino - 6 - hydroxy - 4 - carboxymethylaminopyrimidine): —, at *p*H 1.0; ---, at *p*H 11.0.

*Anal.* Calcd. for $C_6H_7O_2N_5$: C, 39.79; H, 3.87; N, 38.7. Found: C, 39.77; H, 4.17; N, 38.5.

The compound is soluble in about 5000 parts of boiling water, readily in warm 2.5 *N* hydrochloric acid, from which the monohydrochloride crystallizes on cooling as needles.

*Anal.* Calcd. for $C_6H_7O_2N_5 \cdot HCl$: Cl, 16.3. Found: Cl, 16.7.

The sulfate crystallized in colorless prisms from 3 *N* sulfuric acid as a tetrahydrate. Three moles of water were lost at 120°, leaving a monohydrate which does not lose the remaining mole of water at 150°.

*Anal.* $(C_6H_7O_2N_5)_2 \cdot H_2SO_4 \cdot 4H_2O$: Calcd. for 3 $H_2O$, 10.03. Found: 10.03 (after drying at 150° for two hours). Calcd. for $(C_6H_7O_2N_5)_2 \cdot H_2SO_4 \cdot H_2O$: C, 30.13; H, 3.76. Found: C, 30.44; H, 3.77.

The picrate crystallized in bundles of small, dark yellow needles when aqueous picric acid was added to a hot aqueous solution of β-dihydroxanthopterin. After recrystallization from 30% aqueous acetic acid containing 0.3% picric acid, the picrate sinters at about 185° and melts with decomposition at about 265°.

**Oxidation of β-Dihydroxanthopterin.**—Attempts to oxidize β-dihydroxanthopterin to xanthopterin catalytically in alkaline solution or in glacial acetic acid, as described by O'Dell, *et al.*, for the oxidation of α-dihydroxanthopterin,[4] led only to recovery of the starting material. With silver oxide considerable decomposition occurred.

Treatment of β-dihydroxanthopterin with neutral permanganate solution resulted in the consumption of two equivalents of permanganate to form a soluble compound with no absorption band in the ultraviolet. This product, which is presumably a glycol, gives a strong ninhydrin reaction after being boiled with alkali.

A solution of 250 mg. of β-dihydroxanthopterin in 5 ml. of concentrated sulfuric acid was heated at 210° for fifteen minutes. The mixture was allowed to cool and then poured over 25 g. of ice. An amorphous brown precipitate was centrifuged off. The supernatant liquid was neutralized to about *p*H 6 with sodium hydroxide solution and the amorphous orange precipitate removed at once by centrifugation. This precipitate, after purification, consisted of 50 mg. of xanthopterin, as shown by its ultraviolet absorption spectrum. The neutralized reaction mixture, on longer standing, deposited 40 mg. of unreacted β-dihydroxanthopterin also.

**Alkaline Degradation of β-Dihydroxanthopterin to the Acid (VIII).**—A solution of 0.4 g. (0.0022 mole) of β-dihydroxanthopterin in 15 ml. of hot water containing 0.63 g. (0.002 mole) of barium hydroxide octahydrate was heated in a boiling water-bath for six hours and allowed to stand at room temperature overnight. The reaction mixture was diluted to 50 ml. and treated with an excess of sodium sulfate to remove the barium ion. After removal of the barium sulfate the solution was acidified with acetic acid. The yellow crystalline precipitate which formed was filtered off, washed with water and alcohol and air dried (0.2 g.). A sample of this precipitate was purified for analysis by solution in very dilute sodium hydroxide, treatment with carbon and acidification of the hot solution with acetic acid. On cooling, bunches of small colorless needles were formed. The compound does not melt below 350°. It loses its water of crystallization at 120°.

*Anal.* Calcd. for $C_6H_9N_5O_3 \cdot 1.5H_2O$: C, 31.86; H, 5.32; N, 31.0; $H_2O$, 11.95. Found: C, 32.33; H, 6.06; N, 31.0; $H_2O$, 12.20.

When the degradation product (VIII) was boiled with 0.2 *N* hydrochloric acid for a few minutes and the solution neutralized with sodium acetate, the precipitate which formed was identified as β-dihydroxanthopterin by its absorption spectrum.

**Esterification of the Acid (VIII).**—To 12.5 ml. of absolute methanol containing 1 g. of hydrogen chloride was added 150 mg. of VIII. The solution was allowed to stand at room temperature overnight and then evaporated to dryness *in vacuo* below 40°. The solid yellow residue was dissolved in 3 ml. of absolute methanol and precipitated by the slow addition of 125 ml. of absolute ether. The yield of the ester dihydrochloride was 180 mg. (83%). The compound is converted to β-dihydroxanthopterin by heating to about 200°, by solution in alkali, or simply on standing in aqueous solution. Attempts to purify the ester further led in general to less pure material presumably because of the tendency to spontaneous ring closure.

*Anal.* Calcd. for $C_7H_{11}N_5O_3 \cdot 2HCl$: C, 29.38; H, 4.55; Cl, 24.8. Found: C, 29.95; H, 4.50; Cl, 24.0.

The ultraviolet absorption spectrum of the ester (IX) is almost identical with that of the acid (VIII) at *p*H 1 (Fig. 11). When an attempt was made to measure the spectrum of IX at *p*H 11, the spectrum was found to be identical with that of β-dihydroxanthopterin at *p*H 11 (Fig. 4). This ring closure was confirmed when the

alkaline solution was reacidified to *p*H 1 and the spectrum found to be identical with that of β-dihydroxanthopterin at *p*H 1 (Fig. 2).

**α-Dihydroxanthopterin.**—This isomer was prepared by the reduction of leucopterin by sodium amalgam[3] and by the decarboxylation of dihydroxanthopterincarboxylic acid.[2] The ultraviolet absorption spectra of the samples prepared in these two ways are identical and agree with the published spectrum of the product prepared by O'Dell, *et al.*,[4] by the catalytic reduction of xanthopterin (Figs. 1 and 3).

The sample prepared by the reduction of leucopterin was purified *via* the sodium salt as described by Elion, Light and Hitchings[9] and then recrystallized from 250 parts of hot water. The pale yellow elongated prisms which precipitated on cooling contained one mole of water after being dried at 100°. One half of the water of crystallization is lost at 130°, the other half at 150°. When the anhydrous compound is exposed to the air, it quickly regains one-half mole of water to form the stable hemihydrate.

*Anal.* Calcd. for $C_6H_7O_2N_5 \cdot H_2O$: C, 36.2; H, 4.52; $H_2O$, 9.05. Found: C, 36.44; H, 4.44; $H_2O$ (dried at 130° for two hours), 4.52; $H_2O$ (dried at 150° for two hours), 9.10.

When α-dihydroxanthopterin was boiled with glacial acetic acid, the solid material as well as the solution turned dark red. This red product no longer has the spectrum of α-dihydroxanthopterin and has not yet been identified. Its analysis is: C, 36.90; H, 3.42; N, 31.4. Calcd. for $C_7H_8N_5O_4$: C, 37.2; H, 3.54; N, 31.0.

An attempt to cleave α-dihydroxanthopterin by hot barium hydroxide solution led only to the precipitation of an insoluble barium salt which remained unchanged.

The sulfate monohydrate was prepared by the addition of 4 ml. of concentrated sulfuric acid to a solution of 0.5 g. of α-dihydroxanthopterin in 25 ml. of 2 *N* sulfuric acid. It was filtered, washed with acetone and air dried.

*Anal.* Calcd. for $(C_6H_7O_2N_5)_2 \cdot H_2SO_4 \cdot H_2O$: C, 30.13; H, 3.76. Found: C, 29.77; H, 3.73.

The picrate, formed on the addition of one volume of saturated aqueous picric acid solution to a hot aqueous solution of α-dihydroxanthopterin, crystallized as pinkish-orange needles and prisms. It turned brown at about 330° and did not melt at 370°.

**Oxidation of α-Dihydroxanthopterin.**—The spontaneous oxidation of this isomer to xanthopterin in alkaline solution as well as its catalytic oxidation in glacial acetic acid have been previously described.[2,4] It is also oxidized to xanthopterin by silver oxide[3] and by alkaline potassium permanganate.[9] The oxidation with permanganate proceeds beyond the xanthopterin stage if more than two equivalents are used, forming a soluble substance which may be a glycol since it no longer exhibits the ultraviolet absorption band characteristic of the pyrimidine ring structure. After alkaline solutions of this substance have been boiled, the resulting solutions give a strong ninhydrin reaction.

**2,5-Diamino-4,6-dihydroxypyrimidine.**—This compound was prepared by the method of Traube[18] except that the reduction of the 2-amino-5-nitroso-4,6-dihydroxypyrimidine was carried out more easily and in better yield by addition of an excess of sodium hydrosulfite to the ammoniacal suspension of the unisolated nitroso compound rather than by the use of hydrogen sulfide.

**2-Amino-5-chloroacetamido-4,6-dihydroxypyrimidine.**—A mixture of 5 g. of 2,5-diamino-4,6-dihydroxypyrimidine and 13 g. of chloroacetic anhydride was heated in a boiling water bath for one hour, cooled, leached several times with ether and filtered. The insoluble residue was then leached with 150 ml. of sodium acetate–acetic acid buffer of *p*H 5, filtered, washed with water and acetone and dried at 100°. The yield of this crude material was 6.7 g. (80%). A sample was recrystallized from 150 parts of hot water for analysis and dried at 100°.

*Anal.* Calcd. for $C_6H_7N_4O_3Cl \cdot H_2O$: C, 30.44; H, 3.8. Found: C, 30.85; H, 4.05.

**8-Methylguanine.**—This was prepared by the method of Traube[13] from 2,4-diamino-5-acetamido-6-hydroxypyrimidine.

**Ultraviolet Absorption Spectra.**—The spectra were measured with a Beckman spectrophotometer using solutions containing 10 mg. per liter. For solutions of *p*H 1, 0.1 *N* hydrochloric acid was used; for *p*H 3, 0.001 *N* hydrochloric acid; for *p*H 7, a Sörensen phosphate buffer; for *p*H 11, a glycine–sodium hydroxide buffer.

**Acknowledgment.**—We are indebted to Walter S. Ide and Samuel W. Blackman for the microanalyses reported here.

## Summary

The synthesis of 7,8-dihydroxanthopterin from 2,4 - diamino - 5 - chloroacetamido - 6 - hydroxypyrimidine is reported. This isomer, called β-dihydroxanthopterin, differs from the α-dihydroxanthopterin, which is formed by the reduction of pteridine derivatives, in several chemical properties. It is more resistant to oxidation and more stable to acid but more readily cleaved by alkali than the α-isomer. The significance of these observations in relation to the arrangement of the double bonds in pteridine derivatives is discussed.

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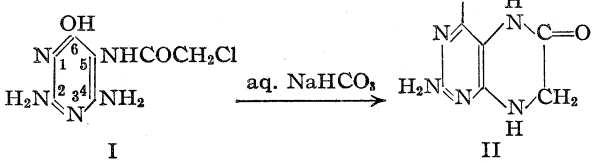
(18) Traube, *Ber.*, **26**, 2556 (1893).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# A New Condensed Pyrimidine System: Some *p*-Oxazino[2,3-*d*]pyrimidines[1]

BY PETER B. RUSSELL, GERTRUDE B. ELION AND GEORGE H. HITCHINGS

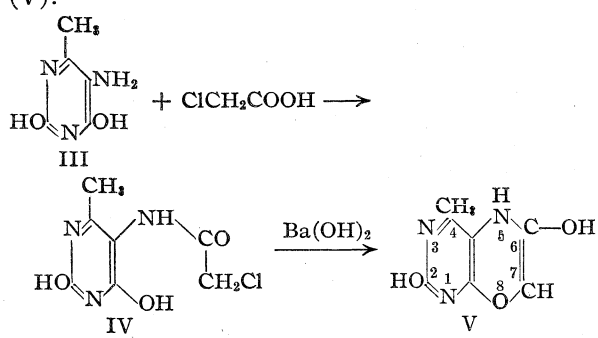
The synthesis of a new isomer of dihydroxanthopterin (II) by the ring closure of 5-chloroacetamido-2,4-diamino-6-hydroxypyrimidine (I) with sodium bicarbonate solution has been reported.[2]




I II

During the investigation of methods for closure of the dihydropyrazine ring other alkaline reagents were studied, and barium hydroxide was found to give a product whose ultraviolet absorption spectrum was different from that of I, II or the $\alpha$-dihydroxanthopterin of O'Dell and co-workers.[3] Although this new compound was not isolated in pure form, the possibility that ring closure involving the 6-hydroxyl group had taken place was suggested. By analogy with the formation of 3-hydroxy-[benz-*p*-oxazine][4] from *o*-chloroacetamidophenol by treatment with potassium hydroxide solution, it appeared probable that the product obtained by the action of barium hydroxide on I was a member of the hitherto unknown group of substances, the *p*-oxazino[2,3-*d*]pyrimidines.

In order to eliminate the possibility of pteridine formation, 5-chloroacetamido-6-hydroxypyrimidines were prepared which did not carry amino groups at position 4 and these were heated with aqueous barium hydroxide. After failure to isolate any of the desired compounds from 5-chloroacetamidouracil or from 5-chloroacetamido-2-amino-6-hydroxypyrimidine, an experiment with 5-chloroacetamido-2,6-dihydroxy-4-methylpyrimidine, (IV) produced a colorless, crystalline compound, $C_7H_7O_3N_3$, which was believed to be 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (V).



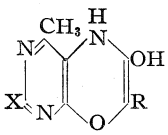

(1) Presented before the Chicago, Ill., meeting of the American Chemical Society, April, 1948.

(2) Hitchings and Elion, THIS JOURNAL, **71**, 467 (1949).

(3) O'Dell, Vandenbelt, Bloom and Pfiffner, *ibid.*, **69**, 250 (1947).

(4) Aschan, *Ber.*, **20**, 1524 (1887).

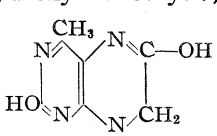
Similar compounds (VI, VII and VIII) were formed from the 2-amino-, 2-methylamino- and 2-dimethylaminopyrimidines corresponding to IV, and two 4,7-dimethyl-*p*-oxazino[2,3-*d*]pyrimidines, IX and X, were prepared from the appropriate 5-$\alpha$-bromopropionamido derivatives. The reaction failed to occur with the 2-methyl analog of IV or with 5-($\alpha$-chlorophenylacetamido)-4-methyl-2,6-dihydroxypyrimidine.



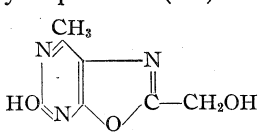

| | | |
|---|---|---|
| VI | X = $NH_2$ | R = H |
| VII | X = $CH_3NH$ | R = H |
| VIII | X = $(CH_3)_2N$ | R = H |
| IX | X = OH | R = $CH_3$ |
| X | X = $NH_2$ | R = $CH_3$ |

In order to prove the structure of these substances, compound V was chosen for more intensive study. The absorption spectrum of V (Fig. 1) was found to have two bands, one of them in the region usually associated with the pyrimidine ring, the second in the higher wave lengths. Hence, the spectrum was consistent with the formulation of the compound as a condensed pyrimidine system. Hydrolysis of V with concentrated hydrochloric acid at 100° resulted in recovery of the pyrimidine (III) showing that there had been no structural changes in the original pyrimidine nucleus during treatment with barium hydroxide. It also ruled out the possibility that one of the nitrogens of the pyrimidine ring may have been alkylated either inter- or intramolecularly by the chloroacetyl group with a subsequent hydrolysis of the amide linkage or linkages. Hydantoin formation would give a product with the observed empirical composition; however, the pyrimidine-N-acetic acids do not hydantoinize.[5] Moreover, such a pyrimidine-N-acetic acid derivative would not be split to the parent pyrimidine III under the rather mild conditions employed.

Additional evidence in favor of the *p*-oxazinopyrimidine structure was obtained when V was heated with concentrated ammonium hydroxide at 120° in a closed system. The product obtained gave an analysis corresponding to the formula $C_7H_8O_2N_4$ and had an absorption spectrum resembling that of a dihydropteridine (Fig. 2), *cf.* ref. (2). It is therefore considered to be 2,6-dihydroxy-4-methyl-7,8-dihydropteridine(XI).




XI




XII

There remained one further possibility to be

(5) Wheeler and Liddle, THIS JOURNAL, **30**, 1154 (1908).

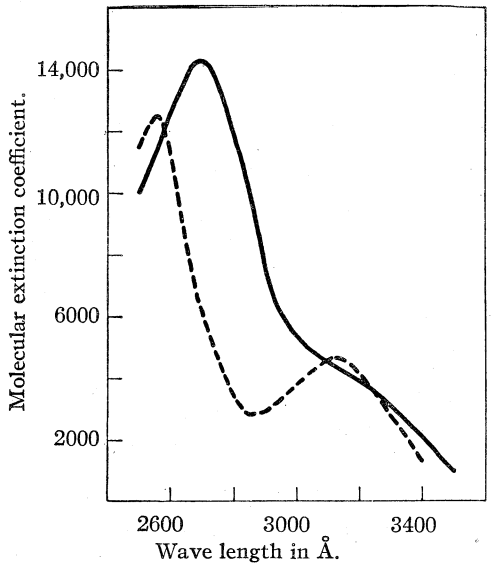
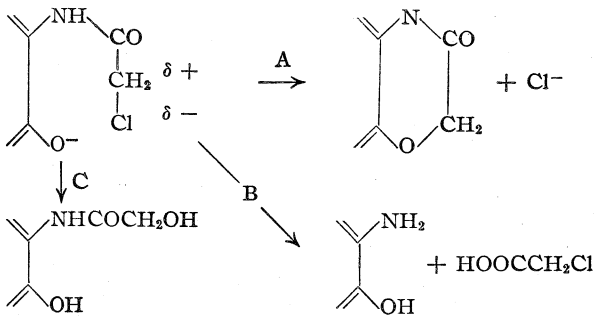


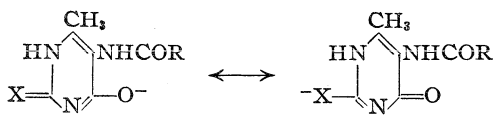

Fig. 1.—Ultraviolet absorption spectra of 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine: - - -, at *p*H 1.0; —, at *p*H 11.0.

considered before the structure of V could be regarded as unequivocally established, namely, that a hydroxymethyloxazolo[2,3-*d*]pyrimidine of type XII had been formed. The mode of formation,[6] the structural requirements for ring closure,[7] and the physical properties[7] of the two groups of compounds are so widely different as to leave little doubt that this oxazolo structure can be eliminated from consideration here.

In view of the limitations of this method for the synthesis of *p*-oxazinopyrimidines, it was decided to investigate further the mechanism of the ring closure. The oxazines are formed as a result of reaction A, but the low yields indicate that other reactions, of which B and C are the most probable, are competing with it.




The extent to which reaction A proceeds would be expected to depend on the ease of ionization of the 6-hydroxyl group, and the acid strength of this group would be governed by resonance of the type shown




Thus a greater excess of barium hydroxide is necessary to obtain the maximum yield of (VI), X = NH, than is necessary for (V), X = O (Fig. 3). Where X is a group incapable of taking part in resonance of this type (*e. g.*, methyl), the formation of the oxazine would be expected only at com-

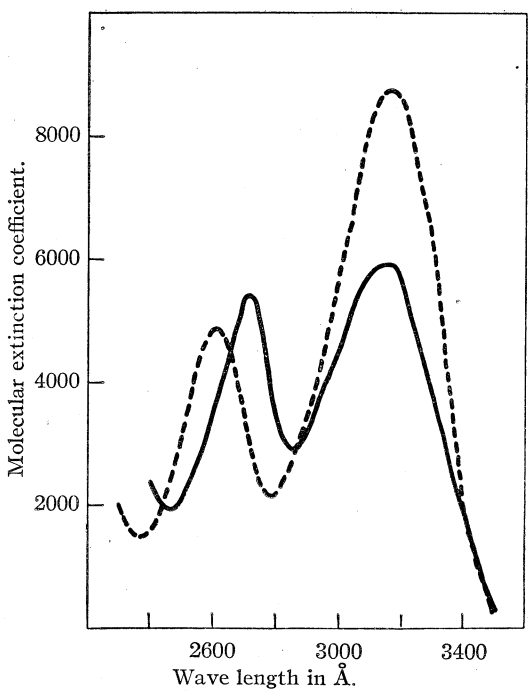



Fig. 2.—Ultraviolet absorption spectra of 2,6-dihydroxy-4-methyl-7,8-dihydropteridine: - - -, at *p*H 1.0; —, at *p*H 11.0.

(6) Johnson, *Am. Chem. J.*, **34**, 203 (1905).
(7) Falco and Hitchings, forthcoming publication.

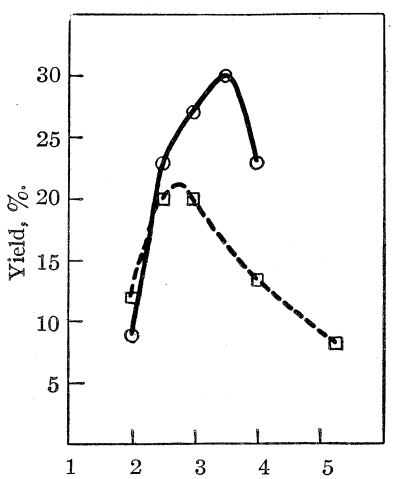



Fig. 3.—Relationship between barium hydroxide concentration and yield of: —⊙—, 2-amino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine; - - -⊡- - -, 2,6-dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine.

paratively high concentrations of barium hydroxide, conditions which favor reactions B and/or C. This may account for the failure to isolate any *p*-oxazinopyrimidine in the case of 5-chloroacetamido-2,4-dimethyl-6-hydroxypyrimidine. Similar considerations may explain the failure of sodium hydroxide and sodium methoxide to effect ring closure in any of several attempts.

## Experimental

**5-Chloroacetamido-2,6-dihydroxy-4-methylpyrimidine (IV).**—An intimate mixture of 0.5 g. of 5-amino-2,6-dihydroxy-4-methylpyrmidine[8] and 2 g. of chloroacetic acid was heated in a boiling water-bath under vacuum for two hours. The cooled mass was extracted with ether, washed with sodium bicarbonate solution and recrystallized from 50% aqueous ethanol. It formed colorless needles, m. p. 257–258° (dec.), (0.75 g., 98%).

*Anal.* Calcd. for $C_7H_8O_3N_3Cl$: C, 38.6; H, 3.5. Found: C, 38.9; H, 3.7.

**2,6-Dihydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (V).**—5-Chloroacetamido-2,6-dihydroxy-4-methylpyrimidine (0.5 g.) was heated with 30 ml. of a solution containing 1.12 g. of barium hydroxide hydrate (3 equivs. of $Ba(OH)_2 \cdot 8H_2O$). After about one-half hour a crystalline barium salt separated; heating was continued for another hour. The warm solution was treated with an excess of sodium sulfate, the barium sulfate filtered off and the solution made faintly acidic with acetic acid. On standing, the oxazinopyrimidine separated as colorless prisms (0.10 g., 30%). On crystallization from water, it formed elongated prisms, m. p., 348–349° (dec.).

*Anal.* Calcd. for $C_7H_7O_3N_3$: C, 46.4; H, 3.9; N, 23.2. Found: C, 46.5; H, 3.7; N, 23.5.

**Hydrolysis of V with Hydrochloric Acid.**—One hundred mg. of V was dissolved in 5 ml. of concentrated hydrochloric acid and the solution was heated on the steam-bath for twenty hours. The hydrochloric acid and water were removed by evaporation to dryness several times in an open dish. The residue was dissolved in 2 ml. of water and saturated sodium acetate solution was added until the *p*H was about 7. Slightly yellow plates separated (80 mg.) with a m. p. of 257° (dec.). Mixed with an authentic sample of 5-amino-2,6-dihydroxy-4-methylpyrimidine (m. p., 256–259°), the m. p. was 258–260°. Its absorption spectrum in acid and in alkaline solution was identical with that of 5-amino-2,6-dihydroxy-4-methylpyrimidine.

**Treatment of V with Ammonium Hydroxide.**—One hundred mg. of V was heated in a sealed tube with 10 ml. of concentrated ammonium hydroxide solution at 120° for six hours. The contents were filtered and evaporated to dryness on the steam-bath. The residue was treated with 5 ml. of water and acidified with acetic acid; the solution had a blue fluorescence. The brownish material was filtered off, dissolved in water, treated with carbon and the filtrate was evaporated to dryness. It decomposed at 305–310° without melting.

*Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.6; H, 4.5; N, 31.1. Found: C, 47.0; H, 4.4; N. 31.2.

**5-α-Bromopropionamido-2,6-dihydroxy-4-methylpyrimidine.**—This was prepared by heating 0.5 g. of 5-amino-2,6-dihydroxy-4-methylpyrimidine with 2.5 g. of α-bromopropionic acid. The product was obtained in almost quantitative yield. It was almost insoluble in hot alcohol. Recrystallized from water it formed colorless needles, m. p. 275–276° (dec.).

*Anal.* Calcd. for $C_8H_{10}O_3N_3Br$: C, 34.9; H, 3.3. Found: C, 35.0; H, 3.3.

**2,6-Dihydroxy-4,7-dimethyl-*p*-oxazino[2,3-*d*]pyrimidine (IX).**—The α-bromopropionamido derivative (0.3 g.) described above was heated with 30 ml. of an aqueous solution of barium hydroxide containing 0.57 g. (3 equiv.) of the hydrate in a boiling water-bath for one and one-half hours. After precipitation of the barium as sulfate, the solution was filtered and acidified with acetic acid. The oxazinopyrimidine crystallized slowly (0.08 g.). When recrystallized from water it formed stout colorless needles, m. p. 338–340° (dec.).

*Anal.* Calcd. for $C_8H_9O_3N_3$: C, 49.2; H, 4.6; N, 21.4. Found: C, 49.3; H, 4.6; N, 21.4.

**5-Benzeneazo-2-amino-6-hydroxy-4-methylpyrimidine.**—Guanidine hydrochloride (19.2 g.) was added to a solution of 44 g. of ethyl benzeneazoacetoacetate[9] in 250 ml. of absolute alcohol. The mixture was stirred while a sodium ethoxide solution (9.2 g. of sodium in 200 ml. of absolute alcohol) was added over three and one-half hours. After the mixture had stood two days at room temperature, the orange solid was filtered off and dissolved in 1 liter of water. The solution was acidified with acetic acid and the precipitate collected. After washing with 1 liter of 5% sodium bicarbonate solution and then with water, it was dried at 100° (30 g.). On recrystallization from pyridine, it formed orange-red prisms, m. p. 274° (dec.).

*Anal.* Calcd. for $C_{11}H_{11}ON_5$: C, 57.6; H, 4.8. Found: C, 57.9; H, 4.8.

**2,5-Diamino-6-hydroxy-4-methylpyrimidine.**—The above azo compound (3.5 g.) was suspended in 100 ml. of 50% aqueous ethanol and reduced catalytically at 60° using a platinum catalyst and two to three atmospheres of hydrogen. Reduction was complete after three hours. The solution was filtered and evaporated to dyness on a steam-bath under diminished pressure. The residue was washed with acetone to remove aniline, and the almost colorless residue recrystallized from water (1.0 g.). The m. p. was 280°. This compound had previously been prepared by Jaeger[10] in poor yield from the corresponding 5-bromo compound and ammonia and reported to have a m. p. of 275°.

*Anal.* Calcd. for $C_5H_8ON_4$: C, 42.9; H, 5.7. Found: C, 43.0; H, 5.8.

**5-Chloroacetamido-2-amino-6-hydroxy-4-methylpyrimidine.**—The above diaminopyrimidine (0.5 g.) was heated with 2 g. of chloroacetic acid in a boiling water-bath under vacuum. After two hours, the mixture was cooled and the excess chloroacetic acid dissolved in ether. The residue was recrystallized from 30% aqueous ethanol and formed colorless needles, m. p. 285–290° (dec.). Yield was 0.73 g., 95%.

*Anal.* Calcd. for $C_7H_9O_2N_4Cl$: C, 38.8; H, 4.2; N, 23.9. Found: C, 38.6; H, 4.6; N, 23.5.

**2-Amino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine (VI).**—The above chloroacetamide (0.4 g.) was dissolved in 10 ml. of water and treated with 20 ml. of an aqueous solution of barium hydroxide (1.04 g. of hydrate). The solution was heated in a boiling water-bath for three hours, the barium removed in the usual manner and the filtrate acidified with acetic acid. The small colorless needles (0.15 g.) after recrystallization from water darkened at about 290° but did not melt below 350°.

*Anal.* Calcd. for $C_7H_8O_2N_4 \cdot 2H_2O$: C, 38.9; H. 5.6; N, 25.9; $H_2O$, 16.7. Found: C, 38.5; H, 5.3; N, 26.1; $H_2O$, 17.2 (dried at 120° *in vacuo*).

**Hydrolysis of VI with Hydrochloric Acid.**—The oxazinopyrimidine, V, (150 mg.) was heated with 5 ml. of concentrated hydrochloric acid on the steam-bath for three hours. The mixture was evaporated to dryness in an open dish. The residue was dissolved in 3 ml. of water and neutralized to *p*H about 6.5 by adding a saturated sodium acetate solution dropwise. The precipitate of fine needles was recrystallized from water and dried at 120°. The melting point was 283° (dec.) and was not depressed on admixture with an authentic sample of 2,5-diamino-6-hydroxy-4-methylpyrimidine.

**5-α-Bromopropionamido-2-amino-6-hydroxy-4-methylpyrimidine.**—This was prepared in a similar manner to the 5-chloroacetamido compound. It was very difficult to

(8) Lythgoe, Todd and Topham, *J. Chem. Soc.*, 315 (1944).

(9) Bülow and Neber, *Ber.*, **45**, 3736 (1912).

(10) Jaeger, *Ann.*, **262**, 365 (1891).

crystallize, solutions tending to form gels on cooling. However, a small sample was obtained as needles from 60% aqueous ethanol. It decomposed at about 300°.

*Anal.* Calcd. for $C_8H_{11}O_2N_4Br$: C, 35.1; H, 4.0. Found: C, 34.8; H, 4.2.

**2-Amino-6-hydroxy-4,7-dimethyl-*p*-oxazino[2,3-*d*]-pyrimidine (X).**—One gram of the crude 5-α-bromopropionamido derivative was heated with 50 ml. of barium hydroxide solution (2 g. of hydrate, 3.5 equivs.). The product was isolated in the usual manner. The fine colorless needles (0.35 g.) melt at 299° (dec.).

*Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.5; H, 5.2; N, 28.9. Found: C, 49.3; H, 5.4; N, 28.9.

**5-*p*-Chlorobenzeneazo-2-methylamino-6-hydroxy-4-methylpyrimidine.**—*p*-Chloroaniline (3.2 g.) was dissolved in 60 ml. of *N* hydrochloric acid, diazotized with sodium nitrite solution (2 g. in 10 ml. of water) and 5 g. of sodium bicarbonate was added. The neutralized diazonium solution was added to a solution of 3.5 g. of 2-methylamino-6-hydroxy-4-methylpyrimidine[11] in 500 ml. of water. The solution was allowed to stand for four to five hours, the orange precipitate filtered off, washed well with water and then alcohol and dried at 100° (5.5 g., 80%). After recrystallization from pyridine, the orange prisms melted at 244° (dec.).

*Anal.* Calcd. for $C_{12}H_{12}ON_5Cl$: C, 51.9; H, 4.3. Found: C, 52.2; H, 4.5.

**5-Amino-2-methylamino-6-hydroxy-4-methylpyrimidine.**—The above azo compound (4.5 g.) was suspended in 20 ml. of ethanol and reduced with hydrogen in the presence of platinum catalyst. The solution was filtered from the catalyst and some insoluble yellow material. The residue was washed with alcohol and the combined filtrate and washings were evaporated to dryness. The residue was washed with a mixture of 60 parts ether and 40 parts acetone. Recrystallized from alcohol it formed almost colorless needles (0.94 g.), m. p. 208–210°.

*Anal.* Calcd. for $C_6H_{10}ON_4$: C, 46.8; H, 6.5. Found: C, 46.5; H. 6.2.

With benzoyl chloride in alkaline solution it gave a benzoyl derivative which separated as colorless needles from water, m. p. 289–290° (dec.).

*Anal.* Calcd. for $C_{13}H_{14}O_2N_4 \cdot H_2O$: C, 56.5; H, 5.8. Found: C, 56.3; H, 5.6.

**5-Chloroacetamido-2-methylamino-6-hydroxy-4-methylpyrimidine.**—The above aminopyrimidine (0.75 g.) was heated with 3 g. of chloroacetic acid in a boiling water bath in vacuum for four hours. The product was worked up as usual and recrystallized from water. The colorless needles melt at 227–228° (dec.) (1.05 g.).

*Anal.* Calcd. for $C_8H_{11}O_2N_4Cl$: C, 41.7; H, 4.8. Found: C, 41.8; H, 4.7.

**2-Methylamino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]-pyrimidine (VII).**—Five hundred mg. of the above chloroacetamide was treated in the usual manner with 1.3 g. of barium hydroxide hydrate in 40 ml. of water. The oxazinopyrimidine was isolated as needles (0.145 g., 35%) decomposing at 340–350° without melting. The crystals contained one-half mole of water of crystallization which was lost at 120° *in vacuo*.

*Anal.* Calcd. for $C_8H_{10}O_2N_4 \cdot {}^1/_2H_2O$: C, 46.3; H, 5.4; N, 27.6. Found: C, 46.3; H, 5.2; N, 27.6. Calcd. for $C_8H_{10}O_2N_4$: C, 49.5; H, 5.2. Found: C, 49.1; H, 5.2.

**2-Dimethylamino-6-hydroxy-4-methylpyrimidine.**—2-Ethylmercapto-4-methyl-6-hydroxypyrimidine[12] (10 g.) was heated with 30 g. of a 33% ethanolic solution of dimethylamine in a sealed tube at 100° overnight. The mixture was evaporated to dryness in an open dish and the residue extracted with ether containing sufficient acetic acid to render the solution faintly acidic. The ethereal solution was filtered, concentrated to about 50 ml., and an equal volume of petroleum ether (b. p. 30–60°) was added. The first crop of needles which separated was slightly purple but successive crops were white, m. p. 106°, yield 9.4 g.

*Anal.* Calcd. for $C_7H_{11}ON_3$: C, 55.0; H, 7.2. Found: C, 55.4; H, 7.2.

**5-Benzeneazo-2-dimethylamino-6-hydroxy-4-methylpyrimidine.**—A solution of 2.6 g. of *p*-chloroaniline in 50 ml. of *N* hydrochloric acid was diazotized with 1.4 g. of sodium nitrite and neutralized with 4.5 g. of sodium bicarbonate. This diazonium solution was added to a solution of 7 g. of the above pyrimidine in 300 ml. of water and the *p*H adjusted to 7 with sodium carbonate. The orange precipitate which separated was filtered off after two hours, washed well with water and dried at 100° (2.3 g.). Recrystallized from pyridine, it formed orange-red prisms, m. p. 217°.

*Anal.* Calcd. for $C_{13}H_{14}ON_5Cl$: C, 53.6; H, 4.0. Found: C, 53.9; H, 4.4.

**5-Amino-2-dimethylamino-6-hydroxy-4-methylpyrimidine.**—The above azo compound (10 g.) in 30 ml. of ethanol was reduced catalytically in two hours using a platinum catalyst at 60°. The catalyst and a small amount of insoluble yellow material was removed by filtration. The mother liquors were concentrated to about 20 ml. and 40 ml. of ether added. The product separated in glistening prisms (4.5 g.) and was reprecipitated from 10 ml. of ethanol by the addition of 30 ml. of ether, m. p. 204–205°.

*Anal.* Calcd. for $C_7H_{12}ON_4$: C, 50.0; H, 7.2. Found: C, 50.2; H, 7.0.

**5-Chloroacetamido-2-dimethylamino-6-hydroxy-4-methylpyrimidine.**—The above aminopyrimidine (0.5 g.) was heated with 2 g. of chloroacetic acid in a boiling water-bath under vacuum. The product was isolated in the usual manner (0.6 g.) and recrystallized from water. The needles melt at 258°.

*Anal.* Calcd. for $C_9H_{13}O_2N_4Cl$: C, 44.3; H, 5.3. Found: C, 44.7; H, 5.7.

**2-Dimethylamino-6-hydroxy-4-methyl-*p*-oxazino[2,3-*d*]pyrimidine.**—The above chloroacetamide (0.3 g.) was heated with 30 ml. of a solution of barium hydroxide (0.63 g. of hydrate, 3.5 equivs.) for two and one-half hours in a boiling water-bath. The product was isolated in the usual manner: white needles, m. p. 311–312° (dec.), yield 0.15 g. On heating in the melting point tube it sublimed at 220–250°, forming fine colorless needles.

*Anal.* Calcd. for $C_9H_{12}O_2N_4$: C, 52.0; H, 5.8. Found: C, 52.0; H, 5.5.

**5-*p*-Chlorobenzeneazo-2,6-dihydroxy-4-phenylpyrimidine.**—One gram of 4-phenyluracil[13] in 2 liters of water was treated with a diazonium solution prepared from 0.6 g. of *p*-chloroaniline in 12 ml. of *N* hydrochloric acid diazotized with 0.4 g. of sodium nitrite and neutralized with 1 g. of sodium bicarbonate. After standing one hour the yellow precipitate was filtered off and washed with water and methanol (0.65 g.). Several recrystallizations from pyridine produced orange-red prisms, m. p. 240° (dec.). Because of the low solubility of 4-phenyluracil and the resultant poor yield of this coupling reaction, the reduction of the azo compound to the corresponding 5-amino compound was abandoned.

*Anal.* Calcd. for $C_{16}H_{11}O_2N_4Cl$: C, 59.1; H, 3.4. Found: C, 59.4; H, 3.5.

**Effect of Concentration of Alkali on the Yield of *p*-Oxazinopyrimidines.**—The chloroacetamidopyrimidines (0.5 g.) were heated with a solution of the required amount of barium hydroxide hydrate in 25 ml. of water in a boiling-water-bath for one and one-half hours. The mixture was then treated with a 10% excess of sodium sulfate, warmed to coagulate the barium sulfate and filtered. The solution was adjusted to *p*H 5–6 with acetic acid and allowed to stand sixteen hours. The crystalline material was collected, washed well with water, then with ethanol and air dried. The dry material was weighed, allowance being

(11) Johnson and Mackenzie, *Am. Chem. J.*, **42**, 363 (1909).

(12) List, *Ann.*, **236**, 14 (1886).

(13) Johnson and Hemmingway, THIS JOURNAL, **37**, 380 (1915).

made for any combined water of crystallization in calculations of yield. Results are reported in Fig. 3.

**Acknowledgment.**—We are indebted to Samuel W. Blackman for the microanalyses which are reported here.

## Summary

The formation of *p*-oxazino[2,3-*d*]pyrimidine derivatives from 6-hydroxy-5-α-chloroacylamidopyrimidines by treatment with aqueous barium hydroxide solution is described. This ring closure has been found to be dependent on the nature of the substituent in the 2-position of the pyrimidine ring.

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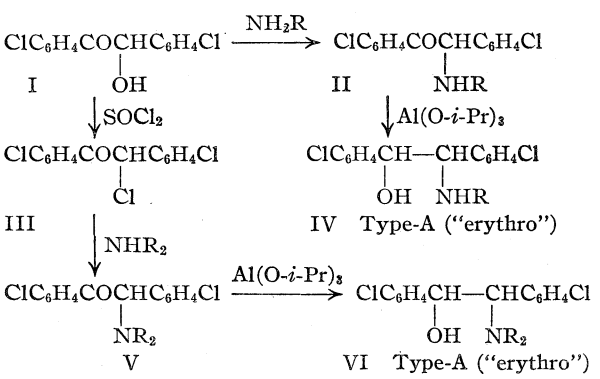
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

# Substituted-Amino Ketones and Alcohols Related to 4,4′-Dichlorobenzoin[1]

BY ROBERT E. LUTZ AND ROBERT S. MURPHEY[2]

In the light of evidence for the necrotizing action against mammalian tumors of several substituted-amino ketones and alcohols derived from benzoin,[3] it seemed worth while to investigate analogous compounds carrying in one or both phenyl nuclei substituents which might have the effect of enhancing the pharmacological activity. The present paper is the first of a series dealing with this phase of the problem. The 4,4′-dichloro series was chosen for study because of the well-known influence of halogen in increasing other types of pharmacological activity such as antimalarial and insecticidal.

The starting material, 4,4′-dichlorobenzoin (I),[4] has to date been obtainable only in poor yields by the benzoin condensation with *p*-chlorobenzaldehyde. By modification of the procedure developed by Willgerodt and Ucke[5] for the preparation of 4,4′-diiodobenzoin, the dichloro analog has been obtained consistently in yields of 80–88%. It is noteworthy that this product is exceptionally easily oxidized to 4,4′-dichlorobenzil upon manipulation involving contact with air.




The secondary amino ketones (II, see table) were made by the action of primary amines on 4,4′-dichlorobenzoin (the Voigt reaction[3,6]). In most runs phosphorus pentoxide was used as a catalyst; however, in one test using ethanolamine, an equally successful preparation resulted when the catalyst was omitted. All of the products were stable as the salts; however, in the form of the bases they underwent ready hydrolysis and oxidation to 4,4′-dichlorobenzil. Only one arylamino ketone, but none of the alkylamino ketones, was obtainable as a crystalline free base.

The amino ketones were reduced by means of aluminum isopropoxide to the amino alcohols (IV). Since only one of the two theoretically possible stereoisomers was isolated in each case, it is to be presumed that the configurations are of the same type (Type-A "erythro") and are analogous to those of the majority of the compounds prepared correspondingly in the parent benzoin series.[3] This presumption is supported by the synthesis of one of these (REL 691) through the *trans*-*p*,*p*′-dichlorostilbene oxide (see below).

4,4′-Dichlorodesyl chloride[4d] (III) was readily made by the action of thionyl chloride on 4,4′-dichlorobenzoin, but in poor yields (*ca.* 33%). It proved to be unstable and exceptionally easily converted into 4,4′-dichlorobenzil under various manipulations in contact with air.

Representative tertiary-amino ketones (V) were made by condensation of 4,4′-dichlorodesyl chloride (III) with the appropriate amine. These were reduced to the amino alcohols (VI) by means of aluminum isopropoxide. Since here also only one of the two possible diastereoisomers was obtained in each case, these compounds are presumed to be of the type-A ("erythro") configuration.

Two ethanolamino ketones were made. The monoethanolamino compound itself (II, R = $CH_2CH_2OH$) was made by the Voigt reaction from 4,4′-dichlorobenzoin, and was readily re-

(1) Agents Causing Necrosis in Tumors, II. This work was carried out under a grant-in-aid from the National Institute of Health, recommended by the National Cancer Institute. The larger part of this work was included in a dissertation for the M.S. degree, University of Virginia, June, 1947.

(2) Holder of National Cancer Institute Junior Research Fellowship, 1947–1948.

(3) Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2015 (1948).

(4) (a) Hantzsch and Glover, *Ber.*, **40**, 1519 (1907); (b) Kenner and Witham, *J. Chem. Soc.*, **97**, 1967 (1910); (c) Gomberg and Van Natta, THIS JOURNAL, **51**, 2241 (1929); (d) Karrer and Forster, *Helv. Chim. Acta*, **30**, 1160 (1947).

(5) Willgerodt and Ucke, *J. prakt. Chem.*, **86**, 281 (1912).

(6) Voigt, *ibid.*, **2**, 34, 2 (1886).

TABLE I

α-SECONDARY AND TERTIARY AMINO-4,4′-DICHLORODESOXYBENZOIN HYDROCHLORIDES (II AND V)

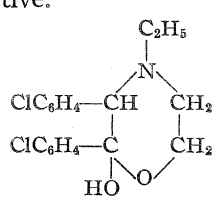
| REL.[a] no. | NHR or $NR_2$ | Method[b] of prepn. | Time of heating, hours | Yield, % | Crystallized from[c] | M. p., °C., cor. | Empirical formula | Analyses, % Carbon (or nitrogen) Calcd. | Carbon (or nitrogen) Found | Hydrogen (or chlorine) Calcd. | Hydrogen (or chlorine) Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 619 | $NHC_4H_9$ | 1a | 4 | 42 | But.–$CH_3OH$ | 249-250 | $C_{18}H_{19}Cl_2NO\cdot HCl$ | 58.00 | 57.73 | 5.41 | 5.27 |
| | | 1b | 1.5 | 49 | But.–$CH_3OH$ | 249-250 | | | | | |
| 626 | $NHC_8H_{17}$ | 1b | 2 | 42 | But.–$CH_3OH$ | 226-227 | $C_{22}H_{27}Cl_2NO\cdot HCl$ | 61.61 | 61.62 | 6.58 | 6.65 |
| 690 | $NHCH_2CH_2OH$ | 1a,d | 0.1 | 89 | But.–$CH_3OH$ | 197-199 | $C_{16}H_{15}Cl_2NO_2\cdot HCl$ | 53.28 | 52.95 | 4.47 | 4.28 |
| | | .. | .. | .. | But.–$CH_3OH$ | 197-199 | | | | | |
| | $NHC_6H_5$(base) | 1a | 2 | 69 | $CH_3OH$ | 107-108 | $C_{20}H_{15}Cl_2NO$ | 3.93 | 3.78 | .. | .. |
| 610 | (Hydrochloride) | .. | .. | .. | EtOH–$H_2O$ | 212-214 | $C_{20}H_{15}Cl_2NO\cdot HCl$ | ... | ... | 9.03 | 9.10 |
| 683 | $NHC_6H_4N(C_2H_5)_2$-*p* | 1a, c | 0.1 | 90 | But.–$CH_3OH$ | 178-180 | $C_{24}H_{24}Cl_2N_2O\cdot 2HCl$ | 5.60 | 5.31 | .. | .. |
| | | 1b | 2 | 84 | But.–$CH_3OH$ | 178-180 | | | | | |
| 632 | $N(C_2H_5)_2$ | 2 | 12 | 59 | But.–$CH_3OH$ | 223-224 | $C_{18}H_{19}Cl_2NO\cdot HCl$[e] | 58.00 | 57.90 | 5.41 | 5.55 |
| 686 | $N(C_2H_5)CH_2CH_2OH$ | 2 | 2 | 64 | But. | 185-186 | $C_{28}H_{16}Cl_2NO_2\cdot HCl$[f] | 55.61 | 55.53 | 5.19 | 5.20 |
| 628 | Piperidyl[d] | 2 | 18 | 65 | EtOH–Acet. | 247-248[g] | $C_{19}H_{19}Cl_2NO\cdot HCl$ | 59.31 | 59.19 | 5.24 | 4.99 |

2-SECONDARY AND TERTIARY AMINO-1,2-DI-(4-CHLOROPHENYL)-ETHANOLS (IV AND VI), BASES AND HYDROCHLORIDES

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $NH_2$[j] | 4e,c | 24 | 68 | EtOH–$H_2O$ | 160-163 | $C_{14}H_{13}Cl_2NO$ | 59.59 | 59.70 | 4.64 | 4.70 |
| 721 | (Hydrochloride) | .. | .. | .. | But.–$CH_3OH$ | 234-235 | $C_{14}H_{13}Cl_2NO\cdot HCl$ | 52.77 | 52.51 | 4.43 | 4.57 |
| | $NHC_4H_9$ | 3 | 5 | 90 | EtOH–$H_2O$ | 129-130 | $C_{18}H_{21}Cl_2NO$ | 4.14 | 3.99 | .. | .. |
| 625 | (Hydrochloride) | .. | .. | .. | But.–$CH_3OH$ | 254-256 | $C_{18}H_{21}Cl_2NO\cdot HCl$ | 57.69 | 57.71 | 5.92 | 6.08 |
| 627 | $NHC_8H_{17}$ | 3 | 4 | 76 | EtOH | 106-107 | $C_{22}H_{29}Cl_2NO$ | 67.00 | 66.69 | 7.41 | 7.43 |
| | (Hydrochloride) | .. | .. | .. | Acet.–ligr. | 182-183 | $C_{22}H_{29}Cl_2NO\cdot HCl$ | 3.25 | 3.24 | .. | .. |
| | $NHCH_2CH_2OH$ | 3 | 3 | 77 | EtOH–$H_2O$ | 104-105 | $C_{16}H_{17}Cl_2NO_2$ | 4.29 | 4.24 | .. | .. |
| | | 4a,c | 20 | 91 | | 104-105[i] | | | | | |
| 691 | (Hydrochloride) | 3 | .. | .. | But.–$CH_3OH$ | 248-249 | $C_{16}H_{17}Cl_2NO_2\cdot HCl$ | 52.98 | 53.06 | 5.00 | 5.21 |
| | | 4a,c | | | | 245-248[i] | | | | | |
| | $NHC_6H_5$ | .. | .. | .. | ... | Oil[h] | $C_{20}H_{17}Cl_2NO$ | 3.91 | 3.96 | .. | .. |
| 611 | (Hydrochloride) | 3 | 1 | 80 | Acet.–$Et_2O$ | 198-199 | $C_{20}H_{17}Cl_2NO\cdot HCl$ | 60.85 | 61.04 | 4.60 | 4.30 |
| | $NHC_6H_4N(C_2H_5)_2$-*p* | .. | .. | .. | EtOH | 139-141 | $C_{24}H_{26}Cl_2N_2O$ | 67.13 | 66.91 | 6.10 | 5.94 |
| 692 | (Dihydrochloride) | 3 | 3 | 92 | But.–$CH_3OH$ | 205-207 | $C_{24}H_{26}Cl_2N_2O\cdot 2HCl$ | 5.58 | 5.57 | .. | .. |
| | $N(C_2H_5)_2$ | .. | .. | .. | EtOH | 90- 91 | $C_{18}H_{21}Cl_2NO$ | 63.91 | 63.80 | 6.26 | 6.18 |
| 682 | (Hydrochloride) | 3 | 8 | 15 | But.–$CH_3OH$ | 226-227 | $C_{18}H_{21}Cl_2NO\cdot HCl$ | 57.69 | 57.91 | 5.92 | 5.76 |
| | Piperidyl[d] | 3 | 6 | 37 | EtOH | 115-115.5 | $C_{19}H_{21}Cl_2NO$ | 65.14 | 65.42 | 6.04 | 6.33 |
| 638 | (Hydrochloride)[d] | .. | .. | .. | EtOH | 254-256 | $C_{19}H_{21}Cl_2NO\cdot HCl$ | 59.00 | 59.01 | 5.74 | 5.74 |
| | $N(C_2H_5)CH_2CH_2OH$ | 4b,d | 10 | 70 | EtOH–$H_2O$ | 101-102 | $C_{18}H_{21}Cl_2NO_2$ | 61.52 | 61.30 | 5.97 | 6.26 |
| 722 | (Hydrochloride) | .. | .. | .. | ...[k] | 189.5-191 | $C_{18}H_{21}Cl_2NO_2\cdot HCl$ | 55.32 | 55.38 | 5.68 | 5.47 |

[a] Code number from this Laboratory. [b] See descriptions in the experimental part. [c] But. = butanone, EtOH = 95% ethanol, acet. = acetone, ligr. = ligroin, $Et_2O$ = ethyl ether. [d] Prepared by James A. Freek. [e] Calcd. for N, 3.76; found, 3.58. [f] Calcd. for N, 3.60; found, 3.63. [g] The base melts at 80–81° *in vacuo*. It was not analyzed. [h] The base was liberated from the pure salt by means of alkali and was isolated by extraction with ether and evaporation of the solvent. It was not distilled. [i] This product gave no mixture melting point depression with the first sample. [j] Unsuccessful attempts were made to prepare this compound through reduction of 4,4′-dichlorobenzil monoxime by stannous chloride and by sodium–alcohol reductions, and to prepare the stereoisomer by condensation of *p*-chlorobenzaldehyde with glycine [*cf.* Erlenmeyer, *Ann.*, **307**, 97 (1899)]. [k] Crystallized from acetone–methanol–isoöctane mixture.

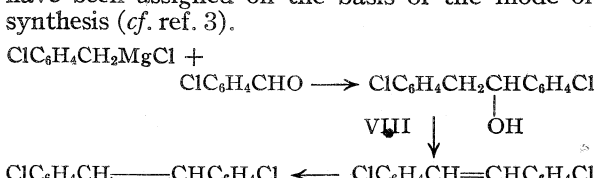
duced by aluminum isopropoxide to the di-alcohol (IV, R = $CH_2CH_2OH$). The ethylethanolamino analog (V, $NR_2$ = $N(C_2H_5)CH_2CH_2OH$), however, evidently has the cyclic structure (VII) since it is not reduced to a significant extent by aluminum isopropoxide under the conditions usually effective.[7]



VII

The corresponding tertiary-amino dialcohol (VI, $NR_2$ = $N(C_2H_5)CH_2CH_2OH$), and also the ethanolamino analog (IV, R = $CH_2CH_2OH$) and the parent amino compound (VI, $NR_2$ = $NH_2$), were successfully made by condensation of *trans*-4,4′-dichlorostilbene oxide (IX) with ethylethanolamine, ethanolamine and ammonia, respectively. The type A ("erythro") configurations are assumed in view of this mode of synthesis.

The *trans*-oxide, used above, was made from *trans*-4,4′-dichlorostilbene (X, known[8]) which has been obtained in a new and improved way by the action of *p*-chlorobenzylmagnesium chloride on *p*-chlorobenzaldehyde and dehydration of the resulting carbinol (VIII). The *trans* configurations have been assigned on the basis of the mode of synthesis (*cf.* ref. 3).



IX *trans* X *trans*

(7) Lutz and Jordan, THIS JOURNAL, **71**, in press (1949).

(8) For preparations of this compound by other methods see (a) Meyer and Hoffmann, *Monatsh.*, **38**, 141 (1917); (b) Pascal and Normand, *Bull. soc. chim.*, **9**, 1029, 1059 (1886); **11**, 21 (1888); (c) Spath, *Monatsh.*, **35**, 463 (1914); (d) Forrest, Stephenson and Waters, *J. Chem. Soc.*, 333 (1946); (e) Meerwein, Büchner and van Emster, *J. prakt. Chem.*, **157**, 237 (1939).

The *p*-diethylaminoanilino ketone hydrochloride [IV, R = $NHC_6H_4N(C_2H_5)_2$-*p*] was made in order to test the influence of an extra basic group. In the form of the free base this compound was extremely unstable; the salt, although relatively much more stable, deteriorated to a red resinous mass on standing in the air. The compound was reduced by means of aluminum isopropoxide to the corresponding alcohol which in contrast proved to be stable in the form of the free base.

The results of pharmacological tests, especially those dealing with tumor necrosis, which are in progress at the National Cancer Institute, will be reported elsewhere.[9]

## Experimental[10]

**The Preparation of 4,4′-Dichlorobenzoin (I).**[4]—Due apparently to the low melting point and high solubility in ethanol, this compound separated as an oil under the usual conditions of the benzoin condensation.[11] For the best results it was important to remove all unreacted *p*-chlorobenzaldehyde. It was advantageous to diminish the reaction time in order to minimize side reactions such as oxidation of the desired product to the corresponding benzil. The compound crystallized well only from petroleum ether.

A saturated aqueous solution of 5 g. of a pure grade of potassium cyanide was added slowly to a refluxing solution of 500 g. of freshly distilled *p*-chlorobenzaldehyde in 300 ml. of methanol. A strongly exothermic reaction ensued. The mixture was refluxed for twenty minutes, and the methanol was evaporated under reduced pressure. The residual red, pasty mass was taken up in benzene. The benzene solution was extracted repeatedly with 20% sodium bisulfite until the extract liberated no aldehyde when treated with alkali; the solution was then washed with water and evaporated under reduced pressure. The residue crystallized as fine, colorless needles from petroleum of boiling range 70–110°; yield 440 g. (88%). After several recrystallizations it melted at 87–88°.[4a,c,d] On standing in air the surface of the white benzoin becomes coated with the yellow benzil.

*Anal.* Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.80; H, 3.58. Found: C, 59.61; H, 3.34.

**4,4′-Dichlorodesyl Chloride (III).**—A solution of 140.5 g. (0.5 mole) of 4,4′-dichlorobenzoin in 50 g. of pyridine at 5° was treated dropwise under cooling with 75 g. (0.63 mole) of thionyl chloride. The resulting viscous yellow mixture was extracted repeatedly with cold water until the test for chloride ion was negative, and was then extracted with petroleum ether to remove unchanged 4,4′-dichlorobenzoin; the product was crystallized from 95% ethanol, yield 53.3 g. (36%), colorless needles of melting point 60–61°.

*Anal.* Calcd. for $C_{14}H_{9}Cl_3O$: C, 56.12; H, 3.03. Found: C, 55.29; H, 2.96.

**4,4′-Dichlorobenzil monoxime** was made from 4,4′-dichlorobenzil by the procedure for the 4,4′-dibromo analog,[12] yield 90%, crystallized from dilute ethanol, m.p. 143–144°.

*Anal.* Calcd. for $C_{14}H_9Cl_2NO_2$: N, 4.76. Found: N, 4.50.

**1,2-Di-(4-chlorophenyl)-ethanol (VIII).**—A solution of 119 g. (0.848 mole) of *p*-chlorobenzaldehyde in 800 ml. of ether was added slowly under stirring to 4-chlorobenzylmagnesium chloride in 700 ml. of ether [made from 154 g. (0.956 mole) of 4-chlorobenzyl chloride and 46 g. (1.89 mole) of magnesium]; the mixture was heated for one hour, hydrolyzed with dilute acetic acid, washed with sodium hydroxide and then with sodium bisulfite, and was concentrated. The residual oil crystallized and the crude product was used in the next experiment. A small sample was recrystallized from isoöctane, hexagonal plates, m.p. 74–75°.

*Anal.* Calcd. for $C_{14}H_{12}Cl_2O$: C, 62.94; H, 4.53. Found: C, 62.99; H, 4.96.

***trans*-4,4′-Dichlorostilbene (X).**[8]—The crude alcohol (VIII) (above) was heated with 1 ml. of 48% hydrobromic acid at 230° for twenty minutes (evolution of water had ceased), and the product was distilled at 215–230° under 10 mm., yield 161 g. After two crystallizations from toluene the yield was 120 g. (57% calculated from VIII), m.p. 175–176°. *Anal.* Calcd. for C, 67.49; H, 4.05. Found: C, 67.55; H, 3.79.

***trans*-4,4′-Dichlorostilbene Oxide (IX).**—A solution of 93.5 g. of X in 3 liters of xylene was added to a solution of 83 g. of perbenzoic acid in 1.1 liters of chloroform. The mixture was allowed to stand for twenty-four hours at room temperature and five hours at 60°. (The reaction was very slow; a number of other solvents were tried but without improvement.) Evaporation to a volume of about 1.5 liters under reduced pressure, washing with sodium hydroxide, drying over sodium sulfate and evaporation of the rest of the solvent, and crystallization of the residual oil from ethanol, gave colorless needles, 50 g. (50%), m.p. 114–115.5°. Treatment in acetone with permanganate to remove unchanged X gave a product melting at 123–124°.

*Anal.* Calcd. for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80. Found: C, 63.41; H, 4.10.

**General Procedures. (1) The Preparation of the Secondary Amino Ketones from 4,4′-Dichlorobenzoin.**—A mixture of 0.25 mole of the benzoin, 0.27 mole of the primary amine and 2 g. of phosphorus pentoxide was heated on a water-bath. (a) When no solvent was used the water formed in the reaction was not removed. (b) When benzene was used as solvent the water formed in the reaction was removed by distillation of the azeotrope; and heating was continued until further distillation failed to give evidence of further formation of water in the reaction. In this case the solvent was removed under diminished pressure before working up the product. (c) In several experiments the amine and catalyst were added to the molten benzoin, and no further heat was applied. (d) In one experiment the catalyst was omitted. The amine was added to the benzoin which had been melted and brought to 110°. Without the application of heat the temperature of the mixture dropped to 85°, and upon slight shaking to mix the materials, it rose sharply to 112°. The mixture was allowed to cool slowly to room temperature and was worked up in the usual way.

α-Anilino-4,4′-dichlorodesoxybenzoin was purified as the base, and the hydrochloride was obtained in the usual way.

In the preparation of the α-monobutylamino-4,4′-dichlorodesoxybenzoin the reaction product was taken up in ether, the unreacted amine was extracted by water, the ether solution was dried over sodium sulfate, and the amino ketone salt was precipitated by the addition of ethereal hydrogen chloride. The corresponding octylamino ketone was purified by removing the unreacted amine under diminished pressure and obtaining the hydrochloride as in the case of the butylamino compound.

**(2) Preparation of the Tertiary-Amino Ketones from 4,4′-Dichlorodesylchloride.**—The α-diethylamino-4,4′-dichlorodesoxybenzoin (V) was prepared by allowing a mixture of 0.4 mole of diethylamine and 0.2 mole of 4,4′-dichlorodesyl chloride (III) to stand at room temperature, with exclusion of air, for the period of time stated in the table. The reaction mixture was dissolved in ether, and the unreacted diethylamine was extracted from this solution by water. The ether solution was dried over

(9) Unpublished work of Shear, Downing, MacArdle, Hartwell, *et al.*, at the National Cancer Institute.

(10) All melting points are "corrected." The microanalyses were carried out by Mrs. Joyce Blume Caliga and by the Clark Microanalytical Laboratory.

(11) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 94.

(12) Biltz, *Ber.*, **43**, 1815 (1910).

sodium sulfate and the amino ketone hydrochloride was precipitated by the addition of ethereal hydrogen chloride, yield 59%.

It was observed that the amino ketones were sensitive compounds and in several experiments the yields were very poor. The diethylamino compound, for example, suffered decomposition with the formation of appreciable amounts of 4,4′-dichlorobenzil. Each successive crystallization of the hydrochloride of this amino ketone from the methanol–butanone mixture involved the formation of significant amounts of 4,4′-dichlorobenzil which was difficultly soluble in the solvent and crystallized out during the manipulation.

In one preliminary experiment V was obtained in only 26% yield upon heating a solution of 0.2 mole of III and 0.424 mole of diethylamine in benzene on the water-bath without the precaution of excluding air.

**(3) Preparation of the 1,2-Di-(4-chlorophenyl)-N-substituted-ethanolamines by Reduction of Amino Ketones.**—The amino ketones prepared as above were reduced to the corresponding alcohols (IV and VI) in the usual way by means of an excess of 1.5 *N* aluminum isopropoxide. The butylamino and octylamino alcohols were purified as the free bases, while all the other amino alcohols were purified as the hydrochlorides.

**(4) The Preparation from 4,4′-Dichlorostilbene Oxide.**—A mixture of X and a large excess of the amine was heated at (a) 130° and (b) 150°, respectively, taken up in (c) benzene or (d) ether, washed with water to remove excess amine, dried over sodium sulfate, and treated with ethereal hydrogen chloride to precipitate the salt. (e) The condensation using 28% concd. aqueous ammonium hydroxide in dioxane as solvent (sealed tube) was at 100°.

## Summary

An improved preparation of 4,4′-dichloro-benzoin and 1,2-di-(4-chlorophenyl)-ethanol, and the syntheses of 4,4′-dichlorodesyl chloride, *trans*-4,4′-dichlorostilbene and 4,4′-dichlorostilbene oxide, are described.

From these compounds a series of secondary and tertiary-amino desoxybenzoins and the corresponding amino and substituted-amino alcohols, have been prepared.

Resistance to aluminum isopropoxide reduction of the ethylethanolamino ketone as contrasted with the facile reduction of the monoethanolamino analog, indicates a cyclic hemiacetal structure for the former.

CHARLOTTESVILLE, VIRGINIA
RECEIVED SEPTEMBER 7, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Polymerization. IX. Metalation during Alfin Polymerization of Butadiene and the Formation of Gel[1]

BY AVERY A. MORTON, RICHARD P. WELCHER,[2] FRANCES COLLINS, SIEGFRIED E. PENNER AND ROBERT D. COOMBS

The previous paper[3] showed that metalation of rubber caused gel to form in proportion to the metalating activity, and the paper[4] before that showed that an Alfin[5] catalyst was a poorer metalating agent than the allylsodium component of the catalyst. It seemed likely, therefore, that the amount of gel formed during Alfin polymerization would have a direct connection with the lack of correct proportioning of alkoxide with alkenylsodium, or, in the absence of a specific combination, would have a connection with the quantity of catalyst in excess of that needed for polymerization. In either event the relation would be expressed by the rule that minimum gel would accompany maximum polymerizing activity. The idea of a specific combination has been confirmed with two moderately active catalysts and that of quantity with an extremely active catalyst that is less sensitive to proportioning.

The first catalyst ($PB_1$)[5] was made from sodium isopropoxide and 1-butenylsodium. Two series of reagents, A and B, were used. A was made by combining the two components after each had stood for some time. Figure 1 shows clearly that in four separate trials during a period of over two months the peak of activity (with reagent no. 4) was also the one with minimum gel. B was made by mixing immediately after preparing the two components separately. Figure 2 shows again the relationship but only after the catalyst had aged for some time (test no. 3). The aging process (in B) unquestionably would have been accelerated if the mixing had been done in the high-speed stirring apparatus. Figure 3 confirms this action of the B series with a mixture of butadiene and isoprene, the latter being added to slow down the action, erase part of the gel formation (isoprene[5] forms little or no gel when polymerized) and bring out the action more distinctly. The particular proportions for maximum activity with A and B have no significance since particle size of the two components was probably not the same. The method of combination was not ideal, but was chosen because it permitted proportioning from stock preparations of the two components. The total amount of each present, therefore, has less significance than the composition of the available surface.

The second catalyst was made from sodium phenylmethyl carboxide and allylsodium and a

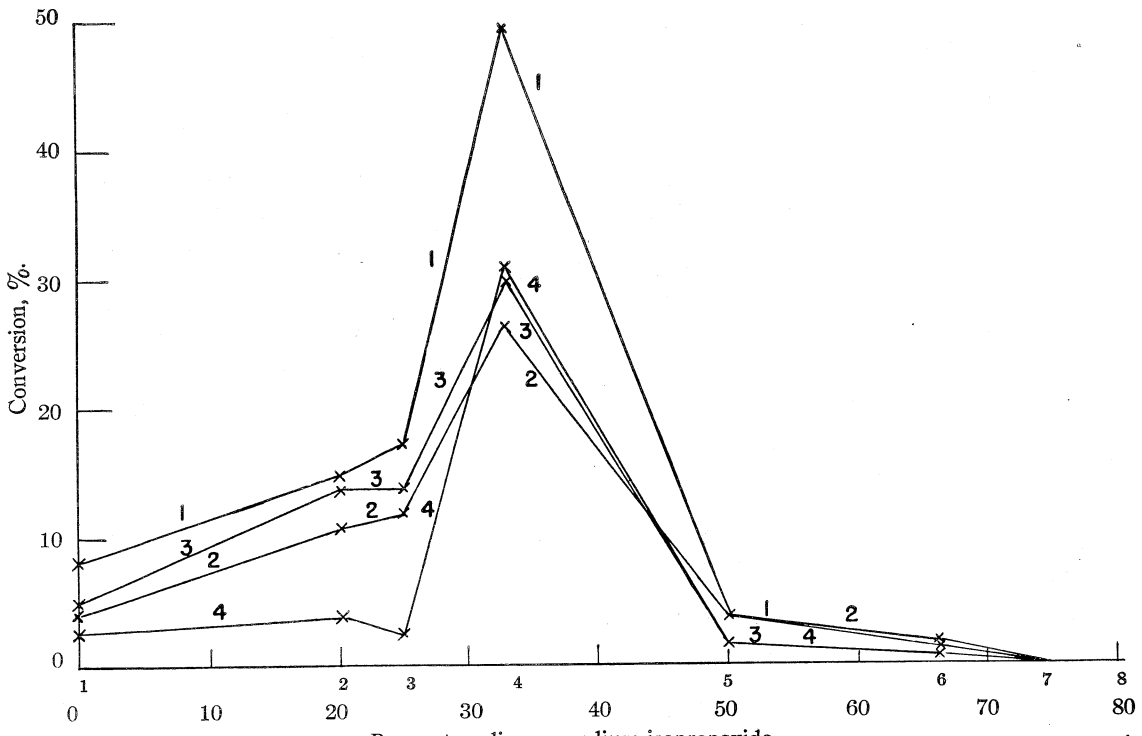
(1) This work was part of the program of research carried out in recent years under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation.

(2) Present address: The American Cyanamid Company, Stamford, Connecticut.

(3) Morton and Ramsden, THIS JOURNAL, **70**, 3132 (1948).

(4) Morton and Holden, *ibid.*, **69**, 1675 (1947).

(5) Morton Magat and Letsinger, *ibid.*, **69**, 950 (1947).




| Reagent no. | 1 | | | | 2 | | | | 3 | | | | 4 | | | | 5 | | | | 6 | | | | 7 | | | | 8 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test no. | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Cat. age, days | 4 | | 7 | 18 | 70 | 6 | | 9 | 20 | 72 | 5 | | 8 | 19 | 71 | 11 | 14 | 25 | 77 | 6 | 9 | 20 | 72 | 5 | 8 | 19 | 71 | 6 | 9 | 20 | 72 | 4 | 7 | 18 | 70 |
| [n] | 0.15 | 0.20 | .. | .. | | 6.2 | 5.8 | 4.4 | .. | | 7.7 | 5.9 | 4.7 | .. | | 5.0 | 6.8 | 5.4 | .. | 2.0 | 0.8 | .. | .. | 2.0 | 2.1 | 2.5 | .. | 1.0 | 0.1 | .. | .. | .. | .. | .. | .. |
| Gel, % | 8 | 11 | .. | .. | | 50 | 59 | 51 | .. | | 65 | 44 | 61 | .. | | 10 | 7 | 7 | .. | 55 | 59 | .. | .. | 79 | 26 | 54 | .. | 58 | 15 | .. | .. | .. | .. | .. | .. |

Fig. 1.—Polymerization of butadiene by $PB_1$ catalyst, series A.

different method was used to adjust the proportions. In the first preparation, C, phenylmethylcarbinol was allowed to react with part of the amylsodium, after which propylene was added to the remainder, so that allylsodium was prepared in the presence of the alkoxide and combination occurred before either component had much chance to agglomerate. This method is the one usually employed for making Alfin catalysts but is less suitable for proportioning the components because of variations in the yields of amylsodium. The product, C, gave good conversion with very low gel (see Table I). D was a similar preparation, the initial behavior of which was clearly similar to those of A and B that had high proportions of alkoxide. Accordingly two small portions of allylsodium, each equal to approximately one-twentieth of the allylsodium originally present, were added, each time with vigorous stirring, and allowed to age for a short or moderate time. A point of maximum activity and zero gel was thus reached (see Table I).

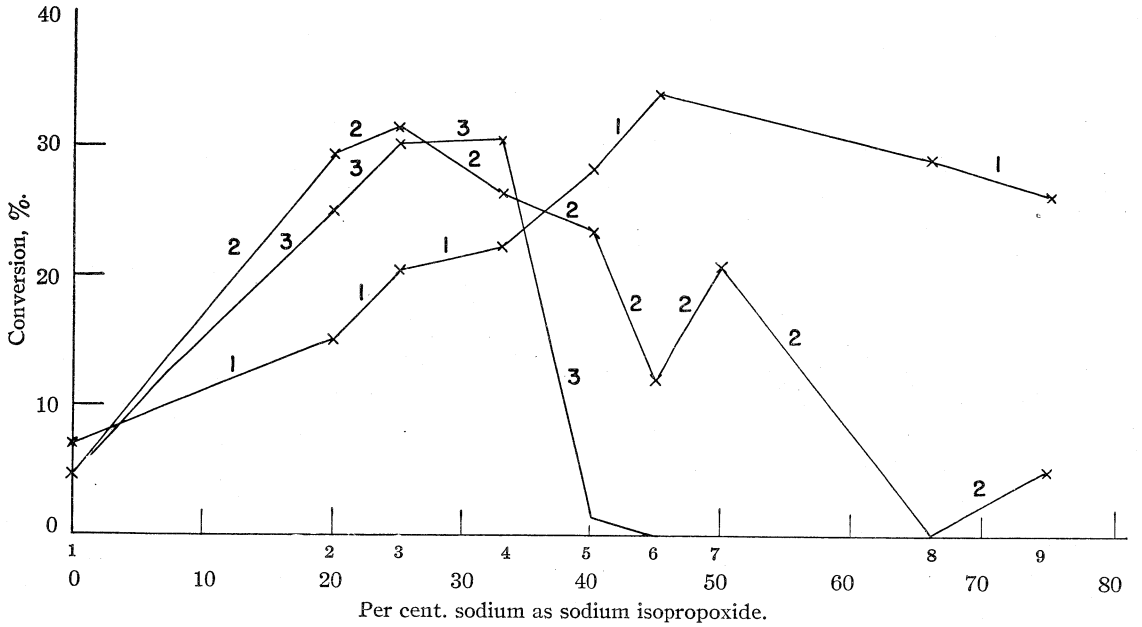
The third catalyst (PP) was from sodium isopropoxide and allylsodium. This pair had extraordinarily high activity, did not lose activity in the presence of excess alkoxide (as do the other two) and gave a product of very high intrinsic viscosity which unquestionably increased the tendency to form gel. The usual percentage of gel from such a catalyst is around 60 to 90. Just once out of well over two hundred preparations of catalyst was one obtained that produced, by bottle polymerization, a rubber with gel as low as 23%. When, however, the quantity of catalyst was reduced to one-fourth, the percentage of gel fell. Values below 20%, some as low as 2%, became

TABLE I

EFFECT OF ADDITION OF ALLYLSODIUM TO INACTIVE CATALYST MADE FROM SODIUM PHENYL METHYL CARBOXIDE AND ALLYLSODIUM

| Catalyst | Additions or other changes | Conversion, % | Intrin. vis. | Gel, % |
|---|---|---|---|---|
| C | | 35 | 6 | 0 to 10 |
| D | As prepared | 16 | 1 | 34 |
| $D_{1-3}$ | D with RNa[a] added and aged 3 days | 19 | 3.8 | 18 |
| $D_{1-18}$ | $D_1$ 15 days later | 28 | 6.0 | 14 |
| $D_2$ | $D_1$ with RNa added | 29 | 5.8 | 13 |
| $D_{2-8}$ | $D_2$ 8 days later | 33 | 5.8 | 0 |
| $D_3$ | $D_{2-8}$ satd. with $C_3H_6$ | 32 | 6.6 | 0 |

*a* R = allyl.




| Reagent no. | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | | 6 | | | 7 | | | 8 | | | 9 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test no. | 1 | 2 | 3[a] | 1 | 2[a] | 3[b] | 1 | 2 | 3[c] | 1 | 2 | 3[a] | 1 | 2 | 3 | 1 | 2[a] | 3 | 1 | 2 | 3 | 1[a] | 2 | 3 | 1 | 2 | 3 |
| Cat. age, days | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 | 3 | 23 | 37 |
| [η] | 0.14 | 0.17 | 0.31 | 2.7 | 4.1 | 7.2 | 6.9 | 8 | 10.6 | 8.0 | 9.6 | 10.7 | 9.6 | 10.6 | 2.5 | 9.7 | 7.4 | .. | .. | 9.8 | .. | 9.3 | .. | .. | 6.5 | 3.9 | .. |
| Gel., % | 27 | 0 | 16 | 32 | 0 | 27 | 14 | 7 | 37 | 12 | 12 | 21 | 35 | 16 | ... | 32 | 41 | .. | .. | 33 | .. | 23 | .. | .. | ... | ... | .. |

[a] 31 min. polymerization time. [b] 32 min., [c] 33 min. All other times, 30 min.

Fig. 2.—Polymerization of butadiene by $PB_1$ catalyst, series B.

common. Conversions, on the other hand, remained high, some as high as 70%. The efficiency was obviously higher and the percentage of gel was lower.

The authors are indebted to Christiana Clapp and Jeanne Kilduff for valuable technical assistance and determination of the constants of the polymers.

## Experiments

**General Methods.**—The operations of preparing amylsodium, metalating the olefins, and polymerizing the dienes have now become routine. The description below will suffice for this paper and others to come, the small variations introduced by each operator having been found to have little effect that exceeds the variation necessarily imposed on any reaction where the reagents are in different phases.

The amylsodium necessary for metalation of the olefins was prepared by drop-wise addition at −10° of 63 ml. (0.5 + mole) of amyl chloride on 23 g. of sodium sand in 500 ml. of pentane under an atmosphere of nitrogen in the high-speed stirring apparatus[6] in the usual manner as described in a previous publication.[5] This size preparation is referred to hereafter as the standard. Larger preparations were made with proportionately larger amounts. They are referred to as two or three times the standard, depending on the amount.

Allylsodium was prepared by bubbling propylene (Phillips Petroleum Company, pure grade) into the amylsodium suspension at 10° to room temperature and with high-speed stirring for about five hours. 1-Butynylsodium was made by addition of 1-butene at −10° to amylsodium. The temperature was then allowed to rise gradually over a one and a half to three and a half hour period to around 20°. Two additions of 60 ml. of 1-butene each per standard batch (total 120 ml.) were thus made in the preparation of Series A reagents; and a single addition of 120 ml. per twice the standard batch was made in preparing the Series B reagents. All reaction mixtures were allowed to stand overnight to complete the metalation.

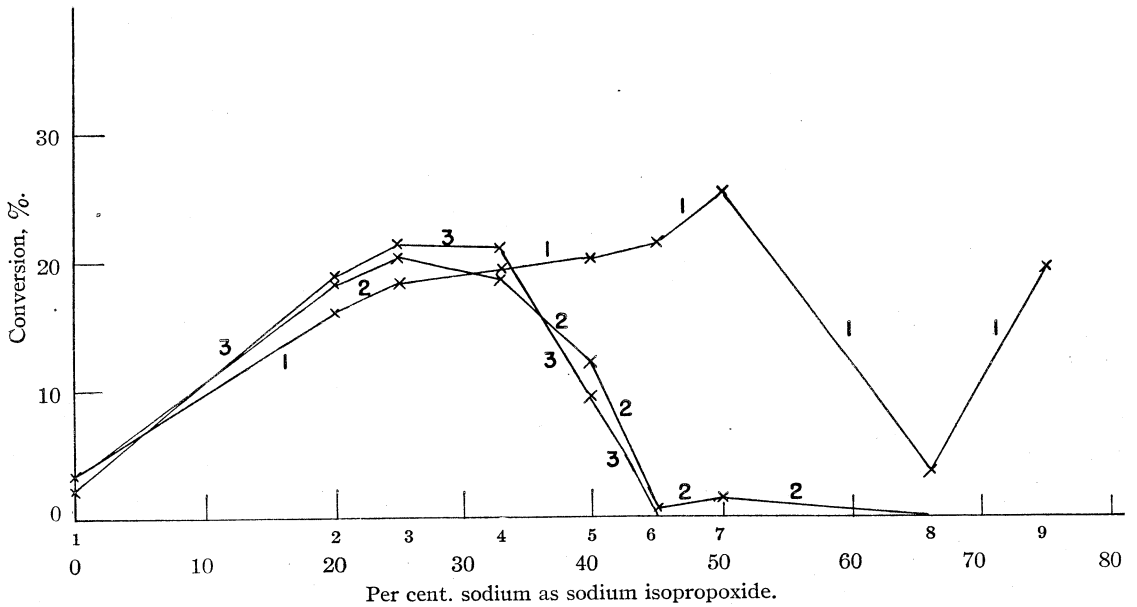
If metalation of the olefin was to be carried out in the presence of an alkoxide, the alcohol was added to the reaction mixture at 0° just before addition of the olefin. The time needed for metalation of the olefin in the presence of alkoxide was only about half that in the absence of alkoxide. The common practice, however, was to allow all such reaction mixtures to stand overnight.

The alkoxide for the stock solutions was prepared by addition of alcohol to amylsodium. This method probably ensured the same state of subdivision that was present in the alkenylsodium suspension, although this precaution might have been unnecessary.

All preparations were transferred from the reaction flask to glass bottles through a siphon tube under pressure of nitrogen. The glass bottle, used for storage, was a common narrow-mouth 500-ml. container, roughly calibrated, which had previously been rinsed with dry pentane and flushed with dry nitrogen. After the contents were transferred to the bottle together with the pentane rinsings from the reaction flask, more pentane was added to bring the volume to a desired amount, the bottle was stoppered with a well rolled cork stopper, and the top covered with a glyptal resin spread. The contents were well shaken, and the mixture set aside until needed. These suspensions settled very little. Some have kept for months without clarifying at the top more than one-quarter inch out of a total height of about 4 in. No appreciable sediment collected in the bottom. The stock preparations were handled in the same way except for proportionately larger bottles.

Before removal of an aliquot portion for compounding or for a polymerization, the bottle was shaken vigorously by

(6) Morton and Redman, *Ind. Eng. Chem.*, **40**, 1190 (1948).




| Reagent no. | 1 | | | 2 | | | 3 | | | 4 | | | 5 | | | 6 | | | 7 | | | 8 | | | 9 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test no. | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Cat. age, days | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 | 10 | 32 | 39 |
| [n] | 0.2 | 0.3 | 0.3 | 2.2 | 6.2 | 7.1 | 4.0 | 5.7 | 6.5 | 4.1 | 7.7 | 8.1 | 4.8 | 6.9 | 6.8 | 5.1 | 1.2 | .. | 5.6 | 4.1 | .. | 3.5 | .. | .. | 5.9 | .. | .. |
| Gel, % | 1 | 6 | 15 | 10 | 22 | 22 | 2 | 2 | 5 | 1 | 16 | 9 | 0 | 29 | 6 | 1 | .. | .. | 0 | .. | .. | 0 | .. | .. | 1 | .. | .. |

Fig. 3.—Polymerization of mixture of 25 parts isoprene and 75 parts butadiene by $PB_1$ catalyst, Series B.

hand. The suspension was then transferred through a siphon tube under nitrogen pressure into the new container or into a transfer tube, if for a polymerization. These transfer tubes, if for 20 ml. or more of suspension, were graduated tubes of about 12 mm. diameter, with a stopcock large enough to permit rapid draining, a size as large as 8 mm. i. d. being preferred. Later, as 5 ml. were used in the tests, the exclusion of traces of moisture became necessary. The tube and siphon was therefore replaced by a two-holed stopper carrying a nitrogen inlet tube and a small pipet, the lower end of which was not constricted. Rapid drainage was thus insured. The suspension was forced into this pipet by nitrogen pressure, the suspension allowed to drain back, and then forced up again to the graduated mark, after which the aliquot part was transferred quickly to the reaction vessel.

The butadiene (Phillips research grade) was condensed in a 28 × 4 cm. test-tube cooled to −72° from which it was poured through a dry cotton plug in a funnel into a graduated dropping funnel. The dry cotton removed a little cloudiness in the liquid butadiene. The diene, which was by that time at a temperature just below its boiling point, was admitted rapidly to the bottle.

Later, as 5 ml. of catalyst was used, and the need for more careful exclusion of water became apparent, the end of the line that led the butadiene into the large test-tube was fitted with a one in. sintered glass disc, the butadiene was collected over anhydrous magnesium sulfate, and was then transferred to the dispensing pipet by pressure of dry gas that forced the butadiene through the sintered glass filter. The dispensing pipet was an ordinary graduated dropping funnel fitted with a three-way stopcock at the bottom and a nitrogen inlet at the top. This stopcock permitted removal of excess butadiene in order to adjust the volume without passing the cold liquid through the delivery tube with consequent condensation of moisture on that member. After delivery of butadiene from the pipet to the reaction bottle, a stream of dry nitrogen was passed through the pipet and delivery tube so that no moisture condensed on the inside of the tube.

Isoprene (Phillips research grade) was freshly distilled and poured from the container as desired.

The polymerization vessel was a 12-oz. soft drink bottle. The order of admission of all components used was 180 ml. of pentane, especially dried with amylsodium (see under PP catalyst) when 5 ml. of catalyst was used, dry nitrogen, catalyst, and butadiene. The bottle was promptly capped, and shaken vigorously by hand for about thirty seconds in order to disperse the catalyst in the medium. The bottle was then transferred to an air-pump shaking machine[7] for moderate agitation. When the desired period (30 min. unless otherwise stated) for polymerizing was over, the bottle was removed, and, in case the mixture had warmed a little, cooled under the water tap for a minute—included in the time of polymerization—then opened with the bottle inverted and so placed that the contents would be blown out by the pressure of unused butadiene into a 2-liter beaker. This blowing-out process was slow and gradual if the polymerization was 70 to 80% complete, and was violent if around 20%. For polymerizations 90% or better the contents were pulled out of the bottle with forceps.

The heat evolved in these reactions was scarcely noticeable to the hand unless the polymerization was 50% or more complete. Above that amount the bottle became warm but not hot. The relatively large volume of solvent used, and the heat of vaporization of pentane inside the bottle apparently kept the temperature within bounds. If a preliminary test showed that a reaction went too fast the quantity of catalyst was reduced. A close regulation of temperature was not deemed essential at this stage of the work where the nature of the several catalysts, their

(7) Morton, *Ind. Eng. Chem., Anal. Ed.*, **6**, 469 (1934).

characteristics and polymerizing activities were being surveyed. An increase in temperature from increased conversion would magnify the greater polymerizing activity shown by a particular catalyst, but in the range studied did not increase the proportion of gel that was formed, and possibly caused only a slight decrease in gel. This point will be clearly seen in the experiments reported for the sodium methylphenyl carboxide and allylsodium pair in which 20, 40 and 60 ml. of catalyst suspension, caused 35, 75 and 82% conversion to products that had 5, 2 and 0% gel, respectively, all with about the same intrinsic viscosity. Such small differences in gel are not regarded at this time as having any real significance.

The 2-liter beaker contained about 500 ml. of petroleum ether, 10 ml. of methanol to destroy the catalyst and 1 to 10 ml. of a reagent ether solution of N-phenyl-β-naphthylamine (PBN), the amount being so varied that the quantity of antioxidant would be 2% of the expected polymer. This mixture was usually allowed to stand overnight in order to soften the rubber gel a little, or the rubber gel was removed, cut into chunks, put into a meat chopper with solid carbon dioxide and cut into small bits in order to hasten the process. The rubber was then stirred mechanically in petroleum ether for five minutes with about 200 ml. of distilled water, more pentane being added in order to get the rubber into solution or homogeneous dispersion. The lower aqueous layer was removed by a siphon and the washing with stirring repeated with another 200 ml. of distilled water. This operation had to be repeated about three or four times before the wash water was neutral to litmus and free from chloride ion. The final pentane solution was milky with scarcely any solid particles if the polymer was free from gel but contained small particles of suspended matter if the gel were high.

An aliquot portion sufficient to contain two grams of rubber in the pentane solute was removed for analysis of intrinsic viscosity and gel. The solvent was removed first at room temperature by a water pump and then overnight by an oil pump, at a temperature not exceeding 40°. The remainder was evaporated on the steam-bath and then in the vacuum oven at room temperature in order to determine the percentage conversion.

Intrinsic viscosities and gels were determined by the method employed[8] by Rubber Reserve Co. on 0.2 g. of the polymer. This method was not developed for polymers that had such high intrinsic viscosities as did some of the products from Alfin polymerization. Use of 0.1 g. of material frequently gave more consistent results.

**$PB_1$ Catalyst** (by R. P. W.).—For Series A the stock suspension of butenylsodium was made by combining three standard preparations as described before. The stock suspension of sodium isopropoxide was also made by combining three lots each obtained by addition of 26 g. of isopropyl alcohol to a standard preparation of amylsodium. For Series B the stock reagents were prepared in single batches, each twice the size of the standard one. Enough pentane was added to each suspension to make the mixture reasonably fluid. The final volumes of the Series A stock solutions were 3600 and 2400 ml. respectively for 1-butenylsodium and sodium isopropoxides and for the corresponding pair of Series B reagents were 2400 and 1600 ml. The estimated amount of 1-butenylsodium per ml. in each preparation was 0.00033 mole and the known amount of sodium isopropoxide was 0.0005 mole.

A better knowledge of the concentration of the components in each stock preparation was unnecessary and probably without significance. The stock reagents differ in their state of aggregation, and the combination to form the catalyst makes a third insoluble product besides the various aggregates in which occlusion of one or another component occurs. Analysis of organosodium reagents is difficult even in the case of soluble compounds—Conant[9] and McEwen[10] claim only 10–15% accuracy in their studies of ether-soluble reagents—and for the case of even more reactive reagents in an insoluble medium, it is much more difficult. For these tests the object was to prepare enough reagents to cover a wide range, and to compound and test them under as uniform conditions as possible and to make enough tests of each reagent over long enough periods of time to insure that a relatively constant state of reactivity has been attained.

As a first approximation, this compounding was done on the assumption that an 80% yield of amylsodium had been obtained and that the conversion to butenylsodium had been quantitative; and the mole percentages of sodium isopropoxide from this reckoning were used as the abscissas in Fig. 1. Had the estimate been correct and had there been no occlusion, all reagents to the left of no. 5 inclusive would have had the same amount of catalyst but would have had increasing amounts of butenylsodium except, of course, reagent no. 1 which contained no isopropoxide. Correspondingly, all reagents to the right of number 5 inclusive would have had a constant amount of catalyst but would have contained increasingly large amounts of isopropoxide. Of the eight reagents prepared, the graph shows that number four actually had the maximum rate of conversion and hence contained the largest number of available catalyst units. Accordingly, reagents 3 and 2 should have contained the same amount of catalyst as no. 4 because each contained the same amount of sodium isopropoxide and more than enough 1-butenylsodium to combine with this alkoxide; and reagents 5 to 8 inclusive should each contain the same amount of catalyst, although less than reagent 4. This method covers a broad range and is largely independent of an exact knowledge of the composition of the stock preparations.

The compounding of the reagents was carried out as shown in Table II.

TABLE II

COMPOUNDING OF REAGENTS FROM STOCK SOLUTIONS

| Reagent no. | Series A Volume in ml. of P[a] | $B_1$[b] | $PB_1$[c] | Series B Volume in ml. of P[a] | $B_1$[b] | $PB_1$[c] |
|---|---|---|---|---|---|---|
| 1 | ... | 540 | 600 | 0 | 360 | 400 |
| 2 | 120 | 720 | 1200 | 80 | 480 | 800 |
| 3 | 120 | 540 | 1200 | 80 | 360 | 800 |
| 4 | 120 | 360 | 600 | 80 | 240 | 400 |
| 5 | 120 | 180 | 600 | 80 | 180 | 400 |
| 6 | 240 | 180 | 600 | 80 | 150 | 400 |
| 7 | 360 | 180 | 600 | 80 | 120 | 400 |
| 8 | 480 | 180 | 1200 | 160 | 120 | 400 |
| 9 | 120 | 180 | 600 | 240 | 120 | 400 |

[a] P refers to the isopropoxide suspension used. [b] $B_1$ refers to the 1-butenylsodium suspension used. [c] $PB_1$ shows the volume of the mixture after pentane has been added as a diluent.

The stock preparations for the Series A reagents stood for several days before the compounding. The mixtures were first shaken together in the bottle by hand but developed no catalytic activity even after two days. Each was then stirred vigorously in the high-speed stirring apparatus. The aging of the reagent, as given in the Table, dates from the time they were stirred together. For the Series B reagents the mixing was done by hand shaking the day after preparation of the stock solutions. They were then catalytically active but did not attain a stable state until some time later.

The quantity of catalyst used in the polymerizations was 20 ml. for the 600 or 400 ml. of $PB_1$ suspension or twice that amount in the case of the 1200 or 800 ml. lots.

**Sodium Methylphenyl Carboxide and Allylsodium** (by F. C.).—Methylphenylcarbinol was prepared by catalytic reduction[11] of acetophenone over Raney nickel at 110° and 1800 lb., which frequently proved unsatisfactory, or by the reactions of benzaldehyde with methylmagnesium iodide

(8) Baker, Mullen and Walker, private communication.

(9) Conant and Wheland, THIS JOURNAL, **54**, 1212 (1932).

(10) McEwen, *ibid.*, **58**, 1124 (1936).

(11) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., p. 30.

according to a typical procedure.[12] The first product boiled at 92° (12 mm.) and had a refractive index, $n^{20}D$ 1.5280, the second one had a refractive index of 1.5282. The recorded[13] value is 1.5275.

The catalyst, C, was prepared by passage of propylene into a standard preparation of amylsodium to which 0.2 mole of methylphenylcarbinol had been added. Twenty ml. of this catalyst caused 35% conversion of 30 ml. of butadiene during one hour to a polymer that had an intrinsic viscosity of 5.8 and a gel of 5%; 40 ml. caused 75% conversion and the viscosity and gel were 5.2 and 2%, respectively; 60 ml. caused 82% conversion and the polymer had 4.9 viscosity and zero gel. The approximate constancy of intrinsic viscosity as the catalyst is doubled and tripled accords with the general behavior of Alfin catalyst. When applied to 20 ml. of isoprene, the conversion values for 20, 40 and 60 ml. of catalyst suspension were 8, 19 and 35% respectively, the corresponding intrinsic viscosities were 1.8, 2.8 and 2.3, and the respective gels were 0.6 and 19%.

In the making of catalyst D, this preparation was repeated with three times the proportions of reactants. The catalytic activity of D as tested by 20, 40 and 60 ml. of catalyst with butadiene was 16, 37 and 43% respectively, the corresponding intrinsic viscosities 1.0, 0.6 and 0.8 and the respective gels were 34, 15 and 33%.

Addition of 30 ml. of standard preparation of allylsodium suspension to 1675 ml. of the above catalyst suspension followed by thirty minutes of high-speed stirring to give D, altered the catalytic activity so that the conversions caused by 20, 40 and 60 ml. of catalyst, after three days of aging, $D_{1-3}$, were 28, 58 and 89%, respectively. The corresponding intrinsic viscosities were 6.0, 5.3 and 4.3 and the respective gels were 14, 19 and 22%. After this suspension had aged for fifteen days, $D_{1-18}$, the corresponding three sets of values were 32, 62, 79%, 6.7, 6.6, 5.3 and 4, 6, 7%. Another quantity of 30 ml. of allylsodium was added to give $D_2$. The remaining tests used only 20 ml. of catalyst suspensions. These results with others are listed in Table I.

**Tests with PP Catalyst** (by R. P. W., S. E. P., and R. D. C.).—Four separate preparations of PP catalyst were made by passage of propylene through standard batches of amylsodium in the presence of different quantities of isopropoxide (see Table III).

Each lot of catalyst was analyzed for its content of organosodium compound by addition of 8 g. of fluorene to 100 ml. of catalyst suspension, followed by high-speed stirring for three hours, standing overnight, carbonation on solid carbon dioxide, recovering the 9-carboxylic acid, and weighing.

The activity of these four catalysts was tested with only 5 ml. of the catalyst suspension. The results recorded in Table II show that the percentages of gels were uniformly low and the activity of the catalyst on the excess alkoxide side decreased no more within one month's time than it did on the excess allylsodium side.

The use of such a small quantity of catalyst as 5 ml. required extra precautions to eliminate moisture or other material that would destroy the catalyst. The pentane was therefore treated with amylsodium in the proportion of 100 ml. per gallon. The mixture was shaken by hand for about a minute and allowed to stand overnight by which time the solid, largely free from its color, had settled to the bottom and left the pentane layer water-white. This pentane was used as a rinse for the polymerization vessel (12 oz. soft drink bottle) as well as for the medium of the reaction. The moisture or air on the wall[14] of these glass bottles would destroy most of the color of 2 ml. of catalyst suspension added to 200 ml. of the above dried pentane within a few minutes of gentle agitation. When 2 ml. more of the catalyst suspension was added, the color of the solid was more permanent, although it, too, was decolorized by overnight standing in the sealed bottle. By rapid handling of all reagents the effect of moisture on the glass walls was minimized. Satisfactory polymerizations were carried out with as little as 3 ml. of catalyst suspension. Below 1.5 ml. of catalyst the amount of polymer formed was as low as 1 mg. even in an indefinitely long period of time.

The results with the above PP catalysts are typical of many now being obtained. Many polybutadienes that contain no gel have been obtained, although occasionally one as high as 70% is still formed.

TABLE III

PREPARATION OF PP CATALYSTS AND POLYMERIZATIONS CAUSED THEREWITH

| Reagent no. | | 1[a] | 2[a] | 3[b] | 4[b] |
|---|---|---|---|---|---|
| Total vol. of cat. suspension, ml. | | 850 | 850 | 875 | 850 |
| Sodium isopropoxide,[c] moles | | .20 | .16 | .12 | .10 |
| Allylsodium,[d] moles | | .12 | .13 | .16 | .19 |
| Catalyst, total[e] moles | | .12 | .13 | .12 | .10 |
| Catalyst used in polymerization, moles × $10^6$ | | 750 | 765 | 685 | 585 |
| Poly. of butadiene[f] | | | | | |
| Test No. 1 | Conversion, % | 71 | 61 | 51 | 28 |
| | Intrinsic viscosity | 8.6 | 17.0 | 15.7 | 11.7 |
| | Gel, % | 4.4 | 11 | 11 | 16 |
| Test No. 2[g] | Conversion, % | 66 | 57 | 49 | 25 |
| | Intrinsic viscosity | 12.8 | 15.1 | 13.9 | 13.0 |
| | Gel, % | 7 | 9 | 4 | [low] |

[a] The color of these suspensions was gray-green to blue-green and the fluidity was high. [b] The color of these two catalysts was slate-blue and the fluidity was low. When used as the polymerization agent they show a tendency to form clumps of insoluble polymer at the beginning of the reaction. [c] The moles of isopropoxide was calculated from the amount of isopropyl alcohol added. [d] Calculated from the weight of fluorene-9-carboxylic acid isolated. [e] Calculated from the quantity of that one of the two components present in lesser amount. [f] Polymerization test one day after preparation of the catalyst. [g] Polymerization test one month after preparation of the catalyst.

## Summary

In Alfin polymerization of butadiene a minimum of gel appears to accompany a maximum of conversion. Incorrect proportioning of the catalyst component or a large excess of catalyst beyond that needed for high efficiency may cause the formation of gel during polymerization.

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(12) Dreger, *Organic Syn.*, Coll. Vol. I, p. 307.

(13) Dechamps, *Bull. soc. chim. Belg.*, **33**, 270 (1924).

(14) Bent and Lesnick, THIS JOURNAL, **57**, 1246 (1935).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Polymerization. X. Metalation of Alkylaryl Hydrocarbons and their Use in the Polymerization of Butadiene[1]

BY AVERY A. MORTON AND ERNEST L. LITTLE, JR.[2]

Alkylaryl compounds are metalated either in the ring or on the alpha carbon of the side chain. If the metal enters the ring, the product can function as a catalyst for the polymerization of butadiene in the same way as did phenylsodium.[3] If it enters the side chain it can function as the Alfin catalyst[4] with sodium isopropoxide, provided that a double bond in the benzene ring can serve in place of the double bond in the olefin. Accordingly a large number of these hydrocarbons were metalated in order to see where metalation occurred, and whether any of the products had interest as a catalyst for the polymerization of dienes.

TABLE I

METALATION OF HYDROCARBONS BY AMYLSODIUM

| Hydrocarbon[a] | Total yield based on $C_5H_{11}Cl$[b] | Total yield based on $C_5H_{11}Na$[c] | Percentage distribution of carboxyl groups: $\alpha$ Carbon | In monometalated products: Ortho | Meta | Para | In dicarbox. acids | In caproic acid |
|---|---|---|---|---|---|---|---|---|
| Et | 19 | 28 | 100 | | | | | |
| Iso | 35 | 53 | | 11.5 | | 88.5 | | |
| *t*-Bu | 31 | 46 | | | 17.3 | 67.1 | 15.6 | |
| *t*-Bu[e] | 48 | 60 | | | 2.7 | 28.3 | 4.5 | 64.5 |
| *p*-Cy | 35 | 52 | 56.7 | | | | 43.3 | |
| $\beta$-Me | 43 | 64 | 100 | | | | | |
| Diben. | 48 | 70 | | | | | 100 | |
| Diph. | 61 | 92 | 100 | | | | | |
| Triph. | 62 | 93 | 100 | | | | | |
| Flu. | 66 | 100 | 100 | | | | | |
| Ace. | | | | | | | 17.5[b] | |

[a] The abbreviations refer respectively to ethylbenzene, isopropylbenzene, *t*-butylbenzene, *p*-cymene, $\beta$-methylnaphthalene, dibenzyl, diphenylmethane, triphenylmethane, fluorene and acenaphthene. The quantity of hydrocarbon added in each case was 0.22 mole except in the second experiment with *t*-butylbenzene in which 0.44 mole was added. [b] In each experiment 0.5 mole of amyl chloride and 1 g. atom of sodium were used in the preparation of amylsodium. In all cases, except the second experiment with *t*-butylbenzene, 0.2 mole of isopropyl alochol was used. Hence the actual amount of amyl chloride is as if only 0.3 mole were used. Yields were calculated on this quantity. [c] The yield of amylsodium is usually around 80% of the amyl chloride used; hence, this amount was assumed to be present. [d] Caproic acid represents unused amylsodium. [e] This experiment was the only one in which no sodium isopropoxide was used. [b] The crude mixture weighed 17.5 g. from which some of the same dicarboxylic observed before and isolated as the dimethyl ether was obtained. Some mono carboxylic acid was possibly present in the crude mixture.

Of the hydrocarbons tested two were metalated in the ring and the remainder in the side alkyl group (see Table I). All except fluorene and acenaphthene had a little catalytic activity (see Table II) but only benzylsodium could be said to be moderately good with respect to percentage conversion and intrinsic viscosity of product. The metalation of toluene to give benzylsodium has previously[5] been shown to yield some disubstitution products as the quantity of toluene is made less. Accordingly the benzylsodium catalyst was prepared with three proportions of toluene (see Table III). The best activity with respect to conversion and the intrinsic viscosity and gel of the product was found with the catalyst that should contain the smallest amount of phenylene disodium.

Acenaphthene and fluorene formed no catalyst. The failure of these compounds to yield a catalyst was confirmed by adding each to an allylsodium–sodium isopropoxide (PP) catalyst and observing the destruction of catalytic activity. Acenaphthene gradually reduced the conversion activity to zero over a 100-day interval during which the intrinsic viscosity of the polymer formed also fell from 15 to 0. Fluorene caused the same changes within one day. In each case carbonation of the destroyed catalyst showed only the expected products from fluorene and acenaphthene. By contract the addition of toluene to the same catalyst caused a drop in intrinsic viscosity to 13 in a period of fifty-one days, and the percentage conversion remained at 100.

Incidental matters of interest with respect to the metalation of the hydrocarbon are (a) the high percentage of para substitution in the metalation of isopropylbenzene and *t*-butylbenzene; (b) the metalation of the methyl group of *p*-cymene in preference to the isopropyl group; (c) the formation of *meso*-$\alpha,\beta$-diphenylsuccinic acid from metalation and carbonation of dibenzyl,

(1) This work was carried out under the auspices of The Office of Rubber Reserve, Reconstruction Finance Corporation.

(2) Present address: Experimental Station, E. I. du Pont de Nemours Co., Wilmington, Del.

(3) Morton and Letsinger, THIS JOURNAL, **69**, 172 (1947).

(4) Morton, Magat and Letsinger, *ibid.*, **69**, 950 (1947).

(5) Morton, Little and Strong, THIS JOURNAL, **65**, 1339 (1943).

TABLE II

CATALYTIC ACTIVITY OF METALATED HYDROCARBONS

| Hydrocarbons[a] | Catalyst age, days | Conver., % | Gel, % | Intrin. vis. |
|---|---|---|---|---|
| None[b] | 1 | 3 | 6 | 1.2 |
| | 1 | 2 | 30 | 1.0 |
| Tol. | 6 | 89 | 23 | 4.0 |
| | 20 | 70 | 29 | 7.4 |
| Tol.[c] | 4 | 100 | 13 | 7.6 |
| | 73 | 48 | 0 | 7.5 |
| *o*-Xy. | 1 | 32 | 28 | 0.7 |
| | 49 | 34 | 51 | 1.3 |
| *m*-Xy. | 1 | 18 | 30 | 1.3 |
| | 48 | 9 | 38 | 2.1 |
| *p*-Xy. | 1 | 43 | 24 | 2.3 |
| | 32 | 33 | 39 | 2.5 |
| *p*-Cy. | 1 | 48 | 46 | 1.4 |
| | 4 | 33 | 28 | 2.1 |
| Et | 1 | 12 | 21 | 0.7 |
| | 3 | 14 | 10 | .6 |
| Iso. | 1 | 4 | 23 | .5 |
| | 5 | 3 | 23 | .8 |
| *t*-Bu | 1 | 1 | 59 | 3.9 |
| *t*-Bu[d] | 1 | 23 | 31 | 0.8 |
| *β*-Me | 1 | 34 | 27 | .5 |
| | 7 | 31 | 24 | .5 |
| Diben. | 3 | 28 | 26 | .5 |
| | 10 | 47 | 64 | 1.0 |
| Diph. | 7 | 20 | 36 | 0.6 |
| | 47 | 5 | 31 | .8 |
| Triph. | 1 | 18 | 52 | .2 |
| | 3 | 14 | 20 | .2 |
| Fl. } No rubber formed | | | | |
| Ace. } | | | | |

[a] The abbreviations in this column have the same significance as those in Table I with addition of toluene (Tol.) and the three xylenes (Xy.). The quantity of hydrocarbon used in each preparation was 0.22 mole, except in the second experiment with toluene where 1 mole was used. [b] Amylsodium only was used in this test. [c] In the preparation of this catalyst 1 mole of toluene was added to the standard preparation of amylsodium. [d] This reagent is the only one that contained no sodium isopropoxide.

TABLE III

VARIATION IN CATALYTIC ACTIVITY OF THE BENZ PP CATALYST AS THE PROPORTION OF PHENYLENE DISODIUM COMPOUND IS INCREASED

| | Increasing quantity of disodium compounds | | | | | |
|---|---|---|---|---|---|---|
| Quantity of toluene used in prepn. of cat. mole | 1 | | 0.22 | | 0.145 | |
| Age of catalyst, days | 4 | 73 | 6 | 20 | 1 | 46 |
| Conversion, % | 100 | 48 | 89 | 70 | 63 | 82 |
| Intrinsic viscosity | 7.6 | 7.5 | 4.0 | 7.4 | 3.9 | 5.2 |
| Gel, % | 13 | 0 | 23 | 29 | 38 | 33 |

indicating that the two sodium ions had taken positions as far apart as possible, (d) the freedom of tarry products[6] from acenaphthene when the metalation–carbonation process is carried out under the present improved conditions and (e) the general success of metalation–carbonation with many of the hydrocarbons such that the process is a good preparative one for certain carboxylic acids.

**Acknowledgment.**—The authors are greatly indebted to Christiana Clapp and Jeanne Kilduff for valuable technical assistance and determination of intrinsic viscosity.

## Experiments

**Metalation of Hydrocarbons.**—The hydrocarbons were Eastman Kodak Co. grade, the physical constants of which either agreed with accepted values or did so after redistillation or recrystallization. Each hydrocarbon (0.22 mole) was added to a standard preparation[13] of amylsodium to which sodium isopropoxide (0.2 mole) had previously been added. Larger amounts were used in the same proportions. The mixture was stirred for four hours after which the contents were transferred to a bottle. Samples were withdrawn when tests of catalytic activity (see Table II) were made, after which the mixture was carbonated by pouring onto solid carbon dioxide. The aqueous layer of the sodium salts was usually extracted once with petroleum ether to remove traces of organic material. Hydrochloric acid was then added. Any solid that precipitated was separated by filtration, the aqueous layer was then extracted with petroleum ether. The remaining aqueous layer was saturated with salt and extracted with ethyl ether. In the following paragraph these three fractions will be referred to as the initial precipitate, the petroleum ether fraction and the ethyl ether fraction. The weights of products are those actually obtained but the percentage yields given in Table I are corrected for the quantity of suspension removed for the polymerization test.

The gray-colored suspension from ethylbenzene yielded 7.3 g. of an oil from the petroleum ether portion. Fractionation gave 6.3 g. of liquid that boiled at 120–125° (4 mm.) and 1 g. of a resinous product. The liquid was identified as *α*-methylphenylacetic acid by its neutralization equivalent of 150.8 (calcd. 150) and the melting point of its amide, 90.7–91.7 cor. (reported[7] value is 91–92°). A yellow gum (1.5 g.) was obtained from the ethyl ether fraction.

The purple colored suspension from isopropylbenzene yielded 19.5 g. of an oil from the petroleum ether portion. Fractionation separated the oil into 13.8 g. that boiled at 104–114° (3 mm.), 4.9 g. that boiled at 114–117° (3 mm.) and 1 g. of a reddish gum. The first fraction was dissolved in 10 ml. of petroleum ether and placed in a refrigerator. Crude crystals of *p*-cuminic acid separated. When recrystallized from 80–20 alcohol–water solution, 11.2 g. of the pure acid, m. p. 115–116° (reported[8] value 115–116°) was recovered. The neutralization equivalent was 163 (calcd. 164). The amide melted at 152–153° cor. (153° reported[9]). The oil recovered from the mother liquor was dissolved in 10 ml. of ethanol and 2 ml. of water and again cooled. *o*-Cuminic acid (2 g.) separated. The neutralization equivalent was 164 (calcd. 164) and the melting point was 48.5–50° (51° reported[10]). The fraction that distilled at 114–117° crystallized in the receiver and, after crystallization from 50 ml. of ethyl alcohol–water (80-20 mixture), yielded 4.1 g. of pure *p*-cuminic acid. The ethyl ether fraction yielded 2 g. of a reddish gum.

The black colored suspension from *t*-butylbenzene yielded 15.5 g. in the initial precipitate and only traces of material from the other two fractions. Extraction of the precipitate with petroleum ether left a residue which yielded 7.1 g. of crystals from 100 ml. of aqueous 80% alcohol. These crystals proved to be *t*-butylbenzoic acid by the neutralization equivalent of 178, the melting point

(6) Morton and Gibb, THIS JOURNAL, **64**, 2250 (1942).

(7) Janssen, *Ann.*, **250**, 136 (1888).

(8) Persoz, *ibid.*, **44**, 312 (1842).

(9) Gattermann and Schmidt, *ibid.*, **244**, 52 (1888).

(10) Kothe, *ibid.*, **248**, 62 (1888).

of 161.5–162.5° (160–161° reported)[11] and by the amide derivative that melted at 170.5–171° uncor. (171° reported[11]). The crystals (8.4 g.) from the mother liquor melted at 85–90° and proved to be a mixture of the *p*-acid with a little of the *m*-isomer. The mixture was first subjected to multiple fractional extraction[12] which divided it into 8 portions. The first seven portions melted at 90–95° the last melted at 290° and yielded 0.8 g. of a dicarboxylic acid after crystallization from aqueous alcohol. The first seven fractions were then recombined and subjected to alternate crystallizations from benzene and then from aqueous 80% alcohol until 2.9 g. of pure *m*-*t*-butylbenzoic acid and 3.9 g. of the pure para isomer were obtained. The *m*-acid was identified by its neutralization equivalent of 179, its melting point of 127–127.5° cor. (reported[13] 127°) and the melting point of its amide 128–129° (reported[13] 130°). The dicarboxylic acid separated in the extraction process possibly contained one carboxyl group ortho to the *t*-butyl group since the principle by which the separation process operates would insure that the strongest acid would be in that portion and *o*-*t*-butylbenzoic acid is much stronger[14] than the other two isomers. Furthermore this position would be the focus of all the directing influences present after initial metalation on the methyl group.

The products from the metalation of *t*-butylbenzene in the absence of isopropoxide yielded no initial precipitate, but the petroleum ether fraction contained 8 g. of *p*-*t*-butylbenzoic acid and 18 g. of caproic acid, the latter from unused amylsodium which was recovered by distillation after the crystals had separated. The residue from the distillation was subjected to alternate crystallizations from benzene and the aqueous alcohol solution until 4.1 g. of the *p*-acid and 1.1 g. of the *m*-isomer were recovered. The ethyl ether fraction yielded 1 g. of a brownish solid from which 0.6 g. of a dicarboxylic acid (m. p. 310–315° in a sealed tube) was obtained after decoloration with carbon and recrystallization from aqueous alcohol.

The green colored suspension from *p*-cymene yielded 9 g. of an oil from the petroleum ether portion. Fractionation at 118–123° (3 mm.) gave 6.5 g. that solidified, had a neutralization equivalent of 176.5 (calcd. 178) and a melting point of 50–51°, near to the 51–52° reported[15] for 4-isopropylphenylacetic acid. The amide melted at 169–170° cor. (170° reported[15]). Two grams of a resinous material was left as a residue from the distillation. The ethyl ether portion yielded 3 g. of a red gum which was treated with decolorizing carbon in boiling water. A dicarboxylic acid (2.5 g.) was recovered, m. p. 189–190° cor.

The purple colored suspension from β-methylnaphthalene yielded 17 g. in the initial precipitate. Recrystallization from water gave 16.5 of β-naphthylacetic acid that melted at 141.0–141.5° (reported[16] 141–142°). The neutralization equivalent was 186 (calcd. 186). The amide melted at 200–201° uncor. (reported[17] 200°).

The brown colored suspension from dibenzyl yielded 1 g. of a yellow gum from the petroleum ether extract and 8 g. of meso-α,β-diphenylsuccinic acid from the ethyl ether extract. Recrystallization of the latter from aqueous alcohol yielded 7.3 g. of pure acid that melted at 229–230° uncor. (reported[18] value is 229–230°). The neutralization equivalent was 135.6 (calcd. 135). The dimethyl ester was prepared with diazomethane and melted at 220.5–221.5° (reported[18] 219–220°).

The yellow colored suspension from diphenylmethane yielded 31.5 g. of diphenylacetic acid in the initial precipitate. When recrystallized from water, it melted at 147.5–148.5° (148° recorded[19]). The neutralization equivalent was 214 (calcd. 212). The amide melted at 167–168° cor. (167.5–168.5° reported[20]). The ether extract yielded 0.5 g. of a red gum.

The red colored suspension from triphenylmethane yielded 37.2 g. of triphenylacetic acid in the initial precipitate. It melted at 266.3–267.3 cor. (267° reported[21]). The methyl ester melted at 185–185.5° cor. (186° reported[21]).

The yellow colored suspension from fluorene yielded 38.7 g. of crude 9-fluorenecarboxylic acid which melted at 220–222° (222–225° reported[22]) when recrystallized from glacial acetic acid. The neutralization equivalent was 210 (calcd. 210). The methyl ester melted at 62–63° (63° recorded[22]).

The green colored suspension from acenaphthene yielded as an initial precipitate 17.5 g. of a yellow solid that was a mixture of acids. Treatment with diazomethane yielded the dimethyl ester of the carboxylic acid already reported.[6]

**The Carbonation Product from Benzylsodium and Sodium Isopropoxide Mixture.**—Phenylacetic acid (0.033 mole) was obtained from the petroleum ether portion. Homoisophthalic acid was obtained from the ethyl ether fraction. No other acids could be found.

**Polymerization Tests.**—The suspensions of metalated hydrocarbons were tested for catalytic activity in the manner described in the previous publication. Twenty ml. of each catalyst was used with 30 ml. of butadiene for one hour. The results are recorded in Tables II and III.

**Effect of Acenaphthene and Fluorene on the PP Catalyst.**—Two molar equivalents of hydrocarbon per estimated mole of catalyst were stirred together for four hours at room temperature. The respective green and yellow colored suspensions were then tested for catalytic activity in the usual way.

**Attempted Use of Cyclohexene.**—Cyclohexene (20 g.) was metalated by a standard quantity of amylsodium to which had been added 7.5 g. of isopropyl alcohol. Before addition of cyclohexene the organosodium reagent (20 ml.) caused the polymerization within one hour of 4% of the butadiene (30 ml.) to a polymer that had an intrinsic viscosity of 0.5 and a gel of 5%. After addition of cyclohexene, the metalated hydrocarbon caused 6% conversion to a polymer that had an intrinsic viscosity of 0.6 and no gel.

## Summary

A number of alkylaryl hydrocarbons have been metalated by amylsodium in order to observe the position of metalation and the behavior of the products as catalysts for the polymerization of butadiene.

Isopropylbenzene and *t*-butylbenzene are metalated in the nucleus. Ethylbenzene, *p*-cymene, β-methylnaphthalene, diphenylmethane and triphenylmethane are metalated on the side carbon atom, preferably on a methyl group if there is more than one possibility.

Benzylsodium yields an Alfin catalyst of moderate activity. Other alkylaryl compounds, when metalated, yield poor catalysts. Acenaphthene and fluorene destroy the activity of an Alfin catalyst and show no catalytic action when metalated.

RECEIVED OCTOBER 4, 1947

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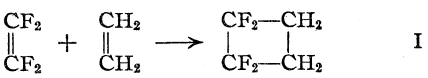
[CONTRIBUTION NO. 252 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

# Synthesis of Tetrafluorocyclobutanes by Cycloalkylation

BY DONALD D. COFFMAN, PAUL L. BARRICK, RICHARD D. CRAMER AND MAYNARD S. RAASCH

## Introduction

Recent publications[1a,b,c,d] have described a new reaction which involves the addition of a fluoroolefin to itself, *e. g.*, the dimerization of tetrafluoroethylene[1a] or of chlorotrifluoroethylene,[1b] and to certain olefin derivatives such as chlorotrifluoroethylene,[1c] acrylonitrile[1d] and methyl methacrylate,[1d] to give cyclobutane derivatives. This new reaction has now been studied in considerable detail, and has been extended to the addition of tetrafluoroethylene to a wide variety of olefins. The general nature of this cycloalkylation method of preparing cyclobutane derivatives has been established. Thus, with ethylene, tetrafluoroethylene gives tetrafluorocyclobutane (I).



I

Analogous reactions of tetrafluoroethylene with various unsaturated compounds have given the corresponding tetrafluorocyclobutanes substituted by halogen, vinyl, ethynyl or other groups.

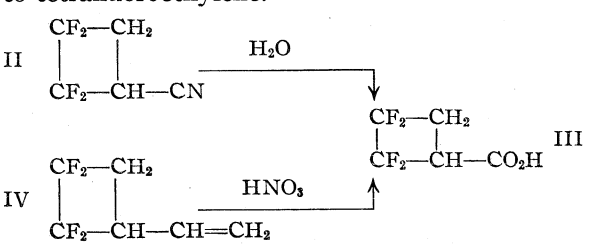
## Generality of the Cycloalkylation

The cycloalkylation of tetrafluoroethylene with unsaturated compounds occurs at a lower temperature and apparently with greater facility than does the dimerization of tetrafluoroethylene.[1a] Under the conditions employed, the synthesis yields 4-membered ring compounds without the competitive dimerization of tetrafluoroethylene to octafluorocyclobutane and without the appreciable formation of 6-membered or larger rings and open-chain polymers. Qualitatively, the ease of reaction varies with the unsaturated reactant. Reactants containing a terminal methylene group combine more readily than do 1,2-disubstituted ethylenes such as 2-butene or trichloroethylene, while reactants having conjugated unsaturation, for example, 1,3-butadiene, acrylonitrile, methyl methacrylate and styrene, are even more reactive.

**Reactions with Vinyl Compounds.**—The cycloalkylation with vinyl and vinylidene compounds is illustrated by the formation of tetrafluorocyclobutane (I) from tetrafluoroethylene and ethylene, and by the substituted tetrafluorocyclobutanes formed in the reaction of tetrafluoroethylene with monolefins such as styrene, with chloroolefins typified by vinyl chloride, and with vinyl acetate, acrolein, allyl alcohol and the related unsaturates listed in Tables I, II, III.

Evidence for the tetrafluorocyclobutane structure is found in the mode of formation, the composition, and the properties of the products. The product from tetrafluoroethylene and a monoölefin has an empirical composition corresponding to that of one molecule of tetrafluoroethylene plus one molecule of olefin. The product is stable to aqueous permanganate, does not react with a solution of bromine in carbon tetrachloride, is unaffected under the usual conditions of catalytic hydrogenation, and its infrared absorption spectra show no absorption bands characteristic of the carbon–carbon double bond. The fluorohydrocarbon is resistant to oxidation as indicated by incomplete combustion in attempts to analyze the cyclobutanes from ethylene, propylene, isobutylene and 2-butene.

Further proof of structure is found in the transformations of products from acrylonitrile and from butadiene. Tetrafluoroethylene and acrylonitrile combine to form in good yield a nitrile which corresponds in composition to cyanotetrafluorocyclobutane (II). On acid hydrolysis, the nitrile gives the saturated tetrafluorocyclobutane carboxylic acid (III). The same acid (III) is obtained by the nitric acid oxidation of the unsaturated product (IV) formed by the addition of one molecule of tetrafluoroethylene to 1,3-butadiene. These transformations establish the identity of (III) as 2,2,3,3-tetrafluorocyclobutane carboxylic acid and of (IV) as 1-vinyl-2,2,3,3-tetrafluorocyclobutane formed by the 1,2-addition of butadiene to tetrafluoroethylene.



**Reactions with 1,3-Dienes.**—As already indicated, cycloalkylation occurs in the reaction of tetrafluoroethylene with terminally unsaturated dienes. The initial 1:1 products are tetrafluorocyclobutanes containing an unsaturated side chain. By further reaction with another molecule of tetrafluoroethylene, a bicyclic product containing two tetrafluorocyclobutane rings is formed. The simplest cases are the products from 1,3-butadiene and from allene. 1,3-Butadiene and tetrafluoroethylene form 1-vinyl-2,2,3,3-tetrafluorocyclobutane (IV) and not the tetrafluorocyclohexene that might have been expected by a Diels–Alder reaction. By hydrogenation, IV was converted to 1-ethyl-2,2,3,3-tetrafluorocyclobutane.

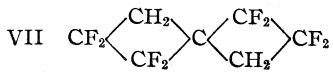
(1) (a) J. Harmon, U. S. Patent 2,404,374 (July 23, 1946); (b) A. L. Henne and R. D. Ruh, THIS JOURNAL, **69**, 279 (1947); (c) P. L. Barrick, U. S. Patent 2,427,116 (September 9, 1947); (d) P. L. Barrick and R. D. Cramer, U. S. Patent 2,441,128 (May 11, 1948).

Reaction of IV with another molecule of tetrafluoroethylene gave 2,2,2′,2′,3,3,3′,3′-octafluorobicyclobutyl (V). Similarly, in reactions with tetrafluoroethylene, allene gave the 1-methylene-2,2,3,3-tetrafluorocyclobutane (VI) and 1,1,2,2,5,5,6,6-octafluorospiro[3.3]heptane (VII).

IV $CF_2(-CF_2)-CH(-CH=CH_2)$

V $CF_2(-CF_2)-CH(-CH(-CF_2)-CF_2)$

VI $CF_2(-CF_2)-C(=CH_2)$

VII 

Isomeric products are obtained from tetrafluoroethylene and unsymmetrical dienes. Thus 2-chloro-1,3-butadiene gave the isomers VIII and IX.

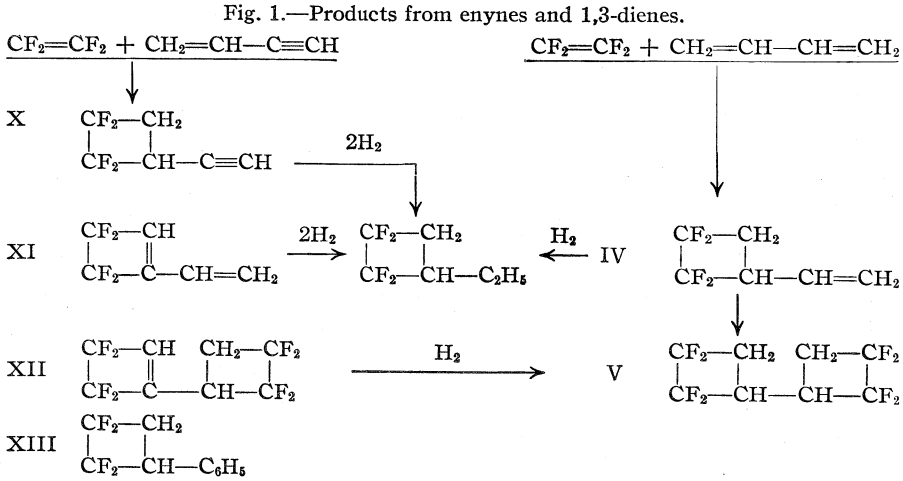
VIII $CF_2(-CF_2)-C(Cl)-CH=CH_2$

IX $CF_2(-CF_2)-CH(-C(Cl)=CH_2)$

The structures of compounds VIII and IX are believed to be those shown in view of (1) their compositions which correspond to a 1:1 tetrafluoroethylene/2-chloro-1,3-butadiene mole ratio; (2) their molecular refractivities which are in agreement with that for a tetrafluorocyclobutane derivative; (3) the conversion of IX to 1-ethyl-2,2,3,3-tetrafluorocyclobutane by hydrogenation; and (4) inability to obtain a chlorine-free product by the hydrogenation of VIII. Two isomeric 1:1 adducts were also obtained from tetrafluoroethylene and 2-fluoro-1,3-butadiene.

**Reactions with Enynes.**—Cycloalkylations with tetrafluoroethylene and an enyne proceed with participation of both the ethylenic and the acetylenic groups of the enyne. The products include the isomeric 1:1 tetrafluoroethylene/enyne adducts and also the bicyclic 2:1 adduct. Four clearly identified products have been obtained from monovinylacetylene. The first of these is 1-ethynyl-2,2,3,3-tetrafluorocyclobutane (X) Fig. 1, formed by reaction of tetrafluoroethylene at the ethylenic linkage of monovinylacetylene. Compound X contained an acetylenic hydrogen as shown by reaction with aqueous silver nitrate. By hydrogenation, X was converted to the 1-ethyl-2,2,3,3-tetrafluorocyclobutane independently synthesized from tetrafluoroethylene and 1,3-butadiene. Monovinylacetylene also reacted by 1,2-addition at the acetylenic linkage with the formation of compound XI. The structure XI was established as 1-vinyl-3,3,4,4-tetrafluorocyclobutene by its polymerizability, by its hydrogenation to 1-ethyl-2,2,3,3-tetrafluorocyclobutane, and by reaction with a second molecule of tetrafluoroethylene to obtain 2′,2′,3′,3′-tetrafluorocyclobutenyl-2,2,3,3-tetrafluorocyclobutane (XII). By hydrogenation, XII gave 2,2,2′,2′,3,3,3′,3′-octafluorobicyclobutyl (V), which was also synthesized from butadiene and two molecules of tetrafluoroethylene. The fourth product obtained from tetrafluoroethylene and monovinylacetylene was 1-phenyl-2,2,3,3-tetrafluorocyclobutane XIII, identical with the adduct of tetrafluoroethylene and styrene. The formation of XIII suggests that under the reaction conditions monovinylacetylene dimerized to styrene[2] which combined with tetrafluoroethylene.

Fig. 1.—Products from enynes and 1,3-dienes.




**Physical Properties.**—The physical properties of selected tetrafluorocyclobutane derivatives are given in Tables I to IV, inclusive. In general, the introduction of fluorine in the cyclobutane ring lowers the refractive index and increases the density of the products. The observed molecular refractivity was calculated by means of the Lorenz–Lorentz equation. The atomic refraction of fluorine was determined by subtracting the sum of the commonly used values (Eisenlohr's) of all the other increments from the experimental value and dividing the difference by the number of fluorine atoms. The atomic refraction of fluorine in these compounds, $AR_F$, varied from 1.04–1.64 and averaged about 1.16.[3] The tetrafluorocyclobutanes containing only carbon, hydrogen and fluorine in Table I have an average $AR_F$ of 1.08 which agrees with the reported value for a fluorohydrocarbon containing four fluorine atoms per molecule.[4] The introduction of other atoms such as chlorine, oxygen, and/or nitrogen, and special configurations such as present in unsaturated substituents

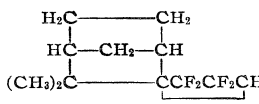
(2) H. B. Dykstra, THIS JOURNAL, **56**, 1625 (1934).

(3) Weissberger, "Physical Methods of Organic Chemistry," Volume I, Interscience Publishers, Inc., New York, N. Y., 1945, p. 679.

(4) Grosse and Cady, *Ind. Eng. Chem.*, **39**, 373 (1947).

TABLE I

REACTION PRODUCTS FROM TETRAFLUOROETHYLENE AND MONO-OLEFINS

| Tetrafluorocyclobutane | B. p., °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | $AR_F$ | Analyses | C | H | F | Reactants[a] (g. $C_2F_4$/g. monoölefin) | Yield % based on $C_2F_4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2CF_2CF_2CH_2$ | 50–50.7 | | 1.3046 | 1.2752 | 18.8 | 1.06 | $C_4H_4F_4$ Calcd. | 37.50 | 3.13 | 59.37 | 35/75 | 40 |
| | | | | | | | Found | [c] | [c] | 59.44 | ethylene | |
| $CH_3CHCF_2CF_2CH_2$ | 68.5–68.8 | | 1.3193 | 1.1961 | 23.5 | 1.08 | $C_5H_6F_4$ Calcd. | 42.25 | 4.22 | 53.53 | 50/125 | 72 |
| | | | | | | | Found | [c] | [c] | 53.73 | propylene | |
| $CH_3CH_2CHCF_2CF_2CH_2$[b] | 91 | | 1.3370 | 1.1506 | 28.0 | 1.06 | $C_6H_8F_4$ Calcd. | 46.15 | 5.13 | 48.72 | | |
| | | | | | | | Found | | | 48.25 | | |
| $(CH_3)_2CCF_2CF_2CH_2$ | 82–83 | | 1.3395 | 1.1446 | 28.4 | 1.15 | $C_6H_8F_4$ Calcd. | 46.15 | 5.13 | 48.72 | 50/125 | 30 |
| | | | | | | | Found | [c] | [c] | 49.21 | isobutylene | |
| $CH_3CH_2CH_2CHCF_2CF_2CH_2$[b] | 113 | | 1.3516 | 1.1190 | 32.62 | 1.05 | $C_7H_{10}F_4$ Calcd. | 49.40 | 5.90 | 44.70 | | |
| | | | | | | | Found | 51.97 | 6.22 | 44.00 | | |
| $CH_3CH_2(CH_3)CCF_2CF_2CH_2$[b] | 107.8 | | 1.3529 | 1.1285 | 32.57 | 1.04 | $C_7H_{10}F_4$ Calcd. | 49.40 | 5.90 | 44.70 | | |
| | | | | | | | Found | 54.23 | 6.83 | 45.98 | | |
| $CH_3CHCF_2CF_2CHCH_3$ | 87.5 | | | | | | $C_6H_8F_4$ Calcd. | 46.15 | 5.13 | 48.72 | 50/125 | 5 |
| | | | | | | | Found | [c] | [c] | 50.35 | butene-2 | |
| $C_6H_5CHCF_2CF_2CH_2$ | 62 | 5 | 1.4512 | 1.2714 | 43.15 | 1.12 | $C_{10}H_8F_4$ Calcd. | 58.83 | 3.92 | 37.25 | 50/125 | 85 |
| | | | | | | | Found | 58.7 | 4.24 | 39.34 | styrene | |
|  | 97–101 | 20 | 1.4352 | | | | $C_{12}H_{16}F_4$ Calcd. | 61.02 | 6.83 | 32.18 | 70/95 | 7 |
| | | | | | | | Found | 61.38 | 7.08 | 31.0 | camphene | |
| $CH_3CH_2CFCF_2CF_2CH_2$[b] | 89–90 | | 1.3295 | 1.2570 | 28.1 | 1.08 | $C_6H_7F_5$ Calcd. | 41.4 | 4.02 | 54.6 | | |
| | | | | | | | Found | [c] | [c] | 54.79 | | |

[a] The reactants were agitated at 150° under autogenous pressure for about eight hours. [b] These products were prepared by hydrogenation of the 1:1 reaction products of tetrafluoroethylene with 1,3-butadiene, 1,3-pentadiene, 2-methyl-1,3-butadiene and 2-fluoro-1,3-butadiene. [c] Extremely low C and H values were obtained due to incomplete combustion of the compounds.

appear to cause some variation in the values for the atomic refraction of fluorine. For example, the tetrafluorocyclobutanes from chloroölefins (Table II) have an average $AR_F$ value of 1.30, while the products of Table III and IV have average $AR_F$ values of 1.20 and 1.12, respectively.

## Experimental

**Preparation of Tetrafluorocyclobutanes.**—The procedure for carrying out the cycloalkylation of tetrafluoroethylene with most of the unsaturated compounds listed in Tables I through IV consisted in charging 100 to 150 g. of the unsaturated compound containing a small amount of polymerization inhibitor, such as hydroquinone or "Terpene B" hydrocarbon,[5] into a 400 ml. high-pressure shaker tube lined with silver or stainless steel. A tube capable of withstanding operating pressures up to 500 atm. should be used when the unsaturated compound to be treated with tetrafluoroethylene is a gas at room temperature. The tube was cooled and evacuated to remove oxygen, and 50 g. of tetrafluoroethylene was added. The reaction mixture was heated under autogenous pressure with agitation at 150° for about eight hours. The pressure varied with the different reactants, but was initially about 45 atm. when the unsaturated compound was a liquid, and decreased as the reaction proceeded. After cooling and releasing any pressure, the liquid product was removed and steam distilled to separate the monomeric products from any non-volatile residue. The steam-volatile tetrafluorocyclobutane derivatives were fractionated.

A detailed study of synthesis conditions was not made. Accordingly, the yields given in the tables are not necessarily optimum. The yields are based on the amount of tetrafluoroethylene charged and are not corrected for the amount of tetrafluoroethylene which did not react. In general where low yields have been reported, reaction was incomplete and for the most part unaccompanied by polymerization of the individual reactants. Typical preparations are described in the following paragraphs.

**Caution.**—Information is not available concerning the toxicity of the various fluorine-containing products described. Acordingly, the products should be regarded with suspicion and handled with appropriate care.

**Analysis.**—It will be noted that the values obtained for carbon in the combustion analyses were frequently higher than the theoretical values. The apparently high carbon values for products containing appreciable proportions of fluorine result from the absorption of hydrogen fluoride formed during combustion and carried over into the Ascarite carbon dioxide absorber. Spongy silver placed in the absorption train preceding the Ascarite is beneficial in minimizing the carry over of hydrogen fluoride, but the silver must be replaced frequently.

**1,1,2,2-Tetrafluorocyclobutane.**—A silver-lined, high-pressure shaker tube was evacuated and charged with 35 g. of tetrafluoroethylene and 75 g. of ethylene. The sealed reactor was then heated under autogenous pressure at 150° with agitation for eight hours. After cooling the tube and bleeding off the gases slowly, there was obtained 17.9 g. of condensate (40% of theory). Characterization showed the condensate to be 1,1,2,2-tetrafluorocyclobutane which had the following properties: b. p. 50–50.7°, $n^{25}D$ 1.3046, $d^{25}_4$ 1.2752, $MR_D$ 18.8.

*Anal.* Calcd. for $C_4H_4F_4$: F, 59.37. Found: F, 59.44.

**Warning.**—Care should be exercised in preparing and heating mixtures of ethylene and tetrafluoroethylene since a violent explosion occurred when a mixture of 50 g. of tetrafluoroethylene and 125 g. of ethylene was heated at 160° and 480 atm. No difficulty was experienced with the other unsaturated compounds. Particular precau-

(5) A terpene fraction consisting principally of dipentene and terpenolene boiling at 176–196° and having refractivity and density values of $n^{20}D$ 1.470–1.478, and $d^{15.5}_4$ 0.855–0.870.

TABLE II

REACTION PRODUCTS FROM TETRAFLUOROETHYLENE AND CHLOROÖLEFINS

| Tetrafluorocyclobutane | B. p., °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | $AR_F$ | Analyses: Calcd. for | C | H | F | Cl | Reactants[a] (g. $C_2F_4$/g. chloroölefin) | Yield, %, based on $C_2F_4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ClHCCF$_2$CF$_2$CH$_2$ | 73–74 | | 1.3462 | 1.4251 | 24.15 | 1.18 | $C_4H_3ClF_4$ | 29.53 | 1.84 | 46.8 | 21.85 | 50/132 vinyl | 23 |
| | | | | | | | Found | 30.43 | 1.86 | 47.56 | 21.78 | chloride | |
| ClCH$_2$CHCF$_2$CF$_2$CH$_2$ | 115–116 | | 1.3745 | 1.3971 | 28.8 | 1.19 | $C_5H_5ClF_4$ | 34.0 | 2.84 | 43.05 | 20.11 | 50/125 allyl | 42 |
| | | | | | | | Found | 33.91 | 3.15 | 44.25 | 20.11 | chloride | |
| ClCH$_2$(CH$_3$)CCF$_2$CF$_2$CH$_2$ | 122–124 | | 1.3846 | 1.3161 | 33.85 | 1.30 | $C_6H_7ClF_4$ | 37.8 | 3.67 | 39.9 | 18.65 | 46/150 methallyl | 45 |
| | | | | | | | Found | 36.98 | 4.51 | 39.97 | 20.41 | chloride | |
| Cl$_2$CCF$_2$CF$_2$CH$_2$ | 84–84.7 | | 1.3702 | 1.5298 | 29.05 | 1.19 | $C_4H_2Cl_2F_4$ | 24.35 | 1.01 | 38.6 | 36.05 | 50/125 vinyli- | 46 |
| | | | | | | | Found | 27.13 | 0.91 | 38.84 | 35.82 | dene chloride[b] | |
| Cl$_2$CCF$_2$CF$_2$CHCl | 109–110.5 | | 1.3995 | 1.5720 | 35.7 | 1.64 | $C_4HCl_3F_4$ | | | 32.82 | 46.00 | 60/100 trichloro- | 18 |
| | | | | | | | Found | | | 33.80 | 44.90 | ethylene[c] | |
| CH$_3$COCClCF$_2$CF$_2$CH$_2$ | 56.7 | 36 | 1.3850 | 1.4478 | 35.75 | 1.36 | $C_6H_5O_2ClF_4$ | 32.65 | 2.28 | 34.5 | 16.15 | 75/100 methyl | 21 |
| | | | | | | | Found | 36.41 | 3.66 | 33.18 | 18.81 | α-chloroacrylate | |

[a] The reactants were agitated at 150° under autogenous pressure for about eight hours. [b] Added 0.5 g. of hydroquinone as polymerization inhibitor. [c] Heated at 225°.

tions should be taken to exclude all oxygen from tetrafluoroethylene and the reaction system.

Propylene, isobutylene and styrene reacted readily, yielding the methyl-, 1,1-dimethyl- and 1-phenyl-2,2,3,3-tetrafluorocyclobutanes, respectively, as given in Table I, whereas butene-2 and camphene were less reactive.

**1-Chloro-2,2,3,3-tetrafluorocyclobutane.**—A stainless steel-lined shaker tube was flushed with nitrogen, evacuated, cooled in a Dry Ice–methanol mixture, and then 132 g. of vinyl chloride and 50 g. of tetrafluoroethylene were added. The sealed tube was heated under autogenous pressure at 150° for eight hours. The tube was cooled and excess gas bled off slowly. The condensate amounted to 19 g. (23% yield) of 1-chloro-2,2,3,3-tetrafluorocyclobutane which had the following properties: b. p. 73–74°, $n^{25}D$ 1.3462, $d^{25}_4$ 1.4251, $MR_D$ 24.15.

*Anal.* Calcd. for $C_4H_3ClF_4$: C, 29.53; H, 1.84; F, 46.8; Cl, 21.85. Found: C, 30.43; H, 1.86; F, 47.56; Cl, 21.78.

Allyl chloride, methallyl chloride, vinylidene chloride, trichloroethylene and methyl α-chloroacrylate reacted with tetrafluoroethylene to yield the corresponding tetrafluorocyclobutanes listed in Table II.

**1-Cyano-2,2,3,3-tetrafluorocyclobutane.**[1d]—A 400 ml. stainless steel-lined shaker tube was flushed with nitrogen and charged with 125 g. of freshly distilled acrylonitrile. The tube was cooled and evacuated. After adding 50 g. of tetrafluoroethylene which contained approximately 0.1 g. of "Terpene B" hydrocarbon,[5] the sealed tube was heated at 150° with agitation under autogenous pressure for about eight hours. The reaction mixture was steam distilled, and the steam-volatile, lower, water-insoluble layer was separated, dried, and distilled. After separating a foreshot of unreacted acrylonitrile, an 84% yield (64 g.) of 1-cyano-2,2,3,3-tetrafluorocyclobutane was obtained which had the following properties: b. p. 148°, $n^{25}D$ 1.3568, $d^{25}_4$ 1.3909. *Anal.* Calcd. for $C_5H_3NF_4$: C, 39.2; H, 1.96; F, 49.7; N, 9.15. Found: C, 37.0; H, 2.07; F, 49.19; N, 9.24. There was also obtained a non-volatile residue (1.2 g.) that contained about 7% fluorine.

The tetrafluorocyclobutanes which contain functional substituents undergo transformations characteristic of such substituents as illustrated by the hydrolysis of 1-cyano-2,2,3,3-tetrafluorocyclobutane to 2,2,3,3-tetrafluorocyclobutane carboxylic acid and by the conversion of this acid to simple carboxylic acid derivatives.

**2,2,3,3-Tetrafluorocyclobutanecarboxylic Acid.**[1d]—Ten grams of 1-cyano-2,2,3,3-tetrafluorocyclobutane was hydrolyzed by warming with 30 ml. of 70% sulfuric acid on a steam-bath for one-half hour. The upper oily layer was separated, and the lower sulfuric acid layer was diluted with cold water and extracted with ether. The combined oil and ether extracts were dried, and the ether was removed. An 87% yield (9.8 g.) of 2,2,3,3-tetrafluorocyclobutane carboxylic acid was obtained having the following properties: b. p. 100–100.5° at 24 mm., $n^{25}D$ 1.3684,[6] $d^{25}_4$ 1.5103.[6] The acid solidified on cooling. It melted at 61.5–63°.

*Anal.* Calcd. for $C_5H_4O_2F_4$: C, 34.9; H, 2.33; F, 44.2; neut. equiv., 172. Found: C, 35.62; H, 2.60; F, 43.91; neut. equiv., 174.8.

2,2,3,3-Tetrafluorocyclobutanecarboxylic acid formed the customary acid derivatives such as the anhydride, the chloride, the amide, and the anilide.[1d]

**Methyl 1-Methyl-2,2,3,3-tetrafluorocyclobutanecarboxylate.**[1d]—A stainless steel-lined shaker tube was flushed with nitrogen and charged with 125 g. of methyl methacrylate containing 0.5 g. of hydroquinone as polymerization inhibitor. The tube was cooled in Dry Ice–methanol mixture, evacuated, and 50 g. of tetrafluoroethylene containing about 0.2 g. of "Terpene B" hydrocarbon[5] was added. The sealed tube was heated under autogenous pressure at 150° for eight hours. At the end of this time, there was no appreciable gas pressure in the tube. The reaction mixture was steam distilled, and the volatile, water-insoluble material was dried over anhydrous sodium sulfate and fractionated. The first fraction was unreacted methyl methacrylate (b. p. 32–36° at 57 mm.). Methyl 1-methyl-2,2,3,3-tetrafluorocyclobutanecarboxylate (64 g. or a 64% yield) was obtained next, boiling at 70° at 56 mm. and having the following properties: $n^{25}D$ 1.3656, $d^{25}_4$ 1.2890, $MR_D$ 34.6.

*Anal.* Calcd. for $C_7H_8O_2F_4$: C, 42.0; H, 4.00; F, 38.0; saponification number, 280.5. Found: C, 35.18; H, 4.24; F, 37.34; saponification number, 280.5. There was also obtained 5 g. of higher boiling liquid (b. p. 135–152° at 52 mm.), and 11 g. of polymer containing 6.8% fluorine.

Saponification of methyl 1-methyl-2,2,3,3-tetrafluorocyclobutane carboxylate with alkali gave the corresponding carboxylic acid[1d] melting at 41–43°.

A wide variety of ethylenically unsaturated oxygen-containing compounds including acrolein, methacrolein, vinyl acetate, allyl alcohol, methyl vinyl ketone, methyl vinyl ether, 2-vinylfuran, safrole and butadiene monoxide have been treated with tetrafluoroethylene to obtain the corresponding tetrafluorocyclobutane derivatives listed in Table III.

**1-Vinyl-2,2,3,3-tetrafluorocyclobutane.**—A stainless steel-lined high pressure shaker tube was flushed with nitrogen, evacuated, and charged with 125 g. of 1,3-buta-

(6) Values were determined on the supercooled liquid.

TABLE III

REACTION PRODUCTS FROM TETRAFLUOROETHYLENE WITH UNSATURATED NITRILES AND OXYGEN COMPOUNDS

| Tetrafluorocyclobutane | B. p., °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | $AR_F$ | Analyses | | C | H | F | N | Reactants[a] (g. $C_2F_4$/g. unsaturant) | Yield, %, based on $C_2F_4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CNCHCF$_2$CF$_2$CH$_2$ | 148 | | 1.3568 | 1.3909 | 24.07 | 1.29 | $C_5H_3NF_4$ | Calcd. for | 39.2 | 1.96 | 49.7 | 9.15 | 75/100 | 84 |
| | | | | | | | | Found | 37.0 | 2.07 | 49.19 | 9.24 | acrylonitrile | |
| CNCH$_2$CHCF$_2$CF$_2$CH$_2$ | 192–195 | | 1.3748 | 1.3459 | 28.2 | 1.16 | $C_6H_5NF_4$ | Calcd. for | 43.1 | 2.99 | 45.5 | 8.38 N | 50/125 | 15 |
| | | | | | | | | Found | 43.01 | 3.59 | 44.89 | 8.60 | allyl cyanide | |
| HC=OCHCF$_2$CF$_2$CH$_2$ | 117–117.5 | | 1.3768 | 1.5089 | 23.7 | 1.13 | $C_5H_4OF_4$ | Calcd. for | 38.5 | 2.56 | 48.75 | | 50/125 | 12 |
| | | | | | | | | Found | 40.5 | 2.57 | 47.67 | | acrolein[b] | |
| HC=O(CH$_3$)CCF$_2$CF$_2$CH$_2$ | 121–122 | | 1.3625 | 1.3113 | 28.8 | 1.25 | $C_6H_6OF_4$ | Calcd. for | 42.35 | 3.53 | 44.7 | | 50/125 | 50 |
| | | | | | | | | Found | 45.44 | 4.25 | 43.27 | | methacrolein[b] | |
| CH$_3$OC=O(CH$_3$)CCF$_2$CF$_2$CH$_2$ | 70 | 56 | 1.3656 | 1.2890 | 34.6 | 1.13 | $C_7H_8O_2F_4$ | Calcd. for | 42.0 | 4.00 | 38.0 | Sap. No. 280.5 | 100/125 | 84 |
| | | | | | | | | Found | 35.18 | 4.24 | 37.34 | 280.5 | methyl methacrylate[b] | |
| CH$_3$C=OOCHCF$_2$CF$_2$CH$_2$ | 138.5–139.5 | | 1.3660 | 1.3310 | 31.2 | 1.44 | $C_6H_6O_2F_4$ | Calcd. for | 38.7 | 3.23 | 40.8 | | 50/125 | 27 |
| | | | | | | | | Found | 36.23 | 3.50 | 41.68 | | vinyl acetate | |
| HOCH$_2$CHCF$_2$CF$_2$CH$_2$ | 155–157 | | 1.3670 | 1.3998 | 25.17 | 1.12 | $C_5H_6OF_4$ | Calcd. for | 38.0 | 3.80 | 48.1 | | 50/125 | 45 |
| | | | | | | | | Found | 39.34 | 3.95 | 47.86 | | allyl alcohol | |
| CH$_3$C=OCHCF$_2$CF$_2$CH$_2$ | 134–135.5 | | 1.3582 | 1.3114 | 28.35 | 1.14 | $C_6H_6OF_4$ | Calcd. for | 42.35 | 3.53 | 44.7 | | 50/125 | 18 |
| | | | | | | | | Found | 41.95 | 4.12 | 43.78 | | methyl vinyl ketone | |
| CH$_3$OCHCF$_2$CF$_2$CH$_2$ | 88–91.8 | | 1.3380 | 1.2612 | 26.0 | 1.30 | $C_6H_6OF_4$ | Calcd. for | 38.0 | 3.80 | 48.1 | | 50/125 | 13 |
| | | | | | | | | Found | 38.72 | 3.46 | 48.05 | | methyl vinyl ether[b] | |
| OCH=CHCH=CCHCF$_2$CF$_2$CH$_2$ | 86.5 | 80 | 1.4073 | 1.3341 | 35.75 | 1.06 | $C_8H_6OF_4$ | Calcd. for | 49.5 | 3.09 | 39.2 | | 50/125 | 77 |
| | | | | | | | | Found | 47.26 | 3.93 | 38.59 | | 2-vinylfuran[b] | |
| *o*-OCH$_2$OC$_6$H$_4$CH$_2$CHCF$_2$CF$_2$CH$_2$ | 133.5–135.5 | 11 | 1.4770 | | | | $C_{12}H_{10}O_2F_4$ | Calcd. for | 54.99 | 3.85 | 29.00 | | 70/110 | 18 |
| | | | | | | | | Found | 54.61 | 3.89 | 29.2 | | safrole | |
| OCH$_2$CHCHCF$_2$CF$_2$CH$_2$ | 74–76 | 67 | 1.3730 | | | | $C_8H_6OF_4$ | Calcd. for | 42.36 | 3.56 | 44.7 | | 70/37 | 9 |
| | | | | | | | | Found | 43.45 | 3.96 | 42.7 | | butadiene monoxide[c] | |

[a] The reactants were agitated at 150° under autogenous pressure for about eight hours. [b] Added 0.5 g. of hydroquinone as polymerization inhibitor. [c] Heated at 135° for ten hours.

diene and 100 g. of tetrafluoroethylene. The tube was heated under autogenous pressure at 125° with agitation for eight hours. After cooling to room temperature and releasing the pressure, the reaction mixture was steam distilled. The volatile water-insoluble liquid was dried and fractionated to give 140 g. (90%) of 1-vinyl-2,2,3,3-tetrafluorocyclobutane having the following properties: b. p. 83–85°, $n^{25}D$ 1.3489, $d^{25}_4$ 1.1866; $MR_D$ 27.87.

*Anal.* Calcd. for $C_6H_6F_4$: C, 46.76; H, 3.92; F, 49.32. Found: C, 46.45; H, 4.11; F, 50.02.

The nitric acid oxidation of 1-vinyl-2,2,3,3-tetrafluorocyclobutane[1d] gave a dense, green oil only sparingly soluble in water. By extraction with sodium bicarbonate solution and acidification, there was obtained 18 g. of an oil denser than water. Distillation gave a colorless product which boiled at 100° at 25 mm. and was identified as 2,2,3,3-tetrafluorocyclobutane carboxylic acid.

*Anal.* Calcd. for $C_5H_4O_2F_4$: C, 34.9; H, 2.33; F, 44.2; neut. equiv., 172. Found: C, 36.9; H, 2.60; F, 44.2; neut. equiv., 180.

**2,2,2′,2′,3,3,3′,3′-Octafluorobicyclobutyl.**—A stainless steel-lined shaker tube was charged with 90 g. of 1-vinyl-2,2,3,3-tetrafluorocyclobutane. After cooling the tube in Dry Ice–methanol mixture and evacuating, 50 g. of tetrafluoroethylene was added and the mixture was heated at 150° under autogenous pressure for eight hours. The tube was cooled to room temperature, and the pressure released. The liquid reaction mixture was fractionated to remove the unchanged 1-vinyl-2,2,3,3-tetrafluorocyclobutane, and then about 14 g. (11% conversion) of 2,2,2′,2′,3,3,3′,3′-octafluorobicyclobutyl distilling at 150–158° was obtained. The material solidified on cooling to room temperature and appeared to melt at 49–50°, but the boiling and melting points were not sharp.

*Anal.* Calcd. for $C_8H_6F_8$: F, 59.84. Found: F, 59.87.

A mixed melting point with the 2,2,2′,2′,3,3,3′,3′-octafluorobicyclobutyl obtained from the hydrogenation of 2′,2′,3′,3′ - tetrafluorocyclobutenyl - 2,2,3,3 - tetrafluorocyclobutane (a tetrafluoroethylene/monovinylacetylene reaction product) showed no depression.

**1-Vinyl-1,2,2,3,3-pentafluorocyclobutane and 1-(1-fluorovinyl)-2,2,3,3-tetrafluorocycobutane.**—A stainless steel-lined shaker tube was evacuated and charged with 128 g. of 2-fluoro-1,3-butadiene and 100 g. of tetrafluoroethylene. It was then heated at 125° with agitation for eight hours. After opening and discharging the tube, the reaction mixture was steam distilled to yield 142 g. of volatile, water-insoluble liquid. Fractionation gave equal amounts (each about 60 g.) of two isomeric products boiling at 85 and 95°, respectively, and 20 g. of a complex mixture of higher boiling products. The two isomeric products had the following properties: b. p. 85°,

TABLE IV

THE 1:1 REACTION PRODUCTS FROM TETRAFLUOROETHYLENE AND DIENES

| Tetrafluorocyclobutane | B. p., °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | $AR_F$ | Analyses | Calcd. for | C | H | F | Cl | Iodine No. | Reactants[a] (g. $C_2F_4$/g. diene) | Yield, %, based on $C_2F_4$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2=CH\overline{CHCF_2CF_2CH_2}$ | 83–85 | | 1.3489 | 1.1866 | 27.87 | 1.14 | | $C_6H_6F_4$ | 46.76 | 3.92 | 49.32 | | | 100/125 1,3-butadiene | 90 |
| | | | | | | | | Found | 46.45 | 4.11 | 50.02 | | | | |
| $CH_2=CH(CH_3)\overline{CCF_2CF_2CH_2}$ | 103 | | 1.3649 | 1.1655 | 32.15 | 1.05 | | $C_7H_8F_4$ | 50.0 | 4.79 | 45.21 | | | 100/68 2-methyl-1,3-butadiene | 83 |
| | | | | | | | | Found | 51.34 | 5.26 | 44.86 | | | | |
| $CH_3CH=CH\overline{CHCF_2CF_2CH_2}$ | 111 | | 1.3698 | 1.1607 | 32.8 | 1.21 | | $C_7H_8F_4$ | 50.0 | 4.79 | 45.21 | | | 100/68 1,3-pentadiene | 68 |
| | | | | | | | | Found | 49.19 | 5.23 | 45.15 | | | | |
| $CH_2=C(Cl)\overline{CCF_2CF_2CH_2}$ | 108 | | 1.3838 | 1.3483 | 32.8 | 1.15 | | $C_6H_5ClF_4$ | 38.21 | 2.67 | 40.30 | 18.80 | | 100/88.5 2-chloro-1,3-butadiene[b] | 51 |
| | | | | | | | | Found | 39.46 | 3.19 | 40.03 | 18.84 | | | |
| $CH_2=CCl\overline{CHCF_2CF_2CH_2}$ | 122–124 | | 1.3868 | 1.3654 | 32.4 | 1.05 | | $C_6H_5ClF_4$ | 38.21 | 2.67 | 40.30 | 18.80 | | | 10 |
| | | | | | | | | Found | 37.37 | | 40.03 | 18.69 | | | |
| $CH_2=CH\overline{CFCF_2CF_2CH_2}$ | 85 | | 1.3405 | 1.2941 | 27.9 | 1.14 | | $C_6H_5F_5$ | 41.85 | 2.91 | 55.24 | | | 100/128 2-fluoro-1,3-butadiene | 35 |
| | | | | | | | | Found | 44.01 | 3.30 | 55.63 | | | | |
| $CH_2=CF\overline{CHCF_2CF_2CH_2}$ | 95 | | 1.3458 | 1.3193 | 27.5 | 1.05 | | $C_6H_5F_5$ | 41.85 | 2.91 | 55.24 | | | | 35 |
| | | | | | | | | Found | 42.90 | 3.14 | 56.36 | | | | |
| $CH_2=\overline{CCF_2CF_2CH_2}$ | 64–66 | | 1.3318 | 1.2288 | 23.4 | 1.17 | | $C_5H_4F_4$ | 42.87 | 2.88 | 54.25 | | | 75/30 allene[c] | 14 |
| | | | | | | | | Found | 43.08 | 3.71 | 53.2 | | | | |
| $\overline{CH=CHCH_2CH_2CHCHCF_2CF_2}$ | 147–149 | | 1.4019 | | | | | $C_8H_8F_4$ | 53.3 | 4.45 | | | | 75/30 dihydrobenzene[b] | 50 |
| | | | | | | | | Found | 54.35 | 4.98 | | | | | |
| $\overline{CH_2CH=CHCHCHCF_2CF_2}$ | 120–123 | | 1.3865 | | | | | $C_7H_6F_4$ | 50.61 | 3.64 | 45.75 | | | 70/46 dicyclopentadiene[d] | 23 |
| | | | | | | | | Found | 51.25 | 3.87 | 44.9 | | | | |
| $CH_2=(CH_3)CH_2O-$ | 70–72 | 19 | 1.3918 | | | | | $C_{10}H_{14}OF_4$ | 53.2 | 6.18 | 33.6 | | 112.3 | 50/150 dimethallyl ether | 20 |
| $CH_2(CH_3)\overline{CCF_2CF_2CH_2}$ | | | | | | | | Found | 54.47 | 6.71 | 32.72 | | 120.2 | | |

[a] The reactants were agitated under autogenous pressure for about eight hours at 100–125°. [b] Added 1.0 g. of hydroquinone as polymerization inhibitor. [c] Heated at 150°. [d] Heated at 190°. A 9% yield of $C_2F_4 \cdot 2C_5H_6$, b. p. 102–107° (17 mm.), $n^{25}D$ 1.4570, was also obtained.

$N^{25}D$ 1.3405, $d^{25}_4$ 1.2941, $MR_D$ 27.9; and b. p. 95°, $n^{25}D$ 1.3458, $d^{25}_4$ 1.3193, $MR_D$ 27.5.

*Anal.* Calcd. for $C_6H_5F_5$: C, 41.85; H, 2.91; F, 55.24. Found for 85° fraction: C, 44.01; H, 3.30; F, 55.63. Found for 95° fraction: C, 42.90; H, 3.14; F, 56.36.

Tetrafluorocyclobutanes from tetrafluoroethylene and other dienes are listed in Table IV.

**1-Ethyl-1,2,2,3,3-pentafluorocyclobutane.**—Fifteen grams of 1-vinyl-1,2,2,3,3-pentafluorocyclobutane (boiling at 85°) was dissolved in 100 g. of absolute ethyl acohol, and was hydrogenated using 4 g. of Raney nickel catalyst and 1500 lb./sq. in. hydrogen pressure at 80°. After removing the catalyst, the solution was diluted with water, the water-insoluble layer was separated, dried over calcium chloride and distilled. 1-Ethyl-1,2,2,3,3-pentafluorocyclobutane was obtained boiling at 89–90° and having the following properties: $n^{25}D$ 1.3295, $d^{25}_4$ 1.2570, $MR_D$ 28.1.

*Anal.* Calcd. for $C_6H_7F_5$: F, 54.6. Found: F, 54.79.

The structure of 1-ethyl-1,2,2,3,3-pentafluorocyclobutane was assigned because of the resistance of fluorine atoms substituted in the cyclobutane ring to elimination by hydrolysis.

Hydrogenation of 1-(1-fluorovinyl)-2,2,3,3-tetrafluorocyclobutane (boiling at 95°) under similar conditions gave a product which was hydrolyzed by water. Hydrolysis with loss of fluorine is evidence that a fluorine atom was present in an aliphatic side chain. The fluorine atoms in a tetrafluorocyclobutane ring are quite resistant to hydrolysis.

**1-Vinyl-1-chloro-2,2,3,3-tetrafluorocyclobutane and 1-(1-chlorovinyl)-2,2,3,3-tetrafluorocyclobutane.**—A silver-lined shaker tube was charged with 100 ml. of water, 88.5 g. of 2-chloro-1,3-butadiene and 1 g. of hydroquinone. After cooling and evacuating, 100 g. of tetrafluoroethylene was added, and the tube was heated with agitation at 100° for about eight hours. The recovered mixture was steam distilled to yield 115 g. of volatile liquid and 11 g. of non-volatile material. Fractionation of the liquid gave two distinct products: (1) 1-vinyl-1-chloro-2,2,3,3-tetrafluorocyclobutane (96 g.): b. p. 108°, $n^{25}D$ 1.3838, $d^{25}_4$ 1.3483, $MR_D$ 32.8, and (2) 1-(1-chlorovinyl)-2,2,3,3-tetrafluorocyclobutane (19 g.): b. p. 122–124°, $n^{25}D$ 1.3868, $d^{25}_4$, 1.3654, $MR_D$ 32.4.

*Anal.* Calcd. for $C_6H_5ClF_4$: C, 38.21; H, 2.67; F, 40.30; Cl, 18.80. Found: (1) C, 39.46; H, 3.19; F, 40.03; Cl, 18.84. (2) C, 37.37; F, 40.03; Cl, 18.69.

The hydrogenation of fraction (1) in absolute ethyl alcohol using Raney nickel catalyst at 80° and 1500 lb./sq. in. pressure gave a product boiling at 113° which analyzed for nearly the theoretical amount of chlorine but which still contained a little unsaturated material as evidenced by oxidation with aqueous permanganate solution. The physical properties of the compound were $n^{25}D$ 1.3690, $d^{25}_4$ 1.2954, $MR_D$ 33.2. The increase in the molecular refraction of 0.4 checks with that expected from saturation of a double bond by two hydrogen atoms.

*Anal.* Calcd. for $C_6H_7ClF_4$: F, 39.9; Cl, 18.65. Found: F, 40.17; Cl, 15.25.

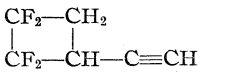
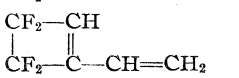
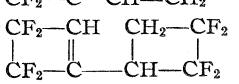
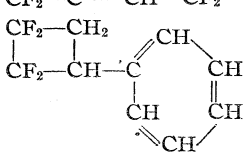
The hydrogenation of fraction (2) in absolute ethyl alcohol using Raney nickel catalyst at 80° and 1500 lb./sq. in. pressure resulted in practically complete removal of the chlorine to yield 1-ethyl-2,2,3,3-tetrafluorocyclobutane boiling at 90–91.5°.

The assignment of the structures for fractions (1) and (2) involves the assumption that chlorine in an aliphatic side chain is more readily eliminated during hydrogenation than is chlorine substituted in the ring.

**1-Ethyl-2,2,3,3-tetrafluorocyclobutane.**—One mole (154 g.) of 1-vinyl-2,2,3,3-tetrafluorocyclobutane was hydrogenated at 80° using about 10 g. of Raney nickel catalyst

TABLE V

REACTION PRODUCTS FROM TETRAFLUOROETHYLENE AND MONOVINYLACETYLENE

| | Product | B. p., °C. | Mm. | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | $AR_F$ | Calcd. for | C | H | F |
|---|---|---|---|---|---|---|---|---|---|---|---|
| X |  | 82–84 | | 1.3553 | 1.2498 | 26.5 | 1.18 | $C_6H_4F_4$ | 47.47 | 2.63 | 50.0 |
| | | | | | | | | Found: | 51.65 | 3.63 | 49.99 |
| XI |  | 98–99 | | 1.3742 | 1.2588 | 27.5 | 1.16 | $C_6H_4F_4$ | 47.37 | 2.63 | 50.0 |
| | | | | | | | | Found: | 46.66 | 2.81 | 51.13 |
| XII |  | 49–50 | 13 | 1.3596 | 1.5147 | 36.6 | 1.27 | $C_8H_4F_8$ | 38.1 | 1.58 | 60.3 |
| | | | | | | | | Found: | 39.52 | 3.31 | 59.02 |
| XIII |  | 60–65 | 9 | | 1.2703 | | | $C_{10}H_8F_4$ | 58.8 | 3.92 | 37.25 |
| | | | | | | | | Found: | 58.71 | 4.41 | 40.35 |

X. This product reacted with dilute aqueous silver nitrate, did not polymerize readily, and on hydrogenation gave 1-ethyl-2,2,3,3-tetrafluorocyclobutane.

XI. This product did not react with aqueous silver nitrate, polymerized readily, and on hydrogenation gave 1-ethyl-2,2,3,3-tetrafluorocyclobutane.

XII. Hydrogenation of XII gave a product identical with the 2,2,2′,2′,3,3,3′,3′ octafluorobicyclobutyl obtained from butadiene and two molecules of tetrafluoroethylene.

XIII. This compound was identical with the 1-phenyl-2,2,3,3-tetrafluorocyclobutane obtained from styrene and tetrafluoroethylene (see Table I).

and 1000–1500 lb./sq. in. hydrogen pressure. The hydrogenation was exothermic. About one mole of hydrogen was absorbed, and 150 g. (96% yield) of 1-ethyl-2,2,3,3-tetrafluorocyclobutane was obtained boiling at 90–91° and having the following properties: $n^{25}D$ 1.3370, $d^{25}_4$ 1.1506, $MR_D$ 28.0.

*Anal.* Calcd. for $C_6H_8F_4$: F, 48.7 Found: F, 48.25.

1-Ethyl-2,2,3,3-tetrafluorocyclobutane was also obtained by hydrogenation of the two isomeric products from tetrafluoroethylene and monovinylacetylene, namely, 1-ethynyl-2,2,3,3-tetrafluorocyclobutane and 1-vinyl-3,3,-4,4-tetrafluorocyclobutene.

**1-Ethynyl-2,2,3,3-tetrafluorocyclobutane and 1-Vinyl-3,3,4,4-tetrafluorocyclobutene.**—A 400-ml. shaker tube was flushed with nitrogen, evacuated, and charged with 50 g. of monovinylacetylene and 50 g. of tetrafluoroethylene (containing less than 20 p. p. m. of oxygen). The sealed tube was heated at 100° for sixteen hours, and was then cooled to room temperature. After releasing the pressure, the light yellow liquid reaction product (82 g.) was removed and steam distilled to obtain about 60 g. of steam-volatile, colorless liquid which was heavier than water, and about 20 g. of light yellow, non-steam-volatile polymer. Analysis of the polymer indicated 26% fluorine, corresponding to a tetrafluoroethylene/monovinylacetylene mole ratio of 1:3.7. Fractionation of the liquid products through a precision column yielded the four products listed in Table V in about a 45:45:5:5 ratio, respectively. There was also a small amount of higher boiling material which was not identified.

**1-Methylene-2,2,3,3-tetrafluorocyclobutane and 1,1,-2,2,5,5,6,6-Octafluorospiro[3.3]heptane.**—Thirty grams of allene and 75 g. of tetrafluoroethylene were heated in a silver-lined shaker tube at 150° under autogenous pressure for eight hours. The excess gas was bled through a Dry Ice-trap, and 18 g. of liquid was obtained from the tube. Fractionation of the liquid gave two distinct products: (1) 1-methylene-2,2,3,3-tetrafluorocyclobutane (14 g.), b. p. 64–66°, $n^{25}D$ 1.3318, $d^{25}_4$ 1.2288, $MR_D$ 23.4, and (2) 1,1,2,2,5,5,6,6-octafluorospiro[3.3]heptane (4 g.), b. p. 107–109°, $n^{25}D$ 1.3325, $d^{25}_4$ 1.5137, $MR_D$ 32.7, $AR_F$, 1.30.

*Anal.* (1) Calcd. for $C_5H_4F_4$: C, 42.87; H, 2.88; F, 54.25. Found: C, 42.98; H, 3.72; F, 52.9. (2) Calcd. for $C_7H_4F_8$: C, 35.01; H, 1.68; F, 63.31. Found: C, 35.69; H, 2.35; F, 61.8.

Fraction (1) instantly decolorized neutral permanganate solution, whereas fraction (2) did not. Ozonolysis of fraction (1) in carbon tetrachloride gave formaldehyde. When 10 g. of fraction (1) was heated with 30 g. of tetrafluoroethylene in a bomb for eight hours at 150° an 18% conversion to fraction (2) was obtained.

**Acknowledgment.**—The authors are indebted to Dr. Paul R. Austin and Dr. W. E. Hanford for helpful suggestions and to Dr. J. W. Stillman under whose supervision the analyses were carried out.

## Summary

A new family of substituted tetrafluorocyclobutanes has been synthesized by the cycloalkylation of tetrafluoroethylene under non-polymerizing conditions with terminally unsaturated ethylenic and acetylenic compounds, and with 1,3-dienes. Typical members of the family include 2,2,3,3-tetrafluorocyclobutane and this fluorohydrocarbon substituted in the 1 position by alkyl, halogen, cyano, carboxy, carbalkoxy, and other groups. As a class, the tetrafluorocyclobutanes are resistant to ring cleavage.

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[CONTRIBUTION NO. 83 FROM THE GENERAL LABORATORIES OF THE UNITED STATES RUBBER COMPANY]

# Rate Constants in Free Radical Polymerizations. I. Methyl Methacrylate

BY MAX S. MATHESON, E. E. AUER, ELLEN B. BEVILACQUA AND E. J. HART

Until recently, the absolute rate constants of vinyl polymerization have not been measured. Now, however, Burnett and Melville[1] and Swain and Bartlett[2] have applied the rotating sector method of Briers, Chapman and Walters[3] to the measurement of the absolute rate constants of vinyl acetate addition polymerization in the liquid phase. A new and elegant method has recently been devised by Bamford and Dewar[4] and applied to the measurement of the absolute rate constants of polymerization of styrene and methyl methacrylate. In their method, changes in intrinsic viscosity of a photopolymerizing system during and after irradiation and knowledge of the molecular weight of a thermal or photopolymer permit the evaluation of all the rate constants. A further very ingenious method applicable to emulsion polymerization has been developed by Smith and Ewart[5] for the measurement of the propagation rate constant. In this Laboratory, we have studied several monomers with the rotating sector method and this paper reports the work on methyl methacrylate.

## Theoretical

The usual studies on polymerization yield the ratios of rate constants rather than their individual values. This is made clear by consideration of the mechanism below, which includes simultaneous initiation by a free radical source such as benzoyl peroxide and by monomer.

| *Free Radical Initiation* | *Rate* |
|---|---|
| $\text{Init.} \xrightarrow{k_d} 2\text{R}\cdot$ | $2k_d\,(\text{Init.})$ |
| $2\text{R}\cdot \xrightarrow{k_r} \text{Stable product}$ | $2k_r\,(R\cdot)$ |
| $\text{R}\cdot + \text{M} \xrightarrow{k_a} \text{M}_1\cdot$ | $2k_a(\text{R}\cdot)\,(\text{M})$ |
| *Initiation by Monomer* | |
| $\text{M} + \text{M} \xrightarrow{k_i} \cdot\text{M}_2\cdot$ | $2k_i(\text{M})^2$ |
| *Propagation* | |
| $\text{M}_r\cdot + \text{M} \xrightarrow{k_p} \text{M}_{r+1}\cdot$ | $k_p(\text{M}_r\cdot)(\text{M})$ |
| $\cdot\text{M}_r\cdot + \text{M} \xrightarrow{k_{p1}} \cdot\text{M}_{r+1}\cdot$ | $k_p(2[\cdot\text{M}_r\cdot])(\text{M})$ |
| *Termination* | |
| $\text{M}_r\cdot + \text{M}_s\cdot \xrightarrow{k_t} \text{M}_{r+s}$ | $2k_t(\text{M}_r\cdot)(\text{M}_s\cdot)$ |
| $\text{M}_1\cdot + \cdot\text{M}_s\cdot \xrightarrow{k_{t1}} \text{M}_{r+s}\cdot$ | $2k_t(2[\cdot\text{M}_s\cdot])(\text{M}_r\cdot)$ |
| $\cdot\text{M}_r\cdot + \cdot\text{M}_s\cdot \xrightarrow{k_{t2}} \cdot\text{M}_{r+s}\cdot$ | $2k_t(2[\cdot\text{M}_r\cdot])(2[\cdot\text{M}_s\cdot])$ |
| *Transfer with Monomer* | |
| $\text{M}_r\cdot + \text{M} \xrightarrow{k_{tr}} \text{M}_r + \text{M}_1\cdot$ | $k_{tr}(\text{M}_r\cdot)(\text{M})$ |
| $\cdot\text{M}_r\cdot + \text{M} \xrightarrow{k_{tr1}} \text{M}_r\cdot + \text{M}_1\cdot$ | $k_{tr}(2[\cdot\text{M}_r\cdot])(\text{M})$ |

where

- Init. = initiator or source of free radicals
- R· = radical from initiator
- M = monomer
- $\text{M}_r\cdot$, $\cdot\text{M}_r\cdot$ and $\text{M}_r$ = respectively, monovalent polymer radical, bivalent polymer radical and stable polymer molecule of $r$ monomer units
- $k$'s = rate constants. Rates are given for formation or consumption of free valencies in initiation or termination, and for consumption of monomer in propagation or transfer.

Implicit in the mechanism are the following assumptions: (1) Although the "Cage" mechanism[6] is given, the essential assumption is that free radical induced initiation is proportional to (Init). Further, monomer initiation gives a biradical.[7] (2) The rate constants of propagation, termination, and transfer are independent of the length[8] or bivalent character of the polymer radicals. (3) The growing polymer radicals terminate by combining.[9] It is further assumed that: (4) Kinetic chains are long. (5) The monomer concentration is constant. In our work, except where specifically stated, no polymerization was carried beyond 5 to 10%. (6) A steady state is attained.

On the basis of the above, one obtains

$$R_i = 2k_d f(\text{Init.}) + 2k_i\,(\text{M})^2 \qquad (1)$$

where $R_i$ = rate of initiation of polymer radicals, $2k_d f(\text{Init.})$ = rate of initiation by initiator, and $f = k_a(\text{M})/(k_r + k_a(\text{M}))$ = constant if (M) held constant.

$$R_p^2 = [k_p^2(\text{M})^2/k_t]\,[k_d f(\text{Init.}) + k_i(\text{M})^2] \qquad (2)$$

where $R_p$ = rate of polymerization $= -\text{d(M)}/dt$.

$$\frac{1}{\bar{P}} = \frac{k_d f(\text{Init.})}{R_p} + C \qquad (3)$$

(1) (a) G. M. Burnett and H. W. Melville, *Nature*, **156**, 661 (1945); (b) *Proc. Roy. Soc. (London)*, **A189**, 456 (1947).

(2) (a) P. D. Bartlett and C. G. Swain, THIS JOURNAL, **67**, 2273 (1945); (b) C. G. Swain and P. D. Bartlett, *ibid.*, **68**, 2381 (1946).

(3) F. Briers, D. L. Chapman and E. Walters, *J. Chem. Soc.*, 562 (1926).

(4) (a) C. H. Bamford and M. J. S. Dewar, *Nature*, **157**, 845 (1946); (b) *Proc. Roy. Soc. (London)*, **A192**, 309 (1948); (c) Discussions of the Faraday Soc. No. 2 (1947), The Labile Molecule, p. 310; (d) M. J. S. Dewar and C. H. Bamford, *Nature*, **158**, 380 (1946).

(5) W. V. Smith and R. H. Ewart, *J. Chem. Phys.*, **16**, 592 (1948).

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(7) P. J. Flory, THIS JOURANL, **59**, 241 (1937).

(8) F. R. Mayo, *ibid.*, **70**, 3689 (1948); R. A. Gregg and F. R. Mayo, *ibid.*, **70**, 2373 (1948).

(9) J. H. Baxendale, S. Bywater and M. G. Evans, *Trans. Faraday Soc.*, **42**, 675 (1946), and M. G. Evans, private communication, give evidence for combination in methyl methacrylate; M. S. Kharasch, H. C. McBay and W. H. Urry, *J. Org. Chem.*, **10**, 401 (1945), show a large proportion of $\text{MeOC}_6\text{H}_4\text{CHCH}_2\text{CH}_3$ radicals dimerize with no evidence of disproportionation.

where $\bar{P}$ = number average degree of polymerization, $C$ = transfer constant = $k_{tr}/k_p$.

These equations show that if $R_p$ and $\bar{P}$ are studied as a function of (Init.) the quantities $k_p^2/k_t$, $k_d f$, and $C$ may be obtained. A further relation to evaluate $k_p$, $k_t$ and $k_{tr}$ individually may be obtained by measuring $\tau_s$, the time average lifetime of the growing polymer radical.

The theory of the rotating sector is fully presented elsewhere.[10] However, some monomers, especially styrene, exhibit "dark" reactions, and we have extended the theory to cover these systems using the mechanism below and following the procedure of Dickinson.[10]

| *Initiation* | *Rate* | *Definitions* |
|---|---|---|
| $S + h\nu \xrightarrow{I_a} 2R\cdot$ | $2qI_a$ | S = sensitizer |
| $2R\cdot \xrightarrow{k_r} S$ | $2k_r(R\cdot)$ | $h\nu$ = quantum of frequency $\nu$ |
| $R\cdot + M \xrightarrow{k_a} M\cdot$ | $2k_a(R\cdot)(M)$ | $I_a$ = absorbed light intensity |
| *Propagation* | | |
| $M\cdot + M \xrightarrow{k_p} M\cdot$ | $k_p(M\cdot)(M)$ | R· = radicals from sensitizer |
| *Termination* | | |
| $M\cdot + M\cdot \xrightarrow{k_t}$ Polymer | $2k_t(M\cdot)^2$ | $q$ = quantum yield of dissociation of S |
| | | M, M·, and $k$'s as previously defined |

**The Assumptions for Photopolymerization in Intermittent Light.**—(1) Initiation: The essential assumption is that the rate of initiation, $R_i$, is proportional to the absorbed light intensity, $I_a$. In our work thermal initiation during light periods in all sector experiments was negligible compared to the photosensitized initiation. During dark periods it is assumed that there is a "dark reaction," whose magnitude is equal to that which would be caused by stray light of intensity $nI_a$ (the dark rate, of course, is induced either by thermal initiation by the monomer as in styrene or by "catalysts" such as peroxides as in methyl methacrylate) where $I_a$ corresponds to the total initiation in the cell when the sector is open and $n$ equals a quantity less than one. Evidence for the mechanism as given has been found by Schulz and Husemann,[11] Schulz and Blaschke[12] and Mark and Josefowitz.[13] (2) Assumptions 2, 4, 5 and 6 of previous mechanism held valid. (3) The irradiating light is absorbed in the cell uniformly, both as to space and as to time during light periods. (4) The magnitude of the "dark" rate of initiation is unaffected by light. (5) The dark–light and light–dark transitions in the cell are instantaneous at the beginning and end of a light flash; precautions to insure the correctness of assumptions 3 to 5 will be found under Experimental Procedure.

From the assumptions about the initiation

$$d(M\cdot)/dt = 2qfI_a - 2k_t(M\cdot)^2 \qquad (4)$$

is derived for the light period while during the dark period the following is derived

$$-d(M\cdot)/dt = 2k_t(M\cdot)^2 - 2qfnI_a \qquad (5)$$

Following Dickinson, we obtain as the final result

$$\frac{(\overline{M\cdot})}{(M\cdot)_s} = \frac{1}{p+1}\cdot\frac{1}{b}\left\{b + n^{1/2}pb + \ln\left[\frac{1+\frac{(M\cdot)_2}{(M\cdot)_s}}{1+\frac{(M\cdot)_2}{(M\cdot)_s n^{1/2}}}\right]\left[\frac{1+\frac{(M\cdot)_1}{(M\cdot)_s n^{1/2}}}{1+\frac{(M\cdot)_1}{(M\cdot)_s}}\right]\right\} \qquad (6)$$

where

$(\overline{M\cdot})/(M\cdot)_s$ = the ratio of $R_p$ in intermittent light to $R_p$ in steady light

since

$(\overline{M\cdot})$ = the time average concentration of M· in intermittent light

and

$(M\cdot)_s$ = the concentration of M· in steady light,

and where

$p$ = ratio of the dark period to the light period = 3 in our work

$b$ = ratio of the time of flash, $t_1$, to the time average duration of growth, $\tau_s$, where $\tau_s$ is the lifetime of the kinetic chain from the initiation of a chain to its termination by mutual interaction with another growing radical

$(M\cdot)_1$ = concentration of M· at the beginning of each dark period

$(M\cdot)_2$ = concentration of M· at the end of each dark period

Further

$$\frac{(M\cdot)_1}{(M\cdot)_s} = \frac{\tanh b + \frac{(M\cdot)_2}{(M\cdot)_s}}{1 + \frac{(M\cdot)_2}{(M\cdot)_s}\tanh b} \qquad (7)$$

and

$$\frac{(M\cdot)_2}{(M\cdot)_s} = \frac{-(1-n)\tanh b\cdot\tanh(n^{1/2}pb)}{2[n^{1/2}\tanh b + \tanh(n^{1/2}pb)]} + \frac{\sqrt{(1-n)^2\tanh^2 b\cdot\tanh^2(n^{1/2}pb) + 4[n^{1/2}\tanh b + \tanh(n^{1/2}pb)][n^{1/2}\tanh b + n\tanh(n^{1/2}pb)]}}{2[n^{1/2}\tanh b + \tanh(n^{1/2}pb)]} \qquad (8)$$

The curves obtained by the use of eqns. (6), (7) and (8) are plotted in Fig. 1 for various values of $n^{1/2}$. $n^{1/2}$ is the ratio of the steady dark rate to the steady light rate. The use of Fig. 1 in the measurement of the kinetic chain lifetime, $\tau_s$, is illustrated under Experimental Procedure.

(10) W. A. Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," Reinhold Publ. Corp., New York, N. Y., 1941, p. 202.

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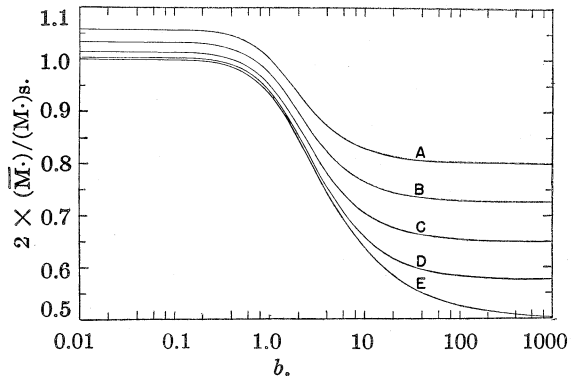



Fig. 1.—The ratio of intermittent light rate to steady light rate as a function of time of flash and dark rate: $A - n^{1/2} = 0.20$, $B - n^{1/2} = 0.15$, $C - n^{1/2} = 0.10$, $D - n^{1/2} = 0.05$, $E - n^{1/2} = 0.0$.

From the mechanism of photopolymerization, the following equations obtain in steady light

$$R_p = k_p(M\cdot)_s(M) \quad (9)$$

$$(M\cdot)_s = R_i\tau_s \quad (10)$$

$$R_i = 2k_t(M\cdot)_s^2 \quad (11)$$

whence

$$R_p\tau_s/(M) = k_p/2k_t \quad (12)$$

Thus, by measuring $\tau_s$ we can get $k_p/2k_t$ whereas by initiator studies we can get $k_p^2/2k_t$ and $k_{tr}/k_p$. The combination yields the individual values of $k_p$, $k_t$ and $k_{tr}$.

## Experimental

**Purification of Materials.**—Rohm and Haas methyl methacrylate was distilled through a 50-plate column under nitrogen: $n^{20}D$ 1.4152, b. p. 45.0° at 105 mm. This product was kept in the dark at −25° until further use. Subsequently, this material was recrystallized five times under dry nitrogen to a constant freezing point 0.3°[13a] above that of the distilled material with an over-all yield for all recrystallizations of 50%. The recrystallized material was stored in an evacuated tube containing 0.1% hydroquinone at −25° in the dark. Recrystallization and all subsequent operations were carried out in a dark room. Earlier experiments showed the necessity for filling the reaction cells by distillation into the cells *in vacuo* and in the absence of light if high dark reactions were to be avoided. Therefore, the vacuum bench and rotating sector equipment were located in a dark room. Eastman Kodak Co. biacetyl was distilled through a Vigreux column and the middle cut retained. Mallinckrodt Chemical Works photographic grade hydroquinone was used without further purification.

**Apparatus.**—A plan view of the rotating sector apparatus is shown diagrammatically in Fig. 2.

This apparatus enables sector studies to be made on two pairs of cells simultaneously, each pair being at a different temperature. The arcs A are Hanovia constant intensity high pressure mercury arcs, Type AH-8 with photocell feedback, supplied from two Sola constant voltage transformers in cascade. Experimentally the intensity was found to be constant to ±1% after a half hour warmup. The a. c. ripple in the light output was shown to be less than 3% of the total intensity. The light was made monochromatic by filters at F, using Corning no. 5840 and no. 738 filters to isolate the 3660 Å. line, except for the slow 30° experiment where the following combination was used: one 5840 + one 738 + three 5113. All lenses were crystal quartz 10 cm. f. l. and 4.6 cm. diameter free aperture. The lenses $L_1$ focused the narrow arc image at the sectors S, so that the transition time from dark to light and *vice versa* was about 2% of the light period. The sectors were made of 11 in. diameter aluminum disks divided into eight equal sectors and every fourth sector cut out to a radial depth of 2 in. These disks were driven by readily interchangeable synchronous motors. By means of these motors the disk speeds could be varied in steps from $^1/_{60}$ to 1800 r. p. m., each step corresponding approximately to a fourfold change in speed. The lenses $L_2$ were placed close to the sectors and considered to be located at the arc image. These lenses focused the image of the $L_1$'s in cells C to assure uniform light intensity over the cell and also to provide for simultaneous transition from dark to light throughout the cell. The images of the $L_1$'s overlapped the front windows of the cells 3 mm. all around. However, at the front of the cell a diaphragm limited the beam to just fill the inside of the cell. These cells were cylindrical cells with plane-polished faces, American Instrument Company Grade 1, 1 cm. internal depth and 3.7 cm. internal diameter. They were surmounted by a 25 cm. length of 2-mm. precision bore capillary. Gaertner M930–342 cathetometers were used to read the liquid levels in the capillaries to 0.01 mm. The cells were placed in holders in the baths B, so designed that inverted clear Pyrex cylindrical Dewars could be placed over the capillaries, the lower end of the Dewar dipping into the bath. Water was drawn up into the Dewar to cover the capillary, and for bath temperatures above room temperature, convection currents within the Dewar kept the temperature at the top of the capillary within 2° of that of the bath, even at a bath temperature of 60°. However, for bath temperatures below room temperature the difference at the top of the capillary was greater, since convection no longer played such an important part in heat transfer up the Dewar, but even in this case a more constant capillary temperature was assured, and in all cases the Dewar served to prevent condensation of the monomer in the capillary tip. Liquid level readings were taken through the transparent Dewar and this arrangement enabled the use of baths of moderate depth.

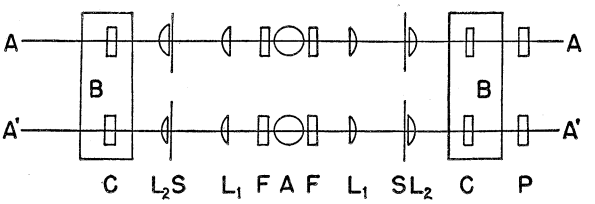



Fig. 2.—Apparatus for rotating sector studies.

During an experiment the constancy of the arcs was checked by the RCA935 photocells shown at P. A 6 cm. diameter quartz lens of 7.5 cm. focal length at the front of the photocell housing intercepted all of the light passing through the cell. The output of the 935 photocells was amplified by General Radio 715AE amplifiers and the amplified output recorded by Esterline Angus 5 ma. Model AW d. c. milliammeters. The output of the arcs was measured behind only one of the baths. The baths were fitted both front and rear with double windows of Corning no. 791 glass, having $^1/_4$″ of sealed air space. The double windows plus an air stream served to eliminate moisture condensation on the windows when the bath was operated at low temperatures. The temperatures of the baths were regulated to ±0.01°. Temperatures below room temperature were obtained by circulating an ethylene glycol–water mixture from an auxiliary American Instrument 4-86LE cooling bath through coils in the baths B. The optical paths in the diagram are designated AA and A′A′ and were thoroughly baffled and sealed against all stray light from other parts of the apparatus or originating externally.

(13a) F. p. of purified monomer −48.2° (Rohm and Haas Co. private communication). Using a thermocouple not absolutely calibrated we obtained a slightly higher value.

**Procedure.**—Filling of cells: Purified monomer was placed in a reservoir containing hydroquinone, and attached to a Pyrex glass vacuum system and degassed to a non-condensable gas pressure of $10^{-4}$ mm., while the monomer was at −80°. The process of melting, refreezing, and pumping on the monomer was repeated several times. The first 10% was distilled off *in vacuo* and rejected. Part of the remaining monomer was then distilled simultaneously into the bulbs B, as shown in Fig. 3. The volume of monomer in B was adjusted at 0° to a volume calibration mark on the bulb. The distilled biacetyl (the sensitizer used in all experiments) was also sealed to the vacuum system in a bulb containing hydroquinone. The required amount of biacetyl (calculated to give not more than 25% absorption in 1 cm. of depth when dissolved in the given volume of monomer in B) was distilled into a calibrated capillary for measuring at 0° and then into B. The apparatus of Fig. 3 was then sealed off at the constriction $C_1$. Next, the apparatus was inverted and the liquid level in the capillary of C adjusted to a suitable height. Both legs were cooled simultaneously to a few degrees above the freezing point of the monomer and the cell C sealed off at constriction $C_2$. The cell was stored at −25° in the dark until used.

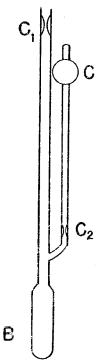


Fig. 3. — Device for filling cells.

**Irradiation.**—The cells were placed in the bath for a sufficient period before irradiation to get an accurate determination of the dark reaction, which in most cases was measured overnight. The cells were initially irradiated with the sectors in the open position to get the rate of polymerization in steady light. Then the sectors were started at known speeds and the rates of polymerization followed in intermittent light. The continuous and sectored irradiations were alternated during the day. Readings were taken at equal time intervals beginning a few minutes after the start of an irradiation so the method of Orthogonal Polynomials[14] could be used to get the least squares slope for the plot of liquid level *versus* time. Our method, it is believed, eliminates not only random reading errors but also errors due to slight heating and cooling effects in the cells at the beginning and end of a given irradiation as a result of the heat of reaction. If the experiments with a given cell were carried out over a period more than one day, the overnight dark reaction was checked each night. It was necessary to take the evening reading at least one hour after the end of an irradiation, otherwise the measured dark rate was affected by the decaying light-induced reaction.

**Densities.**—Since the rate was followed dilatometrically, the densities of monomer and polymer were determined as a function of temperature. The monomer used was freshly distilled, and the pyknometric determinations were carried out immediately in red light to avoid contamination by polymer. Constancy of the monomer density at 0° at the beginning and end of the experiment showed polymerization to be negligible. The polymer was prepared by allowing purified monomer to polymerize in sunlight in a pyrex flask in the presence of a trace of air. After apparent completion of polymerization the polymer was heated *in vacuo* at 100° for sixteen hours, after which the amount of monomer which could be pumped from shavings of the polymer at 100° was negligible. A portion of the polymer was cut to fit a mold and subjected to 2000 p. s. i. at 165° for one hour.

Recently Schulz and Harborth[15] have found the apparent density of polymethyl methacrylate to be greater in solution than in the pure solid state. To check this result two experiments were carried out. In one, freshly distilled monomer containing 0.2% tetrachloroquinone was poured into 100-cc. volumetric flasks containing weighed amounts of polymer and the volume determined after solution of the polymer. In the second experiment the monomer was distilled into 100-cc. volumetric bulbs *in vacuo*, 0.2 g. of benzoquinone being used in each flask as the inhibitor. Air was then introduced into each flask to compress the bubbles formed in the viscous solution. In each case density results were corrected for the small amount of inhibitor present. All of our samples of polymer initiated polymerization of the monomer, probably because of peroxides in them, necessitating the use of considerable inhibitor. The solution density results are given in Table II.

TABLE I

DENSITY OF METHYL METHACRYLATE MONOMER AND POLYMER

(Equation for monomer density, $\rho = 0.9654 - 0.00109\,t - 0.00000097t^2$ ($t$ = °C.)

| Temp., °C. | Monomer density | Temp., °C. | Polymer density[a] Unmolded | Molded |
|---|---|---|---|---|
| 0.38 | 0.9651 | 0.0 | 1.1903 | 1.1907 |
| 20.20 | .9431 | 30.0 | 1.1834 | 1.1835 |
| 30.02 | .9313 | 60.0 | 1.1756 | 1.1747 |
| 40.51 | .9198 | | | |
| 49.74 | .9088 | | | |
| 60.37 | .8956 | | | |

[a] Rohm and Haas Co. has kindly informed us that they find a density of 1.182 ± 0.003 at 25°.

TABLE II

APPARENT DENSITY OF POLYMETHYLMETHACRYLATE AT 30°[a]

| Experiment 1 Wt. % polymer | Density | Experiment 2 Wt. % polymer | Density |
|---|---|---|---|
| 5.26 | 1.195 | 16.09 | 1.227 |
| 10.39 | 1.213 | 26.93 | 1.224 |
| 15.40 | 1.213 | 39.72 | 1.219 |
| 38.78 | 1.218 | | |

[a] Ref. 15 gives 1.213 at 25°.

**Calculation of Results.**—In cases where the dark rate amounted to more than 1% of the steady light rate, two corrections were made. First, least squares values of the rates were corrected for the dark reaction taking place in the unilluminated appendages to the cell, by subtracting the proper fraction of the dark rate, about 20%, from both continuous and sector rates. The ratio of the corrected sector rate to the corrected continuous light rate was then obtained. This is necessary since the theory considers the volume subject to illumination, and in the experimental setup the side tubes and capillary were completely shielded. For all cells used, both the volume in the barrel of the cell and the volume of monomer in the side tubes and capillary were measured. The effect of the dark reaction within the irradiated volume is considered next. By the use of the curves plotted in Fig. 1, the values of $b$ corresponding to the corrected rate ratio were found for values of $n^{1/2}$ of 0, 0.05, 0.10, 0.15 and 0.20 and from these data a plot of $b$ *vs.* $n^{1/2}$ was made ($n^{1/2}$, which will be called the fractional dark rate, is, as noted previously, the ratio of the steady dark rate of polymerization to the steady light rate of polymerization, both rates being

(14) Tables of Orthogonal Polynomial Values Extended to $N$ = 104: R. L. Anderson and E. E. Houseman, Research Bulletin 297, April, 1942, Ames, Iowa.

(15) G. V. Schulz and G. Harborth, *Angew. Chem.*, **59A**, 90 (1947).

limited to the cell barrel). The value of $b$ corresponding to the measured fractional dark rate which obtained during the experiment was then found by interpolation from the plot. The lifetime, $\tau_s$, is the ratio of $t_1$, the time of flash for the given sector speed, to $b$. An example in which a sector speed of 1/15 r. p. m. was used in experiment 19L will make this calculation clear.

| | | | |
|---|---|---|---|
| Rates | Cm./min. | Ratio | .315 |
| Dark | 0.000110 | 2 × Ratio | .630 |
| Dark correction outside cell | .000024 | $t_1$ sec. | 112.5 |
| | | $n^{1/2}$ | .021 |
| Corrected dark rate in cell | .000086 | $b$ measured for $n^{1/2}$ = .021 | 11.5 |
| 11th continuous | .00396 | $\tau_s$ | 9.79 |
| 12th continuous | .00403 | Rate % contraction per hr. | .0724 |
| Av. continuous | .00400 | $\tau_s$ @ 0.5% contraction per hr. | 1.42 |
| Corrected continuous | .00398 | 2 × ratio for $n^{1/2}$ = 0 | .625 |
| 8th sector | .001280 | | |
| Cor. sector | .001256 | | |

In any run ratios were measured at several different sector speeds. In order to obtain an average value of $\tau_s$ from these results, the rate ratios were plotted against the log of the time of flash (log $t_1$) and the position of best fit with the proper theoretical curve of Fig. 1 found. As seen from Fig. 1 and from eqn. (12), the experimental results will depend on the fractional dark rate and the rate of polymerization; therefore, it is necessary to correct the results with each sector to the same $n^{1/2}$ and the same $R_p$ before plotting as above. Further, if a series of experimental points is fitted to one of the curves shown in Fig. 1, the statistical weight for each point will depend in some manner on whether its abscissa corresponds to a flat or steep portion of the theoretical curve at the position of best fit. The points at the extremes of the curves have little effect on the average value of $\tau_s$, but do test whether the theory is obeyed. In view of these considerations it was deemed advisable in adjusting results to a common basis to follow a procedure which would not change appreciably the position of a given point relative to the proper theoretical curve.

The rate ratios were first corrected to the nearest dark rate of Fig. 1. For methyl methacrylate, since the fractional dark rates were small, this meant correcting the given rate ratio to that corresponding to the same experimental value of $b$ but at zero dark reaction ($n^{1/2} = 0$). In the example above the measured ratio for $n^{1/2} = 0.021$ is 0.630 and this is changed to 0.625 at $n^{1/2} = 0.00$, the value of $b$ remaining unchanged at 11.5.

From eqn. (12) $\tau_s$ is inversely proportional to $R_p$, also $b = t_1/\tau_s$, therefore it is seen that if a certain ratio and value of $b$ are measured for a given rate of polymerization, $R_{PA}$, and time of flash, $t_{1A}$, then this result is experimentally the same as obtaining the same ratio and same $b$ at $R_{PB}$ and $t_{1B}$ where $R_{PA}/R_{PB} = t_{1B}/t_{1A}$. On the basis of this, all ratios for a given run were corrected to a common $R_p$ adjusting the $t_1$'s inversely. Then on semi-transparent paper the ratios were plotted *vs.* the log $t_1$ on the same scale as the proper curve of Fig. 1. The plot of ratios *vs.* log $t_1$ was placed over the theoretical curve with ordinates matching and moved back and forth horizontally to several different positions about the position which appeared to give the best fit. At each position the vertical deviations of the experimental points from the curve were measured and the sum of the squares of the deviations calculated. The sum of squares for each position was plotted *vs.* ($t_1$ on experimental curve)/($b$ on theoretical curve) and the position of the minimum taken as $\tau_s$. The agreement between experiment and theory is indicated for a typical run (no. 17L-b) in Fig. 4. The $t_1$ and $b$ scales are displaced with respect to each other so that the best statistical fit of $t_1/b = \tau_s$ is obtained.

The results of all lifetime runs on methyl methacrylate are summarized in Table III. While the samples are small it is believed that the table as a whole indicates that the average results are reproducible to within 25% or less of the indicated values.

TABLE III

LIFETIMES OF POLYMETHYLMETHACRYLATE RADICALS

| Experiment | No. of sectors | Rate % contraction per hr.[a] | $\tau_s$ sec. | Av. $\tau_s$ at 1.0% contraction per hr. | Standard deviation, % |
|---|---|---|---|---|---|
| | | 5° | | | |
| 17L-a | 12 | 0.20 | 3.07 | | |
| 17L-b | 12 | .20 | 2.95 | 0.603 | 2 |
| | | 30° | | | |
| 11L | 4 | .50 | 1.7 | | |
| 15L-a | 2 | .50 | 2.2 | | |
| 15L-b | 6 | .50 | 2.0 | | |
| 16L-a | 4 | .50 | 1.8 | | |
| 16L-b | 4 | .50 | 1.9 | | |
| 18L-a | 4 | .50 | 1.43 | 0.906 | 14 |
| 18L-a | 13 | .10 | 11.5 | | |
| 18L-b | 12 | .10 | 7.2 | | |
| 19L-b | 18 | .10 | 7.25 | 0.831 | 24 |
| | | 50° | | | |
| 16L-b | 4 | 1.0 | 1.40 | 1.40 | |
| | | 60° | | | |
| 11L | 4 | 1.0 | 1.95 | | |
| 15L-a | 4 | 1.0 | 2.15 | | |
| 15L-b | 3 | 1.0 | 1.80 | | |
| 16L-a | 4 | 1.0 | 1.77 | | |
| 17L-a | 4 | 1.0 | 1.20 | | |
| 17L-b | 6 | 1.0 | 2.20 | 1.84 | 22 |

[a] Results in each experiment corrected to the same rate, the selected rate being very close to the experimental rates.

## Results and Discussion

For the case where thermal initiation is rela-

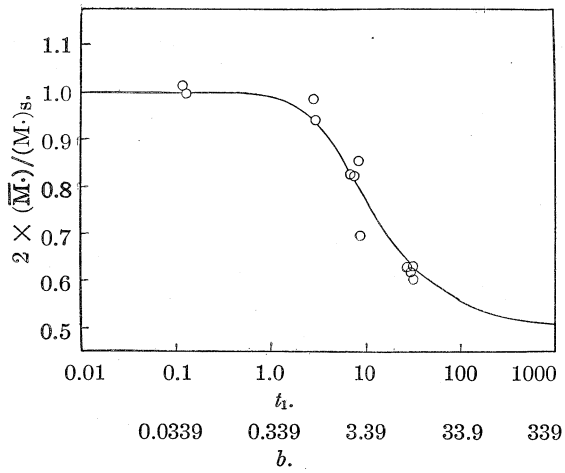



Fig. 4.—Rate of polymerization of methyl methacrylate in intermittent light for different times of flash: Curve, theory for zero dark rate; points, run 17L-b.

tively unimportant as in methyl methacrylate eqn. (2) reduces to

$$R_p = (k_p(M)/k_t^{1/2})\sqrt{k_d f\,(Init.)} \qquad (13)$$

and eqn. (3) to

$$\frac{1}{\bar{P}} = \frac{\sqrt{k_d f\,(Init.)}}{k_p(M)/k_t^{1/2}} + C \qquad (14)^{16a}$$

Schulz[11,12] has previously developed similar equations for this case and shown how by plotting $R_P$ *vs.* $\sqrt{(Init.)}$ and $1/\bar{P}$ *vs.* $\sqrt{(Init.)}$ values of $k_p^2/2k_t$ and $C$ may be obtained. We have combined the data of Schulz and Blaschke[12] with those of Schulz and Harborth[16] to obtain Table IV.

TABLE IV

| | 50°C. | 70°C. |
|---|---|---|
| $k_d f \times 10^7$ | 8.76 | 119 |
| $(k_p^2/2k_t) \times 10^3$ | 4.57 | 11.1 |
| $C \times 10^5$ | 4.77 | 8.07 |

$k$'s in this paper in moles, liters, seconds.

The results in Table IV differ from the average of those given in refs. 12 and 16 for three reasons. First, our calculations are based only on the results at different peroxide concentrations, ignoring the work in which the monomer concentration was varied as the experimental results are acknowledged by the authors to be less accurate at the lower monomer concentrations. Second, our least-squares plot of the data yields values differing slightly from those given for the peroxide studies. Third, although these authors assume termination by combination of radicals, their equation relating the degree of polymerization to kinetic chain length and the transfer constant corresponds to disproportionation. Because of this latter, our values of $k_p^2/2k_t$(or $k_B^2/k_C$) are very nearly half of those given by Schulz and coworkers. The revised values of Table IV constants recently published by Schulz and Harborth are considered by them to be more accurate. However, we have not used these values alone because (1) if only the studies in which the peroxide concentration is varied are used, $k_p^2/2k_t$ from the combined data is but little changed from that calculated from the same studies in ref. 12, (*e. g.* from ref. 12, we calculate $k_p^2/2k_t$ to be $4.52 \times 10^{-3}$ at 50° and $11.2 \times 10^{-3}$ at 70°); (2) a wider range of peroxide concentrations is used in ref. 12 as compared with 16.

If $(R_p\tau_s)/(M)$ is calculated from the data of Table III, the monomer densities of Table I and polymer solution densities of Schulz and Harborth[15,17a] for each experimental temperature, then Table V is obtained. The log of $k_p/2k_t$ is plotted *vs.* $1/T$ in Fig. 5.

TABLE V

| $(k_p/2k_t) \times 10^6$ | °C. |
|---|---|
| 7.78 | 5 |
| 10.94 | 30 |
| 16.06 | 50 |
| 20.60 | 60 |

The upper line was obtained by weighing each experimental point according to the number of

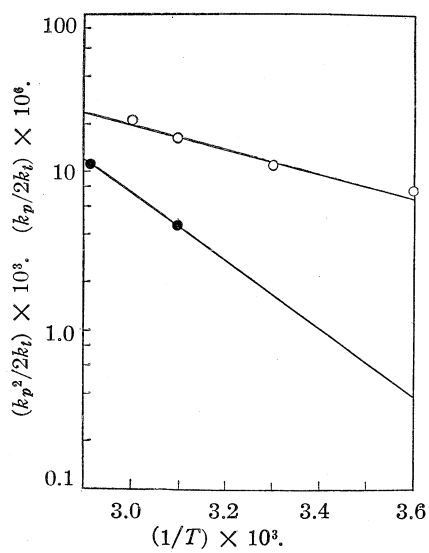



Fig. 5.—Rate constant ratios for methyl methacrylate polymerization: ●, $k_p^2/2k_t$ from data of Schulz and Blaschke[12] and Schulz and Harborth[16]; ○, $k_p/2k_t$, this paper.

(16) G. V. Schulz and G. Harborth, *Die Makromolekulare Chemie*, **1**, 106 (1947).

(16a) The work of Nozaki and Bartlett, THIS JOURNAL, **68**, 1686 (1946), shows that with benzoyl peroxide induced polymerization of styrene, transfer with the initiator occurs, so that eqn. (14) should include a term for this effect. However, the data of Schulz, *et al.*,[12,16] show the plot of $1/\bar{P}$ *vs.* $\sqrt{(Init.)}$ to be a good straight line with no hint of the upward curvature to be expected if transfer with the peroxide were important. F. R. Mayo has pointed out to us that polar effects would favor the transfer reaction of polystyrene radical with benzoyl peroxide as compared with polymethylmethacrylate radical plus the peroxide.

(17a) Use of the solid polymer densities of Table I would lower the calculated values of $k_p$ about 4–8% and change $E_p$ by 200 calories.

runs made in obtaining that point (see Table III), and then calculating the least-squares line. The runs at the low rates of polymerization at 30° were not included in these calculations and would not affect the result much anyway. Also plotted in Fig. 5 is the line for $k_p^2/2k_t$ as obtained from Table IV. From Fig. 5 and a plot of $C$ (Table IV) the values in Table VI have been calculated.

TABLE VI

| | 30° | 60° | $T$ |
|---|---|---|---|
| $k_p$ | 143 | 367 | $5.13 \times 10^6 e^{-6310/RT}$ |
| $2k_t$ | $1.22 \times 10^7$ | $1.87 \times 10^7$ | $1.36 \times 10^9 e^{-2840/RT}$ |
| $k_{tr}$ | $3.75 \times 10^{-3}$ | $22.9 \times 10^{-3}$ | $2.75 \times 10^6 e^{-12280/RT}$ |

In our calculations on our lifetime results the value of (M) was varied from temperature to temperature according to the data of Table I while Schulz and Blaschke appear to have used the same concentration of monomer at all temperatures for the pure monomer disregarding the variation due to expansion with temperature. This means that their values of $R_p$ and $k_p^2/2k_t$ need small corrections before they can be considered to correspond to the rate constants in terms of the actual moles per liter for a given temperature. This correction when made would, however, affect the log of the $k_p^2/2k_t$ *vs.* $1/T$ line only slightly.

The rate constants as represented by the last column of Table VI have the following ratios to the values found by Bamford and Dewar at 0°[4] for methyl methacrylate: for $k_p$ 1.05, $k_t$ 1.52, and for $k_{tr}$ 0.59. The excellent agreement is well within the experimental precision of the two methods. Indeed, if we used termination by disproportionation as do Bamford and Dewar our values of $k_p$ and $k_t$ would double. A consideration of the experimental quantities involved in the determination of the rate constants indicates that the decreasing order of precision is $k_p$, $k_t$, $k_{tr}$. The quantities entering the $k_p$ and $k_t$ values are similar except that $\tau_s$ enters $k_p$ to the first power and $k_t$ to the second, so that the errors in the lifetime are doubled in effect in the determination of $k_t$. In $k_{tr}$ the greatest source of uncertainty derives from the molecular weight measurements since $C$ is determined as the intercept of $1/\bar{P}$ *vs.* $\sqrt{(\text{Init.})}$

The activation energies in Table VI are of about the expected order of magnitude. The frequency factor for the termination reaction, which involves the interaction of two free radicals, approaches normality, whereas the factors for the propagation and transfer reactions, which involve a free radical plus an olefinic compound, are lower. The low frequency factor in the propagation reaction is in accord with the theories of Harman and Eyring.[17]

**Effect of Chain Length on the Termination Constant.**—The theory used in this work assumes the rate constants are independent of the radical chain length. However, Burnett and Melville[1] found that $k_t$ decreased 20% when the radical chain length was doubled in vinyl acetate. Therefore, it seemed desirable to determine whether such an effect existed in methyl methacrylate. In Table III the results of such a test carried out at 30° are given.

The ratio between the experimental rates in the two series of experiments was 6. If $k_t$ decreases 10% as the chain length is doubled it may be calculated that $\tau_s$ measured at the low rate of polymerization should be 40% longer than predicted by eqn. (12) from the value of $\tau_s$ at the high rate of polymerization. Actually, in Table III it is seen that the experimental $\tau_s$ is shorter, not longer, at the low rate of polymerization when the results are corrected to a common rate by eqn. (12). Applying statistics to these admittedly small samples, it is estimated that there is less than a 1% chance that the rate constant does decrease by as much as 10% when the polymer radical length is doubled. We conclude, therefore, that the rate constant for termination is independent of chain length at least up to about 10% conversion.

**Experiments at High Conversion.**—Schulz and Blaschke[18] in investigating the benzoyl peroxide-induced polymerization of methyl methacrylate noted that the rate strongly accelerated after about 20% conversion was obtained at 70°. Trommsdorff[19] subsequently found this rate acceleration to be accompanied by a corresponding increase in the degree of polymerization, and suggested this effect is due to a decrease in the termination constant as the system becomes more viscous. Later, Schulz and Harborth[16] confirmed that even under isothermal conditions at 50 and 70° this strong acceleration persisted and that $\bar{P}$ increased approximately in the same ratio as the rate of polymerization, at least up to 40% conversion and where transfer was not too important. In their interpretation also the growing chains find it more difficult to diffuse together in the viscous medium.

Burnett and Melville[1] found this acceleration to occur at about 25% conversion in the photopolymerization of vinyl acetate and also to appear even earlier in vinyl acetate photopolymerized in a poor solvent such as *n*-hexane.[20] This "gel effect," as they call it, is also attributed by them to a decrease in $k_t$ as the polymer–monomer mixture becomes more viscous. From sector measurements they estimated approximate values of $k_t$ at some point in the gel stage. The results in *n*-hexane were explained as due to a coiling up of the molecule which prevented the active ends of the growing radicals coming together. However,

(17) R. A. Harman and H. Eyring, *J. Chem. Phys.*, **10**, 557 (1942).

(18) G. V. Schulz and F. Blaschke, *Z. physik. Chemie*, **B50**, 305 (1941).

(19) Trommsdorff, "Colloquium on High Polymers," Freiburg, 1944.

(20) Burnett and Melville, *Proc. Roy. Soc. (London)*, **A189**, 494 (1947).

more plausible to us is the explanation Schulz and Harborth used to account for the results of Norrish and Smith[21] on methyl methacrylate polymerizations in poor solvents. They attribute the acceleration to precipitation of the polymer which then absorbs monomer to give an inhomogeneous mixture, portions of which correspond in composition to high conversion.

To test the effect of high conversion on the lifetime of polymethyl methacrylate radicals, two cells were prepared by the usual procedure and irradiated with steady light of the usual intensity at 30° until a conversion of ~37% was attained. At this point, sector measurements were made. Since the rate had increased so much on attaining this conversion, it was necessary to reduce the rate by reducing the light intensity 12.6-fold in order to make accurate measurements of the lifetime. Table VII summarizes the results.

TABLE VII

| Cell | Init. rate contraction, %/hr. | Conversion at which rate increased, % | (Rate at 37% conv.)/(Init. rate), av. | Lifetime measurements $\tau_s$ sec. | Rate contraction %/hr. | Conversion |
|---|---|---|---|---|---|---|
| 1 | 0.496 | 16.0 | | 111 | 0.755 | 33.9 |
| | | | 6.43 | 105 | .946 | 36.3 |
| 2 | .395 | 12.9 | | 100 | .746 | 36.5 |
| Av. | .451 | 14.5 | 6.43 | 105 | .816 | 35.6[a] |

[a] Because irradiation and reaction occur in fixed volume, conversion of 35.6% of the original monomer in the irradiation zone yields a solution corresponding to 33.2% conversion as monomer enters from capillary.

In the work of Schulz and Harborth the increase in molecular weight fully accounts for the accelerated rate and the rate of initiation may be considered constant up to a considerable conversion. The theory of the "cage effect" indicates, however, that $R_i$ may depend upon (M) and the following

TABLE VIII

PHOTOPOLYMERIZATION METHYL METHACRYLATE AT 3660 Å. AND 30° BIACETYL SENSITIZER[a]

| $R_p$ | $\bar{P}$ | Quantum yield $R_p/I_a$ | $Cb$ | $\bar{\nu}$ | $qf$ |
|---|---|---|---|---|---|
| $2.36 \times 10^{-4}$ m./l./sec. | 1963 | 43.1 | $2.6 \times 10^{-5}$ | $1.03 \times 10^3$ | 0.021 |

[a] These experiments yield $k_p/\sqrt{2k_t}$ 30% higher than Fig. 5. [b] From Table IV data. $\bar{\nu}$ = number av. kinetic chain length.

(21) R. G. W. Norrish and R. R. Smith, *Nature*, **150**, 336 (1942).

averages from three experiments enable us to make the assumption as to this dependence.

If $q$, the quantum yield for dissociation of biacetyl, is near 1.0 (experimentally we have found the quantum yield of biacetyl disappearance in ethyl alcohol was approximately 0.7), then $f$ is seen to be low and is therefore $\simeq(k_d/k_r)(M)$. Thus, $R_i$ may be assumed proportional to (M). The result of combining the lifetime data with either the assumption that $R_i$ is constant or is proportional to (M) is given in Table IX.

TABLE IX

| | ($k_p$ initial)/($k_p$ at 33% conversion) | ($k_t$ initial)/($k_t$ at 33% conversion) |
|---|---|---|
| $R_i$ = constant | 0.62 | 216 |
| $R_i \alpha$ (M) | .89 | 151 |

We may conclude that at 33% conversion the propagation constant is unchanged while the termination constant has decreased over 100-fold. Thus, at low conversions we have found the termination constant to be independent of radical chain length while at high conversions the presence of a considerable amount of polymer has decreased the termination constant considerably. It is probable that in the presence of appreciable polymer the termination constant is no longer independent of chain length.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. H. M. Smallwood for his advice and encouragement during the course of this work.

## Summary

The average lifetime of growing polymethyl methacrylate radicals in the photosensitized polymerization of the liquid monomer has been measured as a function of temperature. Combining the lifetime data with studies by Schulz on the rate of polymerization and polymer molecular weight *vs.* free radical initiator concentration gives the rate constants for propagation, termination, and transfer with the monomer. In the initial stages the termination rate constant is independent of chain length. The accelerated polymerization rate occurring in the later stages is due to a decrease in the termination constant.

The theory of the rotating sector has been extended to include those cases having appreciable "dark" rates of polymerization.

PASSAIC, NEW JERSEY RECEIVED JUNE 7, 1948

[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY]

# On the Thermodynamics of Solutions. IV. The Determination of Liquid–Vapor Equilibria by Measuring the Total Pressure[1,2]

BY O. REDLICH AND A. T. KISTER

It has been repeatedly noticed[3] that the knowledge of the total pressure over a binary solution as a function of the composition of the liquid at constant temperature is sufficient for a complete description of the liquid–vapor equilibrium at this temperature. In other words, the activity coefficients can be derived, in principle, from the total pressure without knowledge of the composition of the vapor. In spite of this considerable advantage, the method has not been used very often. One reason is obvious, namely, the difficulty of the calculation. Indeed, none of the various calculation methods appears to be satisfactory. Another reason may have been the suspicion that small experimental errors may entail unduly large errors in the resulting activity coefficients. This question appears to deserve a careful examination.

The present paper is restricted to a special case of some practical importance. The efficiency of distillation columns containing a large number of plates is frequently investigated by means of binary solutions of closely boiling hydrocarbons. The relative volatility of the binary system must be known with a fairly high accuracy since in a column of $n$ plates the error in the resulting efficiency is $n$ times the relative error in the relative volatility. A sufficiently accurate analysis of the liquid and the vapor presents, in general, serious difficulties since the properties of closely boiling hydrocarbons are not sufficiently different. The advantage of the measurement of the total pressure therefore is important. At the same time, convenient calculation methods can be developed for these systems which deviate only slightly from perfect solutions.

## Experimental

To obtain the full advantage of the method, one has to observe two conditions: (a) The composition of the liquid should be obtained by weighing the components. Accordingly the vapor space over the boiling liquid should be small so that the correction for the change of composition by vaporization is negligible or small. (b) Especially for systems of closely boiling components, a differential method is preferable in which the vapor pressure of a solution is directly compared with the vapor pressure of one component boiling at the same temperature. The temperature difference between the two boilers is measured by means of a thermocouple, which requires less vapor space than a resistance thermometer.

The vapor pressure of the component used for reference and the pressure difference between the two boilers are determined by means of a mercury manometer. Capillary depression is eliminated by the use of 20 mm. tubing. The boiling temperature of the reference substance is calculated from the vapor pressure.

Between the manometer legs and the boilers are buffer bulbs (2 liters), Dry Ice traps and short condensers. The manometer and the buffer bulbs are enclosed in an air thermostat. The connecting lines between the manometer and the condensers are filled with nitrogen, the amount of which is precisely controlled by means of needle valves in side lines leading to a nitrogen tank and a vacuum pump. Pressure fluctuations are avoided by maintaining a steady flow rate of the cooling liquid (water or acetone cooled by means of Dry Ice) in the condensers.

The Cottrell boilers (Fig. 1) are enclosed in silvered vacuum jackets j. The kettle is heated by a coil fitting in the cylindrical space h. The thermocouple is introduced into the well w. The liquid thrown up to the well by the Cottrell pump returns through the line r and mixes there with the reflux from the condenser c so that there is practically no holdup of condensed vapor. After the measurement the boiler is drained through the tube d. The boilers are charged each with 85 ml. of liquid. The vapor space up to the level of condensation amounts to 185 ml. The heaters are arranged in series and operate at 60 watts each. The resistances of the heaters are made equal within 1%.

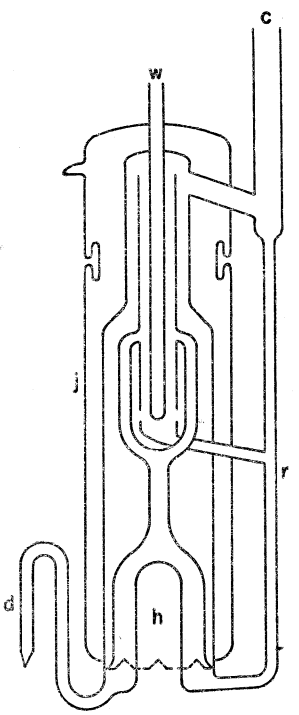


Fig. 1.—Boiler.

The desired boiling temperature is obtained by adjusting the amount of nitrogen in the connecting lines between manometer and boilers. The temperature difference is easily maintained below 0.02° and measured within 0.001°. Only a crude calibration of the thermocouple is therefore required, easily obtained by letting the same pure substance boil in the two boilers at different pressures.

The filling hole is in the connecting line above the Dry Ice-trap so that any contact between vapor and glass stopper is avoided. The solutions, however, are filled into the boiler through a glass tube extending through the trap so that the vapor cannot be carried into the manometer lines.

The purity of the components must be checked by comparing the difference of their vapor pressures with adopted values. Small impurities are harmless if the consistency of the results is maintained by a suitable correction.

The errors introduced by the determination of the pressures and the temperature difference and by weighing influence the total pressure (at about one atmosphere) only by a few thousandths of one per cent. The change of concentration by vaporization into the vapor space is of the

(1) Presented at the Symposium on Thermodynamics and Molecular Structure of Solutions, 114th National Meeting of the American Chemical Society, Division of Physical and Inorganic Chemistry, Portland, Oregon, September 13 and 14, 1948.

(2) Previous papers of this series: *Ind. Eng. Chem.*, **40**, 341, 345 (1948); *J. Chem. Phys.*, **15**, 849 (1947).

(3) See, for instance, R. M. Levy, *Ind. Eng. Chem.*, **33**, 928 (1941).

same order of magnitude for closely boiling systems. The main error, especially for low boiling mixtures, appears to be due to vaporization during the preparation of the solution. The possible error during the filling of *n*- and isopentane into the weighing flask was estimated and a correction of one half its amount was applied. The maximum correction corresponded to 0.025% in the total pressure. Altogether, errors of a few hundredths of one per cent. are to be expected.

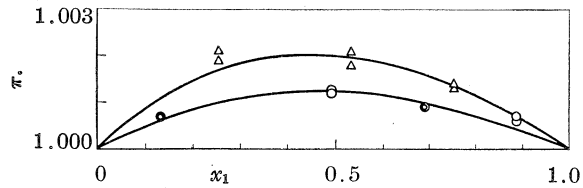



Fig. 2.—Ethylbenzene–*o*-xylene, Δ, $B = 0.0035$; *m*-xylene–*o*-xylene, O, $B = 0.0021$.

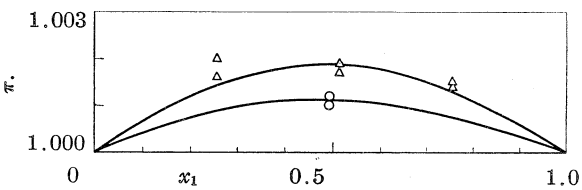



Fig. 3.—Ethylbenzene–*p*-xylene, Δ, $B = 0.0031$; *p*-xylene–*o*-xylene, O, $B = 0.0019$.

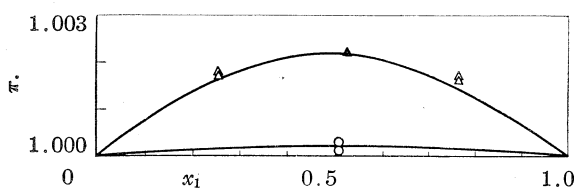



Fig. 4.—Ethylbenzene–*m*-xylene, Δ, $B = 0.0036$; *p*-xylene–*m*-xylene, O, $B = 0.0003$.

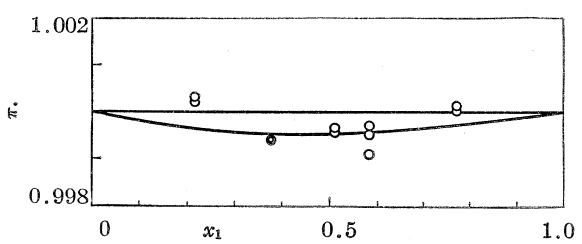



Fig. 5.—Isopentane–*n*-pentane, $B = -0.0008$.

## Results

The results obtained at approximately atmospheric pressure are shown in Figs. 2 to 5. The ordinate is the ratio

$$\pi = P/(x_1P_1 + x_2P_2) \qquad (1)$$

($x_1$ and $x_2$ are the mole fractions of the liquid). The functions $P_1$ and $P_2$ are sufficiently approximated[4] for the present purpose by

$$\ln P_1/p_1^\circ = (V_1 - \beta_1)(P - p_1^\circ)/RT \qquad (2)$$

($p_1^\circ$ vapor pressure, $V_1$ molal volume of the liquid, $\beta_1$ second virial coefficient). Since

$$x_1\gamma_1P_1 = y_1P \qquad (3)$$

($\gamma_1$ activity coefficient), the total pressure is

$$P = x_1\gamma_1P_1 + x_2\gamma_2P_2 \qquad (4)$$

The calculation of the activity coefficients presents no difficulty if, as in the present case, the approximation

$$\log \gamma_1 = Bx_2^2, \quad \log \gamma_2 = Bx_1^2 \qquad (5)$$

is sufficient. In this case we calculate the function $\pi$ of eqn. (1) for a few suitably chosen values of $B$ according to (1), (4) and (5), draw the corresponding curves in a diagram containing the experimental points and find the best value of $B$ by interpolation. This method has the advantage that the influence of experimental errors on the result is immediately seen.

The diagram furnishes a direct indication if the approximation (5) is insufficient and a second term of a Margules series is to be added. In this case the experimental points are consistently above the closest fitting curve in one part of the diagram and consistently below in the other part. The graphical method can be extended to this case without serious difficulty.

For small values of $B$ an even simpler method can be used. Equation (5) is approximated by

$$\gamma_1 - 1 = 2.303\ Bx_2^2, \qquad \gamma_2 - 1 = 2.303\ Bx_1^2 \qquad (6)$$

so that

$$\pi = 1 + 2.303\ Bx_1x_2(x_1P_2 + x_2P_1)/(x_1P_1 + x_2P_2) \qquad (7)$$

This approximation is sufficient for $P_1/P_2 = 1$ if $B < 2.1\ (d\pi)^{1/2}$ and for $P_1/P_2 = \infty$ if $B < 0.6\ (d\pi)^{1/2}$ where $d\pi$ is the permissible error in $\pi$.

The figures contain the curves representing the adopted values of $B$. The vapor pressures of Rossini and his co-workers[5] were used for the calculations. The second virial coefficients were calculated from Berthelot's equation. The values of $B$ may be in error by a few units of the fourth decimal place, corresponding to a maximum error of 0.1% in the relative volatility.

In measurements of this type, the correction for the imperfection of the vapor (Eqn. 2) may be important even at atmospheric pressure. In the system iso- and *n*-pentane the value of $B$ would be $-0.0023$ without the appropriate correction instead of $-0.0008$.

**Acknowledgment.**—The authors are indebted to Mr. L. T. Carleton for valuable advice regarding the construction of the apparatus.

## Summary

Small deviations from the perfect solution are conveniently and accurately determined by measurement of the total pressure. The experimental procedure is described. Results are given for the six binary systems formed by the three xylenes

(4) *Cf.* M. Benedict, C. A. Johnson, E. Solomon and L. C. Rubin, *Trans. Am. Inst. Chem. Engrs.*, **41**, 371 (1945). In other cases better approximations may be required, which will be discussed in the next paper of this series and in a paper by J. A. Beattie (*Chem. Revs.*, 1949).

(5) American Petroleum Institute, Research Project 44 at the National Bureau of Standards, "Selected Values of Properties of Hydrocarbons," Tables No. 1k and 5k (June 30, 1944).

and ethylbenzene and for isopentane–*n*-pentane. The method is useful for systems to be used for determining the efficiency of distillation columns.

RECEIVED AUGUST 30, 1948

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MARYLAND]

# Physical Properties of Some Organic Insect Repellents[1]

BY W. J. SVIRBELY, W. M. EARECKSON III, K. MATSUDA, H. B. PICKARD, I. S. SOLET AND W. B. TUEMMLER

Under the Insecticide and Insect Control Research and Development Program carried out for the Department of National Defense, a large number of organic compounds were prepared and tested for their insect repellent effectiveness. It was thought that a critical study of the physical properties of some successful repellents might be of value in determining whether or not a correlation existed between repellent effectiveness and certain physical characteristics. However, the data required to make such a study were not available. We, therefore, were asked to provide certain physical data for a large number of compounds. The results which we have obtained up to the present are recorded in Table I.

## Experimental

**Purification of Materials.**—About 25 to 30 ml. of starting material (all that was available) was vacuum distilled. A Vigreux column, 1 cm. diameter and 15 cm. long, provided with a chromel heating jacket, was used for all distillations except for isobutyric acid, α-hydroxy-, phenethyl ester and *dl*-malic acid, dibutyl ester. The middle fraction (50–60%) was collected under the conditions given in Table I.

**Refractive Indices.**—Measurements were made using an Abbe refractometer with temperature control. Check results agreeing to 0.0001 unit were obtained. The refractometer was calibrated against water (obs., 1.3325; lit., 1.3325) and with a test plate (obs. 1.5185; manufacturer's value for plate, 1.5185).

**Boiling Points.**—The boiling points were determined by a micro method.[2] The average of five to ten readings for each compound was always within 0.4° of the extreme readings. All boiling points were corrected to 760 mm. Based on the results for the reference materials listed in Table II and on the behavior of the test materials which did not decompose, we estimate the boiling points in Table I to be within 0.3°.

**General Information for Remaining Measurements.**—Due to the limited amounts of material available for the tests, it was necessary to design apparatus whose total volume was not over 2 cc. This necessitated the use of capillary tubing wherever possible. Such apparatus was usually cleaned with acetone, water, potassium chromate–sulfuric acid cleaning solution, water and distilled water. The apparatus was then dried with a current of clean dry air for about an hour while it was kept in the oven at about 45°.

Material was usually introduced into measuring apparatus by suction. All possible precautions to avoid picking up moisture in the course of an experiment were taken.

All thermostats (except the one used for refractive index measurements) were maintained at 35 ± 0.02°.

All thermometers were calibrated against thermometers previously calibrated by the Bureau of Standards.

After the test material was introduced into a measuring apparatus, the unit was allowed to come to temperature equilibrium in a minimum period of fifteen minutes.

**Density.**—Ostwald-Sprengel type pycnometers, volume about 1 ml., were used. Check weighings, agreeing to 0.1 mg., were made on a pycnometer and its contents. The precision is estimated to be 0.01%.

**Viscosity.**—Ostwald viscosimeters, volume between marks was 0.7 to 1.0 ml., were used. Five viscosimeters (small bore capillary) were calibrated with water, while one viscosimeter (large bore capillary) was calibrated with phthalimide, N-*s*-butyl-, after its viscosity was determined. The large bore viscosimeter was used for compounds whose viscosity was greater than 180 millipoises. The times of efflux on check runs agreed to 0.2%. Considering reproducibility and agreement with the value for benzene, we consider the results in Table I to be accurate to at least 0.2%.

**Solubility.**—The method discussed by Sobotka and Kahn[3] was used. The test material is added drop by drop from a calibrated, water-jacketed, 1-ml. microburet, to a definite amount of water contained in a thermostated, glass-stoppered flask, until the end-point is reached (corresponding to the saturation of the water by the test material). Sudan IV was used as the indicator. From the density and volume of the material used, its solubility in grams per 100 ml. of water is calculated. The results, given in Table I, are based on duplicate runs.

A test run made on diethyl succinate gave a value of 1.73 g./100 ml. of water compared to a value of 1.78 g./100 ml. of water obtained by saponification with subsequent titration of a saturated solution of diethyl succinate in water. Benzyl alcohol, *p*-methoxy-, gave a solubility of 3.83 g./100 ml. of water compared to a value of 3.84 g./100 ml. of water obtained from a refractive index calibration curve.

**Surface Tension.**—In the first part of this work, measurements were made by the capillary tube method. The radius of each of six different tubes was determined using both benzene and water as standards. The results for each tube agreed to 0.5%. Heights of liquid in the tube and in the reservoir were measured with a cathetometer reading to 0.1 mm. A duplicate run was made on each material using a different capillary. The reproducibility of data and the agreement with the ring method used on phthalic acid, dimethyl ester and phthalimide, N-*s*-butyl-, indicate that the results given in Table I are within 1% in all cases and within 0.5% in the majority of cases (*i. e.*, those values not designated by the letter R).

Difficulty was experienced in getting equilibrium heights by the capillary tube method in the case of some of the compounds. In those cases, the surface tensions were measured by the ring method, using a Cenco du Noüy precision direct reading tensiometer. The test liquid was placed in a weighing bottle surrounded by a jacket through which the bath water was circulated. The average of eight readings was used in each case to get the approxi-

(1) This research was carried out with funds provided by the U. S. Quartermaster Corps.

(2) Shriner and Fuson, "Identification of Organic Compounds," 2nd edition, John Wiley and Sons, New York, N. Y., p. 93.

(3) Sobotka and Kahn, THIS JOURNAL, **53**, 2935 (1931).

TABLE I

SUMMARY OF DATA

| Compound[d] | Dist. range[b] in °C. | $n^{25}D$ | At 35°: Density in g./ml. | Vis. in poise × $10^3$ | Solubility in g./100 ml. of $H_2O$ | Surf. tens. in dynes/cm. | Interfacial tension against $H_2O$ in dynes per cm. | B. p. in °C. at 1 atm.[c] |
|---|---|---|---|---|---|---|---|---|
| Acetoacetic acid, cyclohexyl ester | 94–95 | 1.4615 | 1.0222 | 48.4 | 0.023 ± 0.004 | 32.9 | 13.1 ± 0.1 | ... |
| Anthranilic acid, methyl ester | 96–97 | 1.5810 | 1.1546 | 60.2 | .290 ± .008 | 41.3 | 13.5 ± .1 | ... |
| Benzaldehyde, *o*-ethoxy-, | 88–89.5 | 1.5409 | 1.0682 | 25.56 | .116 ± .004 | 37.4 | 17.9 ± .05 | ... |
| Benzoic acid, cyclohexyl ester | 119.5 | 1.5200 | 1.0429 | 78.2 | .001 ± .0006 | 35.7 | 26.8 ± .1 | ... |
| Benzoic acid, tetrahydrofurfuryl ester | 132–133 | 1.5209 | 1.1155 | 82.4 | .098 ± .001 | 39.8 | 12.2 ± .1 | ... |
| Benzyl alcohol, *o*-methoxy-, | 97–97.5 | 1.5460 | 1.1113 | 113.4 | 2.64 ± .03 | 42.3 | 5.54 ± .03 | 247.4 |
| Benzyl alcohol, *p*-methoxy-, | 102–103 | 1.5420 | 1.1017 | 93.2 | 3.83 ± .04 | 43.21R | 4.08 ± .05 | 259.1 |
| Benzyl ether | 125.5–126.5 | 1.5601 | 1.0341 | 37.11 | 0.0040 ± .0003 | 38.2 | 26.0 ± .2 | ... |
| Bicyclo(2,2,1)-5-heptene-2,3-dicarboxylic acid, diethyl ester | 117.5–118.5 | 1.4750 | 1.1074 | 100.6 | 0.354 ± .009 | 32.9 | 11.2 ± .1 | ... |
| *cis*-Bicyclo(2,2,1)-5-heptene-2,3-dicarboxylic acid, dimethyl ester | 114–115 | 1.4829 | 1.1637 | 150.2 | 1.32 ± .02 | 36.9 | 8.48 ± .04 | ... |
| Cinnamic acid, isopropyl ester | 107.5–108 | 1.5420 | 1.0046 | 57.9 | 0.004 ± .0005 | 32.7 | ..... | ... |
| Cyclohexaneacetic acid, α-cyano-, ethyl ester | 115–115.5 | 1.4590 | 1.0071 | 90.6 | .033 ± .001 | 33.2 | 20 ± 2 | ... |
| Cyclohexanecarboxylic acid, 1-hydroxycyclopentyl ester | 107 | 1.4748 | 1.0486 | 147.0 | .090 ± .002 | 33.8 | 12.8 ± 0.05 | ... |
| Cyclohexanol, 2-phenyl-, | 107–108 | 1.5242 | 1.0053 | 340.7 | .016 ± .001 | 35.7 | 16 ± 2 | 278.5 |
| 4-Cyclohexene, 1,2-dicarboximide, N-butyl-, | 123.5–124 | 1.5001 | 1.0723 | 299.6 | .226 ± .0006 | 34.7 | 11.4 ± 0.1 | ... |
| *m*-Dioxane, 4-(*p*-methoxyphenyl)-5-methyl-, | 134 | 1.5266 | 1.1053 | 317.6 | .144 ± .003 | 39.2 | 15.2 ± .1 | ... |
| *m*-Dioxane, 5-methyl-5-nitro-2-propyl-,[a] | 110.5–111 | 1.4518 | 1.1103 | 143.1 | .300 ± .002 | 34.3 | 18.8 ± .2 | ... |
| 1,4-Dioxaspirodecane-3-methanol, 6-methyl-, | 103–104 | 1.4713 | 1.0678 | 450 | .422 ± .001 | 32.8 | 3.05 ± .03 | ... |
| 1,3-Dioxolane, 2-hexyl-4-hydroxymethyl-, | 106–111 | 1.4490 | 0.9768 | 131.4 | .157 ± .005 | 28.56R | 2.98 ± .02 | ... |
| 1,3-Dioxolane, 2-hexyl-4-methoxymethyl-, | 89–90.5 | 1.4465 | 1.0027 | 31.43 | .006 ± .0004 | 28.6 | ..... | 249.5 |
| Ethanol, 2-phenoxy-, acetate | 97.5–98.5 | 1.5083 | 1.0908 | 53.0 | .188 ± .004 | 37.8 | 11.1 ± .1 | 257.2 |
| Ethanol, 2,2′-thiodi-, diacetate | 118–118.5 | 1.4675 | 1.1270 | 52.0 | 2.156 ± .003 | 36.5 | 7.66 ± .05 | ... |
| Glycidic acid, β-methyl-β-phenyl-, | 112–113 | 1.5344 | 1.1141 | 159.1 | 0.119 ± .002 | 38.1 | 7.3 ± .1 | ... |
| 1,3-Hexandiol, 2-ethyl-, | 100 | 1.4490 | 0.9300 | 678 | 1.027 ± .002 | 29.02R | 4.6 ± .05 | 243.4 |
| Hydracrylic acid, β-phenyl-, ethyl ester | 123.5–124 | 1.5075 | 1.0881 | 148.2 | 0.805 ± .005 | 35.8 | 8.4 ± .1 | ... |
| Isobutyric acid, α-hydroxy-, phenethyl ester | 110–116 | 1.4950 | 1.0486 | 91.0 | .501 ± .006 | 34.5 | 6.17 ± .05 | 268.6 |
| *dl*-Malic acid, dibutyl ester | 111–120 | 1.4386 | 1.0228 | 85.4 | .057 ± .002 | 29.2 | 9.5 ± .05 | ... |
| 2-Naphthol, 1,2,3,4-tetrahydro-, | 110 | 1.5625 | 1.0784 | 927 | .519 ± .003 | 41.97R | 8.0 ± .1 | 268.6 |
| 1,5-Pentanediol dipropionate | 106.5–107.5 | 1.4286 | 0.9815 | 28.12 | .127 ± .002 | 30.6 | 14.4 ± .1 | 269.6 |
| Phenethyl alcohol, *p*-isopropyl-, | 100.5–101 | 1.5169 | 0.9599 | 150.9 | .0896 ± .0003 | 32.49R | 10.4 ± .1 | 258.2 |
| Phthalic acid, dimethyl ester | 116–116.5 | 1.5137 | 1.1789 | 89.0 | .430 ± .005 | 40.2<br>40.35R | 11.7 ± .05 | 283.6 |
| Phthalimide, N-*s*-butyl-, | 120–121 | 1.5417 | 1.1045 | 177.8 | .025 ± .001 | 36.63R<br>36.6 | 19.0 ± .1 | 294.9 |
| 1,2-Propanediol, 3-(1,3-dimethylbutoxy)-, | 104.5–106 | 1.4419 | 0.9544 | 309.7 | .991 ± .002 | 25.7 | ..... | ... |
| Propanol, 2-(2-cyclohexoxypropoxy)-, | 105.5–106.5 | 1.4530 | 0.9603 | 101.0 | 1.02 ± .05 | 31.1 | 6.00 ± .05 | ... |
| Succinamic acid, N,N-diethyl-, propyl ester | 124.5–125.0 | 1.4509 | 0.9876 | 56.8 | 5.20 ± .13 | 31.7 | 2.40 ± .05 | ... |
| Succinamic acid, N,N-dipropyl-, ethyl ester | 130.5–131 | 1.4517 | 0.9765 | 71.7 | 1.843 ± .005 | 30.8 | 6.3 ± .15 | ... |
| Succinimide, N-amyl-, | 110–111 | 1.4721 | 1.0283 | 131.5 | 1.33 ± .02 | 33.35R | ..... | ... |

[a] *m*-Dioxane, 5-methyl-5-nitro-2-propyl-, is a solid, m. p. 46.5–47.1°. On fractionation, it formed a supercooled liquid. All the data were obtained on the supercooled liquid. [b] The majority of the compounds were distilled at 2 mm. pressure. Compounds 10, 26, 27, 32 in the order listed were distilled at 3.8 mm., 1–2 mm., 0.1–0.3 mm. and 2.4 mm. respectively. [c] Compounds, whose boiling points are not given, decomposed on heating. [d] Source of compounds, numbering them in the order listed in the above table; #26 from American Cyanamid; #12 from Columbia University; #4, 8, 14, 21 from Dow Chemical; #15 from du Pont; #2, 3, 7, 30, 31 from Eastman; #18 from Givaudan-Delawanna; #6, 16, 22, 28 from Harvard U.; #17, 23 from Ohio U.; #9, 10 from Sowa Chemical; #24, 33, 34 from Union Carbide & Carbon; #11, 32 from U. S. Department of Agriculture; #1, 13, 19, 20, 25, 27, 29, 35, 36, 37 from U. of Maryland; #5 from U. of New Hampshire.

mate surface tension. This approximate value was then corrected by the method given by Harkins.[4]

The surface tensions, marked R in Table I, are the values obtained by the ring method. Based on reproducibility of data and on the agreement with the literature values for the reference materials given in Table II, the surface tensions by the ring method are estimated to be accurate within 0.4%.

**Interfacial Tension.**—The interfacial tensions of the test material against water were measured by the drop-volume method.[5] The volume of the pipet in terms of distance between divisions was determined by calibration with mercury. The position of the meniscus was determined with a cathetometer, reading to 0.1 mm. The

(4) (a) Harkins and Jordan, THIS JOURNAL, **52**, 1751 (1930). (b) Weissberger, "Physical Methods of Organic Chemistry," Vol. I, Chapter VI, Interscience Publishers, New York, N. Y., 1945.

(5) Harkins and Humphery, THIS JOURNAL, **38**, 228, 236 (1916).

TABLE II

PHYSICAL PROPERTIES OF REFERENCE LIQUIDS[a]

| Property | Compound | Exp. | Lit. |
|---|---|---|---|
| Viscosity | Benzene | 5.27, 5.26 | 5.26[b] |
| Surface tension ($R$) | Water | 70.56 | 70.85[4b] |
| | Benzene | 26.83 | 26.89[c] |
| B. p. | Nitrobenzene | 210.9 | 210.9[d] |
| B. p. | Decalin | 193.3 | 193.3[d] |
| B. p. | Ethylene glycol | 197.4 | 197.5[d] |
| B. p. | *p*-Methoxy benzyl alcohol | 259.1 | 258.8[d] |
| Interfacial tension at 20° | Chloroform | 29.7 ± 0.5 | 32.8[e] |
| | Chlorobenzene | 35.5 ± 0.2 | 37.4[e] |
| Interfacial tension at 35° | Carbon tetrachloride | 43.2 ± 0.5 | 43.5[e] |

[a] Units and experimental conditions are the same as in Table I unless otherwise specified. [b] "I. C. T.," Vol. V. [c] Hennaut-Roland and Lek, *Bull. soc. chim. Belg.*, **40**, 177 (1931); *C. A.* **25**, 5323 (1931). [d] "I. C. T.," Vol. I. [e] "I. C. T.," Vol. IV.

method of calculation of interfacial tension, including the use of a correction factor was that of Harkins.[4b] Table II indicates the comparison between our values and the literature values for several liquids. The agreement is as close at that reported by investigators using different experimental procedures.[6] The interfacial tension values for those liquids whose densities are only slightly different from that of water were either not determined, or if made, the precision was poor.

## Summary

Physical constants for a large number of organic insect repellents were determined.

(6) Andreas, Hauser and Tucker, *J. Phys. Chem.*, **42**, 1001 (1938).

COLLEGE PARK, MARYLAND

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

# The Use of Radioactive Tracers in a Study of Activator Distribution in Infrared-Sensitive Phosphors[1,2]

BY R. W. MASON, C. F. HISKEY AND ROLAND WARD

The preparation and some of the properties of infrared-sensitive phosphors of the alkaline earth sulfides and selenides have been described by Urbach,[3] Smith,[4] Primak[5] and Stripp.[6] It has been found that reproducible samples are most conveniently prepared by the use of presumably non-reactive fluxes such as lithium fluoride or strontium chloride. The flux effects a complete recrystallization of the base material[5] and serves to introduce the activators during the recrystallization. Since the luminescent properties are quite sensitive to variation in the concentration of the activators, the relationship between these and the brightness of the phosphors under stimulation was investigated.[6] While the results were empirically satisfactory, the absolute activator concentration was not known since the activators at equilibrium conditions must be distributed between the base and the flux. The determination of distribution coefficients of rare earth ions at such low concentrations (0.02% or less) in alkaline earth compounds would be very difficult by the usual analytical procedures, but the availability of radioactive isotopes of europium, cerium and samarium offered a possible solution.

The main difficulty in the application of the tracer technique lay in the separation of the intimately mixed phases. A separation method based on the difference in specific gravities of the base and flux was only partially successful. A much more satisfactory procedure was devised which involved filtration at the fluxing temperature (about 1000°) using a platinum Munroe crucible. Since the method may find some application in studying solubility phenomena in molten salt systems, the procedure is described here in some detail.

## Experimental

**Materials.**—Strontium sulfide and selenide were prepared as previously reported.[3,4] The fluxes, strontium chloride and lithium fluoride, contained only spectroscopic traces of the other alkaline earths and the alkali ions.

## Procedure

(1) **Separation of Base and Flux by Filtration.**—The preparation of a Munroe crucible has been described by Snelling[7] and Swett.[8] Although the platinum mat is reasonably resistant to attack by the phosphor mixtures at 900 to 1100° in a nitrogen atmosphere, it eventually develops pinholes or cracks. These may be sealed by dipping in chloroplatinic acid and heating at 500° or by decomposing a layer of ammonium chloroplatinate on the mat and burnishing and compressing with a glass rod.

The mixtures containing strontium chloride separated readily by gravity filtration but those containing lithium fluoride required suction. For this purpose the apparatus shown in Fig. 1 was constructed. A smooth flange was forged on the Munroe crucible (1) and one end of the

(1) The work described in this paper was carried out under Contract NObs 39045 between the Bureau of Ships and the Polytechnic Institute of Brooklyn.

(2) Abstracted from a thesis by R. W. Mason submitted to the Graduate School of the Polytechnic Institute of Brooklyn, 1948, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) F. Urbach, D. Pearlman and H. Hemmindinger, *J. Optical Soc. Am.*, **36**, 372 (1946).

(4) A. L. Smith, R. D. Rosenstein and R. Ward, THIS JOURNAL, **69**, 1725 (1947).

(5) W. Primak, R. K. Osterheld and R. Ward, *ibid.*, **69**, 1283 (1947).

(6) K. F. Stripp and R. Ward, *ibid.*, **70**, 401 (1948).

(7) W. O. Snelling, *ibid.*, **31**, 456 (1909).

(8) O. D. Swett, *ibid.*, **31**, 928 (1909).

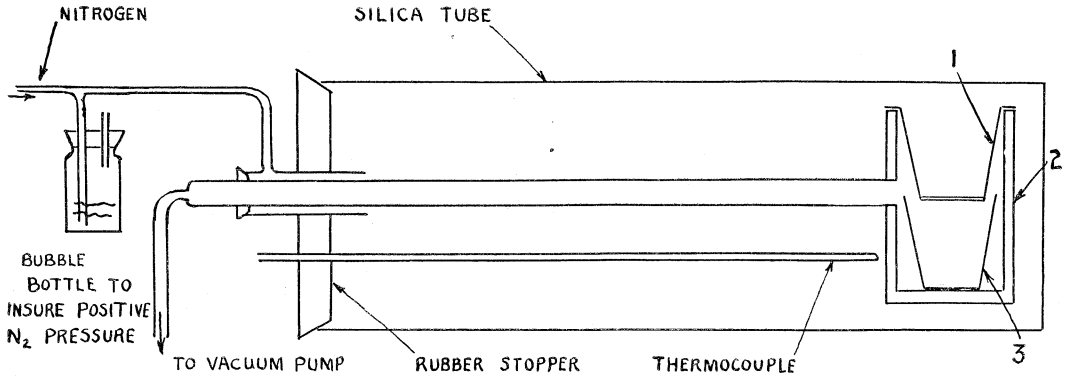



Fig. 1.—Apparatus for suction filtration.

silica tube (2) was faced by grinding with carborundum. The flange seated on this surface gave a sufficiently tight joint so that suction filtration could be rapidly completed. The filtrate was collected in the platinum receptacle (3). The platinum mat usually required repair after two or three suction filtrations. This may have been due to the applied pressure or to the more corrosive action of the lithium salts. It has been found that for some systems nickel is more resistant than platinum. Preliminary experiments showed that filtration could only be accomplished with mixtures containing a much higher proportion of flux than is used in the phosphor preparation (about 10%). For the systems strontium sulfide–strontium chloride and strontium selenide–strontium chloride, 60 to 85 weight per cent. of strontium chloride was found most suitable. Because of the high solubility of strontium sulfide in lithium fluoride, it was necessary with this system to use mixtures in the range of 40 to 60 per cent. flux.

The mixtures for distribution studies were prepared by adding to a weighed quantity of flux europium, cerium or samarium and an adequate amount of the radioisotope as solutions of their chlorides. The mixture was dried at 200° and mixed with the appropriate amount of base. To bring the system as close to equilibrium as possible before filtering, the mixture was pre-heated at the filtering temperature for one hour and cooled in an atmosphere of nitrogen. It was then transferred to the Munroe crucible and heated in a nitrogen atmosphere to the desired temperature. About one-half hour was sufficient for gravity filtration of the mixtures with strontium chloride. The lithium fluoride mixtures were heated for half an hour before filtering by suction which usually took less than a minute.

After cooling under nitrogen, the filtrate and residue were powdered and samples of each reserved for counting and for chemical analysis. The solubilities of the base materials in the molten fluxes are given by analyses of the filtrates.

**(2) Analyses of the Fractions.**—For the strontium chloride–strontium sulfide mixtures, the determination of the sulfide sulfur was made by taking a portion of the fraction, adding it to a standard iodine solution, and after acidification titrating the excess iodine with thiosulfate solution. The strontium chloride was found by difference and the total strontium by conversion to the sulfate. The same general method was followed with the strontium chloride–strontium selenide mixtures except that selenium was determined by oxidation with bromine in acid solution and precipitation as selenium by hydrazonium ion. The lithium fluoride–strontium sulfide mixtures were taken to dryness with sulfuric acid and weighed. The lithium sulfate was dissolved in water and alcohol was added to give a 50% solution. The strontium sulfate was filtered and weighed and the lithium determined by difference. These procedures were checked by more complete standard analyses and were found to be sufficiently precise for this work. The precision was about ±0.2% for the strontium chloride systems and about ±0.5% for the lithium fluoride–strontium sulfide mixtures.

Some of the results are given in Tables I, II and III. From the analyses of the filtrates it can be seen that the solubilities of the strontium sulfide and strontium selenide in the strontium chloride are quite low compared with the solubility of

TABLE I

FILTRATION OF STRONTIUM CHLORIDE–STRONTIUM SULFIDE MIXTURES

| Sample | Temp., in °C. | Weight % SrS in Unfiltered mixtures | Filtrate | Residue |
|---|---|---|---|---|
| 1 | 900 | 25 | 2.6 | 36.3 |
| 2 | 900 | 25 | 2.5 | 33.1 |
| 3 | 900 | 25 | 2.7 | 34.0 |
| 4 | 900 | 25 | 2.5 | 35.4 |
| 5 | 1050 | 20 | 3.7 | 44.5 |
| 6 | 1050 | 20 | 3.7 | 43.5 |
| 7 | 1050 | 40 | 4.1 | 51.4 |
| 8 | 1050 | 40 | 3.7 | 48.0 |

TABLE II

FILTRATION OF STRONTIUM CHLORIDE–STRONTIUM SELENIDE MIXTURES

| Sample | Temp., in °C. | Weight % SrSe in Unfiltered mixtures | Filtrate | Residue |
|---|---|---|---|---|
| 9 | 920 | 40.0 | 5.0 | 49.2 |
| 10 | 920 | 40.0 | 4.7 | 49.7 |
| 11 | 920 | 40.0 | 4.3 | 49.8 |
| 12 | 1050 | 40.0 | 6.1 | 45.7 |
| 13 | 1050 | 25.0 | 5.8 | 43.5 |
| 14 | 1050 | 25.0 | 7.1 | 47.4 |
| 15 | 1050 | 40.0 | 7.1 | 50.0 |

TABLE III

FILTRATION OF LITHIUM FLUORIDE–STRONTIUM SULFIDE MIXTURES: FIFTEEN-GRAM SAMPLES CONTAINING SIXTY WEIGHT PER CENT. SrS

| Sample | Temp., in °C. | Weight % SrS in Filtrate | Residue |
|---|---|---|---|
| 16 | 940 | 35.8 | 82.0 |
| 17 | 1000 | 37.3 | 82.0 |
| 18 | 1000 | 38.3 | 79.0 |
| 19 | 1000 | 37.6 | 80.0 |
| 20 | 1100 | 45.2 | 90.0 |

strontium sulfide in lithium fluoride. The solubilities of the sulfide in the strontium chloride and in the lithium fluoride show an average deviation of about 4%, but for the selenide the average deviation is about 9%. An appreciable increase in solubility with rising temperature is apparent in each of the systems.

(3) **Activator Distribution.**—Samples of the filtrates and residues were prepared for counting by a slight modification of the procedure described by Kamen.[9] In most instances the sample was ground, a 50- or 100-mg. portion suspended in symmetrical tetrachlorethane and filtered through a circular paper in a gooch crucible. The paper, thus covered with an even layer of solid, was transferred to a copper plate, dried and fixed in position with scotch tape. The sample was then bent to fit around the counter tube. The reproducibility was quite satisfactory. It was found that no correction was required for self-absorption. A few samples were prepared by dissolving the sample and evaporating an aliquot on absorbent paper. The precision of the counting including the preparation of samples was about ± 5%.

In Table IV are given the characteristics of the radioactive samples. They were prepared at

TABLE IV

CHARACTERISTICS OF RADIOACTIVE ACTIVATOR SAMPLES[10]

| Irradiated sample | Radioisotopes present | Half-life | Radiation (MEV) Beta | Gamma |
|---|---|---|---|---|
| Europium | Eu 152 | 9.2h | 1.61 | |
| | 154 | 5.8y | 0.34, 0.82 | 1.4 et al. |
| Cerium | Ce 141 | 28d | 0.55 | 0.21 |
| | 143 (Parent of Pr 143) | 33h | 1.35 | 0.50 |
| | Pr 143 | 13.8d | 0.95 | None |
| Samarium | Sm 153 | 47h | 0.73 | 0.1, 0.57 |
| | 155 (Parent of Eu 155) | 25m | 1.9 | 0.3 |
| | Eu 155 | 2y | 0.3 | 0.084 |

the Oak Ridge laboratories by pile irradiation of pure compounds of the elements. The compounds used were europium oxide (furnished by the late Herbert N. McCoy), cerous nitrate and samarium oxide (prepared in Luigi Rolla's laboratory). In counting the cerium samples the beta-radiation was eliminated by means of aluminum foil so that only the gamma-radiation from the cerium isotopes was counted. A standard sample was counted periodically during the course of the measurements. The data, plotted in Fig. 2 against the theoretical decay curve for a twenty-eight day half-life, indicate the possibility that a longer lived contaminant was present, but in negligible amounts. The decay of the samarium sample is shown in Fig. 3 to be close to the theoretical forty-seven hour half-life curve which indicates that the contribution of europium 155 to the total count is unimportant.

(9) M. D. Kamen, "Radioactive Tracers in Biology," Academic Press, New York, N. Y., 1947, p. 152.

(10) Data taken from Radioisotopes Catalog and Price List No. 2, U. S. Atomic Energy Commission, Oak Ridge, Tennessee, revised September, 1947.

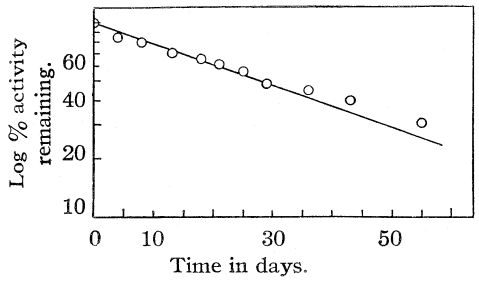



Fig. 2.—The line represents the theoretical decay for twenty-eight day half-life.

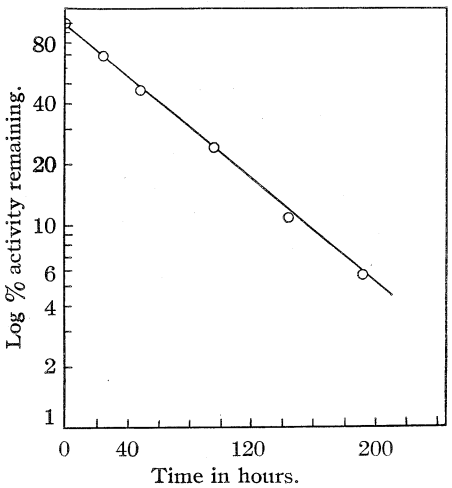



Fig. 3.—The line represents the theoretical decay for forty-seven hour half-life.

The quantities of irradiated europium, cerium and samarium which gave convenient counts in the distribution studies were approximately 10, 200 and 3 parts per million of the base material respectively. Additional quantities of the non-radioactive activators were added so that the distribution could be determined at different activator concentrations.

(a) **Distribution of Europium.**—The data obtained for the calculation of the distribution coefficient of europium in the different systems are listed in Tables V, VI and VII. The numbers in brackets refer to the sample numbers in Tables I, II and III. A four- to eightfold variation in activator concentration was used.

In this report the distribution coefficient is defined as the ratio of the mole fractions of europium in the solid phase and in the liquid phase, *i.e.*

$$K = \left[\frac{n_{Eu}(s)}{(n_{Eu}(s) + n_B)}\right]_{\text{solid phase}} \times \left[\frac{n_{Eu}(l) + n_B + n_F}{n_{Eu}(l)}\right]_{\text{liquid phase}}$$

where $n_{Eu}(s)$ and $n_{Eu}(l)$ are the number of moles of europium in the solid and liquid phases, respectively, and $n_B$ and $n_F$ are the number of moles of base and flux, respectively. This involves the reasonable assumption that none of

the flux dissolves in the base but that only base dissolves in flux. Hence at equilibrium we have the pure base in contact with a saturated solution of the base in the fluid flux. It can be seen that this does not quite represent the distribution in the actual phosphor which consists of a mixture of crystals of pure flux and base. Where the solubility of the base in the flux is low, however, it may be assumed that the distribution coefficient in the solids is not very different.

The distribution coefficient may be calculated from the formula[11]

$$K = \frac{(a + b)[x - y(c/a)]}{y[d - b(c/a)]}$$

where $a$ = moles flux per 100 g. of filtrate
$b$ = moles base per 100 g. of filtrate
$c$ = moles flux per 100 g. of residue
$d$ = moles base per 100 g. of residue
$x$ = counts per standard weight of residue
$y$ = counts per standard weight of filtrate

The values listed for $K$ in Tables V to VII indicate that equilibrium had been fairly well established. With the strontium chloride flux, the activator distribution is not appreciably affected by change of temperature, variation of flux to base ratio or by change of total activator concentration. The concentration of the activator in the liquid phase is somewhat more than one third of the concentration in the solid phase. In the actual phosphor mixture, which contains only about 10% flux, however, about 97% of the added activator resides in the base material.

TABLE V

DISTRIBUTION OF EUROPIUM BETWEEN STRONTIUM CHLORIDE AND STRONTIUM SULFIDE

| | Parts Eu per million parts SrS in unfiltered mixture | Counts per minute: Filtrate | Residue | $K$ |
|---|---|---|---|---|
| (1) | 200 | 1069 | 2045 | 2.8 |
| (2) | 100 | 1158 | 1970 | 2.5 |
| (3) | 400 | 1233 | 2219 | 2.7 |
| (4) | 800 | 1084 | 1977 | 2.6 |
| (5) | 100 | 98.4 | 230 | 3.2 |
| (6) | 400 | 127.0 | 231 | 2.3 |
| (7) | 100 | 68.0 | 157 | 2.8 |
| (8) | 400 | 66.8 | 137 | 2.5 |

(11) This expression is derived from the distribution coefficient defined above in the following manner: (a) It is apparent that the number of moles of activator, $n_{Eu}$, is trivial in comparison to the number of moles of the base or the flux. Thus

$$(K = [n_{Eu}(s)/n_B]_{solid}\,[n_B + n_F)/n_{Eu}(1)]_{liquid}$$

(b) The determination of $[n_{Eu}(s)/n_B]_{solid}$ would, under ordinary filtration techniques, merely involve weighing the undissolved base and making a count to estimate the europium present. Unfortunately, this cannot be done in this case because along with the undissolved base there is always a significant quantity of filtrate retained on the filter, and this filtrate contains dissolved base as well as radioactive Eu. It becomes necessary, therefore, for us to subtract this dissolved base from the total base concentration in the residue and the radioactivity count from the total count observed for the residue. In terms of the analytical quantities $a$, $b$, $c$, $d$, $x$ and $y$ defined previously, the expression for $n_B$ is thus $[d - b(c/a)]$ and for $n_{Eu}(s)$ is $k[x - y(c/a)]$ where $k$ is a proportionality constant. (c) The filtrate is merely analyzed for its count and the number of moles of flux and base in it. The term $[n_{Eu}(l)/(n_F + n_B)]_{liquid}$ is thus equal to $ky/(a + b)$.

TABLE VI

DISTRIBUTION OF EUROPIUM BETWEEN STRONTIUM CHLORIDE AND STRONTIUM SELENIDE

| | Parts Eu per million parts SrSe in unfiltered mixture | Counts per minute: Filtrate | Residue | $K$ |
|---|---|---|---|---|
| (9) | 50 | 761 | 1217 | 2.4 |
| (10) | 100 | 744 | 1142 | 2.3 |
| (11) | 400 | 790 | 1206 | 2.2 |
| (12) | 800 | 677 | 1085 | 2.6 |
| (13) | 100 | 978 | 1503 | 2.5 |
| (14) | 400 | 768 | 1206 | 2.5 |
| (15) | 400 | 937 | 1345 | 2.1 |

TABLE VII

DISTRIBUTION OF EUROPIUM BETWEEN LITHIUM FLUORIDE AND STRONTIUM SULFIDE

| | Parts Eu per million parts SrS in unfiltered mixture | Counts per minute: Filtrate | Residue | $K$ |
|---|---|---|---|---|
| (16) | 150 | 207 | 1647 | 35.3 |
| (17) | 500 | 320 | 1623 | 21.9 |
| (18) | 1000 | 370 | 1690 | 20.7 |
| (19) | 150 | 314 | 1734 | 24.4 |
| (20) | 150 | 611 | 2272 | 13.2 |

In the case of the strontium sulfide–lithium fluoride system, on the other hand, the values of the distribution coefficient (Table VII) are much higher and there is a pronounced decrease with rising temperature. At 1000° the distribution coefficient for this system is more than ten times that for the strontium chloride system. The solubility of the sulfide in the lithium fluoride is also about ten times that in strontium chloride. This means that when the mixture is cooled from 1000° the portion of the sulfide which crystallizes out from solution will have a much lower activator concentration than that which was undissolved at 1000°. With the usual phosphor mixture containing about 10% flux, only 3 to 4% of the sulfide would have dissolved at 1000° and this portion on solidification of the mixture would have an activator concentration about one seventh of that of the main bulk of the sulfide if we assume that no activator remains with the lithium fluoride solid phase. The assumption that the activator concentration in the solid lithium fluoride is essentially zero was justified by the separation of the solid phases into several fractions containing different proportions of flux and base. This was accomplished by taking separate samples of the filtrate and residue from a filtration carried out at 1100° and grinding them under tetrabromoethane to a paste containing particles about 10–20 microns in size. The paste was suspended in a mixture of tetrachloro- and tetrabromoethanes and centrifuged. This was repeated with liquids of progressively higher densities containing more tetrabromoethane so that a series of floating fractions with increasingly higher concentrations of the heavier component were obtained. The fractions were analyzed and counted and the results extra-

polated to the count corresponding to one of the pure components.

The results given in Table VIII are plotted in Fig. 4 which shows two curves, one connecting the points representing the separated fractions of the filtrate and one connecting the points representing the fractions of the residue. The two curves are due to the different concentrations of europium in the residue and filtrate. Both curves extrapolate to zero concentration of europium in the lithium fluoride. The deviation from linearity is probably due to inhomogeneous distribution of the europium.

TABLE VIII

LITHIUM FLUORIDE–STRONTIUM SULFIDE–EUROPIUM SINK-FLOAT SEPARATIONS

| | Sp. gr. of fraction | % of total sample | Wt. % SrS in fraction | Counts per min. per 0.05 g. of fraction |
|---|---|---|---|---|
| Residue from filtration | <2.75 | 0 | .. | .. |
| (69.7% SrS | 2.75–2.85 | 3.5 | 27.8 | 232 |
| 1364 counts per min. | 2.85–2.95 | 18.2 | 27.7 | 482 |
| per 0.05 g. sample) | >2.95 | 78.3 | 89.0 | 1835 |
| Filtrate | <2.77 | 10.7 | 12.9 | 69 |
| (39.7% SrS | 2.77–2.88 | 42.2 | 25.9 | 193 |
| 366 counts per min. | 2.88–2.93 | 17.8 | 25.2 | 195 |
| per 0.05 g. sample) | >2.93 | 29.3 | 81.4 | 814 |

From the results it would appear that in these phosphor systems the assumption can be made that essentially all of the europium added to the mixture finds its way into the lattice of the base material. With the lithium fluoride flux, the phosphor will be slightly inhomogeneous.

**(b) Distribution of Cerium and Samarium.**—The experimental results for the distribution of

TABLE IX

DISTRIBUTION OF CERIUM AND SAMARIUM. COMPOSITION OF FILTRATES AND RESIDUES

| Sample | Temp., in °C. | Unfiltered mixtures | Weight % base in Filtrate | Residue |
|---|---|---|---|---|
| 1 | 1000 | 25.0 SrS | 3.8 SrS | 37.2 SrS |
| 2 | 1000 | 30.0 | 3.8 | 45.0 |
| 3 | 1000 | 40.0 | 3.6 | 47.7 |
| 4 | 1000 | 25.0 | 3.9 | 42.1 |
| 5 | 1000 | 40.0 | 4.7 | 48.7 |
| 6 | 1000 | 25.0 SrSe | 6.5 SrSe | 44.4 SrSe |
| 7 | 1000 | 30.0 | 6.0 | 45.8 |
| 8 | 1000 | 40.0 | 5.5 | 52.8 |
| 9 | 1000 | 25.0 | 7.0 | 43.6 |
| 10 | 1000 | 40.0 | 7.5 | 53.1 |
| 11 | 920 | 60.0 SrS | 28.4 SrS | 73.6 SrS |
| 12 | 1080 | 60.0 | 39.4 | 79.2 |
| 13 | 900 | 60.0 | 25.0 | 74.8 |
| 14 | 1060 | 60.0 | 38.3 | 77.6 |

Experiments 1– 5: SrS–$SrCl_2$
6–10: SrSe–$SrCl_2$
11–14: SrS–LiF

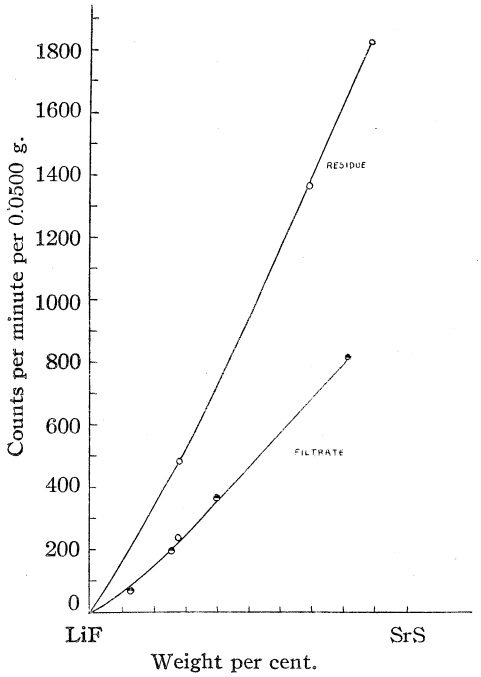



Fig. 4.—Distribution of europium in the LiF–SrS system by sink-float separation of phases.

cerium and samarium in the same systems are given in Tables IX and X. Again it can be seen that the distribution coefficients are much larger for the strontium sulfide–lithium fluoride system than for the systems with the strontium chloride flux. The distribution coefficients for cerium in the strontium sulfide systems are lower than those for samarium.

TABLE X

DISTRIBUTION OF CERIUM AND SAMARIUM IN THE VARIOUS SYSTEMS

| Sample[12] | Parts activator per million parts base in unfiltered mixture | Counts per minute Filtrate | Residue | $K$ |
|---|---|---|---|---|
| 1 | 800 Ce | 128 | 168 | 1.4 |
| 2 | 500 Ce | 122 | 149 | 1.2 |
| 3 | 223 Ce | 91 | 110 | 1.1 |
| 4 | 200 Sm | 540 | 1642 | 4.7 |
| 5 | 25 Sm | 543 | 1186 | 2.7 |
| 6 | 800 Ce | 123 | 216 | 3.0 |
| 7 | 500 Ce | 104 | 142 | 2.0 |
| 8 | 223 Ce | 111 | 122 | 1.3 |
| 9 | 200 Sm | 829 | 1333 | 2.7 |
| 10 | 25 Sm | 1555 | 968 | 0.24 |
| 11 | 200 Ce | 66 | 200 | 15 |
| 12 | 200 Ce | 67 | 239 | 16 |
| 13 | 100 Sm | 219 | 1845 | 45 |
| 14 | 100 Sm | 127 | 1491 | 58 |

There is, however, a marked difference in the distribution coefficients for these activators with changing composition of the original mixtures.

(12) Samples correspond to those in Table IX.

In these experiments, unfortunately, both the percentage base and the activator concentration were changed so that it is not clear from the data whether the distribution coefficients decrease with decreasing activator concentration or decrease with increasing percentage of base. It seems reasonably certain from additional experiments that the latter alternative represents the situation. The solubility of strontium oxide in strontium chloride has been found to be quite high and its presence in the flux causes a pronounced decrease in the distribution coefficient of the activators. The effect with the different activators increases in the order europium–cerium–samarium. The strontium sulfide and selenide contain small amounts of oxide which dissolve in the flux so that increasing proportions of the base material in the original mixtures give rise to increasing concentrations of oxide in the flux. This leads to smaller distribution coefficients. The results of a systematic study of this phenomenon will be presented in a later publication.

**Acknowledgment.**—The authors wish to thank Dr. John R. Dunning and various members of the Radiochemical Laboratories at Columbia University for their friendly coöperation. We are particularly indebted to Mrs. Adele Weil for advice on tracer techniques.

## Summary

A technique for filtering fused salt solutions at 1000° has been described.

The distribution of small quantities of europium, cerium and samarium between phosphor base materials (strontium sulfide and strontium selenide) and saturated solutions of the bases in the fluxes (strontium chloride and lithium fluoride) has been studied in the neighborhood of 1000° with the aid of radioactive tracers.

BROOKLYN 2, N. Y. RECEIVED JULY 3, 1948

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF PITTSBURGH, AND MELLON INSTITUTE]

# Some Physical Properties of Isoquinoline

BY HENRY FREISER[1] AND WILLIAM L. GLOWACKI[2]

This paper is the second in a series[3] describing the work of a program for the determination of physical constants of coal tar bases, sponsored by the Koppers Company.

**Purification of Isoquinoline.**—Seventeen gallons of commercial isoquinoline (Koppers Company 2° isoquinoline having a freezing point of 23.8°) was subjected to eight successive fractional crystallizations until the final material (about 2 kg.) had a freezing point of 26.6°. Further purification was effected by a careful fractional distillation at atmospheric pressure through the rectifying column previously used.[3] Fifty-eight fractions of 30 ml. each were collected at the rate of 30 ml./hr., and after the first three fractions boiled within 0.1°. It is interesting to note that the distillation separated a high-melting impurity more volatile than isoquinoline. This material was identified as naphthalene and is believed responsible for the difficulty encountered in the purification by crystallization. The distillation cuts were further screened by measuring freezing points. For all of the physical properties determined, those central cuts whose freezing points differed by less than 0.05° were combined to give a material having a freezing point of 26.41 ± 0.02° and an estimated purity of at least 99.5 mole per cent.

**Determination of Properties.**—The properties reported here were determined using the same apparatus and procedures previously described.[3]

**Freezing Point.**—The freezing point of pure isoquinoline is estimated at 26.48 ± 0.1°. Quinoline was found to depress the freezing point of isoquinoline by 0.5 ± 0.1° per mole per cent. If the only impurity in the isoquinoline used were quinoline, the material might be as high as 99.8 mole per cent. pure.

**Density and Expansion Coefficient.**—The density values at every 10° from 30 to 80° were found to be 1.09101, 1.08309, 1.07519, 1.06731, 1.05945, and 1.05143 g./ml. with an average reproducibility of 0.00004 g./ml. The values of the expansion coefficient in this temperature range varied from 0.000722 at 30° to 0.000776 at 80°. Values of the density at high temperatures were determined as follows: 1.03540 at 100°, 1.01547 at 125°, 0.99498 at 150°, 0.97421 at 175°, and 0.95300 g./ml. at 200°, with an average reproducibility of 0.00006 g. per ml. The corresponding expansion coefficient values varied from 0.000765 to 0.000899.

**Viscosity.**—The results are presented in Table I.

TABLE I

VISCOSITY OF ISOQUINOLINE

| Temp., °C. | Viscosity, cp. | Temp., °C. | Viscosity, cp. |
|---|---|---|---|
| 30 | 3.2528 | 100 | 1.0230 |
| 40 | 2.6034 | 125 | 0.7787 |
| 50 | 2.1323 | 150 | .6217 |
| 60 | 1.7872 | 175 | .5067 |
| 70 | 1.5269 | 200 | .4223 |
| 80 | 1.3223 | | |

(1) Chemistry Department, University of Pittsburgh.

(2) Present address: Eastern Gas and Fuel Associates, Boston, Mass.

(3) H. Freiser and W. L. Glowacki, THIS JOURNAL, **70**, 2575 (1948).

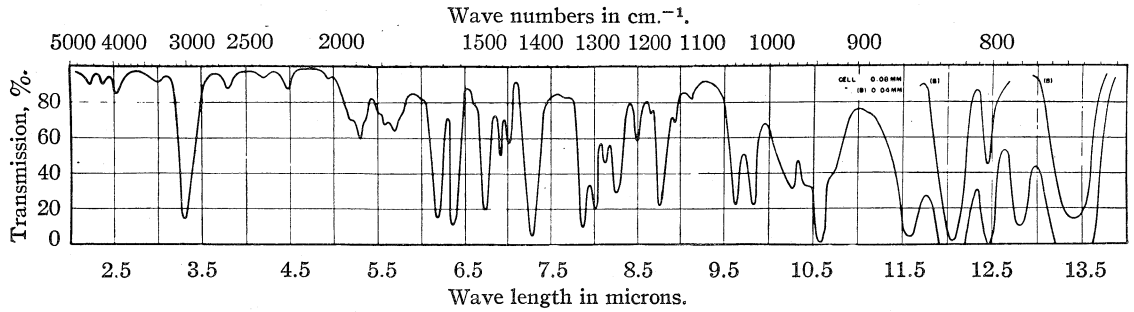



Fig. 1.—Cell, 0.08 mm.; cell 8, 0.04 mm.

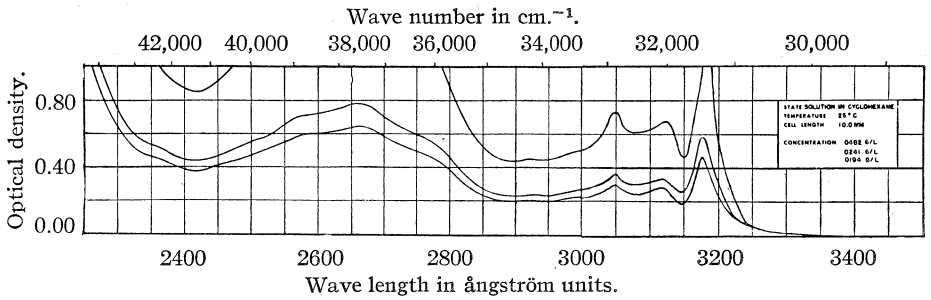



Fig. 2.—State solution in cyclohexane: temperature, 25°; cell length, 10.0 mm.; concn., 0.0482 g./l., 0.0241 g./l., 0.0194 g./l.

**Boiling Point.**[4]—The boiling points of isoquinoline at various pressures were found to be 242.242° at 743.05 mm., 242.026° at 739.33 mm. and 241.832° at 736.14 mm. These values were determined in a differential Swietoslawski ebulliometer using platinum resistance thermometers certified by the National Bureau of Standards to measure the boiling and condensation temperatures of isoquinoline as well as the boiling point of water in a second ebulliometer to establish the pressure value. A further check on the purity of the isoquinoline was obtained in the small difference, 0.007°, between the boiling and condensation temperatures. The average rate of change of boiling temperature with pressure $dT/dp$, calculated from the above values, was 0.0594 ± 0.0009° per mm. From this the boiling point at 760 mm. pressure was calculated at 243.25°. Extrapolation of a plot of values of the temperature difference between the boiling points of isoquinoline and water against the pressure to a value at 760 mm. pressure gave the same result. From the values of the boiling point at 760 mm. pressure and that of $dT/dp$, the heat of vaporization has been calculated by means of the Clausius–Clapeyron equation as 11.7 ± 0.5 kcal. per mole.

**Refractive Index.**—Values of the refractive index of isoquinoline are $n^{30}D$ 1.62078, $n^{30}_{5461\text{ Å.}}$ 1.62806, and $n^{30}_{\infty}$ $1.5799_2$ (calcd.).

**Dipole Moment.**—The dielectric constants $\epsilon$ and densities $d$ of the solutions containing mole fraction $f_2$ of the polar solute and the molar polarization of the solute are given in Table II.

TABLE II

DIELECTRIC POLARIZATION OF ISOQUINOLINE AT 30.0°

| $f_2$ | $\epsilon$ | $d$ | $P_2$ |
|---|---|---|---|
| 0.00000 | 2.2627 | 0.868231 | (168.1 ± 0.3) |
| .006112 | 2.3360 | .870837 | 166.4 |
| .014719 | 2.3954 | .872983 | 164.5 |
| .025562 | 2.4930 | .876380 | 162.1 |
| .029533 | 2.5316 | .877705 | 162.4 |

The sum of $P_E$ and $P_A$ was taken to be 43.3 (the value of the molar refraction at infinite wave length plus 10%), giving a value of the dipole moment of isoquinoline of 2.49 ± 0.01 $D$ in fair agreement with previously determined values.[5]

**Absorption Spectra.**—In Figs. 1 and 2 are presented the infrared and ultraviolet absorption curves, respectively, for isoquinoline. The main infrared absorption maxima are presented in Table III. The main ultraviolet absorption maxima are located at 266, 304, 312, and 318

TABLE III

MAIN INFRARED ABSORPTION MAXIMA OF ISOQUINOLINE

| Microns | $I^a$ | Microns | $I^a$ | Microns | $I^a$ | Microns | $I^a$ |
|---|---|---|---|---|---|---|---|
| 3.30 | m-i | 6.92 | w | 8.50 | w | 10.26 | m |
| 5.30 | w | 7.01 | w | 8.66 | w | 10.59 | i |
| 5.58 | w | 7.29 | i | 8.77 | m | 11.58 | i |
| 5.69 | w | 7.87 | i | 8.94 | w | 12.07 | i |
| 6.18 | m-i | 8.01 | m | 9.14 | w | 12.46 | i |
| 6.35 | m-i | 8.13 | m | 9.63 | m | 12.81 | i |
| 6.73 | m | 8.26 | m | 9.83 | m | 13.42 | i |

[a] Approximate intensity: w = weak, m = moderate, i = intense.

(4) The help of Dr. John R. Anderson and Mr. Jack Killoran of Mellon Institute with this measurement is gratefully acknowledged.

(5) R. J. W. LeFevre and J. W. Smith, *J. Chem. Soc.*, 2239 (1932).

millimicrons. The data were obtained by the Koppers Spectrographical Research Laboratory at Mellon Institute under the direction of Dr. J. J. McGovern.


## Summary

1. Isoquinoline has been purified by fractional distillation and extensive recrystallization to a purity of over 99.5 mole per cent.

2. The following properties have been determined for the purified material: f. p., b. p., density, expansion coefficient and viscosity at frequent temperature intervals between 30 and 200°, refractive index at 5893 and 5461 Å. at 30°, the dipole moment, and the infrared and ultraviolet absorption spectra.


PITTSBURGH, PA. RECEIVED JULY 29, 1948

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[CONTRIBUTION FROM PROJECT SQUID, PURDUE DEPARTMENT OF CHEMISTRY AND SCHOOL OF CHEMICAL ENGINEERING]

# 1,3-Dinitropropane

BY J. P. KISPERSKY, H. B. HASS AND D. E. HOLCOMB

## Introduction

Keppler and Meyer[1] reported 1,3-dinitropropane, prepared by reaction between silver nitrite and 1,3-diiodopropane, to be a yellow, unstable, undistillable oil which changed after several days to a viscous, brown material. On the basis of our present knowledge there seemed to be no adequate reason for expecting 1,3-dinitropropane to be instable. The researches of Kornblum and students[2] in this Laboratory have shown that substantial amounts of organic nitrates are formed in the Victor Meyer reaction and can be removed from the nitro compounds by treatment with sulfuric and phosphoric acids.

3-Nitro-1-propyl nitrate and the corresponding nitrite would be expected to be instable because the primary nitro group tautomerizes to an acidic nitronic acid and neither nitrites nor nitrates are stable to acid.

It, therefore, seemed advisable to repeat the synthesis of 1,3-dinitropropane and to apply the recent purification procedures. As a result, 1,3-dinitropropane has been prepared for the first time in pure form. It is a stable, colorless liquid, distillable at low pressures, b. p. 103° at 1 mm., m. p. −21.4°, molal f. p. const. 4.5, ht. of fusion 27, cal./g., $n^{25}D$ 1.4638, density 1.353 g./ml. at 25.5°, $n_D$ 20.0° − 1.4654; 21.6° − 1.4649; 30.0° − 1.4622.

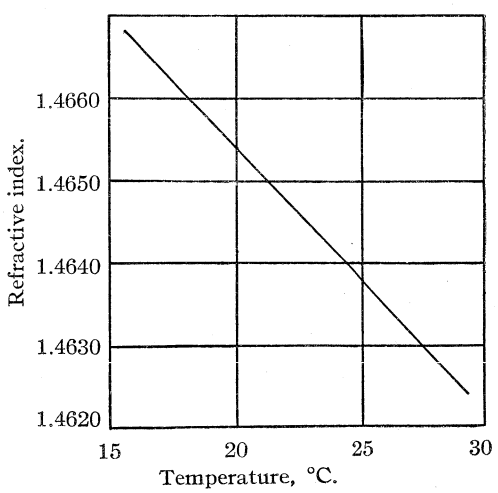



Fig. 1.—Change of refractive index with temperature.

## Experimental

The silver nitrite was prepared according to the directions of McElroy.[3] A slurry was formed of five moles (770 g.) of silver nitrite in 1100 ml. of ether and two moles (592 g.) of 1,3-diiodopropane was added with stirring from a dropping funnel. The flask was cooled externally and the rate of addition regulated to cause gentle refluxing of the ether. After the addition was complete, stirring was continued at room temperature in the dark for twenty hours. Afterward the ether solution was removed by decantation and the residue extracted twice with 300 ml. portions of ether, filtered with suction and washed again with 300 ml. of ether. The ether was evaporated over a steam cone, washed with an equal volume of water and dried over Drierite. The orange-colored liquid residue from two such preparations weighed 300 g.

Distillation in a column resulted in decomposition but an ordinary vacuum distillation gave 90 g. of a fraction b. 100–110° at 1 mm. which gave a positive test with diphenylamine in sulfuric acid. Contrary to Mulliken[4] this color test is not given by pure, primary mononitro paraffins.

The material was then added to three times its volume of 96% sulfuric acid at 0°, stirred for several minutes, poured over ice, and the insoluble layer washed with water. After drying with Drierite the 18 g. remaining distilled at 103° at 1 mm. Qualitative tests showed the presence of nitrogen and absence of halogen. The diphenylamine test now showed the absence of nitrite or nitrate ester.

An estimate of the purity of the sample from the freezing point curve showed it to be 98.2 mole per cent. 1,3-dinitropropane. Nitromethane was added as the known impurity.

*Analysis* by Huffman Microanalytical Laboratories gave the following: Calcd.: H, 4.51; C, 26.87; N, 20.90. Found: H, 4.55, 4.53; C, 26.89, 26.95; N, 21.03, 20.95.

Molar refractivity calculated from Eisenlohr's values is 27.30. Calculated from observed data, 27.33.

Storage of 1,3-dinitropropane at room temperature from September, 1947, to July, 1948, produced no visible alteration.


## Summary

1,3-Dinitropropane has been prepared for the first time in a state of high purity and the common physical constants determined.


RECEIVED AUGUST 6, 1948

(1) Keppler and Meyer, *Ber.*, **25**, 1710 (1892).

(2) Kornblum, Lichtin, Patton and Iffland, THIS JOURNAL, **69**, 307 (1947).

(3) W. R. McElroy, Ph.D. Thesis, Purdue University, 1943.

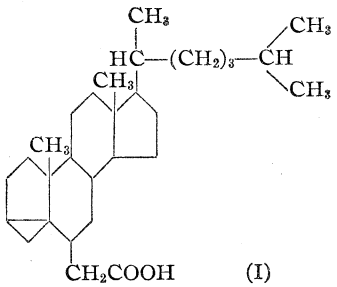
(4) Mulliken, "Identification of Pure Organic Compounds," Vol. II, 1916, p. 28.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

# The Preparation of Isomeric Cholesterylmalonic Acids. III. Rearrangement of *i*-Cholesterylacetic Acid and *i*-Cholesteryl malonamide

BY EMIL KAISER AND J. J. SVARZ

*i*-Sterol derivatives with a substituent connected by a carbon-to-oxygen bond to carbon atom six of the nucleus are known to rearrange to 3-substituted, 5–6 unsaturated sterols by treatment with acids.[1] In this paper the acid rearrangement of such *i*-cholesteryl derivatives is described in which a carbon-to-carbon bond links the substituent to position six of the ring. *i*-Sterols of this type are the *i*-cholesterylmalonic acid[2,3] and the *i*-cholesterylacetic acid (I).



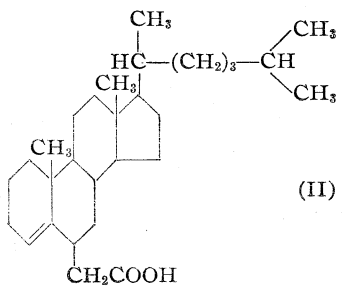

(I)

The *i*-cholesterylacetic acid was prepared by two different procedures. One was the decarboxylation of the *i*-cholesterylmalonic acid. The other method was the saponification of the *i*-cholesterylmalonamide in alkaline glycol solution. The *i*-cholesterylmalonamide not only saponified but was simultaneously decarboxylated to *i*-cholesterylacetic acid.

The *i*-cholesterylacetic acid was dextrorotatory $[\alpha]^{25}D$ + 32°, m.p. 111–112°. When treated with small amounts of sulfuric acid in glacial acetic acid solution a rearrangement occurred. Two compounds were isolated from the reaction mixture. One product was an isomeric cholesterylacetic acid, m.p. 173–174°, $[\alpha]^{25}D$ + 46°. Perbenzoic acid titration showed the presence of one double bond in the compound. The other rearrangement product was also an isomer of the *i*-cholesterylacetic acid, but was found to be neutral to alkali. Perbenzoic acid titration indicated a saturated ring structure. The isomeric neutral product had a m.p. 108–109°, $[\alpha]^{25}D$ + 80.5°.

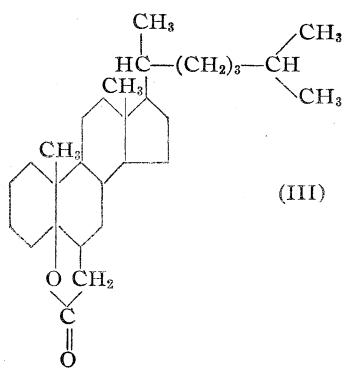
The acid and neutral products of the *i*-cholesterylacetic acid rearrangement were found to be interchangeable. Either of these compounds yielded a mixture of the two derivatives when heated in glacial acetic acid solution in the presence of sulfuric acid. Such an interchange is known to be typical for γ-unsaturated acids and their corresponding lactones.[4,5]

The mechanism of the *i*-cholesterylacetic acid rearrangement is different from the rearrangement mechanism of *i*-derivatives having substituents connected by carbon-to-oxygen[1] or carbon-to-nitrogen[6] bonds to the six position of the sterol nucleus. Cholesteryl-3-acetic acid[2] was not formed in the rearrangement of the *i*-cholesterylacetic acid and both products isolated from the rearrangement mixture were strongly dextro-rotatory. Therefore, a shift of the substituent from the six to the three position did not take place. Only the cyclopropane ring opened up and a γ-unsaturated acid, the $\Delta^4$-cholestene-6-acetic acid (II) was formed. This acid partly lactonized and yielded the cholestane-6-acetic acid lactone, the neutral rearrangement product.




(II)

The cholestane-6-acetic acid lactone was heated to temperatures above 200°[5] to prove a γ or δ configuration. Since cholestene-6-acetic acid was not formed by heating, the lactone was assigned the structure of cholestane-6-acetic acid-γ-lactone (III).




(III)

The acid rearrangement procedure was also applied to the *i*-cholesterylmalonamide. The reaction product was separated into two fractions

(1) (a) Wallis, Fernholz and Gephart, THIS JOURNAL, **53**, 137 (1937). (b) Wagner-Jauregg and Werner, *J. physiol. Chem.*, **213**, 119 (1932). (c) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936).

(2) Kaiser and Svarz, THIS JOURNAL, **67**, 1309 (1945).

(3) Svarz and Kaiser, *ibid.*, **69**, 847 (1947).

(4) Linstead, *J. Chem. Soc.*, 115 (1932).

(5) Linstead and Rydon, *ibid.*, 580 (1933).

(6) Julian, Magnani, Meyer and Cole, THIS JOURNAL, **70**, 1834 (1948).

of different solubilities in methanol. Both fractions were saponified separately with alkali in propylene glycol. From the methanol less soluble fraction the $\Delta^4$-cholestene-6-acetic acid was isolated. The methanol soluble fraction yielded the cholestane-6-acetic acid lactone as the main product.

## Experimental[7,8]

**i-Cholesterylacetic Acid from i-Cholesterylmalonic Acid.**—In a 500-cc. flask immersed in an oil-bath, 10 g. of *i*-cholesterylmalonic acid was heated in a vacuum maintained by a mercury vapor pump. At 168° bath-temperature evolution of carbon dioxide started. The bath-temperature was slowly raised to 175° and kept there for ten minutes. Then the temperature was slowly raised again to 200° and heating continued for ten more minutes. After that the flask was cooled to room temperature and the reaction product crystallized from acetone. After recrystallization from acetone 6.8 g. of *i*-cholesterylacetic acid, m.p. 111.5–112.5°, was obtained.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.28, neut. equiv., 428.0. Found: C, 81.29; H, 11.34; neut. equiv., 428; $[\alpha]^{25}D$ + 32° (in abs. alcohol). Perbenzoic acid titration: one-tenth of a gram dissolved in chloroform did not consume oxygen after seventy-two hours at −4°.

**i-Cholesterylmalonamide.**—The previous procedure was slightly modified. In 10 cc. of thionyl chloride 5 g. of *i*-cholesterylmalonic acid was suspended and the mixture kept at room temperature for two hours. Material still undissolved was brought into solution by heating on the steam-bath for ten minutes. The excess of thionyl chloride was distilled off under reduced pressure and the crude acid chloride transformed into the amide as described before.[3] Yield of crystalline *i*-cholesterylmalonamide was 2.5 g., m. p. 224–226°.

**Saponification of i-Cholesterylmalonamide.**—Twenty grams of potassium hydroxide was dissolved by warming in 100 cc. of propylene glycol. Seven grams of *i*-cholesteryl malonamide was added and the mixture refluxed for ten hours. Saponification of the amide was indicated by evolution of ammonia during the heating. The clear propylene glycol solution was then diluted with water, filtered and acidified with hydrochloric acid. A precipitate was formed which was extracted with ether. The ether extract was washed with water and dried over sodium sulfate. The ether was evaporated, the residue dissolved in methanol and the solution treated with charcoal. After filtration and chilling needles were obtained which were twice recrystallized from methanol; yield 4.2 g., m.p. 110.5–111.5°. The melting point remained unchanged when mixed with *i*-cholesterylacetic acid prepared by pyrolysis of *i*-cholesterylmalonic acid.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.28; neut. equiv., 428.0. Found: C, 81.55; H, 11.40; neut. equiv., 429.8; $[\alpha]^{25}D$ + 32°.

Attempts were made to saponify the *i*-cholesterylmalonamide in isopropyl alcohol. Two grams of potassium hydroxide and 0.5 g. of *i*-cholesterylmalonamide was dissolved in 10 cc. of isopropyl alcohol. The solution was refluxed for ten hours, cooled, diluted with water and filtered. The filtrate was acidified; no precipitation occurred. The solid residue was crystallized from ethyl acetate and identified as *i*-cholesterylmalonamide.

The same result was obtained when heating of the isopropyl alcohol solution was done under pressure at 130°.

**Attempt to Decarboxylate i-Cholesterylmalonic Acid.**—One gram of *i*-cholesterylmalonic acid and 3 g. of potassium hydroxide were refluxed with 10 cc. of propylene glycol for ten hours. *i*-Cholesterylmalonic acid was the sole product isolated from the propylene glycol solution.

**Rearrangement of i-Cholesterylacetic Acid.**—Four grams of *i*-cholesterylacetic acid was dissolved in 120 cc. of glacial acetic acid. Ten drops of concentrated sulfuric acid was added and the solution heated on the steam-bath for two hours. The reaction mixture was cooled and poured into one liter of 10% aqueous sodium chloride solution. The precipitate was filtered off, dried and dissolved in 20 cc. of glacial acetic acid. After filtration the solution was kept at room temperature for several days. Crystals deposited and were removed by filtration. The mother liquor was concentrated to half its volume under reduced pressure. A second crop of crystals was obtained; yield 1.9 g. of $\Delta^4$-cholestene-6-acetic acid, m.p. 173°. After recrystallization from glacial acetic acid the melting point was 173–174°.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.28; neut. equiv., 428.0. Found: C, 81.28; H, 11.36; neut. equiv., 427.3; $[\alpha]^{25}D$ + 46° (in abs. alcohol). Perbenzoic acid titration: one-tenth of a gram dissolved in chloroform consumed 3.32 mg. of oxygen after ninety-six hours at −4°. *Anal.* Calcd. for $C_{29}H_{48}O_2$: 1 g. atom of oxygen (16 g.). Found: 0.89 g. atom of oxygen (14.2 g.). Control: one-tenth of a gram of cholesteryl acetate dissolved in chloroform consumed 3.29 mg. of oxygen after ninety-six hours at −4°. Calcd. for $C_{29}H_{48}O_2$: 1 g. atom of oxygen (16 g.). Found: 0.88 g. atom of oxygen (14.1 g.).

After the $\Delta^4$-cholestene-6-acetic acid crystallized out from the concentrated glacial acetic acid solution, the mother liquor was evaporated to dryness under reduced pressure. The oily residue was dissolved in ether and repeatedly extracted with a 5% potassium hydroxide solution. The combined alkaline extracts, after acidification and crystallization of the precipitates from glacial acetic acid, yielded an additional amount 0.5 g. of $\Delta^4$-cholestene-6-acetic acid, m.p. 173°.

The ether layer was washed with water, dried over sodium sulfate and the ether evaporated. The residue was crystallized from methanol. The cholestane-6-acetic acid-$\gamma$-lactone crystallized in beautiful needles; yield 0.3 g., m.p. 108–109°, mixed melting point with *i*-cholesterylacetic acid 86–88°. Two-tenths of a gram dissolved in ethanol did not consume 0.1 *N* sodium hydroxide solution at room temperature.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.28. Found: C, 81.21; H, 11.28; $[\alpha]^{25}D$ + 80.5°. Perbenzoic acid titration: one-tenth of a gram in chloroform did not consume oxygen after seventy-two hours at −4°.

**Rearrangement of i-Cholesterylmalonamide.**—In 200 cc. of glacial acetic acid 2.25 g. of *i*-cholesterylmalonamide was dissolved and 1 cc. of concentrated sulfuric acid added. The mixture was kept on the steam-bath for one hour. A slight purple color developed. Then 500 cc. of water was added. The precipitate was filtered off, washed with water and dried. The dry material was dissolved in 15 cc. of methanol and the solution kept at −4° for twelve hours. Swollen lumps deposited and were separated by filtration. After drying, 0.55 g. of a slightly colored powder was obtained. This substance was soluble in ether and benzene and was designated as Fraction I.

The mother liquor filtered off from Fraction I was diluted with water. A white precipitate was formed. This precipitate, Fraction II, amounted to 1.55 g.[9]

**Hydrolysis of Fractions I and II.**—One gram of potassium hydroxide was dissolved in 10 cc. of propylene glycol and 0.50 g. of Fraction I was added. The solution was refluxed for two hours, cooled and diluted with 100 cc. of water. The precipitate was filtered off, washed with water and dried. The dry material, weighing 0.3 g., was crystallized from glacial acetic acid. After recrystallization from methanol 0.12 g. of a substance melting 173–174° was obtained. The melting point was not depressed when mixed with $\Delta^4$-cholestene-6-acetic acid, which was obtained from *i*-cholesterylacetic acid.

(7) All melting points are uncorrected.

(8) Microanalyses were made by Mr. C. W. Beazley, Skokie, Illinois.

(9) The rearrangement of *i*-cholesterylmalonamide resulted in loss of nitrogen. Found in *i*-cholesterylmalonamide: N, 6.01; in Fraction I: N, 4.66; in Fraction II: N, 3.02

*Anal.* Calcd. for $C_{29}H_{48}O_2$: neut. equiv., 428.0. Found: neut. equiv., 428.5.

One and a half gram of Fraction II was refluxed in 25 cc. of propylene glycol containing 2.5 g. of potassium hydroxide. After two hours of refluxing the solution was cooled, diluted with 400 cc. of water (clear solution) and acidified. The precipitate was filtered off, washed with water and dried. This substance, weighing 0.95 g. was dissolved in 20 cc. of methanol. After dilution with 100 cc. of water the mixture was extracted with petroleum ether. The petroleum ether was evaporated. The residue was twice crystallized from methanol. Three-tenths of a gram of large needles was obtained, m.p. 108–109°. No melting point depression was observed when mixed with the cholestane-6-acetic acid-γ-lactone, isolated from the *i*-cholesterylacetic acid rearrangement.

**Interchange of $\Delta^4$-Cholestene-6-acetic Acid and Cholestane-6-acetic Acid-γ-lactone.**—(a) Two-tenths of a gram of cholestane-6-acetic acid-γ-lactone was dissolved in 20 cc. of glacial acetic acid containing one-tenth of a cc. of concentrated sulfuric acid. The mixture was heated for one hour on the steam-bath, then diluted with a saturated sodium chloride solution. The precipitate was filtered off, washed with water and dissolved in about 20 cc. of boiling methanol. Crystals deposited in the cold and were separated from the liquid. After recrystallization from glacial acetic acid, 0.05 g. of a substance was obtained with a m.p. of 173–174°; mixed melting point with $\Delta^4$-cholestene-6-acetic acid 173–174°. From the methanol mother liquor 0.06 g. of unchanged cholestane-6-acetic acid-γ-lactone was isolated.

(b) Half a gram of $\Delta^4$-cholestene-6-acetic acid was treated with sulfuric acid in glacial acetic acid solution in an identical manner as the lactone. The acid treated product was first crystallized from glacial acetic acid. Unchanged $\Delta^4$-cholestene-6-acetic acid was recovered, yield, 0.25 g. From the mother liquor a solid was precipitated with saturated sodium chloride solution. This was twice crystallized from methanol. Cholestane-6-acetic acid-γ-lactone was obtained, m.p. 108–109°, yield, 0.1 g.

(c) Two-tenths of a gram of cholestane-6-acetic acid-γ-lactone was heated for eight hours to 205–210°.[5] The brown-colored product was three times recrystallized from methanol, m.p. 108–109°, mixed melting point with cholestane-6-acetic acid-γ-lactone 108–109°. The mother liquors yielded an additional amount of cholestane-6-acetic acid-γ-lactone.

## Summary

*i*-Cholesterylacetic acid was prepared by pyrolysis of *i*-cholesterylmalonic acid and by alkaline hydrolysis of *i*-cholesteryl malonamide. The *i*-cholesterylacetic acid was rearranged in acid solutions. Two products were obtained; the $\Delta^4$-cholestene-6-acetic acid and the cholestane-6-acetic acid-γ-lactone. The mechanism of the *i*-cholesterylacetic acid rearrangement was shown to be different from the rearrangement mechanism of *i*-compounds connected by carbon-to-oxygen or carbon-to-nitrogen bonds to substituents in the six position.

*i*-Cholesterylmalonamide was also rearranged and the rearrangement products saponified. The same compounds were isolated as obtained from the *i*-cholesterylacetic acid rearrangement mixture.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Amine Bisulfite Addition Products of Aldehydes and Ketones. I

BY ROGER ADAMS AND R. D. LIPSCOMB[1]

Aldehydes and ketones are frequently purified through their sodium bisulfite addition products. The adducts are seldom used for identification purposes since they usually do not have sharp melting or decomposition points and suffer the shortcoming of being essentially insoluble in organic solvents. Amine bisulfite addition products of aldehydes and ketones, which have been inadequately investigated, should be formed with equal ease. They offer several possibilities for utilization (1) as compounds for characterization of ketones and aldehydes; (2) for the resolution of aldehydes and ketones and (3) for the replacement of aldehyde and ketone adducts of sodium bisulfite as intermediates in various organic syntheses. The preparation of several representative tertiary amine bisulfites with typical aldehydes and ketones and the characterization of the adducts are described in this first communication.

The procedure usually followed for preparation of the amine bisulfites was to pass sulfur dioxide into the tertiary amines mixed with sufficient water to form the bisulfites. Invariably heat was evolved when sulfur dioxide was first introduced and in many of the conversions, a white solid was observed to separate. This white solid, probably the amine sulfite, gradually dissolved in the reaction mixture as the addition of sulfur dioxide was continued. Whether or not this solid was observed, the reaction mixture always became viscous during the intermediate stage of the conversion. In the final stages, the color of the solution changed to yellow or orange and the viscosity decreased. The reaction was no longer exothermic after the intermediate viscous stage had been reached. The volume of product was often nearly double the volume of starting materials. This volume increase was most noticeable during the latter stages of the reaction.

The resulting mixtures were obviously not pure amine bisulfites but complexes of amine bisulfites with sulfur dioxide. They are relatively stable to air oxidation over long periods of time, probably due to the presence of the excess sulfur dioxide. These mixtures were kept for several years in ordinary reagent bottles in a refrigerator; they may be kept in tightly closed containers at room tem-

(1) An abstract of a thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry. General Aniline and Film Corporation Fellow, 1942–43.

TABLE I

TERTIARY AMINE BISULFITE ADDITION PRODUCTS OF ALDEHYDES AND KETONES

| Bisulfite | Ketone or aldehyde | M. p., °C. | Composition, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|
| -Piperidine | | | | | | |
| N-Methyl- | Cyclohexanone[b] | 90–93 | 48.46 | 48.38 | 9.15 | 9.10 |
| N-*n*-Butyl- | Cyclopentanone | 118 | 54.69 | 54.60 | 9.51 | 9.26 |
| N-*n*-Butyl- | Cyclohexanone | 136 | | | 9.97[c] | 9.41[c] |
| N-*n*-Butyl- | Benzaldehyde | 89–90 | | | 9.73[c] | 9.48[c] |
| N-*n*-Butyl- | Acetone | 102 | 51.21 | 51.38 | 9.67 | 9.62 |
| N-*n*-Butyl- | Methyl *n*-propyl ketone | 69 | | | 10.35[c] | 9.92[c] |
| N-*n*-Butyl- | 2-Ethylhexanal | 78[a] | | | .... | .... |
| N-Benzyl- | Cyclopentanone | 94[a] | | | .... | .... |
| N-Benzyl- | Cyclohexanone | 114 | | | 9.02[c] | 8.95[c] |
| N-Benzyl- | Benzaldehyde | 122–124 | | | 8.82[c] | 8.52[c] |
| N-Benzyl- | Acetone | 100 | 57.12 | 56.81 | 8.00 | 8.07 |
| N-Lauryl- | Cyclohexanone | 103 | 63.69 | 63.70 | 10.93 | 10.97 |
| N-Lauryl- | Benzaldehyde | Oil | | | | |
| N-Lauryl- | Acetone | 95 | 58.35 | 58.35 | 11.02 | 10.49 |
| N-Lauryl- | Methyl *n*-propyl ketone | 81[a] | | | | |
| N-Cetyl- | Cyclohexanone[b] | 107 | 66.21 | 66.38 | 11.32 | 11.87 |
| N-Cetyl- | Acetone | 75–78 | 64.09 | 62.56 | 11.43 | 11.39 |
| -Morpholine | | | | | | |
| N-*n*-Butyl- | Cyclohexanone | 118 | | | 9.98[c] | 10.10[c] |
| N-*n*-Butyl | Benzaldehyde | 114–117[a] | | | | |
| N-*n*-Butyl- | Acetone | 88–89 | | | 11.31[c] | 11.25[c] |
| N-*n*-Butyl- | Methyl *n*-propyl ketone | 85–87 | 50.1 | 50.0 | 9.38 | 9.10 |
| N-Benzyl- | Acetone | 103[a] | | | | |
| Pyridine | Cyclohexanone | 99 | | | 12.36[c] | 12.40[c] |
| Pyridine | Acetone | 85[a] | | | | |
| Pyridine | Benzaldehyde | Oil | | | | |

[a] These compounds were, in general, less stable than the others, and decomposed sufficiently on standing a short time to vitiate the analyses. [b] These compounds gave analyses indicating the probable presence of a molecule of water of crystallization which was not removed by drying at 50–60° or by recrystallization from ether–ethanol mixtures. [c] % sulfur

perature. In open bottles at room temperature, sulfur dioxide is evolved, the color is gradually lost and the mixtures become more viscous. The amine bisulfite complexes are, in general, insoluble in ether and carbon tetrachloride, slightly soluble in benzene, soluble in methanol and ethanol and very soluble in chloroform and water. With an increase of the carbon content of the amine, the solubility of the amine bisulfite in benzene increases but the solubility in water decreases only slightly.

Bisulfites from trimethylamine, triethylamine, N-*n*-butylpiperidine, N-*n*-butylmorpholine, N-benzylpiperidine, N-methylpiperidine, N-laurylpiperidine, N-cetylpiperidine and pyridine were studied. The amine bisulfite complexes varied in color from yellow to orange, and in viscosity from the very limpid N-butylmorpholine bisulfite to the extremely viscous N-benzylmorpholine bisulfite. Several amines gave abnormal results and have not yet been further studied; dimethylaniline and sulfur dioxide reacted to form a red unstable liquid, triethanolamine gave an intermediate glass which could not be completely converted to the bisulfite, quinaldine and sulfur dioxide formed an orange powder, and tetrahydroquinoline an orange, low-melting crystalline solid.

The reaction of the amine bisulfites with aldehydes and ketones was carried out following a general procedure. The bisulfite reagent was mixed with a slight excess of the carbonyl compound. After crystallization started, the mixture was allowed to stand for some time at room temperature. In most cases where the aldehyde or ketone was reactive, mixing was followed immediately by evolution of heat and sulfur dioxide and an accompanying loss of orange color. Crystallization and loss of color often set in at once, or within a few minutes, although in a few instances as much as forty-eight hours was required for crystals to appear. Once crystallization had started, it was observed to proceed rapidly throughout the liquid. Only with the trimethylamine and triethylamine bisulfites and one or two others were "non-crystallizable oils" obtained with aldehydes and ketones, and these were not further investigated. As typical ketones and aldehydes, the following were used: acetone, cyclohexanone, cyclopentanone, benzaldehyde, methyl *n*-propyl ketone, and 2-ethylhexanal.

The addition products could often be obtained pure merely by alternately suspending the crystals in dry ether and collecting them on a filter. In general, they were recrystallized from absolute

ethanol or ethanol–ether mixtures. They all formed well-defined small white needles or plates which possessed sharp melting points. Two of those studied indicated the probability of crystallization with one molecule of water of crystallization which was not removed by recrystallization from ethanol–ether mixtures or drying in air at 50–60°; at least the analyses conformed to this assumption. The N-lauryl- and N-cetylpiperidine bisulfite derivatives were much less soluble in water than the others presumably owing to the long hydrocarbon side-chain. At the same time they were the most stable of the compounds prepared. The stability of the adducts varied considerably. Gradual decomposition, in some cases, started within a few days but others showed no appreciable change over a period of many months. Like the sodium bisulfite addition products, these amine bisulfite addition products are readily decomposed by the action of dilute mineral acids or bases, and the amines are readily recovered.

The melting points of all the compounds prepared (Table I) were within the temperature range from 69 to 136°. A wider range would be preferable if the melting points are to be used for identification purposes. Other amine bisulfites more satisfactory from this standpoint may be found.

## Experimental

**Triethylamine and Trimethylamine Bisulfites.**—A mixture of 0.22 mole of triethylamine and 0.55 mole of water was immersed in an ice-bath, and a stream of sulfur dioxide was passed slowly into the mixture for two hours. A strongly exothermic reaction at the beginning was followed by crystallization of a white solid in the upper amine layer. As the reaction progressed, the solid dissolved and the mixture became one phase, at first colorless, then yellow, and finally orange. The viscosity passed through a stage comparable to that of molasses, then decreased until the mixture was limpid.

This product did not form solid derivatives with acetone, benzaldehyde or *p*-chlorobenzaldehyde although reactions occurred with the evolution of heat.

The formation of trimethylamine bisulfite was essentially comparable except that the amine and water were used in molar ratios. The addition of acetone, cyclohexanone or benzaldehyde resulted in oils which could not be purified.

**Alkylated Piperidines and Morpholines.**—Piperidine and morpholine were alkylated by dissolving the amine (1.2 moles) in 125–200 ml. of dry benzene, and adding the appropriate alkyl halide (0.6 mole) dropwise with stirring at room temperature. When the addition was completed the mixture was stirred and warmed under reflux for several hours. The morpholine or piperidine hydrohalide, which precipitated from the solution, was collected on a filter and washed with benzene. Finally, the combined filtrate and washings were fractionally distilled to obtain the pure N-alkylamine.

The constants of these products, compared with those found in the literature, are shown in Table II.

**N-*n*-Butylpiperidine Bisulfite.**—N-*n*-Butylpiperidine, b. p. 67–67.5° (18 mm.), which contained one molecular equivalent of water was cooled in an ice-bath and sulfur dioxide was introduced. The gas inflow was continued for fifteen minutes after the upper layer had disappeared. The product was light orange and only slightly viscous.

In a similar manner, N-methylpiperidine and pyridine were converted to their bisulfites.

TABLE II

ALKYLATED PIPERIDINES AND MORPHOLINES

| Amine | B. p., °C. (lit.) | B. p., °C. (found) | Ref |
|---|---|---|---|
| N-Methylpiperidine | 105.9 | 105–107 | 2 |
| N-*n*-Butylpiperidine | 175.8 | 67–67.5 (18 mm.) | 2 |
| N-*n*-Laurylpiperidine | 161 (5 mm.) | ..... | 3 |
| N-*n*-Cetylpiperidine | 176–177 (1 mm.) | 175–179 (1 mm.) | 3 |
| N-Benzylpiperidine | 245 | 117–119 (13 mm.) | 4 |
| N-*n*-Butylmorpholine | 67–68 (10 mm.) | 67–67.5 (11 mm.) | 5 |
| N-Benzylmorpholine | 135–136.5 (14 mm.) | 129–131 (13 mm.) | 6 |

**N-*n*-Butylmorpholine Bisulfite.**—N-*n*-Butylmorpholine, b. p. 67–67.5° (11 mm.), was converted to its bisulfite in the same manner as described for the *n*-butylpiperidine. The intermediate viscosity, however, was much greater in this case and the final product was deeper orange in color.

**N-*n*-Benzylpiperidine Bisulfite.**—When sulfur dioxide was passed into N-*n*-benzylpiperidine, b. p. 117–119° (13 mm.), the reaction mixture became so viscous that when this stage was reached the gas was allowed to flow in a slow stream over the surface of the liquid for two days with occasional stirring. Toward the end the viscosity decreased.

**N-*n*-Benzylmorpholine Bisulfite.**—N-*n*-Benzylmorpholine, b. p. 129–131° (13 mm.), exhibited the same characteristics as *n*-benzylpiperidine when treated with sulfur dioxide. The viscosity was such that only by prolonged treatment with sulfur dioxide could part of it be converted to the bisulfite.

**N-Lauryl- and N-Cetyl-piperidine Bisulfites.**—When N-laurylpiperidine and N-cetylpiperidine were used, white solids formed as intermediates which made it necessary to pass the sulfur dioxide over the surface for a long period. The supernatant orange-colored liquid which formed on the surface was poured off from time to time until the conversion was complete.

**Formation of Bisulfite Addition Products.**—The general procedure consisted in addition of a slight excess of aldehyde or ketone to the amine bisulfite complex at room temperature. The color of the reagent was discharged completely only in the presence of an excess of the aldehyde or ketone. Usually, solution took place and the mixture became clear with a slight evolution of heat and a copious evolution of sulfur dioxide. In about one to five minutes the mixture had become colorless, and white crystals usually appeared. After fifteen minutes following solidification, dry ether was added and the crystals filtered. They were then recrystallized from absolute ethanol or absolute ethanol–ether mixtures and dried at 50°.

Some of the reaction mixtures required one hour or more before crystallization started; in particular, benzaldehyde, methyl *n*-propyl ketone or 2-ethylhexanal with N-*n*-butylpiperidine bisulfite, benzaldehyde with N-benzylpiperidine bisulfite and cyclohexanone with N-methylpiperidine bisulfite. The N-benzylmorpholine bisulfite was so insoluble as to require excess of acetone to take it into solution. Pyridine bisulfite and benzaldehyde did not decolorize, and no product crystallized.

The yields in practically all the reactions were entirely satisfactory, and losses by recrystallization were only slight.

## Summary

A variety of tertiary amines, N-methyl-, N-*n*-butyl-, N-benzyl-, N-lauryl-, and N-cetyl-piperidines, N-butyl- and N-benzyl-morpholines were converted to their bisulfites. These bisulfites were allowed to react with representative aldehydes

(2) Magnusson and Schierz, University of Wyoming, Pub., **7**, 1 (1940); *C. A.*, **34**, 6867 (1940).

(3) Stross and Evans, THIS JOURNAL, **64**, 2511 (1942).

(4) Clarke, *J. Chem. Soc.*, **99**, 1927 (1911).

(5) Blicke and Zienty, THIS JOURNAL, **61**, 771 (1939).

(6) Mason and Zief, *ibid.*, **62**, 1450 (1940).

and ketones; acetone, cyclopentanone cyclohexanone, methyl *n*-propyl ketone, benzaldehyde and 2-ethylhexanal.

The amine bisulfite adducts were characterized. In general they are white crystalline solids, readily crystallized from ethanol or ethanol–ether mixtures. Like the corresponding sodium bisulfite adducts, they are decomposed with acids or alkalies into the amines.

URBANA, ILLINOIS RECEIVED AUGUST 9, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Amine Bisulfites. II. Their Use as Resolving Agents for Aldehydes and Ketones

BY ROGER ADAMS AND JOHN D. GARBER[1]

The addition products formed from tertiary amine bisulfites and aldehydes or ketones have been described in the first communication.[2] The extension of this study to certain primary amine bisulfites has now been made. The bisulfites of benzylamine, *s*-butylamine, β-phenethylamine, α-phenethylamine, and β-naphthol phenylaminomethane have been allowed to react with acetone, cyclopentanone, cyclohexanone, 3-methylcyclohexanone, benzaldehyde, heptaldehyde, isovaleraldehyde and valeraldehyde. The reactions usually proceeded smoothly and the adducts are white crystalline compounds, readily purified from absolute ethanol or ethanol–water mixtures in the case of the higher molecular weight substances. The melting points range between 100 and 160° as shown in Table I. Although stereoisomers in certain of the adducts are possible one form predominated, for only a single substance was isolated in good yield.

The gradation in properties of the compounds listed in Table I is interesting. It was noticed that if the molecular weight of either the amine or carbonyl compound was increased, the salt-like properties of the bisulfite addition compound became more indefinite, and the solubility in water and ethanol decreased. The stability also was found to vary between wide limits, an observation which made the temperature of recrystallization an important factor. Thus, the *s*-butylamine bisulfite of *n*-valeraldehyde was formed in the usual manner, but the solid, after isolation, immediately began to evolve sulfur dioxide. It could be recrystallized, but by the time the sample was dry enough for analysis it was impure again. On the other hand, the addition compounds of β-naphthol phenylaminomethane bisulfite with most of the carbonyl compounds listed could be boiled in ethanol without appreciable decomposition.

When sulfur dioxide was allowed to bubble through an equimolar mixture of the amine and water, usually with the addition of a little ether or in certain cases of ethanol, a white precipitate was formed. This product, chiefly the amine sulfite, was not isolated, but the introduction of sulfur dioxide was continued until a homogeneous, yellow, viscous liquid was produced. It is postulated that the yellow color of the resulting product is due to a complex, perhaps of the type $(RNH_2)_x:(SO_2)_y$. Such a complex, in the presence of water and a suitable carbonyl compound, reacts to form an amine bisulfite addition compound. The evolution of sulfur dioxide in the latter reaction may be cited as evidence that $y$ is greater than $x$. Moreover, Bright and Jasper[3] have shown that the 1:1 trimethylamine–sulfur dioxide complex is colorless.

The procedure for forming the adducts with aldehydes and ketones was essentially that previously described.[2] A few isolated experiments were unsuccessful. No reaction product could be isolated from the following combinations: camphor or carbethoxycyclohexanone and *dl*-α-phenethylamine bisulfite; glucose and *dl*-*s*-butylamine bisulfite; benzaldehyde and aniline bisulfite; propiophenone and benzylamine bisulfite (too unstable). In a few instances indicated in the table, no crystalline products formed.

If an optically active amine bisulfite were allowed to react with a racemic aldehyde or ketone, it is apparent that the product would be a mixture of four stereoisomers since a new asymmetric carbon holding the hydroxyl group would be introduced.

$$\underset{dl}{RCHO} + \underset{d \text{ or } l}{R'NH_3SO_3H} \longrightarrow \underset{dl\ dl}{RCHOHSO_3H_3NR'}\ \underset{d \text{ or } l}{}$$

Whether or not all four isomers are formed is of minor significance since the success in resolution will depend upon the ease of isolation of a single optically pure product. If this could be accomplished, a relatively simple method of resolving racemic aldehydes and ketones would be available.

Woodward, Kohman and Harris[4] have enumerated the known resolving reagents for ketones and aldehydes, most of which suffer the disadvantages of difficulty in preparation and of failure to give crystalline derivatives with many carbonyl compounds. They proposed a new reagent *l*-menthyl N-aminocarbamate, which was used by them merely to resolve *dl*-camphor, but which probably will prove to be a much more satisfactory general reagent than any of the others. Sobotka,

(1) An abstract of a thesis submitted in partial fulfillment of requirements for the degree of Doctor of Philosphy, 1943.

(2) Adams and Lipscomb, THIS JOURNAL, **70**, 519 (1948).

(3) Bright and Jasper, *ibid.*, **65**, 1262 (1943).

(4) Woodward, Kohman and Harris, *ibid.*, **63**, 120 (1941).

*et al.*,[5] have employed this reagent successfully in the resolution of *dl*-α-ionone.

Of the three optically active amines thus far studied, the two forms of α-phenethylamine were found to be very satisfactory, particularly with respect to the formation and purification of the bisulfites and the adducts with aldehydes and ketones. *l*-Menthylamine and *d*-β-naphthol phenylaminomethane were employed with indifferent success.

When the bisulfite addition compound of *d*-α-phenethylamine and *dl*-3-methylcyclohexanone was crystallized four times from ethanol an optically pure fraction was obtained in 29% yield. This salt was decomposed and the ketone converted to a semicarbazone, $[\alpha]^{20}D$ −21.0°. Adams, Smith and Loewe[6] previously reported a value of −20.7° for the *d*-3-methylcyclohexanone derivative. When the *l*-α-phenethylamine bisulfite addition compound of the *dl*-ketone was treated in a similar manner, the semicarbazone of *l*-3-methylcyclohexanone was isolated.

*p*-*s*-Butylbenzaldehyde was prepared in yields of 66% from N-methylformanilide and the aryl lithium compound that resulted from the action of lithium on *p*-iodo-*s*-butylbenzene.[7] The bisulfite of *d*-α-phenethylamine formed a well-crystallized product with *p*-*s*-butylbenzaldehyde and a constant melting fraction amounting to 40–48% of the total mixture was isolated. This may indicate that a large portion of the crude reaction product consisted primarily of a single compound. However, decomposition of the salt, gave a *s*-butylbenzaldehyde of such low rotation, $[\alpha]^{33}D$ −0.19°, semicarbazone $[\alpha]^{28}D$ −2.3° that the effectiveness of the resolution is in doubt. The salt may have been a compound composed of two diastereoisomers and only partial resolution was thus realized.

*l*-Menthylamine bisulfite with *p*-*s*-butylbenzaldehyde yielded a salt which appeared to be pure but, upon decomposition, only optically inactive aldehyde was recovered. This same aldehyde reacted with *d*-β-naphthol phenylaminomethane bisulfite abnormally to form a Schiff base instead of the desired addition compound. The Schiff base is a well-crystallized and easily purified substance with a high optical rotation, $[\alpha]^{30}D$ +240°. This type of Schiff base may offer a convenient intermediate for resolution of certain aldehydes and possibly ketones and is being explored. Sobotka, *et al.*,[5] refer to their attempts (unpublished) to resolve α-phenylpropanol with *d*-β-naphthol phenylaminomethane. The regeneration of the aldehyde in optically active form was unsuccessful because of the conditions of hydrolytic scission. This particular aldehyde is prone to racemization through enolization induced by the reagents used.

An improved synthesis for *dl*-β-methylhydrocinnamaldehyde[8] was developed. β-Bromoisopropylbenzene[9,10] was prepared in 60% yields by the action of allyl bromide on benzene in the presence of sulfuric acid. When the Grignard reagent was formed and allowed to react with N-methylformanilide, there was isolated 35% of the theoretical amount of β-methylhydrocinnamaldehyde. The crude product that resulted from the action of *d*-α-phenethylamine bisulfite on this racemic aldehyde yielded after one recrystallization a fraction $[\alpha]^{32}D$ −20.7°. This fraction was decomposed and the resulting aldehyde was converted to the optically active 2,4-dinitrophenylhydrazone, $[\alpha]^{27}D$ −39.6°. The enantiomorph was obtained by the use of the *l*-amine bisulfite in a similar series of reactions.

A quantitative procedure for the determination of sulfur in these addition compounds has been investigated. The "sulfites" and "bisulfites" first reported by Schiff[11] were analyzed for sulfur gravimetrically. He reported that an iodine titration method gave irreproducible results. Since the initial work of Ripper,[12] a great deal has been done on the quantitative determination of aldehydes by means of sodium bisulfite. In a comparison of the modified Ripper method with the excess iodine method, Parkinson and Wagner[13] reported that in general the latter was superior.

Notwithstanding the fact that the reverse reaction of decomposition was involved in the present investigation, the excess iodine method was chosen as a basis for the determination of sulfur. Eventually, a procedure was developed which gave excellent results. The sample was decomposed with aqueous alkali and the solution was poured into water containing a 10% excess of

$$RCHOHSO_3H_3NR' + 2OH^- \longrightarrow RCHO + R'NH_2 + SO_2^= + 2H_2O$$

standard iodine and a slight excess of acid. Back-titration with standard sodium thiosulfate followed immediately. Although several of the addition compounds listed in Table I gave rather poor sulfur analyses, this was undoubtedly due to the difficulty encountered in preparing a pure analytical sample.

## Experimental

**Amine Bisulfite Addition Compounds.**—The following general procedure was adopted for the formation of the amine bisulfite addition compounds listed in Table I. Sulfur dioxide was bubbled through a mixture of amine (0.10 mole) and ether (25 ml.) that contained a slight excess of water (0.11 mole.) The introduction of sulfur dioxide was continued until the initially formed solid was replaced by a homogeneous yellow liquid. This bisulfite solution was poured into an excess (0.20 mole) of the carbonyl compound. Immediately the solution was decolorized, sulfur dioxide was evolved, the reaction mixture became very warm and soon solidified.

It was found more convenient to use ethanol rather than ether in the preparation of the β-naphthol phenyl-

(5) Sobotka, Block, Cahnmann, Feldbau and Rosen, THIS JOURNAL, **65**, 2061 (1943).

(6) Adams, Smith and Loewe, *ibid.*, **64**, 2087 (1942).

(7) Boedtker, *Bull. soc. chim. France*, [4] **45**, 645 (1929).

(8) v. Braun, Grabowski and Kirchbaum, *Ber.*, **46**, 1266 (1913).

(9) Truffault, *Compt. rend.*, **202**, 1286 (1936).

(10) W. J. Shenk, Jr., private communication.

(11) Schiff, *Ann.*, **140**, 125 (1866).

(12) Ripper, *Monatsh.*, **21**, 1079 (1900).

(13) Parkinson and Wagner, *Ind. Eng. Chem., Anal. Ed.*, **6**, 433 (1934).

TABLE I

AMINE BISULFITE ADDITION COMPOUNDS

| Amine | M. p., °C. | Sulfur, % Calcd. | Found | M. p., °C. | Sulfur, % Calcd. | Found | M. p., °C. | Sulfur, % Calcd. | Found | M. p., °C. | Sulfur, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Acetone | | | Cyclopentanone | | | Cyclohexanone | | | 3-Methylcyclohexanone | | |
| Benzyl- | 93–94 | 12.1 | 13.0 | 109–110 | 11.8 | 11.7 | 128–128.5 | 11.0 | 11.1 | 127–128 | 10.6 | 10.6 |
| *dl*-α-Phenethyl- | 91–93 | Unstable | | 115–116 | 11.1 | 11.1 | 128–129 | 10.6 | 10.6 | 122–125 | 10.0 | 10.2 |
| β-Phenethyl- | 110–111 | 12.1 | 12.3 | 119–119.5 | 11.0 | 11.1 | 131–132 | 10.6 | 10.6 | 124–126 | 10.1 | 10.2 |
| *dl*-*s*-Butyl- | 55–65 | Unstable | | 108–110 | 13.1 | 13.4 | 140–142 | 12.5 | 12.6 | 128–129 | 11.9 | 12.0 |
| Heptyl- | | | | 110–111 | 11.4 | 11.4 | | | | | | |
| *dl*-β-Naphthol phenylaminomethane | 117–118 | 8.62 | 8.23 | 126–127 | 7.40 | 7.71 | 142–142.5 | 7.38 | 7.45 | 162–164 | 7.13 | 7.23 |
| | Benzaldehyde | | | Heptaldehyde | | | Isoveraldehyde | | | *n*-Valeraldehyde | | |
| Benzyl- | 119–120 | 11.0 | 10.8 | 104–105 | 10.3 | 10.6 | 105–110 | 10.6 | 11.6 | 107–108 | 11.1 | 11.6 |
| *dl*-α-Phenethyl- | 105–106 | 10.3 | 10.4 | 104–106 | 10.3 | 10.1 | 115–116 | 10.4 | 11.1 | 104–106 | 9.82 | 11.1 |
| β-Phenethyl- | 121–122 | 10.3 | 10.4 | 128–129 | 10.3 | 10.1 | 109–112 | 10.1 | 11.1 | 106–108 | 10.1 | 11.1 |
| *dl*-*s*-Butyl- | 110–111 | 12.1 | 12.2 | 91–96 | Unstable | | 118–122 | 12.0 | 13.3 | Decomposed | | |
| Heptyl- | 106–107 | 10.6 | 10.4 | | | | | | | | | |
| *dl*-β-Naphthol phenylaminomethane | 124–139 | 6.97 | 7.32 | 141–142 | 7.03 | 7.19 | 143–144 | 6.59 | 7.67 | 139–140 | 6.58 | 7.67 |

aminomethane bisulfite addition compounds. In all cases the product was collected by filtration and washed with ether before it was recrystallized from either absolute ethanol or an ethanol–water mixture.

**Analytical Method for the Determination of Sulfur.**—The sample (0.3 g.) of amine bisulfite addition compound was weighed into a small erlenmeyer flask and treated with 10 ml. of water. It was immaterial whether complete solution was effected. After 5 ml. of 5% aqueous potassium hydroxide had been added, the flask was stoppered and allowed to stand at room temperature for one hour. It was found that this time could be shortened considerably without affecting the results. The alkaline reaction mixture was poured into an aqueous solution of a 10% excess of standard iodine and just enough 5% sulfuric acid to neutralize the alkali used originally and also the amine formed by the decomposition of the sample. One drop excess of the acid solution was then added, and the iodine titrated with standard sodium thiosulfate. Analyses were carried out in which the sample was heated at 50° with alkali. This modification gave excellent results if the flask was swept out with nitrogen before it was stoppered and heated.

***d*-α-Phenethylamine Bisulfite Addition Compound of *d*-3-Methylcyclohexanone.**—The bisulfite solution was formed in the usual manner from 12 g. of *d*-α-phenethylamine,[14] 2.7 g. of water and 20 ml. of ether. To the viscous, yellow liquid was added 22 g. of *dl*-3-methylcyclohexanone in one portion. Immediately, bubbles of sulfur dioxide were evolved and much heat was produced. Crystallization was induced by scratching and cooling the solution, and after the reaction mixture had solidified ether was added and the paste broken down with a spatula. A yield of 30 g. (96%) of the *d*-α-phenethylamine bisulfite addition compound of *dl*-3-methylcyclohexanone, m.p. 106–113°, resulted. Four recrystallizations of this racemic addition compound from the minimum amount of absolute ethanol at 40° yielded 4.3 g. (29%) of the *d*-α-phenethylamine bisulfite addition compound of *d*-3-methylcyclohexanone, m. p. 126–127°.

*Anal.* Calcd. for $C_{15}H_{25}O_4NS$: C, 57.11; H, 7.99. Found: C, 57.20; H, 7.24. *Rotation.* 0.1068 g. made up to 5 ml. with water at 26° gave $\alpha_D$ + 0.03°; *l*, 1; $[\alpha]^{26}D$ + 1.4°.

**Semicarbazone of *d*-3-Methylcyclohexanone.**[6]—A sample of 0.8 g. of the purified addition compound was decomposed with 10 ml. of 20% hydrochloric acid at 45°. The ketone was extracted with ether, and converted to the semicarbazone in the usual manner. This derivative was recrystallized several times from aqueous ethanol, m.p. 183–183.5°.

*Anal.* Calcd. for $C_8H_{15}ON_3$: C, 56.78; H, 8.94. Found: C, 57.04, H, 9.09. *Rotation.* 0.0738 g. made up to 5 ml. with ethanol at 20° gave $\alpha_D$ −0.31°; *l*, 1; $[\alpha]^{20}D$ −21.0°.

***l*-α-Phenethylamine Bisulfite Addition Compound of *l*-3-Methylcyclohexanone.**—Identically the same procedure was used for the formation of the *l*-amine bisulfite and the corresponding addition compound as was used in the case of the *d*-amine. From 12 g. of *l*-α-phenethylamine and 22 g. of *dl*-3-methylcyclohexanone was obtained 29 g. (93%) of the bisulfite addition compound, m. p. 106–113°. The crude material was recrystallized four times from the minimum amount of absolute ethanol at 40°, and 3.9 g. (27%) of the pure bisulfite addition compound of *l*-α-phenethylamine and *l*-3-methylcyclohexanone was removed by filtration, m. p. 126–127°.

*Anal.* Calcd. for $C_{15}H_{25}O_4NS$: C, 57.11; H, 7.99. Found: C, 57.16; H, 8.02. *Rotation.* 0.2137 g. made up to 5 ml. with water at 28° gave $\alpha_D$ −0.06°; *l*, 1; $[\alpha]^{28}D$ −1.4°.

**Semicarbazone of *l*-3-Methylcyclohexanone.**—This compound was prepared from 0.8 g. of the *l*-amine bisulfite addition compound of the *l*-ketone in the same manner as its stereoisomer. After the product had been recrystallized several times from aqueous ethanol the semicarbazone of *l*-3-methylcyclohexanone was pure, m. p. 183–183.5°.

*Rotation.* 0.0840 g. made up to 5 ml. with ethanol at 20° gave $\alpha_D$ + 0.35°; *l*, 1; $[\alpha]^{20}D$ +20.8°.

***p*-Iodo-*s*-butylbenzene.**[7]—A mixture of 160 g. of *s*-butylbenzene, 127 g. of iodine, 39 g. of iodic acid, 50 ml. of water and 350 ml. of glacial acetic acid was allowed to reflux in a 1-l. flask (ground glass connections) equipped with a water-cooled condenser. Heating was continued for several hours and then the solution was decanted from the excess iodine into an equal volume of water. The lower layer was separated and boiled with an equal volume of methanolic potassium hydroxide for thirty minutes. The lower layer was separated, washed with water, dried over anhydrous magnesium sulfate, filtered and distilled *in vacuo*. A total of 84 g. (53%) of *s*-butylbenzene was recovered from the fore-run, and 81 g. (55%, based on *s*-butylbenzene actually consumed) of *p*-iodo-*s*-butylbenzene was obtained, b. p. 115–118° (12 mm.); $n^{30}D$ 1.5642.

***p*-*s*-Butylbenzaldehyde.**—The technique of Adams and Carlin[15] for the preparation of aldehydes from aryl lithium

(14) Ingersoll, *Org. Syntheses*, Coll. Vol. II, p. 506.

(15) Adams and Carlin, THIS JOURNAL, **65**, 360 (1943).

compounds and N-methylformanilide[16] was used. A 500-ml. three-necked round-bottomed flask was provided with a mercury-sealed Hershberg wire stirrer, a reflux condenser, a nitrogen inlet tube and an outlet tube fitted with a stopcock. The stirrer and condenser mounts were each equipped with ground glass joints, and the top of the reflux condenser was made so that a special ground glass joint dropping funnel could be inserted. A rapid stream of dry, oxygen-free nitrogen was passed through the flask, which contained 25 ml. of anhydrous ether; and, simultaneously, 2.78 g. of lithium was cut into small pieces and allowed to fall through the central neck. The rate of flow of nitrogen was reduced to one bubble (through a 6″ column of sulfuric acid) per second, the stirrer started and a solution of 46 g. of *p*-iodo-*s*-butylbenzene in 60 ml. of anhydrous ether was added at such a rate that refluxing was maintained throughout the addition.

The solution was stirred for one hour, and then a mixture of 26 g. of N-methylformanilide with an equal volume of ether was added dropwise. Enough heat was generated to cause the solvent to reflux. The solution was stirred overnight and then poured into a mixture of 200 ml. of water, 11 ml. of concentrated sulfuric acid and 100 g. of ice. The ether layer was separated and the aqueous layer was extracted three times with 100-ml. portions of ether. The combined ether extract was dried over anhydrous sodium sulfate, filtered and the solvent removed. The fraction that boiled at 116–118° (15 mm.) was *p*-*s*-butylbenzaldehyde, $n^{25}D$ 1.5240; yield 19.8 g. (66%).

**d-α-Phenethylamine Bisulfite Addition Compound of l-p-s-Butylbenzaldehyde.**—Sulfur dioxide was passed into a mixture of 25.4 g. of *d*-α-phenethylamine, 4.0 g. of water and 75 ml. of ether. The amine bisulfite solution was poured into 44 g. of slightly yellow *dl*-*p*-*s*-butylbenzaldehyde. After the reaction mixture had solidified, 300 ml. of ether was added, the flask stoppered and the mixture allowed to stand overnight in the ice-box. The addition compound was collected on a filter and washed with ether until white. The yield was 71 g. (92%) of crude product, m. p. 90–95°. A solution of 20 g. of the above addition product in 350 ml. of chloroform at 45° was allowed to stand at room temperature but no crystals appeared. After addition of 200 ml. of dry ether, the solution was placed in an ice-box overnight. It thus yielded 4 g. of white crystals, m. p. 103–104°. Further recrystallization from either chloroform or ethanol failed to yield a fraction of higher melting point.

*Anal.* Calcd. for $C_{19}H_{27}O_4NS$: S, 8.79. Found: S, 8.68. *Rotation.* 0.3911 g. made up to 25 ml. with ethanol at 27° gave $\alpha_D + 0.11°$; *l*, 2; $[\alpha]^{27}D + 3.52°$.

**l-p-s-Butylbenzaldehyde.**—A sample of 10 g. of the addition compound from *d*-α-phenethylamine bisulfite and *l*-*p*-*s*-butylbenzaldehyde, m. p. 103–104°, was decomposed with 75 ml. of 5% hydrochloric acid, and the aldehyde extracted with ether. The combined ether extract was dried over anhydrous magnesium sulfate, filtered and distilled under diminished pressure. The yield of *l*-*p*-*s*-butylbenzaldehyde, b. p. 115–116° (13 mm.), $n^{25}D$ 1.5247, was 2.6 g. (59%).

*Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: C, 81.16; H, 8.94. *Rotation.* 2.1345 g. made up to 6.63 ml. with ethanol at 33° gave $\alpha_D -0.06°$; *l*, 1; $[\alpha]^{33}D -0.19°$.

**Semicarbazone of l-p-s-Butylbenzaldehyde.**—A small sample of addition compound, m. p. 103–104°, was decomposed with 15% sulfuric acid. The aldehyde was recovered by an ether extraction and converted to the semicarbazone. Two recrystallizations from ethanol yielded a white product, m. p. 206–207°.

*Anal.* (racemic modification) Calcd. for $C_{12}H_{17}ON_3$: C, 65.73; H, 7.81. Found: C, 65.63; H, 7.91. *Rotation.* 0.0765 g. made up to 10 ml. with ethanol at 28° gave $\alpha_D -0.01°$; *l*, 1; $[\alpha]^{28}D -1.3°$.

**Reaction of d-β-Naphthol Phenylaminomethane Bisulfite and dl-p-s-Butylbenzaldehyde.**—In a 125-ml. erlenmeyer flask which contained 15 ml. of a 50% mixture of ethanol and ether and 3.0 g. of water, 5 g. of *d*-β-naphthol phenylaminomethane, $[\alpha]^{28}D + 45.8°$, was added. Sulfur dioxide was introduced until the solid dissolved and the solution had a characteristic yellow color. To this bisulfite solution was added 5 g. of *dl*-*p*-*s*-butylbenzaldehyde. There was no evidence of reaction after the mixture had stood in the ice-box for a week, but when the flask was kept at room temperature for two days, beautiful acicular crystals appeared, m. p. 164–165°, which may be recrystallized from ethanol. Since this product did not decolorize iodine, it was assumed that it was not a bisulfite addition compound.

*Rotation.* 0.1069 g. made up to 10 ml. with chloroform at 30° gave $\alpha_D + 2.56$; *l*, 1, $[\alpha]^{30}D +240°$.

Since it was thought the product might be a Schiff base it was synthesized by a direct method. To a solution of 0.2 g. of *d*-β-naphthol phenylaminomethane in 15 ml. of ethanol was added a few drops of *dl*-*p*-*s*-butylbenzaldehyde and one drop of 10% aqueous sodium hydroxide. The precipitate, which formed immediately, was recrystallized several times from ethanol, m. p. 166–166.5°. The mixture of this product and the one obtained above showed no depression when melted.

*Anal.* Calcd. for $C_{28}H_{27}ON$: C, 85.46; H, 6.92. Found: C, 85.31; H, 7.09.

**l-Menthylamine Bisulfite Addition Compound of dl-p-s-Butylbenzaldehyde.**—Sulfur dioxide was passed into a mixture of 14.3 g. of *l*-menthylamine (Eastman Kodak Co.), 3.0 g. of water and 25 ml. of ether. When the formation of the amine bisulfite was complete, 18 g. of *dl*-*p*-*s*-butylbenzaldehyde was added. Although there was very little heat effect, the reaction mixture soon solidified. The product was collected on a filter and washed thoroughly with absolute ether, m. p. 109–114°. The yield was 11.6 g. (32%).

*Rotation.* 0.2220 g. made up to 25 ml. with ethanol at 27° gave $\alpha_D -0.21°$; *l*, 2; $[\alpha]^{27}D -11.6°$.

A solution of 11 g. of the crude product from the *d*-amine bisulfite and the *dl*-aldehyde in 50 ml. of absolute ethanol at 50° was allowed to stand at room temperature. When this solution was filtered, 7 g. of addition compound, m. p. 112–115°, was obtained. This fraction was dissolved in the minimum amount of ethanol at 45° and the resulting solution again allowed to stand at room temperature. A crop that weighed 1.02 g. was isolated, m. p. 117–118°. The semicarbazone of the aldehyde obtained by decomposition of this fraction was optically inactive.

*Anal.* Calcd. for $C_{21}H_{37}O_4NS$: S, 8.02. Found: S, 7.80. *Rotation.* 0.1375 g. made up to 10 ml. with ethanol gave $\alpha_D -0.16$; *l*, 1; $[\alpha]^{33}D -11.6°$.

**β-Bromoisopropylbenzene.**[9,10]—A 1-l., three-necked flask was fitted with a mercury-sealed Hershberg wire stirrer, a water-cooled condenser and a dropping funnel. Into the flask was introduced 420 ml. of benzene (dried over anhydrous calcium chloride) and 81.5 ml. of concentrated sulfuric acid. The stirrer was started and the temperature maintained at 40 ± 2° throughout the addition of 175 g. (1.45 moles) of allyl bromide. Vigorous stirring was continued for five hours and then the reaction mixture was allowed to stand overnight. The benzene layer was separated, washed consecutively with 30 ml. of concentrated sulfuric acid, 50 ml. of water which was saturated with sodium sulfate, 50 ml. of 10% aqueous sodium hydroxide and finally with 50 ml. of water. The benzene layer was placed in a 1-l. round-bottomed flask arranged for steam distillation. When no more oil appeared in the condensate, the layers were separated and the water layer extracted with 100 ml. of benzene. The combined organic extract was dried over anhydrous magnesium sulfate, filtered and the solvent removed. The yield of β-bromoisopropylbenzene was 166 g. (58%); b. p. 109–111° (16 mm.); $n^{25}D$ 1.5462.

**β-Methylhydrocinnamaldehyde.**[8]—The Grignard reagent was formed from 6.0 g. of magnesium, 51 g. of β-bromoisopropylbenzene and 100 ml. of dry ether. After this solution was heated under reflux for one hour, 35 g. of

(16) Fieser and Jones, *Org. Syntheses*, **20**, 66 (1940).

N-methylformanilide in an equal volume of ether was added. A vigorous reaction ensued, and when the addition was complete the solution was heated under reflux for two hours. The Grignard reaction mixture was decomposed with 100 ml. of 5 *N* sulfuric acid. When all of the solid had dissolved, the ether layer was separated and shaken for thirty minutes with an equal volume of saturated sodium bisulfite. The sodium bisulfite addition compound was collected on a filter and washed with ether. Upon decomposition of the salt with aqueous sodium bicarbonate, a yield of 13 g. (35%) of *dl*-β-methylhydrocinnamaldehyde, b. p. 92–93° (14 mm.), $n^{30}D$ 1.5106, was obtained.

*Anal.* Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.08; H, 8.56.

The 2,4-dinitrophenylhydrazone of *dl*-β-methylhydrocinnamaldehyde was prepared in the usual manner. The crude product was dissolved in ether and extracted with three portions of 1:1 hydrochloric acid. The ether layer was separated, the solvent removed and the residue recrystallized several times from ethanol; yellow crystals, m. p. 123–123.5°.

*Anal.* Calcd. for $C_{16}H_{16}O_4N_4$: C, 58.53; H, 4.91. Found: C, 58.35; H, 5.09.

***d*-α-Phenethylamine Bisulfite Addition Compound of *l*-β-Methylhydrocinnamaldehyde.**—The amine bisulfite was formed by the action of sulfur dioxide on 4.5 g. of *d*-α-phenethylamine, 1.0 g. of water and 15 ml. of ether. When bisulfite formation was complete, 6.0 g. of crude *dl*-β-methylhydrocinnamaldehyde was added in one portion. The solid addition product was isolated by filtration and washed with ether, m. p. 95–115°; yield 7.0 g. (54%).

All of the crude bisulfite addition compound of the *d*-amine and the *dl*-aldehyde was dissolved in 30 ml. of 95% ethanol at 45°. When the solution was allowed to stand at room temperature, 1.78 g. of glistening, white crystals were isolated, m. p. 131.5–132°.

*Anal.* Calcd. for $C_{18}H_{25}O_4NS$: S, 9.12. Found: S, 9.20. *Rotation.* 0.0870 g. made up to 5 ml. with ethanol at 32° gave $\alpha_D$ −0.36; *l*, 1; $[\alpha]^{32}D$ −20.7°.

**2,4-Dinitrophenylhydrazone of *l*-β-Methylhydrocinnamaldehyde.**—Approximately 0.5 g. of the first fraction of the *d*-amine bisulfite addition compound of *l*-β-methylhydrocinnamaldehyde was decomposed and converted to the 2,4-dinitrophenylhydrazone, which was purified in the same manner as the corresponding derivative of the *dl*-aldehyde. A yellow crystalline product was isolated, m. p. 97–97.5°.

*Rotation.* 0.0681 g. made up to 10 ml. with chloroform at 27° gave $\alpha_D$ −0.27°; *l*, 1; $[\alpha]^{27}D$ −39.6°.

***l*-α-Phenethylamine Bisulfite Addition Compound of *d*-β-Methylhydrocinnamaldehyde.**—Sulfur dioxide was passed into 4.8 g. of *l*-α-phenethylamine, 1.0 g. of water and 10 ml. of ether. To the resulting solution 5.0 g. of pure *dl*-β-methylhydrocinnamaldehyde, b. p. 93–94° (16 mm.), was introduced. The reaction mixture solidified when allowed to stand in the ice-box for a few hours and the product was filtered, m. p. 88–115°; yield, 7.2 g. When a mixture of 6 g. of the bisulfite addition compound of the *l*-amine and the *dl*-aldehyde in 20 ml. of absolute ethanol and 0.25 ml. of water at 45° was allowed to stand at room temperature, 1.03 g. of acicular crystals were formed, m. p. 130–131°.

*Anal.* Calcd. for $C_{18}H_{25}O_4NS$: S, 9.12. Found: S, 9.05. *Rotation.* 0.1411 g. made up to 10 ml. with ethanol at 32° gave $\alpha_D$ + 0.30; *l*, 1; $[\alpha]^{32}D$ +21.3°.

## Summary

1. Several primary amines were converted to their bisulfites and these were added to various aldehydes and ketones. The adducts were usually white crystalline products, melting in the range 100–160°, and readily purified from ethanol or ethanol–water mixtures.

2. The optically active forms of α-phenethylamine were converted to their bisulfites and when they reacted with *dl*-3-methylcyclohexanone or *dl*-β-methylhydrocinnamaldehyde yielded products from which pure salts were isolated. Upon decomposition, the optically active aldehyde or ketone resulted. Only partial resolution of *dl*-*p*-*s*-butylbenzaldehyde was affected in the same manner.

3. *d*-β-Naphthol phenylaminomethane and *l*-menthylamine bisulfites did not give satisfactory results in the resolution of the three aldehydes and ketones used.

4. *p*-*s*-Butylbenzaldehyde was prepared from the aryl lithium compound, resulting from the action of lithium on *p*-iodo-*s*-butylbenzene, and N-methylformanilide. A new synthesis of β-methylhydrocinnamaldehyde from the Grignard of β-bromoisopropylbenzene and N-methylformanilide appears to be an improvement over those previously used.

5. A satisfactory quantitative method for determination of sulfur in the adducts of amine bisulfites and aldehydes or ketones is described.

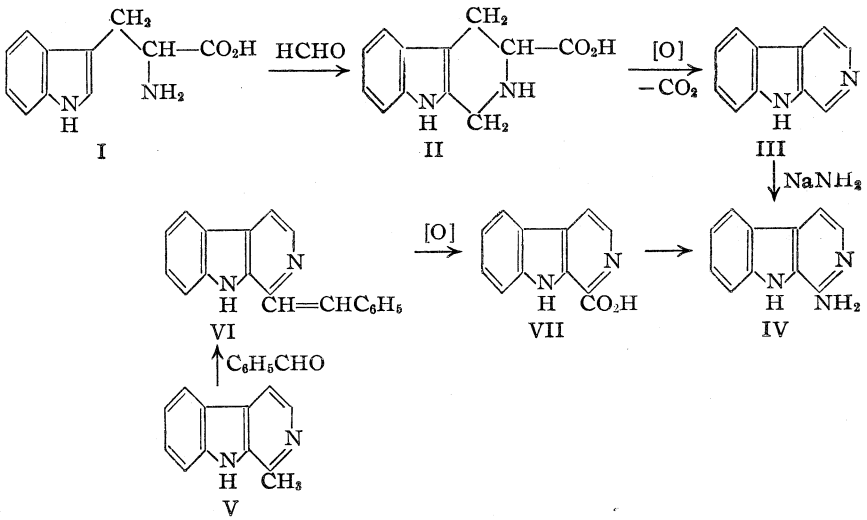
URBANA, ILLINOIS RECEIVED AUGUST 9, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Synthesis of β-Carbolines. V. 1-Amino-β-carboline[1]

BY H. R. SNYDER, HOWARD G. WALKER[2] AND FRANK X. WERBER[3]

In preceding papers[1,4] syntheses of the isomeric 3- and 6-amino derivatives of harman were reported. These amines were prepared by the degradation of an acid (Curtius reaction) and the reduction of a nitro compound, respectively. Although the direct amination, by alkali amides, of higher heterocyclic bases containing the pyridine nucleus has been found to have only limited applicability,[5] it was of interest to test the possible use of the reaction in the β-carboline series. Accordingly, norharman (III) has been subjected to the action of sodium amide; reaction occurred readily, and the product has been shown to be 1-amino-β-carboline (IV).




The preparation of norharman (III) was carried out according to Harvey, Miller and Robson[6] in direct analogy to the synthesis of harman,[4] without isolation of the intermediate tetrahydrocarboxylic acid (II). *dl*-Tryptophan (I) was condensed with formaldehyde and the 1,2,3,4-tetrahydronorharman - 3 - carboxylic acid so formed (II) was converted directly to III by dehydrogenation and decarboxylation with aqueous potassium dichromate. Amination of III with sodium amide proceeded in 89% yield to give 1-amino-β-carboline (IV). Acetylation of IV with acetic anhydride in pyridine solution produced a diacetyl derivative, the detailed structure of which has not yet been elucidated.

Chichibabin and Oparina[7] have shown that 1-aminoisoquinoline is obtained by direct amination of isoquinoline. It thus seemed reasonable to assume that the β-carboline nucleus would be attacked at the 1-position. All approaches to the structure proof were based on this assumption. Diazotization followed by hydrolysis, or direct hydrolysis of the amine with acid or base, might be expected to lead to the 1-hydroxy-β-carboline prepared by Elderfield and Hageman.[8] All attempts in this direction were unsuccessful, however. 9 - Methyl - 1 - hydroxy - β - carboline[9] might be prepared by methylation and subsequent diazotization of the amine, but methylation with diazomethane failed, so that this approach was abandoned. Similarly, no identifiable products were obtained in attempts to replace the amino group with bromine, nor was it found possible to hydrolyze any of the resulting crude reaction products to the hydroxy compound.

An unequivocal synthesis of 1-amino-β-carboline has been carried out by the method shown in the accompanying diagram. Harman (V) was oxidized to β-carboline-1-carboxylic acid (VII) essentially by the method of Kermak, Perkin and Robinson,[9] who condensed harman with benzaldehyde and oxidized the condensation product (VI) with potassium permanganate. The acid (VII) could be degraded to 1-amino-β-carboline by application of the Curtius reaction.[10] Preliminary experiments indicated that the more direct route to the carbonylazide—treatment of the acid chloride with sodium azide—was not feasible because of the extreme insolubility of the acid, which made conversion to the acid chloride unsatisfactory. The acid was readily esterified, however, and the methyl ester reacted with hydrazine almost instantaneously, without application of heat. Although the hydrazide was very insoluble it was readily transformed into the azide by treatment with nitrous acid in a large

(1) For the preceding paper see Snyder, Parmerter and Walker, THIS JOURNAL, **70**, 237 (1948).

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(4) Snyder, Parmerter and Katz, THIS JOURNAL, **70**, 222 (1948).

(5) Leffler, in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, pp. 91-104.

(6) Harvey, Miller and Robson, *J. Chem. Soc.*, 153 (1941).

(7) Chichibabin and Oparina, *J. Russ. Phys.-Chem. Soc.*, **50**, 543 (1920).

(8) Elderfield and Hageman, private communication.

(9) Kermak, Perkin and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(10) See Smith, in Adams, "Organic Reactions," Vol. III, John Wiley and Sons, New York, N. Y., 1946, p. 337 ff.

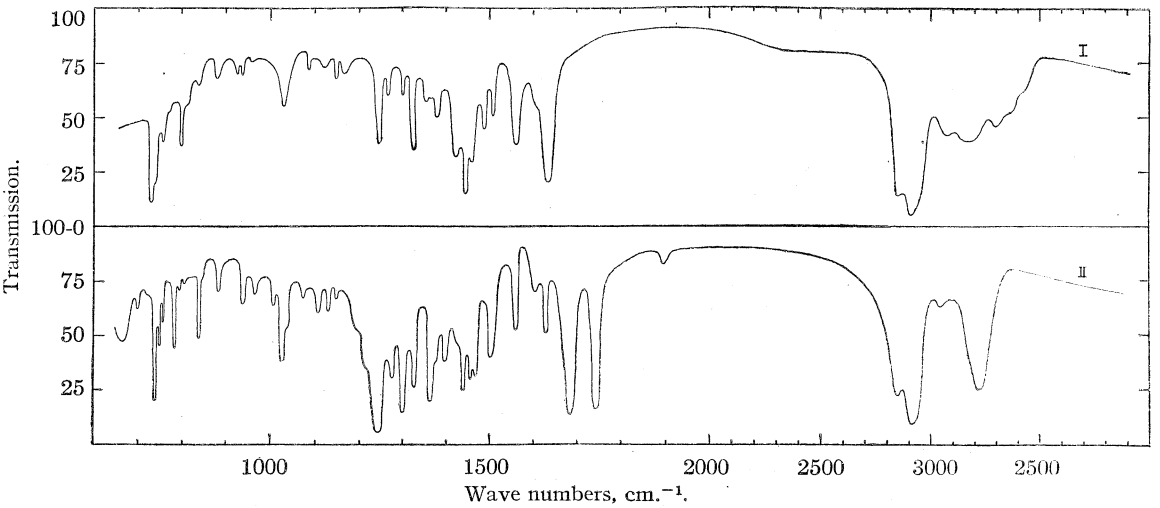



Fig. 1.—I, 1-Amino-β-carboline, suspended in mineral oil; II, diacetyl derivative of 1-amino-β-carboline, suspended in mineral oil.

volume of water. The azide was quite stable at room temperature. Attempted conversion to the amine in dilute acetic acid gave the *sym*-urea, which could be converted to the amine by hydrolysis with concentrated aqueous potassium hydroxide, but only in low yields. Conversion to the amine by preparation and hydrolysis of the ethyl carbamate was the most successful of the methods tried. The amine (IV) thus obtained melted two degrees lower than that formed by direct amination of norharman, but a mixture of the two samples melted at an intermediate temperature. Infrared absorption[11] spectra of the two amines were identical (see Fig. 1).

The diacetyl derivative of the amine obtained by the indirect route was also prepared; this substance and the compound derived from the direct-amination product melted at the same point, alone or mixed, and their infrared absorption curves were identical in every detail (Fig. 1).

## Experimental[12]

**Norharman.**—The general procedure of Harvey, Miller and Robson[6] was followed. Ten grams (0.049 mole) of *dl*-tryptophan was dissolved in 500 ml. of 0.1 *N* sodium hydroxide containing 5.6 ml. (0.07 mole) of aqueous formalin (40%). The solution was incubated at 37° for forty-six hours. It was neutralized with 4 ml. of glacial acetic acid, transferred to a 5-l. flask, and diluted with water to a volume of 2.5 l. The suspension was heated to boiling, and most of the 3-carboxy-1,2,3,4-tetrahydro-β-carboline dissolved. A mixture of 500 ml. of 10% aqueous potassium dichromate and 100 ml. of glacial acetic acid was added to the slowly boiling solution, with stirring, over a period of forty-five minutes. The solution darkened, carbon dioxide was evolved, and a brown precipitate appeared soon after the addition was started. Boiling was continued for two minutes after the addition was complete. The mixture was cooled and the excess dichromate was destroyed with sodium bisulfite. Sodium carbonate was added to definite alkalinity and the product was extracted exhaustively with about 2.5 l. of ether. The extracts were dried over magnesium sulfate and the solvent removed. After one recrystallization from aqueous methanol the slightly yellow, crystalline norharman weighed 2.80 g. (34%), m.p. 199–201°.

**1-Amino-β-carboline.**—Sodium amide was prepared according to the standard procedure,[5] from 1.81 g. (0.0788 mole) of sodium and 30 ml. of liquid ammonia in a 200-ml. three-necked flask fitted with mercury-sealed stirrer and reflux condenser. After the ammonia had evaporated, 3.31 g. (0.0197 mole) of norharman and 90 ml. of dimethylaniline were added, and the mixture was stirred and heated at 140–150° for twenty-four hours. The contents of the flask were allowed to cool, and 50 ml. of 5% sodium hydroxide solution and 100 ml. of water were added cautiously. Low-boiling petroleum ether was added to precipitate all material in the organic layer, the mixture was cooled in an ice-bath, and the crystalline product was collected. It was washed with low-boiling petroleum ether and dried in a vacuum desiccator; there was obtained 3.31 g. (89%) of material, m.p. 193–197°. Recrystallized from a methanol–water mixture it melted at 198–200°. A mixture of the crude reaction product and norharman melted at 142–159°. A sample of the product was recrystallized once more from methanol–water, yielding white platelets, m.p. 199.5–200.5° (dec.).

*Anal.* Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95. Found: C, 72.22; H, 4.79.

The diacetyl derivative was prepared according to a standard method of acetylation.[13] Recrystallized four times from benzene, it melted at 196–197.5°. A sample mixed with 1-amino-β-carboline melted at 135–150°.

*Anal.* Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.56; H, 4.58; N, 15.59.

**Benzalharman.**[9,14]—Harman,[4] 9.94 g. (0.055 mole), and 55 ml. of distilled benzaldehyde were placed in a 500-ml. round-bottomed flask and the mixture was refluxed gently for four hours, with a condenser short enough to permit the slow evaporation of the water formed in the reaction. After cooling, the brown mixture was diluted with 200 ml. of ether, and dilute hydrochloric acid was added to precipitate the yellow hydrochloride of benzalharman. It was separated, washed with ether and water, and recrystallized from 95% ethanol. The hydrochloride

(11) We are indebted to Mrs. Agatha R. Johnson for the infrared absorption data.

(12) All melting points are corrected. Microanalyses by Miss Theta Spoor and Mr. H. S. Clark.

(13) Shriner and Fuson, "Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, N. Y., 1948, p. 165, Procedure B.

(14) Barger and Scholtz, *J. Chem. Soc.*, 614 (1933); Leonard and Elderfield, *J. Org. Chem.*, 7, 556 (1942).

was suspended in 40 ml. of 95% ethanol, neutralized with dilute aqueous ammonia (1:5 ammonium hydroxide–water), and the free base was collected. The yield of yellow crystalline benzalharman was 12.6 g. (84%), m.p. 197–199°.

**β-Carboline-1-carboxylic Acid.**—The permanganate oxidation method of Kermak, Perkin and Robinson[9] was used. Benzalharman, 12.7 g. (0.046 mole) was dissolved in 50 ml. of pyridine, the solution was cooled in ice and stirred during the dropwise addition of enough saturated aqueous potassium permanganate to leave a pink color for one hour (approx. 300 ml.). The exact amount added depends on rapidity of addition, temperature and other factors. Five ml. of 95% ethanol was added and the mixture was heated on the steam-bath to destroy excess permanganate. The dark suspension was filtered hot and the filtrate was concentrated to a volume of 100 ml. and acidified with dilute hydrochloric acid. The canary-yellow hydrochloride was collected. The manganese dioxide residue was suspended in 100 ml. of water and acidified with hydrochloric acid; the mixture was treated with sodium bisulfite to dissolve the manganese dioxide, and the additional hydrochloride precipitate was collected. (Direct treatment of the original mixture with sodium bisulfite, to circumvent the necessity for removal of the manganese dioxide by filtration, resulted in lower yields.) The combined hydrochloride precipitates were dissolved in 1500 ml. of hot 5% aqueous potassium hydroxide, the solution was filtered, cooled, and the free acid was precipitated with acetic acid. The material was collected, washed with water, and dried; it weighed 3.4 g., m. p. 235°. The acidic mother liquor yielded an additional 0.9 g. of product (total crude yield, 43%). β-Carboline-1-carboxylic acid is a bright yellow, crystalline powder whose insolubility in all solvents tried made recrystallization impossible.

**1-Carbomethoxy-β-carboline.**—β-Carboline-1-carboxylic acid, 3.9 g., was suspended in 300 ml. of anhydrous methanol saturated with hydrogen chloride. The mixture was refluxed for twenty hours and concentrated to a volume of 100 ml. under reduced pressure and at room temperature. It was diluted with an equal volume of ice water, made barely alkaline with sodium bicarbonate, and extracted with chloroform. The extract was dried over magnesium sulfate and the solvent was removed. The yield of crude ester was 1.50 g., m.p. 152–157°. A small sample was sublimed *in vacuo* and recrystallized three times from dilute methanol; m.p. 165.3–166.0°.

*Anal.* Calcd. for $C_{13}H_{10}O_2N_2$: C, 69.02; H, 4.46; N, 12.39. Found: C, 69.02; H, 4.18; N, 12.41.

The magnesium sulfate residue was combined with the extracted water solution, and the mixture was concentrated and acidified with acetic acid. One and one-half grams of β-carboline-1-carboxylic acid was recovered.

**β-Carboline-1-carbonyl Hydrazide.**—The remainder of the crude ester from the previous preparation, 1.35 g., was dissolved in a mixture of methanol and water and the solution was slowly added to 7 ml. of 85% hydrazine hydrate. Precipitation of the hydrazide started immediately and was allowed to go to completion in the refrigerator overnight. The product was collected, m.p. 215–236°. One recrystallization from dioxane gave 1.20 g. of hydrazide, m.p. 265–267°. A sample recrystallized repeatedly from dioxane melted at 268–269.5° (dec.).

*Anal.* Calcd. for $C_{12}H_{10}ON_4$: C, 63.71; H, 4.46. Found: C, 63.47; H, 4.30.

**β-Carboline-1-carbonyl Azide.**—β-Carboline-1-carbonyl hydrazide, 0.95 g., was added to 146.1 ml. of dilute hydrochloric acid (6.1 ml. of the concentrated acid in 140 ml. of water), and the suspension was filtered to remove the insoluble residue. The filtrate was cooled to 0° in an ice–salt-bath, and 0.33 g. of sodium nitrite in 5 ml. of water was added over a period of five minutes. The suspension of azide-hydrochloride was allowed to stand in the cooling bath for two hours, made definitely alkaline with saturated aqueous sodium carbonate, and the solid was collected and washed with water. After drying to constant weight in a vacuum desiccator the product weighed 0.86 g.; it was quite stable at room temperature, but slowly decomposed at temperatures of 70–100°.

**Ethyl β-Carboline-1-carbamate.**—The crude azide, 0.86 g., was refluxed for three hours in 13 ml. of absolute ethanol diluted with 4 ml. of dry xylene. The mixture was filtered hot and the residue was washed with hot 95% ethanol. The combined filtrate and washings were concentrated to a volume of 15 ml., and 0.38 g. of fluffy yellow needles was collected, m.p. 283–285° (dec.), with characteristic shrinking at 181–183°. Examination of the residue from the hot reaction mixture, weighing 0.16 g., revealed it to be a less soluble crystalline modification of the major reaction product. Its melting point and infrared-absorption curve were identical with those of the ethanol-soluble portion, and mixtures of the two samples showed no melting point depression. A small amount of the soluble modification, recrystallized repeatedly from ethanol, melted at 285–288° (dec.), shrinking at 184–186°.

*Anal.* Calcd. for $C_{14}H_{13}O_2N_3$: N, 16.46: Found: N, 16.36.

**1-Amino-β-carboline.**—A suspension of 0.33 g. of crude carbamate in 7 ml. of 20% aqueous potassium hydroxide was refluxed for two hours. The mixture was allowed to cool, and the crude amine was collected and washed with cold water. After one recrystallization from dilute ethanol (Norite) there was obtained 0.21 g. of colorless needles, m.p. 199–201 (dec.). A sample recrystallized to constant melting point melted at 196.5–198.5° (dec.). Mixed with the amine prepared by direct amination of norharman it melted at 198–200°.

*Anal.* Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95. Found: C, 72.32; H, 5.14.

The diacetyl derivative was prepared[13] and recrystallized repeatedly from benzene. It melted at 195.5–197.5°, alone or mixed with a sample derived from the amination product of norharman.

*Anal.* Calcd. for $C_{15}H_{13}O_2N_3$: N, 15.72. Found: N, 15.54.

## Summary

1-Amino-β-carboline has been prepared by direct amination of norharman, and the structure of the product has been proved by an independent synthesis.

URBANA, ILLINOIS RECEIVED JULY 14, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF FREDERICK STEARNS AND COMPANY, DIVISION OF STERLING DRUG, INC.]

# Preparation of N-Substituted 1-(3′,4′-Dihydroxyphenyl)-2-aminoethanols[1]

BY JOHN R. CORRIGAN,[2a] MARIE-JO LANGERMANN[2b] AND MAURICE L. MOORE[2c]

In a previous report[3] from these laboratories we have described the preparation of a series of N-substituted 1-(*p*-hydroxyphenyl)-2-aminoethanols. Our investigations were prompted by an observation of Konzett[4] that 1-(*p*-hydroxyphenyl)-2-isopropylaminoethanol was more active as a broncholdilator than the N-methyl analog (Synephrine). Konzett[4] also studied the broncholytic properties of several N-alkyl analogs of epinephrine and reported that 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol possessed ten times the bronchodilator activity of its N-methyl analog (epinephrine) against pilocarpine-induced bronchial spasm in dogs. The chemical synthesis of these N-alkyl epinephrine analogs (alkyl = ethyl, propyl, isopropyl, butyl and isobutyl) has not been reported. We have, therefore, extended our investigations to include the preparation of a series of N-substituted 1-(3′,4′-dihydroxyphenyl)-2-aminoethanols.

All of the amino alcohols in this series were obtained from the corresponding amino ketone hydrochlorides by catalytic hydrogenation with palladium-on-charcoal in aqueous solution. By careful removal of the solvent from the reduction solutions most of the amino alcohol hydrochlorides were isolated in crystalline form. In certain cases where the hydrochlorides resisted crystallization it was found necessary to precipitate the relatively unstable amino alcohol bases from the reduction solutions with ammonia. These bases, which were filtered if solid or extracted with butanol or ether if gummy, were converted to the acetate salts with glacial acetic acid in alcohol–ether solution. The properties of these amino alcohol salts are shown in Table I.

TABLE I

N-SUBSTITUTED DERIVATIVES OF 1-(3′,4′-DIHYDROXYPHENYL)-2-AMINOETHANOL 3,4-$(HO)_2C_6H_3CHOHCH_2NHR$ AS SALTS

| R | M. p., °C., dec. | Formula | Analyses, % Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|
| $CH_2CH_3$ | 171–172 | $C_{10}H_{16}O_3NCl$ | 5.99 | 5.88 | 15.17 | 15.02 |
| $CH_2CH_2CH_3$ | 159–160 | $C_{13}H_{21}O_5N$[a] | 5.17 | 5.14 | ... | ... |
| $CH(CH_3)_2$ | 170–172 | $C_{11}H_{18}O_3NCl$ | 5.66 | 5.56 | 14.31 | 14.56 |
| $CH_2CH_2CH_2CH_3$ | 143.5–144.5 | $C_{12}H_{20}O_3NCl$ | 5.35 | 5.24 | 13.54 | 13.57 |
| $CH_2CH(CH_3)_2$ | 143.5–144.5 | $C_{12}H_{20}O_3NCl$ | 5.35 | 5.24 | 13.54 | 13.32 |
| $CH(CH_3)CH_2CH_3$ | 167–169 | $C_{14}H_{23}O_5N$[a] | 4.91 | 4.78 | ... | ... |
| $C(CH_3)_3$ | 179–180 | $C_{14}H_{23}O_5N$[a] | 4.91 | 4.93 | ... | ... |
| $CH_2CH_2CH_2CH_2CH_3$ | 123–124 | $C_{13}H_{22}O_3NCl$ | 5.08 | 5.04 | 12.86 | 12.72 |
| $CH(CH_3)CH(CH_3)_2$ | 142–144 | $C_{15}H_{25}O_5N$[a] | 4.68 | 4.36 | ... | ... |
| $CH(CH_2CH_3)_2$ | 141–143 | $C_{15}H_{25}O_5N$[a] | 4.68 | 4.74 | ... | ... |
| Cyclopentyl | 180–181 | $C_{13}H_{20}O_3NCl$ | 5.12 | 5.21 | 12.95 | 13.05 |
| Cyclohexyl | 174–176 | $C_{14}H_{22}O_3NCl$ | 4.87 | 4.98 | 12.32 | 12.22 |

[a] Acetate salt.

The amino ketones were prepared by condensing ω-chloro-3,4-dihydroxyacetophenone with various primary amines and were isolated as the hydrochloride salts. The reactions were usually carried out in ethanol or isopropanol. However it was found that ω-*t*-butylamino-3,4-dihydroxyacetophenone hydrochloride was isolated in higher yield when the condensation was run in dioxane instead of alcohol. The reaction temperatures were generally around 60–80° and the yields of amino ketone hydrochlorides varied between 15 and 55%. Properties of the aminoketone hydrochlorides are listed in Table II.

We are indebted to Dr. A. M. Lands and coworkers in the Pharmacological Research Laboratories for a preliminary report of the pharmacological activity of these compounds. The N-isopropyl, N-*s*-butyl, and N-*t*-butyl analogs of epinephrine are the most active vasodepressor and bronchodilator members of this series. In general the most potent vasodepressor compounds were also the most active bronchodilators. The N-*n*-butyl derivative, however, is a very effective bronchodilator although its depressor activity is only 1/20 that of the N-isopropyl analog.

An extensive pharmacological study of 1-(3′,4′-

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting, New York, N. Y., on September 17, 1947.

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(3) Corrigan, Langermann and Moore, THIS JOURNAL, **67**, 1894 (1945).

(4) Konzett, *Arch. Exptl. Path. Pharmakol.*, **197**, 27 (1940).

TABLE II

N-SUBSTITUTED DERIVATIVES OF ω-AMINO-3,4-DIHYDROXYACETOPHENONE HYDROCHLORIDE, 3,4-$(HO)_2C_6H_3COCH_2NHR \cdot HCl$

| R | M. p., °C., dec. | Formula | Analyses, % Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|
| $CH_2CH_3$ | 240–242 | $C_{10}H_{13}O_3N \cdot HCl$ | | | | |
| $CH_2CH_2CH_3$ | 234–236 | $C_{11}H_{15}O_3N \cdot HCl$ | 5.70 | 5.69 | 14.43 | 14.40 |
| $CH(CH_3)_2$ | 239–242 | $C_{11}H_{15}O_3N \cdot HCl$ | 5.70 | 5.64 | 14.43 | 14.62 |
| $CH_2CH_2CH_2CH_3$ | 206–208 | $C_{12}H_{17}O_3N \cdot HCl$ | 5.39 | 5.11 | 13.65 | 13.15 |
| $CH_2CH(CH_3)_2$ | 214–216 | $C_{12}H_{17}O_3N \cdot HCl$ | 5.39 | 5.26 | 13.65 | 13.66 |
| $CH(CH_3)CH_2CH_3$ | 226–227 | $C_{12}H_{17}O_3N \cdot HCl$ | 5.39 | 5.57 | 13.65 | 13.77 |
| $C(CH_3)_3$ | 233–235 | $C_{12}H_{17}O_3N \cdot HCl$ | 5.39 | 5.19 | 13.65 | 13.49 |
| $CH_2CH_2CH_2CH_2CH_3$ | 201–202 | $C_{13}H_{19}O_3N \cdot HCl$ | 5.12 | 5.26 | 12.95 | 13.02 |
| $CH(CH_3)CH(CH_3)_2$ | 231–233 | $C_{13}H_{19}O_3N \cdot HCl$ | 5.12 | 5.04 | 12.95 | 12.76 |
| $CH(CH_2CH_3)_2$ | 198–201 | $C_{13}H_{19}O_3N \cdot NCl$ | 5.12 | 5.44 | 12.95 | 13.61 |
| Cyclopentyl | 213–214 | $C_{13}H_{17}O_3N \cdot HCl$ | 5.17 | 5.15 | 13.09 | 12.86 |
| Cyclohexyl | 256–258 | $C_{14}H_{19}O_3N \cdot HCl$ | 4.90 | 4.74 | 12.40 | 12.35 |

dihydroxyphenyl)-2-isopropylaminoethanol has shown it to be 1.5 to 2 times more active than epinephrine against histamine-induced asthma in guinea pigs and in addition its LD50 is approximately 450 mg./kg. by intraperitoneal administration in white mice as compared with 4 mg./kg. for epinephrine. This compound is a potent vasodepressor and also possesses marked antispasmodic properties.

## Experimental[5]

Most of the amines in this work were supplied through the courtesy of Commercial Solvents Corporation and Sharples Chemicals, Inc. *t*-Butylamine was prepared by catalytic hydrogenation of 2,2-dimethylethylenimine.[6] Cyclopentylamine, 3-amylamine, and 2-methyl-isobutylamine were obtained from the appropriate ketones by catalytic hydrogenation in ammoniacal alcohol solution.

**ω-Isopropylamino-3,4-dihydroxyacetophenone Hydrochloride** (I).—A mixture of 37.5 g. (0.2 mole) of ω-chloro-3,4-dihydroxyacetophenone, 39 g. (0.66 mole) of isopropylamine, and 125 ml. of isopropanol was heated with stirring to 65–70° at which point the heat was removed to allow the reaction to proceed spontaneously. The amino ketone base which separated after completion of the reaction was converted to the hydrochloride salt by the addition of concentrated hydrochloric acid to the reaction solution. After cooling overnight the amino ketone hydrochloride was filtered, washed with acetone, and dried; m. p. 239–242°, dec., yield 26.5 g. (54%).

(5) All melting points are uncorrected.

(6) Campbell, Sommers and Campbell, THIS JOURNAL, **68**, 140 (1946).

**1-(3′,4′-Dihydroxyphenyl)-2-isopropylaminoethanol Hydrochloride** (III).—Fifteen grams (0.06 mole) of (I) was dissolved in 150 ml. of hot water, 1 g. of 10% palladium-on-Nuchar catalyst added, and the warm solution hydrogenated under 50 pounds pressure. After filtering the catalyst, the water was carefully removed by distillation under reduced pressure. Acetone was distilled from the concentrate to remove residual water. The residue which solidified was recrystallized from alcohol–ether or 90% isopropyl alcohol to give a white crystalline product which melted at 170–172° dec., yield 11.5 g. (78%).

## Summary

1. A number of ω-alkylamino-3,4-dihydroxyacetophenones have been prepared from ω-chloro-3,4-dihydroxyacetophenone and various primary amines in alcohol or dioxane.

2. A series of N-alkyl 1-(3′,4′-dihydroxyphenyl)-2-aminoethanols has been obtained by the catalytic hydrogenation of the corresponding ketones.

3. Most of these amino alcohols possess broncholytic and vasodepressor activity with the isopropyl, *t*-butyl and *s*-butyl derivatives being the most active on both counts. The *n*-butyl compound is one of the most active in the series as a bronchodilator although it is a relatively weak vasodepressor. One of these compounds, 1-(3′,4′-dihydroxyphenyl)-2-isopropylaminoethanol is now in clinical use.

DETROIT, MICH. RECEIVED SEPTEMBER 23, 1948

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Dialkylaminoalkyl Esters of Trisubstituted Acetic Acids

BY A. A. LARSEN, A. WAYNE RUDDY, B. ELPERN AND MILDRED MACMULLIN

In connection with studies directed toward the synthesis of compounds possessing antispasmodic activity a series of dialkylaminoalkyl esters of 2,2-diphenylalkanoic acids, 2,2-diphenyl-4-pentenoic acid and 2-cyclohexyl-2-phenylbutanoic acid was prepared. The 2,2-diphenylalkanoic acids were prepared by the following sequence of reactions.

$C_6H_5CH_2CN \longrightarrow C_6H_5CHBrCN \longrightarrow$
$(C_6H_5)_2CHCN \longrightarrow (C_6H_5)_2CRCN \longrightarrow (C_6H_5)_2CRCO_2H$

Diphenylacetonitrile was obtained in about 80% yield from phenylacetonitrile. Subsequent alkylation with sodamide gave upward of 80% of the tertiary nitriles. Hydrolysis of these nitriles was best accomplished by refluxing with 70% sulfuric acid for about sixty hours.[1] Increased concentrations of sulfuric acid led to the formation of water soluble products, probably sulfonated material. Use of less concentrated acid and shorter periods of heating gave an increased amount of the corresponding amides. Wieland and Dorrer[2] employed 75% sulfuric acid for the hydrolysis of 2,2-diphenylpropanenitrile; however, their period of heating was short and the principal product isolated was the amide. Hydrolysis with alkali and water or alcohols was attended with little success, resulting in low yields of the amides. Hydrolysis of the nitriles in a sealed tube with hydrochloric and sulfuric acids gave the desired product, but was less convenient than the method employed.

2-Cyclohexyl-2-phenylbutanoic acid was readily obtained by alkylation of cyclohexylphenylacetonitrile followed by hydrolysis of the tertiary nitrile to the acid. 2,2-Diphenyl-4-pentenoic acid was prepared from allyl diphenylacetate by rearrangement with sodamide.[3] The unsaturated acid obtained in this manner had the same melting ing point as that reported by Ramart,[4] which was prepared by allylation of benzyl diphenylacetate followed by hydrolysis to the acid.

The various acids were converted to the corresponding acyl chlorides upon treatment with thionyl chloride and then allowed to react with an excess of the appropriate amino alcohol to give the desired esters (Table I).

## Experimental

**Preparation of the 2,2-Diphenylalkanoic Acids.**—The general procedure employed here is suitably illustrated by the preparation of 2,2-diphenylbutanoic acid.

A well-stirred mixture of 193 g. (1 mole) of diphenylacetonitrile[5] and 48 g. (1.2 moles) of sodamide in 600 ml. of dry benzene was refluxed for two hours. The deep red-colored mixture was cooled to 60° and 312 g. (2 moles) of ethyl iodide was added as rapidly as possible. The reaction mixture was then refluxed for several hours. Upon working up there was obtained 196 g. (88%) of 2,2-diphenylbutanenitrile, b. p. 145–147° (0.3 mm.), $n^{25}D$ 1.5660.

A mixture of 111 g. (0.5 mole) of the above nitrile and 686 g. of 70% (d. 1.61) sulfuric acid was heated with stirring at 150° until a test portion remained clear when diluted with water and made alkaline. The reaction mixture was cooled to 100° and poured onto ice and water with vigorous stirring. The solid material was filtered off by means of a large fluted filter paper and washed repeatedly with water to leave a practically colorless product. The crude acid was taken up in 2% sodium hydroxide, filtered and slowly reprecipitated with dilute sulfuric acid. The white 2,2-diphenylbutanoic acid after drying weighed 86 g. (71%) and melted from 170–173°. A small portion when recrystallized from benzene melted at 174–175°.[6]

In a similar manner, 2,2-diphenylpropanenitrile[2] (95% yield, b. p. 127–130° (1.5 mm.), $n^{25}D$ 1.5713), 2,2-diphenylpropanoic acid[2,4] (66% yield, m. p. 173–175°), 2,2-diphenylpentanenitrile[5] (81% yield, b. p. 126–130° (0.2 mm.), $n^{25}D$ 1.5634), and 2,2-diphenylpentanoic acid[7] (56% yield, m. p. 156–157°) were also prepared.

**2-Cyclohexyl-2-phenylbutanoic Acid.**—Cyclohexylphenylacetonitrile[8] was alkylated with ethyl bromide and sodamide in the same manner as that employed for the alkylation of diphenylacetonitrile to give 2-cyclohexyl-2-phenylbutanenitrile (94%), b. p. 120–126° (1 mm.), $n^{25}D$ 1.5264.

*Anal.* Calcd. for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.47; H, 9.44; N, 6.20.

After this nitrile was refluxed with 70% sulfuric acid the reaction mixture was poured onto ice and water, the layers separated and the acid extracted with dilute alkali. Upon acidification the alkali extracts gave the desired acid which when recrystallized from dilute methanol melted at 121–123° (64% based on unrecovered nitrile).

*Anal.* Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; neut. equiv., 246. Found: C, 77.94; H, 9.10; neut. equiv., 246.

When this acid was refluxed for two hours with excess thionyl chloride there was obtained a 90% yield of 2-cyclohexyl-2-phenylbutanoyl chloride, b. p. 119–120° (1 mm.), $n^{25}D$ 1.5418.

*Anal.* Calcd. for $C_{16}H_{21}ClO$: Cl, 13.39. Found: Cl, 13.28.

**2,2-Diphenyl-4-pentenoic Acid.**[4]—A mixture of 10 g. (0.04 mole) of allyl diphenylacetate and 1.5 g. (0.04 mole) of sodamide in 75 ml. of dry benzene was refluxed for thirty hours. After the reaction mixture was diluted with water, extracted with benzene, and the alkaline layer acidified, an oil separated out which soon solidified. The crude acid weighed 7.7 g. and melted from 120–130°. After two recrystallizations from methanol it melted at 142–143°.

*Anal.* Calcd. for $C_{17}H_{16}O_2$: neut. equiv., 252. Found: neut. equiv., 249.

**Preparation of the Basic Esters.**—The same general procedure outlined below was used to prepare all the esters listed in Table I except that the acid chloride from 2-cyclohexyl-2-phenylbutanoic acid was prepared in one lot and distilled before using. Yields of the basic esters varied from 40–70%.

(1) Bockmühl and Ehrhart, U. S. Patent 2,230,774 (Feb. 4, 1941).

(2) Wieland and Dorrer, *Ber.*, **63B**, 407 (1930).

(3) Hauser and Hudson, "The Acetoacetic Ester Condensation," "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 272.

(4) Ramart, *Compt. rend.*, **178**, 396 (1924).

(5) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947).

(6) Klingemann, *Ann.*, **275**, 85 (1893).

(7) Danilov, *J. Russ. Phys.-Chem. Soc.*, **52**, 369 (1920); *C. A.*, **18**, 1484 (1924).

(8) Hancock and Cope, "Organic Syntheses," **25**, 25 (1945).

TABLE I

BASIC ESTER HYDROCHLORIDES $R-C(C_6H_5)(R')-CO_2R''\cdot HCl$

| R | R′ | R″ | M. p., °C.[a] | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $-CH_3$ | $-C_6H_5$ | $-CH_2CH_2N(CH_3)_2$ | 178–180 | $C_{19}H_{24}NO_2\cdot HCl$ | 68.36 | 68.48 | 7.24 | 7.15 | 10.63 | 10.42 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH_2CH_2N(CH_3)_2$[b] | 164–165 | $C_{20}H_{26}NO_2\cdot HCl$ | 69.05 | 69.16 | 7.53 | 7.45 | 10.19 | 10.21 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH_2CH_2N(C_2H_5)_2$ | 124–126 | $C_{22}H_{29}NO_2\cdot HCl$ | 70.29 | 70.43 | 8.05 | 8.09 | 9.43 | 9.46 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH_2CH_2NC_5H_{10}$ | 146–147 | $C_{23}H_{29}NO_2\cdot HCl$ | 71.23 | 71.25 | 7.77 | 7.89 | 9.14 | 8.92 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH_2CH_2CH_2N(C_2H_5)_2$ | 152–153 | $C_{23}H_{31}NO_2\cdot HCl$ | 70.83 | 71.13 | 8.27 | 8.16 | 9.09 | 9.21 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH_2CH_2CH_2NC_5H_{10}$ | 143–144 | $C_{24}H_{31}NO_2\cdot HCl$ | 71.70 | 71.98 | 8.02 | 8.12 | 8.82 | 9.00 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH(CH_3)CH_2N(CH_3)_2$ | 165–166 | $C_{21}H_{27}NO_2\cdot HCl$ | 69.70 | 69.97 | 7.80 | 7.96 | 9.79 | 9.53 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH(CH_3)CH_2N(C_2H_5)_2$ | 117–118 | $C_{23}H_{31}NO_2\cdot HCl$ | 70.83 | 70.81 | 8.27 | 8.16 | 9.09 | 8.96 |
| $-C_2H_5$ | $-C_6H_5$ | $-CH(CH_3)CH_2NC_5H_{10}$[c] | 218–219 | $C_{24}H_{31}NO_2\cdot HCl$ | 71.70 | 71.53 | 8.02 | 8.04 | 8.82 | 8.83 |
| $-C_2H_5$ | $-C_6H_{11}$ | $-CH_2CH_2N(CH_3)_2$ | 170–171 | $C_{20}H_{31}NO_2\cdot HCl$ | 67.87 | 67.65 | 9.11 | 9.00 | 10.02 | 10.09 |
| $-C_2H_5$ | $-C_6H_{11}$ | $-CH_2CH_2N(C_2H_5)_2$ | 185–186 | $C_{22}H_{35}NO_2\cdot HCl$ | 69.17 | 69.27 | 9.50 | 9.67 | 9.28 | 9.23 |
| $-C_2H_5$ | $-C_6H_{11}$ | $-CH_2CH_2NC_5H_{10}$ | 158–159 | $C_{23}H_{35}NO_2\cdot HCl$ | 70.11 | 70.29 | 9.21 | 9.18 | 9.00 | 8.95 |
| $-CH_2CH_2CH_3$ | $-C_6H_5$ | $-CH_2CH_2N(CH_3)_2$ | 176–177 | $C_{21}H_{27}NO_2\cdot HCl$ | 69.70 | 69.85 | 7.80 | 7.64 | 9.79 | 9.73 |
| $-CH_2CH=CH_2$ | $-C_6H_5$ | $-CH_2CH_2N(CH_3)_2$[d] | 147–148 | $C_{21}H_{25}NO_2\cdot HCl$ | 70.08 | 70.05 | 7.28 | 7.64 | 9.85 | 10.02 |

[a] All melting points are corrected. [b] The methiodide melted at 159–160°. *Anal.* Calcd. for $C_{21}H_{28}INO_2$: C, 55.63; H, 6.22; N, 3.09. Found: C, 55.61; H, 6.17; N, 2.90. [c] The methiodide melted at 211–213°. *Anal.* Calcd. for $C_{25}H_{34}INO_2$: C, 59.17; H, 6.75; N, 2.76. Found: C, 59.19; H, 6.75; N, 2.99. [d] *Anal.* Calcd. for $C_{21}H_{25}NO_2\cdot HCl$: bromine uptake, 1 mole. Found: bromine uptake, 0.98 mole.

A solution of 10 g. (0.04 mole) of 2,2-diphenylbutanoic acid in 25 ml. of thionyl chloride was refluxed for three hours. The solution was concentrated and then reconcentrated several times with benzene to remove the excess thionyl chloride. The residue was finally taken up in 40 ml. of dry benzene, decolorized with charcoal and refluxed for ten hours with 7.4 g. (0.08 mole) of dimethylaminoethanol. The reaction mixture was made alkaline with 10% sodium hydroxide, extracted with benzene and the benzene extracts washed well with water and finally concentrated at the water pump. The residue was taken up in dry ether and the hydrochloride of the basic ester precipitated with alcoholic hydrogen chloride. After washing with ether, the hydrochloride was recrystallized twice from ethyl acetate to give 8.3 g. (57%) of product, m. p. 164–165°.


## Summary

A number of basically substituted esters of 2,2-diphenylalkanoic acids, 2,2-diphenyl-4-pentenoic acid and 2-cyclohexyl-2-phenylbutanoic acid have been prepared.

Procedures for the hydrolysis of certain tertiary nitriles to the corresponding acids have been investigated.


RENSSELAER, N. Y. RECEIVED AUGUST 20, 1948

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[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

# A Synthesis of Adenine. The Incorporation of Isotopes of Nitrogen and Carbon[1]

BY LIEBE F. CAVALIERI, JOHN F. TINKER AND AARON BENDICH

The earlier procedure[2] used for the synthesis of adenine labeled with isotopic nitrogen in the 1 and 3 positions[3] suffered from the disadvantage that the yields in certain steps were variable. This procedure as well as others[4,5] has been re-investigated and the synthesis now developed (Fig. 1) provides uniformly reproducible and satisfactory yields. This synthesis has been used for the incorporation of isotopes of carbon and of nitrogen into adenine.

Formamidine hydrochloride was prepared in nearly quantitative yield according to the reactions shown in Fig. 1. It will be noted that the atom per cent. excess of $N^{15}$ in the formamidine hydrochloride is one half of that in the ammonia used, and that the isotope is distributed equally between the two nitrogen atoms. The condensation of formamidine hydrochloride and phenylazomalononitrile, to give I was carried out in *n*-butanol in the presence of sodium butoxide. In our hands, the yield of I was consistently lower when the condensation was carried out in ethanol containing sodium ethoxide.[2]

The previously described catalytic hydrogenation of 4,6-diamino-5-phenylazopyrimidine (I) to 4,5,6-triaminopyrimidine (II)[2] was found to be sensitive to impurities and variable yields were obtained. Upon investigation of other methods it was found that reduction with zinc and water proceeded smoothly with crude I.

A two-step cyclization of 4,5,6-triaminopyrimidine (II) to adenine (IV) was accomplished by

(1) The authors gratefully acknowledge the assistance of the James Foundation of New York, Inc., the National Cancer Institute of the U. S. Public Health Service, the United States Office of Naval Research and the Barker Welfare Foundation.

(2) Baddiley, Lythgoe and Todd, *J. Chem. Soc.*, 387 (1943).

(3) Brown, Roll, Plentl and Cavalieri, *J. Biol. Chem.*, **172**, 469 (1948).

(4) Traube, *Ann.*, **331**, 64 (1904).

(5) Hoffer, "Jubilee of Emil Barell," 428 (1946); *C. A.*, **41**, 4108 (1947).

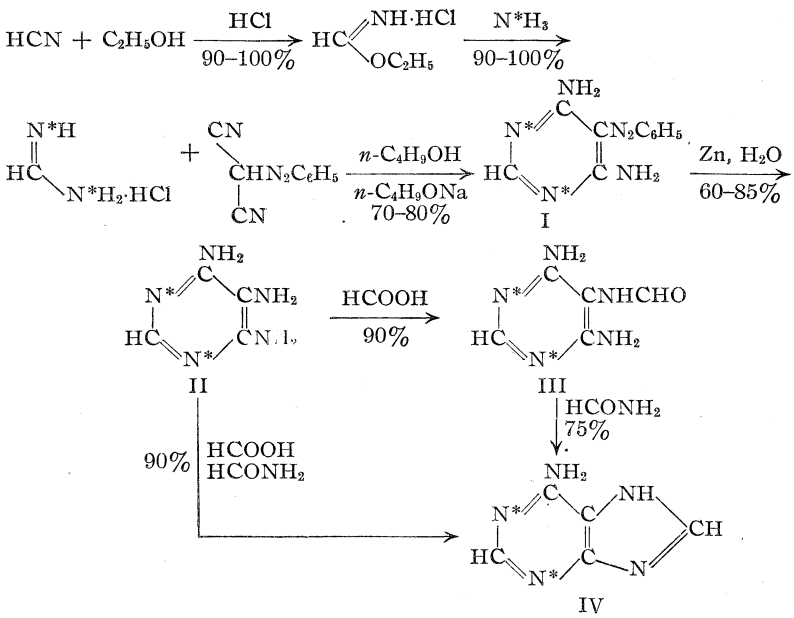



Fig. 1.—N* is $N^{15}$.

Baddiley, Lythgoe and Todd.[2] These investigators prepared the sulfur analog of III, 4,6-diamino-5-thioformylaminopyrimidine, by the reaction of II with potassium dithioformate and this derivative was cyclized to adenine by refluxing with either water or pyridine. In this Laboratory the product which resulted when the cyclization was carried out in water[3] revealed the presence of adenine and of 4,6-diamino-5-formylaminopyrimidine, when investigated by counter-current distribution. Cyclization with pyridine yielded, in addition to adenine, a small amount of 4,6-diamino-5-formylaminopyrimidine and unchanged starting material. The cyclization of 4,5,6-triaminopyrimidine (II) directly to adenine (IV) with formic acid[4] gave, in our hands, maximum yields of 35–40%. The conversion to adenine was most readily accomplished by heating II with a dilute solution of formic acid in anhydrous formamide.[6] Alternatively, the reaction could also be carried out in two steps. 4,6-Diamino-5-formylaminopyrimidine (III) was formed in quantitative yield when II was warmed gently with 98% formic acid. III was then cyclized to adenine in the presence of anhydrous formamide.

In hydrolysis experiments it was noted that when 4,6-diamino-5-formylaminopyrimidine (III) was heated with 1 *N* hydrochloric acid some adenine was produced together with a larger quantity of the hydrolysis product, 4,5,6-triaminopyrimidine. However, in the presence of concentrated hydrochloric acid, III was converted completely to 4,5,6-triaminopyrimidine.

Still another synthetic route which was investigated was based upon the condensation of malononitrile and thiourea to give 2-thio-4,6-diaminopyrimidine which was then nitrosated to 2-thio-4,6-diamino-5-nitrosopyrimidine.[4,6] The treatment of the latter compound with Raney nickel resulted in simultaneous desulfurization and the reduction of the nitroso group to yield 47% of 4,5,6-triaminopyrimidine (II). When 2-thio-4,5,6-triaminopyrimidine, prepared from the nitroso derivative by hydrosulfite reduction,[6] was desulfurized by Raney nickel treatment, a 78% yield of triaminopyrimidine (II) was obtained. The preparation of thiourea from isotopic ammonia is readily carried out but, although this synthesis could be useful for the incorporation of isotopic ammonia, the over-all yields based on malononitrile are less than for the method described in the experimental section.

The incorporation of isotopic carbon into malononitrile and thence into phenylazomalononitrile has also been accomplished (Fig. 2) and the incorporation of either $C^{13}$ or $C^{14}$ into the 4 and 6 carbons of the adenine molecule has been carried out by this synthesis.

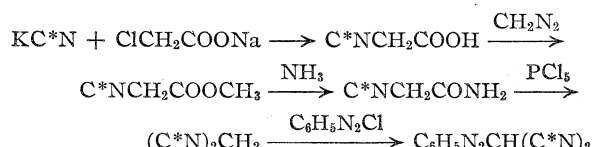



Fig. 2.—C* is $C^{13}$, $C^{14}$.

## Experimental

**Ethyl Formimino Ether Hydrochloride.**—A four-necked flask was equipped with a mercury-sealed stirrer, a sintered glass gas-dispersion tube, a calcium chloride drying tube, and an inlet tube for the introduction of hydrogen cyanide. The flask was surrounded by a bath (alcohol–Dry Ice) kept at −10 to −20°. A mixture of one pound of commercial anhydrous ether and 225 cc. (3.86 moles) of absolute ethyl alcohol was placed in the flask. The stirrer was set in motion and the generation of hydrogen cyanide from 4 moles of sodium cyanide was begun.[7] When approximately 3.5 moles of the hydrogen cyanide was collected, a vigorous stream of anhydrous hydrogen chloride was passed in and continued for ten minutes after the first appearance of turbidity (total time, thirty to forty-five minutes). The mixture was then allowed to warm overnight, without stirring, during which time the bath temperature reached 10°. The bath was cooled to −20° and the solvent was removed through the gas dispersion tube by suction. The residual solid was washed with two one-half pound portions of ether, and the ether removed as before. The white crystalline product (285 g., 90% based on hydrogen cyanide, in an experiment where it was measured accurately) was dried briefly in air and stored in a tightly stoppered bottle. The compound slowly loses weight on exposure to air.

(6) Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3109 (1948).

(7) "Organic Synthesis," Coll. Vol. I, John Wiley & Sons, Inc. New York, N. Y., 1932, p. 307.

*Anal.* Calcd. for $C_3H_7ON \cdot HCl$: Cl, 38.0. Found: Cl, 38.9.

**Formamidine Hydrochloride.**—Ethyl formimino ether hydrochloride (17.0 g., 0.18 mole) and 35 cc. of commercial absolute ethanol were placed in a dry Carius tube equipped with an inlet tube reaching an inch below the surface of the ethanol. The inlet tube was arranged so as to be easily detached. The tube was immersed in a Dry Ice-bath and connected to an ammonia generator. The generator consisted of a flask provided with a condenser and an inlet tube for the introduction of air. A drying tower filled with pellets of potassium hydroxide was placed on top of the condenser. Ammonium nitrate (8.8 g., 0.11 mole containing *ca.* 25 atom per cent. excess $N^{15}$ in the ammonium group) which had been dried over calcium chloride was dissolved in 5–10 cc. of water and decomposed carefully by the addition of 11 cc. of 12 *N* potassium hydroxide. A brisk stream of air was drawn through the apparatus into an acid trap containing 5% aqueous boric acid and methyl violet indicator. Fifteen minutes after the addition of the potassium hydroxide, a water-bath was placed around the generating flask, the rate of air-sweep was decreased somewhat and the bath was warmed gradually to boiling in twenty minutes. After the bath had boiled for fifteen minutes, it was removed and the solution was boiled over a direct flame for fifteen minutes. Little or no ammonia remained in the generator.

The bomb tube, with its inlet tube detached and included, was sealed and heated for two hours at 100°, during which time the tube was shaken occasionally. The tube was cooled, opened and any excess ammonia was collected in the aqueous boric acid trap by drawing a stream of dry air through the inlet tube for thirty minutes while the tube was surrounded by a bath at 55–60°. Usually with this ratio of reactants no excess ammonia was collected. Ammonia which was not recoverable varied from 0 to 8%. The hot ethanolic solution was filtered (the residue is 99% pure ammonium chloride), the alcohol was evaporated by means of a stream of dry air, and the residual formamidine hydrochloride was dried *in vacuo* over phosphorus pentoxide and sulfuric acid.

*Anal.* Calcd. for $CH_4N_2 \cdot HCl$: Cl, 44.1. Found: Cl, 43.8. (The analysis was carried out on material containing no excess $N^{15}$.)

**4,6-Diamino-5-phenylazopyrimidine (I).**—In a one-liter erlenmeyer flask was placed 29 cc. (46.5 g., 0.15 mole) of aniline and 85 cc. (1.02 moles) of concentrated hydrochloric acid. Ice was added to the mixture to maintain a temperature of 0 to 5°. Sodium nitrite (29.0 g., 0.50 mole, assay 97%) in 50 cc. of water was added in small portions, while stirring. After ten minutes, 51 g. (0.63 mole) of anhydrous sodium acetate in 100 cc. of water was added, followed by 33 g. (0.50 mole) of malononitrile[8] in 25 cc. of ethanol. After thirty minutes the phenylazomalononitrile[9] was collected by filtration, washed with cold water and dried in air. The material may be recrystallized from benzene (5 cc. per g.) although the crude material could be used for the following reaction. The yield of recrystallized material was 48–52 g., 55–60%. A three-necked flask was provided with a Hershberg stirrer, a reflux condenser (protected with a drying tube) and two separatory funnels (one on top of the other). Formamidine hydrochloride prepared from 0.11 mole of ammonia was placed in the flask. To this was added 20 g. (0.118 mole) of phenylazomalononitrile in 30 cc. of *n*-butanol (dried by distillation). In the bottom separatory funnel (connected to a drying tube) was placed 2.9 g. (0.13 mole) of sodium. Dry *n*-butanol (100–150 cc.) from the upper funnel was added to the sodium in small portions. The sodium butoxide solution was added to the reaction mixture in several portions, and the mixture refluxed gently for four hours. The mixture was cooled to 5° and the solid collected by filtration. The cake was washed alternately with water and alcohol and dried for a short time at 110°; yield, 15–18 g., 70–80%. This material was used in the next step without further purification, since the compound was difficult to recrystallize. When carefully dried ethanol was used as a solvent for the reaction[2] the yield was frequently as low as 30%.

**4,5,6-Triaminopyrimidine Sulfate (II).**—4,6-Diamino-5-phenylazopyrimidine (4.0 g., 0.0186 mole) was added to a boiling solution of 40 cc. of water and 6 cc. of ethyl cellosolve containing 4 g. of zinc dust. The mixture was boiled for 60–90 seconds while stirring. Sulfuric acid (6 cc. of 18 *N*) was added to the hot solution as rapidly as possible and the mixture decolorized with norite and filtered immediately. A lower yield resulted when the material was left in contact with acid. Upon cooling 2.4–3.4 g. (55–78%) of precipitate was collected. The 4,5,6-triaminopyrimidine sulfate thus obtained was used for the next step. The material could be recrystallized from 2 *N* sulfuric acid (20 cc. per g.) with an 85% recovery.

*Anal.* Calcd. for $C_4H_7N_5 \cdot H_2SO_4 \cdot H_2O$: N, 28.8. Found: N, 28.7.

**4,6-Diamino-5-formylaminopyrimidine.**—4,5,6-Triaminopyrimidine (1.0 g., 0.008 mole) was warmed gently with 2 cc. of 98% formic acid until all the solid had gone into solution. The excess formic acid was removed by evaporation at room temperature and the residue recrystallized from ethanol; yield, 1.15 g., 95%. The distribution constant in *n*-butanol–1 *N* phosphate, *p*H 6.5, for this material was 0.16.[3,10]

*Anal.* Calcd. for $C_5H_6ON_5$: C, 39.09; H, 4.51; N, 45.68. Found: C, 39.21; H, 4.61; N, 45.73.

**4,6-Diamino-5-thioformylaminopyrimidine.**—This compound was prepared according to the procedure of Baddiley, Lythgoe and Todd.[2] The distribution constant was 0.96.[10]

*Anal.* Calcd. for $C_5H_6N_5S$: C, 35.68; H, 3.99; N, 41.49; S, 18.79. Found: C, 35.49; H, 4.17; N, 41.39; S, 18.95.

**Adenine Sulfate (IV).**—(a) 4,5,6-Triaminopyrimidine sulfate (II) (0.78 g.) and 9 cc. of anhydrous formamide containing 0.3 cc. of 98% formic acid was heated in a bomb tube at 160–165° for two and one-half hours. The contents of the tube were chilled and the insoluble portion united with the residue on concentration of the filtrate *in vacuo* at *ca.* 150°. The residues were recrystallized from *ca.* 12 cc. of 2 *N* $H_2SO_4$; yield, 0.62 g. (95%).

(b) 4,5,6-Triaminopyrimidine sulfate (II) (5.0 g., 0.0207 mole) was dissolved in 25 cc. of anhydrous formic acid while warming the mixture gently. The solution was evaporated to dryness by warming gently in a stream of air. The 4,6-diamino-5-formylaminopyrimidine was transferred to a Carius tube and 20 cc. of formamide added. The tube was sealed and heated at 170° for two and one-half hours. The contents of the tube were cooled and the mixture filtered. The filtrate was evaporated to dryness and the two solid residues were recrystallized from 2 *N* sulfuric acid; yield, 3.1–3.5 g. (77–87%). The yield was lowered when the 4,5,6-triaminopyrimidine sulfate was boiled with formic acid or when the heating period in the formamide was greater than two and one-half hours.

*Anal.* Calcd. for $(C_5H_5N_5)_2 \cdot H_2SO_4 \cdot H_2O$: N, 36.3; S, 8.28. Found: N, 36.3; S, 8.50.

Atom per cent. excess $N^{15}$, 4.82. Counter-current distribution revealed that the adenine sulfate was 98–100% homogeneous with respect to ultraviolet absorbing impurities.[10]

**Cyanoacetamide.**[12]—In a 50-cc. flask was placed 590 mg. of sodium cyanide (90%) and approximately 2.7 millicuries of $C^{14}$ in the form of sodium cyanide (147 mg.) containing about 80 mg. of sodium hydroxide. Five cc. of a 3.2 *N* solution of chloroacetic acid (neutralized with sodium carbonate) was added and the mixture was boiled

(8) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 379.

(9) Topham, *J. Chem. Soc.*, 315 (1944).

(10) Tinker and Brown, *J. Biol. Chem.*, **173**, 585 (1948).

(11) Corrected for content of isotopic nitrogen.

(12) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 173.

gently for five minutes. The solution was allowed to cool somewhat and 2 cc. of concentrated hydrochloric acid was added. The mixture was evaporated to dryness *in vacuo* at 60–70°. The solid was extracted twenty times with 5-cc. portions of ether and the ether solution was added gradually to an ethereal solution of diazomethane (prepared from 4.5 g. of nitrosomethylurea). The solution was allowed to evaporate while standing overnight at room temperature. The residual oil was treated with 2 cc. of concentrated ammonia and warmed gently. An additional 2 cc. of ammonia was added and the solution was allowed to remain at room temperature overnight. The reaction mixture was evaporated to dryness *in vacuo* at room temperature and dried over phosphorus pentoxide for forty-eight hours; yield 400 mg., 42% over-all yield, based on the cyanide used.

**Malononitrile.**[8]—The cyanoacetamide was placed in a sublimation apparatus together with 400 mg. of phosphorus pentachloride. The system was evacuated by means of a water pump and the apparatus was immersed in a boiling water-bath. After the reaction had subsided, chloroform (cooled to −5° by means of a chloroform–Dry Ice-bath) was circulated through the cold finger. With the aid of an oil-bath the reaction mixture was heated to 160° and maintained there until the sublimation was complete (ten minutes).

**Phenylazomalononitrile.**—The malononitrile was allowed to melt from the cold finger into a 50-cc. glass-stoppered erlenmeyer and rinsed with a few cc. of methanol. Five cc. of 1 *M* phenyldiazonium acetate solution was added and the flask kept in an ice-bath overnight. The product was collected by filtration, washed with cold water and dried in the air; yield, 200 mg., 20% based on the cyanoacetamide used.

**Adenine Sulfate.**—The phenylazomalononitrile thus prepared was utilized in the preparation of adenine according to the directions described above. The final yield of adenine sulfate was 75[13] mg., which represents an over-all yield of 3.8% based upon the cyanide used. The product possessed an activity of approximately 7000 counts/min./milligram when a film of 1.93 micrograms/cm.$^2$ was prepared by evaporation of an aqueous solution on an aluminum planchet and counted with a thin window (1.9 mg./cm.$^2$) Geiger–Müller counter.

**Acknowledgment.**—The authors wish to acknowledge the advice of Dr. George Bosworth Brown, the coöperation of Dr. Harold Beyer in the isotope determinations, and the assistance of Alice Angelos, Rosco Funk, Jr., and Thelma Kaplan.

## Summary

Various syntheses of adenine have been investigated and a satisfactory procedure for the introduction of isotopes of nitrogen and carbon has been developed.

The preparation from isotopic carbon of cyanoacetamide and malononitrile is described.

(13) Of this amount, 32 mg. was obtained from the filtrate by washout dilution with 450 mg. of non-radioactive adenine.

NEW YORK, N. Y. RECEIVED AUGUST 19, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF ANIMAL AND PLANT PATHOLOGY, THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, PRINCETON, NEW JERSEY, AND THE DEPARTMENT OF PHYSICS,[1] UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA]

# The Hydration, Size and Shape of Tobacco Mosaic Virus[2a,2b]

BY H. K. SCHACHMAN[3] AND MAX A. LAUFFER

## Introduction

On the basis of indirect evidence, several investigators have speculated about the degree of hydration of tobacco mosaic virus,[4a,b,c] but there has been no direct experimental attack on this problem. The ultracentrifuge furnishes a possible means for the direct determination of the density of the virus in solution by a study of the effect of varying solvent density on the change of sedimentation rate.[5a,b] The combination of this solution density with the apparent partial specific volume permits an evaluation of the hydration of the virus.

A certain amount of ambiguity arises in a precise evaluation of the size and shape of any molecule because of the difficulty in determining the relative contributions of hydration and anisometry to the physical chemical properties of the material in question. In the case of tobacco mosaic virus, the application of several physical technics, including ultracentrifugation, X-ray diffraction, viscosity, birefringence of flow and diffusion, has led to the evaluations of size and shape which were largely substantiated by direct observation in the electron microscope.[6] These computations, however, were predicated upon the assumption of little or no hydration of the virus particles, an assumption made because X-ray measurements could be interpreted to mean that the particles did not swell when placed in solution.[7]

In view of the apparent success of the centrifugation method of determining the hydration of viruses, it seemed worthwhile to determine the hydration of tobacco mosaic virus and then to re-examine the other physical chemical properties in the light of this result.

(1) Contribution No. 11p-47 of the Department of Physics, University of Pittsburgh.

(2) (a) Paper delivered before the division of Biological Chemistry at the 111th meeting of the American Chemical Society, April, 1947; (b) aided in part by a grant from the National Foundation for Infantile Paralysis.

(3) Junior Research Fellow of the National Institute of Health; present address: University of California, Berkeley California.

(4) (a) R. Markham, K. M. Smith and D. Lea, *Parasitology*, **34**, 315 (1942); (b) F. C. Bawden and N. W. Pirie, *Proc. Roy. Soc. (London)*, **B123**, 274 (1937); (c) N. W. Pirie, *Advances in Enzymol.*, **5**, 1 (1945).

(5) (a) J. E. Smadel, E. G. Pickels and T. Shedlovsky, *J. Exp. Med.*, **68**, 607 (1938); (b) D. G. Sharp, A. R. Taylor, I. W. McLean, Jr., D. Beard and J. W. Beard, *Science*, **100**, 151 (1944).

(6) M. A. Lauffer, THIS JOURNAL, **66**, 1188 (1944).

(7) J. D. Bernal and I. Fankuchen, *J. Gen. Physiol.*, **25**, 111 (1941).

## Materials and Methods

Tobacco mosaic virus freshly isolated by differential centrifugation, according to the method of Stanley,[8] was examined in the ultracentrifuge at a concentration of 3.0 mg. per cc. in solvents of varying density. Different concentrations of crystalline bovine serum albumin in *p*H 4.7, 0.2 *M* acetate buffer, were used as solvents. Some of the bovine serum albumin was obtained through the courtesy of Dr. Hans Neurath of Duke University Medical School, and some of it was purchased directly from Armour and Company, Chicago, Illinois. Experiments on two other samples of tobacco mosaic virus, isolated in similar fashion, were conducted at *p*H 7.0 in 0.01 *M* phosphate buffer containing sucrose in varying concentrations. One of these samples, A, was also examined in several concentrations of bovine serum albumin at *p*H 7.0 in 0.01 *M* phosphate buffer. The studies were carried out in an air driven ultracentrifuge of the Bauer–Pickels type, equipped with the Svensson optical system. Specific gravities of the solutions were obtained by the use of a 2-cc. pyknometer, and viscosities were determined in an Ostwald type viscometer.

## Experimental Results

Figure 1 shows the relation of sedimentation rate to the density of the suspending medium for the studies on tobacco mosaic virus suspended in serum albumin solutions of various concentrations.

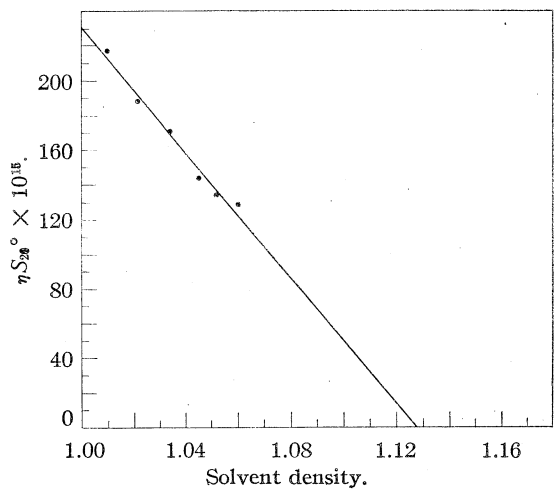



Fig. 1.—Sedimentation constants corrected for solution viscosity of tobacco mosaic virus in serum albumin solutions plotted as a function of solution density. The *p*H was maintained at 4.7 by means of 0.2 *M* acetate buffer. Straight line was fitted by method of least squares.

In Fig. 2 are plotted the results for tobacco mosaic virus in a medium containing sucrose at different concentrations. The ordinate in these graphs is the sedimentation constant corrected for the viscosity to correspond to a value in a solvent with the viscosity of water at 20°. The abscissa is the density of the suspending medium at 20°.

The rate at which particles suspended in a strictly homogeneous medium sediment in a centrifugal field should be directly proportional to the difference between the densities of the particles and of the medium. If the medium causes no alteration in size, shape and density of the particles,

(8) W. M. Stanley, THIS JOURNAL, **64**, 1804 (1942).

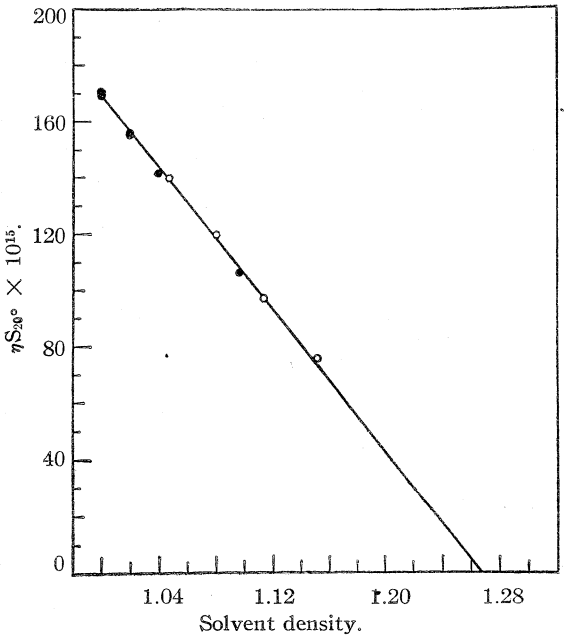



Fig. 2.—Sedimentation constants corrected for solution viscosity of tobacco mosaic virus in sucrose solutions plotted as a function of solution density. The *p*H was maintained at 7.0 with 0.01 *M* phosphate buffer. Straight line was fitted by method of least squares.

then the decrease in sedimentation constant, $S$, multiplied by viscosity, $\eta$, is directly proportional to the increase in density of the solution, $\rho_s$. In general, it can be shown that eqn. 1

$$\eta S = \frac{M(\rho - \rho_s)}{6\pi N \left(\frac{3VM}{4\pi N}\right)^{1/3} \left(\frac{f}{f_0}\right) \rho} \qquad (1)$$

where $M$ is the anhydrous molecular weight of the sedimenting particles, $V$ is the partial specific volume of the material, $\rho$ is the density of the particles, $N$ is the Avogadro number, and $(f/f_0)$ is the friction ratio, which is a function of the anisometry and hydration of the particles, describes the relationship. Equation 1 can be used to evaluate the hydrated molecular weight, if $V$ and $\rho$ are the specific volume and density of the hydrated particles. In this case the friction ratio is only a function of anisometry. If the sedimenting particles are unaltered by the medium, a plot of $\eta S$ *vs.* $\rho_s$ according to eqn. 1 should yield a straight line. The slope of the line is a function of size, shape and the density of the particles, and the intercept at $\eta S = 0$ is dependent only on the density of the particles.

That the curve in Fig. 1 shows this linear dependence of $\eta S$ on $\rho_s$ suggests that the medium has little or no effect on the size, shape, and density of the particles. It cannot be said with complete certainty, however, that the physical characteristics of the virus were not altered by the serum albumin. A complex precipitates at *p*H values between about 4 and 5 when the ionic strength is

considerably lower than in the present experiments. Also the virus is precipitated by serum albumin at *p*H values above 5 when the ionic strength is about 0.1.[9]

Similarly, the linearity of the curve in figure 2 suggests that the medium has not altered the virus. Smadel, Pickels and Shedlovsky[4] obtained a non-linear dependence of sedimentation rate on the density of the medium when they studied the sedimentation of the elementary bodies of vaccinia in sucrose solutions. They suggested as one explanation of their results that the sucrose solutions caused an osmotic withdrawal of water from the particles with a consequent increase in particle density. Studies[10,11] on the influenza viruses showed similar behavior. It was this concept of osmotic influence of the medium on the virus particles that prompted Sharp, *et al.*,[5] to use serum albumin rather than sucrose as a means of obtaining solvents of different densities. Because of the higher molecular weight of serum albumin as compared to sucrose, it was expected that such an osmotic withdrawal of water, if real, would be considerably reduced. The resultant straight lines in plots of $\eta S$ *vs.* $\rho_s$ for the sedimentation of the influenza viruses in serum albumin solutions[5,11] lend support to the suggestion of Smadel, Pickels and Shedlovsky.

Extrapolation of the curve in Fig. 1 yields a value of $\rho_s = 1.13$ g./cc. for the density of solution in which virus particles do not sediment. If no alteration of the virus has occurred, the density of the virus in aqueous solution can be considered as equal to 1.13 g./cc. Similarly, extrapolation of the results presented in Fig. 2 indicates that the density of the virus in aqueous solution is about 1.27 g./cc. Preparation A, which also appeared to have a density of 1.27 g./cc. in solutions containing sucrose, was studied in serum albumin solutions of low ionic strength at *p*H 7.0, and a value about 1.1 was obtained by extrapolation. This result is in reasonable agreement with that obtained at *p*H 4.7 and presented in Fig. 1.

For the case of non-linear dependence of corrected sedimentation constant on density, Smadel, Pickels and Shedlovsky suggested the construction of a tangent to the curve at the point corresponding to the density of dilute buffer. The value of $\rho_s$ at which this tangent intercepts the abscissa can then be taken as the density of the virus particles in a solvent devoid of sucrose.[12] Sharp, *et al.*, demonstrated a discrepancy between the two methods for influenza virus and concluded that the lower value obtained in serum albumin was more reliable.

The data of Fig. 1 show a value of about 230 $S$[14] for the sedimentation constant of tobacco mosaic virus in the absence of serum albumin. In a previous study[6] a value of 185$S$ was found for the sedimentation constant of tobacco mosaic virus in the unaggregated state, and it was shown that boundaries corresponding to higher sedimentation constants could be attributed to dimers and trimers. The high value obtained for the tobacco mosaic virus indicates that the virus particles are in a polymerized state. Inasmuch as the aggregation is predominantly end-to-end, the hydrodynamic density of the polymerized virus probably would not differ from that of the virus in the monomeric state. The data of Fig. 2 indicate that the virus studied at *p*H 7.0 is unaggregated.

If no contraction occurs on the combination of a strictly homogeneous medium and the dry virus, the degree of hydration can be calculated from the partial specific volume of the virus and the density obtained from the sedimentation experiments. Inherent in these calculations is the assumption that the bound water is not unlike the body of water acting as solvent. If a volume, $v$, of anhydrous virus with density $\rho$ becomes associated with a volume $\Delta v$ of water with density $\rho_w$ to form a hydrated particle of density $\rho_s$, the total volume of the hydrated virus particle will be $(v + \Delta v)$ and its mass will be $(v\rho + \Delta v\rho_w)$. The data of sedimentation rate in serum albumin solutions lead to a hydration value of about 1.9 ml. of water per ml. of dry virus or 66% by volume on a wet basis. Similar calculations for the sedimentation in sucrose solutions lead to the value of about 0.37 ml. of water per ml. of dry virus or 27% water by volume on a wet basis.

## Discussion

**The Hydration of Tobacco Mosaic Virus.**—The vastly different hydrodynamic densities obtained in the sucrose and in the serum albumin solutions indicate a marked difference in the apparent hydration of tobacco mosaic virus in the two media. The following considerations, which were proposed in a private communication by Kauzmann,[15] show that this difference can possibly be attributed to a region in the medium surrounding a virus particle which, for purely geo-

(9) M. A. Lauffer, *Arch. Biochem.*, **13**, 145 (1947); *J. Biol. Chem.*, **174**, 481 (1948).

(10) M. A. Lauffer and W. M. Stanley, *J. Exp. Med.*, **80**, 531 (1944).

(11) D. G. Sharp, A. R. Taylor, I. W. McLean, Jr., D. Beard and J. W. Beard, *J. Biol. Chem.*, **159**, 29 (1945).

(12) In the studies in serum albumin solutions a correction was made for the sedimentation of the serum albumin. This correction was made according to the suggestion of Sharp, Taylor and Beard[13] by subtracting the sedimentation constant of serum albumin from the measured sedimentation constant of the virus before multiplying by the viscosity. This correction seems reasonable at high concentrations of serum albumin where the virus is sedimenting very slowly, but such a correction does not seem valid when the virus is sedimenting in a very dilute serum albumin solution. If the correction were not made, the points at high serum albumin concentrations would no longer fall on a straight line, and a tangent to the curve at the density of the buffer would be necessary. In that case, a result not significantly different from the 1.13 g./cc. obtained in Fig. 1 would still be obtained.

(13) D. G. Sharp, A. R. Taylor and J. W. Beard, *J. Biol. Chem.*, **163**, 289 (1946).

(14) The symbol $S$ represents the Svedberg unit defined as $10^{-13}$ cm. per sec. per cg. unit of centrifugal field.

(15) The authors wish to acknowledge their indebtedness to Dr. W. Kauzmann of Princeton University and to express their appreciation to him for his contributions to this problem.

metrical reasons, cannot be penetrated by serum albumin or sucrose molecules. In other words, the assumption that sucrose and serum albumin solutions are homogeneous media may not be appropriate for the present purpose. In that event, computation based upon the assumption of a homogeneous medium would not be valid.

If serum albumin molecules are considered to be rigid, uncharged spheres of radius $a$, it is clear that the center of a serum albumin molecule will not be able to come closer than a distance $a$ from the surface of a virus particle suspended in a serum albumin solution. This will lead to a region of thickness $2a$ in which the density changes gradually from that of water to that of the serum albumin solution. It can be shown by a statistical procedure that this is equivalent to having each virus particle surrounded by a layer of thickness $a$ of liquid with the density of the medium exclusive of serum albumin. In the case of a virus particle suspended in a sucrose solution, a similar but much thinner equivalent layer of sucrose-free fluid will surround the virus particle. As will be seen in the subsequent more quantitative treatment, this equivalent layer of fluid affects the force operating on a virus particle in a centrifugal field.

If $v$ is defined as the volume of a virus particle, $\Delta v$ as the volume of a shell of thickness $a$ corresponding to the equivalent layer of albumin-free medium as described above, $a$ as the radius of a serum albumin molecule, $\rho$ as the average density of the virus particle including any water of hydration really part of the virus particle, $\rho_s$ as the density of the serum albumin solution, $\rho_w$ as the density of the medium exclusive of serum albumin, $W$ as the mass of a volume $V$ of serum albumin solution, and $W'$ as the mass of the same volume of solution containing a single virus particle, the following considerations apply. The effective force acting on the virus particle in the centrifuge should be proportional to $(W' - W)$, and, when this difference vanishes, the particle should not sediment. For purposes of these considerations, the excess mass of a serum albumin molecule over that of an equal volume of water can be considered to be concentrated at a point in the center of the molecule. Thus, the shell of volume, $\Delta v$, which can contain no centers of serum albumin molecules, must have density $\rho_w$. On the other hand, the density of the solution outside $\Delta v$ is $\rho_s$. Therefore

$$W = V\rho_s \qquad W' = v\rho + \Delta v\rho_w + (V - v - \Delta v)\rho_s$$

The particle will not sediment when $W' - W$ is equal to zero, that is, when the effective weight of the virus particle is $W' - W$ or $v\rho + \Delta v\rho_w - (v + \Delta v)\rho_s$. This equation is identical with that used for the calculation of the hydration per unit volume of dry virus. The apparent hydration in this case, however, is entirely a property of the medium in which the virus is suspended.

Physical studies carried out on serum albumin[16] indicate that the molecule is not spherical but is a rod about 150 Å. long and 38 Å. in diameter.[16] This can be approximated by a cylinder capped by hemispheres, with a diameter, $2a$, of 38 Å. and a total length, $2b$, of 150 Å. Obviously, a virus particle will be surrounded by a layer of medium of thickness, $a$, in which no serum albumin molecule centers can exist and by an additional layer of thickness, $(b - a)$, in which centers of only serum albumin particles oriented in certain ways can be found. It can be shown by a statistical procedure that this amounts to the equivalent of a layer of medium with a thickness of $^1/_2\ (a + b)$ from which serum albumin is excluded entirely. These calculations apply only in those cases in which the radius of curvature of the virus particle is substantially greater than the thickness of the surrounding serum albumin-free medium. Calculations carried out by the method of Schultz[17] show that the thickness of this layer surrounding a cylinder with the diameter of a tobacco mosaic virus particle should still be approximately $^1/_2(a + b)$. Thus, a tobacco mosaic virus particle should be surrounded by the equivalent of a zone of albumin-free medium 47 Å. thick.

Similar effects should also be expected to occur in sucrose solutions. The sucrose molecule is equivalent in size to a sphere of about 4 Å. in radius, but undoubtedly the molecule is somewhat asymmetric, so that perhaps the effective radius is 5 or 6 Å. Thus, in a sucrose solution a tobacco mosaic virus particle should be surrounded by the equivalent of a layer of sucrose-free medium 5 or 6 Å. in thickness because of the inability of sucrose particles to get any closer to the surface.

The apparent water associated with the virus particle in serum albumin solution and in sucrose solution is, of course, a property dependent primarily upon the medium in which the virus finds itself and is not an intrinsic property of the virus particle itself. If there is any intrinsic water of hydration, regardless of the means by which that water is attached to the virus particle, it must be the total water indicated by the sedimentation experiments in sucrose or in serum albumin solution minus that which is to be attributed to the inability of the sucrose or the serum albumin particle centers to approach the virus surface. The apparent hydration of tobacco mosaic virus in serum albumin solution is the equivalent of a layer of water 53 Å. thick surrounding a rod-like particle with an anhydrous diameter of 152 Å. Since a layer approximately 47 Å. thick must be attributed to the inability of the serum albumin molecule centers to touch the surface of a tobacco mosaic virus particle, this leaves only about a 6 Å. shell attributable to the intrinsic hydration of the tobacco mosaic virus particle. Similarly, the results obtained when tobacco mosaic virus was sedimented in a sucrose solution indicate that the virus particle has an apparent hydration equiva-

(16) E. J. Cohn, J. L. Oncley, L. E. Strong and S. Armstrong, Jr., *J. Clin. Invest.*, **23**, 417 (1944).

(17) G. V. Schultz, *Z. Naturforsch.*, **2**, 348 (1947).

lent to a shell 13 Å. thick surrounding the virus rod. However, when the 6 Å. figure corresponding to the probably effective radius of a sucrose molecule is subtracted, a value of only 7 Å. remains as an estimate of the thickness of the layer corresponding to the intrinsic hydration of a tobacco mosaic virus particle. It is apparent that the same order of magnitude is obtained for the intrinsic hydration from the two series of experiments when interpreted in this manner. Thus, the best estimate of the intrinsic hydration of tobacco mosaic virus is about 15% by volume on a wet basis.

X-Ray diffraction measurements have been of value in determining the ultimate virus particle size and the role of associated water. The investigation of tobacco mosaic virus by X-ray scattering has followed two paths. One, the intramolecular structure resulting from large angle scattering and corresponding to small spacings, demonstrated that certain intraparticle spacings were not altered by a change in concentration of the virus from a dry gel to moderately concentrated solutions. Because of the constancy of the internal spacings over a broad concentration region, Bernal and Fankuchen[7] suggested that the particles do not swell appreciably when placed in aqueous solution.

The second problem attacked by Bernal and Fankuchen was a study of the intermolecular pattern as exhibited by small angle scattering. They found that the distance between the particles is inversely proportional to the square root of the concentration by volume. This requires that the particles separate appreciably only in a lateral direction. Despite the large separation distances involved, of the order of 500 Å., there was a regular lattice arrangement in the form of an hexagonal pattern. Thus, the virus particles can exist in solutions and in gels in a regular pattern where the particles are separated by water layers several times the diameter of the particles. The degree of association of the water cannot be determined from X-ray measurements. Centrifuge studies in serum albumin solutions and in sucrose solutions, when interpreted in the manner described above, indicate that the hydrodynamic unit contains an intrinsic hydration equivalent to a shell of water 6 or 7 Å. thick. If one accepts the interpretation of Bernal and Fankuchen of the meaning of the wide angle scattering, most of this water would actually be found in a shell surrounding the virus particle. It is not difficult to conceive of a water layer of such thickness being held to the outside of a virus particle.

**Hydrodynamic Complications.**—The existence of this shell of diluted albumin solution about the sedimenting virus particles causes complications in connection with the viscosity correction to the sedimentation constant. Evidently the virus moves in an environment of somewhat lower viscosity than that of the bulk solution. Therefore it is not correct to multiply the observed sedimentation constant by the over-all relative viscosity of the solution in order to obtain the equivalent sedimentation constant in water. The difference between the over-all viscosity and this effective viscosity is probably considerable, especially in concentrated albumin solutions, but it does not seem to be easy to compute.[18] This consideration contributes an element of uncertainty to the extrapolated value of the solution density corresponding to zero sedimentation rate, and thus casts some doubt upon the reliability of the extent of hydration indicated above.

Finally, the question might be raised whether such a layer of low density will be able to maintain itself as the virus particle moves in the centrifuge. Thus it might seem reasonable to expect that the virus particle would act as a plow in moving through the albumin solution, with albumin molecules piling up in front of the virus and being swept clear at the back. In the centrifuge, a tobacco mosaic virus particle moves at the rate of about $^1/_5 \times 10^{-3}$ cm./sec. Serum albumin has a diffusion constant of about $6 \times 10^{-7}$ sq. cm./sec. This corresponds to a root mean squared displacement of serum albumin molecules, due to kinetic energy, of $\sqrt{12 \times 10^{-7}}$ or $1.1 \times 10^{-3}$ cm. in one second. Thus, in the usual experiment, most of the serum albumin molecules should have time to move out of the path and into the wake of an advancing virus particle.

**The Size and Shape of Tobacco Mosaic Virus.**—The study of macromolecules has invoked such a varied number of physical tools that it has become possible to validate partially certain of them by their combined use on one substance. Tobacco mosaic virus, because of its characteristic shape and large size, serves as an excellent model for study. It was shown that the predictions of the size and shape of the virus particles from viscosity, sedimentation and diffusion data were in substantial agreement with the results obtained from electron microscopy and X-ray diffraction.[6] The generally accepted value, 15.2 mμ, for the diameter of the rod-like particle resulted from small angle scattering of X-rays. Studies in the electron microscope on purified and unpurified tobacco mosaic virus lend support to the concept of a rod-like particle 280 mμ in length by 15.2 mμ in diameter. On the basis of a partial specific volume of 0.73 cc./g., the molecular weight of the anhydrous particle is $41.9 \times 10^6$.

Detailed accounts of the available methods for determining molecular size and shape have been presented elsewhere,[6,19,20] but these are complicated, as mentioned above, by the difficulty in evaluating the relative contributions of hydration and anisometry to the friction ratio. If the value 0.15 ml. of water per ml. of wet virus is used in

(18) J. M. Burgers, *Proc. Acad. Sci., Amsterdam*, **45**, 10 (1942).
(19) M. A. Lauffer and W. M. Stanley, *Chem. Revs.*, **24**, 303 (1939).
(20) J. L. Oncley, *Ann. N. Y. Acad. Sci.*, **41**, 121 (1941).

conjunction with the intrinsic viscosity,[21] ($\eta$), 39 ml./ml.,[6] an axial ratio of 18.3 results for the hydrated particle. This value of the axial ratio can be used in the Perrin equation to yield a friction ratio due to asymmetry of 1.92. Allowing for the fact that a hydrated particle has a frictional resistance greater than that of an anhydrated particle produces a value, 2.01, for the over-all friction ratio. Combination of this ($f/f_0$) value with the sedimentation constant, 185 *S*, leads to $34 \times 10^6$ for the anhydrous molecular weight. This corresponds to a rod about 270 by 14 m$\mu$.[22]

Diffusion and sedimentation data can also be used to predict the size of the anhydrous particles. The calculation of molecular weight by this method is independent of hydration and the value, $31 \times 10^6$, previously reported still obtains. This corresponds to a rod-like particle 250 by 14 m$\mu$ for the case in which 15% by volume of water on a wet basis are associated with the virus.

The size and shape of the particle can be calculated, also, by a combination of viscosity and diffusion data. Results obtained in this manner correspond to a rod-shaped particle 250 by 13 m$\mu$ and a molecular weight of $27 \times 10^6$ when 15% of volume hydration is assumed.

(21) Intrinsic viscosity is defined as the ratio, as the volume fraction approaches zero, of specific viscosity to volume fraction.

(22) This calculation was made on the assumption that hydration increases the thickness but not the length of a virus particle.


## Summary

The hydrodynamic density of tobacco mosaic virus was determined by centrifugation in bovine serum albumin and sucrose solutions of various densities. In both sets of experiments, straight lines could be used to express the dependence of sedimentation rate upon density of the medium. A hydrodynamic density of 1.13 was obtained for the experiments carried out in serum albumin solutions, and a value of 1.27 was obtained for experiments carried out in sucrose solutions. It was shown that this great discrepancy can be attributed to the effect upon the buoyancy of a virus particle produced by a disturbance of the homogeneous distribution of solute molecules in the immediate neighborhood of a virus particle. This effect depends upon the radius of the solute molecule and is therefore greater for serum albumin than for sucrose. When this effect is taken into account, the data can be interpreted to indicate that tobacco mosaic virus has an intrinsic hydration of approximately 15% by volume on a wet basis. The size and shape of the virus particle were calculated by several methods on the basis of this new hydrated model. Excellent agreement was obtained when the calculations from viscosity and sedimentation data were compared with direct measurements obtained by electron microscopy and X-ray diffraction. Calculations involving the diffusion constant gave less satisfactory agreement.


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[CONTRIBUTION FROM DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

# The Separation of the Antibodies, Isoagglutinins, Prothrombin, Plasminogen and $\beta_1$-Lipoprotein into Subfractions of Human Plasma[1a,b]

BY J. L. ONCLEY, M. MELIN, D. A. RICHERT,[1c] J. W. CAMERON[1d] AND P. M. GROSS, JR.[1e]

The separation of the protein and lipoprotein components of human plasma into a series of fractions by the use of a five-variable system, as well as the principles involved in this fractionation, have been described in a previous paper.[2] The procedure developed depends upon the use of organic precipitants (ethanol in this case), low temperatures (0 to $-8°$), low ionic strengths of electrolytes (below 0.16 mole per liter), and accurate control of the *p*H and protein concentration. In this work the albumins were concentrated in Fraction V, fibrinogen in Fraction I, most of the $\alpha$-globulins in Fraction IV-1 and IV-4. Fraction II + III contained isoagglutinins, prothrombin, plasminogen, certain lipoproteins with properties ascribed to the X-protein of plasma, as well as antibodies.[3]

The aim of this study was to devise methods

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(1b) This paper is Number 73 in the series "Studies on the Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross, and Number XIX in the series "Preparation and Properties of Serum and Plasma Proteins" from the same laboratory.

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(2) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, THIS JOURNAL, **68**, 459 (1946).

(3) The importance of these methods for the concentration of antibodies was pointed out in an earlier paper of this series: E. J. Cohn, J. A. Luetscher, Jr., J. L. Oncley, S. H. Armstrong, Jr., and B. D. Davis, *ibid.*, **62**, 3396 (1940).

for large scale subfractionation of as many constituents of Fraction II + III as possible into useful and stable concentrates which could then be made available for more extensive chemical and clinical work.

## I. Isolation of Lipoproteins

Approximately three-quarters of the lipoproteins of plasma were concentrated in Fraction II + III. Measurements at low ionic strengths (0.005 to 0.02) indicated that both the carotenoid-bearing[4] and cholesterol-bearing proteins in this fraction had a minimum solubility at about *p*H 5.9. Isolated lipoprotein fractions, however, were usually isoionic near *p*H 5.5 (Table I).[5] The lipoprotein of Fraction II + III has the peculiar property of sedimenting in the ultracentrifuge with a rate that was very sensitive to the density of the solution. This behavior is characteristic of the so-called "X-protein" of plasma, first described by McFarlane,[6] and later by Pedersen.[7,8]

Processing of Fraction II + III, as of whole plasma, was made difficult by the presence of this lipoprotein. The total fraction could not be dried, or even frozen and thawed, without some denaturation.[10] Ammonium sulfate fractionation had yielded precipitates which either centrifuged poorly[7] or rose to the surface.[11] Separation of the lipoproteins from Fraction II + III thus became of the utmost importance.

This lipoprotein fraction, bearing the carotenoid pigment, cholesterol and most other lipids found in Fraction II + III, was extracted almost quantitatively from the residue of plasminogen, prothrombin, isoagglutinins and γ-globulins at 0.07 mole fraction (20%)[12] ethanol if the *p*H were about 7.6 and the ionic strength about 0.005. This ionic strength was readily achieved by resuspending Fraction II + III in a volume of this solvent equal to or twice that of the plasma from which it was obtained. The resulting precipitate (Fraction II + IIIW) contained considerable cholesterol if the extraction was carried out below *p*H 7, but almost none if at *p*H 7.6 or above, and could then be frozen and dried with little or no denaturation of the protein. The lipoprotein fraction separated was designated Fraction III-0. The advantages of this procedure, which yielded both a lipoprotein concentrate soluble in aqueous solutions and a lipid-poor precipitate, were so great that it became the first step in our subfractionation of Fraction II + III (globulin methods 8 and 9).

The extracted lipoproteins were precipitated at 0.09 mole fraction ethanol, *p*H 5.6 to 5.9. Because of its very low density, quantitative separation of lipoprotein from the suspension was somewhat difficult,[13] but was more complete in the presence of traces of calcium ion. The resulting lipoprotein precipitate contained a large percentage of β-globulin, and 60 to 70% of the fraction behaved as X-protein in the ultracentrifuge. Analyses revealed about 35% total lipid, about half of which was cholesterol and cholesterol esters. Materials with the properties usually ascribed to "plasmin inhibitor" and "antithrombin" were found in this fraction.[14]

Fraction III-0, like Fraction II + III, could not be dried from the frozen state without denaturation. Most of the lipoprotein was, however, precipitated as euglobulin by resuspension in a large volume of water at an ionic strength below 0.002 and at a *p*H between 5.4 and 5.9. The remaining protein (Fraction II + IIIW) could then be precipitated with ethanol, dried from the frozen state, and reconstituted to give a satisfactory solution.

## II. Isolation of γ-Globulin Antibodies

Many antibody molecules fall into the γ-globulin class when studied by electrophoresis.[15] Proteins of this group have the most alkaline isoelectric points and the smallest electrical charges at neutral *p*H values of any of the major components of plasma. The γ-pseudoglobulins from horse serum[16] have an isoelectric point near *p*H 6.4. Human γ-globulin of this isoelectric point appears to be largely euglobulin,

(4) We are indebted to J. W. Mehl of the Department of Biochemistry, University of Southern California School of Medicine, for these observations, which were carried out at the Harvard Plasma Fractionation Laboratory during the summer of 1944.

(5) Euglobulins isoelectric in this range were reported early by W. B. Hardy (*J. Physiol.*, **33**, 251 (1905)), J. Mellanby (*ibid.*, **33**, 338 (1905)), H. Chick, (*Biochem. J.*, **8**, 261 (1914)), and E. J. Cohn (*J. Gen. Physiol.*, **4**, 697 (1922)), and more recently by A. A. Green (THIS JOURNAL, **60**, 1108 (1938)). The β-globulins as a whole were reported by A. Tiselius (*Biochem. J.*, **31**, 313, 1464 (1937)); (*Trans. Faraday Soc.*, **33**, 524 (1937)) to be isoelectric near *p*H 5.1.

(6) A. S. McFarlane, *Biochem. J.*, **29**, 407, 660, 1175, 1202, 1209 (1935).

(7) K. O. Pedersen, "Ultracentrifugal Studies on Serum and Serum Fractions," Almqvist and Wiksells, Boktryckeri AB, Upsala, Sweden, 1945; *J. Phys. and Colloid Chem.*, **51**, 156 (1947).

(8) Solutions containing 86% of X-protein in the ultracentrifuge have been obtained in some of the euglobulin lipoprotein fractions, which were found by electrophoresis to consist largely of $\beta_1$-globulin. Further purification in the air-driven preparative ultracentrifuge has given fractions still having the sechmentation behavior of X-protein and containing as much as 97% $\beta_1$-globulin.[9]

(9) J. L. Oncley, G. Scatchard and A. Brown, *J. Phys. Colloid Chem.*, **51**, 184 (1947).

(10) L. Pillemer, during the time he was working at the Harvard Plasma Fractionation Laboratory, showed that high concentrations of certain agents, especially sucrose, seemed to render such products soluble to a considerable extent.

(11) G. S. Adair and M. E. Adair, *J. Physiol.*, **102**, 17P (1943).

(12) Ethanol concentrations are expressed as mole fraction, and as per cent. by volume at 25°; see Table I, reference 2.

(13) Some additional protein could be precipitated by lowering the *p*H to 4.8 and slightly increasing the ethanol concentration. More albumin and α-globulin and considerably less lipid were found in this fraction.

(14) Measurements of antithrombin activity have been made by J. T. Edsall and S. G. Miller, who also have found appreciable amounts of antithrombin in Fraction IV-1.

(15) See K. Landsteiner, "The Specificity of Serological Reactions," revised edition, Harvard University Press, Cambridge, Massachusetts, 1945, Chapter IV.

(16) E. J. Cohn, T. L. McMeekin, J. L. Oncley, J. M. Newell and W. L. Hughes, Jr., THIS JOURNAL, **62**, 3386 (1940).

human γ-pseudoglobulin being isoelectric near *p*H 7.4 (Table I).

TABLE I

ISOIONIC POINTS OF VARIOUS PROTEIN FRACTIONS[a]

| Fraction | *p*H of solution of Euglobulin | *p*H of solution of Pseudoglobulin |
|---|---|---|
| | β-Globulin | |
| III-0-1,2,3:181 | 5.5 | 4.8 |
| III-0-1,2:S362-3,4 | 5.5 | 5.4 |
| III-0-1:183–184 | 5.2 | 4.6 |
| III-0-3:183–184 | 5.6 | 5.7 |
| III-0-4:S362-3,4 | 5.6 | 5.5 |
| III-0-5:S362-3,4 | 5.7 | 5.5 |
| III-0-5:AVL7 | 5.6 | 5.4 |
| | γ-Globulin | |
| II-1:L371 | 6.4 | 7.3 |
| II-1:LY3 | 6.5 | 7.2 |
| II-2:L371 | 6.5 | 7.6 |
| II-2:122 | 6.5 | 7.4 |
| II-1,2:160A | 6.3 | 7.1 |
| II-1,2:171 | 6.8 | 7.6 |
| II-3:SW1 | 6.4 | 7.4 |
| II-3:42-W3F | 6.2 | 7.0 |

[a] Determined by measuring the *p*H of the pseudoglobulin and euglobulin solutions after exhaustive dialysis, and hence representing the isoionic points of these proteins, rather than the isoelectric points. *Cf.* E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides as Ions and Dipolar Ions," Reinhold Publishing Corporation, New York, N. Y., 1943, p. 446.

Solubility studies have indicated that although γ-globulin was readily precipitated by 0.09 mole fraction (25%) ethanol at neutral reaction, its solubility at *p*H 5 was considerably higher than that of albumin.[17] Sodium acetate was found to dissolve considerably more γ-globulin than sodium chloride of equal ionic strength, and both electrolytes decreased solubility with increasing ionic strength; results similar to those described for the influence of neutral salts on casein and edestin at reactions acid to their isoelectric points.[18] Great dependence of solubility upon the amount of saturating body in the system, as was earlier described for serum globulin[19,20,21] has also been observed and assumed to demonstrate the molecular heterogeneity of the γ-globulin precipitate.

The lipid-poor, readily dried, antibody-rich Fraction II + IIIW has formed an ideal starting material for the separation of γ-globulin (Fraction II) from other components (Fraction III). The γ-globulins have been extracted from these components at *p*H values of 5.8 and lower, usually 5.2. This was desirable because the γ-globulins are more soluble under these conditions than at reactions nearer neutrality, and the other components less, since they have isoelectric points in this *p*H range (5.9 to 4.8).

At any given *p*H an ethanol concentration was chosen which would permit solution of at least 3 g. of γ-globulin per liter, and in which only traces of contaminating substances were soluble.[22] Because of possible instability of various antibody molecules at acid *p*H, most efforts at isolation were carried out above *p*H 5. Reactions acid to *p*H 4.7 led to appreciably increased solubility of β-globulin, unless the ethanol concentration was greater than mole fraction 0.059 (17%). A *p*H value of about 5.2, 0.015 ionic strength, and an ethanol concentration of 0.059 mole fraction (17%) gave a very satisfactory solubility differential between the γ-globulin and the other components. A *p*H of 5.4, 0.005 ionic strength in 0.024 mole fraction ethanol (7.5%) was also satisfactory for this separation. A total Fraction II was precipitated from the supernatant by increasing the ethanol to 0.09 mole fraction and the *p*H to 7.2.

Attempts were made to separate the γ-globulins in Fraction II into subfractions. Addition of 0.05 mole/l. of sodium chloride to the γ-globulin solution at *p*H 5.2, mole fraction ethanol 0.059 (17%), and ionic strength of 0.015,[23] led to the separation of a fraction designated Fraction II-3. After Fraction II-3 had been removed, the solution was adjusted to *p*H 7.2, holding the ethanol and ionic strength constant. The precipitate formed under these conditions was called Fraction II-1. The γ-globulin remaining in solution precipitated at 0.09 mole fraction (25%) ethanol, and was called Fraction II-2.

Some physical–chemical,[9] chemical[25] and immunological[26] properties of these γ-globulin fractions have already been recorded. Clinical studies have indicated the usefulness of Fractions II-1 and II-2 in prophylaxis against measles and

(17) We are indebted to Mrs. M. H. Blanchard of this Laboratory for these studies.

(18) T. B. Osborne, THIS JOURNAL, **24**, 39 (1902); T. B. Osborn and I. F. Harris, *Am. J. Physiol.*, **14**, 151 (1905) (or *ibid.*, **13**, 436 (1905)); K. Linderstrøm-Lang and S. Kodama, *Compt. rend. trav. lab. Carlsberg*, **16**, No. 1 (1925).

(19) W. B. Hardy, *J. Physiol.*, **33**, 251 (1905).

(20) J. Mellanby, *ibid.*, **33**, 338 (1905).

(21) S. P. L. Sörensen, *Compt. rend. trav. lab. Carlsberg*, **15**, No. 11 (1923); THIS JOURNAL, **47**, 457 (1925); "Proteins," The Fleischmann Laboratories, 1925, p. 1.

(22) The γ-globulin fractions obtained by these methods have often been found to contain substances which cause a blood pressure lowering effect upon the blood pressure of certain test animals, especially cats. A number of experiments suggested that the temperature coefficient of solubility of the depressor causing substance was of a larger magnitude than that of the γ-globulin, and made it desirable to use as low a temperature as possible for the separation. L. H. Woodruff, C. A. Janeway and W. Berenberg made the earlier assays of depressor activity. More recently O. Krayer and his associates in the Department of Pharmacology, Harvard Medical School, have investigated these effects. Some studies have also been made by E. Shorr and B. W. Zweifach of the New York Hospital.

(23) The precipitation of γ-globulin under these conditions was predicted from solubility studies,[17] and by work simultaneously carried out at the University of Wisconsin.[24] Fraction II-3 was not extracted from Fraction II + III by the earlier methods, which had been carried out in the presence of the lipoprotein now concentrated in Fraction III-0 and at higher ionic strengths.

(24) H. F. Deutsch, L. J. Gosting, R. A. Alberty and J. W. Williams, *J. Biol. Chem.*, **164**, 109 (1946).

(25) J. W. Williams, M. L. Petermann, G. C. Colovos, M. B. Goodloe, J. L. Oncley and S. H. Armstrong, Jr., *J. Clin. Invest.*, **23**, 433 (1944).

(26) J. F. Enders, *ibid.*, **23**, 510 (1944).

epidemic jaundice.[27] Fraction II-3 has been shown effective in measles prophylaxis,[28] but studies in prophylaxis against epidemic jaundice have not yet been completed. Although differences among these γ-globulin fractions were observed in the above-mentioned studies, further fractionation of purified γ-globulin must be undertaken to explore more fully the possibility of separating the γ-globulin antibodies from one another.

## III. Separation of Isoagglutinins, Prothrombin and Plasminogen

Solubility studies of anti-A, anti-B and anti-Rh isoagglutinins indicated a minimum solubility near 6.3, and a strong solvent action of neutral salts in water or in ethanol–water mixtures at that *p*H, and at reactions acid to the isoelectric point[29,30] Under most conditions employed, the solubility of the fractions containing the isoagglutinins was considerably lower than that of other γ-globulins. Quantitative measurements indicate, however, that less than 1% of even the most highly purified fractions were agglutinating antibody.[31]

Highly purified human prothrombin has thus far not been prepared. However, as Mellanby's important observations suggested, it appears to be a euglobulin with a minimum solubility near *p*H 4.8, dissolved by most electrolytes in aqueous solutions when the ionic strength was 0.08 mole per liter or greater.[32,33] Most investigators have reported inactivation of prothrombin at reactions acid to *p*H 4.8 and alkaline to *p*H 10. If it is assumed that human prothrombin has the same activity as the bovine prothrombin highly purified by Seegers and reported to be 1500 u./mg,[33] then fractions with activities of less than 30 u./mg., routinely prepared in the course of this work, contained less than 2% prothrombin.[34] Although there was no need to purify this component further, when it is prepared to yield human thrombin for clinical purposes[35] the fractions containing prothrombin which have been obtained must be considered only as starting material for further chemical investigations.

Plasma, or a fraction of plasma, has been rendered proteolytic by the use of certain reagents[36]; the activated enzyme termed plasmin (fibrinolysin), and the inactive enzyme (or precursor), plasminogen.[37] Under most conditions investigated, plasminogen precipitated with prothrombin. The observation that plasminogen was adsorbed by fibrin made possible its separation from prothrombin.

The separation of the isoagglutinins from prothrombin and plasminogen was made possible by utilizing the different isoelectric points of these materials. At *p*H 5.4 there were large differences in solubility, and the solubilities of the two components to be separated can be adjusted to suitable values by the variation of the ionic strength of an aqueous solution. Since it has been observed that prothrombin was considerably less soluble in sodium acetate buffers[38] than in sodium chloride solution with *p*H adjusted to the same value, and since a specific effect of the acetate ion upon the solubility of the isoagglutinins was not noted, it was found advantageous to use acetate buffers for this step. This separation was effected by completely dissolving Fraction III in a small volume of acetate buffer of about 0.2 ionic strength, and then precipitating the prothrombin and plasminogen (Fraction III-2,3) together with most of the remaining fibrinogen and a part of the other proteins present by diluting this solution

(27) C. W. Ordman, C. G. Jennings, Jr., and C. A. Janeway, *J. Clin. Invest.*, **23**, 541 (1944); C. A. Janeway, *Bull. N. Y. Acad. Med.*, **21**, 202 (1945); *J. Am. Med. Assoc.*, **126**, 674 (1944); M. Greenberg, S. Frant and D. D. Rutstein, *ibid.*, **126**, 944 (1944); J. Stokes, Jr., and J. R. Neefe, *ibid.*, **127**, 144 (1945).

(28) C. A. Janeway, personal communication.

(29) The presence of anti-A and anti-B isoagglutinins in Fraction II + III was noted by W. C. Boyd, and reported in some detail by J. F. Enders, *J. Clin. Invest.*, **23**, 510 (1944), (*cf.* table on p. 515, compiled by W. C. Boyd), and by L. Pillemer, J. L. Oncley, M. Melin, J. Elliott and M. C. Hutchinson, *J. Clin. Invest.*, **23**, 550 (1944).

(30) Studies of the anti-Rh isoagglutinins have been carried out in collaboration with L. K. Diamond, Department of Pediatrics, Children's Hospital, Boston, Mass.

(31) E. A. Kabat, private communication. See also E. A. Kabat and A. E. Bezer, *J. Exptl. Med.*, **82**, 207 (1945).

(32) For a discussion of the earlier literature see J. T. Edsall, R. M. Ferry and S. H. Armstrong, Jr., *J. Clin. Invest.*, **23**, 557 (1944).

(33) A recent survey of the properties of prothrombin has been made by W. H. Seegers, E. C. Loomis and J. M. Vandenbelt, *Proc. Soc. Exptl. Biol. and Med.*, **56**, 70 (1944); and *Arch. Biochem.*, **6**, 85 (1945).

(34) The assay of thrombin and prothrombin was briefly described by Edsall, Ferry and Armstrong.[32] More recently, it has been defined in terms of a standard thrombin reference preparation, whose activity is fixed by definition. This new thrombin unit is identical within the limits of experimental error with the thrombin unit described by Seegers,[33] and has been officially adopted by the National Institute of Health (defined in detail in Minimum Requirements for Dried Thrombin, National Institute of Health, August 28, 1945). See the reports on the determination of prothrombin in "Blood Clotting and Allied Problems," Josiah Macy, Jr., Foundation New York, 1948.

(35) E. A. Bering, Jr., *J. Clin. Invest.*, **23**, 586 (1944); O. T. Bailey and F. D. Ingraham, *ibid.*, **23**, 591 (1944); F. D. Ingraham and O. T. Bailey, *J. Neurosurg.*, **1**, 23 (1944); F. D. Ingraham, O. T. Bailey and F. E. Nulsen, *ibid.*, **1**, 171 (1944); O. T. Bailey, F. D. Ingraham, O. Swenson, J. J. Lowrey and E. A. Bering, Jr., *Surgery*, **18**, 347 (1945).

(36) In Fraction III-3, the separation of which is described below, D. A. Richert found a slow spontaneous activation of plasminogen to plasmin, even in sterile solution, without the addition of chloroform, streptokinase, or any other activator. The final concentration of plasmin obtained in this way was about one-third of the maximum obtainable on complete activation with streptokinase. Chloroform treatment of Fraction III-3 did not give any increase in the rate or in the final amount of activation, as compared with the control sample without added activator. This is perhaps explainable by the fact that the lipids present in Fraction II + III were previously separated in Fraction III-O. The function of the chloroform in whole plasma or crude plasma fractions may well be due to its extraction of fat soluble inhibitors which normally prevent the spontaneous conversion of plasminogen to plasmin. For further discussion of the proteolytic enzyme system of plasma, see J. T. Edsall, "Advances in Protein Chemistry," **3**, 449–51 (1947).

(37) In order to describe the protease system the revised terminology suggested by L. R. Christensen and C. M. MacLeod, *J. Gen. Physiol.*, **28**, 559 (1945), has been followed.

(38) These observations were made by L. Pillemer, D. J. Mulford, J. T. Edsall, S. G. Miller and D. A. Richert.

with water to an ionic strength of about 0.08.[39]

The recovery of isoagglutinin in the supernatant solution from Fraction III-2,3 was accomplished by raising the *p*H to 6.3 (minimum solubility of the isoagglutinins), and adding a small amount of ethanol. The recovery of the isoagglutinins was quite satisfactory, and the precipitate so obtained (Fraction III-1) was dried from the frozen state without deterioration.

Prothrombin and plasminogen were separated by dissolving Fraction III-2,3 in about 0.1 ionic strength sodium chloride and sufficient buffer to bring the *p*H to about 6.9. Under proper conditions a fibrin clot[40] formed and was removed by centrifugation. This clot lysed in a few hours at room temperature, or after standing overnight in the cold room, and contained a large part of the plasminogen.[41]

The supernatant solution from the clot contained most of the prothrombin, which could be reprecipitated by lowering the *p*H and adding a small amount of ethanol, or could be dried from the frozen state. Prothrombin was not stable indefinitely, but could be readily converted to thrombin by suitable agents.[32,42]

## IV. Procedures for the Subfractionation of Fraction II + III[43]

Studies of the subfractionation of Fraction II + III involving isoelectric precipitation at various ionic strengths, but without the use of ethanol, yielded fairly active prothrombin fractions, but failed to yield concentrated antibody-containing fractions which were free of lipid. Various methods involving precipitation with ethanol, with careful control of the *p*H, ionic strength and temperature, were then introduced. Only the last methods have led to the separation of all protein components in conditions approximating the native state. For this reason it has not seemed desirable to describe in detail earlier attempts at complete fractionation. Since they may be useful for specific purposes, however, they have been briefly outlined.[44] Although developed for the fractionation of normal human plasma, they have also been applied with some success to certain types of convalescent human plasma and to the plasma of certain animals. Modifications of these methods may lead to more satisfactory separations of the comparable proteins of different species, because of their somewhat different concentrations and solubilities.

**Method 1** for preparing the total Fraction II + III for immunological studies was introduced in 1942. The precipitated Fraction II + III, removed and stored at a temperature of −5°, contained approximately 35% protein by weight, 0.062 mole fraction (18%) ethanol, and 0.06 ionic strength of salts (largely sodium chloride with some citrate and bicarbonate). This material was suspended in about an equal volume of 0.1 *M* sodium chloride solution previously chilled to 0°, and dialyzed against 0.1 *M* sodium chloride at 0° for two or three days with frequent changes of dialysate to remove the ethanol present in the precipitated material. During dialysis a clot of fibrin usually formed and was removed by filtration and centrifugation. The precipitate was then washed with cold 0.5 *M* sodium chloride solution, recentrifuged, and the supernatant solution was added to the dialyzed material. The resulting protein solution, containing only traces of ethanol, was adjusted to 0.15 *M* sodium chloride, approximately 15% of protein by dry weight. It could be sterilized by filtration through Seitz type filter pads. Thrombin was largely removed during clotting, and prothrombin was removed by the filtration.

**Method 2** made available γ-globulin and thrombin. Fraction II + III was suspended in cold sodium chloride solution, allowed to clot, and clarified. Prothrombin (Fraction III-2) was removed by adjusting to *p*H 4.7–5.3 and an ionic strength of about 0.08. The remaining α- and β-globulin (Fraction III-1) was removed at 0° by adjusting the *p*H to 5.7, the ionic strength to 0.015 or 0.03 and the ethanol concentration to about 0.051 mole fraction (15%). The volume used was about twice that of the original plasma. The γ-globulin (Fraction II) was then precipitated by increasing the ethanol concentration to mole fraction 0.091 (25%), which precipitated Fraction II-2. By then adjusting the *p*H to 7.0, Fraction II-1 was precipitated.

**Method 3** involved suspension of Fraction II + III paste, clotting of fibrinogen, and removal of thrombin by methods similar to those used in Method 2. Fraction III-1 was then removed at more acid *p*H (5.2 to 4.5), lower volume (approximately equal to the volume of original plasma), and ethanol concentrations from 0.04 to 0.07 mole fraction (12 to 20%) (Table II). The total γ-globulin was usually precipitated in one fraction, but in some cases Fractions II-1 and II-2 were removed separately.

**Method 4** involved suspension of Fraction II + III in a volume of water twice that of the original plasma at *p*H 5.9, 0.005 ionic strength, 0°. The resulting euglobulin precipitate represented about half the total protein, and contained considerable γ-globulin. The supernatant solution, precipitated by bringing the ethanol concentration to 0.1 mole fraction (30%), contained large amounts of γ-globulin and lipoprotein.

**Method 5** was developed to make isoagglutinins available in good yield. Suspension, clotting of fibrinogen, and removal of prothrombin were accomplished as in Methods 2 and 3, except that Fraction III-2 was precipitated at a slightly lower ionic strength (0.06). Fraction III-1, containing β-globulin, lipoprotein and isoagglutinin, was precipitated in a volume 1.8 times that of the plasma represented, at *p*H 6.3, 0.015 ionic strength, 0.026 mole fraction (8%) ethanol, 0°. The ethanol was removed by suspending the precipitate in about 20 volumes of water at 0°, *p*H 6.3, and ionic strength less than 0.001. The resulting lipoprotein-rich precipitate could not be dried without denaturation, but the paste could be suspended in 0.15 *M* sodium chloride and adjusted to *p*H 7.2. The γ-globulin was precipitated as in Method 3.

(39) These conditions are very nearly those used in the original Mellanby procedure.[20] A similar procedure, using somewhat lower ionic strengths, was used in the isolation of the C'1 component of complement from guinea pig serum, L. Pillemer, E. E. Ecker, J. L. Oncley and E. J. Cohn, *J. Expll. Med.*, **74**, 297 (1941).

(40) If sufficient thrombin had been formed by converting agents in the plasma, spontaneous clotting occurred. If insufficient thrombin were present, a small amount was added at this point.

(41) The products of the lysis of the fibrin clot have been studied by W. H. Seegers, M. L. Nieft and J. M. Vandenbelt, *Arch. Biochem.*, **7**, 15 (1945), who found two main components called α- and β-fibrin. The α-fibrin, *pI* = 5.5, has an electrophoretic behavior similar to fibrinogen; the β-fibrin, *pI* = 4.2, is somewhat more like α-globulin or albumin.

(42) See L. E. Strong, Encyclopedia of Chemical Technology, Vol. II, p. 571–572. The Interscience Encyclopedia, Inc., New York, N. Y., 1948.

(43) The materials and method used for these subfractionations are completely described in ref. 2.

(44) Detailed procedures for carrying out most of these methods have been published in the Bulletin of the Blood Substitutes Committee, Committee on Medical Research, Office of Scientific Research and Development. They will be made available upon request.

TABLE II

CONDITIONS FOR THE SEPARATION OF FRACTION III-1 FROM γ-GLOBULIN

| Method | pH | Ionic strength, moles/l. | Ethanol concn. Mole fraction | Ethanol concn. Vol. %(25°) | Temperature, °C. | Volume compared to plasma |
|---|---|---|---|---|---|---|
| 2 | 5.7 | 0.015–0.03 | 0.051 | 15 | 0 | 2.0 |
| 3A | 5.1 | .040 | .048 | 14 | −3 | 1.0 |
| 3B[a] | 5.2 | .059 | .040 | 12 | −3 | 1.0 |
| 3C | 5.2 | .036 | .051 | 15 | −5 | 0.9 |
| 3D | 5.2 | .036 | .059 | 17 | −3 | .9 |
| 3E | 5.2 | .036 | .059 | 17 | −5 | .9 |
| 3F | 5.2 | .036 | .059 | 17 | −6 | .9 |
| 3G | 4.8 | .036 | .070 | 20 | −7 | .9 |
| 3H[a] | 4.5 | .036 | .070 | 20 | −7 | .9 |
| 5 | 6.3 | .015 | .026 | 8 | 0 | 1.8 |
| 8 | 5.4 | .005 | .024 | 7.5 | −2 | 0.7 |
| 9 | 5.2 | .015 | .059 | 17 | −6 | 0.7 |

[a] The γ-globulin fraction obtained from these conditions was found to contain considerable β-globulin as impurity.

**Method 6** was used to obtain a satisfactory isoagglutinin fraction when other fractions were not desired. Fraction II + III was suspended and taken to *p*H 6.3, 0.01 ionic strength, 0.024 mole fraction (7.5%) ethanol, 0°, and a volume about 0.6 times that of the original plasma. Isoagglutinins were precipitated along with lipoprotein. The resuspended precipitate was adjusted to *p*H 7.2 in water at 0°, 0.005 ionic strength, and a volume 0.7 times that of plasma. Much of the lipoprotein and γ-globulin were soluble under these conditions, but the isoagglutinins remained in the precipitate. This precipitate was dissolved in 0.1 *M* sodium chloride, and thrombin was added to remove fibrinogen as a fibrin clot.

**Method 7** recovered only the isoagglutinin fraction. Fraction II + III was suspended at 0° or 25° in a volume of water eight times that of the plasma, *p*H 6.3, and an ionic strength of 0.005. The water was saturated with toluene. The isoagglutinin fraction settled in about twenty-four hours. Resuspension under the same conditions was sometimes desirable. Fibrinogen and most of the γ-globulin and lipoprotein were removed by this procedure.

**Method 8** was similar to method 9, except that Fraction III was removed at *p*H 5.4, 0.005 ionic strength, 0.024 mole fraction (7.5%) ethanol, −2°, and a volume 0.7 times the volume of plasma represented.

**Method 9** evolved from the combination of method 8 with the modification of method 3 to a lower ionic strength developed at the University of Wisconsin[24] for the separation of Fraction III from γ-globulin. This method is given in detail in the remainder of this section.

**Precipitate II + III** from standard preparations of normal serum albumin (human) is used as the starting material for this preparation.[45] Each kilogram of this precipitate is suspended in 2 kg. of water containing ice (about one-quarter of the water should be frozen, in the form of very fine ice crystals). When the suspension is fairly uniform, add 3 kg. of water (cooled to 0°) to which 112 cc. of 0.5 *M* disodium phosphate (*p*H 9.2) has been added.[46] The suspension should be stirred slowly and kept at a temperature of 0° until all lumps are dissolved and a nearly complete solution is obtained. After the suspension is complete, add it to 20 kg. of water (cooled to 0°), and stir slowly at 0° for thirty to sixty minutes. The *p*H of this suspension[47] should be 7.6 ± 0.2. Then bring to 20% ethanol by adding 15 liters of 53.3% ethanol keeping the temperature as low as possible until −5° is reached. This suspension should stand at −5° with a slow stirring for several hours before centrifuging. Centrifuge at a rate of about 30 liters per hour.

**Precipitate III-O** is precipitated from the supernatant from precipitate II + IIIW by bringing the *p*H to about 5.7, with *p*H 4 calcium acetate buffer,[48] and the ethanol concentration to 25%. This suspension should be allowed to stand for about forty-eight hours at −5° before centrifugation, and then centrifuged at a rate of about 20 liters per hour. The supernatant solution still contains appreciable protein, a large part of which is precipitated by adjusting the *p*H to 4.8, and the ethanol concentration to 35%.

**Precipitate II + IIIW** is resuspended in acetate buffer[49] and taken to *p*H 5.2, 0.015 ionic strength and 17% ethanol. This can be done by suspending each kilogram of precipitate II + IIIW in 2 kilograms of water and ice, as before, and then adding 2 kg. of cold water to which 0.35 mole of sodium acetate has been added. When this suspension is complete, add sufficient *p*H 4 acetate buffer,[51] diluted with one liter of cold water per kilogram of precipitate II + IIIW, to lower the *p*H of the suspension to 5.0 ± 0.1 and stir for several hours. Then add 13.5 liters of cold water and then 8.66 liters of 53.3% ethanol per kilogram of precipitate II + IIIW, raising the ethanol concentration to 17%. The temperature should be lowered during the addition of the ethanol, keeping the suspension near the freezing point until it is cooled to −6°. The precipitate is re-

(45) This method can also be applied to precipitate II + III or I + II + III from special lots of plasma or serum, such as convalescent serum or plasma, or to various similar fractions obtained by these methods. Occasionally, where materials have been stored in the frozen or dry state, the original suspension will yield a considerable quantity of insoluble material consisting of denatured protein and lipid. In these cases, material can be centrifuged and clarified with filtration through Seitz-type pads in a solution of 1 or 2 per cent. protein and 0.15 *M* sodium chloride at *p*H about 7. The clarified solution can then be taken to −5°, *p*H 6.8, 25% ethanol, ionic strength 0.1 just as plasma would be treated (but omitting the removal of Fraction I), and the precipitate corresponding to the usual Fraction II + III can then be used in this preparation.

(46) A sodium glycinate buffer solution was also used for this *p*H adjustment. See ref. 53.

(47) Because of the low ionic strength of this suspension, the *p*H value obtained depends considerably upon the method of reading in the glass electrode. We have used the value obtained by dilution of the suspension just before the alcohol addition with an equal volume of 0.02 *M* sodium chloride solution. Dilution with an equal volume of 0.15 *M* sodium chloride solution will give a *p*H nearer 7.2

(48) The *p*H 4 calcium acetate buffer is that used in the fractionation of plasma except that the sodium acetate is replaced by calcium acetate. It consists of 4.0 *M* acetic acid and 0.4 *M* calcium acetate, and is diluted before use.

(49) When we are dealing with plasma collected so that it contains a high titer of the various anti-Rh isoagglutinins[50] it is often advantageous to process the Fraction II + IIIW by a modification of Method 7. The procedure which has been used follows:

Precipitate II + IIIW is resuspended in water and taken to *p*H 6.3, 0.005 ionic strength, using acetate buffer. This can be done by suspending each kilogram of precipitate II + IIIW in two liters of cold water and ice. When this suspension is complete, pour it with good stirring into 90 liters of 0.005 ionic strength *p*H 6.3 acetate buffer per liter of starting II + IIIW paste. This resulting suspension may be held at either 0° or 25°. It is usually carried out at 0°, but where there is a large amount of fibrinogen present in the precipitate II + IIIW the 25° extraction procedure is advantageous. When the extraction is carried out at room temperature, the buffer is saturated with toluene as a bacteriostatic agent (approximately 0.5 cc. per liter). The dilute suspension is then stirred for about an hour, and then allowed to settle overnight. The precipitate is suspended in a small amount of *p*H 6.3 buffer of 0.005 ionic strength (sodium acetate), frozen and dried in vacuum.

This method can also be applied to precipitate III as obtained from method 9 for the subfractionation of Fraction II + III.

The use of this material as a reagent for blood typing has been discussed in an earlier paper.[50]

(50) J. L. Oncley, M. Melin, J. W. Cameron, D. A. Richert and L. K. Diamond, *Ann. N. Y. Acad. Sci.*, **47**, 899 (1946).

(51) The *p*H 4.0 sodium acetate buffer is that used in the fractionation of plasma.[3] It consists of 4.0 *M* acetic acid and 0.8 *M* sodium acetate.

moved by centrifugation at a rate of about 30 liters per hour and at a temperature of −6.0 ± 0.5°. The effluent from this centrifugation should then be clarified by filtration[52] at a temperature of −6.0 ± 0.5°.

Each kilogram of precipitate III is suspended in 2 kg. of water and ice, and then diluted with 2 kg. of 0.5 ionic strength *p*H 5.4 acetate buffer cooled to 0°. The suspension is stirred until uniform, and then diluted with 7.5 kg. of 0° water. This suspension should be at *p*H 5.4, ionic strength 0.08, and 0 to +1°, and should be stirred for several hours. The precipitate is removed by centrifugation at a relatively slow rate of speed and at 0 to +1°.

**Precipitate III-2,3** should be suspended as soon as possible in 1 liter of 0° water per kilogram of precipitate and the *p*H adjusted to 6.8 to 7.0 with sodium glycinate buffer.[53] Then add 1 liter of 0° water containing enough sodium chloride to give a total ionic strength of 0.1. After one to two hours of stirring, test the solution for preformed thrombin and remove a sample to see if the fibrinogen has clotted. To do this, centrifuge a small sample and then add thrombin to the supernatant solution to see whether more fibrin is formed. If all the fibrinogen has clotted, do not add additional thrombin. If there is fibrinogen still left in solution, then add enough thrombin to give a total amount (including that already present) of 10,000 units per kilogram of Fraction III-2,3. Stir this suspension for an additional hour and centrifuge at 0° for about an hour, or at a very slow rate if continuous centrifugation is required. The supernatant containing Fraction III-2 can either be dried directly if prothrombin is desired, or immediately converted to thrombin before drying. To accomplish the conversion of prothrombin to thrombin, calcium chloride and thromboplastin are added, according to the directions given elsewhere,[42] and the temperature is raised to 20–25°. This solution is then clarified, sterilized and dried.

**Precipitate III-3** should be suspended[54] in sodium chloride and bicarbonate solution to give an ionic strength of 0.15 and a *p*H of 7.1 ± 0.1, and allowed to stand at 0° until all of the fibrin has been lysed. After clarification and sterilization, this material can be dried from the frozen state.

Each kilogram of the supernatant from precipitate III-2 is adjusted to *p*H 6.3 by the addition of sodium bicarbonate (approximately 20 cc. of 1 *M* sodium bicarbonate should be required), and then the ethanol is adjusted to 15% by the addition of an equal volume of 30% ethanol, keeping the temperature at or near the freezing point until lowered to −5°, where it should be maintained. The precipitate can then be removed by centrifugation at −5°, and at a speed of about 80 liters per hour.

**Precipitate III-1** can be dried from the frozen state, and reconstituted to about 5% protein in isotonic saline at *p*H 7 for a blood grouping solution if the pool were group specific and of sufficiently high titer.[50,55]

Each kilogram of filtrate from precipitate III is taken to about 0.06 ionic strength by the addition of 50 millimoles of sodium chloride, holding the *p*H at 5.2, the ethanol concentration at 17%, and the temperature at −6°.

**Precipitate II-3** can be removed by centrifugation of the above suspension at a rate of about 50 liters per hour and at a temperature of −5°. It may be dried from the frozen state[56] preferably without the addition of sodium chloride or glycine.

Each kilogram of filtrate from precipitate II-3 is taken to *p*H 7.4 ± 0.2 by addition of about 15 millimoles of sodium bicarbonate, and to 20–25% ethanol by the addition of 40–114 cc. of 95% ethanol. The temperature is maintained at −5°.

**Precipitate II-1,2**[57] can be removed by centrifugation of the above suspension at a rate of about 50 liters per hour, and at a temperature of −5°. It may be dried from the frozen state preferably without the addition of sodium chloride or glycine.

**Precipitate II.**—A total Fraction II, rather than the Fractions II-1,2 and II-3, can be prepared from the filtered effluent from precipitate III by increasing the *p*H to 7.4 ± 0.2 with sodium bicarbonate solution, and the ethanol concentration to 25% with 95% ethanol. The temperature should be maintained at −5°. The precipitate may be removed by centrifugation at the same rate as recommended for Fractions II-1,2 and II-3.

## V. Distribution of Proteins in the II + III Subfractions

Analyses of the various steps in the fractionation procedure have been carried out by the same methods already reported in a previous study of this series (2). The results obtained during the fractionation of a large lot of Fraction II + III prepared by method 6 for the fractionation of citrated plasma (2) are recorded in Table III. Nitrogen determinations and volume measurements were made on all suspensions and supernatant solutions obtained during subfractionation, and of all resuspended precipitates. Values for the protein in the precipitates are calculated from the analyses of the resuspended precipitates, and the protein lost in centrifugation or filtration, and the protein remaining in the supernatant solutions at the end of the process were calculated from the analyses of the suspensions or supernatant solutions. These results are tabulated as the percentage of total protein nitrogen in the fraction referred to the protein nitrogen in the Fraction II + III used for subfractionation. To convert these values to the amount of protein by nitrogen (N × 6.25) which would have been obtained from a liter of plasma, we have used the value of 15.1 g. of Fraction II + III per liter of plasma previously reported.[58] The nitrogen factors estimated from nitrogen and dry weight determinations of each resuspended precipitate are also recorded in Table IV. Using these nitrogen factors, instead of 6.25 as used in Table III, we obtain the values recorded in the last column of Table

(52) We have used Seitz S-1 pads and 0.5% 505 filter aid and sometimes K-5 pads and 1% Hyflow filter aid for this filtration. The filter pad should be washed with 0.30 *M* sodium chloride and then with 0.01 *M* acetic acid, and finally with 0.05 ionic strength *p*H 5.2 acetate buffer in 17% ethanol. The *p*H of the final washings should be checked to see that it is 5.2 after filtration (this can be easily done with a spot-plate and suitable indicator solution). This washing procedure is essential because the low ionic strength of the solution and changes in *p*H at this point can substantially lower the recovery of γ-globulin.

(53) Sodium glycinate buffer is prepared by half-neutralizing a glycine solution with sodium hydroxide. The solution we have used contains 1 mole of glycine and 0.5 mole sodium hydroxide per liter. It has a *p*H of about 9.5 and has the advantage of causing less of a drift in *p*H upon aeration than is observed when sodium bicarbonate is used to increase the alkalinity.

(54) The suspension of this material is conveniently carried out using a Waring blendor to break up the fibrin clot.

(55) M. Melin, *J. Clin. Invest.*, **24**, 662 (1945).

(56) We have found it helpful to suspend precipitate II-3 and II-1,2 in 1.5 volumes of water–ice mixture (1.3 of water frozen). If this mixture is kept cold during the suspension, most of the globulin remains undissolved, and does not "lump up" upon freezing.

(57) Fraction II-1,2 represents the more soluble part of the γ-globulin and is taken off at conditions used for preparation of Fraction II by earlier methods. Such material has been used clinically in both measles and epidemic jaundice. This fraction should be dissolved to make solutions containing 16.5 g. of γ-globulin per 100 cc. and sterilized by Seitz filtration.

(58) See Ref. 2, Table VII.

TABLE III

DISTRIBUTION OF PROTEINS IN SUBFRACTIONS OF FRACTION II + III

| Experiment | Per cent. of total protein nitrogen in fraction 1 | 2 | 3 | 4 | Mean | G. N × 6.25 per liter of plasma |
|---|---|---|---|---|---|---|
| II + III | (100) | (100) | (100) | (100) | (100) | (15.1) |
| II + IIIW | 66.0 | 65.0 | 62.5 | 61.5 | 63.7 | 9.6 |
| Cent. loss | 0.7 | 1.0 | 0.9 | 1.5 | 1.0 | |
| III-0 | 24.4 | 26.2 | 22.7 | 24.3 | 24.4 | 3.7 |
| Cent. loss | 0.6 | 0.8 | 1.8 | 0.7 | 1.0 | |
| Supernatant | 8.3 | 7.0 | 12.1 | 12.0 | 9.9 | |
| III | .... 26.8 | .... | .... 24.2 | .... | 25.5 | 3.9 |
| Cent. loss | .... 1.2 | .... | .... 2.0 | .... | 1.6 | |
| Filt. loss | .... 2.8 | .... | .... 2.0 | .... | 2.4 | |
| II-3 | .... 20.9 | .... | .... 16.9 | .... | 18.9 | 2.9 |
| Cent. loss | .... 0.2 | .... | .... 0.2 | .... | 0.2 | |
| II-1,2 | .... 13.2 | .... | .... 15.5 | .... | 14.4 | 2.2 |
| Cent. loss | .... 0.1 | .... | .... 0.1 | .... | 0.1 | |
| Supernatant | .... 0.4 | .... | .... 0.9 | .... | 0.6 | |
| III-1 | .... 11.9 | .... | .... 11.2 | .... | 11.6 | 1.8 |
| Cent. loss | .... 0.6 | .... | .... 0.5 | .... | 0.5 | |
| Supernatant | .... 1.3 | .... | .... 0.7 | .... | 1.0 | |
| III-2 | .... 8.8 | .... | .... 7.2 | .... | 8.0 | 1.2 |
| Cent. loss | .... 0.9 | .... | .... 0.7 | .... | 0.8 | |
| III-3 | .... 2.7 | .... | .... 2.6 | .... | 2.7 | 0.4 |
| Cent. loss | .... 0.6 | .... | .... 1.3 | .... | 0.9 | |

V(b) for the grams of protein per liter of plasma recovered in fractions.

We have recorded the electrophoretic analyses of the various II + III sub-fractions in Table V(a). In some cases the separations between these components is incomplete, especially in the case of the $\beta_1$-globulin and the $\beta_2$-globulin + fibrinogen components. The protein distributions in Tables V(b) and V(c) have been corrected for the nitrogen factor, but not for the refractive index increment of the components. Recent papers in this series[59] have indicated that these refractive index corrections would be small, and they can properly be neglected at this time. The unusually high mobilities assigned to the $\beta_1$ component in the lipid-rich fractions has also been discussed.[59]

TABLE IV

ESTIMATES OF NITROGEN AND CHOLESTEROL IN SUBFRACTIONS OF FRACTION II + III OF HUMAN PLASMA

| Fraction | Grams protein/gram nitrogen (1) | (2) | (3) | (4) | Mean | Wt. per cent. Nitrogen | Cholesterol |
|---|---|---|---|---|---|---|---|
| II + III | 7.9 | 7.8 | 7.8 | 7.8 | 7.8 | 12.8 | 6.0 |
| II + IIIW | —6.8— | | 6.7 | 6.7 | 6.7 | 14.9 | 1.8 |
| III-O | 10.5 | 10.4 | 9.9 | 9.8 | 10.1 | 9.9 | 12. |
| II-1,2 | —6.2[a]— | | | | 6.2[b] | 16.0 | <0.06 |
| II-3 | —6.2[a]— | | | | 6.2[b] | 16.0 | <0.06 |
| III | —7.1— | | —7.0— | | 7.0 | 14.3 | 3.5 |
| III-1 | —7.3— | | —7.2— | | 7.3 | 13.8 | 3.7 |
| III-2 | —6.8— | | —6.6— | | 6.7 | 13.0 | 3.0 |
| III-3 | —6.5— | | —6.7— | | 6.6 | 15.2 | 1.2 |

[a] After filtration of combined 16.5% γ-globulin solution. [b] Also value of E. Brand, B. Kassell and L. J. Saidel, *J. Clin. Invest.*, **23**, 437 (1944).

(59) S. H. Armstrong, Jr., M. J. E. Budka and K. C. Morrison, THIS JOURNAL, **69**, 416 (1947); S. H. Armstrong, Jr., M. J. E. Budka, K. C. Morrison and M. Hasson, *ibid.*, **69**, 1747 (1947).

TABLE V

DISTRIBUTION OF PLASMA PROTEINS INTO II + III SUBFRACTIONS BY METHOD 9

| Fraction | A | α | $\beta_1$ | $\beta_2 + \phi$ | γ | Total |
|---|---|---|---|---|---|---|
| | (a) Per cent. of fraction | | | | | |
| II + III | 4 | 6 | 35 | 18 | 37 | 100 |
| III-0 | 6 | 5 | 68 | 16 | 5 | 100 |
| II + IIIW | 2 | 8 | 15 | 19 | 56 | 100 |
| II-1,2 | 0 | 0 | 0 | 2 | 98 | 100 |
| II-3 | 0 | 0 | 0 | 4 | 96 | 100 |
| III | 3 | 15 | 33 | 34 | 15 | 100 |
| III-1 | 2 | 18 | 15 | 45 | 14 | 100 |
| III-2 | 1 | 20 | 65 | 12 | 2 | 100 |
| III-3 | 3 | 20[a] | 39 | 37[b] | 2 | 100 |
| (b) Grams per liter of plasma recovered in fractions | | | | | | |
| II + III | 0.7 | 1.1 | 6.5 | 3.4 | 6.9 | 18.6 |
| III-0 | 0.3 | 0.3 | 4.1 | 1.0 | 0.3 | 6.0 |
| II + IIIW | 0.2 | 0.8 | 1.6 | 1.9 | 5.8 | 10.3 |
| II-1,2 | 0 | 0 | 0 | 0 | 2.2 | 2.2 |
| II-3 | 0 | 0 | 0 | 0.1 | 2.8 | 2.9 |
| III | 0.1 | 0.7 | 1.5 | 1.5 | 0.6 | 4.4 |
| III-1 | 0 | 0.4 | 0.3 | 1.0 | 0.3 | 2.1 |
| III-2 | 0 | 0.3 | 0.8 | 0.2 | 0 | 1.3 |
| III-3 | 0 | 0.1 | 0.1 | 0.2 | 0 | 0.4 |
| (c) Grams per liter of plasma estimated in plasma | | | | | | |
| II + III | 0.8 | 1.1 | 6.6 | 3.5 | 7.0 | 19.0 |
| II | 0 | 0 | 0 | 0.1 | 5.4 | 5.5 |
| III-1 | 0.1 | 0.5 | 0.4 | 1.2 | 0.4 | 2.6 |
| III-2 | 0 | 0.4 | 1.0 | 0.2 | 0.1 | 1.7 |
| III-3 | 0 | 0.2 | 0.3 | 0.3 | 0 | 0.8 |
| III-0 | 0.5 | 0.5 | 5.7 | 1.3 | 0.4 | 8.4 |
| Total | 0.6 | 1.6 | 7.4 | 3.1 | 6.3 | 19.0 |

[a] Including β-fibrin.[61] [b] Including α-fibrin.[61]

In order to estimate the composition of plasma from these data, we have also calculated the amounts of each of these subfractions present in a liter of plasma (Table V(c)), using the data in Table III to estimate the losses. Although the lost material probably does not have the same electrophoretic composition as the isolated subfractions, we have calculated the distribution of proteins using this assumption, and the total found in the corrected subfractions is near to that observed for the Fraction II + III.

The distribution of the lipoprotein components has been followed by cholesterol determinations in most of these fractions, as recorded in Table IV. These values, when combined with the yield of the fractions from Table V(c), indicate that about 85% of the cholesterol of II + III, or about two-thirds of the cholesterol of plasma, is concentrated into Fraction III-0. The purified $\gamma$-globulin fractions (II-1,2 and II-3) contain less than one-fourth molecule of cholesterol per molecule of $\gamma$-globulin.

TABLE VI

DISTRIBUTION OF CERTAIN ANTIBODIES INTO II + III SUBFRACTIONS BY METHOD 9

| Fraction | Weight of fraction | Typhoid agglutinin O | Typhoid agglutinin H | Influenza A Hirst test | Influenza A mouse Prot. | Diphtheria Antitoxin | Streptococcal Antitoxin |
|---|---|---|---|---|---|---|---|
| (a) Preparation 184 (Ratio to IIG141) | | | | | | | |
| II-1,2 | | 1.1 | 1.5 | 0.6 | 0.7 | 0.8 | 1.0 |
| II-3 | | 4.6 | 1.3 | 1.2 | .9 | .6 | 0.9 |
| III-1 | | 40 | 0.9 | 0.7 | .1 | .3 | ... |
| III-2,3 | | 20 | 0.7 | .2 | .1 | .1 | ... |
| III-0 | | ... | ... | .2 | .1 | .1 | ... |
| Plasma | | 4.6 | 0.3 | .3 | .2 | .1 | ... |
| (b) Preparation S362 (Ratio to IIG141) | | | | | | | |
| II-1,2 | | 1.0 | 1.0 | 1.0 | 1.0 | 1.2 | 1.0 |
| II-3 | | 3.8 | 1.4 | 1.0 | 0.7 | 1.3 | 0.8 |
| III-1 | | 41 | 3.8 | 0.7 | .5 | 0.5 | ... |
| III-2 | | 10 | 0.6 | 0.3 | .1 | .1 | ... |
| III-0 | | 0.7 | 0.2 | 0.2 | .1 | .1 | ... |
| II + III | | 10 | 1.5 | 1.3 | .3 | .7 | ... |
| (c) Preparation 184 (per cent. of plasma) | | | | | | | |
| II-1,2 | 3.8 | 1 | 18 | 7 | 15 | 20 | |
| II-3 | 4.6 | 5 | 18 | 19 | 22 | 25 | |
| III-1 | 4.0 | 36 | 12 | 9 | 3 | 8 | |
| III-2,3 | 3.8 | 17 | 8 | 2 | 2 | 1 | |
| III-0 | 12.7 | ... | ... | 6 | 6 | 10 | |
| Total | 28.9 | 59 | 56 | 43 | 48 | 64 | |
| (d) Preparation S362 (per cent. of II + III) | | | | | | | |
| II-1,2 | 13 | 1 | 9 | 10 | 39 | 21 | |
| II-3 | 16 | 6 | 15 | 13 | 34 | 29 | |
| III-1 | 14 | 59 | 35 | 7 | 23 | 10 | |
| III-2 | 9 | 9 | 4 | 2 | 2 | 1 | |
| III-3 | 4 | ... | .. | .. | ... | .. | |
| III-0 | 44 | 2 | 2 | 8 | 10 | 7 | |
| Total | 100 | 77 | 65 | 40 | 108 | 68 | |

## VII. Distribution of Antibodies and Physiologically Active Components

Studies of the antibody content of the various fractions have been reported by Enders.[26] More extensive studies are now available.[60] Nearly all antibodies which have been studied are found concentrated into Fractions II-1,2, II-3 or III-1, and Fractions I, III-0, III-2, III-3, IV-1, IV-4 and V are found to contain only traces of antibody. Table VI gives the results obtained on two preparations which were carefully studied. The results are first compared with a reference solution containing the same concentration of protein Table VI (a) and (b), and then with the plasma (or Fraction II + III for preparation S362) from which it was fractionated. The totals recorded in Table VI (c) and (d) represent the amount of antibody accounted for in the various fractions. Deviations from 100% represent destruction of activity, loss into other fractions, and the collected errors of these tests. The latter cause probably is the most significant. Errors in antibody assay are most serious when the activity is low, such as is found in plasma, and Fractions III-0, III-2 and III-3.

Table VII summarizes a much larger number of tests made on Fractions II-1,2, II-3 and III-1. The antibody content of the fraction, compared

TABLE VII

AVERAGE ANTIBODY CONTENT OF FRACTIONS II-1,2, II-3 AND III-1

Comparison with equal weights of plasma protein[a]

| | II-1,2 | II-3 | III-1 |
|---|---|---|---|
| Isoagglutinins | (0.2) | (0.4) | 16 |
| Typhoid O agglutinin | 0.4 | 1.2 | 16 |
| Typhoid H agglutinin | 8 | 8 | 4 |
| Influenza A, Hirst test | 4 | 4 | 3 |
| Influenza A, mouse protection | 9 | 12 | 4 |
| Influenza A, complement fixation | 7 | (7) | .. |
| Mumps, complement fixation | 8 | (8) | .. |
| Diphtheria antitoxin | 10 | 7 | 4 |
| Streptococcal antitoxin | 9 | 9 | .. |

[a] Antibody concentration of solutions of Fractions II-1,2 or II-3 containing 165 mg. protein/ml., compared with plasma, will be 2.5 times these values. Values for Fraction II-1,2 compared with plasma from Enders[6] and additional data obtained more recently (about 30 preparations). Values for Fraction II-3 were obtained largely by comparison of Fraction II-3 with II-1,2 (about 13 preparations). Values for Fraction III-1 compared with plasma or Fraction II-1,2 and II-3 obtained in about 4 preparations.

(60) We wish to thank Professor John F. Enders and his group in the Department of Bacteriology and Immunology at the Harvard Medical School—Miss Julia C. Sullivan, Miss Bettie Griffith, and Miss Jeanne E. Beauchamp—for making most of these studies. Studies of anti-A, anti-B, anti-Rh$_0$, anti-Rh', and anti-Rh'' isoagglutinins were made by Dr. L. K. Diamond, Children's Hospital, Boston, Dr. W. C. Boyd, Boston University School of Medicine, Boston, and some of us (M. Melin, J. W. Cameron, and D. A. Richert). The distribution of the following antibodies has been studied: (a) On most preparations: agglutinins against typhoid O antigen; agglutinins against typhoid H antigen; antibody causing inhibition of the hemagglutinin of influenza A virus, strain PR8; mouse protection (neutralizing) antibody against influenza A virus, strain PR8; diphtheria antitoxin (interdermal neutralization test on rabbits). (b) On many preparations: complement-fixing antibody against the virus of mumps; complement-fixing antibody against influenza A virus, strain PR8; (c) on selected preparations: agglutinins against H pertussis, phase 1, strain 484, Philadelphia; streptococcal antitoxin (interdermal neutralization test on rabbits); antibody against streptococcal hemolysin; isoagglutinins against cells of human blood groups A and B; isoagglutinins against cells of human blood groups Rh$_0$, Rh' and Rh''.

with the content of the same weight of plasma protein has been recorded.

TABLE VIII

ASSAY FOR PROTHROMBIN AND PLASMINOGEN ACTIVITY

Values are in units/cc. plasma

| Run | Plasma | (II + III) | II + III Susp. | II + IIIW | III | III-2 | III-3 |
|---|---|---|---|---|---|---|---|
| | | | Prothombin | | | | |
| 171 | 82 | 63 | 75 | 70 | 46 | .. | .. |
| 173 | 100 | 54 | 91 | 60 | .. | .. | .. |
| 175 | ... | 95 | 89 | 50 | 41 | .. | .. |
| 176 | 58 | 83 | 86 | 60 | 37 | .. | .. |
| 177 | 72 | 61 | 38 | 17 | .. | .. | .. |
| 178–179 | 88 | 58 | 18 | 190 | 35 | .. | .. |
| 180–181 | 56 | 68 | 32 | 55 | 37 | 34 | .. |
| 182–183–184 | 68 | 73 | 24 | 18 | 27 | .. | .. |
| 185–186 | 63 | 78 | 53 | 31 | 21 | .. | .. |
| S362-1,2 | ... | .. | 62 | 73 | 81 | 78 | .. |
| | | | Plasminogen | | | | |
| S-362-1,2 | ... | .. | 32 | 27 | 30 | (21) | 14 |

Typical assays for prothrombin and plasminogen activity are recorded for the various fractions in Table VIII.[61] Assays for both of these substances are somewhat uncertain, probably due largely to the presence of inhibitors which make it difficult to completely convert prothrombin to thrombin and plasminogen to plasmin without decomposition. Little or no prothrombin and plasminogen is found in any fraction other than III-2 and III-3.

(61) These studies have been made by Miss S. G. Miller and one of us (D. A. Richert), under the supervision of Professor J. T. Edsall. The methods used are recorded elsewhere.[34,36]

## Summary

1. The properties of various protein components of Fraction II + III of normal human plasma are reviewed.

2. Methods are outlined for the separation of Fraction II + III into a series of subfractions by low-temperature ethanol precipitation, in which careful control of the *p*H, temperature, and concentration of ethanol, salt and protein have been achieved. The subfractions so obtained have led to satisfactory separation and concentration of the following components: γ-globulin antibodies in Fraction II, isoagglutinins in Fraction III-1, prothrombin in Fraction III-2, plasminogen in Fraction III-3 and $\beta_1$-lipoprotein in Fraction III-0.

3. Studies of the distribution of components into these subfractions are tabulated. They have involved measurements of protein nitrogen, dry weight of protein, cholesterol, prothrombin activity, plasminogen activity and various antibody activities.

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# Filter Paper Chromatography

BY HENRY B. BULL, J. WILFRID HAHN AND VICTOR H. BAPTIST

Consden, Gordon and Martin[1] reported a very ingenious method for the separation of amino acids by filter paper chromatography in which phenol or some other appropriate organic solvent sweeps the applied amino acids along the filter paper, capillarity causing the organic solvent to move. The positions of the amino acids are located by spraying the filter paper with a solution of ninhydrin and heating the filter paper strips. The amino acids develop colors, the intensity and tint of which depend upon a number of factors. A review of filter paper chromatography has recently appeared.[2]

The present paper reports an attempt to make filter paper chromatography of amino acids quantitative. The percentage light intermission along the chromatogram is measured and this transmission has been plotted on semi-log graph paper against the distance along the filter paper strips, and the areas of the segments above the plotted curve measured with a planimeter. It has been found that the areas so determined are over a limited concentration range a simple function of the concentration of the amino acids. The various factors which influence the reliability of this method are reported.

(1) Consden, Gordon and Martin, *Biochem. J.*, **38**, 224 (1944).

(2) Consden, *Nature*, **162**, 359 (1948).

## Experimental

Carl Schleicher and Schuell quantitative filter paper number 507 was cut against the machine direction into strips 7.20 mm. wide and 60 cm. long. One end of the filter paper strip was placed in the bottom of an oblong butter dish and a thick glass strip placed on top of the paper to hold it in position. It was found convenient to use 5 such strips hanging at about 2 cm. intervals over each side of the butter dish. The lower ends of the filter paper strips were attached to small metal clamps affixed to a metal rod. 0.0135 cc. of the amino acid solution adjusted to a *p*H 5 to 7 was placed on a marked spot on the filter paper strip with a Blodgett pipet about 4 cm. from the edge of the butter dish. The filter strips were in a horizontal position during this operation. The amino acid solutions were air dried on the filter paper and the butter dish, with the filter paper strips hanging vertically, was placed on a stage in a tall glass jar. The jar had a layer of 80% aqueous solution of Merck reagent grade of phenol on the bottom. Eighty per cent. aqueous solution of phenol was poured into the butter dish to cover the ends of the filter paper strips. A second glass jar was inverted over this jar and the joint between the jars sealed with vaseline.

After about forty-eight hours, the phenol solution had nearly reached the ends of the filter paper strips. The strips were removed and the flow distance of the phenol marked with a pencil. The strips were allowed to air dry until they were no longer "wet" with phenol. They were then placed in an oven provided with a circulating fan for two minutes at 90°. The filter paper strips were removed and stretched in a horizontal position and sprayed with a solution containing 0.40 g. of ninhydrin, 10 g. of phenol and 90 g. of *n*-butyl alcohol. After the "wet" appearance of the strips had disappeared, they were sprayed on the reverse side and allowed to dry until the "wet" appearance had disappeared. The strips were then placed in an oven at 90° for ten minutes. They were then placed over an enclosed steam-bath for five minutes. The color had now reached its maximum.

The filter paper strips were mounted on a glass slide 4 cm. wide, 0.5 cm. thick and 70 cm. long blacked out except for a groove 7.2 mm. wide in which the filter paper strip was placed and fastened at both ends with Scotch tape. The glass strip was then passed between an illuminated slit 6 mm. high and 5 mm. wide and the phototube. An electronic photometer model 512 and photometer tube "D" of the Photovolt Corporation of New York was used in this work. The Photovolt Corporation has since generously placed at our disposal a densitometer specially constructed for this type of measurement, the details of which can be obtained from this Corporation.

The percentage light transmission was read every 5 mm. along the filter paper; thus the entire filter paper strip was scanned except for 0.6 mm. along each edge. A light filter whose maximum transmission was at 570 mμ was placed in front of the slit.

The light transmission through the filter paper was then expressed in per cent. of the light transmitted through a "blank" filter paper strip which had been carried through the entire procedure except that no amino acid had been applied to it. The per cent. transmission was then plotted on semi-log graph paper against the distance along the filter paper strips. The areas above the plotted curve and 100% transmission were measured with a planimeter and this area multiplied by the standard color-area of the particular amino acid to obtain the concentration of the amino acid. The amino acid was identified by its $R_F$ value as defined by Consden, *et al.*[1]. In case there remained doubt as to the identity of a color band on the chromatogram, known amino acids were added to the amino acid mixture and the position of the increase in areas of the light transmission against distance plot noted.

## Discussion

The various factors which influence the success of this method and which have been investigated by us are as follows:

**Filter Paper.**—About 15 brands of filter paper were studied. The suitability of these filter papers varied widely. As a result of this investigation we concluded that the ideal paper must be dense so that the rate of flow of phenol would be slow, otherwise the resolution of the amino acids on the strip will not be sharp. Further, the filter paper must be uniform with a good light transmission. And lastly, the filter paper must be free of impurities which give rise to extraneous colors. The filter paper which was found to fulfill these conditions best is the Carl Schleicher and Schuell quantitative filter paper number 507 cut against the machine direction.

**Resolving Solvent.**—We have confined our studies entirely to freshly made aqueous phenol solutions using Merck reagent grade. In the beginning part of this research, we employed phenol saturated with water in the butter dish and water saturated with phenol in the bottom jar. This arrangement was abandoned for several reasons but principally because the $R_F$ values of the amino acids were too erratic, and the system was much too sensitive to minor temperature changes. As noted in the experimental part of this paper, 80% aqueous phenol, both in the butter dish and in the bottom of the jar, seemed to yield the best results.

Various phenol concentrations were investigated, using identical concentrations in the butter dish as well as in the bottom of the jar. The $R_F$ values of the various amino acids are shown in Table I as a function of the phenol concentration, the *p*H of the applied amino acid solutions being 5.0.

TABLE I

$R_F$ VALUES AS A FUNCTION OF THE PHENOL CONCENTRATION EXPRESSED IN GRAMS OF PHENOL PER 100 G. OF AQUEOUS SOLUTION

| Amino acid | Phenol concentration 60 | 65 | 70 | 75 | 80 | 85 |
|---|---|---|---|---|---|---|
| Serine | 0.73 | 0.33 | 0.34 | 0.31 | 0.30 | 0.32 |
| Glycine | .73 | .38 | .40 | .35 | .36 | .38 |
| Methionine | .92 | .73 | .74 | .70 | .70 | .72 |
| Phenylalanine | .92 | .80 | .80 | .75 | .76 | .78 |
| Lysine | .63 | .37 | .30 | .25 | .23 | .19 |
| Arginine | .63 | .45 | .41 | .35 | .33 | .28 |
| Alanine | .74 | .53 | .53 | .53 | .52 | .52 |
| Leucine | .94 | .77 | .78 | .75 | .74 | .73 |
| Glutamic | .63 | .36 | .35 | .31 | .32 | .23 |
| Theonine | .70 | .48 | .47 | .44 | .44 | .38 |
| Aspartic | .63 | .18 | .18 | .13 | .14 | .077 |
| Valine | .88 | .72 | .70 | .69 | .69 | .67 |

The amino acids most sensitive to changes in phenol concentration are aspartic, glutamic, lysine and arginine. Indeed, these are the amino acids whose $R_F$ values are the most variable under all conditions.

*p*H.—The *p*H of the amino acid solutions was adjusted with the addition of sodium hydroxide or with hydrochloric acid, and the $R_F$ values determined using 80% aqueous phenol. These results are shown in Table II.

TABLE II

$R_F$ VALUES AS A FUNCTION OF THE *p*H OF THE AMINO ACID SOLUTIONS APPLIED TO THE FILTER STRIPS

| Amino acid | $R_F$ values at *p*H 3.30 | 5.00 | 8.60 |
|---|---|---|---|
| Aspartic | 0.17 | 0.14 | 0.15 |
| Lysine | .28 | .23 | .32 |
| Serine | .35 | .30 | .33 |
| Glutamic | .33 | .32 | .30 |
| Arginine | .37 | .33 | .40 |
| Glycine | .40 | .36 | .38 |
| Threonine | .47 | .44 | .48 |
| Alanine | .55 | .52 | .55 |
| Valine | .70 | .69 | .72 |
| Methionine | .74 | .70 | .70 |
| Leucine | .76 | .74 | .75 |
| Phenylalanine | .78 | .76 | .74 |

As will be noted from Table II, the $R_F$ values of the amino acids are largely independent of the *p*H of the amino acid solutions. The color developed was also independent of the *p*H from values of 4 to about 7.5. More alkaline *p*H values changed the blue purple color characteristic of all amino acids tested to a red purple, and at *p*H values of about 9 the color became a brick red. At *p*H values acid to about 4, a red color was also obtained.

**Developing Solution.**—Various developing solutions were studied and the solution which appeared to give the maximum color intensity and which was most reliable in performance had a small amount of phenol added to it; the composition of this solution is given in the experimental part. This solution must be freshly prepared to obtain uniform colors.

**Color Development.**—It has been our objective to develop the maximum color intensity possible for a given amino acid concentration. When the filter-paper strips are heated at 90° in the oven, they reach a constant level of color intensity in about five minutes, and this intensity remains essentially unchanged for at least thirty-five minutes of heating. However, when the strips are removed from the oven after the constant level of intensity has been attained and the color intensity measured in the densitometer after successive intervals, it is found that the color intensity increases with time at room temperature. This increase in optical density of the filter strips amounted to about 30% after twenty-four hours. The increase in optical density with time was finally recognized as probably being due to moisture uptake by the paper from the atmosphere. It was then found that a five-minute treatment in the steam oven after the dry oven brought the strips to their final color intensity. This final color was stable within experimental error for at least forty-eight hours provided the strips were protected from light.

**Color Developed.**—Contrary to some reports in the literature, the tint of the color developed with ninhydrin was as near as could be determined exactly the same for all the amino acids investigated, provided the *p*H of the amino acid solution was within the range of 4 to 7.5. Figure 1 shows the per cent. transmission for colors developed by alanine and by aspartic acid on the filter paper as a function of the wave length of the light. The colors developed by a number of other amino acids were investigated, and were found to be practically identical with the two shown in Fig. 1.

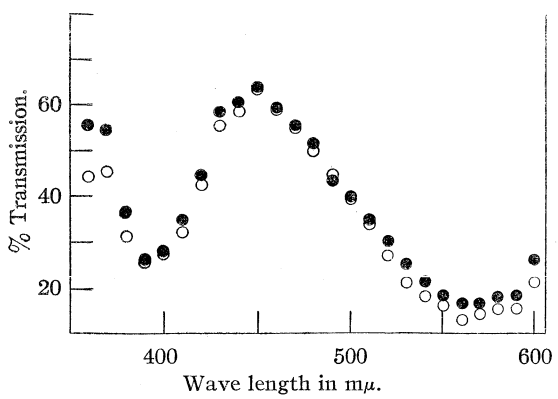



Fig. 1.—Per cent. light transmission through the color bands of alanine (open circles) and of aspartic acid (solid circles) on the filter paper as a function of the wave length of light.

There is a broad minimum in the optical transmission in the neighborhood of 570 mμ and this is the reason for using a light filter of this wave length in the densitometer.

**Amino Acid Concentration.**—As noted above, the per cent. light transmission was plotted on semi-log graph paper (Keuffel and Esser No. 358-51) against the distance along the filter paper strip allowing the space between each line on the graph paper to equal 2 mm. The areas between the plotted curve and 100% transmission were measured with a planimeter in square inches. These areas were then divided by the amount of amino acid in micromoles and this ratio was plotted against the area in square inches. It was found that the points for arginine, serine, valine, glutamic acid, leucine, threonine, alanine and lysine fell about a line whose least square equation is

$$A/C = 380.4 - 9.10A \qquad (1)$$

where $A$ is the area in square inches and $C$ is the amount of the amino acid in micromoles. The probable per cent. error for 68 determinations extending from 0.67 to 13.5 micrograms of the above acids was ±8.82. The per cent. errors were more or less independent of concentration.

The results for aspartic acid, phenylalanine, methionine and glycine did not follow equation 1. All of these acids developed less color than the first group of amino acids although when $A/C$ was plotted against $A$, linear relations were obtained. The equations for these amino acids are

| | | |
|---|---|---|
| Aspartic | $A/C = 340 - 10.0A$ | (2) |
| Phenylalanine | $A/C = 210 - 6.5A$ | (3) |
| Methionine | $A/C = 160 - 0.5A$ | (4) |
| Glycine | $A/C = 275 - 12.3A$ | (5) |

We did not attempt to evaluate the errors associated with equations 2, 3, 4 and 5. Since these acids did not develop the maximum color, the amount of color which is developed is probably very much dependent on how the reaction is carried out.

The addition of sodium chloride up to 0.1 $N$ had no significant influence on the color developed by alanine, but 0.2 $N$ sodium chloride produced a reddening of the color and reduced the area about 10%. The $R_F$ values for all the amino acids were independent of the amounts of the amino acids present.

**Mixtures of Amino Acids.**—The greatest utility of paper chromatography is in the study of mixtures of amino acids such as are obtained in protein hydrolysates. Shown in Fig. 2 is a

light transmission curve plotted on a semi-log scale against the distance in cm. along the filter paper strip. The mixture consisted of 3.38 micrograms each of arginine hydrochloride, valine, leucine, threonine, alanine and lysine hydrochloride.

There was too much overlapping of the arginine and the threonine for separate resolutions, but the sum of the micromoles of these two acids was 0.048 and the same calculated by the use of equation 1 is 0.043 micromole. The amounts of the other amino acids in micrograms were lysine hydrochloride 3.78, alanine 2.84, valine 3.51, and leucine 3.32. Where there was overlapping of the amino acid curves as shown in Fig. 2, a vertical line is drawn between the two overlapping amino acids from the peak transmission to the 100% transmission line and the respective areas assigned on the basis of this line. Providing there is not excessive overlapping, this treatment yielded good results.

All resolutions of amino acids on filter paper strips were done at room temperature and no thermostating was attempted. We have been unable to detect any important influence of temperature using 80% aqueous phenol except that the phenol moved faster at higher temperatures, and if this rate became too high the separation of the amino acids was not sharp. The rate we have tried to maintain was about 40 cm. or less in forty-four hours. If temperature gradients exist, the filter paper strips should be arranged so that they face the gradient; otherwise, the amino acid bands will be distorted.

**Acknowledgments.**—We are grateful to Corn Products Refining Company for the support of J. Wilfrid Hahn and to Swift and Company for the support of Victor H. Baptist. We wish to thank Dr. K. K. Jones for the loan of a photospectrometer, and Drs. L. S. Fosdick and C. O. Rupe for gifts of pure amino acids. The Carl Schleicher and Schuell Company and the Photovolt Corporation have been most helpful.

## Summary

1. A new arrangement of the filter paper chromatography of Consden, Gordon and Martin is described.

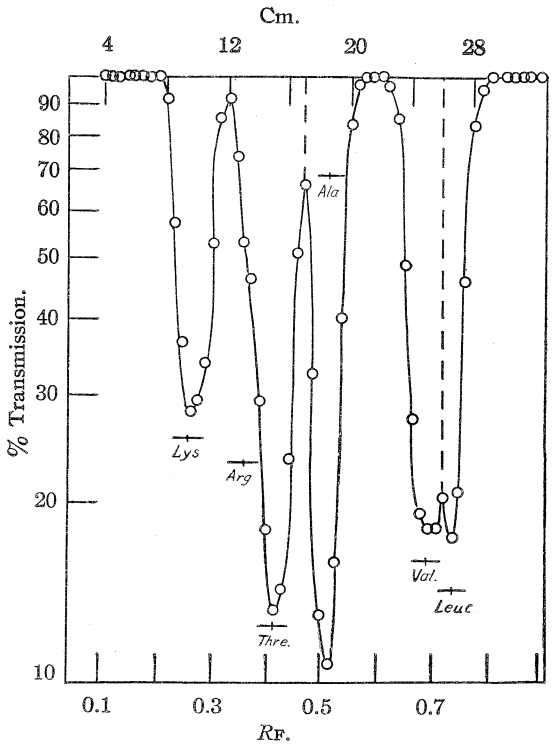



Fig. 2.—Optical transmission curve for a mixture of 3.38 micrograms each of lysine hydrochloride, arginine hydrochloride, threonine, alanine, valine and leucine.

2. The main features of this new approach consist in the use of a superior grade of filter paper, of 80% aqueous phenol, and attention to the details of color development.

3. It appears that arginine, serine, valine, glutamic acid, leucine, threonine, alanine and lysine give the same micromolar color values, and by the technique described it is possible to estimate these acids in the range of 0.67 to 13.5 micrograms with a probable per cent. error of a single determination of ±8.82. Aspartic acid, phenylalanine, methionine and glycine yield lower micromolar color values.

4. The application of this method to amino acid mixtures is described.

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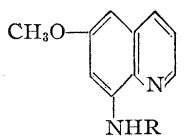
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Synthesis of 6-Methoxy-8-aminoquinoline Derivatives; Ethyleneimine Rearrangements in Attachment of Monoalkylaminoalkyl Side Chains[1]

BY ARTHUR C. COPE, HAROLD R. NACE,[2] WILLIAM R. HATCHARD, W. H. JONES, MARK A. STAHMANN AND RICHARD B. TURNER

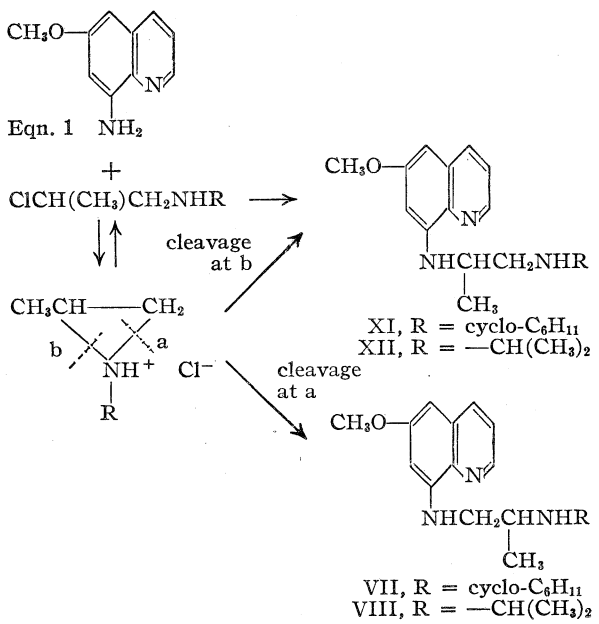
This paper describes the synthesis of a number of 6-methoxy-8-aminoquinoline derivatives[3] related to Plasmochin (I) but containing *primary* aminoalkyl (II and III) or *secondary* aminoalkyl side chains (IV-X) attached to the 8-amino group. Rearrangement is possible in the alkylation reactions through which VII, VIII, IX and X were prepared if ethyleneimines are formed as intermediates, as was proved to have occurred in two of the four cases by unequivocal syntheses of each of these compounds.

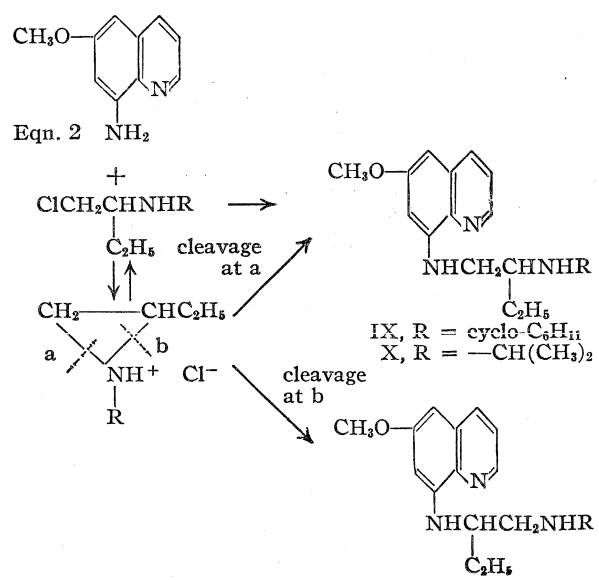
The *primary* aminoalkyl side chains in II and III were introduced by alkylation of 6-methoxy-8-aminoquinoline with phthalimidoalkyl halides, followed by removal of the phthalyl group as phthalhydrazide by treatment first with hydrazine hydrate then hydrochloric acid.[4] The primary amino group in II was converted to the isopropylamino group in the synthesis of IV by reductive alkylation with acetone in the presence of Adams platinum catalyst.



I, R = $-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
II, R = $-(CH_2)_4NH_2$
III, R = $-CH_2CH(OH)CH_2NH_2$
IV, R = $-(CH_2)_4NHCH(CH_3)_2$
V, R = $-(CH_2)_2NHC_6H_{11}$-(cyclo)
VI, R = $-(CH_2)_2NHCH(CH_3)_2$

Secondary aminoalkyl side chains in V-X (Table II) were introduced by the alkylation of 6-methoxy-8-aminoquinoline with secondary aminoalkyl chloride hydrochlorides.[5] It is evident from the following equations that the alkylation reactions could proceed by direct displacement of the chlorine of the aminoalkyl chloride, as in an alkylation by a simple alkyl halide, or that an ethyleneimine might be formed as an intermediate. Either course would lead to the same product from an alkylaminoethyl chloride, as in the syntheses of V and VI by alkylation of 6-methoxy-8-aminoquinoline with cyclohexylaminoethyl chloride hydrochloride and isopropylaminoethyl chloride hydrochloride, respectively. The two paths could lead to the same or different products in cases where an intermediate ethyleneimine would have an unsymmetrical structure, ac-




(1) Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Institute of Tecinology.

(2) Abbott Laboratories Fellow, 1947-1948.

(3) Prepared as part of the antimalarial program sponsored by the Committee on Medical Research. The antimalarial activity in avian malaria of each of the compounds designated by an SN number in the Experimental Part is reported in "Antimalarial Drugs 1941-1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(4) By the procedure of Ing and Manske, *J. Chem. Soc.*, 2348 (1926). The preparation of II by this procedure has been described by Robinson and Tomlinson (ref. 18).

(5) By modifications of the method described by Rohrman and Shonle, THIS JOURNAL, **66**, 1642 (1944).

TABLE I

ALKYLAMINOALKYL CHLORIDE HYDROCHLORIDES

| No. | Compound | Yield, %[b] | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found | Chlorine, % Calcd. | Chlorine, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Cyclo-$C_6H_{11}NHCH_2CH_2Cl\cdot HCl$[a,c] | 91[d] | 219.5–220[e] | $C_8H_{17}NCl_2$ | 48.5 | 48.4 | 8.65 | 8.60 | 7.07 | 7.08 | 35.8 | 35.8 |
| 2 | $(CH_3)_2CHNHCH_2CH_2Cl\cdot HCl$[f] | 82[g] | 187.5–188[e] | $C_5H_{13}NCl_2$ | 38.0 | 38.0 | 8.29 | 8.37 | 8.86 | 8.81 | 44.9 | 44.8 |
| 3 | Cyclo-$C_6H_{11}NHCH_2CH(CH_3)Cl\cdot HCl$[m,n] | 43 | 220–222[o] | $C_9H_{13}NCl_2$ | | | | | | | | |
| 4 | $(CH_3)_2CHNHCH_2CH(CH_3)Cl\cdot HCl$[h] | 37 | 184.5–185.5[i] | $C_6H_{15}NCl_2$ | 41.87 | 42.0 | 8.78 | 8.77 | 8.14 | 7.92 | 41.2 | 41.3 |
| 5 | Cyclo-$C_6H_{11}NHCH(C_2H_5)CH_2Cl\cdot HCl$[j] | 77 | 155–156[k] | $C_{10}H_{21}NCl_2$ | 53.09 | 53.23 | 9.36 | 9.32 | 6.19 | 6.05 | 31.4 | 31.4 |
| 6 | $(CH_3)_2CHNHCH(C_2H_5)CH_2Cl\cdot HCl$[j] | 90 | 115.5–117[l] | $C_7H_{17}NCl_2$ | 45.17 | 44.93 | 9.21 | 9.22 | 7.52 | 7.32 | 38.1 | 38.2 |

[a] Survey number SN 15,288; see ref. 3 for significance. [b] Of material with the melting point tabulated unless otherwise noted. [c] Thionyl chloride added during two hours and the mixture heated under reflux for two hours. [d] M. p. 212–212.5° (uncor.). [e] Recrystallized from ethanol. [f] Heated under reflux for one and one-half hours. [g] M. p. 176–177° (uncor.). [h] The mixture was allowed to stand overnight at room temperature after the thionyl chloride was added. [i] Recrystallized from ethanol and from chloroform. [j] Heated under reflux for half an hour. [k] Recrystallized from ethanol–ether and from carbon tetrachloride–petroleum ether. The m. p. tabulated was observed on rapid heating. Slow heating produced softening at this temperature and decomposition at 238–240°. [l] Recrystallized from ethanol–ethyl acetate and from ethyl acetate. [m] Described by Hancock, Hardy, Heyl, Wright and Cope, THIS JOURNAL, **66**, 1751 (1944). [n] Heated under reflux for one and one-half hours. [o] Recrystallized from ethanol; m. p. uncor.

cording to the point at which it opened in the alkylation.[6]

Displacement reactions of tertiary aminoethyl halides have been established as proceeding through intermediate quaternary ethyleneimmonium salts in a number of instances.[7] Ross[8] has shown that one unsymmetrical quaternary ethyleneimmonium salt reacted by cleavage under basic conditions between the nitrogen and the least substituted carbon atom (corresponding to cleavage at point *a* in the tertiary ethyleneimines represented as intermediates in equations 1 and 2). In other cases intermediate quaternary ethyleneimmonium salts apparently cleaved between the nitrogen and the most highly substituted carbon atom (as at point *b* in equations 1 and 2),[9] while in still other cases similar unsymmetrical quaternary ethyleneimmonium intermediates cleaved at both positions to give mixtures of isomeric products.[10] More recently secondary ethyleneimines have been shown to rupture preferentially but not exclusively at the primary carbon atom in reactions with amines, catalyzed by ammonium chloride.[11]

The alkylation reactions in which VII-X were prepared differ from others studied earlier in that the alkylating agents are secondary aminoalkyl chlorides, and the possible intermediates would be tertiary ethyleneimines or their hydrochlorides. Independent syntheses of VII-X by methods noted below established their structures, which correspond to cleavage of the ethyleneimines between the nitrogen and the least substituted carbon atom (point *a*, equations 1 and 2). Another possibility in the synthesis of IX and X, in which rearrangement did not occur, is direct displacement of the chlorine without intervention of a cyclic intermediate. It should be noted that yields of VII-X were not high, and the presence of isomers (derivable by cleavage of the intermediates at point *b*) in the solutions from which they were isolated is not excluded.

The secondary aminoalkyl chloride hydrochlorides with which 6-methoxy-8-aminoquinoline was alkylated in the syntheses of V-X were prepared from the corresponding aminoalcohol hydrochlorides and thionyl chloride (Table I). Evidence that rearrangement did not occur in the preparation of the chlorides was obtained for the last four compounds in Table I, which could have isomeric structures if the ethyleneimmonium chlorides formulated in equations 1 and 2 were formed as intermediates. These four compounds were heated with an excess of aqueous silver nitrate, which converted them to nitric acid salts of alkylaminoalcohols (any intermediate nitric acid esters which may have been formed were hydrolyzed under the reaction conditions). The alkylaminoalcohols which were obtained when the solutions were made basic were proved to be identical with the original alkylaminoalcohols from which the chlorides were prepared by a direct comparison of physical properties and of the hydrochlorides, which were prepared as solid derivatives. Rearrangement under the acidic conditions of these transformations is unlikely, and formation of the original alkylaminoalcohols of two structural types (two primary and two secondary alcohols) makes it very improbable that ethyleneimmonium salts were intermediates in the reaction with silver nitrate, for the cyclic imines which would be of the same structural type in all four cases would have to undergo

(6) The alkylaminoalkyl chlorides were used as hydrochlorides, which would be less susceptible to the rearrangement than the corresponding bases. In alcohol solution containing 6-methoxy-8-aminoquinoline, however, an equilibrium would be set up in which all of the basic species present would be present as bases and salts in amounts dependent upon their concentrations, basic strengths and solubilities of their hydrochlorides. Presence of the hydrogen chloride is not shown in the equations except in the ethyleneimmonium salts, which would be formed as a first step in self alkylation regardless of whether subsequent cleavage at a or b occurred in the salt or the corresponding base.

(7) (a) Bergmann, Fruton, Golumbic, Stahmann and Stein, *J. Org. Chem.*, **11**, 518–591 (1946); (b) Bartlett, Ross, Swain and Davis, THIS JOURNAL, **69**, 2971–2982 (1947).

(8) Ross, *ibid.*, **69**, 2982 (1947).

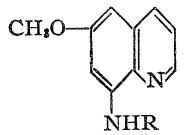
(9) Kerwin, Ullyot, Fuson and Birkle, *ibid.*, **69**, 2961 (1947).

(10) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946); Schultz, Robb and Sprague, *ibid.*, **69**, 188, 2454 (1947).

(11) Clapp, *ibid.*, **70**, 184 (1948).

two different types of cleavage to lead to these products.

Two of the possible alkylation products of equation 1 were prepared by first adding 6-methoxy-8-aminoquinoline to 1-nitro-1-propene to give 6-methoxy-8-(2-nitroisopropylamino)-quinoline (XIII).[12] XIII was reductively al-



XIII, R = $-CH(CH_3)CH_2NO_2$
XIV, R = $-CH_2CHOHCH_3$
XV, R = $-CH_2COCH_3$



XVI, R = $-CH_2CH(CH_3)N$



XVII, R = $-CH_2CH(CH_3)NH_2$



XVIII, R = $-CH_2CH(C_2H_5)N$



XIX, R = $-CH_2CH(C_2H_5)NH_2$

kylated with cyclohexanone and with acetone in the presence of Adams platinum catalyst[13] to give XI and XII, which were isolated as the dihydrochlorides. The dihydrochlorides and dipicrates of XI and XII differed in m.p. and showed depressions in mixed m.p. with the corresponding derivatives prepared from the alkylation products (equation 1), which accordingly could be assumed to be the isomers VII and VIII. Attempts to prepare known samples of VII and VIII by a similar procedure beginning with the addition of 6-methoxy-8-aminoquinoline to 2-nitro-1-propene were unsuccessful, for a pure crystalline addition product could not be isolated. Attempts to utilize 6-methoxy-8-(2-hydroxypropylamino)-quinoline (XIV) or 6-methoxy-8-acetonylaminoquinoline (XV) as intermediates in the synthesis of VII and VIII also were unsuccessful. XIV was prepared from 6-methoxy-8-aminoquinoline and propylene oxide, but could not be oxidized to XV under the conditions which were investigated. XV was obtained in very low yield by alkylation of 6-methoxy-8-aminoquinoline with bromoacetone, and could be converted to a crystalline semicarbazone and phenylhydrazone, which by reduction might have been converted to 6-methoxy-8-(2-aminopropylamino)-quinoline (XVII). The low yield in the preparation of XV led to abandonment of this route in favor of successful syntheses of VII and VIII through XVII as an intermediate which began with 2-phthalimido-1-propanol, prepared from phthalic anhydride and 2-amino-1-propanol. Reaction of this compound with phosphorus pentabromide yielded 2-phthalimido-1-bromopropane, which with 6-methoxy-8-aminoquinoline gave 6-methoxy-8-(2-phthalimidopropylamino)-quinoline (XVI). Removal of the phthalyl group in XVI[14] yielded 6-methoxy-8-(2-aminopropylamino)-quinoline (XVII). Reductive alkylation of XVII with cyclohexanone and with acetone gave samples of VII and VIII of known structure, which were proved to be identical with the alkylation products (equation 1) by comparison of the m.p. and mixed m.p. of the dihydrochlorides and dipicrates, and of the free base in the case of VII (a crystalline solid).

Similar syntheses which gave samples of IX and of X of known structure utilized as intermediates 2-amino-1-butanol, 2-phthalimido-1-butanol and 2-phthalimido-1-bromobutane, which with 6-methoxy-8-aminoquinoline yielded 6-methoxy-8-(2-phthalimidobutylamino)-quinoline (XVIII). Removal of the phthalyl group in XVIII gave 6-methoxy-8-(2-aminobutylamino)-quinoline XIX, which was reductively alkylated with cyclohexanone and with acetone to give IX and X. These samples of IX and X yielded dihydrochlorides and dipicrates which were identical (m.p. and mixed m.p.) with corresponding derivatives prepared from the products obtained from alkylation according to equation 2, and the crystalline samples of IX from the two sources were identical.

Difficulty was encountered in some instances in obtaining hydrochlorides with constant melting or decomposition points in this series (VII-X) and although their mixed melting points indicated the identities noted, comparison of the crystalline bases (VII and IX) and the picrates of VII-X obtained by the two methods of synthesis furnished more satisfactory proofs of identity.

## Experimental[14]

**6-Methoxy-8-(4-aminobutylamino)-quinoline Dihydrochloride Hemihydrate (II, SN 3, 883).**—4-Bromobutylphthalimide[15] was prepared from tetramethylene dibromide[16] and potassium phthalimide[17] and recrystallized from ligroin; yield 48%, m.p. 78–79°. A mixture of 60.0 g. of 6-methoxy-8-aminoquinoline and 97.0 g. of 4-bromobutylphthalimide was heated in a bath at 120–125° for six hours. The temperature of the reaction mixture was observed and heating was discontinued in the early stages if necessary to avoid a rapid spontaneous rise in temperature. After cooling, the mixture was heated under reflux with 350 ml. of ethanol to dissolve oily material, cooled and filtered. The orange hydrobromide was converted to the free base by shaking with methylene chloride and a dilute solution of potassium carbonate. The extract was washed with sodium chloride solution, filtered through sodium sulfate and concentrated. Crystallization of the residue from ethanol gave 55.0 g. (43%) of light yellow prisms, m.p. 92–94°. Several recrystalliza-

(12) Analogous to the addition of aniline to nitroethylene to give N-(2-nitroethyl)-aniline reported by Wieland and Sakellarios, *Ber.*, **52**, 903 (1919).

(13) Emerson and Uraneck, THIS JOURNAL, **63**, 749 (1941), have reported the reductive alkylation of nitromethane with ketones to give secondary amines.

(14) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mr. Philip H. Towle, Mrs. Louise W. Spencer and Mrs. C. K. Fitz for analyses.

(15) Gabriel and Maas, *Ber.*, **32**, 1269 (1899).

(16) Wilson, *J. Chem. Soc.*, 50 (1945).

(17) By the procedure described for preparing β-bromoethylphthalimide in "Organic Syntheses," Coll. Vol. I, second ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 119.

tions from ethanol gave an analytical sample of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline, m.p. 94–94.5°.

*Anal.* Calcd. for $C_{22}H_{21}O_3N_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.2; H, 5.73; N, 11.1.

The hydrobromide of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline melted at 210–211° (dec.) after several crystallizations from ethanol. Robinson and Tomlinson[18] report m.p. 196–198° (dec.).

*Anal.* Calcd. for $C_{22}H_{21}O_3N_3 \cdot HBr$: N, 9.21; Br, 17.51. Found: N, 9.08; Br. 17.6.

A solution of 55.0 g. of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline and 10.0 g. of 85% hydrazine hydrate in 500 ml. of ethanol was heated under reflux for two hours. The solvent was removed under reduced pressure and the residue was heated on a steam-bath with 200 ml. of 4.0 *N* hydrochloric acid for one hour. The mixture was cooled, filtered to remove phthalhydrazide, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethanol yielded 41.9 g. (87%) of II, m.p. 209–211° (dec.). An analytical sample purified by several crystallizations from ethanol had m.p. 213–214° (dec.) (ref. 18 reports m.p. 208° (dec.)).

*Anal.* Calcd. for $C_{14}H_{19}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 51.38; H, 6.78; N, 12.84; Cl, 21.66; $H_2O$, 2.75. Found: C, 51.2; H, 6.48; N, 12.7; Cl, 21.6; $H_2O$, 2.59 (by loss in weight on drying at 1 mm. and 110°).

**6-Methoxy-8-(4-isopropylaminobutylamino)-quinoline Dihydrochloride (IV, SN 13,275).**—The above dihydrochloride hemihydrate (II) (19.6 g.) was converted to the free base by shaking with ether and a dilute solution of potassium carbonate. The ether solution was dried over sodium sulfate, the ether was distilled and the residual oil was dissolved in 60 ml. of ethanol. Acetone (5 ml.) was added and the solution was added to the platinum catalyst prepared by hydrogenating 1.5 g. of platinum oxide in ethanol. Hydrogenation began rapidly at atmospheric pressure and became very slow after about thirty minutes; 78% of the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and 70 ml. of 1.96 *N* ethanolic hydrogen chloride was added to the filtrate. After concentration, the filtrate was diluted with ether and yielded 15.5 g. (72%) of IV, m.p. 185–187° (dec.). An analytical sample was crystallized several times from ethanol–ether; m.p. 189–190° (dec.).

*Anal.* Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl$: C, 56.66; H, 7.55; N, 11.66; Cl, 19.68. Found: C, 56.6; H, 7.62; N, 11.6; Cl, 19.7.

**6-Methoxy-8-(3-amino-2-hydroxypropylamino)-quinoline (III, SN 12,943).**—A mixture of 174 g. of 6-methoxy-8-aminoquinoline, 120 g. of 3-chloro-2-hydroxypropylphthalimide[19] and 300 ml. of *n*-butanol was heated under reflux for sixty-eight hours. The mixture was cooled and poured into 800 ml. of water containing 1.2 moles of hydrochloric acid, with stirring. The suspension was stirred with 500 ml. of benzene for thirty minutes, the benzene was decanted, and the process was repeated with 200 ml. of benzene. The mixed hydrochlorides were collected by filtering the aqueous suspension, dried, and converted to the free bases by dissolving in 1200 ml. of boiling ethanol and 130 ml. of pyridine. After cooling overnight the solids were separated by filtration and redissolved in 500 ml. of boiling ethanol and 100 ml. of pyridine. The hot solution was filtered and 400 ml. of hot water was added slowly. On cooling, 54 g. (29%) of 6-methoxy-8-(3-phthalimido-2-hydroxypropylamino)-quinoline separated, m.p. after recrystallization from 700 ml. of ethanol 142–143°.

*Anal.* Calcd. for $C_{21}H_{19}O_4N_3$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.8; H, 5.1; N, 11.1.

A solution of 46 g. of 6-methoxy-(3-phthalimido-2-hydroxypropylamino)-quinoline and 8.5 ml. of hydrazine hydrate in 460 ml. of ethanol was heated under reflux for ninety minutes. The ethanol was removed under reduced pressure and the residue heated under reflux for fifteen minutes with 420 ml. of water containing 0.3 mole of hydrochloric acid. After cooling and separating phthalhydrazide by filtration, 400 ml. of 1.0 *N* sodium hydroxide was added. After cooling for one hour the crystalline product was separated; yield of III 29 g. (92%), m.p. after recrystallization from 750 ml. of boiling ethanol 157–158°.

*Anal.* Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.13; H, 6.93; N, 16.99. Found: C, 62.9; H, 6.9; N, 17.1.

The hydrochloride was prepared from III and after recrystallization from ethanol–ether had m.p. 189–190°.

*Anal.* Calcd. for $C_{13}H_{17}O_2N_3 \cdot 2HCl$: C, 48.76; H, 5.98. Found: C, 48.5; H, 6.4.

**Alkylaminoalkyl Chloride Hydrochlorides.**—The following general procedure was used in preparing the compounds listed in Table I. The aminoalcohol[20] (0.3–1.0 mole) was dissolved in dry alcohol-free chloroform (750 ml. per mole) and placed in a three-necked flask fitted with a stirrer, reflux condenser and gas delivery tube dipping beneath the surface of the liquid. The solution was stirred and saturated with dry hydrogen chloride. The gas delivery tube was replaced with a dropping funnel and thionyl chloride (2.0 to 3.0 molar equivalents) was added with stirring and cooling. The solution was heated under reflux or allowed to stand as stated in the footnotes, the solvent and excess thionyl chloride were removed under reduced pressure, and the residue was crystallized to constant melting point from the solvent noted.

Evidence confirming the structures of the last four alkylaminoalkyl chloride hydrochlorides listed in Table I was obtained by converting them into the corresponding aminoalcohols in the following manner. 1-Isopropylamino-2-chloropropane hydrochloride (9.3 g., 0.056 mole), 39.2 g. (0.23 mole) of silver nitrate and 100 ml. of water were heated under reflux for eighteen hours. The mixture was filtered and the silver chloride (15.6 g., 97.5%) was washed with water. Saturated sodium chloride solution was added to the combined filtrate and washings until no more silver chloride precipitated. After filtering and washing the silver chloride with water, the combined filtrate and washings were made basic with sodium hydroxide and extracted with ether. The extracts were dried over magnesium sulfate and treated with dry hydrogen chloride in acetone to convert the aminoalcohol into its hydrochloride. On concentration 4.8 g. of 1-isopropylamino-2-propanol hydrochloride separated, m.p. 143.5–145°. The m.p. of this sample was not depressed on mixture with a known sample prepared from the aminoalcohol[20b] and hydrogen chloride in acetone and purified by crystallization to constant m.p. from acetone and acetone–methylene chloride; m.p. 144.5–146.5°.

*Anal.* Calcd. for $C_6H_{16}ONCl$: C, 46.90; H, 10.50; N, 9.12; Cl, 23.08. Found: C, 46.80; H, 10.57; N, 8.81; Cl, 23.2.

By a similar procedure 1-cyclohexylamino-2-chloropropane hydrochloride (20 g.) was converted to 1-cyclohexylamino-2-propanol (11.4 g., 77%), b.p. 125° (20 mm.), which solidified on cooling and was identified as the hydrochloride, m.p. and mixed m.p. with a known sample[20b] 162.5–164°. Likewise 2-isopropylamino-1-chlorobutane hydrochloride (20.6 g.) yielded 10.3 g. (68%) of 2-isopropylamino-1-butanol, b.p. 88° (20 mm.), m.p. 43–46°. This aminoalcohol was converted to the hydrochloride as a solid derivative, m.p. 99.5–101°. Its m.p. was not depressed on mixture with a known sample prepared from 2-isopropylamino-1-butanol[20c] and hydrogen chloride in acetone and recrystallized from acetone; m.p. 100–101.5°.

*Anal.* Calcd. for $C_7H_{18}ONCl$: C, 50.14; H, 10.82; N, 8.35; Cl, 21.15. Found: C, 50.28; H, 10.58; N, 8.29; Cl, 21.2.

On treatment with silver nitrate under similar conditions 2-cyclohexylamino-1-chlorobutane hydrochloride

(18) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(19) Gabriel and Ohle, *Ber.*, **50**, 820 (1917).

(20) (a) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942); (b) **66**, 1454 (1944); (c) Hancock and Cope, *ibid.*, **66**, 1738 (1944).

TABLE II

6-METHOXY-8-AMINOQUINOLINE DERIVATIVES PREPARED BY ALKYLATION WITH ALKYLAMINOALKYL CHLORIDE HYDROCHLORIDES

| Alkylating agent No.[a] | Moles | 6-Methoxy-8-aminoquinoline, moles | Formula of product | Survey number[b] | Yield, %[c] | M. p., °C. |
|---|---|---|---|---|---|---|
| 1 | 0.22 | 0.20 | V | SN 13,705 | 12 | 229–229.5 (dec.)[h] |
| 2 | .11 | .10[l] | VI | SN 13,704 | 20 | 228.5–229 (dec.)[h] |
| 3 | .17 | .16 | VII | SN 13,707[e] | 20[f] | 229–230 (dec.)[h] |
| 4 | .10 | .10 | VIII | SN 13,706[d] | 18 | 232.5–233.5 (dec.)[h] |
| 5 | .16 | .16[k] | IX | SN 13,709 | 14[g] | 208–209 (dec.)[h] |
| 6 | .134 | .134 | X | SN 13,708 | 16 | 177–179[i,j] |

[a] Identified by these numbers in column 1, Table I. [b] Number by which the compound is designated in ref. 3. [c] Designated as XI in ref. 3 but the correct structure is VII. [d] Designated as XII in ref. 3 but the correct structure is VIII. [e] Yield of analytically pure material crystallized to constant m. p. Yields of fairly pure products were considerably higher. [f] Yield of the free base, distilled at 0.03 mm. and a bath temperature of 180–200° and recrystallized from ethanol–water; m. p. 93–94°. *Anal.* Calcd. for $C_{19}H_{27}ON_3$: C, 72.81; H, 8.69; N, 13.41. Found: C, 73.15; H, 8.66; N, 13.3. [g] Eight per cent. was isolated as the free base, distilled at 0.03–0.04 mm. and a bath temperature of 170–185° and recrystallized from ethanol–water; m. p. 62–63°. *Anal.* Calcd. for $C_{20}H_{29}ON_3$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.50; H, 8.89; N, 12.7. The remainder (6%) was isolated as the dihydrochloride. [h] Recrystallized from absolute ethanol. [i] Recrystallized from absolute ethanol–ether. [j] Dried at 60° and 1 mm. overnight. Analysis indicated that the salt was a hemihydrate. Drying at 118° and 1 mm. caused partial loss of hydrogen chloride. [k] The reactants were heated in 40 ml. of refluxing *n*-butanol for sixty-eight hours. [l] The period of reflux was forty-seven hours.

(13.35 g.) yielded 7.4 g. (73%) of 2-cyclohexylamino-1-butanol, b.p. 128–129° (25 mm.). The hydrochloride was prepared as a derivative, m.p. 158.5-160.5°. The m.p. of this sample was not depressed on mixture with a known sample prepared from 2-cyclohexylamino-1-butanol[20c] and hydrogen chloride in acetone–ethanol and recrystallized from methylene chloride–acetone and ethanol–ether; m.p. 161–162°.

*Anal.* Calcd. for $C_{10}H_{22}ONCl$: C, 57.81; H, 10.68; N, 6.75; Cl, 17.07. Found: C, 57.97; H, 10.49; N, 6.57; Cl, 17.0.

**Alkylation of 6-Methoxy-8-aminoquinoline with Alkylaminoalkyl Chloride Hydrochlorides.**—The 6-methoxy-8-aminoquinoline derivatives V-X listed in Table II were prepared by the procedure described by Rohrmann and Shonle,[5] modified as described below and in the foot notes. Absolute ethanol solutions of the reactants were heated under reflux for sixty to sixty-seven hours, after which the ethanol was removed under reduced pressure. Water was added to the residue, which was made strongly basic with 20% sodium hydroxide, in some cases saturated with potassium carbonate,[21] and extracted with ether or methylene chloride.[22] The extracts were dried over magnesium sulfate, concentrated, and the residue was distilled in a short-path modified Hickmann molecular-type pot still. In each case 6-methoxy-8-aminoquinoline was separated as a low boiling fraction. V, VII and IX distilled as higher boiling fractions, VII and IX under conditions noted in the footnotes and V at 0.015 mm. and a bath temperature of 155–180°. V was converted to the dihydrochloride and purified by recrystallization, while VII and IX were purified by the methods described in the footnotes. In the distillation of VI, VIII and X, decomposition began after removal of the 6-methoxy-8-aminoquinoline, so the undistilled residues were dissolved in ethanol and hydrochloric acid was added to convert the products to dihydrochlorides, which were purified by recrystallization.

Dipicrates (Table III) were prepared from VII, VIII, IX and X prepared by alkylation (Table II) in order to obtain additional crystalline derivatives for comparison with dipicrates of these compounds obtained from the unequivocal syntheses described below. The bases and picric acid (2.2 molar equivalents) in absolute ethanol were heated to the reflux temperature. The dipicrates separated on cooling, and were purified by recrystallization to constant m.p. from the solvents noted in Table III.

(21) There was some evidence that the bases were partially converted to carbonates in the presence of potassium carbonate, which was omitted in later preparations.

(22) In the preparation of V, 6-methoxy-8-aminoquinoline was separated from the more basic product by preparing a solution of the crude product in 500 ml. of water and 200 ml. of ethanol, adding concd. hydrochloric acid until the solution was acid to congo red, then sodium acetate until the solution was slightly basic to congo red, and extracting with eight 100-ml. portions of ether. See Elderfield, *et al.* THIS JOURNAL, **68**, 1521 (1946).

### Synthetic Proofs of Structure

**6-Methoxy-8-(2-nitroisopropylamino)-quinoline (XIII).**—A solution of 3.5 g. of freshly distilled 1-nitro-1-propene[23] in 50 ml. of ether was added to 7 g. of 6-methoxy-8-aminoquinoline dissolved in 50 ml. of ether, and the solution was heated under reflux for twenty-four hours. The ether was removed under reduced pressure; the residue crystallized on cooling and scratching. Crystallization from 40 ml. of absolute ethanol gave 7.5 g. (72%) of light yellow needles, m.p. 84–85°.

*Anal.* Calcd. for $C_{13}H_{15}O_3N_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 60.03; H, 6.01; N, 16.15.

**6-Methoxy-8-(2-cyclohexylaminoisopropylamino)-quinoline Dihydrochloride (XI).**—A solution of 1 g. of XIII and 0.75 g. of cyclohexanone in 15 ml. of ethanol was added to the platinum catalyst prepared by reducing 0.1 g. of platinum oxide in 5 ml. of ethanol, and the mixture was shaken with hydrogen. After twenty-two hours hydrogen absorption stopped at 98% of the theoretical value. The catalyst was separated and ethanolic hydrogen chloride added to the filtrate, which was concentrated and diluted with ether. One recrystallization of the yellow product from absolute ethanol gave 0.6 g. (40%) of XI; m.p. 207.5–208.5° (dec.), which was raised to a constant m.p. of 210–211° (dec.) by two recrystallizations from absolute ethanol.

*Anal.* Calcd. for $C_{19}H_{27}ON_3 \cdot 2HCl$: C, 59.06; H, 7.57; N, 10.88; Cl, 18.35. Found: C, 59.19; H, 7.44; N, 11.09; Cl, 18.35.

A mixed m.p. of XI with the product of alkylation (VII, equation 1; Table II, m.p. 226–228° (dec.)) was depressed to 196–200° (dec.).

XI was heated with 2.2 equivalents of picric acid in ethanol and converted to the dipicrate, which was recrystallized from 95% ethanol to a constant m.p. of 171.5–172.5° (dec.).

*Anal.* Calcd. for $C_{31}H_{33}O_{15}N_9$: N, 16.34. Found: N, 16.38.

A mixed m.p. of XI dipicrate with the dipicrate of the

(23) Schmidt and Rutz, *Ber.*, **61**, 2146 (1928).

TABLE II (*Continued*)

| Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|
| $C_{18}H_{27}ON_3Cl_2$ | 58.06 | 58.09 | 7.31 | 7.78 | 11.29 | 11.23 | 19.05 | 19.07 |
| $C_{15}H_{23}ON_3Cl_2$ | 54.2 | 54.4 | 6.98 | 6.95 | 12.7 | 12.6 | 21.3 | 21.3 |
| $C_{19}H_{29}ON_3Cl_2 \cdot 0.5H_2O$ | 57.72 | 57.74 | 7.88 | 7.64 | 10.63 | 10.93 | 17.94 | 18.07 |
| $C_{16}H_{25}ON_3Cl_2$ | 55.48 | 55.3 | 7.28 | 7.66 | 12.13 | 11.8 | 20.48 | 20.32 |
| $C_{20}H_{31}ON_3Cl_2$ | 59.99 | 60.12 | 7.81 | 7.90 | 10.50 | 10.5 | 17.7 | 17.3 |
| $C_{17}H_{27}ON_3Cl_2 \cdot 0.5H_2O$ | 55.28 | 55.6 | 7.64 | 7.72 | 11.38 | 11.2 | 19.20 | 19.4 |

TABLE III

DIPICRATES OF 6-METHOXY-8-AMINOQUINOLINE DERIVATIVES PREPARED BY ALKYLATION

| Dipicrate of: | M. p., °C. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|
| VII | 186–186.5 (dec.)[a] | $C_{31}H_{33}O_{16}N_9$ | 48.25 | 48.16 | 4.31 | 4.36 |
| VIII | 188.5–189 (dec.)[a] | $C_{28}H_{29}O_{15}N_9$ | 45.97 | 45.86 | 4.00 | 4.31 |
| IX | 164.5–165[a] | $C_{32}H_{35}O_{15}N_9$ | 48.92 | 48.63 | 4.49 | 4.49 |
| X | 140.5–141[b] | $C_{29}H_{31}O_{15}N_9$ | 46.71 | 46.71 | 4.19 | 4.46 |

[a] Recrystallized from a mixture of two parts of absolute ethanol and one part of acetone. [b] Recrystallized from a mixture of four parts of absolute ethanol and one part of acetone.

alkylation product (VII, equation 1; Table III, m.p. 186–186.5° (dec.)) was depressed to 162–162.5° (dec.).

**6-Methoxy-8-(2-isopropylaminoisopropylamino)-quinoline Dihydrochloride (XII).**—Hydrogenation of a solution of 1 g. of XIII and 0.45 g. of acetone in 15 ml. of ethanol in the presence of 100 mg. of prereduced platinum oxide required twenty-two hours, and 96.5% of hydrogen was absorbed. The product was isolated in the same manner as XI and recrystallized from ethanol; yield 0.45 g. (35%), m.p. 217.5–218.5° (dec.).

*Anal.* Calcd. for $C_{16}H_{23}ON_3 \cdot 2HCl$: C, 55.48; H, 7.28; N, 12.13; Cl, 20.48. Found: C, 55.56; H, 7.41; N, 12.10; Cl, 20.60.

A mixed m.p. of XII with the product obtained by alkylation (VIII, equation 1; Table II, m.p. 239–240° (dec.)) was depressed to 207–207.5° (dec.).

XII was converted to the dipicrate, which was recrystallized from 2:1 ethanol–acetone; m.p. 184–185° (dec.).

*Anal.* Calcd. for $C_{28}H_{29}O_{15}N_9$: C, 45.97; H, 4.00. Found: C, 46.09; H, 4.12.

A mixed m.p. of XII dipicrate with the dipicrate of the alkylation product (VIII, equation 1; Table III, m.p. 188.5–189° (dec.)) was depressed to 169–170° (dec.).

**6-Methoxy-8-(2-hydroxypropylamino)-quinoline (XIV).**—Propylene oxide (7 g.) was added to a solution of 17.4 g. of 6-methoxy-8-aminoquinoline in 50 ml. of dioxane and 10 ml. of water. The solution was heated under reflux for twenty-four hours, concentrated under reduced pressure, and the residue distilled from a Hickmann molecular-type pot still. 6-Methoxy-8-aminoquinoline (12.5 g.) distilled at a bath temperature of 110–130° (0.02–0.025 mm.), followed by XIV as a very viscous orange oil (6.8 g., 29%) at a bath temperature of 130–145° (0.02–0.025 mm.).

*Anal.* Calcd. for $C_{12}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.21; H, 6.97; N, 12.01.

Attempts to oxidize XIV to XV with chromic acid in acetic acid, potassium permanganate in acetone, cyclohexanone and aluminum isopropoxide in benzene, and benzophenone and potassium *t*-butoxide in benzene were unsuccessful.

**6-Methoxy-8-acetonylaminoquinoline (XV).**—A solution of 34.8 g. of 6-methoxy-8-aminoquinoline and 13.7 g. of bromoacetone in 250 ml. of ether was heated under reflux for a total of forty-four hours and filtered at intervals to remove insoluble salts (principally 6-methoxy-8-aminoquinoline hydrobromide). The ether filtrate was concentrated under reduced pressure. Semicarbazide hydrochloride (5 g.) and sodium acetate (10 g.) were added to a solution of the residue in 75 ml. of ethanol, followed by water to the point of turbidity (50 ml.). The mixture was boiled for ten minutes, cooled, and the solid which separated was recrystallized to constant melting point from benzene–petroleum ether to yield 3.0 g. of XV semicarbazone, m.p. 171.5–173.5°.

*Anal.* Calcd. for $C_{14}H_{17}O_2N_5$: C, 58.52; H, 5.97; N, 24.38. Found: C, 58.65; H, 5.99; N, 24.09.

XV semicarbazone (1 g.) was hydrolyzed by heating on a steam-bath with 20 ml. of 3 *N* hydrochloric acid for thirty minutes. The solution was cooled, made alkaline with potassium carbonate, and extracted with methylene chloride. The XV in the extract was purified by crystallization from methylene chloride–ether and ether; m.p. 92.5–93.5°.

*Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.85; H, 6.16; N, 12.23.

XV (0.1 g.) was converted to the phenylhydrazone as an additional derivative, which was purified by four crystallizations from ethanol–water; yield 0.055 g., m.p. 133.5–135°.

*Anal.* Calcd. for $C_{19}H_{20}ON_4$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.40; H, 6.50; N, 17.54.

**6-Methoxy-8-(2-phthalimidopropylamino)-quinoline (XVI).**—XVI was prepared and isolated by the procedure described for 6-methoxy-8-(4-phthalimidobutylamino)-quinoline, from 19 g. of 2-phthalimido-1-bromopropane[24] and 13.6 g. of 6-methoxy-8-aminoquinoline, which were heated in a nitrogen atmosphere at 145–150° for six hours. The product crystallized from ethanol as light yellow needles; yield 5.35 g. (21%), m.p. 142–144°. An analytical sample recrystallized twice from ethanol had a constant m.p. of 145–145.5°.

*Anal.* Calcd. for $C_{21}H_{19}O_3N_2$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.48; H, 5.33; N, 11.76.

**6-Methoxy-8-(2-aminopropylamino)-quinoline Dihydrochloride (XVII).**—A solution of 7 g. of XVI and 1.4 g. of 85% hydrazine hydrate in 150 ml. of absolute ethanol was heated under reflux for two hours and then concentrated under reduced pressure. The residue was heated on a steam-bath for one hour with 200 ml. of 2 *N* hydrochloric acid, cooled, and filtered to remove the phthalhydrazide, which was washed with water. The filtrate and washings were concentrated under reduced pressure, treated with dilute sodium hydroxide to liberate XVII as the free base, and extracted with methylene chloride. The extracts were washed with sodium chloride solution, dried over sodium sulfate, and concentrated. A solution of the residue in ethanol was made acid to congo red with hydrogen chloride in ethanol. XVII separated as bright orange crystals on cooling; yield 4.0 g. (68%), m.p. 230.5–233° (dec.). Two recrystallizations from absolute ethanol gave an analytical sample with a constant m.p. of 230.5–231.5° (dec.).

(24) Gabriel and Ohle, *Ber.*, **50**, 812 (1917).

*Anal.* Calcd. for $C_{13}H_{17}ON_3 \cdot 2HCl$: C, 51.32; H, 6.30; N, 13.81; Cl, 23.31. Found: C, 51.34; H, 6.41; N, 13.89; Cl, 22.85.

**6-Methoxy-8-(2-cyclohexylaminopropylamino)-quinoline (VII).**—One gram of XVII was converted to the free base by shaking with dilute sodium hydroxide and methylene chloride. The extract was dried, the solvent removed, and a solution of the residue and 1 ml. of cyclohexanone in 15 ml. of ethanol was shaken with hydrogen and 100 mg. of prereduced platinum oxide. The theoretical amount of hydrogen was absorbed in ten minutes, and then the rate decreased sharply. The catalyst was removed, the filtrate concentrated to a volume of 15 ml., and water was added slowly. VII separated as light brown needles; yield 0.66 g. (65%), m.p. 92–93°. Crystallization from ethanol–water after treatment with Darco gave 0.62 g. of VII as white needles, m.p. 93–93.5°, which was not depressed on mixture with a sample of VII melting at 93–94° prepared by alkylation (equation 1, Table II).

*Anal.* Calcd. for $C_{19}H_{27}ON_3$: C, 72.81; H, 8.69; N, 13.41. Found: C, 72.43; H, 8.41; N, 13.60.

The dihydrochloride of VII prepared in this way was recrystallized twice from absolute ethanol and dried to constant weight at 40° and 1 mm.; m.p. 229–230°; mixed m.p. with VII dihydrochloride prepared by the alkylation reaction (equation 1, m.p. 229–230° (dec.), Table II) was not depressed. A mixed m.p. with XI dihydrochloride (m.p. 210–211° (dec.)) was depressed to 200–201° (dec.). Analysis indicated that VII dihydrochloride was a hemihydrate.

*Anal.* Calcd. for $C_{19}H_{27}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 57.72; H, 7.65. Found: C, 57.80; H, 7.61.

The dipicrate of VII from this source was recrystallized from 2:1 ethanol–acetone as bright orange crystals, m.p. 186–186.5° (dec.); mixed m.p. with the dipicrate of VII prepared by alkylation (equation 1; m.p.186–186.5° (dec.), Table III) was unchanged; mixed m.p. with XI dipicrate (m.p. 171.5–172.5° (dec.)) was depressed to 162–168.5° (dec.).

*Anal.* Calcd. for $C_{31}H_{33}O_{15}N_9$: C, 48.25; H, 4.31; N, 16.34. Found: C, 48.39; H, 4.52; N, 16.10.

**6-Methoxy-8-(2-isopropylaminopropylamino)-quinoline Dihydrochloride (VIII).**—One gram of XVII dihydrochloride was converted to the free base and reductively alkylated with acetone (1 ml.) in 15 ml. of absolute ethanol by the procedure described for VII. The theoretical amount of hydrogen was absorbed in one hundred minutes. VIII was isolated as the dihydrochloride in yellow needles, m.p. 234.5–235° (dec.); yield 0.9 g. (79%). A mixed m.p. with VIII dihydrochloride prepared by alkylation (equation 1; m.p. 232.5–233.5° (dec.), Table II) was 233–233.5° (dec.). A mixed m.p. with the isomeric XII dihydrochloride (m.p. 217.5–218.5° (dec.) was depressed to 205–207° (dec.)).

*Anal.* Calcd. for $C_{16}H_{23}ON_3 \cdot 2HCl$: C, 55.48; H, 7.28; N, 12.13; Cl, 20.48. Found: C, 55.11; H, 7.46; N, 12.37; Cl, 20.45.

The dipicrate prepared from this sample of VIII was recrystallized from 2:1 absolute ethanol–acetone and dried to constant weight at 40° and 1 mm.; m.p. and mixed m.p. with the dipicrate of VIII prepared by alkylation (equation 1; m.p. 188.5–189° (dec.), Table III) 188.5–189°.

*Anal.* Calcd. for $C_{28}H_{29}O_{15}N_9$: C, 45.97; H, 4.00; N, 17.23. Found: C, 46.23; H, 4.44; N, 17.04.

**2-Phthalimido-1-hydroxybutane.**—Phthalic anhydride (41.5 g.) was added in portions with cooling to a solution of 25 g. of 2-amino-1-butanol in 100 ml. of methanol. The methanol was removed by distillation and the residue was heated at 20 mm. in a bath at 180–200° until no more water distilled. Distillation of the residue gave 37 g. (60%) of 2-phthalimido-1-hydroxybutane as a very viscous straw-colored liquid, b.p. 155–159° (1 mm.); $n^{25}D$ 1.5613; $d^{25}_4$ 1.2107. $MD$ calcd. 57.18, found 58.66. A redistilled sample was analyzed; b.p. 180° (4 mm.); $n^{25}D$ 1.5617.

*Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.78; H, 5.99; N, 6.48.

**2-Phthalimido-1-bromobutane.**—2-Phthalimido-1-hydroxybutane (45 g.) was added dropwise to 88.4 g. of phosphorus pentabromide, and after the addition the mixture was heated on a steam-bath until it became homogeneous. After cooling, 200 ml. of water was added, followed by potassium carbonate until the mixture was alkaline. The product was extracted with ether, dried over magnesium sulfate and distilled; yield 37 g. (64%), b.p. 159–162° (2 mm.). A redistilled sample of the viscous straw-colored liquid had b.p. 159–160° (2 mm.); $n^{25}D$ 1.5736.

*Anal.* Calcd. for $C_{12}H_{12}O_2NBr$: C, 51.08; H, 4.29; N, 4.97; Br, 28.33. Found: C, 51.05; H, 4.36; N, 4.97; Br, 28.16.

**6-Methoxy-8-(2-phthalimidobutylamino)-quinoline (XVIII).**—A mixture of 25 g. of 2-phthalimido-1-bromobutane and 17 g. of 6-methoxy-8-aminoquinoline was heated in a nitrogen atmosphere at 145–155° for twelve hours. The mixture was heated under reflux with 50 ml. of absolute ethanol, cooled, and filtered to remove 6-methoxy-8-aminoquinoline hydrobromide (11.3 g.). The filtrate was made acid to congo red with concd. hydrochloric acid and yielded a yellow crystalline salt (9.6 g.) which was converted to the free base (XVIII). After crystallization the yield of the yellow product was 6.9 g. (21%), m. p. 112–113°. Three recrystallizations from absolute ethanol gave an analytical sample with a constant m. p. of 113.5–114° (with previous softening).

*Anal.* Calcd. for $C_{22}H_{21}O_3N_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.31; H, 5.70; N, 11.25.

**6-Methoxy-8-(2-aminobutylamino)-quinoline Dihydrochloride (XIX).**—The procedure described for preparing XVII was used to convert 7.5 g. of XVIII to XIX; yield 5.0 g. (78%), m. p. 231–232° (dec.). After one recrystallization from absolute ethanol an analytical sample had a constant m. p. of 235–235.5° (dec.).

*Anal.* Calcd. for $C_{14}H_{19}ON_3 \cdot 2HCl$: C, 52.84; H, 6.65; N, 13.20; Cl, 22.28. Found: C, 52.86; H, 6.94; N, 13.39; Cl, 22.13.

**6-Methoxy-8-(2-cyclohexylaminobutylamino)-quinoline (IX).**—The reductive alkylation procedure described for preparing VII was applied to XIX (1 g.) and 1 ml. of cyclohexanone; hydrogenation was complete in fifteen minutes. IX was isolated as silky-white needles by crystallization from ethanol–water; yield 0.6 g. (58%), m. p. 61–61.5°. Recrystallization from ethanol–water raised the m. p. to 62–62.5°; mixed m. p. with IX prepared by alkylation (equation 2; Table II, m. p. 62–63°) was not depressed.

*Anal.* Calcd. for $C_{20}H_{29}ON_3$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.41; H, 8.95; N, 13.22.

The dihydrochloride of this sample of IX, recrystallized from absolute ethanol and dried to constant weight at 70° and 1 mm. had a constant m. p. and mixed m. p. with IX dihydrochloride prepared by alkylation (equation 2; Table II, m. p. 208–209° (dec.)) of 208–209° (dec.).

*Anal.* Calcd. for $C_{20}H_{29}ON_3 \cdot 2HCl$: C, 59.99; H, 7.81; N, 10.50. Found: C, 59.78; H, 7.92; N, 10.52.

The dipicrate of this sample of IX had a constant m. p. of 165–166° after one recrystallization from 2:1 ethanol–acetone and a mixed m. p. with IX dipicrate derived from the alkylation product (equation 2; m. p. 164–165°, Table III) was not depressed.

*Anal.* Calcd. for $C_{32}H_{35}O_{15}N_9$: C, 48.92; H, 4.49. Found: C, 48.63; H, 4.46.

**6-Methoxy-8-(2-isopropylaminobutylamino)-quinoline Dihydrochloride (X).**—One gram of XIX was reductively alkylated with acetone during two hours by the procedure described for preparing VIII. X was obtained in a yield of 0.8 g. (70%), m. p. 161.5–166° (with previous softening). Three recrystallizations from ethanol gave an analytical sample with a constant m. p. of 171–171.5° (with previous softening). The salt lost weight on drying

and appeared to be a hydrate; a sample dried at 40° and 1 mm. analyzed correctly for a hemihydrate.

*Anal.* Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 55.28; H, 7.64; N, 11.38; Cl, 19.20. Found: C, 55.76; H, 7.36; N, 11.66; Cl, 19.12.

A mixed m. p. of this sample of X with X prepared by alkylation (equation 2; Table II, m. p. 177–179°) was 172–173°.

The dipicrate prepared from this sample of X, recrystallized from 4:1 ethanol–acetone and dried at 70° and 1 mm. had a m. p. of 137–138° (with previous softening) and was not depressed on mixture with X dipicrate prepared from the alkylation product (equation 2; Table III, m. p. 140.5–141°).

*Anal.* Calcd. for $C_{29}H_{31}O_{15}N_9$: C, 46.71; H, 4.19. Found: C, 46.76; H, 4.44.

## Summary

A number of derivatives of 6-methoxy-8-aminoquinoline have been prepared which are substituted on the 8-amino group by primary or secondary aminoalkyl side chains. A rearrangement proceeding through a tertiary ethyleneimine intermediate has been observed to occur in the alkylation of 6-methoxy-8-aminoquinoline with 1-alkylamino-2-chloropropane hydrochlorides (equation 1). 6-Methoxy-8-(alkylaminoalkylamino)-quinolines of known structure have been synthesized by first attaching primary aminoalkyl side chains to the 8-amino group through intermediate phthalimido compounds, and then reductively alkylating the primary aliphatic amino group with acetone and with cyclohexanone in the presence of Adams platinum catalyst and hydrogen. A 6-methoxy-8-(nitroalkylamino)-quinoline also has been reductively alkylated with these ketones under the same conditions.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

# The Adsorption of Water Vapor on Activated Charcoal

BY EDWIN O. WIIG AND A. J. JUHOLA[1]

There will be presented in the papers that follow a method for measuring pore size distribution of charcoal which assumes that water on charcoal is held by capillary condensation. The main support for this assumption is that the pronounced hysteresis in the adsorption isotherm can best be accounted for by explanations based on the capillary condensation theory.[2,3,4,5] The results reported in this paper of studies of the changes in the density of adsorbed water with change in relative pressure and of the changes in the dimensions of an activated charcoal during adsorption and desorption lend further support to this theory.

## I. Linear Expansion of Charcoal

The change in length of charcoal rods as water and also various other vapors are adsorbed has been studied by numerous investigators.[6] In most of these investigations, which will be discussed later, relatively large carbon rods were employed whereas in the present work an activated gas mask adsorbent was used.

This charcoal, N-19, was prepared from hardwood sawdust, zinc chloride activated, extruded as rods 1/16 inch diameter, calcined at 600°, washed and calcined at 850°. It had an ash content of 0.2%, an apparent density of 0.48, a particle density of 0.80, a carbon density (by helium) of 2.09 and a surface area of 1300–1700 sq. m./g.

**Determination of Linear Expansion of Charcoal.**—The principal part of the apparatus for measuring the linear expansion of charcoal during adsorption and desorption is shown in Fig. 1. The inner tube A is filled with the extruded charcoal rods, 2–5 mm. long and 1.6 mm. diameter, placed end to end. The ends of each granule were squared off with emery cloth before being placed in the tube. B is a short piece of wire with squared-off ends placed on top of the charcoal column. Changes in length of the column during adsorption and desorption were observed by following with a cathetometer the movement of the upper edge of the wire with respect to a reference mark on the inner tube. The length of the charcoal column was 960 mm. and its weight was 0.920 g.

The tube assembly, which was weighed at intervals to determine the water content, was attached to an apparatus similar to that shown in Fig. 4 for the necessary evacuation of the sample, adsorption, desorption, measurement of the relative vapor pressure, etc. The charcoal column was thermostated at 24.4° with a water-cooled jacket.

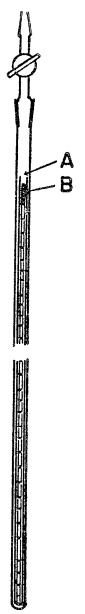



Fig. 1.—Apparatus for measuring linear expansion of charcoal.

## Results

The per cent. change in length of the charcoal column as a function of the relative pressure is shown in Fig. 2. It will be observed that, starting with dry char, as the humidity is increased the charcoal first contracts and then at $p/p_0 \sim 0.68$ begins to expand

(1) Present address: The Barrett Division, Allied Chemical and Dye Corp., Philadelphia, Pennsylvania.

(2) E. O. Kraemer in H. S. Taylor's "A Treatise on Physical Chemistry," D. Van Nostrand Co., New York, N. Y., 1931, Chap. XX.

(3) McBain, THIS JOURNAL, **57**, 699 (1935).

(4) Cohan, *ibid.*, **66**, 98 (1944); includes an excellent bibliography.

(5) Emmett and DeWitt, *ibid.*, **65**, 1253 (1943); Emmett and Anderson, *ibid.*, **67**, 1492 (1945).

(6) Meehan, *Proc. Roy. Soc.* (*London*), **115A**, 199 (1927); Bangham and Fakhoury, *ibid.*, **A130**, 81 (1930); *J. Chem. Soc.*, 1324, (1931); Bangham, Fakhoury and Mohamed, *Proc. Roy. Soc.*, **A138**, 162 (1932); **A147**, 152 (1934); **A147**, 175 (1934); Bangham and Razook, *ibid.*, **A166**, 572 (1938); McBain, Porter and Sessions, THIS JOURNAL, **55**, 2294 (1933); Haines and McIntosh, *J. Chem. Phys.*, **15**, 28 (1947); Schwab and Karkalos, *Z. Elektrochem.*, **47**, 345 (1941).

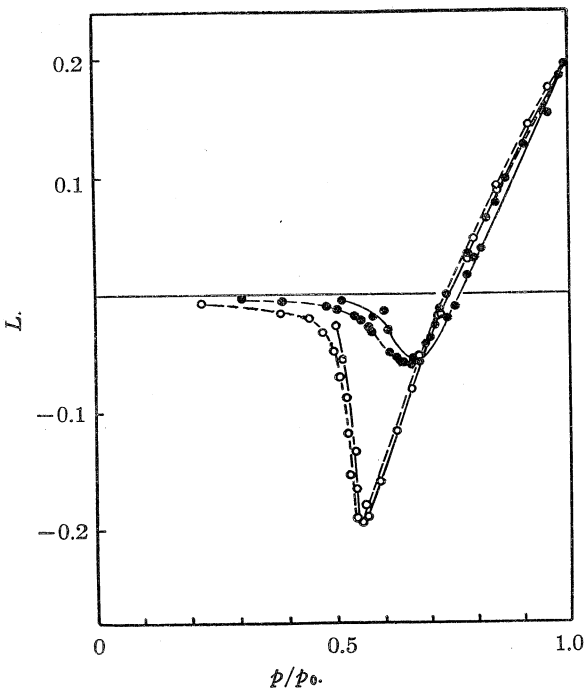



Fig. 2.—Percentage linear expansion $L$ of charcoal N-19 as a function of the relative vapor pressure of adsorbed water: ●, adsorption points; O, desorption points; solid curve, first adsorption and desorption; broken line curve, second adsorption and desorption.

until at $p/p_0 \sim 1$ it is 0.2% longer than at the start. Determinations on the adsorption wave were repeated to make certain the contraction was real. Contraction was again observed but the second set of determinations (broken line curve) did not quite coincide with the first. This displacement of the curve to the left may be due to the same cause as the displacement to the left of the second and subsequent adsorption curves of isotherms as in Fig. 5. On desorption a much greater contraction is obtained.

Except for the results of Haines and McIntosh,[6] which appeared while this work was in progress and with which the present observations are in essential agreement, the contraction obtained here would seem to disagree with the expansion noted by earlier workers. The experimental conditions are quite different, however, and appear to account for the differences in behavior. Most of the charcoals were not as highly activated as are modern chars. Meehan's[5] charcoal was prepared from three-inch cubes of yellow pine which were slowly dried and then heated uniformly for approximately four hours in a charcoal packed cylinder having small gas vents in its ends. After gradual cooling the charcoal so obtained was trimmed to approximately two-inch cubes. Some of the experiments of Bangham,[6] *et al.*, were carried out with rods cut from this charcoal. It would appear doubtful that such cubes could be completely carbonized near the center. Any oxygen structure remaining in the charcoal might easily produce immediate swelling as in wood itself. The oft quoted observation of Bangham and Fakhoury[6] that the first traces of water admitted to their char caused a marked expansion was made on an 80 × 8 × 8 mm. rod of German willow charcoal of pre-World War I manufacture. Again there is no way of knowing how thoroughly carbonized such charcoal might be. This charcoal was untreated except that between experiments it was "submitted to prolonged vacuum-heating at 220°" in the extensometer. On heating one of Meehan's charcoals to 1000° Bangham observed on adsorbing methanol at 20° that no measurable expansion occurred until 0.059 g. of methanol per g. of carbon had been adsorbed, then marked expansion set in at 0.07 g. per g., followed by a steady increase thereafter. This is in contrast with greater expansion on less rigorously treated samples.

McBain, Porter and Sessions[6] report only expansion for a rod (60 mm. long × 25 mm. diameter) of activated sugar charcoal. However, in the lower relative pressure range, where contraction was observed in the present investigation, these workers chose to hold the water vapor pressure constant and heated the charcoal to 37–61° to reduce the relative humidity. Since the surface tension changes with temperature, any contraction that might have occurred at lower temperatures may have been missed. Bangham observed no expansion by water vapor absorbed at 100° and a decrease in expansion by methanol at 50° compared to 0°. Also, Haines and McIntosh[6] found an expansion with dimehtyl ether at 20° but an initial contraction with a more sensitive extensometer at 6.5°. Using relatively large rods of a zinc chloride activated charcoal similar to that employed here, Haines and McIntosh observed no change in length with increase in water vapor pressure until $p/p_0 = 0.75$ was reached, after which expansion increased regularly. On subsequent desorption contraction below the original length and then expansion to the original length occurred as reported here. However, in a footnote they report that with their more sensitive electrical condenser arrangement for measuring the change in length of the charcoal rod a slight initial *contraction* was observed in the lower relative pressure range, analogous to the larger contraction in the present work.

The thermal effects which Haines and McIntosh observed on admitting vapors to charcoal might also contribute to the difference in behavior of the large rods of other investigators and the very small rods used here. With long relatively thick rods the vapor penetration must advance crosswise radially. The thermal effects should consequently be lengthwise. If the temperature is lower toward the center of the rod then perhaps contraction sets in crosswise and expansion, due to the higher temperature, lengthwise. Eventually the rod should reach equilibrium but the at-

tainment of equilibrium between a radial contraction and a lengthwise expansion might be slow, especially when one considers that charcoal is, as X-ray data indicate,[7] probably composed of small graphite platelets. At any rate, in the second condenser arrangement of Haines and McIntosh, where the thermal effect was smaller, a slight contraction rather than expansion was observed with water.

## II. The Density of Adsorbed Water

The density of water adsorbed on silica gel has been reported by Ewing and Spurway[8] to vary from 0.5408 for larger amounts of water to 1.0285 for smaller quantities. Danforth and DeVries[9] found densities for carbon tetrachloride adsorbed on activated charcoal which began at about 1.9, fell to a minimum of 1.36 and then rose to 1.58 as the vapor pressure was increased. Similar results were obtained with acetone. Morrison and McIntosh[10] have recently reported the density of water adsorbed on several activated charcoals. Their values, however, are quite different from those reported here.

Two charcoals were used in the present work: N-19, on which the linear expansion measurements were made; N-291-AY-1, a zinc chloride activated wood charcoal which was extruded through a seven-inch die in one step of its preparation and later crushed to small particles. The pore size distribution, etc., of this char are reported in detail in the following paper.

**Determination of the Density of Adsorbed Water.**—In principle the determination consisted of measuring by helium displacement the volume of a known weight of dry charcoal followed by similar volume measurements with varying amounts of adsorbed water.

The charcoal (16–20 mesh) contained in adsorption tube T, Fig. 3, was degassed at 360° for several hours, stopcock A closed and the thermostat water jacket J placed around T. In the case of charcoal N-291-AY-1 the adsorption tube had a volume of about 32 cc. and held 7.380 g. char. To obtain much greater accuracy the sample was increased tenfold for N-19. Gas buret B, with the mercury level at one of the constrictions between the bulbs, and the system to A were filled with helium to nearly atmospheric pressure, usually about 740 mm. as measured by mercury manometers 1 and 3. The pressure on both sides of the dibutyl phthalate null manometer 5 was adjusted to that of B. Stopcock A was opened to admit helium to the charcoal and the mercury level in B raised to increase the helium pressure to the initial pressure as determined by the null manometer. After equilibrium was reached, mercury was drained from B until the initial level was obtained and the mercury weighed. The volume of the weighed mercury was the volume of T, with or without charcoal as the case might be.

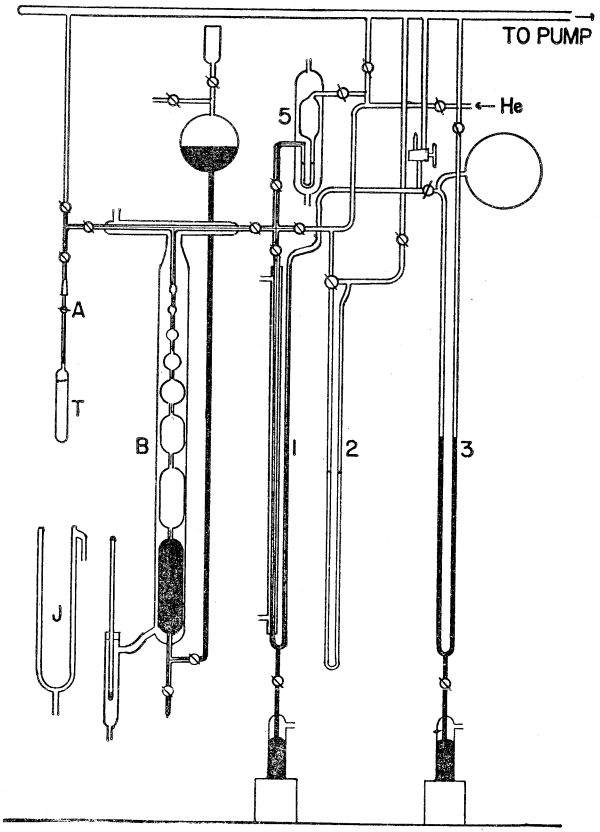



Fig. 3.—Apparatus for measuring apparent volume of adsorbed water.

When the charcoal contains adsorbed water a slightly different procedure was followed since a vapor pressure correction was necessary in the calculations. The water vapor was allowed to expand from T into B and over to dibutyl phthalate manometer 2, where its pressure was measured after attainment of equilibrium. Dead space corrections were negligible. The buret system to stopcock A was evacuated and from this point on the determination was the same as for dry char. Tube T contained a fine capillary below A which prevented diffusion of water vapor through the helium into B. The vapor pressure correction was introduced into the calculations through the relationship

$$V_t = \frac{P}{P - p} V_h$$

where $P$ is the helium pressure, $p$ the vapor pressure of the adsorbed water, $V_h$ the volume of weighed mercury, and $V_t$ the volume of tube T. An indication of the accuracy of the measurements is given by two sets of experiments with smaller than 16 mesh Pyrex glass particles in place of charcoal in tube T. The volume by helium displacement of, *e. g.*, 2.5 and 5.0 g. water on the glass

(7) Clark and Johnstone, O. S. R. D. Formal Report, Dec. 9, 1942; Hofman, Ragoss and Sinkel, *Kolloid Z.*, **96**, 231 (1941).
(8) Ewing and Spurway, THIS JOURNAL, **52**, 4635 (1930).
(9) Danforth and DeVries, *ibid.*, **61**, 873 (1939).
(10) Morrison and McIntosh, *Canadian J. Res.*, **24**, 137 (1946).

gave 0.997 for the density of water at 24° as compared to the accepted value of 0.9973.

**Determination of Water Adsorption Isotherms.**—The apparatus for determining the isotherms, which are needed in connection with both the density of adsorbed water and the linear expansion of charcoal, is shown in Fig. 4. Manometers M and N contained dibutyl phthalate, M measured $P$, the vapor pressure of adsorbed water, and N measured $P_0$, the saturation vapor pressure of water. A and C were three-way stopcocks with one of the outlets sealed to a capillary tube as shown in the diagram. During evacuation the stopcocks were turned so that gases passed through the larger outlets while during adsorption or desorption the stopcocks were turned so the water vapor passed through the capillaries. The purpose of the capillaries was to slow down the adsorption or desorption process sufficiently so that the pressure of the vapor surrounding the charcoal was not greatly different from the equilibrium pressure. The amount of water adsorbed was determined by weighing tube T. Flask B, containing water, and T were submerged in a water-bath maintained at about 24°, slightly below room temperature. While precautions were taken to prevent rapid changes in temperature, no effort was made to keep the bath at exactly constant temperature, since Coolidge[11] has shown that the water adsorption isotherm is not affected by temperature changes near room temperature.

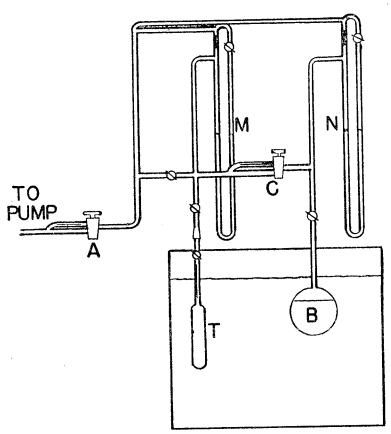



Fig. 4.—Apparatus for measuring water adsorption.

## Results

For the two charcoals studied the water adsorption isotherm is presented in Figs. 5 and 6, the apparent volume of adsorbed water in Figs. 7 and 8 and the density of adsorbed water in Table I. The latter, consistently less than unity, is in disagreement with the values 1.01 to 1.16, 0.95 to 1.04, 0.99 to 1.15 and 0.98 to 1.17 obtained by Morrison and McIntosh on four different charcoals but in line with their values of 0.95, 0.94 and 0.93 at 100% relative humidity. The present data would appear to be reliable; the high results

(11) Coolidge, THIS JOURNAL, 49, 708 (1927).

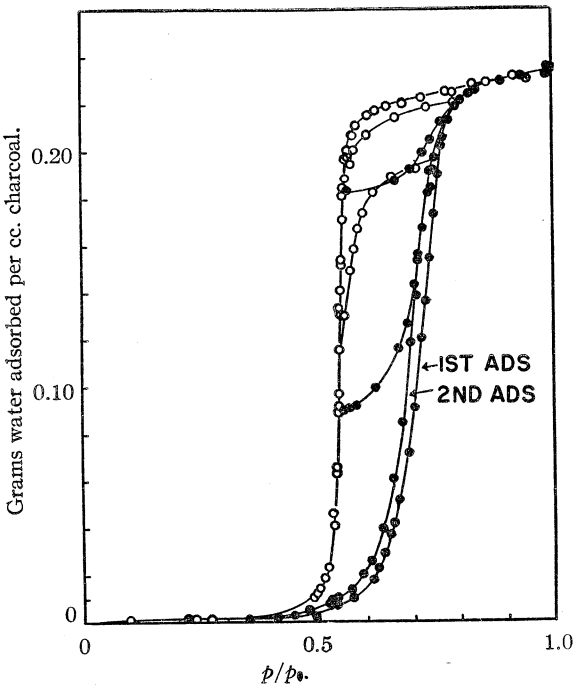



Fig. 5.—Water adsorption isotherm, charcoal N291-AY-1: ●, adsorption; O, desorption.

mentioned could be caused by either or both of two possible sources of error.[12] At first sight it might appear strange that the volume (or density) of adsorbed water does not reach the normal

TABLE I

DENSITY OF ADSORBED WATER ON THE ADSORPTION AND DESORPTION BRANCHES OF THE ISOTHERM

| Relative pressure | N-291-AY-1 Adsorp. | N-291-AY-1 Desorp. | N-19 Adsorp. | N-19 Desorp. |
|---|---|---|---|---|
| 0.35 | | | | 0.90 |
| .40 | | | 0.79 | .82 |
| .50 | | 0.85 | .82 | .85 |
| .60 | 0.90 | .90 | .85 | .89 |
| .70 | .91 | .91 | .89 | .91 |
| .80 | .92 | .92 | .91 | .91 |
| .90 | .93 | .93 | .92 | .92 |
| .99 | .93 | .93 | .92 | .92 |

(12) Small amounts of acid spray from the sulfuric acid solutions (stirred to hasten equilibrium) which were used to control the water vapor pressure might, as suggested by Emmett (private communication) have contaminated the water adsorbed on the charcoal. A more likely source of error is to be found in the method used to determine the volume of the adsorbed water by helium displacement. In making this determination helium, at high pressure and mixed with water vapor of the same partial pressure as that over the charcoal, was admitted to the charcoal tube. This has the effect of yielding a total water vapor pressure in the charcoal tube greater than the original partial pressure. Some of this extra water vapor should be adsorbed, resulting in a somewhat greater pressure drop, hence a smaller volume for the adsorbed water and an increased density. Though the system was open for twenty-four hours to allow attainment of equilibrium, the back diffusion of water vapor through two stopcocks and tubing filled with helium at relatively high pressure would be very slow. As the water content of a given char increases the effect of the extra pressure decrease will be smaller and the density will decrease, as was observed in general. *Cf.* Tuck, McIntosh and Maass, *Canadian J. Res.*, **26**, 20 (1948).

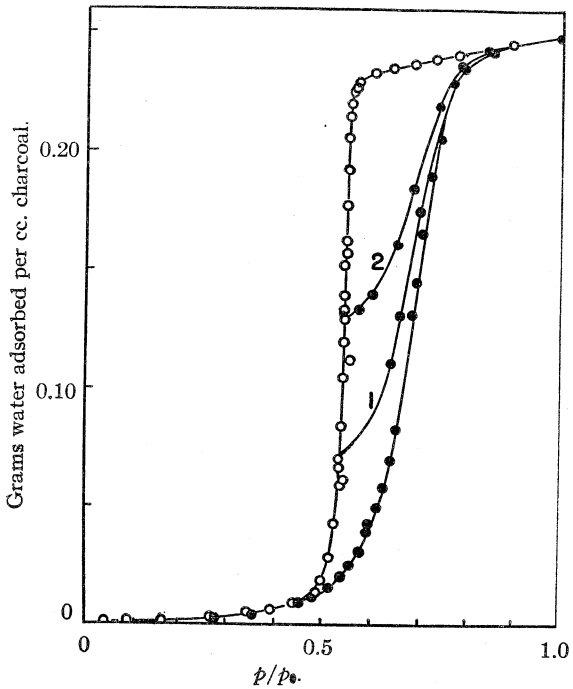



Fig. 6.—Water adsorption isotherm for charcoal N-19: ● adsorption; O desorption; 1 and 2 scanning curves.

value for liquid water at $P_0$. However, since the water molecules in general cannot exactly fit the pores, there will be larger voids between water molecules in pores than are present in the normal

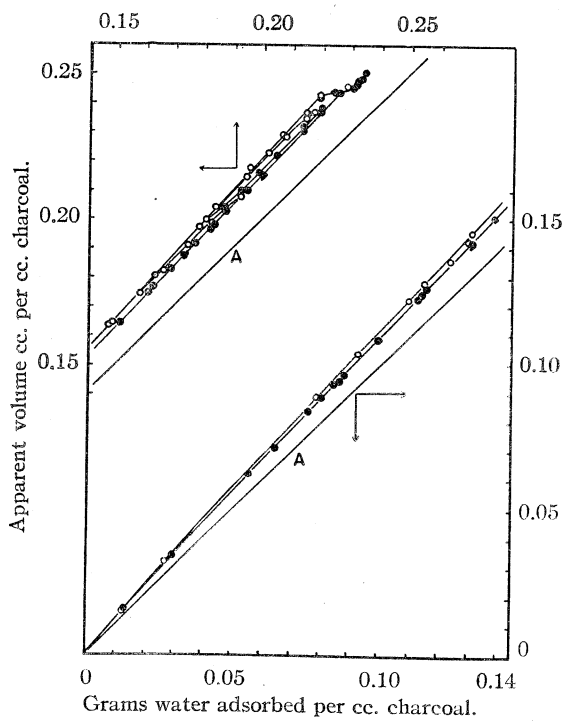



Fig. 7.—Apparent volume of adsorbed water at 24° on charcoal N291: ●, adsorption points; O, desorption points; curve A, normal volume of water.

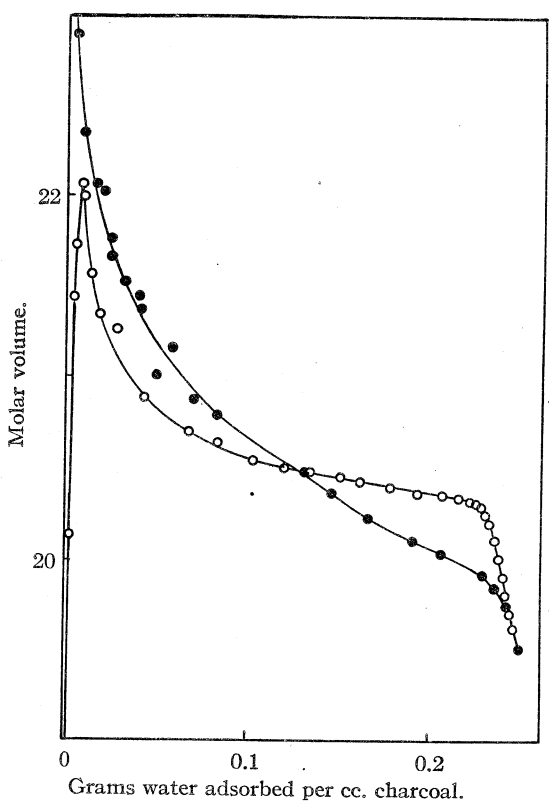



Fig. 8.—Molar volume of adsorbed water in equilibrium with vapor pressures on the main hysteresis loop of the isotherm: ●, adsorption; O, desorption; charcoal N-19.

liquid state. Since these chars have a large volume of small pores, the voids prevent the attainment of the normal density.

## Discussion

The results of the measurements of the linear expansion of charcoal suggest that the expansion is a function of the relative vapor pressure and the weight of adsorbed water. It was found that the experimental data approximately obey the equation

$$L = kw(\ln p/P_0 - B) \qquad (1)$$

where $L$ is the per cent. linear expansion, $B$ is $\ln p_a/P_0$ where $p_a$ is the vapor pressure when $L = 0$ (*i. e.*, where $L$ changes from negative to positive), $w$ is the weight of adsorbed water per cc. of charcoal and $k$ is a constant. When the quantity $w(\ln p/P_0 - B)$ is plotted against $L$ as shown in Fig. 9, an essentially straight line is obtained, the slope of which gives $k$ a value of 2.8. The greatest deviation from this equation, indicated by the dotted line curve, occurs during contraction on adsorption at low partial pressures; the rest of the experimental points obey the equation quite well.

The contraction of the carbon structure can readily be accounted for by the capillary condensation theory which requires a contraction pressure or tension on the adsorbent. When the latter predominates—as in the intermediate pressure

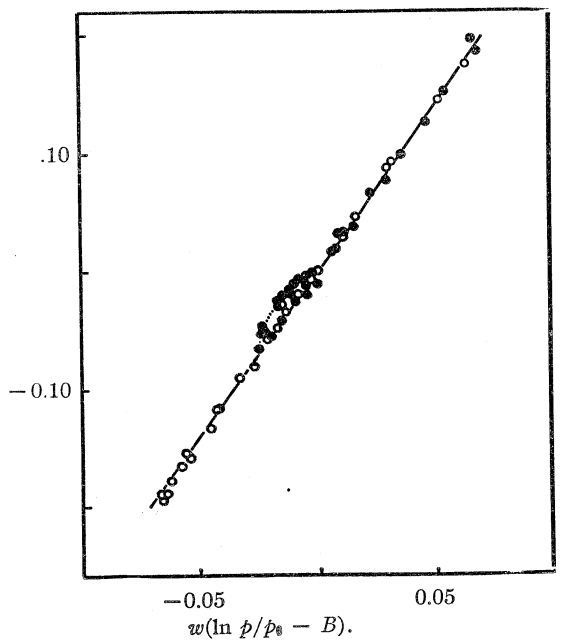



Fig. 9.—Percentage linear expansion $L$ of charcoal as function of logarithm of relative vapor pressure and weight of adsorbed water $w$ per cc. of charcoal: $B$ constant; ●, adsorption points; O, desorption points.

range, in which the pores are filled but in which the curvature of the menisci is still appreciable—contraction results but, as the tension is reduced, owing to decreased curvature of the menisci, the swelling pressure predominates and a net expansion results which increases to $P_0$. The constant $B$ may then be considered due to the swelling pressure similar to the swelling of any solid by a liquid.

A helpful picture which fits in with the data in the succeeding papers is as follows. The water molecules in pores behave as rigid spheres and due to the relative size of the pores as compared to the water molecules, there are larger voids between the molecules than exist in the normal liquid phase. Owing to their mutual attraction (hydrogen bonding), the molecules tend to squeeze into these voids and the result is an outward pressure exerted against the pore wall which appears as expansion of the charcoal. When the meniscus of the condensed water is in small pores, the meniscus exerts a negative pressure on the liquid which partially balances the mutual attraction between the molecules and, therefore, they do not tend to squeeze into the voids. The result is that the charcoal does not expand but rather contracts. As more water is adsorbed, the meniscus moves to larger pores, thereby decreasing the negative pressure (or increasing the hydrogen bonding since the molecules approach each other closer), and as a result the charcoal expands. It follows that if there were no voids between the water molecules there would be no expansion of the charcoal at the higher relative pressures. The length of the charcoal column during adsorption would pass through a minimum and come to its normal length at saturation.

According to the capillary rise equation a liquid is under a tension or negative pressure $P$ which varies inversely with the pore diameter $D$

$$P = -\frac{4\sigma \cos\theta}{D} \qquad (2)$$

where $\sigma$ is the surface tension and $\theta$ the contact angle of the liquid with the wall. Assuming adsorption of water by capillary condensation and the validity of the Kelvin equation

$$D = \frac{4V\sigma \cos\theta}{RT \ln P_0/p} \qquad (3)$$

where $V$ is the molar volume of adsorbed water, and substituting for $D$ in equation (2) one obtains

$$P = \frac{RT}{V} \ln p/P_0 \qquad (4)$$

During the contraction of charcoal the pressure on the carbon is equal to the pressure on the adsorbed liquid, equation (4), with the sign changed. If the per cent. linear expansion, $L$, is directly proportional to this negative pressure and to the amount of water adsorbed, then at constant temperature

$$L = k'\frac{w}{V} \ln p/P_0 \qquad (5)$$

This differs from equation (1) in that it contains the variable $V$ and constant $B$ is lacking. In the adsorbed water density studies it was observed that the maximum variation of $V$ was less than 5%, hence for approximate calculations $V$ may be considered constant. If then constant $B$ is attributed to the void effect mentioned earlier, equation (1) has some theoretical foundation.

If the water adsorption isotherms of the two charcoals in Figs. 5 and 6 are compared with the volume curves of adsorbed water on the same char in Figs. 7 and 8, it is evident that over nearly the complete range the volume (or density) is some function of the relative pressure. According to equation (4) any change in the relative pressure produces a change in pressure $P$ on the adsorbed liquid. The change in volume per unit volume of adsorbed water depends on this change in pressure on the liquid and the coefficient of compressibility $\beta$

$$\beta(P_2 - P_1) = -\frac{v_2 - v_1}{v_1} \qquad (6)$$

By proper combination of equations (4) and (6) one obtains

$$\beta RT\left(\frac{1}{V_2}\ln\frac{p_2}{P_0} - \frac{1}{V_1}\ln\frac{p_1}{P_0}\right) = -\frac{v_2 - v_1}{v_1} \qquad (7)$$

Values of $\beta$ are available only for positive pressures. Since $\beta$ increases with increasing tension or negative pressure, this change in $\beta$ was estimated from calculations based on the van der Waals equation, using $a = 7003$ and $b = 0.811$, and on equation (6). In making these calculations it was

assumed that the van der Waal's $P-V$ relationship would be an extension into the negative pressure range of its known behavior in the positive pressure range.

To test the relationship in (7) on charcoal N-291-AY-1 the value of the right side of the equation was calculated from the curves in Fig. 7. For a given weight of adsorbed water the volume on the desorption curve was taken as $v_2$ and on the adsorption curve as $v_1$. This gave the change in volume per unit volume when the relative vapor pressure was decreased from $p_1/P_0$ on the adsorption side of the isotherm to $p_2/P_0$ on the desorption side. The molar volumes $V_1$ and $V_2$ were calculated from $v_1$ and $v_2$, respectively.

In Fig. 10 the calculated values of the right side of equation (7) are presented graphically by the lower curve and the left side of the equation by the upper curve. Although the experimental accuracy of the volume measurements, shown by the vertical lines through the experimental points, does not warrant a quantitative comparison, the similarity in shape of the two curves does give a qualitative indication that equation (7) may be essentially correct.

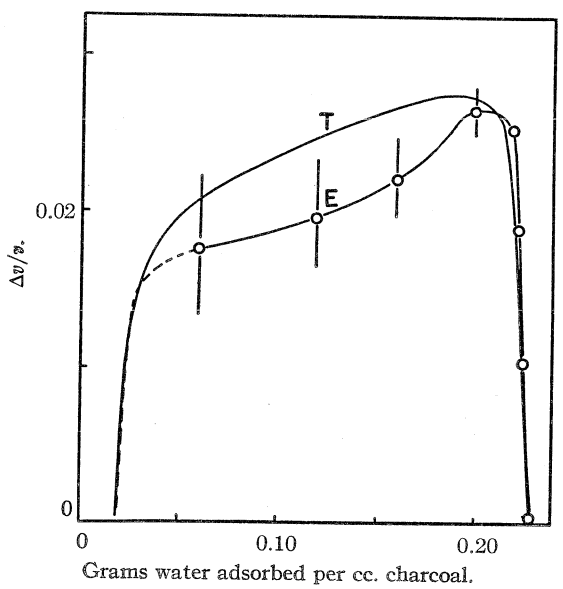



Fig. 10.—Change in volume per unit volume $\Delta v/v$ of the apparent volume of adsorbed water as observed experimentally and calculated from the isotherm: E, experimental; T, calculated; charcoal N291-AY-1.

The water density data obtained on N-19 were treated in a somewhat different manner. Figure 11 shows the molar volume of adsorbed water in equilibrium with relative water vapor pressures on the main desorption branch and the two scanning curves of the isotherm (Fig. 6) as a function of weight of water adsorbed. In Fig. 12 the solid line curves are the accumulated change in volume per unit volume of adsorbed water, starting at saturation in Fig. 11 and proceeding to lower moisture contents along the desorption and scanning curves 1 and 2. The broken line curves were calculated from the left side of equation (7) as for

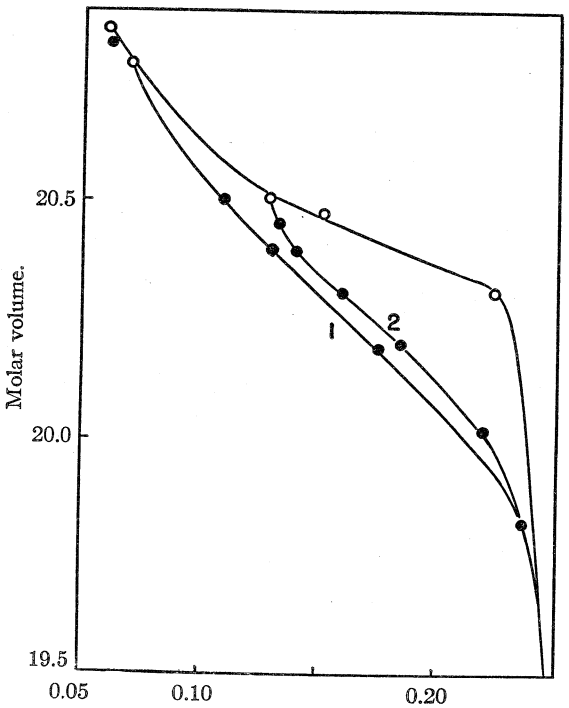



Fig. 11.—Molar volume of adsorbed water in equilibrium with relative vapor pressures on the main desorption and two scanning curves of the isotherm: ●, adsorption; ○, desorption; charcoal N-19.

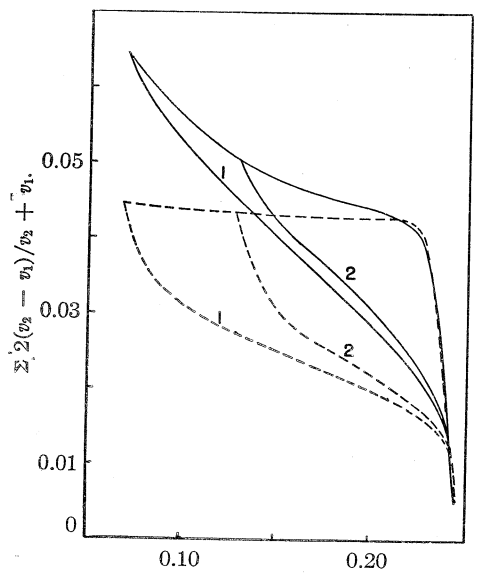



Fig. 12.—Change in volume per unit volume of adsorbed water in equilibrium with the desorption side and scanning curves of the isotherm: solid curves, experimental; broken line curves, theoretical; charcoal N-19.

charcoal N-291-AY-1. The agreement is good between the theoretical and experimental volume change in the range 0.21 to 0.25 g. water adsorbed per cc. charcoal but at lower moisture contents the experimental and theoretical curves begin to diverge.

The choice of N-19 for this study may have been an unfortunate one since an extra variable, which apparently did not exist in N-291-AY-1, appears to influence the molar volume of adsorbed water on this charcoal. For N-291-AY-1 the molar volume on the desorption side for a given weight of adsorbed water was always found to be greater than on the adsorption side. On N-19, however, the molar volume on adsorption at moisture contents below 0.13 g. was found to be greater than on the desorption side, as shown by the curves in Fig. 8. This crossing of the two curves may be attributed to the water adsorbed below 0.01 g. of moisture content, desorption side, having a very low molar volume. It appears that on adsorption, as more and more water is adsorbed, the previously adsorbed water molecules rearrange themselves into a closer packed state which is retained on desorption.

In order to avoid the complicating effects due to this rearrangement of the water molecules in the determination of the effect of the relative pressure on the molar volume, calculations were made only with data from the main desorption branch of the hysteresis loop and the two scanning curves. In Fig. 13 the differences between the curves in Fig. 12 were plotted against weight of water adsorbed in an attempt to cancel out the

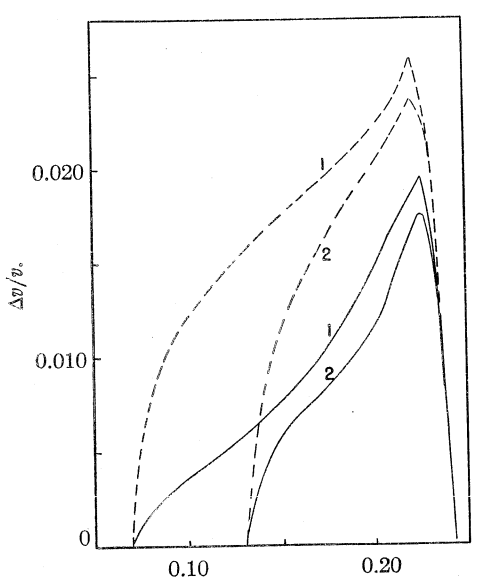



Fig. 13.—Change in volume per unit volume of the adsorbed water when the relative vapor pressure is decreased from the adsorption to the desorption side of the isotherm: solid curves, experimental; broken line curves, theoretical, charcoal N-19.

contribution of the submicro volume (which is apparently the volume of voids between water molecules in small pores) to the molar volume. Curve 1 in Fig. 13 was obtained by plotting the difference between scanning curve 1 and its desorption curve in Fig. 12 against the weight of water adsorbed. The other curves were obtained similarly. These curves represent the change in volume per unit volume for a given weight of adsorbed water when the relative pressure is increased from points on the desorption branch of the isotherm to points on the scanning curves. For N-19, Fig. 13, as for N-291-AY-1 in Fig. 10, a similarity exists between the theoretical and experimental curves, and again the magnitudes of the theoretical values are greater. These studies would appear to show that a definite relationship does exist between the relative vapor pressure and the molar volume of adsorbed water but the exact quantitative relation is complicated by the factors discussed above.

The evidence presented in this paper for the initial contraction of charcoal on exposure to water vapor, for a density of adsorbed water close to that of liquid water and for the similarity of experimental adsorbed water volume relationships with those calculated on the basis of capillary condensation would seem to constitute rather strong support for the capillary condensation theory. Additional support for the theory has recently been claimed by Broad and Foster[13] through their observation that isotherms of water and deuterium oxide on charcoal are identical (within 3%).

**Acknowledgment.**—The authors wish to express their thanks to the Chemical Corps Technical Command for sponsoring this work and in particular for a fellowship held by one of us (A. J. J.). They are also indebted to Professor T. L. Hill for valuable suggestions.

## Summary

Charcoal exposed to water vapor has been found to undergo an initial contraction followed by a subsequent expansion as the vapor pressure is increased. The per cent. linear expansion of the charcoal has been shown to be a function of the relative vapor pressure and the amount of water adsorbed. This relationship is expressed approximately by the equation

$$L = k'w\ (\ln p/P_0 - B)$$

which was partially justified on theoretical grounds by the capillary condensation theory.

The change in the volume per unit volume of adsorbed water was found to vary with the relative vapor pressure qualitatively according to a relationship derived from theoretical considerations based on the capillary condensation theory. For the density of water adsorbed on charcoal a value slightly less than unity was obtained.

RECEIVED JULY 23, 1948

(13) Broad and Foster, *J. Chem. Soc.*, 372 (1945).

[CONTRIBUTION FROM THE ROHM AND HAAS CO.]

# An X-Ray Diffraction Study of the Copper Chromites and of the "Copper-Chromium Oxide" Catalyst[1]

BY JAMES D. STROUPE

The "copper–chromium oxide" hydrogenation catalyst, effective for the liquid phase hydrogenation of some types of organic compounds,[2,3] is normally prepared by decomposing a copper ammonium chromate at low temperatures to give a material reported as "copper–chromium oxide," "copper chromite," "copper oxide–chromite," etc.[2] Of the descriptive names for the catalyst "copper–chromium oxide" appears to be the most generally accepted and will be used to designate the normal catalyst in the following discussions. In order to determine its real composition and to investigate its behavior by means of X-ray diffraction a similar study of the pure copper chromites has been necessary.

It is the primary purpose of this paper to report the characteristic powder diffraction data for cupric and cuprous chromites, to clarify the composition of the normal catalyst by means of positive identification of its components through their powder diffraction patterns and to further apply these data to the study of catalyst transformations during use and reclamation. All diffraction work was carried out on G.E. and Norelco apparatus using CuK$\alpha$ radiation.

## Cupric Chromite and Cuprous Chromite

Following the Groger[4] method for preparing the copper chromites, separate samples of precipitated chromate were given ignition treatments ranging from one hour at 700° to several hours at 1100°. After each ignition the crystalline product was leached with hot, concentrated hydrochloric acid until cupric ion no longer appeared in the filtrate and the diffraction pattern of cupric oxide could no longer be detected in that of the solid residue.

The washed products which had received the extremes of ignition treatment were found to be single, structurally different, crystalline compounds whose chemical analyses very closely checked those calculated for cupric chromite ($CuCr_2O_4$-low temperature) and cuprous chromite ($Cu_2Cr_2O_4$[5] high temperature), respectively. Tables IB and IC list the diffraction data for these compounds.

From their characteristic diffraction patterns, both chromites were identified in samples which had received intermediate ignition treatment, the cuprous salt systematically replacing the cupric chromite at higher temperatures. Since the unwashed products contained only cupric oxide in addition to the chromites, high temperature interaction of cupric oxide with cupric chromite to give cuprous chromite was indicated. Behavior of this system was determined by an extensive series of ignitions made in air. The three most important typical reactions, determined through positive diffraction identification of all solid components, are discussed below.

(1) Pure cupric chromite prepared by the Groger method was ignited at temperatures increasing from 700 to 1100°. The material was found to be relatively stable at low temperatures but to break down to give cuprous chromite and chromic oxide at high temperatures according to the simplified reaction

$$2CuCr_2O_4 \xrightarrow{>900^\circ} Cu_2Cr_2O_4 + Cr_2O_3 + [O]$$

(2) An intimate equimolar mixture of cupric chromite and cupric oxide behaved quite differently under the above ignition conditions. At temperatures below 900° these components were observed to combine slowly to form only cuprous chromite and oxygen; above 900°, this reaction could readily be driven to completion

$$CuCr_2O_4 + CuO \xrightarrow{>900^\circ} Cu_2Cr_2O_4 + [O]$$

(3) Though the cuprous chromite obtained in the above fashion was found to be entirely stable at room conditions it was completely reoxidized to the original components by "annealing" in air for several hours at temperatures between 600 and 700°. Thus

$$[O] + Cu_2Cr_2O_4 \xrightarrow{600\text{–}700^\circ} CuO + CuCr_2O_4$$

From the second observation the mechanism of formation of cuprous chromite at high temperatures in the Groger synthesis is apparent. Together with the final one these direct diffraction results verify the high temperature equilibrium claimed by L. and P. Wohler[6] from oxygen pressure measurements on a closed system originally containing an equi-molar mixture of cupric oxide and cupric chromite.

$$CuO + CuCr_2O_4 \underset{\text{"red heat"}}{\rightleftharpoons} Cu_2Cr_2O_4 + [O]$$

## The "Copper-Chromium Oxide" Catalyst

Preparation of the "copper–chromium oxide" catalyst by thermal decomposition of copper am-

(1) Presented before the Inorganic and Physical Section at the American Chemical Society Meeting, Atlantic City, April, 1947.

(2) "Organic Syntheses," Vol. XIX, John Wiley & Sons, Inc., New York, N. Y., 1939, pp. 31–35.

(3) Adkins, "Reactions of Hydrogen with Organic Compounds," The University of Wisconsin Press, Madison, Wis., 1937.

(4) Groger, *Z. anorg. Chem.*, **58**, 412 (1902); **76**, 30 (1912).

(5) The double formula $Cu_2Cr_2O_4$ will be used instead of $CuCrO_2$ to more directly indicate the oxide composition ($Cu_2O \cdot Cr_2O_3$).

(6) L. and P. Wohler, *Z. physik. Chem.*, **62**, 445–453 (1908).

monium chromate was first described by Adkins and Connor[7] and by Lazier.[8] Many other ways of combining the oxides of copper and chromium have since been tried with varied success in catalytic application[2,3] but the most efficient catalysts have usually been obtained by some modification of the method originally suggested and blocked out below

$$\underset{\text{(Reactants)}}{Cu(NO_3)_2 \text{ soln.} + (NH_4)_2CrO_4 \text{ soln.}} \longrightarrow \underset{\text{(Intermediate precipitate)}}{\text{Complex chromates}} \xrightarrow[\text{decomposition}]{\text{low temperature}} \underset{\text{(Catalyst)}}{\text{"Copper–chromium oxide"}}$$

Connor, Folkers and Adkins[9] early suggested the partial replacement of copper by barium, and Calingaert and Edgar[10] claimed the following near quantitative reactions to describe the two step process.

$$2CuSO_4 + Na_2Cr_2O_7 + 4NH_3 + 3H_2O \longrightarrow 2Cu(OH)NH_4CrO_4 + Na_2SO_4 + (NH_4)_2SO_4 \quad (1)$$

$$2Cu(OH)NH_4CrO_4 \xrightarrow[\text{decomposition}]{\text{Low temp.}} \underset{\text{(Catalyst)}}{Cr_2O_3 \cdot 2CuO} + N_2 + 5H_2O \quad (2)$$

It is possible to carry out the decomposition step under sufficiently controlled low temperatures (350°) to secure "copper–chromium oxide" catalysts which are amorphous. At slightly higher ignition temperatures the presence of a fraction of very small crystallites is indicated by weak and broad diffraction bands. Ordinarily, however, the exothermic nature of the decomposition reaction makes its temperature control difficult and the normal ignited catalyst batch usually is a mixture of completely crystallized components.

Though one cannot determine the composition of amorphous catalysts by X-ray diffraction, it appears significant that only very slight differences in absolute chemical composition between amorphous and crystalline "copper–chromium oxide" catalysts can be detected and that a constant Cu:Cr ratio is maintained. Accordingly it seems reasonable to assume that the component composition of amorphous catalysts may be very similar to that of the crystalline catalysts normally prepared for production applications. Typical behavior of both the simple catalyst prepared according to the directions of Calingaert and Edgar and of the similarly obtained barium-modified catalyst has been determined by X-ray diffraction.

**Intermediate Precipitate.**—The barium-free intermediate was found to be a single, crystalline material having a chemical composition closely approximating the formula $Cu(OH)NH_4CrO_4$.[10] Partial (10%) replacement of copper by barium caused precipitation of crystalline barium chromate which appeared to remain substantially unchanged during catalyst decomposition, use and reclamation and therefore has been omitted from the discussion of the subsequent steps.

**Normal Catalyst.**—Decomposition of the above precipitate and ignition at 500° for two hours produced the finely divided, black, crystalline normal catalyst. From its diffraction data cupric oxide and cupric chromite were readily identified and their relative line intensities found to indicate an equimolar ratio. This latter result was closely checked by chemical analyses and is further substantiated by those reported by Calingaert and Edgar in their previous analytical study. Without claiming any such real compound they indicated the catalyst composition to be $Cr_2O_3 \cdot 2CuO$. The true mode of combination determined by the diffraction data is $CuCr_2O_4 + CuO$. Catalyst batches ignited above 600° were found already to show the expected partial combination of cupric oxide with cupric chromite to form cuprous chromite and at very high temperatures (1100°) this conversion was completed.

**Used Catalyst.**—X-Ray data from catalysts which had been used in a typical liquid phase hydrogenation below 300° often showed crystalline cupric chromite to have been largely reduced to the cuprous chromite in a reaction with cupric oxide competing with the reduction of this oxide to crystalline, metallic copper. The red color of such used catalysts has long been claimed—and is proved by the identifiable diffraction pattern of metallic copper—to be due to the finely divided metal and many empirical attempts have been made to prevent this reduction. The very low temperature reaction of cupric oxide with cupric chromite to produce the cuprous salt has not previously been considered and should be taken into account in further efforts to develop the catalyst and explain its behavior.

**Reclaimed Catalyst.**—It has been economically feasible to reclaim used "copper–chromium oxide" catalyst by burning off the residual organic materials with alcohol in open pans and reigniting the catalyst for two hours at 600°. Diffraction data from samples taken at various stages of the reclamation process show that the copper is readily reoxidized but that the cuprous chromite remains unchanged. From the previous study of the copper chromites it was apparent that, to obtain a catalyst composition identical with that of new material, a relatively long, low temperature "annealing" treatment would be necessary. A four to six hour annealing at 650° in air was found sufficient to reoxidize the cuprous chromite of the used catalyst to the cupric salt giving a material chemically and structurally identical with the original catalyst.

## Summary

The reactions involved in the copper chromite

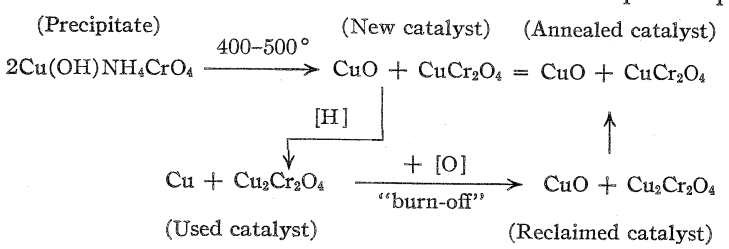
(7) Adkins and Connor, THIS JOURNAL, **53**, 1090–1095 (1930).

(8) Lazier, U. S. Patent 1,746,782 (1930).

(9) Connor, Folkers and Adkins, THIS JOURNAL, **53**, 2012 (1931); **54**, 1138 (1932); U. S. Patent 2,091,800 (1937).

(10) Calingaert and Edgar, *Ind. Eng. Chem.*, **26**, 878 (1934).

system may be summarized in a sketch of the following type




## The Copper Chromite "Spinel"[11]

Cupric chromite has often been spoken of as a likely spinel-former though a careful check of the diffraction literature has failed to turn up data to prove the point. Among the most recent of such assertions are those of Selwood[12] who discussed the "spinel" obtained by high temperature ignition of an oxide mixture and of the "copper–chromium oxide" catalyst. Samples kindly provided by him and thought to be representative of the treatment given his samples no. 16 and no. 17 have been carefully re-examined in this Laboratory by X-ray diffraction methods. The "spinel" prepared by high temperature vacuum ignition of a 1:1 mechanical mixture of copper oxide and chromic oxide is heterogeneous containing free chromic oxide and cuprous chromite; that prepared by high temperature vacuum ignition of the normal copper chromite catalyst is identical in chemical composition and crystalline structure with the cuprous chromite obtained by our similar ignitions in air. These high temperature catalysts do not have the typical spinel composition; furthermore there is strong indication that the cuprous chromite really formed crystallizes on an hexagonal lattice instead of the cubic one required by the spinel structure.

Thin, single crystal plates of the cuprous chromite prepared in this laboratory by high temperature ignition of an equimolar mixture of cupric oxide and cupric chromite are optically isotropic in the plate view, anisotropic in the edge view, show a typical uniaxial interference figure and are characterized by angles of 60 and 120° between bounding edges. Laue data secured from plates mounted perpendicular to the X-ray beam show perfect hexagonal symmetry and axial lengths of the indicated hexagonal cell $a_0 = 2.975$ Å., $c_0 = 17.096$ Å. have been calculated from single crystal oscillation and powder back reflection data. A rough density measurement of 7.0 g./cc. by carbon tetrachloride displacement indicates two $Cu_2Cr_2O_4$ per unit cell. All lines of the CuK$\alpha$ powder diffraction pattern of this compound have been successfully indexed on the basis of the hexagonal cell and further work on the single crystal data is in progress.

(11) The "Spinel" structure is based upon a face-centered cubic unit cell containing eight $R_2MX_4$($Cr_2CuO_4$ in this case).

(12) P. W. Selwood, F. N. Hill and Harold Boardman, THIS JOURNAL, **68**, 2055 (1946).

In the following table are listed the interplanar spacings ("d") and estimated line intensities (I) found to be characteristic of (A) $Cu(OH)NH_4CrO_4$, (B) $CuCr_2O_4$ and (C) $Cu_2Cr_2O_4$, respectively. Line spacings have been approximately corrected for sample absorption and line intensities relate only to the strongest line of each pattern and do not permit direct intercomponent comparison.

TABLE I

DIFFRACTION DATA

| (A) $Cu(OH)NH_4CrO_4$ "d" | I | (B) $CuCr_2O_4$ "d" | I | (C) $Cu_2Cr_2O_4$ "d" | I | HK·L |
|---|---|---|---|---|---|---|
| 7.1 Å. | 100 | 4.87 Å. | 15 | 5.69 Å. | <5 | 00·3 |
| 4.96 | 10 | 3.017 | 25 | 2.85 | 40 | 00·6 |
| 2.69 | 40 | 2.874 | 35 | 2.570 | 20 | 10·0 |
| 3.28 | 55 | 2.556 | 100 | 2.470 | 100 | 10·2 |
| 2.945 | 15 | 2.401 | 60 | 2.210 | 40 | 10·4 |
| 2.737 | 25 | 2.134 | 25 | 1.911 | 5 | 10·6 |
| 2.622 | 20 | 1.960 | 10 | 1.646 | 45 | 10·8 |
| 2.542 | 30 | 1.706 | 15 | 1.488 | 35 | 11·0 |
| 2.365 | 10 | 1.629 | 40 | 1.439 | 5 | 11·3 |
| 2.304 | 20 | 1.589 | 15 | 1.426 | 30 | 00·12 |
| 1.962 | 10 | 1.505 | 30 | | | 10·10 |
| 1.848 | 5 | 1.442 | 40 | 1.319 | 20 | 11·6, $\bar{1}$2·6 |
| 1.832 | 5 | 1.293 | 5 | 1.275 | 15 | 02·2 |
| 1.774 | 15 | 1.276 | 15 | 1.234 | 10 | 02·4 |
| 1.645 | 15 | 1.195 | 5 | | | 20·6 |
| 1.545 | 10 | 1.106 | 5 | 1.172 | <5 | 10·13 |
| 1.483 | 10 | 1.067 | 10 | | | 11·9 |
| 1.456 | 5 | 1.031 | <5 | 1.105 | 15 | 10·14 |
| 1.383 | 5 | 0.985 | 5 | | | 02·8 |
| 1.315 | <5 | .955 | 10 | 1.030 | 20 | 02·10 |
| 1.285 | 5 | .930 | <5 | | | 11·12, $\bar{1}$2·12 |
| 1.143 | <5 | .885 | 5 | 0.988 | 5 | 10·16 |
| 1.102 | 5 | .857 | 15 | .968 | 15 | 21·2, $\bar{1}$3·2 |
| | | | | .949 | 10 | 00·18 |
| | | | | | | 21·4, $\bar{1}$3·4 |
| | | | | .886 | 20 | 02·14 |
| | | | | | | 21·8, $\bar{2}$3·8 |
| | | | | .858 | 15 | 30·0 |
| | | | | .846 | 20 | 21·10, $\bar{1}$3·10 |
| | | | | .822 | 20 | 02·16 |
| | | | | | | 30·6 |
| | | | | .811 | 15 | 10·10 |
| | | | | .801 | 30 | 11·18 |

**Acknowledgment.**—The author wishes to thank Dr. A. J. Vander Weyden of the University of Denver for many carefully prepared samples of catalysts and components.

## Summary

Cupric chromite and cuprous chromite have been prepared, chemically analyzed, characterized by their X-ray powder diffraction data and found to be related in the following way.

$$CuO + CuCr_2O_4 \underset{600\text{–}700^\circ}{\overset{900^\circ}{\rightleftharpoons}} Cu_2Cr_2O_4 + [O]$$

Crystalline $Cu(OH)NH_4CrO_4$ precipitated in the first step of the preparation of "copper–chromium oxide" catalyst, is decomposed at relatively low temperatures to produce an equimolar mixture of cupric oxide and cupric chromite, the normal catalyst. Very high temperature ignition of the catalyst causes their complete combination to form cuprous chromite. Microscopic and X-ray data indicate the latter substance to crystallize in the hexagonal system with two $Cu_2Cr_2O_4$ per unit cell, $a_0 = 2.975$ Å., $c_0 = 17.096$ Å.

Normal "copper–chromium oxide" catalysts used in typical low temperature hydrogenations show partial or complete reduction to metallic copper and cuprous chromite. Ordinary reclamation processes succeed only in removing organic matter and re-oxidizing the copper but complete return to the chemical composition of the original catalyst can be accomplished by a relatively long, low temperature "annealing" treatment.

RECEIVED JUNE 16, 1948

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[CONTRIBUTION FROM INSTITUTT FOR UORGANISK KJEMI, NORGES TEKNISKE HÖGSKOLE]

# The Equilibrium $CaCO_{3(melt)} = CaO_{(s)} + CO_2$. The Activity Coefficients of Calcium Carbonate in Alkali Carbonate Melts

BY H. FLOOD, T. FÖRLAND AND B. ROALD

## Experimental

The equilibrium diagram of the system calcium carbonate–sodium carbonate–carbon dioxide ($p_{CO_2}$ = 1 atm.) has been examined by P. Niggli,[1] and later by W. Eitel.[2] A sketch of the diagram is shown in Fig. 1a. Only the right-hand side of the diagram is of interest in connection with the questions to be treated here. At the composition ratio 1:1, a compound ($CaCO_3 \cdot Na_2CO_3$) appears which is decomposed at temperatures above 817°. Solid calcium carbonate does not dissolve appreciable amounts of sodium carbonate. The solubility of calcium carbonate in the melt increases with the temperature (compare the curve DA). At about 900° the carbon dioxide tension of solid calcium carbonate exceeds 1 atm. Above this temperature only calcium oxide, not calcium carbonate, can exist in equilibrium with the melt. The composition of the melt in equilibrium with calcium oxide at 1 atm. carbon dioxide pressure is given by the curve AB. The curve AB has been only roughly estimated in the previous publications. Thus in the diagram of W. Eitel it is drawn with the curvature the wrong way.

By assuming calcium oxide insoluble[3] in the melt, however, the curve AB can be determined by a simple gravimetric procedure.

Starting with a melt, for instance, of composition and temperature corresponding to the point $N_1$, $T_1$ (compare Fig. 1b), and raising the temperature to $T_2$, calcium oxide will be precipitated and carbon dioxide expelled until the composition of the melt corresponds to $N_2$. This composition is given by the amount of carbon dioxide expelled, which is determined by weighing. By further raising of the temperature to $T_3$ another composition corresponding to $N_3$ will be found after adjustment of the equilibrium, etc. In this way the curve AB may be determined.

The experiments were carried out in an apparatus previously used in the investigation on the reactions of polyacids with alkali carbonate[4] (compare also ref. 1). As precipitated calcium oxide proved to re-dissolve very slowly in the melts, the experiments were always carried out at rising temperatures.

The platinum crucible with the weighed charge was placed in the heating zone of the furnace and kept there at a constant temperature about twenty minutes. Then it was quickly as possible removed, cooled in a desiccator and weighed (in a weighing bottle).

In addition to the system mentioned, the system with potassium carbonate was examined. Also a few experiments with lithium carbonate were carried out. The results are given in Table I and a graphical representation is shown in Fig. 2. The potassium and sodium systems give results with smaller limits of error than the lithium system. It seems that basic lithium melts may cause an attack on the platinum crucible.

TABLE I

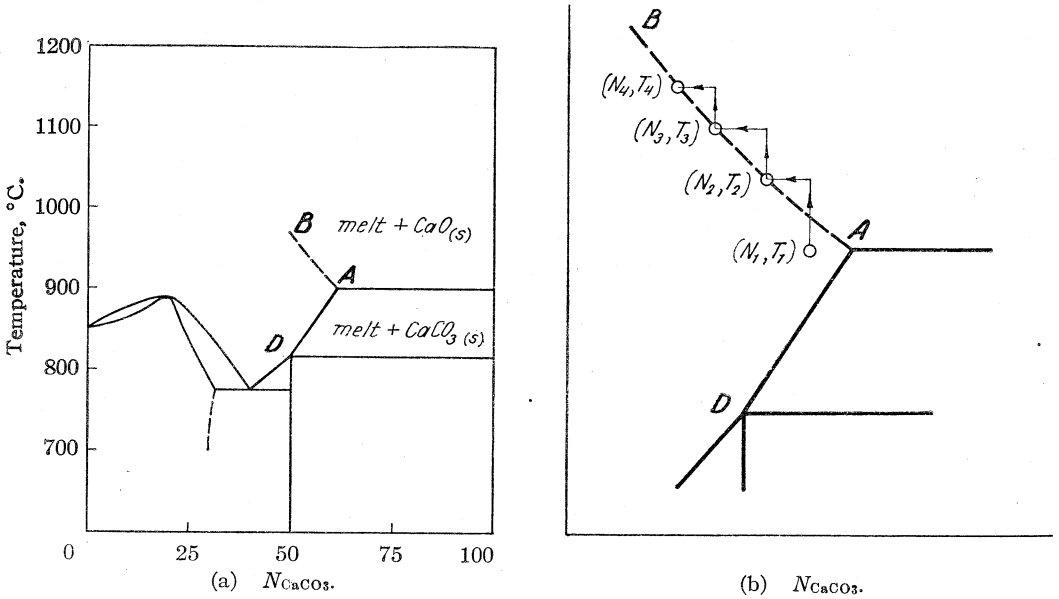
| Experiment | Temperature, °C. | Mol. $10^{-3}$ CaO precip.-$CO_2$ expelled | $CaCO_3$ | $K_2CO_3$ | $N_{CaCO_3}$ |
|---|---|---|---|---|---|
| | | A. $K_2CO_3$–$CaCO_3$ | | | |
| I | 20 | 0 | 11.10 | 5.62 | (66.4) |
| | 971 | 3.98 | 7.12 | 5.62 | 55.9 |
| | 1078 | 7.88 | 3.22 | 5.62 | 36.4 |
| II | 20 | 0 | 6.18 | 3.47 | (64.0) |
| | 1008 | 2.93 | 3.25 | 3.47 | 47.9 |
| | 1063 | 3.91 | 2.27 | 3.47 | 39.5 |
| | 1105 | 4.43 | 1.75 | 3.47 | 33.5 |
| | | B. $Na_2CO_3$–$CaCO_3$ | | | |
| I | 20 | 0 | 9.18 | 9.04 | (50.4) |
| | 964 | 1.60 | 7.58 | 9.04 | 45.6 |
| | 1044 | 5.67 | 3.51 | 9.04 | 28.0 |
| II | 20 | 0 | 9.68 | 8.47 | (53.3) |
| | 1005 | 5.01 | 4.67 | 8.47 | 35.5 |
| | 1097 | 7.52 | 2.16 | 8.47 | 20.3 |
| | | C. $Li_2CO_3$–$CaCO_3$ | | | |
| I | 20 | 0 | 7.00 | 12.04 | (36.8) |
| | 971 | 1.35 | 5.65 | 12.04 | 32.0 |
| | 1034 | 4.23 | 2.77 | 12.04 | 18.7 |
| II | 20 | 0 | 8.36 | 13.57 | (38.1) |
| | 1018 | 4.19 | 4.17 | 13.57 | 23.5 |

(1) P. Niggli, *Z. anorg. Chem.*, **98**, 241 (1916).

(2) W. Eitel, *Tschermak's Min. Petr. Mitt.*, **38**, 1 (1925).

(3) A correction can be made for the solubility of calcium oxide in the melt by examining the amount of expelled carbon dioxide at temperatures and compositions just below the curve AB. The experiments indicated that the correction was negligible.

(4) H. Flood, T. Förland and B. Roald, unpublished.




Figs. 1a and b.—The equilibrium diagram of the system calcium carbonate–sodium carbonate when $p_{CO_2}$ = 1 atm.

## Discussion

The data given in Table I and Fig. 2 can be used for a discussion of the deviations of the melts from ideal solutions. We denote by $p'_{CO_2}$ the carbon dioxide pressure above a molten mixture of calcium carbonate and alkali carbonate in presence of solid calcium oxide according to the equilibrium

$$CaCO_3(m) = CaO(s) + CO_2(g)$$

On the other hand, the carbon dioxide pressure $p_{CO_2}$ according to the equilibrium

$$CaCO_3(s) = CaO(s) + CO_2(g)$$

is fairly well investigated. K. K. Kelley and C. T. Anderson[5] give the following formula for $p_{CO_2} = K$

$$RT \ln K = 42.500 + 1.52T \log T + 2.155.10^{-3}T^2 - 0.0205.10^5T^{-1} - 34.58T$$

In the following we denote the activities of calcium carbonate in the solid state by $a_s$, in the liquid state by $a_l$ and in molten mixtures by $a_m$. Then

$$a_m/a_s = p'_{CO_2}/K \qquad (1)$$

and when the carbon dioxide pressure above the melt is 1 atm.

$$a_m/a_s = 1/K \qquad (2)$$

Introducing $a_l$ in numerator and denominator we have

$$\frac{a_m}{a_l}\frac{a_l}{a_s} = \frac{1}{K} \qquad (3)$$

and

$$RT \ln \frac{a_m}{a_l} + RT \ln \frac{a_l}{a_s} + RT \ln K = 0$$

(5) K. Kelley and C. T. Anderson, Bull. 384, Bureau of Mines (1935).

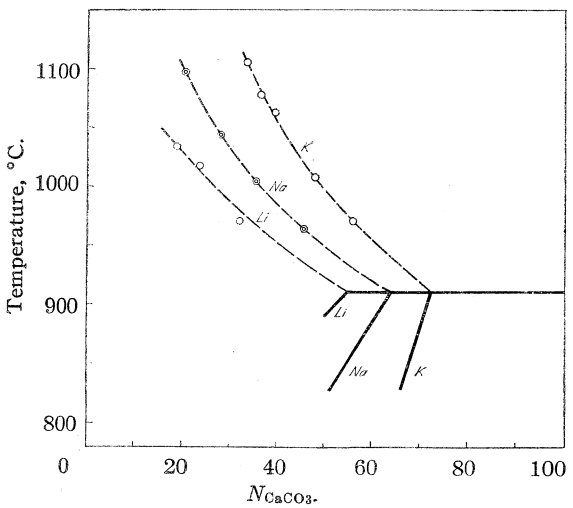



Fig. 2.—The equilibrium diagrams of the systems calcium carbonate–potassium carbonate, calcium carbonate–sodium carbonate and calcium carbonate–lithium carbonate when $p_{CO_2}$ = 1 atm.

The term $RT \ln \frac{a_l}{a_s}$ is the change in free energy for the process

$$CaCO_3(s) \longrightarrow CaCO_{3(\text{pure liquid})}$$

at the same temperature. If we denote the heat absorbed in the melting process by $\Delta H$, and $T_0$ is the melting point for calcium carbonate, we have

$$RT \ln \frac{a_m}{a_l} + RT \ln K + \Delta H \left(1 - \frac{T}{T_0}\right) = 0 \qquad (4)$$

neglecting the variation of $\Delta H$ with the temperature.

Now we will choose $CaCO_{3\,(\text{pure liquid})}$ as stand-

ard state. Introducing $f_1$ for the activity coefficient and $N_1$ for the mole fraction of calcium carbonate in the molten mixture, we get $a_1 = 1$ and

$$RT \ln f_1 = -RT \ln N_1 - RT \ln K - \Delta H \left(1 - \frac{T}{T_0}\right) \quad (5)$$

This equation contains two unknown $f_1$ and $\Delta H$. $T_0$ has been found by Smyth and Adams to be 1340°.[6] J. H. Hildebrand and E. J. Salstrom[7] have investigated mixtures of silver bromide–alkali bromide by aid of e. m. f. measurements. They find that the melts behave as "regular solutions"; this means that the entropy of mixing is the same as for an ideal mixture. This is expressed by the equation

$$RT \ln f_{AgBr} = bN^2_{Alk.\ Br.}$$

where $f$ is the activity coefficient, $N$, the mole fraction and $b$ a constant individual for each alkali metal. In the rubidium and potassium systems $b$ is positive, but in the sodium and lithium systems $b$ is negative. Hildebrand and Salstrom connect this with the fact that the ionic radii of the two former are larger than the radii of the two latter alkali metal ions.

We will now examine if similar simple rules are valid in the molten carbonate mixtures. From eqn. 5 we have

$$\frac{RT \ln N_1K}{1 - \frac{T}{T_0}} + \frac{RT \ln f_1}{1 - \frac{T}{T_0}} + \Delta H = 0$$

If the melt behaves as a "regular solution," we should get a straight line by plotting $-RT \ln N_1K/1 - (T/T_0)$ against $N_2^2/1 - (T/T_0)$ ($N_2$ is the mole fraction of alkali carbonate). Compare Fig. 3. It appears from the diagram that the experimental values, at least in the case of potassium and the sodium systems, are well represented by straight lines, with a mutual intercept for $N_2^2 = 0$, giving

$$\Delta H = 3.400 \pm 600 \text{ cal.}$$

We may therefore write

$$RT \ln f_1 = bN_2^2$$

where $b$ is an individual constant for each alkali carbonate system. The melts in fact seem to behave as regular solutions.

(The principal error in this calculation is caused by inaccuracies in the estimation of the temperature. The temperature in the heating zone was constant during the adjustment of the equilibrium with an accuracy of ±1°. This leads to an uncertainty in the computation of $K$ corresponding to d log $K$/d$T$ = 0.01. At 1000° this corresponds to ±70 cal.)

The slopes of the straight lines give values of $b$. The $b$-values of Hildebrand and Salstrom for the bromide systems, which also are given in Table II, show that the deviations from ideal solution are distinctly smaller in the bromide mixtures where the mixing cations are of equal electric charge than in the carbonate mixtures where the electric charges are different.

TABLE II

| | $CaCO_3 + (Alk.)_2CO_3$, cal. | $AgBr + Alk.\ Br$, cal. |
|---|---|---|
| K | −11500 | −1480 |
| Na | − 5500 | +1050 |
| Li | − 2400 | +1880 |

Having found the values of $\Delta H$ and $b$, we are able to give the formula for the calculation of the curve AB (Fig. 1) at any carbon dioxide pressure. For a carbon dioxide pressure ($p'_{CO_2}$) above the melt different from 1 atm., eqn. 3 will have the form

$$\frac{a_m}{a_1} \cdot \frac{a_1}{a_s} = \frac{p'_{CO_2}}{K}$$

and eqn. 5 will have the form

$$RT \ln p'_{CO_2} = RT \ln K + RT \ln N_1 + RT \ln f_1 + \Delta H \left(1 - \frac{T}{T_0}\right)$$

substituting for $RT \ln f_1$ we get

$$RT \ln p'_{CO_2} = RT \ln K + RT \ln N_1 + bN_2^2 + \Delta H \left(1 - \frac{T}{T_0}\right)$$

which is the equation for the curve AB at any carbon dioxide pressure. The limit $p'_{CO_2} = K$ corresponds to the co-existence of $CaCO_3$(s), (CaO(s)) and $CaCO_3$–$(Alk)_2CO_3$ melt. This gives the equation

$$RT \ln N_1 + b(1 - N_1)^2 + \Delta H(1 - T/T_0) = 0$$

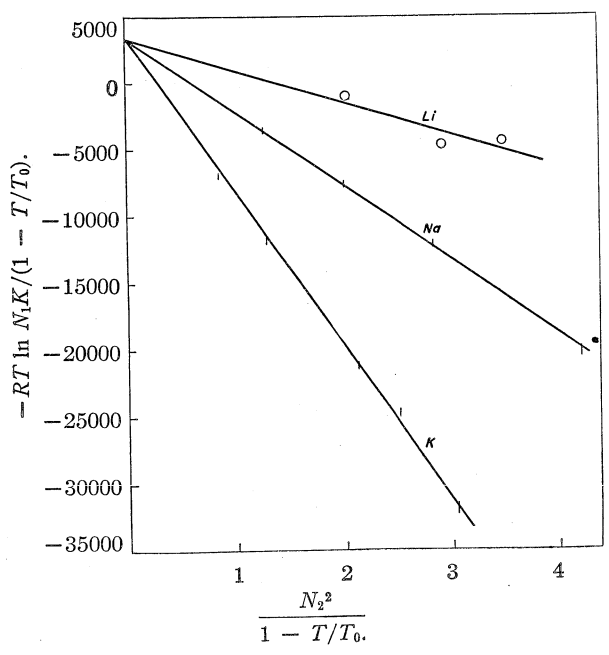



Fig. 3.

(6) F. H. Smyth and L. H. Adams, *ibid.*, **45**, 1167 (1923).

(7) J. H. Hildebrand and E. J. Salstrom, THIS JOURNAL, **54**, 4257 (1932).

(This result may also be derived from the Clausius–Clapeyron formula considering the melt as a regular solution.) The calculated curve checks only fairly with W. Eitel's measurements of the same phase diagram. However, there is also quite a difference in decomposition temperature for $CaCO_3(s)$ at $p_{CO_2} = 1$ atm. given by W. Eitel (900°) and given by K. Kelley (884°). Our calculations are based upon K. Kelley's data.

The authors express their thanks to Det Videnskapelige Forskningsfond av 1919 and Norges tekniske høgskoles Fond for grants.

## Summary

1. By means of a simple gravimetric procedure the composition of calcium carbonate–alkali carbonate melts in equilibrium with solid calcium oxide at a carbon dioxide pressure of 1 atm. has been determined.

2. On the basis of these results calculation of the activity coefficient of calcium carbonate in the melt is discussed. It follows that the carbonate mixtures behave as regular solutions.

3. The heat of fusion of calcium carbonate is calculated to 3400 cal.

TRONDHEIM, NORWAY RECEIVED AUGUST 4, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

# Reactions of the Silver Salts of Carboxylic Acids with Iodine in the Presence of Some Tertiary Amines

BY RALPH A. ZINGARO, JUDSON E. GOODRICH, JACOB KLEINBERG AND CALVIN A. VANDERWERF

Recent reports[1,2] that monopyridine iodine (I) *p*-nitrobenzoate is toxic *in vitro* to certain fungi have reawakened interest in base stabilized iodine salts of organic acids.[3]

The purpose of the present work was the preparation of a series of positive iodine salts of organic acids, using pyridine or α- or β-picoline as the coördinating agents, with the intent of finding new compounds which may be effective against bacteria and fungi. Thirty-one of these salts have been prepared and pertinent data concerning them are collected in the tables. The percentage yields are based on the silver salt used and not on the amount of iodine which reacted.

In those cases where pyridine was the coördinating agent, the aromatic acids used were selected in such a way as to permit comparisons of the effects on the yield of desired product of various substituents at different positions on the aromatic acid ring.

In many of the reactions where the yield of iodine salt was low, recovery of appreciable free acid was realized even under rigorously anhydrous conditions. For example, in the attempt to prepare α-picoline iodine (I) *p*-bromobenzoate, *p*-bromobenzoic acid was recovered in over 70% yield. This may mean that the formation of the iodine compound and the formation of the free acid are competing reactions.

TABLE I

DERIVATIVES OF α- AND β-PICOLINE IODINE (I)

| | α | | | | β | | | |
|---|---|---|---|---|---|---|---|---|
| | M. p., °C. (uncor.) | Yield, % | Iodine, % Calcd. | Iodine, % Found | M. p., °C. | Yield, % | Iodine, % Calcd. | Iodine, % Found |
| Benzoate | 122–124dec. | 9 | 37.2 | 37.1 36.9 | 123–126dec. | 24 | 37.2 | 37.1 37.2 |
| *o*-Nitrobenzoate | 116–119dec. | 14 | 32.9 | 32.7 32.6 | 88–91 | 36 | 32.9 | 33.0 33.0 |
| *m*-Nitrobenzoate | 139–143 | 53 | 32.9 | 33.0 32.8 | 134–137dec. | 32 | 32.9 | 32.5 32.5 |
| *p*-Nitrobenzoate | 163–165dec. | 14 | 32.9 | 32.9 32.9 | 188–191dec. | 52 | 32.9 | 33.0 32.8 |
| 3,5-Dinitrobenzoate | 159–162dec. | 64 | 29.4 | 29.3 29.2 | 164–167dec. | 32 | 29.4 | 29.1 29.1 |
| *p*-Chlorobenzoate | 113–116dec. | 21 | 33.8 | 34.2 34.0 | 129–132dec. | 17 | 33.8 | 33.6 33.5 |
| *p*-Bromobenzoate | ..... | .. | .. | .. .. | 127–129dec. | 14 | 30.2 | 30.3 30.2 |
| *p*-Iodobenzoate | 118–121dec. | 30 | 27.2 | 27.2 26.9 | 116–120dec. | 50 | 27.2 | 27.0 27.5 |

(1) Kleinberg, Novak and Gerberg, *Proc. Soc. Exp. Biol. Med.*, **58**, 238 (1945).

(2) Kleinberg and Meyer, *Science*, **104**, 398 (1946).

(3) The following references describe the intermediate complex compounds formed by the action of iodine on the silver salts of organic acids, the various types of decomposition of these substances, mechanisms proposed for these reactions, and the use of pyridine as a coördinating base in the formation of positive iodine salts of organic acids: (a) Simonini, *Monatsh.*, **14**, 81 (1893); (b) Wieland and Fischer, *Ann.*, **446**, 49 (1925); (c) Hershberg, *Helv. Chim. Acta*, **17**, 351 (1934); (d) Prévost, *Compt. rend.*, **196**, 1129 (1933); (e) Birckenbach and Meisenheimer, *Ber.*, **69B**, 723 (1936); (f) Carlsohn, "Über eine neue Klasse von Verbindungen des positiv einwertigen Iods," Verlag von S. Hirzel, Leipzig, 1932.

## Experimental

**Preparation of Reagents.**—Since positive iodine compounds decompose in the presence of water, anhydrous conditions must be maintained throughout in their preparation. The chloroform and Skellysolve A were dried over calcium chloride and distilled; the commercial absolute ether was dried over sodium and distilled. The pyridine and α- and β-picoline were dried over sodium hydroxide pellets for two weeks and distilled, the distillates boiling at 114.5 and 128.1° at 740 mm. and 141.7° at 735 mm., respectively, being collected.

**Preparation of Silver Salts of the Acids.**—The organic acid was dissolved in hot alcohol and a hot aqueous solu-

TABLE II[a]

DERIVATIVES OF MONOPYRIDINE IODINE (I)

| Salt | M. p., °C. (uncor.) | Yield, % | Per cent. Iodine as $I^+$ Calcd. | Found | |
|---|---|---|---|---|---|
| *o*-Nitrobenzoate | 120–121 | 36 | 34.1 | 33.9 | 34.0 |
| *m*-Nitrobenzoate | [b] | 55 | 34.1 | 34.1 | 33.8 |
| 3,5-Dinitrobenzoate | 157dec. | 64 | 30.0 | 30.0 | 29.7 |
| α-Naphthoate | 109–112d. | 48 | 33.6 | 33.5 | 33.5 |
| *p*-Chlorobenzoate | 105–109d. | 47 | 35.1 | 35.3 | 35.1 |
| 2,4-Dichlorobenzoate[c] | 105–113d. | 18 | 32.0 | 31.6 | 31.6 |
| *p*-Bromobenzoate | 142–145 | 62 | 31.2 | 30.8 | 30.9 |
| *m*-Bromobenzoate | 84–93dec. | 9 | 31.2 | 31.0 | 30.9 |
| *p*-Iodobenzoate | 152–155d. | 58 | 28.0 | 27.7 | 27.7 |
| *m*-Iodobenzoate | 94–96dec. | 8 | 28.0 | 27.9 | 27.9 |
| *p*-Fluorobenzoate | 158–162 | 50 | 36.8 | 36.8 | 36.7 |
| *m*-Fluorobenzoate | 81–84 | 37 | 36.8 | 36.8 | 36.5 |
| *o*-Fluorobenzoate[d] | [b] | 11 | 36.8 | 36.5 | 36.4 |
| *p*-Methylbenzoate | 118–121d. | 60 | 37.1 | 37.1 | 37.0 |
| Acid phthalate[e] | [b] | 69 | 34.4 | 34.2 | 34.2 |
| Stearate | 64–66 | 51 | 25.9 | 25.9 | 25.6 |

[a] The success of the reaction for the synthesis of the iodine salt appears to decrease with decreasing electron withdrawing power of the ring substituents. Moreover, the yield of the desired product seems to depend upon the position of the substituent, decreasing in the order $p > m > o$. The reaction is unsuccessful when applied to acids which contain *o*-substituents exhibiting weak +I or +T effects, and to acids substituted in any position by groups, such as hydroxy and amino, which exhibit strong +T effects. [b] Decomposes over a wide range. [c] These compounds were prepared by treating the silver salts with a large excess of pyridine and less than the theoretical amount of iodine. If treated under ordinary conditions, a residue was obtained from which the acid could be isolated by extracting with Skellysolve A and removing the excess iodine with mercury. [d] This compound could not be salted out of solution, but the residue remaining after evaporation of the chloroform gave the compound after continuous washing with Skellysolve A and ether. These washings on evaporation yielded crystals identified as the acid. [e] This compound salted out of solution as a heavy, viscous liquid which crystallized on standing in the cold.

tion of sodium carbonate was added until the solution tested basic to litmus. Nitric acid was then added dropwise until the solution tested acid to litmus. Any solid present was filtered off and a hot aqueous solution of an equivalent amount of silver nitrate was added. The silver salt was removed by filtration, washed with distilled water and alcohol, and dried at 70°.

**Preparation of Positive Iodine Compounds.**—To a suspension of a few grams of the silver salt of the acid in dry chloroform, iodine was added with shaking until the solution remained light orange in color. A slight excess of the coördinating base was then added and the addition of iodine was continued until the solution again remained colored after shaking. The silver iodide was filtered and a volume of Skellysolve A from one to four times the volume of the solution, depending upon the solubility of the compound being prepared, was added. The solution was allowed to stand overnight in the dark and the solid which had precipitated was filtered, washed with ether (or with Skellysolve if the compound was soluble in ether), and dried *in vacuo* over sulfuric acid. The positive iodine compounds are white or pale yellow crystalline solids.

**Analysis of Positive Iodine Compounds.**—To a 0.05-g. sample of the iodine compound, an excess of potassium iodide solution was added. Five ml. of carbon tetrachloride was then added and the solution acidified with a few drops of acetic acid. The organic acid which separated was retained in the carbon tetrachloride layer and did not interfere with the analysis. Finally, the free iodine in the solution was titrated with a 0.01 *N* sodium thiosulfate solution.

**Acknowledgment.**—The authors wish to thank the Upjohn Company for their grant during the time this work was carried out.

## Summary

Thirty-one new compounds of positive univalent iodine coördinated with pyridine or α- or β-picoline have been prepared.

LAWRENCE, KANSAS RECEIVED SEPTEMBER 15, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

# Transference Numbers of Zinc and Cadmium Sulfates at 25°, as Functions of the Concentration

BY GERARD M. WOLTEN AND CECIL V. KING

The method of determining transference numbers by means of the ratio of the electromotive forces of concentration cells with transference to those without[1] is thought by some[2] to be capable of great accuracy.

To throw further light on this method and to provide additional data on transference numbers, we have applied this method to solutions of zinc sulfate and cadmium sulfate at 25°.

## Experimental

To measure the e. m. f.'s of zinc and cadmium sulfate concentration cells with transference, of the type MHg, $MSO_4(m')$, $MSO_4(m'')$, MHg, where MHg indicates an amalgam, we used a cell of the same design as used by Stokes and Levien.[3] A Leeds and Northrup type K-1 potentiometer and a no. 2500B galvanometer, with 8000 to 10,000 ohms in series for suitable damping, were used. To shield against electric leakage and stray currents, the equipotential shielding method of White[4] was used. The thermostat was kept at 25.00 ± 0.02°. All cells reached equilibrium within one hour and stayed constant for at least several hours. Duplicate cells were reproducible within 0.05 mv., each cell being constant within 0.03 mv. or better.

### Materials

Zinc, zinc sulfate, and cadmium sulfate were the "C. P. Analysed" reagent grade of the J. T. Baker Chemical Co. C. P. triply distilled mercury was obtained from F. W. Berk & Co. Cadmium was obtained from the Udylite Corp. and by spectrographic analysis shown to be 99.95%

(1) Harned and Dreby, THIS JOURNAL, **61**, 3113 (1939).

(2) Taylor and Taylor, "Elementary Physical Chemistry," 3rd ed., D. Van Nostrand Co., New York, N. Y., 1942, p. 388.

(3) Stokes and Levien, THIS JOURNAL, **68**, 333 (1946).

(4) White, *ibid.*, **36**, 2011 (1914).

pure. Distilled water was redistilled from a quartz vessel and swept with nitrogen. The concentrations of the zinc sulfate solutions were determined by titration with potassium ferrocyanide, using diphenylamine as internal indicator.[5] The titrations were performed upon weighed samples of the solutions, so that the molalities followed immediately. The solutions of concentrations lower than 0.5 molal were made by weight dilution from the more concentrated ones. The solutions of cadmium sulfate were made by dissolving the required amounts of anhydrous salt in known weights of water, since it is a standard analytical procedure to determine cadmium quantitatively by weighing it as the sulfate.[6] From the works of Puschin,[7] Bijl,[8] Henderson and Stegeman,[9] Bray,[10] Cowperthwaite and LaMer,[11] and LaMer and Parks,[12] it is evident that all of the amalgams used in this work exhibit an unvarying e. m. f. over a wide range of concentrations of the metal in mercury, including the concentrations used here. Since it was thus unnecessary to reproduce the amalgam concentrations exactly for each run, it was found most convenient to prepare the amalgams in small batches, using a fresh one for each determination. This eliminated any problems of proper storage of these materials. The amalgams were made by heating about 35 g. of mercury and enough zinc or cadmium to make 6 or 8% amalgams, respectively. The heating was done in a stream of nitrogen.

## Experimental Results

CONCENTRATION CELLS WITH TRANSFERENCE AT 25°

TABLE I

Zinc sulfate, $m' = 2.059$ molal

| $m''$ | E. m. f., v. |
|---|---|
| 2.270 | 0.00200 |
| 2.059 | .00000 |
| 1.640 | − .00370 |
| 1.333 | − .00515 |
| 0.9693 | − .01050 |
| .4852 | − .01940 |
| .1055 | − .03052 |
| .05079 | − .03827 |
| .05054 | − .03834 |
| .01020 | − .06310 |
| .005052 | − .07769 |
| .001130 | − .09300 |
| .0005669 | − .09937 |

TABLE II

Cadmium sulfate, $m' = 1.003$ molal

| $m''$ | E. m. f., v. |
|---|---|
| 2.886 | 0.02009 |
| 2.503 | .01722 |
| 2.013 | .01103 |
| 1.526 | .00693 |
| 1.003 | .00000 |
| 0.5025 | − .00960 |
| .09852 | − .02295 |
| .04924 | − .03755 |
| .009911 | − .05601 |
| .004983 | − .06543 |
| .001259 | − .08129 |
| .0007394 | − .08637 |

The corresponding concentration cells without transference are of the type

$$MHg, MSO_4(m'), PbSO_4(s), PbHg, PbSO_4(s), MSO_4(m''), MHg$$

The e. m. f. of such a cell is the difference between the e. m. f.'s of two cells of the type

$$MHg, MSO_4(m), PbSO_4(s), HgPb$$

where $m$ first assumes the value $m'$ and then $m''$. Bray[10] investigated such cells for M = Zn, and LaMer and Parks[12] for M = Cd. From these data, the e. m. f.'s of zinc sulfate and cadmium sulfate concentration cells without transference have been calculated. If one chooses identical concentrations for the reference electrodes of both types of cells, one can then use the well-known relationship $dE_t/dE = t$, to calculate the transference number ($t$) of the ion with respect to which the terminal electrodes are not reversible, the sulfate ion in this case. $E_t$ denotes the e. m. f. of a cell with and $E$ the e. m. f. of a cell without transference. For the computation of the differential coefficient, we used the method of Rutledge,[13] following the example of Stokes and Levien.[3,14] Unlike graphical methods of differentiating, the method of Rutledge enables one to utilize the full degree of accuracy of the original data. In this case, the gain is slight, but we like to draw attention to the method, which is an intriguing one.

## Discussion

The anionic transference numbers of zinc sulfate and of cadmium sulfate are shown graphically in Figs. 1 and 2, where they are compared with the values obtained by Hittorf, Jahn and co-workers.[15]

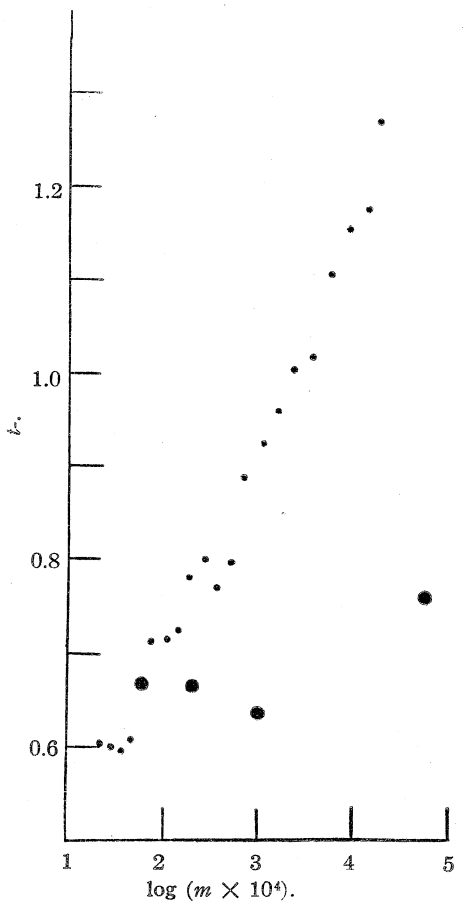



Fig. 1.—Zinc sulfate: small circles, present data; large circles, data of Hittorf, *et al.*

(5) "Scott's Standard Methods of Chemical Analysis," 5th ed., Vol. I, D. Van Nostrand Co., New York, N. Y., p. 1064 ff.
(6) *Ibid.*, p. 202.
(7) Puschin, *Z. anorg. Chem.*, **36**, 210 (1903).
(8) Bijl, *Z. physik. Chem.*, **41**, 641 (1902).
(9) Henderson and Stegeman, THIS JOURNAL, **40**, 84 (1918).
(10) Bray, *ibid.*, **49**, 2372 (1927).
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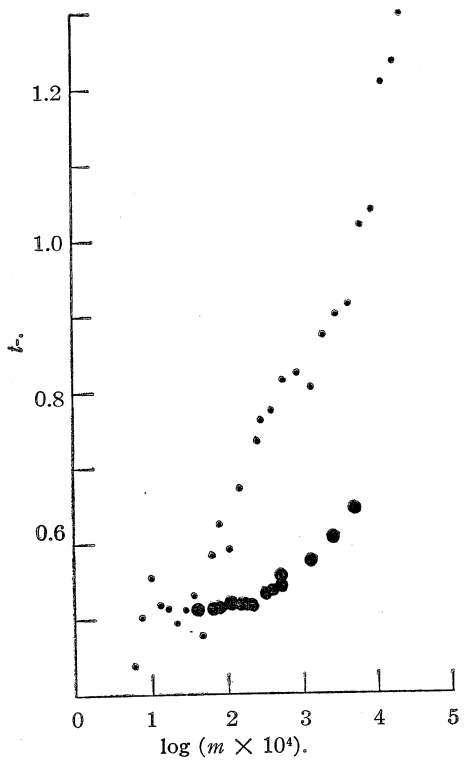



Fig. 2.—Cadmium sulfate: small circles, present data; large circles, data of Redlich and Goldlust, as reported by Jahn.[15]

We have no explanation to offer for the discrepancy. We can, however, point out that the presence of complex-formation, which our results indicate, is strongly supported by the low values of the activity coefficients. According to Masaki and Ikkatai,[16] Bray,[10] and LaMer and Parks,[12] the activity coefficients of both zinc and cadmium sulfate are about 0.08 in a 0.3 molal solution. This is approximately the concentration above which our results indicate negative cationic transference numbers. It has also been shown by McBain and Van Rysselberghe[17] that the cations in solutions of magnesium, zinc and cadmium sulfates form negatively charged complexes in the presence of excess alkali sulfate. The cationic and the anionic transference numbers must necessarily add up to unity. We have determined the anionic transference number. The cationic transference number can be determined in a quite similar manner, by means of the cell

$PbHg, PbSO_4(s), MSO_4(m'), MSO_4(m''), PbSO_4(s), PbHg$

The use of lead amalgam requires the rigid exclusion of air,[10] and a cell must be used which makes this possible. Such a cell vessel differs from the one used in the present investigation. For this reason, measurements on the above cell have not been included in this work, but it is hoped to make such a report in a future communication from this department.

## Summary

The transference numbers of zinc and cadmium sulfate have been investigated at 25° by the method of electromotive forces.

WASHINGTON SQUARE COLLEGE
NEW YORK 3, N. Y. RECEIVED[18] JULY 14, 1948

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(17) McBain and Van Rysselberghe, THIS JOURNAL, **52**, 2326 (1930).

(18) Original manuscript received December 18, 1947.

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[CONTRIBUTION NO. 57 FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF TENNESSEE]

# The Salts of Perrhenic Acid. II. The Iron Family and Manganese[1]

BY WILLIAM T. SMITH, JR., AND GROVER E. MAXWELL

The perrhenates of cobalt, nickel and manganese have been previously prepared and the colors and compositions of these salts reported.[2,3,4]

This paper deals with a more extensive examination of the composition and properties of the perrhenates of these metals in the divalent state as well as the perrhenates of iron in both di- and trivalent states.

**Preparation of the Salts.**—The carbonate or hydroxide of the metal was treated with a solution of perrhenic acid[5] and the hydrated salt was crystallized from the solution by evaporation at room temperature. All of these salts are deliquescent at the prevailing humidity in Knoxville during summer and were consequently crystallized by evaporation in a vacuum. In winter the crystallizations take place spontaneously in contact with the ambient air. The preparation of ferrous perrhenate was first attempted in an atmosphere of hydrogen. In spite of the precautions, approximately 10% of the iron present was oxidized to the ferric state, and the perrhenate so obtained suddenly became very viscous and black on evaporation at room temperature in a vacuum. This black semi-solid was very soluble in water giving a brown solution which on repeated evaporation gave the black semi-solid again. This solid was very soluble in ether although tests showed that neither the pure ferrous nor ferric perrhenate was

(1) This paper is based on a thesis presented by Grover E. Maxwell to the Graduate School of the University of Tennessee in partial fulfillment of the requirements for the M.S. degree, August 4, 1948.

(2) Briscoe, Robinson and Rudge, *J. Chem. Soc.*, 2211 (1931).

(3) Druce, *ibid.*, 966 (1938).

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(5) Smith and Long, THIS JOURNAL, **70**, 354 (1948).

TABLE I

PROPERTIES OF THE PERRHENATES

| Compound | Color | Soly., g./100 g. $H_2O$ at approx. 27° | F. p., °C. | Density, g./cc. at approx. 25° | Composition, % Found | Calcd. |
|---|---|---|---|---|---|---|
| $Co(ReO_4)_2$[a] | Deep purple | 299 | 816 | 5.33 | Co, 10.54 | 10.53 |
| $Co(ReO_4)_2 \cdot 3H_2O$[a] | Pinkish-red | 462 | | | $H_2O$, 8.65 | 8.79 |
| $Co(ReO_4)_2 \cdot 4H_2O$ | Purple-red | 548[d] | | 3.90 | $H_2O$, 11.54 | 11.40 |
| | | | | | $ReO_4$, 79.9 | 79.3 |
| $Ni(ReO_4)_2$[a] | Yellow | 310 | | | | |
| $Ni(ReO_4)_2 \cdot 2H_2O$ | Light green | 408 | | | $H_2O$, 6.04 | 6.04 |
| $Ni(ReO_4)_2 \cdot 4H_2O$[a] | Green | 567[d] | | 3.95 | $H_2O$, 11.36 | 11.40 |
| | | | | | Ni, 9.14 | 9.27 |
| | | | | | $ReO_4$, 80.0 | 79.3 |
| $Mn(ReO_4)_2$[b] | Pink | 340 | 861 | 5.12 | Mn, 9.70 | 9.90 |
| | | | | | $ReO_4$, 90.1 | 90.1 |
| $Mn(ReO_4)_2 \cdot 2H_2O$ | Pink | 464[d] | | 4.32 | $H_2O$, 6.30 | 6.10 |
| $Fe(ReO_4)_2$ | Dark red | 233 | | | Fe, 10.4 | 10.0 |
| | | | | | $ReO_4$, 89.0 | 90.0 |
| $Fe(ReO_4)_2 \cdot 4H_2O$ | Orange | 355[d] | | 3.64 | $H_2O$, 11.6 | 11.5 |
| $Fe(ReO_4)_3$ | Black | 270 | | | Fe, 6.80 | 6.92 |
| | | | | | $ReO_4$, 91.9 | 93.1 |
| $Fe(ReO_4)_3 \cdot 2H_2O$ | Black | 318 | | | $H_2O$, 4.35 | 4.27 |
| $Fe(ReO_4)_3 \cdot 4H_2O$[c] | Light purple | 376[d] | | 4.13 | $H_2O$, 8.44 | 8.21 |

[a] Briscoe and co-workers[2] reported these compounds and also the pentahydrates of cobalt and nickel perrhenates. [b] This compound has been previously reported.[3] The trihydrate of manganese perrhenate was also reported by the same investigator but was not found in this investigation. [c] One sample of ferric perrhenate on rapid evaporation yielded a brown hydrate. On dehydration the product was also brown. [d] Solubilities of the lower hydrates and anhydrous salts were calculated from these measurements on the actual equilibrium system.

very soluble in this solvent. The possibility of this product being a covalent complex is being investigated. A more satisfactory method for producing ferrous perrhenate was the reduction of ferric perrhenate in solution with powdered electrolytic iron. The reduction, decantation and crystallization were carried out in a vacuum. On one such preparation of ferrous perrhenate the concentrated solution separated into two immiscible liquid phases. Both phases produced crystals of the same appearance and composition.

The anhydrous salts and lower hydrates were produced by dehydration of the salts which crystallized from water solution.

**Analysis of the Salts.**—The analyses were all duplicated and good checks were obtained. The method used for rhenium was a modification[5] of the method of Willard and Smith.[6] The iron was determined gravimetrically as ferric oxide.[7] The method used in determining cobalt as the pyrophosphate and oxide was one described by Schoeller.[8] The standard dimethylglyoxime method[9] was used for nickel. The pyrophosphate method[10] was used for manganese.

The determination of water in the different hydrates was made by dehydration. Ferrous perrhenate tetrahydrate was dehydrated over calcium chloride at room temperature. No inflection points in the dehydration curves were observed. No further significant loss in weight occurred in an oven at 105°. Ferric perrhenate tetrahydrate lost water over calcium chloride at room temperature. There is a decided break in the curve at a loss in weight corresponding to the conversion to the dihydrate. The rate at which water was lost from the dihydrate was approximately one-fiftieth of the rate observed for the tetrahydrate. The dihydrate becomes anhydrous on heating in an oven at 105°. Cobalt perrhenate tetrahydrate on drying over calcium chloride yields the trihydrate. The trihydrate loses water very slowly over fresh calcium chloride and was found to maintain a constant weight over somewhat spent calcium chloride. The anhydrous salt is obtained on heating in an oven at 105°. Although six samples were dehydrated under varying conditions the previously reported pentahydrate[2] was not observed. The tetrahydrate of nickel perrhenate is the most stable of the tetrahydrates of the perrhenates of the iron family. Some samples of this hydrate remained over calcium chloride for several months with only slight visible evidence of efflorescence on the corners of some crystals. This hydrate has been reported to be stable[2] at 100° but it was found in this study that heating to 100° yields the anhydrous salt and heating at 80° to constant weight yields the dihydrate. The pentahydrate which has been previously reported[2] was not found. Manganous perrhenate crystallizes

(6) Willard and Smith, *Ind. Eng. Chem., Anal. Ed.*, **11**, 305 (1939).

(7) Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 5th ed., 1939, Vol. I, p. 467.

(8) Schoeller, *Analyst*, **69**, 8 (1944).

(9) Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley and Sons, Inc., New York, N. Y. 1929 p. 216.

(10) Kolthoff and Sandell, "Textbook of Quantitative Analysis," The Macmillan Co., New York, N. Y., 1938, p. 350.

water solutions as the dihydrate. The dehydration curve for this salt over calcium chloride gave no indication of a lower hydrate. After dehydrating the salt to constant weight over calcium chloride no further loss in weight was observed at 105° in an oven. The results of the analyses are presented in Table I.

**Density Determination.**—The densities of the solid salts were determined by displacement of benzene at 25°. The pycnometer, containing the salt and benzene, was placed in a desiccator and the system evacuated until the benzene boiled for a few minutes. After the removal of dissolved and adherent bubbles of gas in this manner, the temperature of the system was allowed to rise to 25° before weighings were made. The method was checked using salts of known density. Results indicate that the method is good to about 0.5%. The densities for the hydrates which crystallized from water and anhydrous salts which had been fused were determined.

**Solubility Determinations.**—The solubility was determined by evaporation of water from weighed quantities of the saturated solutions. Since all of the salts are very soluble (see Table I) the solubility was determined at only one temperature, approximately 27°. The solubilities of the salts other than those which exist in equilibrium with the saturated solution were calculated from the data on those that do exist in the equilibrium mixture. While the solubilities are all of the same order there is a distinct increase in solubility of the salts in the following order: ferrous, ferric, cobalt, nickel and manganese.

**Freezing Points.**—None of the hydrates listed in Table I are stable at the melting point. In fact, all of them decompose to form anhydrous salts at or below 105°. Three of the anhydrous salts decomposed without melting. The decompositions resulted in the volatilization of the rhenium as heptoxide. Ferrous perrhenate, the least stable, decomposed rapidly in a low bunsen flame. A full bunsen flame was necessary to rapidly decompose ferric perrhenate while nickel perrhenate required an oxygen flame for rapid decomposition. The anhydrous cobalt and manganese perrhenates can be melted, although some decomposition occurs at the temperatures required. Despite the decomposition excellent checks on the freezing points were obtained (see Table I). The decomposition products apparently are insoluble in the molten perrhenates. The method used for determining the freezing points has been previously described.[5] The thermocouple gave standard Chromel–Alumel voltages at the freezing point of sodium chloride, 800.4 ± 0.5°.[11]

**Microscopic Examination of Crystals.**—All of the salts which were obtained by primary crystallization either from water solution or from the fused substance were examined in polarized light with a microscope. These crystals are all anisotropic.

**Magnetic Susceptibility Measurements.**—The unusual colors of the ferrous and ferric perrhenates indicate some different type of structure from that in most salts of iron. Magnetic susceptibility measurements were made in an attempt to throw some light on the structure. The molar magnetic susceptibility of ferric perrhenate in a saturated solution was found to be $14{,}000 \times 10^{-6}$ and for the solid tetrahydrate $15{,}200 \times 10^{-6}$. This gives 5.83 and 6.08, respectively, as the magnetic moments. The molar susceptibility for the ferrous perrhenate tetrahydrate was measured as $11{,}300 \times 10^{-6}$ which gives a magnetic moment of 5.21. According to Selwood[12] a moment of 4.90 corresponds to four unpaired electrons per molecule and 5.92 to five unpaired electrons. Thus, within the limits of experimental error, the iron apears to be in the states normally found in simple salts. The magnetic susceptibility measurements were made using a modification of the Curie–Cheneveau balance.[13,14] The modification consisted principally in having the magnet stationary and measuring the torsion on a wire necessary to pull a sample of given volume and shape from the field between the poles of the magnet. Solid ferrous ammonium sulfate which has about the same susceptibility as the perrhenates measured was used in standardizing the apparatus.

## Summary

The perrhenates of the iron family and manganese have been prepared and the formulas verified by analysis. The solids which crystallize from solution at room temperature are the tetrahydrates of ferrous, ferric, cobalt and nickel perrhenates and the dihydrate of manganese perrhenate. The dihydrates of nickel and ferric perrhenates and the trihydrate of cobalt perrhenate were also isolated. All of these salts are deliquescent at high summer humidities. All of the hydrates produced anhydrous salts at 105° or below. The densities of those substances obtained by primary crystallization were determined. The solubilities have been measured at room temperature. Freezing points have been obtained for the salts which could be melted under atmospheric pressure. Microscopic examinations of all primary crystals revealed they are optically anisotropic. The unusual colors of the perrhenates of iron are indicative of complex formation, although magnetic susceptibility measurements indicate that if complex linkages do exist in these compounds they have an ionic rather than a covalent nature.

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(11) Roberts, *Phys. Rev.*, **23**, 386 (1924).

(12) Selwood, "Magnetochemistry," Interscience Publishers, Inc., New York, N. Y., 1943, p. 144.

(13) Selwood, *ibid.*, p. 10.

(14) Cheneveau, *Phil. Mag.*, **20**, 357 (1910).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ST. JOHN'S UNIVERSITY]

# Quantitative Determination of Cobaltammine Ammonia. Application to the Determination of Ferrocyanide Ion

BY HAROLD A. HORAN AND HENRY J. EPPIG[1]

A modification of the analytical method ingeniously employed by Brönsted[2] for solubility measurements with the cobaltic ammines, can be adapted advantageously to the volumetric determination of anionic constituents which form quantitatively insoluble, filterable precipitates with common ammines such as hexammine cobalt (III) chloride. The determination of ferrocyanide ion by this adaptation is presented in the experimental part of this paper. Although the cobaltic ammines have been used for the gravimetric determination of anions,[3] the thermal instability of the precipitated ammines generally precludes weighing of the compounds as such. The necessary conversion to a suitable weighing form sacrifices time and an advantageous ratio of compound weight found per unit weight of constituent sought. The proposed volumetric procedure has the advantages of speed and accuracy. In essence the method is that commonly used for the determination of combined ammonia in ammonium salts, the presence of the many ammonia groups in the ammine compound serving to increase the accuracy of the calculated anion. The latter is simply precipitated with a cobaltic ammine cation. After filtering and washing, the precipitated ammine is decomposed with alkali under conditions such that its ammonia is quantitatively evolved and determined by the standard alkalimetric procedure. The anion is then calculated from the known ratio of ammonia to anion in the compound. As pointed out by Horan,[3d] the hexammines are more reliable as precipitants than the substituted complex ions such as $Co(NH_3)_nX_m$, X = Cl, $NO_3$, etc., and $n + m = 6$. The proposed methods are accordingly limited to hexammine precipitants.

In the initial stages of this work the quantitative evolution and determination of cobaltammine ammonia presented a problem which has been recognized by many, including those who first investigated the compounds nearly a century ago. Although Genth[4] originally employed simple alkaline decomposition of the ammine and absorption of the evolved ammonia in hydrochloric acid, Gibbs and Genth[5] later reported difficulty with this method. They indicated a loss of ammonia in the course of the decomposition, due to oxidation by tervalent cobalt. Even after prior reduction by agents such as sulfurous acid, this method was found to be unsatisfactory. Krok[6] and Jörgensen[7] experienced low ammonia analyses by this method, and Jörgensen showed that alkaline decomposition in the presence of the reducing agent stannous chloride did not obviate the difficulty; nitrogen results were at best 1% low. It seems paradoxical that Brönsted in his earlier works[2,8] used simple alkaline decomposition for the evolution of ammonia, and without a reducing agent. Later, Brönsted[9] claimed, contrary to Jörgensen,[7] that "accurate ammonia determinations for all compounds of this type can be carried out by decomposing with alkali, with or without addition of reducing agents such as stannous chloride." Neusser[10] referred to "incomplete decomposition" into ammonia when certain cobaltic ammines were decomposed by means of alkali. Recently Lamb and Mysels[11] mentioned a method developed by Lamb and Damon.[12] It involves a preliminary reduction of the cobalt in hot acid solution by means of stannous chloride, after which the solution is made alkaline and the ammonia quantitatively evolved. This modification, however, requires an extra step as compared with the direct alkaline decomposition which is the basis of the methods suggested in the present paper.

Repeated experiments in this Laboratory with several types of carefully purified cobaltic ammines, using varied concentrations of alkali and observing proper experimental and mechanical precautions,[13] confirm the conclusions of Gibbs and Genth,[5] namely, that accurate and precise ammonia values cannot be obtained when the compounds are decomposed by means of alkali alone. This is the case with solid samples or solutions of the compounds; it is characteristic of the cobaltic ammines in general, and can be ascribed to oxidation of ammonia by tervalent cobalt.[14] We have found, however, that alkaline

(1) Present address: Picatinny Arsenal, Dover, New Jersey.

(2) Brönsted, *K. Vetenskaps Akad. Nobelinstitut*, **5**, 25, 10 (1919).

(3) (a) Parks, Dissertation, Columbia University, 1930; (b) Hynes, Malko and Yanowski, *Ind. Eng. Chem., Anal. Ed.*, **8**, 356 (1936); (c) Furman and State, *ibid.*, **8**, 420 (1936); (d) Horan, THIS JOURNAL, **61**, 2022 (1939); (e) Spacu and Pop, *Z. anal. Chem.*, **120**, 322 (1940).

(4) Genth, *Nordamerika Monatsvericht*, II, 8 (1851).

(5) Gibbs and Genth, *Am. J. Sci.*, [2] **23**, 240 (1857).

(6) Krok, *Lunds Univ., Arsskrift*, VII, 3 (1870).

(7) Jörgensen, *J. prakt. Chem.*, [2] nf, **18**, 246 (1878); *Z. anorg. Chem.*, **5**, 160 (1894).

(8) Brönsted, *D. kgl. Danske Vedersk Selsk, Math-fysike Meddel* II [10], 21 (1919); IV [4], 23 (1921).

(9) Brönsted and Peterson, THIS JOURNAL, **43**, 2266 (1922).

(10) Neusser, *Z. anorg. Chem.*, **207**, 386 (1932).

(11) Lamb and Mysels, THIS JOURNAL, **67**, 470 (1945).

(12) Unpublished work, privately communicated by Dr. A. B. Lamb.

(13) (a) Davisson, *Ind. Eng. Chem.*, **11**, 465 (1919); (b) Moose, Dissertation, Columbia University, 1935; (c) Miller, *Ind. Eng. Chem., Anal. Ed.*, **8**, 50 (1936).

(14) This effect of tervalent cobalt on ammonia in alkaline solution can be readily observed by treating a solution of an ammonium salt and a tervalent cobalt compound, for instance potassium cobalt (III) oxalate $[K_3Co(C_2O_4)_3]$, with sodium hydroxide.

decomposition of stable hexammine and pentammine cobaltic salts in the presence of the soluble, alkaline-stable reductant, arsenious oxide, proceeds with the quantitative evolution of ammonia. Volumetric determinations of the latter, when the compounds are decomposed in this manner, are highly accurate and reproducible. The adaptation to determinations of cobaltammine precipitated anions is simple and direct, and the results obtained are excellent. The procedure is presently described for the determination of ferrocyanide. The precipitate which forms upon addition of hexammine cobalt (III) ion to ferrocyanide ion has the composition indicated by the formula $[Co(NH_3)_6]_4[Fe(CN)_6]_3 \cdot H_2O$.[15] Eight moles of ammonia are equivalent to one of ferrocyanide.

## Experimental

**Materials.**—The following ammines were prepared and carefully purified: hexammine cobalt(III) chloride,[16] hexammine cobalt(III) nitrate,[17] bromopentammine cobalt(III) bromide,[18] chloropentammine cobalt(III) chloride[19] and carbonatotetrammine cobalt(III) chloride.[20] The compounds were analyzed for cobalt and anion. *Anal.* Calcd. for $Co(NH_3)_6Cl_3$: Co, 22.03; Cl, 39.78. Found: Co, 22.05, 22.05; Cl, 39.74, 39.77. Calcd. for $Co(NH_3)_6(NO_3)_3$: Co, 16.98; $NH_3$ + $NO_3$ as N, 36.32. Found: Co, 16.98, 17.00; N, 36.23, 36.28. Calcd. for $[Co(NH_3)_5Br]Br_2$: Co, 15.36; Br (total), 62.46. Found: Co, 15.39, 15.37; Br (total), 62.42, 62.49. Calcd. for $[Co(NH_3)_5Cl]Cl_2$: Co, 23.53; Cl (ionized), 42.47. Found: Co, 23.59, 23.52; Cl (ionized), 42.42, 42.43. Calcd. for $[Co(NH_3)_4CO_3]Cl$: Co, 26.49; Cl, 15.93. Found: Co, 26.53, 26.44; Cl, 15.88, 15.89.

An aqueous solution of hexammine cobalt(III) chloride, containing 4.0 g. of the solid in 96 ml. of water, was prepared for use in the determination of ferrocyanide.

**Apparatus.**—For determination of ammonia, weighed samples were decomposed with sodium hydroxide solution in a 500-ml. Kjeldahl flask which was connected through a Davisson scrubber trap[13a] to a water condenser; the latter was fitted with an improved adapter[13c] at its outlet. The entire apparatus was made of Pyrex glass, in order to avoid rubber connections: 250 ml. of redistilled water, free of ammonia and ammonium salts, together with a suitable amount of sodium hydroxide was present in the flask at the outset. Most of the air within the apparatus was expelled[13c] before the sample was allowed to enter the alkaline solution. The distillate was received under standard sulfuric acid.

Typical results which were obtained with hexammine cobalt(III) chloride, when the decomposition was effected with different amounts of sodium hydroxide, are given in Table I. Similar results were obtained with other hexammines and also with the substituted ammines listed above.

**Potassium Ferrocyanide.**—Merck reagent potassium ferrocyanide was first purified by recrystallization from water between 25 and 0°, and then treated according to Loftfield and Swift[21] for final purification. The salt was dried to constant weight at 95° in an atmosphere of pure dry nitrogen. An exact weight of the salt was dissolved in sufficient water to make a solution of known total weight. The solution was measured from a weight buret, and the weight of potassium ferrocyanide taken was then calculated. Several different solutions were used in the course of this work; a typical composition was 1.3900 g. of the salt in 98.0355 g. of aqueous solution.

Table I

Ammonia Analyses; Samples Decomposed with Alkali Alone

Calcd. for $Co(NH_3)_6Cl_3$: $NH_3$, 38.20

| Sodium hydroxide present in flask | $NH_3$, found, % | |
|---|---|---|
| 5 ml. of 50% NaOH solution | 37.50 | 37.66 |
| 10 ml. of 50% NaOH solution | 37.85 | 37.78 |
| 25 ml. of 50% NaOH solution | 37.84 | 37.90 |
| 200 g. NaOH, solid | 37.95 | 37.90 |

**Arsenious Oxide.**—Merck reagent was used without further purification.

Blanks containing the redistilled water, sodium hydroxide and arsenious oxide (7.0 g.) were distilled into standard acid, and the amounts of the latter which were consumed were estimated by back titration. These were less than 0.03 ml. of 0.1 *N* acid.

**Standard Sulfuric Acid and Sodium Hydroxide Solutions.**—Solutions of these were prepared in 0.1 *N* and in 0.05 *N* concentrations, and were standardized by the usual methods. Methyl red was used as the indicator in ammonia determinations.

**Accurate Ammonia Analyses of the Cobaltic Ammines.** The failure to recover completely the ammonia of these compounds when the decomposition was effected by alkali alone (Table I), was the result of a reaction between tervalent cobalt and ammonia; no detectable nitrogen remained in the residues from such decompositions.

Preliminary experiments demonstrated that the stable, alkaline soluble reductant, arsenious oxide, reacted with many of the cobaltic ammines forming a clear, deep-purple colored solution. The evolution of ammonia in these cases was quantitative. The following procedure was finally adopted for accurate ammonia analyses. The Kjeldahl flask of the previously described apparatus was charged with 250 ml. of redistilled water, 15 g. of sodium hydroxide and 7 g. of arsenious oxide. A weighed sample (*ca.* 0.2 g.) of the ammine was suspended in the neck of the flask while most of the air within the apparatus was displaced[13c] by rapidly bringing the solution to the boiling point. The sample was released; reduction took place rapidly. Distillation was continued until about 80% of the solution was distilled over into the standard acid. The condenser was briefly steamed, rinsed and the titration of the remaining acid performed. Results are given in Table II.

Table II

Accurate Cobaltammine Ammonia Analyses in the Presence of Arsenious Oxide

| Ammine used | $NH_3$, % Calcd. | $NH_3$, % Found | |
|---|---|---|---|
| $Co(NH_3)_6Cl_3$ | 38.20 | 38.17 | 38.21 |
| $Co(NH_3)_6(NO_3)_3$ | 29.44 | 29.45 | 29.47 |
| $[Co(NH_3)_5Br]Br_2$ | 22.19 | 22.18 | 22.20 |
| $[Co(NH_3)_5Cl]Cl_2$ | 33.99 | 33.93 | 33.95 |
| $[Co(NH_3)_4CO_3]Cl$[a] | 30.61 | 30.43 | 30.48 |

[a] In connection with the low results obtained with this relatively unstable tetrammine, it should be noted that decomposition proceeded with the immediate formation of a small amount of dark brown precipitate, instead of the immediate formation of a homogeneous purple mixture.

**Determination of Ferrocyanide by the Cobaltammine–Ammonia Method.**—A suitable amount of potassium ferrocyanide solution (containing no more than 0.2 g. of the

(15) (a) Gibbs and Genth, *J. prakt. Chem.*, **72**, 161 (1857); (b) Braun, *Ann.*, **125**, 182 (1863); (c) Ephraim and Mosimann, *Ber.*, **54**, 396 (1921); (d) Steinmetz, *Z. Kryst.*, **57**, 233 (1922).

(16) Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Hasse and Son, Copenhagen, 1941, p. 241.

(17) Jörgensen, *J. prakt. Chem.*, 2, **23**, 227 (1881).

(18) Booth, "Inorganic Synthesis," McGraw-Hill Book Co., New York, N. Y., 1939, Vol. I, p. 186.

(19) Hynes, Yanowski and Schiller, This Journal, **60**, 3053 (1938).

(20) Lamb and Damon, *ibid.*, **59**, 385 (1937).

(21) Loftfield and Swift, *ibid.*, **60**, 3083 (1938).

salt) was discharged from a weight buret into a 50-ml. beaker and this solution, which contained a known amount of the salt, was diluted to 20 ml. with water. Hexammine cobalt(III) chloride solution was added dropwise with stirring, sufficient to provide an excess of 20–30% over that required to form $[Co(NH_3)_6]_4[Fe(CN)_6]_3$. The beaker was placed in cold water (about 4°) for twenty minutes, and the precipitate allowed to settle. The latter was quantitatively filtered on a dense filter paper (Whatman No. 5) and washed thoroughly with approximately 45 ml. of cold water. The filter paper containing the precipitate was folded carefully, tied with a thin wire and suspended in the neck of the Kjeldahl flask of the apparatus described above. The flask contained 250 ml. of redistilled water, 15 g. of sodium hydroxide and 7 g. of arsenious oxide. After rapidly bringing the contents of the flask to the boiling point in order to expel most of the air,[13c] the filter paper was released. The liberated ammonia was distilled rapidly into the standard acid in the receiver. The final steps were as described above under accurate ammonia analyses: 0.1 *N* acid was used for the larger amounts of ferrocyanide; 0.05 *N* acid was used for amounts less than 0.1 g.

Blank determinations with ferrocyanide included were not measurably different from those mentioned above under arsenious oxide. Results are given in Table III. They were calculated from the ammonia analyses found, on the basis of eight moles of ammonia equivalent to one mole of potassium ferrocyanide.

TABLE III

DETERMINATION OF FERROCYANIDE BY THE COBALTAMMINE–AMMONIA METHOD

| $K_4Fe(CN)_6$ taken, g. | $K_4Fe(CN)_6$ found, g. | $K_4Fe(CN)_6$ taken, g. | $K_4Fe(CN)_6$ found, g. |
|---|---|---|---|
| 0.1914 | 0.1916 | 0.0532 | 0.0532 |
| .1845 | .1847 | .0528 | .0527 |
| .1782 | .1781 | .0539 | .0540 |
| .1609 | .1609 | .0186 | .0187 |
| .1048 | .1045 | .0174 | .0173 |
| .1125 | .1125 | .0185 | .0183 |

## Discussion

The results in Table III show that the proposed method for the determination of ferrocyanide is very reliable even when semi-micro quantities of this anion are under consideration. In such instances no special equipment is required, and it is unnecessary to use standard solutions of extreme dilution. These are decided advantages over the usual oxidation–reduction methods generally used for this constituent, since the oxidimetric gram-equivalent weight of potassium ferrocyanide is very high, 368.34; in determinations of quantities of the order of 0.025 g. one must use 0.01 *N* oxidizing agent and a micro buret. Furthermore, the cobaltammine–ammonia method permits results of higher precision and accuracy than the corresponding gravimetric method[3b] which uses hexammine cobalt(III) ion as the precipitant for ferrocyanide. This follows since the present method takes advantage of a found/sought mole ratio of $8NH_3/1K_4Fe(CN)_6$, in comparison to the unfavorable 0.503/1.00 (wt. ignited oxides found/wt. potassium ferrocyanide taken) factor of the gravimetric procedure. An additional disadvantage of the latter is the adverse influence caused by small, uncontrollable variations in the composition of the ignited residues.

The reliability of the weighing forms used in most gravimetric cobaltammine methods is questionable. Since the precipitates are generally unstable on drying at 100° the compounds are either dried at room temperature after the final removal of the aqueous phase with volatile organic solvents, or they are converted to mixed oxides of cobalt by ignition. In the first instance loosely bound or lattice water[22] may be removed to an indefinite degree; in the second, the existence of several oxides of cobalt, *viz.*, CoO, $Co_2O_3$, $Co_3O_4$, with uncertain ranges of thermal stability[23] is a source of indeterminate error.

In view of the large number of ammonia groups present, it is suggested that adaptations similar to that suggested for ferrocyanide ion should make it possible to determine accurately several other anions, which are quantitatively precipitated by hexammine cobalt(III) chloride.

## Summary

A direct, accurate, volumetric method for the quantitative evolution and determination of ammonia in the stabile hexammine and pentammine cobalt(III) salts is presented.

Use of this method for ammonia present in hexammine cobalt(III) ferrocyanide which has been quantitatively precipitated from a solution containing ferrocyanide ion, serves as a convenient and accurate means of estimating this anion.

Suggestions are made relative to similar modifications of cobaltammine methods for the determination of other anions.

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(22) Emeléus and Anderson, "Modern Aspects of Inorganic Chemistry," D. Van Nostrand Co., New York, N. Y., 1938, p. 163.

(23) Ephraim–Thorne, "Inorganic Chemistry," Nordeman Publishing Co., Inc., New York, N. Y., 1939, p. 439.

[CONTRIBUTION NO. 12 FROM THE THERMODYNAMICS LABORATORY OF THE PETROLEUM EXPERIMENT STATION, BUREAU OF MINES, BARTLESVILLE, OKLA.]

# Low Temperature Thermal Data on Eight $C_8H_{16}$ Alkylcyclohexanes

BY HUGH M. HUFFMAN, SAMUEL S. TODD AND GEORGE D. OLIVER[1]

In continuation of the program of the Bureau of Mines,[2] to investigate the thermodynamic properties of petroleum hydrocarbons and related substances, low-temperature thermal studies have been made on eight $C_8H_{16}$ alkylcyclohexanes over the temperature range 12 to 300°K. This investigation of a group of isomers represents one of the most comprehensive studies of isomers yet made in the field of low temperature calorimetry. A number of interesting and unusual phenomena were observed which will be discussed. Insofar as the authors are aware this is the first published work on the low temperature heat capacity of these substances.

## Experimental

**The Materials.**—The materials used in this investigation were API–NBS "best" samples prepared by the A.P.I. Research Project 6 at the National Bureau of Standards[3] and certified by them in regard to their purity.

**The Apparatus.**—The measurements were made in the apparatus described by Ruehrwein and Huffman.[4] Very briefly, the method is as follows: About 0.4 mole of the material under investigation was contained in a sealed copper calorimeter, which was mounted in the adiabatic calorimetric system. A measured amount of electrical energy was supplied to the calorimeter, and at all times the temperature of the environment was maintained at that of the calorimeter to prevent heat interchange. The initial and final temperatures of the calorimeter were measured by means of a platinum resistance thermometer. The electrical measurements required for determining the resistance of the thermometer and for the electrical energy were made on a "White" double potentiometer in conjunction with a high-sensitivity galvanometer and accurately calibrated resistances. The potential was in terms of a bank of six saturated cadmium cells, which had been certified by the National Bureau of Standards. Time measurements were made with an electric stopclock driven by alternating current, the frequency of which was controlled with an accuracy of 0.001%. The precision of the measurements was, in general, better than 0.1%; and above 30°K., it is believed that the accuracy uncertainty, unless otherwise stated, should not be greater than 0.2%. The energy measurements were made in terms of the international joule and were converted to calories by dividing by 4.1833.

Melting-point studies were made on all of these compounds as a part of the routine measurements and the results are summarized in Table I. It should be borne in mind that the equilibrium temperatures given correspond to triple points since the material in all cases was sealed in the calorimeter under its own vapor pressure. Three of these

TABLE I

$C_8H_{16}$ ALKYLCYCLOHEXANE MELTING POINT SUMMARY

| % liq. | $T_{obs.}$ | $T_{calcd.}$ |
|---|---|---|
| **Ethylcyclohexane** | | |
| 16.86 | 161.8315 | 161.8279 |
| 41.37 | .8354[a] | .8354 |
| 71.32 | .8375 | .8376 |
| 90.37 | .8382[a] | .8382 |
| 100.0 | | .8385 |
| Pure | | 161.8406 |
| $N_x = 0.0382\,\Delta T$ | | |
| Impurity = 0.008 ± 0.004 mole % | | |
| **1,1-Dimethylcyclohexane** | | |
| 24.3 | 239.393 | 239.158 |
| 40.0 | .491 | .414 |
| 53.7 | .540 | .515 |
| 76.4 | .603[a] | .603 |
| 79.2 | .604 | .611 |
| 92.0 | .638[a] | .638 |
| 100.0 | | .652 |
| Pure | | 239.811 |
| $N_x = 0.00423\,\Delta T$ | | |
| Impurity = 0.07 ± 0.03 mole % | | |
| ***cis*-1,2-Dimethylcyclohexane** | | |
| 8.3 | 223.2257 | 223.1420 |
| 37.9 | .2483[a] | .2483 |
| 70.6 | .2618 | .2621 |
| 88.5 | .2654[a] | .2654 |
| 100.0 | .2668 | |
| Pure | | 223.278 |
| $N_x = 0.00397\,\Delta T$ | | |
| Impurity = 0.0045 ± 0.002 mole % | | |

(1) Present address: Carbide and Carbon Chemical Corporation, Oak Ridge, Tennessee.

(2) Knowlton and Huffman, THIS JOURNAL, **66**, 1492 (1944).

(3) These samples of API–NBS hydrocarbons have been made available by the American Petroleum Institute and the National Bureau of Standards through the A. P. I. Research Project 44 on the "Collection, analysis, and calculation of data on the properties of hydrocarbons." The samples were purified at the National Bureau of Standards by the A. P. I. Research Project 6 on the "Analysis, purification and properties of hydrocarbons," under the supervision of Frederick D. Rossini, from material supplied by the following laboratories:

*Ethylcyclohexane, cis-1,3-dimethylcyclohexane, trans-1,3-dimethylcyclohexane, 1,1-dimethylcyclohexane, cis-1,2-dimethylcyclohexane* and *trans-1,2-dimethylcyclohexane*, by the A. P. I. Research Project 45 on the "Synthesis and properties of hydrocarbons of low molecular weight" at the Ohio State University, under supervision of Cecil E. Boord.

*cis-1,4-Dimethylcyclohexane* and *trans-1,4-dimethylcyclohexane*, by the Standard Oil Development Co., Elizabeth, N. J. through the courtesy of W. J. Sweeney.

(4) Ruehrwein and Huffman, THIS JOURNAL, **65**, 1620 (1943).

TABLE I (*Continued*)

| % liq. | $T_{obs.}$ | $T_{calcd.}$ |
|---|---|---|
| | *trans*-1,2-Dimethylcyclohexane (I) | |
| 17.8 | 184.9546 | 184.9470 |
| 47.6 | .9762[a] | .9762 |
| 71.5 | .9817[a] | .9820 |
| 91.4 | .9848 | .9845 |
| 100.0 | | .9853 |
| Pure | | 184.994 |
| $N_x = 0.0368\Delta T$ | | |
| Impurity = 0.030 ± 0.005 mole % | | |
| | II | |
| 16.6 | 184.9515 | 184.9423 |
| 45.6 | .9713[a] | .9707 |
| 68.8 | .9767 | .9769 |
| 88.1 | .9793[a] | .9793 |
| 100.0 | | .9804 |
| Pure | | 184.988 |
| Impurity = 0.028 ± 0.005 mole % | | |
| | *trans*-1,3-Dimethylcyclohexane | |
| 18.2 | 182.929 | 182.920 |
| 39.2 | .997[a] | .997 |
| 66.6 | 183.023 | 183.024 |
| 85.5 | .033[a] | .033 |
| 100.0 | | .037 |
| Pure | | 183.063 |
| $N_x = 0.0354\Delta T$ | | |
| Impurity = 0.090 ± 0.010 mole % | | |
| | *cis*-1,3-Dimethylcyclohexane | |
| 16.78 | 197.5565[a] | 197.5565 |
| 38.99 | .5778 | .5774 |
| 68.63 | .5845 | .5842 |
| 90.85 | .5864[a] | .5864 |
| 100.0 | | .5870 |
| Pure | | 197.593 |
| $N_x = 0.0333\Delta T$ | | |
| Impurity = 0.021 ± 0.005 mole % | | |
| | *cis*-1,4-Dimethylcyclohexane | |
| 19.08 | 185.6916 | 185.6871 |
| 45.50 | .7138[a] | .7138 |
| 69.72 | .7205 | .7204 |
| 91.73 | .7235[a] | .7235 |
| 100.0 | | .7243 |
| Pure | | 185.733 |
| $N_x = 0.0324\Delta T$ | | |
| Impurity = 0.028 ± 0.005 mole % | | |
| | *trans*-1,4-Dimethylcyclohexane | |
| 2.79 | 236.126[a] | 236.126 |
| 12.28 | .197 | .196 |
| 37.53 | .209 | .210 |
| 66.47 | .212 | .213 |
| 88.70 | .214[a] | .214 |
| 100.00 | | .215 |
| Pure | | 236.217 |
| $N_x = 0.026\Delta T$ | | |
| Impurity = 0.007 ± 0.005 mole % | | |

[a] Calculations based on these experimental points.

compounds have small cryoscopic constants, and consequently the triple points may be expected to differ significantly from the melting points which are observed when the liquid materials are saturated with air at atmospheric pressure.

In the case of ethylcyclohexane, which has a low cryoscopic constant, the melting point study was repeated several times to test the precision of the measurements. The results of this study are shown in Fig. 1 which is a plot of $T$ against $1/F$, where $T$ is the absolute temperature and $F$ is the fraction melted. The extreme experimental difference is seen to be slightly greater than 0.002° but in any single series of measurements the precision of measurement is much better than this. In addition to the melting point measurements a single freezing-point[5] measurement was made. This point was approximately 0.015° below the melting-point curves. These data tend to confirm the hypotheses that equilibrium temperatures may be a resultant of the way the material is treated and not necessarily a true equilibrium.

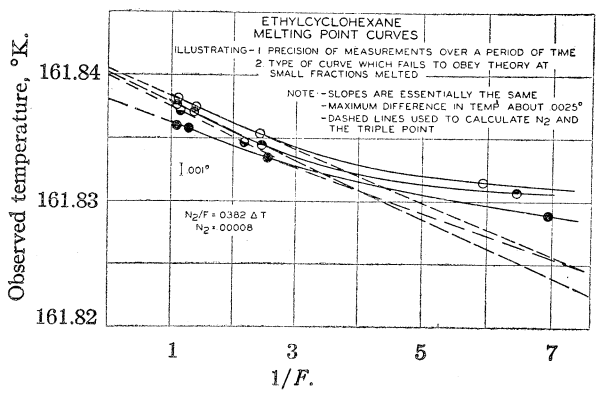



Fig. 1.—Melting point curves for ethylcyclohexane.

In the case of *trans*-1,2-, *trans*-1,3- and *trans*-1,4-dimethylcyclohexane there is some uncertainty in the melting points for pure material and for the mole fraction of impurity in the sample because in none of these materials was it possible to obtain an unambiguous value for the heat of fusion. The uncertainty due to this factor will not be very great in the absolute sense.

## Results

The experimentally determined heat capacities are given in Table II. In Table III are listed specific heat data at integral temperatures as selected from a smooth curve drawn through all of the data. The specific heat data for crystalline *trans*-1,3-dimethylcyclohexane may be less accurate than that of the other compounds for reasons which will be discussed later.

The molal heats of fusion of these compounds are given in Table IV. The uncertainties given are in all cases precision uncertain-

(5) Freezing point means the equilibrium was approached after crystallizing a portion of the material rather than melting.

TABLE II

THE MOLAL HEAT CAPACITY OF THE $C_8H_{16}$ ALKYLCYCLOHEXANES

0°C. = 273.16°K., mol. wt. = 112.208

| $T$, °K. | $\Delta T$ | $C_p$ cal. deg.$^{-1}$ | $T$, °K. | $\Delta T$ | $C_p$ cal. deg.$^{-1}$ |
|---|---|---|---|---|---|
| **Ethylcyclohexane** | | | | | |
| 12.00 | 1.512 | 1.116 | 123.73 | 8.568 | 21.599 |
| 12.61 | 1.989 | 1.270 | 131.86 | 8.930 | 22.670 |
| 13.79 | 2.153 | 1.559 | 132.55 | 9.066 | 22.739 |
| 15.11 | 3.057 | 1.915 | 140.59 | 8.535 | 23.807 |
| 18.34 | 3.468 | 2.819 | 141.41 | 8.661 | 23.854 |
| 19.73 | 2.995 | 3.233 | 148.15 | 6.577 | 24.808 |
| 21.72 | 3.317 | 3.828 | 149.91 | 8.328 | 24.936 |
| 23.09 | 3.724 | 4.221 | 154.63 | 6.380 | 25.693 |
| 25.56 | 4.357 | 4.955 | Liquid | | |
| 26.95 | 3.993 | 5.353 | 167.35 | 6.223 | 39.125 |
| 30.38 | 5.288 | 6.280 | 171.66 | 6.278 | 39.409 |
| 31.01 | 4.110 | 6.450 | 174.55 | 8.188 | 39.542 |
| 35.90 | 5.756 | 7.688 | 179.95 | 10.309 | 39.922 |
| 41.76 | 5.953 | 9.025 | 183.18 | 9.073 | 40.090 |
| 47.74 | 6.021 | 10.281 | 192.68 | 9.910 | 40.740 |
| 53.80 | 6.081 | 11.461 | 193.07 | 9.877 | 40.724 |
| 55.24 | 5.142 | 11.721 | 202.86 | 9.699 | 41.434 |
| 59.92 | 6.158 | 12.558 | 212.95 | 10.486 | 42.199 |
| 60.90 | 6.172 | 12.696 | 223.34 | 10.286 | 43.052 |
| 67.45 | 6.930 | 13.767 | 233.53 | 10.095 | 43.934 |
| 74.84 | 7.848 | 14.872 | 243.98 | 10.797 | 44.885 |
| 82.78 | 8.025 | 16.078 | 254.66 | 10.578 | 45.929 |
| 90.90 | 8.219 | 17.255 | 265.13 | 10.360 | 46.986 |
| 98.86 | 7.702 | 18.313 | 270.92 | 6.847 | 47.566 |
| 103.87 | 6.261 | 18.985 | 275.38 | 10.161 | 48.073 |
| 106.88 | 8.341 | 19.370 | 279.40 | 10.098 | 48.490 |
| 110.00 | 5.990 | 19.790 | 285.46 | 9.975 | 49.176 |
| 115.00 | 7.900 | 20.417 | 289.39 | 9.887 | 49.611 |
| 115.44 | 8.007 | 20.486 | 295.34 | 9.773 | 50.302 |
| 123.17 | 8.442 | 21.530 | 299.19 | 9.715 | 50.746 |
| **1,1-Dimethylcyclohexane** | | | | | |
| Crystals I | | | 121.45 | 9.470 | 20.878 |
| 12.31 | 1.533 | 1.051 | 131.04 | 9.723 | 22.281 |
| 14.10 | 2.110 | 1.512 | 141.61 | 11.410 | 23.909 |
| 15.15 | 3.484 | 1.812 | Crystals II | | |
| 16.25 | 2.229 | 2.128 | 154.15 | 7.027 | 33.286 |
| 18.94 | 3.164 | 2.949 | 165.61 | 11.175 | 34.350 |
| 18.98 | 4.204 | 2.957 | 176.64 | 10.876 | 35.258 |
| 22.73 | 4.423 | 4.129 | 187.37 | 10.591 | 36.167 |
| 23.98 | 5.838 | 4.479 | 190.04 | 64.737 | 36.462 |
| 27.13 | 4.374 | 5.375 | 197.84 | 10.350 | 37.091 |
| 29.97 | 6.139 | 6.115 | 208.07 | 10.098 | 38.084 |
| 31.32 | 4.866 | 6.449 | 216.88 | 29.411 | 38.953 |
| 31.67 | 4.701 | 6.528 | 218.05 | 9.860 | 39.090 |
| 36.55 | 7.009 | 7.637 | 226.07 | 7.328 | 39.988 |
| 36.88 | 6.229 | 7.695 | 227.79 | 9.672 | 40.123 |
| 42.88 | 5.778 | 8.856 | 228.35 | 6.529 | 40.230 |
| 43.46 | 6.802 | 8.964 | 230.80 | 10.132 | 40.473 |
| 48.76 | 5.970 | 9.894 | 232.62 | 5.767 | 40.733 |
| 50.66 | 7.611 | 10.199 | Liquid | | |
| 55.21 | 6.944 | 10.936 | 242.74 | 5.279 | 44.094 |
| 58.16 | 7.362 | 11.405 | 246.71 | 5.359 | 44.483 |
| 61.76 | 6.163 | 11.974 | 249.32 | 5.273 | 44.712 |
| 65.52 | 9.038 | 12.548 | 250.57 | 10.393 | 44.823 |
| 67.66 | 5.617 | 12.890 | 260.69 | 10.141 | 45.868 |
| 75.69 | 11.298 | 14.057 | 260.86 | 10.172 | 45.908 |
| 86.97 | 5.229 | 15.821 | 270.72 | 9.926 | 46.914 |
| 87.49 | 12.303 | 15.866 | 270.92 | 9.951 | 46.982 |
| 94.27 | 9.365 | 16.885 | 279.75 | 8.128 | 47.902 |
| 101.05 | 14.815 | 17.852 | 280.78 | 9.767 | 48.028 |
| 103.28 | 8.663 | 18.186 | 287.81 | 7.989 | 48.828 |
| 112.16 | 9.100 | 19.508 | 295.73 | 7.859 | 49.708 |
| 118.81 | 20.714 | 20.475 | 303.53 | 7.732 | 50.664 |
| ***cis*-1,2-Dimethylcyclohexane** | | | | | |
| | | | 136.27 | 15.200 | 23.082 |
| Crystals I | | | 140.69 | 10.638 | 23.654 |
| 11.92 | 1.740 | 0.873 | 141.66 | 4.672 | 23.686 |
| 13.63 | 1.768 | 1.283 | 142.62 | 9.236 | 23.884 |
| 13.69 | 1.733 | 1.308 | 147.02 | 6.037 | 24.378 |
| 15.55 | 2.115 | 1.777 | 151.07 | 10.115 | 24.944 |
| 16.68 | 4.253 | 2.088 | 151.67 | 8.844 | 25.007 |
| 18.33 | 3.457 | 2.560 | 151.93 | 16.116 | 25.007 |
| 20.60 | 3.589 | 3.241 | 153.72 | 7.400 | 25.284 |
| 21.68 | 3.252 | 3.560 | 160.93 | 7.036 | 26.331 |
| 24.88 | 3.152 | 4.487 | 167.87 | 6.860 | 27.449 |
| 25.11 | 5.438 | 4.552 | Crystals II | | |
| 28.24 | 3.569 | 5.409 | 175.48 | 8.811 | 37.185 |
| 30.33 | 4.993 | 5.968 | 182.98 | 10.396 | 37.514 |
| 32.12 | 4.174 | 6.407 | 183.70 | 9.678 | 37.533 |
| 35.23 | 4.804 | 7.164 | 184.23 | 8.699 | 37.569 |
| 40.60 | 5.929 | 8.334 | 185.69 | 5.727 | 37.700 |
| 46.57 | 5.994 | 9.512 | 187.30 | 18.926 | 37.797 |
| 52.18 | 5.241 | 10.549 | 193.28 | 9.489 | 38.241 |
| 54.89 | 4.131 | 11.021 | 194.42 | 12.017 | 38.314 |
| 57.91 | 6.217 | 11.552 | 202.68 | 9.309 | 38.977 |
| 59.96 | 5.997 | 11.894 | 205.84 | 10.832 | 39.223 |
| 65.06 | 6.863 | 12.742 | 211.90 | 9.134 | 39.727 |
| 65.68 | 5.438 | 12.863 | 215.69 | 8.856 | 40.030 |
| 71.52 | 6.245 | 13.777 | Liquid | | |
| 71.60 | 6.228 | 13.795 | 228.30 | 4.960 | 43.480 |
| 77.59 | 5.752 | 14.767 | 233.46 | 8.379 | 43.934 |
| 77.66 | 6.147 | 14.769 | 234.86 | 8.157 | 44.065 |
| 82.94 | 4.940 | 15.597 | 241.59 | 9.896 | 44.704 |
| 84.04 | 6.513 | 15.777 | 243.75 | 9.639 | 44.767 |
| 88.51 | 6.199 | 16.469 | 252.40 | 9.713 | 45.569 |
| 90.72 | 6.841 | 16.783 | 254.08 | 11.022 | 45.736 |
| 95.25 | 7.279 | 17.446 | 262.02 | 9.534 | 46.514 |
| 97.71 | 7.141 | 17.786 | 264.98 | 10.777 | 46.802 |
| 102.98 | 8.188 | 18.551 | 271.46 | 9.352 | 47.423 |
| 105.31 | 8.052 | 18.875 | 275.66 | 10.597 | 47.849 |
| 113.88 | 9.099 | 20.058 | 280.74 | 9.201 | 48.361 |
| 123.55 | 10.242 | 21.403 | 286.50 | 11.098 | 48.982 |
| 124.63 | 5.116 | 21.497 | 289.86 | 9.043 | 49.317 |
| 131.28 | 8.185 | 22.442 | 297.48 | 10.865 | 50.168 |
| 133.97 | 8.066 | 22.735 | 298.82 | 8.879 | 50.333 |
| **Unstable crystals II** | | | | | |
| 12.19 | 1.029 | 1.496 | 77.58 | 8.450 | 15.480 |
| 13.32 | 1.259 | 1.828 | 81.03 | 5.242 | 16.313 |
| 13.73 | 1.163 | 1.973 | 83.97 | 7.670 | 16.830 |
| 14.91 | 1.976 | 2.308 | 85.12 | 5.041 | 17.216 |
| 15.77 | 2.919 | 2.588 | 85.85 | 6.129 | 17.425 |
| 17.36 | 2.933 | 3.063 | 86.38 | 3.903 | 17.525 |
| 18.90 | 3.333 | 3.549 | 90.39 | 3.550 | 18.825 |
| 20.61 | 3.585 | 4.090 | 91.81 | 5.791 | 20.376 |
| 22.96 | 4.803 | 4.795 | 92.78 | 1.239 | 21.693 |

TABLE II (*Continued*)

| T, °K. | ΔT | $C_p$ cal. deg.$^{-1}$ | T, °K. | ΔT | $C_p$ cal. deg.$^{-1}$ |
|---|---|---|---|---|---|
| 24.33 | 3.855 | 5.179 | 92.88 | 2.426 | 23.584 |
| 27.85 | 4.962 | 6.143 | 93.97 | 1.136 | 26.911 |
| 28.05 | 3.579 | 6.200 | 94.57 | 0.946 | 33.884 |
| 32.09 | 4.482 | 7.187 | 95.56 | 1.033 | 33.302 |
| 33.09 | 5.518 | 7.420 | 97.41 | 5.411 | 32.787 |
| 38.76 | 5.818 | 8.647 | 100.30 | 3.790 | 33.247 |
| 44.63 | 5.927 | 9.770 | 102.77 | 5.297 | 33.226 |
| 50.60 | 6.012 | 10.841 | 107.29 | 10.208 | 33.404 |
| 55.22 | 4.710 | 11.666 | 108.90 | 6.960 | 33.401 |
| 56.64 | 6.080 | 11.888 | 116.64 | 8.540 | 33.680 |
| 57.42 | 8.179 | 12.027 | 117.79 | 10.777 | 33.790 |
| 60.43 | 5.705 | 12.554 | 125.10 | 8.369 | 34.059 |
| 60.63 | 5.665 | 12.570 | 128.49 | 10.622 | 34.242 |
| 62.25 | 7.308 | 12.847 | 133.39 | 8.211 | 34.480 |
| 65.58 | 8.140 | 13.408 | 139.49 | 11.390 | 34.817 |
| 65.89 | 5.215 | 13.479 | 141.53 | 8.065 | 34.890 |
| 67.49 | 7.715 | 13.761 | 149.72 | 8.316 | 35.276 |
| 69.63 | 7.455 | 14.090 | 150.76 | 11.140 | 35.344 |
| 70.91 | 4.839 | 14.330 | 157.96 | 8.177 | 35.733 |
| 73.70 | 8.113 | 14.827 | 161.77 | 10.882 | 36.002 |
| 74.83 | 6.957 | 15.022 | 166.56 | 9.018 | 36.352 |
| 75.87 | 5.073 | 15.242 | 172.49 | 10.571 | 37.063 |
| 76.21 | 7.651 | 15.292 | | | |

*trans*-1,2-Dimethylcyclohexane

| | | | | | |
|---|---|---|---|---|---|
| 11.99 | 1.928 | 0.827 | 140.66 | 9.016 | 23.807 |
| 14.07 | 3.686 | 1.288 | 143.79 | 7.817 | 24.117 |
| 14.14 | 2.417 | 1.299 | 145.10 | 9.715 | 24.412 |
| 16.56 | 2.466 | 1.909 | 149.23 | 9.802 | 24.913 |
| 18.43 | 5.097 | 2.426 | 149.89 | 9.458 | 25.047 |
| 19.49 | 3.400 | 2.721 | 151.46 | 7.520 | 25.178 |
| 23.49 | 4.619 | 3.907 | 154.60 | 9.281 | 25.676 |
| 28.04 | 4.480 | 5.185 | 155.74 | 7.494 | 25.770 |
| 30.50 | 6.425 | 5.835 | 159.15 | 9.050 | 26.300 |
| 32.69 | 4.798 | 6.402 | 159.32 | 10.383 | 26.254 |
| 37.24 | 7.070 | 7.503 | 161.46 | 8.950 | 26.471 |
| 44.16 | 6.765 | 8.983 | 163.70 | 8.909 | 26.865 |
| 51.30 | 7.507 | 10.354 | 172.45 | 8.587 | 28.011 |
| 54.95 | 6.865 | 10.986 | | Liquid | |
| 58.68 | 7.260 | 11.661 | 183.68 | 7.812 | 39.603 |
| 59.04 | 7.201 | 11.706 | 188.64 | 5.820 | 39.924 |
| 62.13 | 7.484 | 12.229 | 192.39 | 9.612 | 40.170 |
| 65.87 | 7.122 | 12.866 | 194.50 | 7.722 | 40.275 |
| 66.18 | 7.082 | 12.922 | 196.34 | 9.568 | 40.427 |
| 69.94 | 8.140 | 13.498 | 202.85 | 11.320 | 40.901 |
| 73.69 | 7.941 | 14.098 | 203.12 | 9.500 | 40.909 |
| 76.47 | 7.426 | 14.537 | 206.29 | 10.342 | 41.129 |
| 82.56 | 9.796 | 15.469 | 214.06 | 11.094 | 41.721 |
| 84.41 | 8.456 | 15.771 | 216.54 | 10.153 | 41.908 |
| 92.09 | 9.278 | 16.960 | 225.05 | 10.875 | 42.596 |
| 92.54 | 7.792 | 16.998 | 227.05 | 10.863 | 42.757 |
| 94.33 | 7.947 | 17.223 | 235.81 | 10.655 | 43.515 |
| 100.62 | 8.381 | 18.157 | 237.80 | 10.645 | 43.678 |
| 101.05 | 8.553 | 18.202 | 246.36 | 10.435 | 44.487 |
| 102.03 | 7.440 | 18.347 | 248.33 | 10.425 | 44.639 |
| 102.05 | 10.654 | 18.377 | 256.68 | 10.221 | 45.504 |
| 110.76 | 10.021 | 19.592 | 258.65 | 10.215 | 45.678 |
| 111.52 | 9.868 | 19.737 | 266.80 | 10.021 | 46.519 |
| 113.25 | 11.735 | 20.037 | 268.76 | 10.003 | 46.749 |
| 120.46 | 9.376 | 20.972 | 275.91 | 8.188 | 47.521 |
| 121.07 | 9.244 | 21.108 | 278.67 | 9.802 | 47.818 |
| 124.56 | 10.893 | 21.587 | 284.83 | 9.657 | 48.488 |
| 129.58 | 8.867 | 22.222 | 288.37 | 9.611 | 48.892 |
| 130.92 | 10.451 | 22.418 | 293.61 | 7.899 | 49.497 |
| 135.13 | 10.241 | 23.044 | 297.89 | 9.421 | 50.019 |
| 139.17 | 10.317 | 23.550 | 301.44 | 7.770 | 50.453 |

*cis*-1,3-Dimethylcyclohexane

| | | | | | |
|---|---|---|---|---|---|
| 11.75 | 1.741 | 0.879 | 109.54 | 8.616 | 19.645 |
| 13.18 | 1.840 | 1.247 | 118.34 | 9.001 | 20.910 |
| 13.71 | 2.200 | 1.384 | 127.11 | 8.524 | 22.165 |
| 15.51 | 2.800 | 1.899 | 135.83 | 8.924 | 23.313 |
| 15.94 | 2.254 | 2.013 | 144.52 | 8.455 | 24.482 |
| 18.63 | 3.137 | 2.831 | 151.85 | 6.024 | 25.411 |
| 18.93 | 4.038 | 2.922 | 153.30 | 9.113 | 25.640 |
| 22.06 | 3.714 | 3.902 | 158.81 | 7.898 | 26.540 |
| 23.29 | 4.699 | 4.279 | 162.68 | 9.683 | 27.127 |
| 25.88 | 3.927 | 5.026 | 166.56 | 7.603 | 27.669 |
| 28.35 | 5.416 | 5.720 | 171.21 | 7.427 | 28.294 |
| 29.86 | 4.027 | 6.112 | 174.49 | 8.428 | 28.827 |
| 33.97 | 5.817 | 7.132 | 182.14 | 7.060 | 30.178 |
| 39.86 | 5.966 | 8.427 | | Liquid | |
| 45.87 | 6.039 | 9.582 | 204.19 | 5.433 | 41.042 |
| 51.93 | 6.095 | 10.690 | 206.28 | 7.229 | 41.212 |
| 54.44 | 6.603 | 11.122 | 211.37 | 8.930 | 41.562 |
| 55.68 | 5.640 | 11.344 | 214.36 | 8.916 | 41.738 |
| 58.06 | 6.157 | 11.752 | 220.67 | 9.655 | 42.277 |
| 61.37 | 7.246 | 12.305 | 230.66 | 10.331 | 43.076 |
| 61.73 | 6.477 | 12.396 | 240.88 | 10.120 | 44.076 |
| 68.22 | 6.491 | 13.442 | 250.91 | 9.925 | 45.003 |
| 68.85 | 7.720 | 13.536 | 260.73 | 9.719 | 46.025 |
| 75.01 | 7.102 | 14.499 | 263.29 | 9.646 | 46.295 |
| 76.35 | 7.281 | 14.715 | 270.35 | 9.525 | 46.972 |
| 82.38 | 7.624 | 15.674 | 272.84 | 9.464 | 47.213 |
| 84.14 | 8.291 | 15.954 | 279.79 | 9.363 | 47.992 |
| 90.09 | 7.805 | 16.853 | 282.22 | 9.295 | 48.240 |
| 92.67 | 8.780 | 17.243 | 289.14 | 9.326 | 49.054 |
| 98.18 | 8.374 | 18.028 | 290.93 | 8.122 | 49.268 |
| 101.14 | 8.165 | 18.463 | 298.31 | 9.015 | 50.029 |
| 106.45 | 8.157 | 19.221 | 299.48 | 8.982 | 50.157 |

*trans*-1,3-Dimethylcyclohexane

| | | | | | |
|---|---|---|---|---|---|
| 12.41 | 1.442 | 1.107 | 150.60 | 9.268 | 25.250 |
| 13.57 | 0.700 | 1.403 | 152.62 | 8.342 | 25.603 |
| 14.14 | 2.040 | 1.558 | 153.98 | 8.459 | 25.742 |
| 15.93 | 3.090 | 2.037 | 155.90 | 8.173 | 26.030 |
| 16.27 | 2.208 | 2.132 | 159.69 | 8.896 | 26.411 |
| 18.96 | 3.163 | 2.904 | 160.80 | 8.019 | 26.748 |
| 19.46 | 3.992 | 3.059 | 162.23 | 8.048 | 26.906 |
| 22.43 | 3.780 | 3.973 | 162.48 | 4.988 | 26.958 |
| 23.83 | 4.768 | 4.362 | 162.50 | 5.022 | 26.890 |
| 26.36 | 4.027 | 5.101 | 164.04 | 7.794 | 27.197 |
| 28.98 | 5.538 | 5.764 | 166.48 | 7.849 | 27.327 |
| 30.44 | 4.133 | 6.124 | 167.04 | 5.839 | 27.528 |
| 34.72 | 5.941 | 7.181 | 167.22 | 4.827 | 27.817 |
| 40.73 | 6.080 | 8.503 | 169.61 | 6.709 | 28.545 |
| 46.84 | 6.172 | 9.645 | 171.93 | 4.579 | 29.957 |
| 53.04 | 6.210 | 10.819 | | Liquid | |
| 55.47 | 5.015 | 11.268 | 187.65 | 5.666 | 41.064 |
| 59.28 | 6.274 | 11.896 | 188.87 | 9.326 | 41.184 |
| 61.01 | 6.058 | 12.217 | 190.27 | 7.499 | 41.285 |
| 61.09 | 7.088 | 12.236 | 190.44 | 5.625 | 41.312 |

TABLE II (*Continued*)

| T, °K. | ΔT | $C_p$ cal. deg.$^{-1}$ | T, °K. | ΔT | $C_p$ cal. deg.$^{-1}$ |
|---|---|---|---|---|---|
| 67.45 | 6.836 | 13.299 | 190.76 | 9.281 | 41.260 |
| 68.32 | 7.373 | 13.422 | 190.79 | 9.276 | 41.271 |
| 74.72 | 7.690 | 14.447 | 194.52 | 7.462 | 41.518 |
| 75.81 | 7.607 | 14.596 | 196.97 | 7.434 | 41.695 |
| 81.95 | 6.783 | 15.602 | 198.64 | 9.244 | 41.774 |
| 83.52 | 7.800 | 15.836 | 202.86 | 9.203 | 42.098 |
| 88.98 | 9.325 | 16.682 | 208.72 | 10.904 | 42.525 |
| 89.43 | 8.164 | 16.763 | 211.61 | 8.310 | 42.734 |
| 91.41 | 7.992 | 17.044 | 219.52 | 10.700 | 43.327 |
| 97.30 | 7.588 | 17.906 | 220.23 | 8.930 | 43.397 |
| 97.94 | 8.603 | 17.971 | 229.96 | 10.529 | 44.142 |
| 99.51 | 8.191 | 18.199 | 230.65 | 10.494 | 44.189 |
| 105.36 | 8.527 | 19.069 | 240.40 | 10.338 | 45.034 |
| 106.75 | 9.016 | 19.246 | 241.04 | 10.289 | 45.091 |
| 107.63 | 8.057 | 19.352 | 250.64 | 10.145 | 45.928 |
| 113.48 | 7.708 | 20.214 | 250.69 | 9.011 | 45.926 |
| 115.50 | 8.472 | 20.470 | 260.17 | 9.940 | 46.824 |
| 115.92 | 8.539 | 20.535 | 260.69 | 9.953 | 46.905 |
| 121.45 | 8.230 | 21.345 | 270.01 | 9.744 | 47.860 |
| 124.18 | 8.895 | 21.693 | 270.54 | 9.762 | 47.887 |
| 124.69 | 8.977 | 21.726 | 279.67 | 9.573 | 48.792 |
| 129.49 | 7.852 | 22.425 | 280.22 | 9.583 | 48.860 |
| 132.86 | 8.456 | 22.884 | 289.16 | 9.398 | 49.831 |
| 137.59 | 8.348 | 23.534 | 289.71 | 9.413 | 49.929 |
| 141.53 | 8.885 | 24.040 | 298.47 | 9.223 | 50.910 |
| 144.10 | 8.703 | 24.418 | 299.04 | 9.243 | 50.973 |
| 145.75 | 7.989 | 24.654 | | | |

*cis*-1,4-Dimethylcyclohexane

| | | | | | |
|---|---|---|---|---|---|
| 12.29 | 1.655 | 0.942 | 119.37 | 8.294 | 20.960 |
| 13.22 | 2.012 | 1.158 | 127.47 | 7.912 | 22.024 |
| 14.21 | 2.206 | 1.406 | 135.62 | 8.389 | 23.127 |
| 15.70 | 2.972 | 1.813 | 144.62 | 9.602 | 24.323 |
| 16.44 | 2.291 | 2.016 | 154.01 | 9.159 | 25.526 |
| 18.84 | 3.320 | 2.723 | 162.72 | 8.044 | 26.520 |
| 19.17 | 3.178 | 2.836 | 167.92 | 5.775 | 27.331 |
| 22.73 | 4.482 | 3.942 | 173.61 | 5.611 | 28.188 |
| 27.31 | 4.312 | 5.288 | | Liquid | |
| 27.38 | 4.810 | 5.312 | 189.49 | 5.527 | 41.663 |
| 32.11 | 4.663 | 6.588 | 193.18 | 5.509 | 41.853 |
| 37.10 | 5.321 | 7.789 | 194.50 | 7.285 | 41.938 |
| 42.59 | 5.646 | 8.945 | 196.80 | 9.088 | 42.059 |
| 48.32 | 5.814 | 10.064 | 199.58 | 7.284 | 42.207 |
| 53.79 | 5.133 | 11.066 | 206.15 | 8.926 | 42.582 |
| 55.51 | 4.954 | 11.362 | 206.71 | 10.761 | 42.645 |
| 59.43 | 6.147 | 12.029 | 214.66 | 8.096 | 43.138 |
| 60.99 | 5.992 | 12.293 | 217.38 | 10.568 | 43.336 |
| 67.16 | 6.362 | 13.298 | 223.92 | 10.438 | 43.782 |
| 73.45 | 6.218 | 14.280 | 227.87 | 10.400 | 44.072 |
| 79.23 | 5.386 | 15.212 | 234.28 | 10.277 | 44.518 |
| 80.14 | 7.152 | 15.320 | 238.17 | 10.213 | 44.877 |
| 85.28 | 6.711 | 16.132 | 248.30 | 10.039 | 45.700 |
| 87.43 | 7.421 | 16.468 | 258.24 | 9.846 | 46.614 |
| 92.54 | 7.818 | 17.214 | 268.39 | 10.453 | 47.624 |
| 94.98 | 7.682 | 17.557 | 277.25 | 7.267 | 48.479 |
| 100.66 | 8.414 | 18.341 | 278.44 | 9.474 | 48.556 |
| 102.96 | 8.293 | 18.679 | 285.57 | 9.366 | 49.313 |
| 108.97 | 8.398 | 19.510 | 287.52 | 8.695 | 49.532 |
| 111.17 | 8.113 | 19.832 | 294.85 | 9.201 | 50.302 |
| 117.73 | 9.300 | 20.700 | 303.22 | 7.536 | 51.273 |

*trans*-1,4-Dimethylcyclohexane

| | | | | | |
|---|---|---|---|---|---|
| 12.27 | 1.889 | 0.881 | 150.82 | 8.207 | 25.536 |
| 13.96 | 1.937 | 1.286 | 159.26 | 8.659 | 26.765 |
| 14.41 | 2.411 | 1.378 | 167.70 | 8.225 | 28 043 |
| 16.61 | 3.364 | 1.954 | 175.77 | 7.919 | 29.319 |
| 16.83 | 2.454 | 2.010 | 184.00 | 8.544 | 30.848 |
| 19.75 | 3.389 | 2.835 | 192.36 | 8.178 | 32.515 |
| 20.39 | 4.209 | 3.028 | 200.77 | 8.649 | 34.567 |
| 23.44 | 3.987 | 3.923 | 205.67 | 6.727 | 35.917 |
| 24.97 | 4.956 | 4.373 | 211.11 | 8.058 | 37.835 |
| 27.52 | 4.180 | 5.080 | 213.00 | 7.929 | 38.713 |
| 30.30 | 5.709 | 5.795 | 217.92 | 5.851 | 41.201 |
| 31.96 | 4.687 | 6.223 | 218.86 | 7.440 | 41.825 |
| 36.21 | 6.106 | 7.241 | 220.61 | 7.282 | 43.056 |
| 42.39 | 6.251 | 8.583 | 222.47 | 4.972 | 44.500 |
| 48.67 | 6.310 | 9.800 | 227.43 | 6.358 | 50.913 |
| 55.01 | 6.371 | 10.957 | 227.47 | 5.053 | 50.896 |
| 55.03 | 5.491 | 10.966 | 230.31 | 2.956 | 57.296 |
| 61.04 | 6.525 | 12.001 | 232.80 | 2.026 | 68.360 |
| 67.94 | 7.272 | 13.171 | 234.38 | 1.125 | 80.632 |
| 75.49 | 7.840 | 14.397 | 235.41 | 0.935 | 99.52 |
| 83.12 | 7.422 | 15.664 | 236.00 | 0.2504 | 300.5 |
| 90.68 | 7.695 | 16.873 | | Liquid | |
| 98.52 | 7.970 | 18.036 | 242.16 | 5.494 | 44.787 |
| 102.99 | 7.609 | 18.662 | 244.77 | 7.224 | 44.961 |
| 105.54 | 6.064 | 19.071 | 248.52 | 7.238 | 45.358 |
| 106.24 | 7.482 | 19.173 | 252.83 | 8.901 | 45.656 |
| 110.38 | 7.185 | 19.764 | 262.09 | 9.619 | 46.501 |
| 112.14 | 7.163 | 20.103 | 271.63 | 9.453 | 47.448 |
| 119.63 | 7.824 | 21.139 | 281.00 | 9.289 | 48.395 |
| 127.73 | 8.372 | 22.282 | 290.21 | 9.127 | 49.370 |
| 135.03 | 6.242 | 23.311 | 299.25 | 8.965 | 50.391 |
| 142.44 | 8.563 | 24.358 | | | |

ties. The accuracy uncertainty may be considerably greater because of premelting and other effects.

Two of these compounds, 1,1-dimethylcyclohexane and *cis*-1,2-dimethylcyclohexane, had isothermal transitions of considerable magnitude. The transition temperature was studied in the usual way by observing the equilibrium temperatures corresponding to various fractions transposed. The transition temperatures are 153.15 ± 0.05°K. and 172.5 ± 0.1°K., respectively. Duplicate measurements were made of the heats of transition and these values are given in Table V.

The thermal data obtained over the temperature range 12 to 298.16°K. were used to calculate the entropies of these compounds in the liquid state. The results of these calculations are summarized in Table VI.

In order to compare the experimental values with those obtained from theoretical considerations it is necessary to convert the experimental values to the hypothetical gaseous standard state of one atmosphere and 298.16°K. This has been done using the data from the A.P.I. Research Project 44 tables[6] and the results are given in

(6) Selected Values of Properties of Hydrocarbons, Circular of the National Bureau of Standards C461, p. 172.

TABLE III

SMOOTHED HEAT CAPACITIES OF $C_8H_{16}$ ALKYLCYCLOHEXANES, CAL./DEG./MOLE

| T, °K. | Ethylcyclo-hexane | 1,1-dmch. | *cis*-1,2-dmch. | *trans*-1,2-dmch. | *cis*-1,3-dmch. | *trans*-1,3-dmch. | *cis*-1,4-dmch. | *trans*-1,4-dmch. |
|---|---|---|---|---|---|---|---|---|
| 12 | 1.12 | 0.98 | 0.89 | 0.83 | 0.94 | 1.01 | 0.89 | 0.82 |
| 13 | 1.36 | 1.22 | 1.14 | 1.04 | 1.19 | 1.26 | 1.11 | 1.04 |
| 14 | 1.62 | 1.48 | 1.38 | 1.27 | 1.46 | 1.52 | 1.36 | 1.28 |
| 15 | 1.88 | 1.76 | 1.63 | 1.51 | 1.75 | 1.78 | 1.62 | 1.54 |
| 20 | 3.31 | 3.27 | 3.06 | 2.87 | 3.27 | 3.22 | 3.10 | 2.91 |
| 25 | 4.79 | 4.78 | 4.52 | 4.34 | 4.78 | 4.72 | 4.63 | 4.38 |
| 30 | 6.18 | 6.12 | 5.87 | 5.71 | 6.15 | 6.02 | 6.03 | 5.72 |
| 35 | 7.47 | 7.30 | 7.11 | 6.97 | 7.37 | 7.24 | 7.30 | 6.96 |
| 40 | 8.64 | 8.32 | 8.20 | 8.11 | 8.46 | 8.36 | 8.42 | 8.08 |
| 45 | 9.72 | 9.24 | 9.21 | 9.15 | 9.42 | 9.30 | 9.43 | 9.10 |
| 50 | 10.74 | 10.09 | 10.15 | 10.11 | 10.34 | 10.26 | 10.38 | 10.04 |
| 55 | 11.68 | 10.90 | 11.06 | 11.01 | 11.22 | 11.18 | 11.28 | 10.96 |
| 60 | 12.56 | 11.68 | 11.91 | 11.87 | 12.08 | 12.05 | 12.14 | 11.82 |
| 65 | 13.38 | 12.47 | 12.74 | 12.72 | 12.92 | 12.88 | 12.95 | 12.68 |
| 70 | 14.16 | 13.24 | 13.54 | 13.52 | 13.72 | 13.70 | 13.74 | 13.50 |
| 75 | 14.92 | 14.01 | 14.34 | 14.30 | 14.50 | 14.49 | 14.53 | 14.32 |
| 80 | 15.68 | 14.76 | 15.15 | 15.08 | 15.30 | 15.28 | 15.30 | 15.14 |
| 85 | 16.41 | 15.51 | 15.92 | 15.84 | 16.08 | 16.07 | 16.10 | 15.96 |
| 90 | 17.12 | 16.25 | 16.68 | 16.58 | 16.84 | 16.84 | 16.85 | 16.76 |
| 95 | 17.80 | 16.98 | 17.41 | 17.32 | 17.57 | 17.57 | 17.57 | 17.52 |
| 100 | 18.46 | 17.70 | 18.13 | 18.06 | 18.30 | 18.28 | 18.27 | 18.26 |
| 110 | 19.79 | 19.18 | 19.52 | 19.48 | 19.72 | 19.71 | 19.67 | 19.72 |
| 120 | 21.10 | 20.66 | 20.91 | 20.91 | 21.16 | 21.12 | 21.03 | 21.19 |
| 130 | 22.42 | 22.14 | 22.26 | 22.28 | 22.55 | 22.50 | 22.38 | 22.60 |
| 140 | 23.73 | 23.66 | 23.55 | 23.66 | 23.88 | 23.86 | 23.72 | 24.01 |
| 150 | 25.04 | 25.21 | 24.81 | 25.00 | 25.26 | 25.23 | 25.02 | 25.42 |
| 160 | 26.36 | 33.89 | 26.06 | 26.32 | 26.72 | 26.60 | 26.32 | 26.89 |
| 170 | 39.30 | 34.71 | 27.29 | 27.62 | 28.17 | 27.97 | 27.61 | 28.40 |
| 180 | 39.90 | 35.54 | 37.27 | 28.89 | 29.66 | 29.33 | 28.90 | 30.08 |
| 190 | 40.54 | 36.39 | 37.99 | 40.00 | 31.14 | 41.25 | 41.69 | 32.02 |
| 200 | 41.22 | 37.29 | 38.76 | 40.68 | 40.76 | 41.91 | 42.24 | 34.36 |
| 210 | 41.97 | 38.27 | 39.56 | 41.40 | 41.46 | 42.62 | 42.84 | 37.40 |
| 220 | 42.77 | 39.29 | 40.38 | 42.18 | 42.21 | 43.37 | 43.51 | 42.64 |
| 230 | 43.62 | 40.40 | 43.64 | 43.00 | 43.05 | 44.15 | 44.25 | 56.44 |
| 240 | 44.52 | 43.83 | 44.48 | 43.87 | 43.97 | 45.00 | 45.00 | 44.60 |
| 250 | 45.48 | 44.79 | 45.38 | 44.82 | 44.92 | 45.88 | 45.86 | 45.44 |
| 260 | 46.46 | 45.80 | 46.32 | 45.82 | 45.92 | 46.84 | 46.78 | 46.32 |
| 270 | 47.49 | 46.85 | 47.28 | 46.88 | 46.96 | 47.82 | 47.75 | 47.28 |
| 280 | 48.56 | 47.94 | 48.29 | 47.96 | 48.02 | 48.85 | 48.75 | 48.29 |
| 290 | 49.68 | 49.05 | 49.35 | 49.08 | 49.14 | 49.95 | 49.79 | 49.35 |
| 298.16 | 50.62 | 50.01 | 50.24 | 50.05 | 50.04 | 50.87 | 50.69 | 50.25 |
| 300 | 50.84 | 50.23 | 50.44 | 50.27 | 50.24 | 51.09 | 50.90 | 50.46 |
| 310 | 52.02 | | | | | | | |

Table VII. The entropies calculated by Pitzer, *et al.*,[7] have been included for comparison.

## Discussion

A number of interesting phenomena were noted in studying these compounds and will be discussed in the following section. As mentioned previously, *cis*-1,2-dimethylcyclohexane undergoes an isothermal transition at 172.5°K. The rate of transition from the high temperature form (crystals II) of *cis*-1,2-dimethylcyclohexane to the low temperature form (crystals I) was extremely slow. The maximum rate of transition occurred at a temperature 10 to 15° below the transition temperature. Even at this temperature, approximately one week was required to complete the transformation. Because of the slowness of the transition it was readily possible to supercool crystals II without any significant formation of crystals I. Consequently, heat capacity measurements were made on both crystalline forms from liquid hydrogen temperature up to the transition temperature, 172.5°K.

A plot of the molal heat capacity of both crystalline forms is shown in Fig. 2. The most interesting part of the plot is the rapid rise in the heat capacity of crystals II at about 95°K. This rapid change in the heat capacity over a short tempera-

(7) C. W. Becket, K. S. Pitzer and R. W. Spitzer, THIS JOURNAL, **69**, 2488 (1948).

TABLE IV

$C_8H_{16}$ ALKYLCYCLOHEXANES: MOLAL HEATS OF FUSION, CAL./MOLE

| Compound | Expt. I | Expt. II | Expt. III | Mean[e] |
|---|---|---|---|---|
| Ethylcyclohexane | 1992.0 | 1991.5 | | 1991.7 ± 0.3 |
| 1,1-Dimethylcyclohexane | 482.6 | 484.1 | 483.6[c] | 483.4 ± 0.8 |
| *cis*-1,2-Dimethylcyclohexane | 393.5 | 392.9 | 392.9 | 393.2 ± 0.3 |
| *trans*-1,2-Dimethylcyclohexane | 2507.4 | 2507.9 | | 2507.6[a] ± 0.3 |
| *cis*-1,3-Dimethylcyclohexane | 2587.2 | 2585.0 | | 2586.1 ± 1.1 |
| *trans*-1,3-Dimethylcyclohexane | .... | .... | | 2358[b] |
| *cis*-1,4-Dimethylcyclohexane | 2224.6 | 2225.9[c] | 2222.7 | 2224.4 ± 1.7 |
| *trans*-1,4-Dimethylcyclohexane | .... | .... | | 2947.2[d] |

[a] In addition to this value three other expts. gave a value of 2490.8 ± 2.0 cal./mole. See text for discussion. [b] See text for discussion of erratic values of heat of fusion. [c] From melting point measurement. [d] The rapid rise in heat capacity before the triple point precludes an accurate value for the heat of fusion, see text. [e] These values are precision uncertainty.

TABLE V

MOLAL HEATS OF TRANSITION, CAL./MOLE

| Compound | I | II | Mean |
|---|---|---|---|
| 1,1-Dimethylcyclohexane | 1430.7 | 1430.0 | 1430.3 ± 0.4 |
| *cis*-1,2-Dimethylcyclohexane | 1971.1 | 1975.7 | 1973.4 ± 2.3 |

TABLE VI

ENTROPY SUMMARY: $C_8H_{16}$ ALKYLCYCLOHEXANES, CAL./DEG./MOLE

| | | |
|---|---|---|
| **Ethylcyclohexane** | | |
| $S_{12}$ (Debye, 4°, $\theta$ = 95.25) | 0.398 | |
| $\Delta S_{12-161.84}$ (graphical) | 27.909 | |
| $\Delta S_{161.84}$ (1991.7/161.84) | 12.306 | |
| $\Delta S_{161.84-298.16}$ (graphical) | 26.522 | |
| $S_{298.16}$ (liquid) | 67.135 | |
| **1,1-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 6°, $\theta$ = 117.5) | 0.327 | |
| $\Delta S_{12-153.15}$ (graphical) | 25.509 | |
| $\Delta S_{153.15}$ (1430.3/153.15) | 9.339 | |
| $\Delta S_{153.15-239.81}$ (graphical) | 16.515 | |
| $\Delta S_{239.81}$ (483.4/239.81) | 2.016 | |
| $\Delta S_{239.81-298.16}$ (graphical) | 10.167 | |
| $S_{298.16}$ (liquid) | 63.873 | |
| ***cis*-1,2-Dimethylcyclohexane** | | |
| Crystals II (Unstable Modification) | | |
| $S_{12}$ (Debye, 4.5°, $\theta$ = 90.4) | 0.519 | |
| $\Delta S_{12-172.50}$ (graphical) | 37.852 | |
| $S_{172.50}$ | 38.371 | 38.371 |
| Residual entropy at 0°K. | | 2.053 |
| Crystals I, (stable modification) | | |
| $S_{12}$ (Debye, 6°, $\theta$ = 120.6) | 0.303 | |
| $\Delta S_{12-172.50}$ (graphical) | 28.681 | |
| $\Delta S_{172.50}$ (1973.4/172.50) | 11.440 | 40.424 |
| $\Delta S_{172.50-223.28}$ (graphical) | 9.947 | |
| $\Delta S_{223.28}$ (393.2/223.28) | 1.761 | |
| $\Delta S_{223.28-298.16}$ (graphical) | 13.391 | |
| $S_{298.16}$ (liquid) | 65.523 | |
| ***trans*-1,2-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 5°, $\theta$ = 115.5) | 0.286 | |
| $\Delta S_{12-184.99}$ (graphical) | 30.502 | |
| $\Delta S_{184.59}$ (2507.6/184.99) | 13.555 | |
| $\Delta S_{184.99-298.16}$ (graphical) | 20.959 | |
| $S_{298.16}$ (liquid) | 65.302 | |
| ***cis*-1,3-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 6°, $\theta$ = 117.9) | 0.323 | |
| $\Delta S_{12-197.59}$ (graphical) | 33.410 | |
| $\Delta S_{197.59}$ (2586.1/197.59) | 13.088 | |
| $\Delta S_{197.59-298.16}$ (graphical) | 18.342 | |
| $S_{298.16}$ (liquid) | 65.163 | |
| ***trans*-1,3-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 5°, $\theta$ = 107.90) | 0.349 | |
| $\Delta S_{12-183.06}$ (graphical) | 30.89 | |
| $\Delta S_{183.06}$ (235.8/183.06) | 12.88 | |
| $\Delta S_{183.06-298.16}$ (graphical) | 21.91 | |
| $S_{298.16}$ (liquid) | 66.03 | |
| ***cis*-1,4-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 6°, $\theta$ = 121.15) | 0.299 | |
| $\Delta S_{12-185.73}$ (graphical) | 31.169 | |
| $\Delta S_{185.73}$ (2224.4/185.73) | 11.977 | |
| $\Delta S_{185.73-298.16}$ (graphical) | 21.359 | |
| $S_{298.16}$ (liquid) | 64.804 | |
| ***trans*-1,4-Dimethylcyclohexane** | | |
| $S_{12}$ (Debye, 5°, $\theta$ = 114.67 | 0.292 | |
| $\Delta S_{12-236.22}$ (graphical) | 40.350 | |
| $\Delta S_{236.22}$ (2947.2/236.22) | 12.476 | |
| $\Delta S_{236.22-298.16}$ (graphical) | 10.944 | |
| $S_{298.16}$ (liquid) | 64.062 | |

TABLE VII

MOLAL ENTROPY AT 298.16°K., CAL. DEGREE$^{-1}$ MOLE$^{-1}$

| Substance | Experimental Lig. | Experimental Vap. | Calcd.[7] Vap. |
|---|---|---|---|
| Ethylcyclohexane | 67.14 | 91.46 | 91.44 |
| 1,1-Dimethylcyclohexane | 63.87 | 87.22 | 87.24 |
| *cis*-1,2-Dimethylcyclohexane | 65.52 | 89.47 | 89.51 |
| *trans*-1,2-Dimethylcyclohexane | 65.30 | 88.75 | 88.65 |
| *cis*-1,3-Dimethylcyclohexane | 65.16 | 88.72 | 88.54 |
| *trans*-1,3-Dimethylcyclohexane | 66.03 | 89.96 | 89.92 |
| *cis*-1,4-Dimethylcyclohexane | 64.80 | 88.64 | 88.54 |
| *trans*-1,4-Dimethylcyclohexane | 64.06 | 87.45 | 87.19 |

ture interval is very similar to that behavior which is characteristic of organic glasses. A similar case was observed by Kelly[8] in his investigation of cyclohexanol, *i. e.*, the unstable crystals II could be easily supercooled to liquid hydrogen temperature and showed the glassy bump.

Since crystals II have a low heat of fusion, 393 cal. per mole, and a high heat capacity, about 6% less than that of the liquid at the melting point, it seems reasonable to postulate that the molecules are free to rotate in the lattice. However, as the material is cooled it is possible that the restrictions to rotation become greater and a major part of the rotation is frozen in a short temperature interval, thereby causing the rapid change in the

(8) K. K. Kelley, THIS JOURNAL, 51, 1400 (1929).

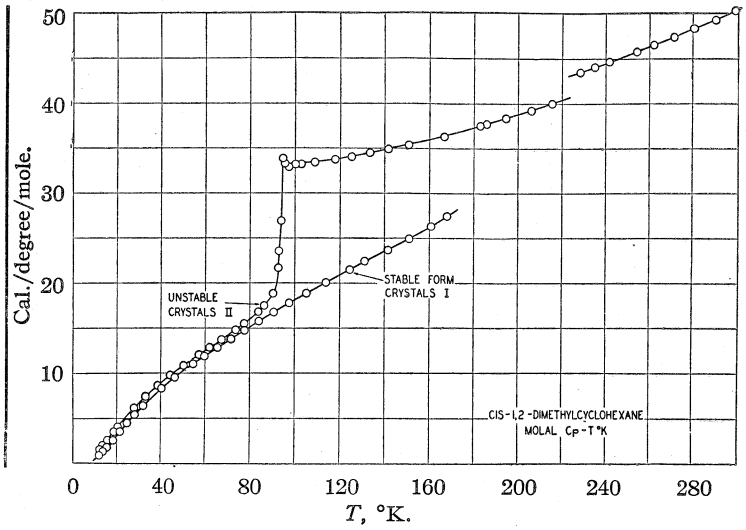



Fig. 2.—Heat capacity curves for the two different forms of *cis*-1,2-dimethylcyclohexane.

heat capacity. When crystals II were rapidly cooled and maintained under adiabatic conditions for a long period of time at a temperature about 10° below that of the rapid rise in heat-capacity curve, heat was evolved. This liberation of energy could be associated with the decrease in the energy of the crystals as the molecules reorient themselves toward equilibrium positions in the crystal lattice.

Since heat-capacity measurements were made on both crystalline forms from liquid-hydrogen temperature, the entropy of crystals II was calculated graphically at 172.5°K. over two different paths. These calculations showed the super-cooled crystals II to have a residual entropy of 2.06 E.U. at 0°K. Since *cis*-1,2-dimethylcyclohexane is a mixture of *d* and *l* forms, a part of this residual entropy can be explained if it is assumed that crystals II is a solid solution of the *d* and *l* forms that persist to 0°K. Thus the value for the entropy of mixing, 50-50 mixture, which is $R$ ln 2 would account for 1.38 E.U. of the observed residual entropy. This leaves approximately 0.6 E.U. unaccounted for and it is possible that imperfect orientation of the molecules is responsible for this difference. However, since there is no positive evidence that a solid solution is formed, it is possible that all of the residual entropy is due to the randomness or disorder of the rapidly cooled crystals.

The *trans*-1,4-dimethylcyclohexane heat-capacity curve, as shown in Fig. 3, has an unusually rapid rise in the temperature region below the melting point. The highest experimental heat-capacity point has an approximate value of 300 cal./mole at 236.0°K. It was first thought that this rapid rise in the curve was due to premelting. However, from the melting point studies, the amount of impurity was calculated to be 0.007 mole per cent. on the assumption that the system obeys Raoult's law. The premelting effect due to this amount of impurity would change the molal heat capacity only 0.1 or 0.2 cal./deg. at 236.0°K., which is insignificant as compared to the magnitude of the experimental value observed. Hence, the unusually steep slope of the curve cannot be due to premelting.

It appears unlikely that the observed behavior is associated with an impurity and hence it is believed that it is characteristic of the material and may be explained as follows. Since the shape of the curve is similar to the low temperature side of a *lambda* point we can assume that a second order transition started but melting took place before the transition was completed.

Egan and Kemp[9] observed a similar effect in the heat-capacity curve of ethylene and explained it in a like manner.

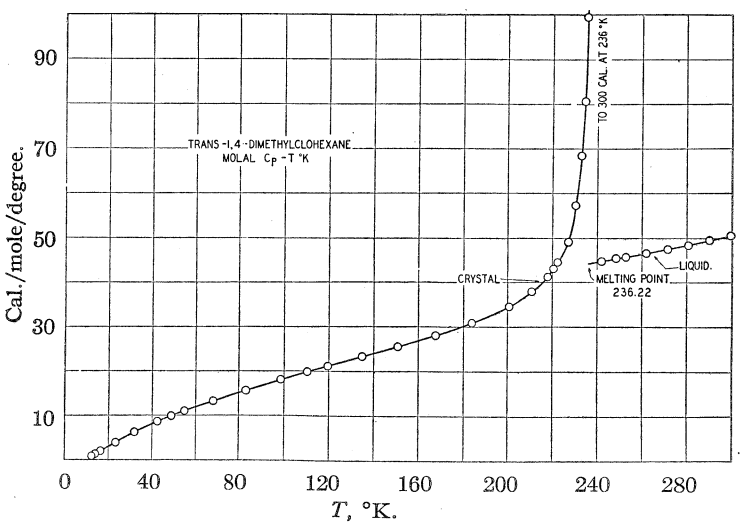



Fig. 3.—Heat capacity curve for *trans*-1,4-dimethylcyclohexane showing high heat capacity of crystals below the melting temperature.

Because of this rapid rise, it was impossible to extrapolate the heat-capacity curve to the melting point with any great reliability. Consequently, it was impossible to calculate an accurate value for the heat of fusion by the usual methods. This uncertainty will be reflected to some extent in the accuracy of the calculated melting point and the amount of impurity; but fortunately, the amount of impurity is probably small so that the accuracy

(9) C. J. Egan and J. D. Kemp, THIS JOURNAL, **59** 1264 (1937).

will not be greatly affected in the absolute sense and the reliability of the results will depend principally on how closely the system obeys Raoult's law.

In the study of *trans*-1,2-dimethylcyclohexane four measurements of the heat of fusion and two melting-point determinations were made. The heats of fusion fell into two internally consistent groups which appeared to be related to the manner in which crystallization was initiated. If the liquid material was cooled rapidly to about 85°K. and crystallization was initiated by slowly heating the undercooled liquid, crystals were obtained which gave the high heat of fusion. However, if crystallization was initiated by allowing the liquid to cool slowly across the vacuum and crystallization to take place spontaneously, crystals were obtained which gave the lower value for the heat of fusion. Melting-point studies were made on crystals obtained by both of these methods. These data gave melting points (for pure material) which differed by only 0.006° which is not a very large difference but greater than the expected error of the measurements. The higher melting point was associated with the material having the lower heat of fusion. If it is assumed that there are two crystalline forms of this material, the above data show that the high melting form, although the stable form at its melting point, will have to become the unstable modification at some lower temperature. Furthermore, if both forms obey the third law, the high-melting form, with the low heat of fusion, will have to have a higher heat capacity in some portion of the temperature range or will have to undergo a transition in order to gain the necessary entropy. Our measurements show that above 90°K. the high melting form does have the higher heat capacity by a small but significant amount. In the temperature range 50 to 90° the heat capacity of the two forms are identical within the experimental error. Assuming the postulate of two crystalline forms is correct, the entropy was calculated over the two paths and found to differ by only 0.04 cal./degree which is within the experimental error.

This explanation is substantiated further by an unpublished investigation made in this Laboratory on ethylcyclopentane in which were found, very definitely, two crystalline forms with melting points differing by 0.7°, the stable high-melting form having the lower heat of fusion by approximately 170 cal./mole. The high-temperature form has the higher heat capacity over the entire temperature range from 12° to the m. p. and the entropies over the two paths are identical.

In the case of *trans*-1,3-dimethylcyclohexane it was found impossible to obtain a satisfactorily reproducible value for the heat of fusion. A great many experiments were tried in which the method of crystallizing was varied as widely as was experimentally convenient. At this time it is not possible to explain the reason for the observed behavior of this material. However, the authors are inclined to believe that it is probably due to a very slow rate of crystallization as the crystallization approaches completion. Because of the above effect, the thermal data on this compound are much less reliable than is characteristic of data from this Laboratory. The value for the heat of fusion given in Table IV is the highest value observed but not necessarily the correct value. The value of the entropy calculated from these data will also be less reliable than usual.

Table VII shows that the experimental and calculated values[6] of the entropies are in excellent agreement when the old labels on *cis* and *trans*-1,3-dimethylcyclohexane are interchanged as proposed by Pitzer and Beckett.[10]

## Summary

The heat capacities of eight $C_8H_{16}$ alkyl cyclohexanes have been given over the temperature range 12 to 300°K.

Melting points, transition temperatures, heats of fusion, and heats of transition for these compounds have been given.

Entropy values have been calculated for the liquid and gaseous state at 298.16°K.

RECEIVED AUGUST 30, 1948

(10) K. S. Pitzer and C. W. Beckett, THIS JOURNAL, **69**, 977 (1947); F. D. Rossini and K. S. Pitzer, *Science*, **105**, 647 (1947).

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY, EMERYVILLE, CALIFORNIA]

# Thermal Cracking of Higher Paraffins

BY H. H. VOGE AND G. M. GOOD

The decomposition of paraffins with two to eight carbon atoms has been quite well explained as being predominantly a chain reaction involving free radicals. The radical theory accounts for the products,[1,2] the inhibition of cracking by nitric oxide[3,4] and olefins,[4] and the initiation of cracking by mercury dimethyl[5] and other materials that readily produce radicals.[6] In addition, alkyl radicals have been detected in hydrocarbon systems undergoing decomposition at reduced pressures.[2,7] The cracking of paraffins containing more than eight carbon atoms has not been adequately tested against the theory, yet such materials offer a more stringent test of predicted products of reaction. Although a few examples of the cracking of higher hydrocarbons are to be found in the literature, such as the fine early studies of Gault and Hessel[8] and Gault and Sigwalt,[9] they are not adequate for detailed comparison. The data given in the present paper enable comparisons to be made between predicted and observed products of cracking and also furnish rates of cracking that lead to a general equation for the cracking velocities of normal paraffins. The experiments were made in connection with a study of catalytic cracking,[10] and supplied data on *n*-dodecane, an isododecane, and *n*-hexadecane. The results are compared with those predicted by the radical chain theory and by the alternative theory of Burk.[11]

## Experimental

All experiments were made in a system for flowing reactants. The equipment and procedure were essentially as described previously.[10a,12] The reactor tubes were of 18–8 chromium–nickel steel (A.I.S.I. type 302) of $^1/_2$, 1, or 1$^1/_2$-inch iron pipe size. Temperature control in the center of the tube was within ±3° of the specified value. The reactor tubes were vertical, and were filled with clean, dense quartz chips of 6–14 mesh (inch) size to aid heat transfer and prevent laminar flow. In the run at elevated pressure, the system was initially pressured with nitrogen, and at the end of the experiment, the pressure was reduced to atmospheric before the commencement of the usual nitrogen flush.

Analysis of gases was by low temperature distillation followed by sulfuric-acid absorption for olefins or infrared spectrophotometry for isomeric olefins and paraffins. Liquid products were distilled in a column of 14 mm. i.d. and 76 cm. length, packed with $^3/_{16}$ inch diameter helices. The fractions were analyzed for olefins by bromine number (bromine in carbon tetrachloride method), and for aromatics by ultraviolet absorption, or in some cases by acid absorption corrected for olefins or by refractive dispersion.

Although the cracking experiments were made in "stainless steel" tubes, there was no evidence of catalysis by the tube walls, which were maintained in an oxidized condition by treatment with air at 500–600° in the regenerations following each run of two to ten hours' duration. In other experiments not reported here, it has been noted that when stainless steel tubes develop catalytic activity, usually at 550° or above, they do so quite suddenly, and produce large amounts of hydrogen and carbon. No such effects were observed in the present experiments. The non-catalytic properties of oxidized stainless steel tubes have also been mentioned by Marschner,[13] who showed that they gave the same results as Pyrex in the cracking of *n*-octane. Nevertheless, we are uncertain whether all the coke and hydrogen arose from uncatalyzed reactions, and have not attached significance to the quantities of these materials.

**Results of Cracking *n*-Hexadecane.**—The *n*-hexadecane (cetane) was from du Pont, with $n^{20}D$ 1.4346, $d^{20}_4$ 0.7741, m.p. 17.0°, and b.p. 287.7° at 761.3 mm. Results from two cracking runs at atmospheric pressure, and one at a pressure of 21 atmospheres absolute, are shown in Table I, while Table II gives the products as moles from each 100 moles of hexadecane cracked. Conversions were computed from the amount of material in the range $C_1$ through $C_{14}$, together with hydrogen and coke. The $C_{15}$ material was not included because the amount was not always determined; actually the $C_{15}$ fraction was 0.9% of the charge in the run at 21 atmospheres, and should be less in the other runs at lower conversions. Material other than hexadecane in the products boiling above 273° was also quite small, as judged by the refractive index of that fraction from the run at 31.5% conversion, which was $n^{20}D$ 1.4360 (hexadecane feed 1.4346).

Reaction velocity constants were computed for a first order reaction, since the first order law, $kt = \ln 100/100 - C$, where $C$ is the percentage conversion, is known to hold approximately for the thermal decomposition of paraffins at a given pressure. The residence time, $t$, is not directly measurable in a flow system, and therefore the proper equation for a flow system, first given by Benton,[14] was used. This is

$$kG/V = N \ln (100/100 - C) - (N - 1)\, C/100$$

where $k$ is the rate constant in sec.$^{-1}$, $G$ is the void hot volume of the reactor in cc., $V$ is the influx gaseous flow rate in cc. per sec. at reaction temperature and pressure, $N$ is the moles of product per mole of hexadecane cracked, and $C$ is the percentage conversion. The void volume of the quartz chips was 45% of the gross volume. In computing the volume G, correction was made for the temperature profile, by weighting small sections of the tube in accordance with relative reaction velocities at the observed temperatures, to get an equivalent volume at 500°. This was done by assuming an activation energy of 60 kcal. per mole. Actually, about 95% of the equivalent volume was between 495 and 503°. After $k$

(1) W. G. Appleby, W. H. Avery and W. K. Meerbott, THIS JOURNAL, **69**, 2279 (1947), and references cited therein.

(2) F. O. Rice and K. K. Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore, 1935.

(3) L. A. K. Staveley and C. N. Hinshelwood, *Trans. Faraday Soc.*, **35**, 845 (1939), and earlier work by the same authors.

(4) L. S. Echols and R. N. Pease, THIS JOURNAL, **61**, 1024 (1939).

(5) F. E. Frey, *Ind. Eng. Chem.*, **26**, 200 (1934).

(6) E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, N. Y., 1946.

(7) G. C. Eltenton, *J. Chem. Phys.*, **15**, 455 (1947).

(8) H. Gault and F. A. Hessel, *Ann. Chim.*, [10] **2**, 319 (1924).

(9) H. Gault and R. Sigwalt, *Annales de l'Office National des Combustibles Liquides*, **2**, 309, 543 (1927).

(10) (a) B. S. Greensfelder and H. H. Voge, *Ind. Eng. Chem.*, **37**, 514 (1945); (b) B. S. Greensfelder, H. H. Voge and G. M. Good, *ibid.*, **37**, 1168 (1945).

(11) R. E. Burk, *J. Phys. Chem.*, **35**, 2446 (1931).

(12) (a) H. H. Voge, G. M. Good and B. S. Greensfelder, *Ind. Eng. Chem.*, **38**, 1033 (1946); (b) H. J. Henriques, *ibid.*, **39**, 1564 (1947).

(13) R. F. Marschner, *Ind. Eng. Chem.*, **30**, 554 (1938).

(14) A. F. Benton, THIS JOURNAL, **53**, 2984 (1931).

TABLE I

THERMAL CRACKING OF *n*-HEXADECANE AT 500°

| | | | |
|---|---|---|---|
| Conditions | | | |
| Pressure, atm. abs. | 1 | 1 | 21 |
| LHSV[a,b] | 0.046 | 0.10 | 3.0 |
| Flow, moles/l./hr.[b] | 0.156 | 0.337 | 10.1 |
| Duration, hr. | 10.5 | 4.5 | 2.0 |
| Material balance, %w | | | |
| Gas through $C_4$ | 17.9 | 11.9 | 13.8 |
| $C_5$-$C_9$ liq. (to 152°) | 14.2 | 9.8 | 18.0 |
| $C_{10}$-$C_{14}$ liq. (to 255°) | 9.0 | 9.4 | 14.3 |
| $C_{15}$ liq. (to 273°) | 57.6 | 69.3 | 0.9 |
| $C_{16}$ and higher | | | 51.0 |
| Coke | 1.3 | 0.7 | 0.9 |
| Loss | 0.0 | −1.1 | 1.1 |
| Computed data, no loss basis | | | |
| Conversion, % (through $C_{14}$) | 42.4 | 31.5 | 47.5 |
| Rate constant, $k$, sec.$^{-1}$ | 0.0026 | 0.0032 | .. |
| Residence time, sec. | 211 | 118 | 84 |
| Olefin contents of liquid fractions, %w | | | |
| $C_5$ | 94 | 99 | 63 |
| 42–99° | 91 | 90[c] | 68 |
| 99–125° | .. | .. | 67 |
| 152–174° | .. | .. | 70 |
| Aromatic contents of liquid fractions, %w | | | |
| 42–99° | 2 | 1 | 2 |
| 99–125° | 4 | 3 | 6 |
| 125–152° | .. | .. | 12 |
| Above 255° | .. | .. | 0 |

[a] Liquid hourly space velocity. [b] LHSV and flow rate based on void space (45% of gross volume) at 495–503°. [c] 42–74° fraction.

had been computed from the above equation, the residence time, $t$, was obtained from the usual first order law. Since the first order law probably does not hold exactly, $k$ and $t$ are approximations. The values of $k$ in the two experiments at atmospheric pressure, 0.0026 and 0.0032 sec.$^{-1}$ agree moderately well, and are also in approximate agreement with an earlier rough value of 0.004[10a] at 4% conversion. The experiment at 21 atmospheres led to a higher value of 0.0078, but since this has not been checked, it is not now taken as indicating that cracking rate increases with pressure. The primary interest in the experiment at 21 atmospheres lies in the nature of the products.

The products from thermal cracking of hexadecane, listed in Table II, cover the full range from methane upward, but methane, ethylene, ethane and propylene are especially prominent at atmospheric pressure. The elevated pressure of 21 atmospheres causes an increased saturation of the fractions, and a general shift of products toward higher molecular weights. Analyses of a few of the liquid fractions, included in Table I, indicate that olefin contents were very high for the atmospheric pressure runs. In the run at 21 atmospheres, olefin contents were lower and aromatic and paraffin contents were higher.

## Radical Theory of Cracking

Rice and Rice[2] noted that the products from the cracking of *n*-hexadecane as observed by Gault and co-workers[8,9] were in general agreement with the predictions of the radical chain theory. The present data permit a much more detailed comparison, and show that while the simple theory of Rice and Rice[2] overemphasizes certain products, the

TABLE II

PRODUCTS FROM THERMAL CRACKING OF *n*-HEXADECANE

| | | | |
|---|---|---|---|
| Pressure, atm. abs. | 1 | 1 | 21 |
| Conversion, % | 42.4 | 31.5 | 47.5 |
| Products, moles per 100 moles of hexadecane converted | | | |
| $H_2$ | 16.5 | 16.7 | 17.4 |
| $CH_4$ | 50.9 | 53.0 | 23.3 |
| $C_2H_4$ | 84.0 | 76.9 | 14.9 |
| $C_2H_6$ | 56.6 | 52.6 | 38.0 |
| $C_3H_6$ | 59.0 | 47.4 | 27.1 |
| $C_3H_8$ | 16.5 | 13.0 | 36.5 |
| $C_4H_6$ | 1.7 | 1.6 | 0.9 |
| *i*-$C_4H_8$ | 1.6 | 1.6 | 0.8 |
| *n*-$C_4H_8$ | 18.5 | 16.6 | 18.3 |
| *i*-$C_4H_{10}$ | 0.6 | 0.8 | 0.8 |
| *n*-$C_4H_{10}$ | 2.7 | 2.0 | 13.0 |
| *t*-$C_5H_{10}$ | 2.8 | 2.8 | 2.2 |
| *s*-$C_5H_{10}$ | 12.0 | 5.7 | 12.1 |
| *i*-$C_5H_{12}$ | 0.4 | 0.1 | 1.0 |
| *n*-$C_5H_{12}$ | 0.6 | | 7.1 |
| $C_6$ (42–74°) | 26.5 | 24.3 | 26.3 |
| $C_7$ (74–99°) | 14.5 | 16.2 | 18.6 |
| $C_8$ (99–125°) | 12.7 | 13.4 | 12.2 |
| $C_9$ (125–152°) | 10.5 | 10.1 | 13.2 |
| $C_{10}$ (152–174°) | 5.7 | 10.9 | 11.0 |
| $C_{11}$ (174–196°) | 5.2 | 9.3 | 9.2 |
| $C_{12}$ (196–217°) | 7.5 | 7.3 | 8.2 |
| $C_{13}$ (217–238°) | 7.2 | 7.7 | 6.2 |
| $C_{14}$ (238–255°) | 3.1 | 4.9 | 7.0 |
| Total | 417.3 | 394.9 | 325.3 |

improved theory of Kossiakoff and Rice[15] gives better agreement.

According to the radical chain theory, small alkyl radicals accumulate to a steady state concentration. These radicals remove hydrogen atoms from paraffin molecules, leaving a large radical which will decompose rapidly in definite ways, ultimately regenerating a small radical which continues the chain. Reasonable values for the parameters determining products were set forth by Kossiakoff and Rice,[15] and almost the same values have been adopted here. The rate of removal of secondary hydrogen is taken to be greater than that of primary hydrogen by a factor of 3.66 at 500° (exp $(2000/RT)$). The total rate of removal of each type is proportional to the number of such atoms multiplied by this factor. The relative rate of removal of a tertiary hydrogen at 500° is 13.4 (exp $(4000/RT)$).

Radicals formed by removal of hydrogen atoms rupture at a carbon–carbon bond that is removed by one carbon atom from the hydrogen-deficient carbon (that is, at a beta bond). There are good reasons why the rupture occurs only at the beta bonds.[16] No carbon–hydrogen bonds are made or broken when rupture occurs, and the products are always an olefin and a smaller radical. When alternative beta bonds are available, the relative rates of cracking are determined by the resonance

(15) A. Kossiakoff and F. O. Rice, THIS JOURNAL, **65**, 590 (1943).

(16) C. E. H. Bawn, *Trans. Faraday Soc.*, **34**, 598 (1938); F. O. Rice and E. Teller, *J. Chem. Phys.*, **6**, 489 (1938); **7**, 199 (1939).

stabilizations of the radicals that crack off. For simplicity in view of lack of accurate knowledge, the relative rates of cracking have been taken as follows, corresponding to $\exp(1700/RT)$, and powers thereof.

| Radical cracked off | Relative rate |
|---|---|
| Methyl | 1 |
| Ethyl and higher primary | 3 |
| Secondary | 9 |
| Tertiary | 27 |

The theory described so far may be called the simple chain theory. It is compared with experimental results in Table III. The amount of ethylene predicted is much too great. Most of this ethylene arises from the breakdown of large primary alkyl radicals, which, according to the simple theory, continue to split off ethylene until they are reduced to the methyl or ethyl radicals that appear in the final products as methane or ethane. An amplification of the theory introduced by Kossiakoff and Rice[15] overcomes this difficulty by assuming that the large radicals, although too short-lived to be converted to paraffins, are sufficiently long-lived to undergo isomerization prior to rupture. In the present work it is assumed as by Kossiakoff and Rice, that the radical position can only shift by a coiling mechanism to a carbon atom separated by three or more carbon atoms from the original position. Therefore, $C_3$, $C_4$ and $C_5$ radicals do not isomerize; among the hexyl radicals only the 1- and 2-forms are taken to be interconvertible; for the heptyl, the 1-, 2- and 3-; and for the higher radicals, all possible isomers obtainable by a shift of a hydrogen atom. Branched chain radicals are not formed from straight chains by these isomerizations. In computing the equilibrium among the radicals immediately prior to their cracking, the secondary are estimated to be 4,000 cal. per mole more stable than the primary, and the tertiary another 4,000 cal. per mole more stable than the secondary. Thus the relative weights at 500° are 1, 13.4 and 47.7 for primary, secondary and tertiary, and of course these weights have to be multiplied by the appropriate statistical factor.[15]

TABLE III

EXPERIMENTAL AND THEORETICAL PRODUCTS FROM HEXADECANE

| Product | Moles per 100 moles cracked: Experimental | Theoretical: Simple | Theoretical: With isom. |
|---|---|---|---|
| $CH_4$ | 53.0 | 50.7 | 61.2 |
| $C_2H_4$ | 76.9 | 338.7 | 99.9 |
| $C_2H_6$ | 52.6 | 49.4 | 38.8 |
| $C_3H_6$ | 47.4 | 13.5 | 50.3 |
| $C_3H_8$ | 13.0 | 0 | 0 |
| $C_4H_6$ | 1.6 | 0 | 0 |
| $i$-$C_4H_8$ | 1.6 | 0 | 0 |
| $n$-$C_4H_8$ | 16.6 | 10.1 | 27.2 |
| $C_4H_{10}$ | 2.8 | 0 | 0 |
| $C_5H_{10}$ | 8.5 | 6.8 | 14.9 |
| $C_5H_{12}$ | 0.1 | 0 | 0 |
| $C_6$ | 24.3 | 6.8 | 16.5 |
| $C_7$ | 16.2 | 6.8 | 14.0 |
| $C_8$ | 13.4 | 6.8 | 12.3 |
| $C_9$ | 10.1 | 6.8 | 10.9 |
| $C_{10}$ | 10.9 | 6.8 | 9.9 |
| $C_{11}$ | 9.3 | 6.8 | 8.9 |
| $C_{12}$ | 7.3 | 6.8 | 7.8 |
| $C_{13}$ | 7.7 | 6.8 | 7.1 |
| $C_{14}$ | 4.9 | 6.8 | 7.0 |
| $C_{15}$ | ... | 3.4 | 3.5 |
| Total hydrocarbon | 378.2 | 533.8 | 390.2 |
| $H_2$ | 16.7 | 0 | 0 |

In computing the predicted products from the cracking of $n$-hexadecane by the amplified radical theory of Kossiakoff and Rice, every radical formed in the process of decomposition was taken to isomerize to equilibrium before cracking further, except for the $C_7$ and smaller, as noted above. The restriction on the degree of isomerization of the smaller radicals is rather arbitrary, since it is conceivable that isomerization may occur by a simple shift of a hydrogen atom rather than by a coiling mechanism. In the case of $n$-hexadecane, however, this restriction makes little difference because of the relatively small number of isomerizations excluded. Table III shows that the products predicted by the chain theory with radical isomerization agree well with those observed in cracking at atmospheric pressure. Comparison has been made with the run of 31.5% conversion, but the other run agrees about as well. It would be more desirable to compare experimental cracking at very low conversions, since the theory is for the initial cracking and does not take into account secondary decomposition of initial products. However, secondary cracking reactions will change the theoretical values of Table III less than 15% at conversions below 30% according to some unpublished calculations made with the simple radical theory by Drs. R. S. Rasmussen and D. P. Stevenson of these laboratories.

The agreement obtained using radical isomerization is suggestive, but is not a full proof of this step for alternative, more complex, explanations of the products are conceivable.

A graphical comparison of theoretical and experimental results from hexadecane is given in Fig. 1, in which products are grouped by carbon number. As noted above, agreement is quite good. The more detailed data of Table III show a few discrepancies. For example, the theoretical amount of ethylene is somewhat high, even with radical isomerization. Likewise some propane is obtained, indicating that the theoretical assumption that all propyl radicals decompose is not correct. Other deviations are minor, such as the failure to predict traces of butadiene and isobutylene, present in the experimental products in amounts scarcely greater than the error of analysis. One of the most important predictions of the theory is the absence of paraffins above ethane.

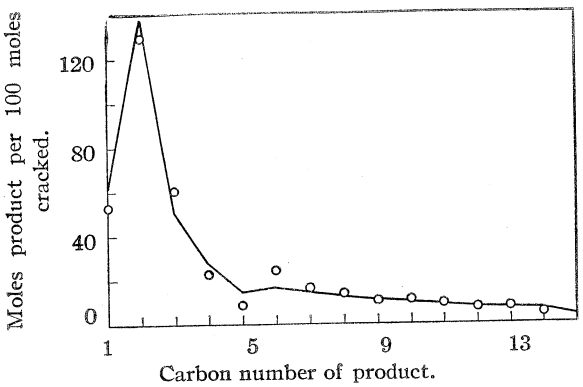



Fig. 1.—Experimental and theoretical product distributions from hexadecane at 500°: circles, experimental, 31.5% conversion; line, theoretical, with radical isomerization.

With the exception of propane, this is well borne out. Very small amounts of paraffins are found in the $C_4$, $C_5$, and liquid fractions. Similar results have been observed for the thermal cracking of paraffin wax at low pressures and in the presence of steam diluent.[17] The wax consists primarily of normal paraffins, $C_{20}$ to $C_{28}$, and liquid products from cracking are 90% olefinic, or more.

No attempt was made to compute the products from cracking at elevated pressure. Certain qualitative aspects are in good agreement with the principles of the radical chain theory, such as the presence of paraffins above ethane, and the higher average molecular weight. At 21 atmospheres it is thought that some of the higher radicals are converted to paraffins before they can decompose. This also accounts for the lesser amount of ethylene.

## Cracking of Dodecanes

Products from the thermal cracking of an isododecane were given in a previous paper.[10a] The isododecane was made by hydrogenation of the trimer of isobutene obtained in the polymerization with cold sulfuric acid, and there are valid reasons for believing that the predominant structure present was 2,2,4,6,6-pentamethylheptane. Calculations of the products theoretically expected from this structure were made under the same assumptions employed above. The experimental and theoretical products are compared in Table IV. The agreement is a little better without radical isomerization, but there is not a large difference between the two cases as there was with *n*-hexadecane. The correspondence of calculated and experimental products is considered fairly good. It is of interest that no $C_2$ is predicted and very little is found. Also, butane is predicted in the observed quantity, in contrast with normal paraffins where no paraffinic products above ethane are theoretically expected.

Experimental results from thermal cracking of *n*-dodecane at 550°, previously published,[10a] are in qualitative agreement with the results from *n*-hexadecane and with the amplified radical chain theory.

TABLE IV

EXPERIMENTAL AND THEORETICAL PRODUCTS FROM ISODODECANE

Experimental results from cracking at 500° and atmospheric pressure (ref. 10a), with 15.1% conversion

| | Moles per 100 moles cracked | | |
|---|---|---|---|
| | | Theoretical | |
| Product | Experimental | Simple | With isom. |
| $C_1$ | 53 | 73 | 73 |
| $C_2$ | 7 | 0 | 0 |
| $C_3$ | 20 | 17 | 7 |
| $i$-$C_4H_8$ | 86 | 57 | 43 |
| $n$-$C_4H_8$ | 5 | 0 | 0 |
| $i$-$C_4H_{10}$ | 25 | 27 | 27 |
| $n$-$C_4H_{10}$ | | 0 | 0 |
| $C_5$ | | 0 | 0 |
| $C_6$ | | 0 | 0 |
| $C_7$ | | 24 | 29 |
| $C_8$ | 76 | 27 | 27 |
| $C_9$ | | 0 | 0 |
| $C_{10}$ | | 0 | 0 |
| $C_{11}$ | | 32 | 37 |
| Total hydrocarbon | 272 | 257 | 243 |
| Hydrogen | 24 | 0 | 0 |

## Direct Fission Theory and Rates of Cracking

Before the development of the chain theory, Burk[11] suggested that cracking might occur by direct fission of a paraffin into a smaller paraffin and an olefin. He also proposed[11,18] a general equation for the rate of cracking of normal paraffins, namely, $k = (n - 1)v \exp(-E/RT)$, where $k$ is the first order rate constant, $n$ is the number of carbon atoms, and $v$ and $E$ are constants for the homologous series. It is now clear that the direct fission theory does not explain the products of cracking, for it predicts only two moles of product per mole cracked, and a mixture of olefins and paraffins for all carbon numbers two or more below that of the paraffin cracked (except, of course, for $C_1$). The rate equation was tested by Burk, Laskowski and Lankelma[18] with available data by computing values of $E$ from the known values of the reaction rates, $k$, and a constant value of $v$. They obtained $E$'s varying from 59 to 65 kcal. From the approximate constancy of $E$, they concluded that the data supported the equation and mechanism of Burk.

The rate constant obtained in this work for hexadecane has been combined with a few other values from the literature in another test of the above equation. The present test has been made by plotting values of $k/(n - 1)$ against $n$ for a single temperature. According to the Burk equation for the rate of cracking, a horizontal line should result. Data for the plot are given in Table V, and Fig. 2 shows the result. It is seen

(17) For example, A. J. van Peski, U. S. Patent 2,172,228 (1939).

(18) R. E. Burk, L. Laskowski, and H. P. Lankelma, THIS JOURNAL, 63, 3248 (1941).

that $k/(n-1)$ increases in a regular fashion with increasing $n$. It is concluded that the equation is not a very good approximation. Instead, the following empirical relationship, taken from the straight line drawn in Fig. 2, may be written for the rate of cracking of normal paraffins at 500°

$$k\ (\text{sec.}^{-1}) = (n-1)(1.57\,n - 3.9) \times 10^{-5}$$

and atmospheric pressure, for $4 \leq n \leq 16$. Actually the agreement of the experimental points with this line in Fig. 2 is better than can be expected, considering the variations in $k$ normally met. It is not thought that the above empirical equation represents the true relationship for $n$-paraffins, but simply that it is a useful approximation. It should also be stressed that expression of the rates by means of first order constants in itself is an approximation, because the most careful work shows first order rate constants usually decrease somewhat with increasing depths of cracking.

TABLE V

THERMAL CRACKING RATES FOR $n$-PARAFFINS, $C_nH_{2n+2}$

| $n$ | Ref. | First order rate const., sec.$^{-1}$: $k$ at temp., °C. | $k$ at 500° | $k \times 10^5/(n-1)$ |
|---|---|---|---|---|
| 4 | 4 | $2.06 \times 10^{-4}$, 520 | $0.80 \times 10^{-4}$ | 2.7 |
| 4 | 19 | $1.32 \times 10^{-4}$, 513 | $0.66 \times 10^{-4}$ | 2.2 |
| 7 | 1 | $5.5 \times 10^{-3}$, 552 | $3.8 \times 10^{-4}$ | 6.3 |
| 8 | 13 | $3.9 \times 10^{-3}$, 538 | $6.0 \times 10^{-4}$ | 8.6 |
| 12 | 10a | $1.8 \times 10^{-2}$, 550 | $16.8 \times 10^{-4}$ | 15.3 |
| 16 | 20 | $3.2 \times 10^{-3}$, 500 | $32 \times 10^{-4}$ | 21.3 |

The rate constants given in Table V are from experiments in which conversion lay between 10 and 32% (except for dodecane at 41%) and the pressure was atmospheric or very close to atmospheric. If rates at 500° were not given, they were converted from the nearest available temperature, using the activation energy given by the same author, or 60 kcal. if no other was stated. Although this procedure is not as satisfactory as would be measurements on a number of homologs in one apparatus at one temperature, it is considered sufficiently accurate for the test presented here.

(19) E. W. R. Steacie and I. E. Puddington, *Can. J. Research*, **B16**, 176 (1938).

(20) This work.

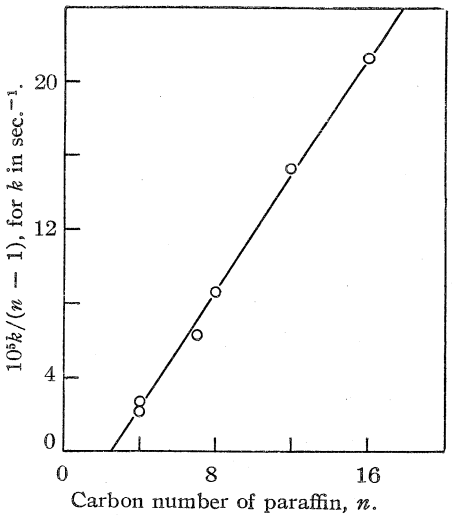



Fig. 2.—Variation of cracking rate constant with carbon number for $n$-paraffins at 500°.

**Acknowledgment.**—Dr. B. S. Greensfelder gave valuable encouragement. Mrs. S. S. Tornbom assisted in the performance of the experiments.

## Summary

The thermal cracking of $n$-hexadecane was observed in a system for flowing reactants at 500° and pressures of one and 21 atmospheres absolute. Detailed analyses of the products are given, and those at one atmosphere are shown to be in good agreement with the predictions of the Rice radical chain theory as amplified by Kossiakoff and Rice. Earlier data for the products from an isododecane are also shown to agree with the theory. Rates of cracking for homologous normal paraffins are approximately represented by first order rate constants, which do not fit an equation proposed by Burk, but lead to the empirical relationship $k$ (sec.$^{-1}$) $= (n-1)(1.57\,n - 3.9) \times 10^{-5}$ for rates at 500°.

EMERYVILLE, CALIF. RECEIVED MAY 4, 1948

[CORNELL UNIVERSITY AND THE S. A. M. LABORATORIES OF THE MANHATTAN PROJECT, ITHACA, N. Y., AND COLUMBIA UNIVERSITY, NEW YORK, N. Y.]

# The Thermal Polymerization of Hexafluorobutadiene[1]

BY MAURICE PROBER[2] AND WILLIAM T. MILLER, JR.

The unsaturated fluorocarbons have been of especial interest in this Laboratory because of their high order of reactivity, and consequent suitability for study and for use as synthetic intermediates, in marked contrast to corresponding chloro compounds. Hexafluoro-1,3-butadiene, the first fluorocarbon diolefin prepared[3] and investigated, was found to exhibit a chemical reactivity in many ways rivaling its hydrogen analog. It underwent radical chain type and thermal polymerization and was readily halogenated and attacked by neutral permanganate in contrast to the comparatively inert hexachloro-1,3-butadiene.[4] The present paper reports on the thermal reactions of hexafluoro-1,3-butadiene and of its dimer and trimer.

The thermal polymerization of conjugated hydrocarbons has already been studied in the case of a number of dienes.[5-17] At elevated temperatures there was appreciable formation of dimers and in some cases trimers. High molecular weight products were also formed in the liquid phase thermal reactions unless special precautions were taken to remove peroxides and oxygen. Dimerization may be generally represented by 1,4-addition of one molecule of a diene to a double bond of a second molecule and the dimers of butadiene, isoprene and 2,3-dimethylbutadiene, and the trimer of butadiene all have been reported to have cyclohexene structures.[5,8,12,15,18] However, 1-phenyl-1,3-butadiene appears to be an exceptional case and a cyclopentene structure has been assigned to its thermal dimer.[17,18a] Kinetic studies of vapor phase thermal diene dimerizations have indicated a homogeneous second order reaction.[6,7,9]

**Thermal Reactions of Hexafluorobutadiene.**—On the basis of preliminary work, the thermal reactions of hexafluoro-1,3-butadiene have now been investigated over the temperature range of 150 to 180°. The reactions were carried out by heating the diene in steel bombs with not more than trace amounts of water or oxygen normally present. The reaction products were hexafluorocyclobutene, dimers which distilled at 98 to 100°, trimers which distilled at 64 to 66° at 10 mm., and some higher boiling material. The higher boiling fractions were viscous liquids which indicated that the degree of polymerization was low. In the higher temperature runs small amounts of a compound boiling below the dimer fraction but with the empirical formula $C_8F_{12}$ was isolated as well. The reaction product was readily separated into its major components, which differed by four carbon units, by fractional distillation. The recovered butadiene fraction was analyzed by chlorination and separation of the resulting dichloride and tetrachloride by fractional distillation. Experimental data are summarized in Table I.

These data indicated that the yields of the different products were strongly influenced by reaction temperature. Similar observations have been made for the thermal dimerization of butadiene,[10] but a comparison of the reactivity of the two dienes is complicated by the side reactions in the case of hexafluorobutadiene to form cyclobutene and trimer. Intramolecular cyclization became more pronounced as the reaction temperature was increased, and at 500° and atmospheric pressure, hexafluorobutadiene was quantitatively converted to hexafluorocyclobutene when passed through a heated tube with a five to fifteen second contact time.[19] Under comparable conditions, butadiene undergoes dimerization.[20] Although a trimer has been obtained by heating vinylcyclohexene and butadiene, the yield was very poor.[18] Formation of a trimer proceeded more rapidly with hexafluorobutadiene, and as shown above this fraction constituted a considerable portion of the reaction product. As might be expected

(1) Based on the thesis submitted by Maurice Prober to the Graduate School of Cornell University in partial fulfillment of the requirements for the Ph.D. degree, June 1946. This work was largely carried out for the Manhattan Project under Contract No. OEMsr-237 and Supplement No. 1 at Cornell University and under Contract No. W-7405-Eng.-50 at S. A. M. Laboratories, Columbia University. The Cornell contracts were administered through Division 9 of the National Defense Research Committee.

(2) Present address: General Electric Company, Schenectady, N. Y.

(3) Miller, Ehrenfeld, Phelan, Prober and Reed, *Ind. Eng. Chem.*, **39**, 401 (1947).

(4) Fruhwirth, *Ber.*, **74**, 1700 (1941).

(5) Lebedev, *Bull. soc. chim.*, **12**, 780 (1912).

(6) Vaughan, THIS JOURNAL, **54**, 3863 (1932).

(7) Harkness, Mears and Kistiakowsky, *J. Chem. Phys.*, **5**, 682 (1937).

(8) Lebedev and Sergjenko, *Chem. Zentr.*, **107**, II, 59 (1936).

(9) Kistiakowsky and Ransom, *J. Chem. Phys.*, **7**, 725 (1939).

(10) Robey, Wiese and Morrell, *Ind. Eng. Chem.*, **36**, 3 (1944).

(11) Wallach, *Ber.*, **24**, 1538 (1891).

(12) Lebedev and Skavronskai, *Bull. soc. chim.*, **16**, 82 (1914).

(13) Whitby and Crozier, *Can. J. Res.*, **6**, 203 (1932).

(14) Aschan, *Ann.*, **461**, 9 (1928).

(15) Wagner-Jauregg, *ibid.*, **488**, 178 (1931).

(16) Whitby and Gallay, *Can. J. Res.*, **6**, 280 (1932).

(17) Bergmann, *J. Chem. Soc.*, 1359 (1935).

(18) Alder and Rickert, *Ber.*, **71**, 373 (1938).

(18a) Since this paper was prepared, Foster and Schreiber, THIS JOURNAL, **70**, 2303 (1948), have described the preparation of cyclooctadienes from 2-chloro-1,3-butadiene, in moderate yield, and from 1,3-butadiene and 2,3-dichloro-1,3-butadiene, in small yields, and have drawn our attention to the isolation of an 8-carbon ring dimer from chloroprene still residues by Brown, Rose and Simonsen, *J. Chem. Soc.*, 101 (1944).

(19) F. H. Winslow and W. T. Miller, Jr., unpublished work.

(20) Moor, Strigaleva and Shilyaeva, *C. A.*, **30**, 365 (1936).

TABLE I

THERMAL POLYMERIZATION OF HEXAFLUOROBUTADIENE

| No. | Reaction conditions Time, hr. | Temp., °C. | Conversion,[a] % | Products[b] Cyclobutene $C_4F_6$ | Low b. p. $C_8F_{12}$ | Dimer $C_8F_{12}$ | Trimer $C_{12}F_{18}$ | High b. p. residue |
|---|---|---|---|---|---|---|---|---|
| 1[c] | 44 | 150 | 83 | 6.4 | 0 | 67 | 19 | 1.5 |
| 2[d] | 44 | 150 | 79 | 6.7 | 0 | 67 | 15 | 1.1 |
| 3[c,e] | 44 | 150 | 77 | 6.9 | 0 | 65 | 18 | 1.9 |
| 4[f] | 5 | 160 | 39 | 5.3 | 0 | 88 | 3.6 | 0.2 |
| 5[d,f] | 5 | 160 | 37 | 5.6 | 0 | 89 | 3.2 | 0.5 |
| 6[d,f] | 18 | 180 | 94 | 14 | 2.0 | 40 | 30 | 3.9 |
| 7[d,f] | 18 | 180 | 94 | 14 | 2.5 | 38 | 33 | 4.1 |
| 8[d,f] | 44 | 180 | 99[g] | 14 | 5.1 | 33 | 34 | 6.0 |

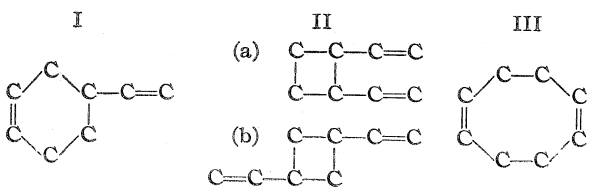
[a] Conversions are calculated on the basis of all reaction products recovered including intermediate fractions. [b] Yields expressed as weight per cent. of hexafluorobutadiene converted. [c] Charged under nitrogen. [d] Charged under air. [e] Catechol, 0.3 g., added. [f] Dissolved gases removed by distillation. [g] Complete reaction; the conversion is less than 100% because of losses in handling.

on the basis of a stepwise reaction mechanism, heating hexafluorobutadiene with excess dimer yielded considerably more trimer than was obtained directly.

The presence of oxygen or an anti-oxidant such as catechol did not affect the composition of the products as shown in Table I by the results of reactions 1, 2 and 3 further supporting a molecular type thermal reaction and in all cases the residues were indicated as very low polymers. These results differ considerably from those observed with the hydrocarbon dienes where the presence of oxygen generally leads to appreciable yields of high polymer.

With the exception of hexafluorocyclobutene, the structures of the thermal reaction products of hexafluorobutadiene have not been proved. The lack of related compounds was a major handicap to this work. However, some progress was made toward assigning structures to the dimer products. Analyses and molecular weight determinations confirmed the molecular formula, $C_8F_{12}$, and the presence of more than one isomer was indicated by the absence of a sharp boiling point and failure to obtain a plateau in the cooling curve. Chlorination confirmed this conclusion, and yielded tetrachloride, and hexachloride in approximately 2.5 to 1 molar ratio. Both chlorides were saturated to permanganate in acetone. The presence of structural isomeric chlorides was not excluded.

The dimer skeletons derivable from hexafluorobutadiene without carbon–carbon or carbon–fluorine bond rearrangements, which are capable of yielding tetrachlorides are listed below.




Little direct evidence was available to indicate a preferred structure. All of the hydrocarbon dimers formed from dienes which have been examined[5,8,13,14,15] with the exception of the dimer from 1-phenylbutadiene[17] have been indicated as cyclohexene ring compounds. By analogy, hexafluorobutadiene would undergo a similar reaction to form structure I. However, one of the interesting differences between fluorocarbon and hydrocarbon chemistry is the more ready formation of cyclobutane structures with the highly fluorinated systems. Examples are the cyclobutane dimer formed by heating tetrafluoroethylene,[21] chlorotrifluoroethylene,[21,22] or unsym.-dichlorodifluoroethylene,[21,22] and the cyclization of hexafluorobutadiene to hexafluorocyclobutene described above. In addition, the thermal reactions of the dimer fraction could be best explained by assuming a cyclobutane structure for at least one of the isomers.

No data were collected with specific reference to the non-planar cycloöctadiene structure III. It is planned to continue work on the hexafluorobutadiene dimer structures by oxidation. Different acids should be obtained from I, II and III.

The preparation of the hexachloride, $C_8Cl_6F_{12}$, from the dimer fraction indicated the presence of a dimer with a structure formed by rearrangement as well as condensation. Formation of hexachloride by ring cleavage of tetrachloride was unlikely because chlorination at 0 and 100° yielded the same tetrachloride: hexachloride ratios and because of the observed difficulty of cleaving known fluorinated cyclobutane compounds with chlorine.

The absence of a sharp boiling point also indicated the presence of more than one isomeric trimer.

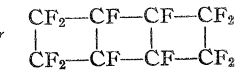
**Thermal Reactions of Hexafluorobutadiene Dimers.**—When the hexafluorobutadiene dimer fraction was heated in a glass bomb at 200° for one hundred and sixty-four hours, 40% was converted into a remarkable isomeric compound,

(21) Harmon, U. S. Patent 2,404,374, July 23, 1946.

(22) Henne and Ruh, THIS JOURNAL, **69**, 279 (1947). The thermal dimerization of tetrafluoro- and of the chlorofluoroethylenes to form cyclobutanes was also carried out independently by Miller and his associates as a part of the fluorocarbon war research program.

$C_8F_{12}$, which boiled at 80° and melted at 40°. Reheating the recovered high boiling $C_8F_{12}$ yielded a total conversion for the two cycles of about 65% of the original fraction to the low boiling isomer. The purified low boiling compound was entirely stable to permanganate and to chlorination. Its formula was checked by molecular weight determinations and by analysis. These facts require a fused tricyclic structure such as IV. Such a compound could be formed by

IV



intramolecular condensation of *cis*-dodecafluoro-1,2-divinylcyclobutane, IIa, or dodecafluoro-1,5-cycloöctadiene, III, without rearrangement of groups. Evidence for the ready formation of cyclobutane rings in fluorinated systems has been presented above. The stability of a simple cyclobutane ring was also demonstrated by passing 1,2-dichlorohexafluorocyclobutane and excess chlorine through a heated glass tube. No reaction occurred until pyrolysis temperatures approaching 500° were reached. The relatively high melting point of 40° of the saturated $C_8F_{12}$ suggested a symmetrical structure, but no other direct chemical evidence was available to support the structure postulated for this unusual material. However, preliminary X-ray diffraction studies on the crystalline $C_8F_{12}$ compound by Professor J. L. Hoard and Mr. R. W. Broge of this Laboratory have yielded results which are consistent with the tricyclic structure proposed above.

In addition to the low boiling isomer, a white infusible polymer was isolated in low yield from the bomb reactions of hexafluorobutadiene dimer. This polymer was insoluble in acetone, pentane, ethyl alcohol, carbon tetrachloride, benzene, $C_8F_{16}$, and 1,1,2-trichlorotrifluoroethane and decomposed on heating above 300°.

A 60% yield of the low boiling saturated $C_8F_{12}$ isomer was obtained by passing the dimer fraction through a hot tube at 500°. The recovered dimer fraction was recycled, but did not yield additional low boiling $C_8F_{12}$. The recovered material was chlorinated and yielded only tetrachloride, indicating the absence of triene, and it was considered significant that the physical properties of this tetrachloride fraction were not identical with those of the tetrachloride fraction isolated by direct chlorination of hexafluorobutadiene dimer as described above. Approximately five per cent of the dimer fraction underwent depolymerization in the hot tube reaction. The $C_4F_6$ product isolated was hexafluorocyclobutene which, under the conditions of the experiment would have been formed from hexafluorobutadiene. No products boiling higher than $C_8F_{12}$ were obtained from the hot tube reactions.

**Thermal Reactions of the Hexafluorobutadiene Trimer.**—The trimer was found to undergo polymerization when heated at 300° in a sealed tube. After one hundred and sixteen hours, approximately 35% $C_{12}F_{18}$ fraction was recovered, 30% boiled from 175 to 200° at 10 mm., probably $C_{24}$ fractions, and the remainder did not distil at a bath temperature of 300° under 1.5 mm. pressure. Less than 5% low boiling material was formed and the recovered $C_{12}F_{18}$ was indicated as approximately equivalent in unsaturation to the starting material by permanganate titration. Partial depolymerization occurred when the trimer was passed through a hot tube at 520°.

## Experimental

**Hexafluorobutadiene.**—Hexafluorobutadiene was prepared by dechlorination of 1,2,3,4-tetrachlorohexafluorobutane. The tetrachloride was gradually added to a hot stirred suspension of zinc dust in absolute alcohol and the diene fractionally distilled out as formed utilizing a partial condenser topped by a short packed column. The product was refluxed over phosphorus pentoxide to remove alcohol and then redistilled through a 70 × 1.2 cm. glass helix packed low temperature column. The fraction b. p. 6.5 to 7.5° (uncor.) was taken for polymerization studies.

**Thermal Reactions.**—The polymerization bombs were steel "lecture" cylinders[23] in which the conventional valve was replaced by a plug bearing inlet and outlet tubes equipped with brass needle valves. The bombs were thoroughly washed and dried before each run, but the walls were coated with iron oxide. The diene was distilled through a drying tube packed with "Drierite" directly into the bombs under dry oxygen-free nitrogen. The nitrogen was purified by passing it through a series of wash bottles containing Fieser solution,[24] lead acetate solution, and concentrated sulfuric acid, followed by a phosphorus pentoxide tube. In those experiments where the effect of oxygen was tested, a slow stream of dry air was passed through the bomb after it had been charged with diene. The vapor phase was about 200 cc. After the first three experiments this procedure was discarded in favor of charging the bomb under dry air and distilling out 10 to 20 g. of diene to sweep out dissolved gases. The polymerization bombs were heated in a constant temperature oven controlled to ±0.5°, and the reaction times include the time necessary for the bomb to warm up from room temperature. At the conclusion of a run, the bombs were cooled rapidly to room temperature and the contents transferred to a cold still pot under a carbon dioxide atmosphere. It was preferable to carry out the transfer and distillations under an inert atmosphere to avoid oxidation since perfluoro olefins in general undergo ready oxidation to yield acid halide type products in air. The reaction product was distilled through a 75 × 1.0 helix packed column with Dry Ice trap in series. The Dry Ice trap condensate consisted of recovered hexafluorobutadiene and hexafluorocyclobutene, b. p. 0.0°.[25] This mixture was analyzed by chlorination under a Dry Ice reflux condenser with illumination from a quartz mercury vapor lamp. The 1,2-dichlorohexafluorocyclobutane, b. p. 60.4,[26] resulting from the cyclobutene and the 1,2,3,4-tetrachlorohexafluorobutane, b. p. 134.1°,[27] resulting from the diene were readily separated by fractional distillation. The dimer fraction, $C_8F_{12}$, was collected from 96 to 100° with most of it distilling from 98 to 100°.

*Anal.* Calcd. for $C_8F_{12}$: C, 29.56; mol. wt., 324. Found: C, 29.3, 29.6; mol. wt., 326, 331.

In the higher temperature runs, a lower boiling dimer was

(23) As supplied by the Mathieson Company.

(24) Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 395.

(25) Harmon[21] has reported b. p. 5 to 6°; Henne and Ruh[22] have reported b. p. 1.13°.

(26) Harmon[21] has reported b. p. 58–59°; Henne and Ruh[22] have reported b. p. 59.87°.

(27) Determined by J. M. Phelan.

collected over the boiling range 80 to 85°. The behavior of this compound is described below. In the first five runs, the trimer fraction was too small for convenient fractional distillation, and was separated from the higher boiling residue by simple distillation. It was collected over the boiling range 165 to 185° and distilled largely from 175 to 180°. In subsequent runs the residue from the $C_8F_{12}$ distillation was fractionally distilled at 10 mm. and the trimer, $C_{12}F_{18}$, collected, b. p. 62 to 68°, largely b. p. 64 to 66°.

*Anal.* Calcd. for $C_{12}F_{18}$: C, 29.65. Found: C, 29.7, 29.8.

The quantitative results for the hexafluorobutadiene polymerizations are given in Table I. The amounts of hexafluorobutadiene charged for the eight reactions for which data are given was as follows: Reaction (1), 305 g.; (2), 253 g.; (3), 196 g.; (4), 328 g.; (5), 327 g.; (6), 350 g.; (7), 390 g.; (8), 418 g.

**Hexafluorobutadiene Dimer.**—The dimer fraction of b. p. 96 to 100°, as indicated above, was utilized for the following experiments.

**Chlorination.**[28]—Chlorine, 41 g., was passed into 81.7 g. $C_8F_{12}$ while the reaction mixture was illuminated by a mercury vapor lamp. The light source was placed about one foot away to minimize heating effects and the chlorination flask was maintained at 0 to 5° by circulating ice water through a cold finger. The reaction product was washed with 5% sodium hydroxide solution, dried, and fractionally distilled at 20 mm. pressure to yield the following fractions: 6.5 g., Dry Ice-trap condensate; 2.6 g., b. p. 55 to 90.5°; 59.7 g., b. p. 90.5 to 94.0°; 4.3 g., b. p. 94.0 to 138.0°; 27.0 g. b. p. 138.0 to 139.5°; 3.1 g., residue.

The same general procedure as above was carried out with 81.5 g. of $C_8F_{12}$. However, the liquid was maintained at reflux during the chlorination and varied in temperature from 100° at the beginning to over 200° at the end of the run. The reaction product was washed with 5% sodium hydroxide solution, dried, and refractionally distilled at 20 mm. pressure to yield the following fractions: 7.1 g. Dry Ice-trap condensate; 4.9 g., b. p. 91 to 94°; 68.0 g., b. p. 94 to 127° but principally at 94 to 97°; 1.7 g., b. p. 127 to 138°; 25.8 g., b. p. 138 to 140°.

A heart cut from redistillation of the combined fractions of b. p. 90 to 97° at 20 mm. was found to be saturated to potassium permanganate in acetone; b. p. 203°, 90.5 to 91.5° at 20 mm., $n^{20}D$, 1.3870.

*Anal.* Calcd. for $C_8Cl_4F_{12}$: C, 20.62. Found: C, 20.6, 20.7.

A heart cut from redistillation of the fraction of b. p. 138 to 140° at 20 mm. was also saturated to permanganate in acetone; b. p. 261°, 139 to 140° at 20 mm.; $n^{20}D$ 1.4040.

*Anal.* Calcd. for $C_8Cl_6F_{12}$: C, 17.88; Cl, 39.63. Found: C, 18.0, 18.1; Cl, 39.6, 39.3.

The molar ratio of tetrachloride to hexachloride was estimated as 2.5 to 1.0 for the low temperature reaction and 2.8 to 1.0 for the high temperature chlorination; agreement within experimental error.

**Thermal Reactions.**—Hexafluorobutadiene and its unsaturated dimer, $C_8F_{12}$, reacted as follows.[29] A steel bomb was charged with 40 g. of $C_8F_{12}$ and 10 g. $C_4F_6$ and heated for twelve hours at 170°. No unreacted hexafluorobutadiene remained, and 39.8 g. of $C_8F_{12}$ and 7.5 g. of $C_{12}F_{18}$ were obtained. The yield of $C_{12}F_{18}$ was considerably higher than that derived solely from $C_4F_6$ under comparable conditions and indicated that formation of $C_{12}F_{18}$ proceeded through interaction of $C_8F_{12}$ and $C_4F_6$.

The unsaturated dimer of hexafluorobutadiene was partially converted by heating into an isomeric saturated compound.

A sealed glass bomb tube containing 56.7 g. of $C_8F_{12}$, b. p. 96 to 100° was heated at 200° for one hundred and sixty-four hours. The volatile reaction products were distilled out of the bomb to leave 2 g. of white solid residue. Upon slow heating the solid began to darken at 300° and underwent slow decomposition at 400° without melting. The solid was insoluble in acetone, pentane, ethyl alcohol, carbon tetrachloride, $C_8F_{16}$ (satd.), 1,1,2-trichlorotrifluoroethane and benzene. The liquid product was separated into the following fractions by distillation through a small Vigreux column: 19.0 g., b. p. 82 to 86° (solid at room temperature); 6.7 g., b. p. 86 to 96°; 15.3 g., b. p. 96 to 100°; 3.7 g. residue. The 98 to 100° portion of the recovered $C_8F_{12}$ was reheated under the same conditions to yield additional low boiling $C_8F_{12}$. However, no infusible solid was formed in this reaction.

The isomerization of hexafluorobutadiene dimer was also carried out in the vapor phase. The 30-cm. middle section of a 60 × 3 cm. glass tube was heated by an electric combustion tube furnace and the midpoint temperature maintained at 500 ± 10° while 187.7 g. of $C_8F_{12}$, b. p. 96 to 100°, was passed through the tube at a rate of 11.7 ± 1.8 g. per hour. No carbonization and only slight etching of the tube was observed. The reaction product, 184 g., was collected at room temperature. Only 0.2 g. was recovered from a Dry Ice trap and nothing condensed in a liquid oxygen trap arranged in series. Distillation yielded the following fractions: 12.1 g. Dry Ice trap-condensate; 114.3 g., b. p. 78 to 83°; 7.7 g., b. p. 83 to 95°; 44.0 g., b. p. 95 to 101°; 3.1 g. residue. The fraction of b. p. 78 to 83° was chlorinated but very little chlorine absorption was observed. The chlorination product was fractionally distilled and neglecting a small forerun and residue boiled sharply at 80°. This fraction had a freezing point of 40.1° (cooling curve) and was saturated to permanganate in acetone.

*Anal.* Calcd. for $C_8F_{12}$: C, 29.65; mol. wt., 324.1. Found (80° b. p. fraction): C, 29.8, 29.9; mol. wt., 321, 323.

The Dry Ice trap condensate was shown to consist of hexafluorocyclobutene and low boiling $C_8F_{12}$.

The fraction of b. p. 95 to 101° was recycled through the hot tube at 500° and the product fractionally distilled to yield: 0.2 g. of Dry Ice trap condensate; 3.7 g., b. p. 89 to 95°; 36.4 g., b. p. 95 to 100°; 2.0 g. residue. No low boiling $C_8F_{12}$ was recovered. The fraction of b. p. 95 to 100° was chlorinated and distilled at 20 mm. pressure to yield: 1.2 g. Dry Ice trap condensate; 37.0 g., b. p. 96 to 100°; 0.7 g. residue. The composition of the fraction b. p. 96 to 100° at 20 mm., $n^{20}D$ 1.3952, was shown to be $C_8Cl_4F_{12}$.

*Anal.* Calcd. for $C_8Cl_4F_{12}$: C, 20.62; Cl, 30.44. Found: C, 20.5; Cl, 30.7.

**Hexafluorobutadiene Trimer.**—The trimer of hexafluorobutadiene underwent polymerization on heating. A 50.0-g. sample of $C_{12}F_{18}$, b. p. 65 to 66° at 10 mm. was heated at 300° for one hundred and sixteen hours in a sealed glass tube. Distillation of 48.6 g. of the product through a short Vigreux column at 10 mm. yielded the following fractions: 4.2 g., Dry Ice trap condensate; 16.8 g., b. p. 62 to 68°; 26.3 g., residue. The unsaturation of the recovered $C_{12}F_{18}$ fraction, b. p. 62 to 68° at 10 mm., and the starting material were compared by measuring the volume of potassium permanganate solution required to produce a lasting pink color under identical conditions. No difference in unsaturation was detected. Distillation of 24.0 g. of the residue from a Claisen flask yielded 7.1 g., b. p. 175 to 200° at 10 mm., and a residue which did not distill with a final bath temperature of 320° and 1.5 mm. pressure. By comparison with the boiling points reported for fluorocarbons,[30] the distillate was indicated as probably a $C_{24}$ fraction. When the trimer was passed through a nickel tube at 520° with a contact time of ten seconds, depolymerization occurred. Approximately 15% was converted into hexafluorocyclobutene and 20% into the low boiling $C_8F_{12}$ isomer.

(28) The chlorination experiments were carried out by R. L. Ehrenfeld.

(29) This experiment was carried out by Oscar Blum.

(30) Grosse and Cady, *Ind. Eng. Chem.*, **39**, 367 (1947).

**Acknowledgment.**—We are greatly indebted to Mr. Oscar Blum, Mr. R. L. Ehrenfeld, and Dr. F. H. Winslow for permission to quote from their experimental work and to Miss Pearl Foster, Dr. Frank McKenna, Mr. J. M. Phelan, and Mrs. Rebecca Teston for analytical determinations.

## Summary

Hexafluorobutadiene has been shown to be a highly reactive compound resembling in general butadiene rather than the relatively inert hexachlorobutadiene.

The thermal reactions of hexafluorobutadiene were investigated over the temperature range 150 to 180° and hexafluorocyclobutene, dimers, which were formed in largest amount, and trimers isolated as the principal products.

Hexafluorobutadiene dimer and trimer fractions were shown to be mixtures of isomers. On heating, the dimer was partially converted into a remarkable lower-boiling saturated and highly stable isomer for which a fused tricyclic structure was proposed. Hexafluorobutadiene trimer polymerized slowly on heating. Both dimer and trimer were partially depolymerized by passing through a hot tube.

ITHACA, N. Y. RECEIVED AUGUST 21, 1948

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[CONTRIBUTION FROM THE LABORATORY OF EXPERIMENTAL THERAPEUTICS, U. S. PUBLIC HEALTH SERVICE, AND JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH]

# Disproportionation of Aromatic Stiboso Compounds. I. Mechanism[1]

BY H. H. JAFFE[2] AND G. O. DOAK[2]

Stibosobenzene and its derivatives are known to disproportionate in the solid state at moderately elevated temperatures according to the equation[3]

$$4ArSbO \longrightarrow (Ar_2Sb)_2O + Sb_2O_3$$

In order to determine the mechanism of this reaction and possibly to elucidate the effect of structure on the stability of the carbon–antimony bond we have chosen to investigate the rate of the above reaction. The present paper is concerned with stibosobenzene alone: the effect of substitution will be presented in a later paper.

## Experimental

Benzenestibonic acid, prepared by a method described previously,[4] was reduced in concentrated hydrochloric acid and ethyl alcohol with sulfur dioxide in the presence of a trace of hydriodic acid. The resulting solution of phenyldichlorostibine was hydrolyzed by dilute aqueous ammonia or sodium hydroxide.[3] The precipitated stibosobenzene was washed with 10 to 12 liters of water, alcohol and ether, and dried *in vacuo*.

Stibosobenzene, prepared in this manner, was obtained as an amorphous colorless solid, soluble in formic and acetic acids, but insoluble in other common organic solvents and in water. So far it has not been possible to prepare it in a crystalline state. The compound does not possess a well-defined melting point, but sinters at approximately 154°, although this temperature varies somewhat with the rate of heating. The molecular weight is unknown. Cryoscopic measurements in formic and acetic acids gave anomalously large depressions, probably due to reaction with the solvents. By analogy with antimony trioxide which exists in a bimolecular and a polymolecular form,[5] and with aromatic arsenoso compounds, which have molecular weights four times the formula weight,[6] stibosobenzene is probably not monomolecular.

In preliminary experiments it was demonstrated that the disproportionation of stibosobenzene at 100° yielded bis-(diphenylantimony)-oxide in quantitative yield. The product was identified by melting point and analysis. In an atmosphere of nitrogen no side reaction could be detected. It was further shown that extraction of a mixture of stibosobenzene, antimony trioxide and bis-(diphenylantimony)-oxide with five portions of ether (40 ml. each) permitted quantitative recovery of the bis-(diphenylantimony)-oxide, without contamination with stibosobenzene or antimony trioxide.

To determine the rate of disproportionation, samples of stibosobenzene (0.25 to 0.75 g.) were permitted to rearrange in large test-tubes in an atmosphere of nitrogen in a constant temperature bath maintained at fixed temperatures between 75 and 100°. Samples were withdrawn at accurately measured intervals, chilled in ice and extracted with ether. The extracts were evaporated *in vacuo* at room temperature and dried to constant weight. The bis-(diphenylantimony)-oxide was weighed and analyzed and the fraction of the original material that had rearranged was obtained from these data. The rate constants, $k_2$, were calculated from equation (1) below by the method of least squares using from 6 to 14 experimental points.

(1) Presented before the Division of Physical and Inorganic Chemistry at the New York Meeting of the American Chemical Society, September 17, 1947.

(2) Present address: Syphilis Experimental Laboratory, School of Public Health, University of North Carolina, Chapel Hill, North Carolina.

(3) H. Schmidt, *Ann.*, **421**, 174 (1920).

(4) G. O. Doak and H. G. Steinman, THIS JOURNAL, **68**, 1987 (1946).

(5) A. F. Wells, "Structural Inorganic Chemistry," Clarendon Press, Oxford, 1945, p. 416.

(6) F. F. Blicke and F. D. Smith, THIS JOURNAL, **52**, 2946 (1930).

## Results and Discussion

**Kinetics.**—The rearranged fraction $(1 - x)$ plotted against time $(t)$ resulted in an S-shaped curve. This could be reduced to a linear relationship by plotting $\ln(1/x - 1)$ against $t$ (except for the first portion of the curve) (Figs. 1a and b), corresponding to a rate law

$$-dx/dt = k_2(x)(1 - x) \qquad (1)$$

or in the integrated form

$$\ln\left(\frac{1 - x}{x}\right) = k_2(t - t_{1/2}) \qquad (1a)$$

where $t_{1/2}$ is the time required for one half of the original material to rearrange. The early portion of the curve deviated from the expected straight line in different directions depending on whether sodium hydroxide or ammonia was used in the synthesis. An explanation of this phenomenon will be suggested below.

The rate constants determined from equation (1) in a series of experiments using a single preparation of stibosobenzene were constant within the limits of experimental error (Table I). The constants obtained with different preparations varied over a wide range (Table II). In spite of this variation, the same rate law was found to apply in more than fifty experiments with eleven separate preparations.

TABLE I

THE RATE OF DISPROPORTIONATION OF A SINGLE PREPARATION OF STIBOSOBENZENE AT 78°

| $10^4k_2$ sec.$^{-1}$ | Standard error |
|---|---|
| 3.11 | 0.20 |
| 3.16 | .20 |
| 2.96 | .20 |

TABLE II

THE RATE OF DISPROPORTIONATION OF VARIOUS PREPARATIONS OF STIBOSOBENZENE AT 78°

| $10^4k_2$ sec.$^{-1}$ | Standard error | $10^4k_2$ sec.$^{-1}$ | Standard error |
|---|---|---|---|
| a. Hydrolyzed with Aqueous Ammonia | | b. Hydrolyzed with Sodium Hydroxide | |
| 4.73 | 0.29 | 0.514 | 0.15 |
| 3.08 | .09 | .651 | .059 |
| 1.24 | .27 | .254 | .011 |
| 3.52 | .17 | 1.44 | .04 |
| 5.21 | .11 | 2.06 | .09 |
| 4.63 | .14 | | |

The variation of the rate constants in different preparations is probably due to small amounts of impurities which could not be removed since stibosobenzene could not be purified. Tables III and IV show the effect of the addition of various substances to the rate of the reaction. It is seen that bases and bis-(diphenylantimony)-oxide are effective catalysts. The effect of hydrogen chloride and other strong acids could not be investigated because stibosobenzene reacts with acids to form ether soluble compounds.

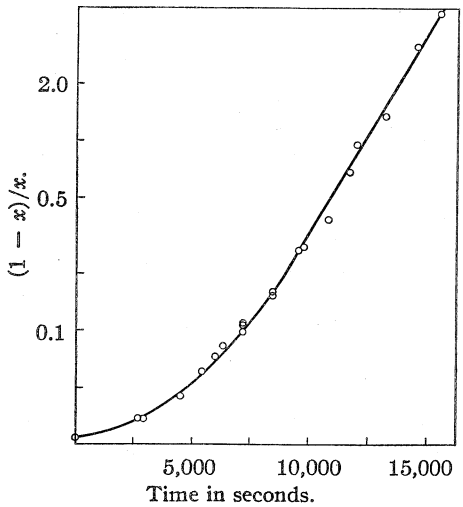



Fig. 1a.—The disproportionation of stibosobenzene at 78°: preparations hydrolyzed with aqueous ammonia.

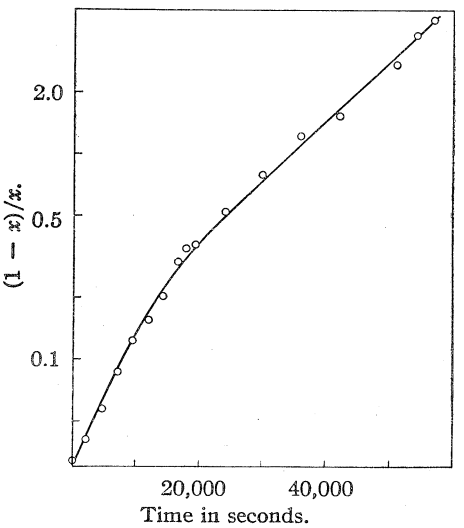



Fig. 1b.—The disproportionation of stibosobenzene at 78°: preparations hydrolyzed by sodium hydroxide.

The rate constant of one preparation of stibosobenzene was determined at three temperatures (Table V). The plot of ln $k_2$ against $1/T$ (Fig. 2) permits calculation of the apparent energy of activation, $E$, which was 23.5 ± 1.5 kcal./mole.

TABLE III

THE EFFECT OF VARIOUS SUBSTANCES ON THE RATE OF DISPROPORTIONATION OF STIBOSOBENZENE AT 78°

| Nature of substance | Amount: weight fraction of stibosobenzene | $10^4k_2$ sec.$^{-1}$ | $10^4k_2(0)$[a] sec.$^{-1}$ |
|---|---|---|---|
| $C_6H_5SbO_2H_2$ | 0.1 | 4.49 | 4.69 |
| Powdered pyrex | .1 | 4.56 | 4.69 |
| $NH_3$ | .1 atm. | 3.73 | 3.41 |

[a] Rate constant for same preparation of stibosobenzene without catalyst.

**Mechanism.**—From the experimental data several possible mechanisms for the reaction

TABLE IV

THE EFFECT OF VARIOUS SUBSTANCES ON THE RATE OF DISPROPORTIONATION OF STIBOSOBENZENE

| Substance added | Amount: weight fraction of stibosobenzene | $(1 - x)_t$[a] | $(1 - x)_t$[b] |
|---|---|---|---|
| Vacuum | .. | 0.358 | 0.367 |
| $Sb_2O_3$ | 0.1 | .466 | .492 |
| Zn dust | .2 | .367 | .367 |
| $Na_2SO_3$ | .02 | .369 | .367 |
| *d* | .1 | .360 | .367 |
| CuCl | .02 | .365 | .367 |
| Succinic acid | .1 | .500 | .492 |
| $NaOAc \cdot 3H_2O$ | .1 | .774 | .492 |
| $Na_2CO_3$ | .1 | .522 | .492 |
| $[(C_6H_5)_2Sb]_2O$ | .2 | .417 | .101 |
| NaOH | .75 | .215 | .127 |
| $C_5H_5N$ | .2 | .940 | .367 |
| $NH_3$ | *c* | .645 | .367 |

[a] Fraction rearranged after *t* min. at 78°. [b] Fraction of stibosobenzene without added catalyst rearranged after same time. [c] Under partial pressure of $NH_3$. [d] Mixture of equal parts of KBr, KCl, KI and $(NH_4)_2SO_4$.

TABLE V

THE EFFECT OF TEMPERATURE ON THE RATE OF DISPROPORTIONATION OF STIBOSOBENZENE

| $T$, °K. | $10^4 k_2$, sec.$^{-1}$ | Standard error |
|---|---|---|
| 350.6 | 5.21 | 0.11 |
| 362.1 | 12.8 | 1.0 |
| 373.2 | 33.4 | 1.5 |

can be suggested. The simplest interpretation of rate law (1) is a bimolecular, autocatalytic reaction. However no plausible reaction between stibosobenzene and bis-(diphenylantimony)-oxide to form more of the latter product can be written. The fact that most of the effective catalysts for the reaction are liquids at the experimental temperatures (pyridine, sodium acetate and bis-(diphenylantimony)-oxide) suggests that the reaction occurs in solution, the supposed catalyst functioning by virtue of its solvent power for stibosobenzene. The catalysis by dry ammonia and sodium hydroxide is an argument against such a mechanism. Further, the kinetics of such a reaction would be expected to be first order with respect to the solvent, to give a break

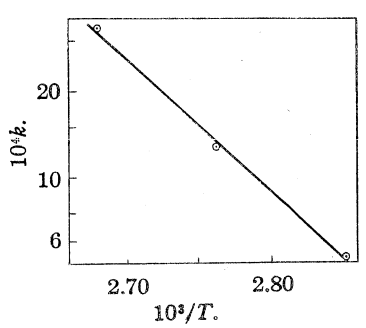



Fig. 2.—The effect of temperature on the rate of disproportionation of stibosobenzene.

when the solvent is no longer saturated with stibosobenzene, and thereafter to be first order with respect to stibosobenzene. No such break has been observed in following the reaction to completion.[7]

Reactions occurring in the solid phase have usually been interpreted as interface reactions,[8] which follow the rate law

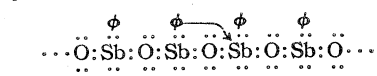
$$-\frac{dx}{dt} = \frac{d(1-x)}{dt} = k(1-x)^{2/3}$$

in the early portion of the reaction, and later approach the rate law

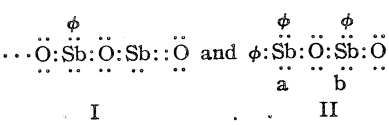
$$-dx/dt = k'x^{2/3}$$

The rate of disproportionation of stibosobenzene did not conform with these kinetics. Also as an interface reaction catalysis by both products would be expected, while it was shown (Table IV) that antimony trioxide was not a catalyst, although bis-(diphenylantimony)-oxide was. Further the reaction obeyed the same rate law whether the catalytic product, the bis-(diarylantimony)-oxide, was liquid at experimental temperatures (stibosobenzene), or solid (the *p*-chloro and *p*-methyl derivatives).

Another possible mechanism, which seems to afford the best interpretation of the experimental facts, is a chain reaction; the initiating step of which is the transfer of a phenyl group ($\phi$) from one antimony atom to an adjacent one



followed by splitting at the oxygen atom to yield fragments I and II.

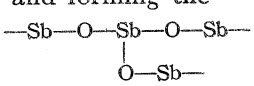


I II

The fragment I then attacks an adjacent antimony atom of stibosobenzene:



causing the shift of a phenyl group, thus propagating the chain, and forming the



grouping characteristic of antimony trioxide.[5]

Resonance with two phenyl groups lowers the electron density on antimony atom a in fragment II, compared with the antimony atoms in stibosobenzene. By an inductive effect the electron

(7) The disproportionations of the *p*-Cl- and *p*-$CH_3$- derivatives of stibosobenzene (to be reported in a later paper) obey the same rate law, although the corresponding bis-(diarylantimony)-oxides are solid at the experimental temperature. This is a further argument against the above mechanism.

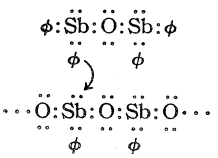
(8) *Cf.* G. M. Schwab, H. S. Taylor and R. Spence, "Catalysis" D. Van Nostrand Company, New York, N. Y., 1937, p. 324 ff.

density on antimony atom b is also lowered. This makes it less likely for this atom to lose a phenyl group than to gain one, thus forming bis-(diphenylantimony)-oxide.

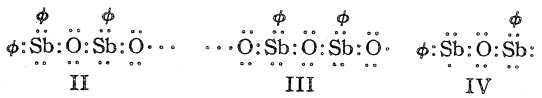
The chain breaking reaction may be the recombination of a phenyl group with an antimony atom of fragment I, or the attack of the oxygen atom of fragment I on an antimony atom of another such fragment, or both.

The proposed mechanism considers the shift of a phenyl group as the first step in the reaction. It is not known at the present time whether this phenyl group shifts with or without its electron pair, or with only one electron. The formation of fragments I and II would result in any case.

The autocatalysis by the product, bis-(diphenylantimony)-oxide, may be interpreted in terms of the following mechanism. A phenyl group migrates from a molecule of bis-(diphenylantimony)-oxide to an adjacent one of stibosobenzene.



followed by a break at the antimony–oxygen bond. This process results in fragments II, III and IV.



II III IV

Fragment III has a reactive oxygen atom which can propagate the chain in the same manner as fragment I above, while fragment IV may act as a chain breaker. The reaction according to the above mechanisms would be expected to obey the rate law

$$-dx/dt = k'x[k_1'x + k_2'(1 - x)] \qquad (2)$$

where $k'$ is the resultant rate constant of the chain propagating and chain breaking reactions, and $k_1'$ and $k_2'$ are the rate constants of the chain initiating steps (the thermal dissociations of stibosobenzene and bis-(diphenylantimony)-oxide respectively). Using $k_1 = k'k_1'$ and $k_2 = k'k_2'$ equation (2) can be written

$$-dx/dt = k_1x^2 + k_2x(1 - x) \qquad (2a)$$

If $k_2 \gg k_1$ equation (2a) will reduce to equation (1) except when $(1 - x) \ll x$, *i. e.*, for the first portion of the reaction.

The rate curves for all the preparations of stibosobenzene hydrolyzed with aqueous ammonia followed equation (2a) throughout (Fig. 1a). Equation (2a) can be integrated to give

$$\ln (k_2/x - k_2 + k_1) = k_2(t - C) \qquad (2b)$$

It is easily seen that this reduces to (1a) if $k_2 \gg k_1$, and that as a good approximation

$$C = t_{1/2} - (\ln k_2)/k_2$$

Substitution of this value for $C$ and solving for $k_1$ leads to the expression

$$k_1 = k_2\left[1 - \frac{1}{x} + e^{-k_2(t_{1/2} - t)}\right] \qquad (2c)$$

which permits calculation of $k_1$. Six experimental points (Fig. 1a) give $k_1 = 0.102 \pm 0.008 \times 10^{-4}$ sec.$^{-1}$. For the same preparation of stibosobenzene $k_2$ was found to be $4.68 \pm 0.14 \times 10^{-4}$ sec.$^{-1}$, and therefore $k_1 = 0.02\ k_2$, which bears out the assumption that $k_2 \gg k_1$. Since all experimental curves for stibosobenzene preparations hydrolyzed by ammonia gave the same characteristic curvature it seems probable that the ratio $k_1/k_2$ remains approximately constant regardless of the amount of catalyst present.

The early portion of the rate curves obtained with preparations hydrolyzed with sodium hydroxide showed a rapid initial rate, an effect opposite to that obtained with preparations hydrolyzed with aqueous ammonia (Fig. 1b). In spite of this the rate constants $k_2$ calculated from equation (1) from the main portion of the curve, but neglecting the early portion, were slower than those from the products hydrolyzed with ammonia (Table II). This may be explained by the assumption that sodium hydroxide molecules, while actually catalyzing the reaction more than ammonia molecules, cannot freely diffuse through the reaction mixture, and are thus effectively prevented from catalyzing more than the initial phase of the reaction. It might be possible to remove all traces of catalyst by partially rearranging samples of stibosobenzene, and extracting the bis-(diphenylantimony)-oxide together with the entrapped catalyst. The rate constant of the resulting product might then approximate that of pure stibosobenzene, free from catalyst.

To test this postulate large samples of stibosobenzene (10–15 g.) prepared by hydrolysis with sodium hydroxide were permitted to rearrange partially, extracted with ether and dried. The amount of stibosobenzene in the resulting mixture was determined by antimony analysis. The rate of disproportionation of the stibosobenzene in these mixtures containing antimony trioxide was then determined in the usual manner. A definite reduction of the rate constant was observed, which was not due to negative catalysis by antimony trioxide, since increasing amounts of the latter did not further retard the reaction. Nevertheless, the rate constants obtained from two different mixtures prepared in this manner were not in agreement (Table VI). It appears that the deter-

TABLE VI

THE RATE OF DISPROPORTIONATION OF STIBOSOBENZENE AT 78° AFTER PARTIAL DISPROPORTIONATION

| Original material | | Resulting material | |
|---|---|---|---|
| $10^4k_2$, sec.$^{-1}$ | Standard error | $k_2 \times 10^4$ sec.$^{-1}$ | Standard error |
| 2.06 | 0.09 | 0.341 | 0.015 |
| 0.254 | .011 | .155 | .008 |

mination of the true rate constant for the disproportionation of stibosobenzene awaits the preparation of pure samples of the compound.

**Acknowledgment.**—The authors wish to acknowledge the assistance by Claire T. Brooks and Joseph J. Holechek throughout the course of this work. The interest of Harry Eagle is also gratefully acknowledged.

## Summary

1. The kinetics of the disproportionation of stibosobenzene were determined. From 20 to 100% completion the reaction was shown to obey a rate law: $-dx/dt = k_2x(1 - x)$, where $x$ is the fraction of stibosobenzene remaining at time $t$.

2. Preparations of stibosobenzene hydrolyzed with aqueous ammonia obeyed a rate law: $-dx/dt = k_1x^2 + k_2x(1 - x)$ over the entire course of the reaction, and the ratio $k_1/k_2$ was found to be 0.02.

3. The reaction was shown to be catalyzed by the product, bis-(diphenylantimony)-oxide, and by bases such as sodium hydroxide, ammonia and pyridine.

4. Rate constants were reproducible for each preparation, but varied widely with different preparations, an effect which is probably due to traces of impurities.

5. The apparent energy of activation was found to be 23.5 kcal./mole.

6. As mechanism of the reaction a chain reaction is proposed which is initiated by the thermal dissociation of phenyl groups from stibosobenzene and bis-(diphenylantimony)-oxide.

RECEIVED[9] SEPTEMBER 29, 1948

(9) Original manuscript received May 5, 1948.

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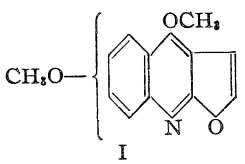
[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN, AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALCUTTA, INDIA]

# On the Constitution of the Active Principles Isolated from the Matured Bark of *Aegle marmelos*, Correâ

BY ASIMA CHATTERJEE AND SUDHANGSU SEKHAR MITRA

The tree *Aegle marmelos*, Correâ (*Rutaceae*) commonly known as Bael, is indigeneous to India and found wild all over the Sub-Himalayan forests, in Central and South India. Its wood is yellowish-white with a strong aromatic scent. It is reputed to be a valuable Ayurvedic medicine for dysentery and various intestinal complaints. The bark as well as the fruits are used for this purpose. An examination of the fruits by various workers has revealed the occurrence of a coumarin[1] termed "marmelosin" which is identical with imperatorin,[2] a furocoumarin isolated from *Imperatoria ostruthium*[3] and *Angelica archangelica*.[4] The isolation of three crystalline constituents of the *Aegle marmelos* bark was described earlier.[5] We wish to report that one is an alkaloid identical[6] with γ-fagarine[7]; the second compound is marmesin, a coumarin which has not been isolated so far from other natural sources; and the third compound is umbelliferone.

Hydrochloric acid washing of ethereal bark extracts yielded a basic portion from which an alkaloid, m. p. 142.5–143°, was separated in 0.3% yield, which has been shown by Chakravarty[6] to be identical with γ-fagarine[7] (I).




I

The remaining ether extract upon concentration and standing in the refrigerator deposited crystals of marmesin, m. p. 189.5°, in a 0.6% yield. The mother liquor, after alkali washings and steam distillation, deposited umbelliferone m. p. 230° (yield, 0.06%).

The molecular formula of marmesin appeared to be $C_{14}H_{14}O_4$ which was confirmed by Rast's method and also by titration. Marmesin is optically active, $[\alpha]^{34}D$ +26.8° (in chloroform). This compound does not contain methoxy or methylenedioxy groups. It yields a monoacetyl derivative and readily undergoes dehydration producing anhydromarmesin. These facts indicate the presence of an hydroxyl group. Since the compound does not react with ferric chloride or diazomethane, it must contain an alcoholic group. Marmesin is neutral to litmus and is insoluble in aqueous alkali but readily dissolves in alcoholic alkali with a stable yellow color. This solution precipitated, on acidification, the original substance indicating a lactone structure. Marmesin dissolves in concentrated sulfuric acid with a yellow color and a deep violet fluorescence. When refluxed with aqueous alkali and a little mercuric oxide, marmesin passed into solution and, on acidification with hydrochloric acid, yielded an acid which did not undergo ring closure to give the

(1) B. B. L. Dikshit and S. Dutt, *J. Indian Chem. Soc.*, **7**, 759 (1930); **9**, 271 (1932).

(2) E. Späth, P. K. Bose, W. Grüber and N. C. Guha, *Ber.*, **70**, 1021 (1937).

(3) E. Späth and H. Holsen, *ibid.*, **66**, 1137 (1933).

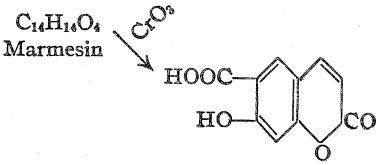
(4) E. Späth and F. Vierhapper, *ibid.*, **70**, 248 (1937).

(5) A. Chatterjee (née Mookerjee), *Current Science*, **12**, 209 (1943).

(6) K. K. Chakravarty, *J. Indian Chem. Soc.*, **21**, 401 (1944).

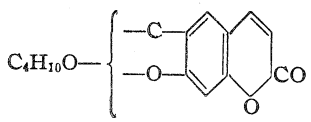
(7) V. Deulofeu, R. Labriola and J. Langhe, THIS JOURNAL, **64**, 2326 (1942).

original substance. Consequently, a corresponding *trans* coumaric (*trans*-marmesic acid) acid, $C_{14}H_{16}O_5$, must have been formed under the influence of mercuric oxide. All these reactions are indicative of a coumarin ring which was secured by the oxidation of marmesin with chromic acid to umbelliferone-6-carboxylic acid (II).



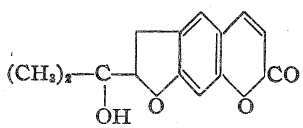

II

Consequently, the partial structure for marmesin can now be represented by (III).



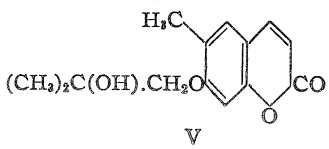

III

When fused with alkali, marmesin yields resorcinol, and, upon mild oxidation with chromic acid, acetone. The latter indicates that the group, $(CH_3)_2C(OH)$–, might be a part of the $C_4H_{10}O$-residue. The presence of a dimethylhydroxymethyl radical would also explain the easy dehydration of marmesin. One of the two phenolic hydroxyl groups which appears in resorcinol and umbelliferone-6-carboxylic acid is apparently involved in an ether linkage which in all probability leads to structure (IV) for marmesin.



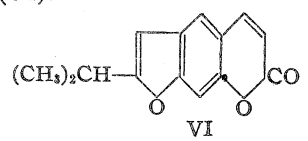

IV

By catalytic hydrogenation marmesin yields dihydromarmesin ($C_{14}H_{16}O_4$); however, anhydromarmesin adds four atoms of hydrogen ($C_{14}H_{16}O_3$). This observation eliminates structure (V).




V

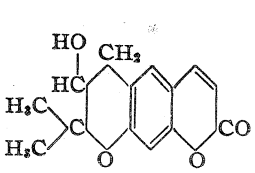
Formula (IV) represents a substituted dihydrofurocoumarin where the $(CH_3)_2C(OH)$-group is attached to the $\beta$-carbon atom in the dihydrofuran ring which has been also confirmed by the established identity of anhydromarmesin with desoxyoreoselone[8] (VI).



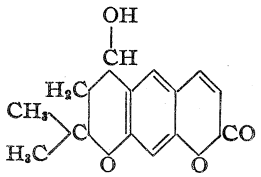

VI

(8) E. Späth, K. Klager and C. Schlösser, *Ber.*, **64**, 270 (1931); E. Späth and K. Klager, *ibid.*, **66**, 749 (1933).

The possibility of an alternate structure (VII) or (VIII) involving a chroman ring can be ruled out since anhydromarmesin is not identical with xanthyletin.[9] From the study of marmesin it appeared that it might be an optical isomer of L-nodakenetin,[10] the degradation product of the glucoside nodakenin, isolated from *Peucedanum decursivum*.[11] Therefore, our marmesin sample was compared with authentic nodakenetin obtained from Dr. W. Grüber (Vienna) to whom our thanks are due. Although the two compounds and their corresponding derivatives are very similar, they show a large melting point depression (35°). The mixture of the two samples in equal amounts shows no optical activity. It should be mentioned that free nodakenetin has not yet been found in nature but only as the glucoside mentioned[11]; however, its D-isomer, marmesin, occurs in the free state.




VII




VIII

An interesting observation was made in connection with umbelliferone, *viz.*, that the latter was not present as such in the residual oil but could be obtained from it by steam distillation or saponification.[12] It is, therefore, probable that the bark of *Aegle marmelos* contains another as yet not isolated coumarin which can be readily hydrolyzed to umbelliferone.

## Experimental

**Extraction of the Matured Bark of Aegle Marmelos.**—Two kg. of air-dried, powdered bark was extracted with ether for forty-eight hours in a Soxhlet apparatus. The deep-brown extract was shaken with 0.1% hydrochloric acid (300 ml.) to remove $\gamma$-fagarine. This was repeated (about 5 times) until the acid digest gave only an insignificant precipitate with Dragendorff's reagent. Then the brown ether solution (P) was washed with water, dried over sodium sulfate, concentrated to 500 ml. and kept in a refrigerator for four weeks.

**Isolation of Marmesin.**—The brown ethereal solution (P) deposited 12 g. of marmesin which was filtered off, and the mother liquor (Q) was kept for further investigation. Marmesin was purified by successive crystallizations from acetone, ethyl alcohol, benzene, and ethyl acetate when rhombic plates of a constant m. p. 189.5° were obtained. It sublimes unchanged in a 0.1 mm. vacuum at 150–160°. It is freely soluble in chloroform, fairly in acetone or alcohol, sparingly in benzene, ethyl acetate, ether, and is insoluble in petroleum ether or water; $[\alpha]^{34}D$ +26.8° (in chloroform).

*Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.30; H, 5.69; mol. wt., 246. Found: C, 68.42; H, 5.74; mol. wt. (Rast), 252, 250.

**Molecular Weight by Titration.**—Marmesin (0.15 g.) was dissolved in 5 ml. of alcohol and refluxed for half an hour

(9) E. Späth, P. K. Bose, E. Dobrovolny and A. Chatterjee (née Mookerjee), *ibid.*, **72**, 1452 (1939).

(10) E. Späth and P. Kainrath, *ibid.*, **69**, 2062 (1936).

(11) J. Arima, *Bull. Chem. Soc. Japan*, **4**, 16 (1929).

(12) E. Späth and L. Socias, *Ber.*, **67**, 59 (1934).

with 25 ml. of 1 *N* aqueous potassium hydroxide. The pale yellow solution was cooled and the excess of alkali was back titrated with sulfuric acid (phenolphthalein). Found: mol. wt., 250, 253.

**Action of Dilute Alkali on Marmesin.**—Marmesin (0.25 g.) in 5 ml. of methyl alcohol was mixed with 40 ml. of 1% aqueous potassium hydroxide and refluxed for half an hour. The substance passed into solution and gradually became yellow. It was acidified with hydrochloric acid (congo red), allowed to stand overnight, and extracted with ether. The dry residue of this extract crystallized from acetone in colorless, rhombic plates which melted at 189–189.5°, alone or when mixed with a pure specimen of marmesin.

**Acetylation of Marmesin.**—A mixture of marmesin (0.25 g.), 5 ml. of acetic anhydride and 0.5 g. of freshly fused sodium acetate was refluxed for five hours. The mixture was poured into ice-cold water and stirred. The separated solids were collected, washed with ice-cold water and crystallized from hot water. The colorless flakes (0.25 g.), m. p. 130°, were washed with cold water and dried.

*Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.55. Found: C, 66.91, H, 5.42.

**Dehydration of Marmesin.**—Marmesin (0.25 g.) dissolved in 50 ml. of dry benzene was refluxed with 2.5 g. of phosphorus pentoxide for five hours. The decanted, clear solution was concentrated to 5 ml. Transparent plates of anhydromarmesin separated which were filtered and washed with cold benzene; constant m. p., 138–140°.

*Anal.* Calcd. for $C_{14}H_{12}O_3$: C, 73.69; H, 5.26. Found: C, 73.80; H, 5.60.

**Catalytic Hydrogenation of Marmesin.**—Marmesin (0.3 g.), dissolved in glacial acetic acid (10 ml.), was treated with hydrogen and Adams platinum oxide catalyst (0.1 g.) which had been saturated previously with hydrogen. The absorption of hydrogen (30.0 ml. at 30°, 760 mm.) corresponded almost exactly to 1 $H_2$. The solution was filtered, diluted with water and extracted with ether. The ethereal solution was washed successively with sodium bicarbonate and water, dried over sodium sulfate, concentrated to 5 ml., diluted with 1 volume of petroleum ether, and kept overnight. Colorless, rhombic plates separated, m. p. 135°.

*Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.75; H, 6.45. Found: C, 68.34; H, 6.20.

**Catalytic Hydrogenation of Anhydromarmesin.**—Anhydromarmesin (0.450 g.) in 10 ml. of glacial acetic acid was treated as above in the presence of 0.15 g. of catalyst. Within a few minutes 98.0 ml. of hydrogen was absorbed (30°, 760 mm.) corresponding to 4 gram atoms of hydrogen. The solution was treated as described in the previous section. The product crystallized from a mixture of benzene and petroleum ether in colorless flakes, m. p. 116–117°.

*Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.40; H, 6.90. Found: C, 72.70, H, 7.07.

***trans*-Coumaric Acid Derivative of Marmesin (*trans*-marmesic acid).**—A mixture of marmesin (0.39 g.), 30 ml. of aqueous 2 *N* sodium hydroxide and a little mercuric oxide was refluxed for two hours and filtered. The yellow filtrate was acidified with hydrochloric acid (congo red) and kept overnight. The precipitated yellowish-green flakes were recrystallized from dilute methyl alcohol and melted at 204° (dec.).

*Anal.* Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.02. Found: C, 63.95; H, 6.31.

**Fusion of Marmesin with Potassium Hydroxide; Isolation of Resorcinol.**—Marmesin (1.00 g.) was fused with potassium hydroxide (5.00 g.) in a nickel crucible and heated to 250° on a metal-bath for one hour. The product was cooled and digested with water. The brown solution was acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with 10% aqueous sodium bicarbonate and then with water, dried and concentrated. The separated crystals were recrystallized from alcohol and petroleum ether (b. p. 60°) and then from ethyl acetate (m. p. 109°). They gave a violet color with ferric chloride and reduced ammoniacal silver nitrate. The sample gave no melting point depression with resorcinol.

*Anal.* Calcd. for $C_6H_6O_2$: C, 65.45; H, 5.45. Found: C, 65.50; H, 5.61.

**Oxidation of Marmesin with Chromic Acid.**—A solution of marmesin (0.5 g.) in glacial acetic acid (8 ml.) was added to chromic acid (0.25 g. in 10 ml. of 50% acetic acid) and kept at room temperature for sixty hours in a closed flask. The mixture was cooled in ice and was slowly almost neutralized with strong sodium hydroxide. The solution was distilled until 15 ml. was collected in a receiver containing 4 drops of freshly distilled benzaldehyde and 4 drops of 10% sodium hydroxide. On keeping the mixture overnight in the refrigerator, a semi-solid separated that was extracted with ether. The dried extract was evaporated. The oily residue was treated with 2 drops of benzaldehyde (in dilute, acetone-free methyl alcohol) and cooled in ice when immediately glistening needles separated which were recrystallized from dilute methanol (acetone-free); pale yellow, shining needles, m.p. 112°. The substance was identified as dibenzal acetone by the mixed melting point test.

**Isolation of Umbelliferone-6-carboxylic Acid by Oxidation of Marmesin.**—Marmesin (1.5 g.) was treated with 300 ml. of 3% sulfuric acid and the mixture was heated. To the boiling mass, 5 g. of potassium bichromate (in 60 ml. of water) was slowly added and the brown-red solution was refluxed for six hours. Then the dark-green solution was cooled and shaken with ether to remove unchanged marmesin. The green aqueous filtrate was concentrated on a water-bath to 100 ml. and kept overnight at 0°. The separated pale yellow solid (0.5 g.) was washed with cold water. It crystallized from methyl alcohol in colorless needles, m.p. 260° (dec.). It gave a violet color with ferric chloride and dissolved readily in aqueous alkali or alkali bicarbonate (with effervescence) with a stable yellow color. The compound was identified as umbelliferone-6-carboxylic acid by m.p. and mixed m.p. tests.[13]

*Anal.* Calcd. for $C_{10}H_6O_5$: C, 58.27; H, 2.95. Found: C, 58.52; H, 3.23.

**Methylation of Umbelliferone-6-carboxylic Acid.**—The compound (0.05 g.) in methanol was treated with excess diazomethane (in ether). After two days, the solvent was removed, and the residue crystallized from a mixture of ether and methyl alcohol. The pale yellow needles melted at 165–166° and gave no depression with dimethyl-7-hydroxy-coumarincarboxylic acid (m.p. 168°).

**Decarboxylation of 7-Hydroxy-coumarin-6-carboxylic Acid.**—Umbelliferone 6-carboxylic acid (0.2 g.) isolated from chromic acid oxidation products of marmesin, was heated above its m.p. to 265–270° for thirty minutes. From the brown mass a colorless solid distilled at 150–160° (0.1 mm.). It crystallized from dilute methyl alcohol in needles, m.p. 230°. It had the same melting point when mixed with synthetic umbelliferone.

*Anal.* Calcd. for $C_9H_6O_3$: C, 66.64; H, 3.74. Found: C, 66.21; H, 3.98.

The methyl derivative of the decarboxylation product, prepared by the action of diazomethane, melted at 118–119° and showed no change when mixed with synthetic methyl-umbelliferone.

**Isolation of Umbelliferone from the Fraction (Q).**—The mother liquor, Q, left after removal of marmesin, was freed from the solvent, and the oil (R) obtained weighed 300 g. Two hundred grams of this oil was steam-distilled for twelve hours when an oil (6 ml.) was collected, having a bitter taste, and a pleasant smell, resembling that of a mixture of eucalyptus and lemon oil. After removal of this essential oil, the residue was cooled and a crystalline substance (0.80 g.) obtained. It was purified by crystallizations from methyl alcohol, ethyl acetate and

(13) H. von Pechmann, *Ber.*, **17**, 932 (1884).

water, yielding shining needles of umbelliferone, m.p. 230°.

**Isolation of Umbelliferone from Oil (R) by Saponification.**—To the oil (100 g.) (15°), 200 ml. of 20% methanolic potassium hydroxide was added with constant shaking. The mixture was allowed to stand for forty-five minutes, poured into 1.5 liters of ice-water and extracted five times with ether to remove unsaponifiable matter. The alkaline aqueous portion was acidified with hydrochloric acid (congo red) and distilled *in vacuo* to remove the greater portion of methyl alcohol. The next day the separated oil was extracted with ether and the extract was washed with 2 × 100 ml. of 25% potassium carbonate (W). The ethereal extract was washed with water, dried and distilled. Only a very small, gummy residue was left.

**Isolation of Umbelliferone from Fraction (W).**—The brown potassium carbonate washings (W) were acidified with hydrochloric acid (congo red) whereby the solution became turbid. It was extracted with 100 ml. of ether; the extract was twice washed with water, dried and distilled. A brownish, solid residue of umbelliferone (0.4 g.), mixed with a little viscous oil, was left, which crystallized from dilute methanol in silky, colorless needles; m.p. 230°.

**Acknowledgment.**—It is a pleasure to thank Professor L. M. Parks for suggestions and the laboratory facilities granted, and Professor A. H. Uhl, Professor S. N. Bose, Professor P. C. Mitter, and Dr. P. K. Bose for their interest in this investigation.

## Summary

From the matured bark of *Aegle marmelos*, Correâ, three crystalline compounds have been isolated in pure state: 1, The alkaloid γ-fagarine; 2, A coumarin which had not been observed before in the free state in nature. It is an optical isomer of nodakenetin; and 3, Umbelliferone.

MADISON, WISCONSIN, AND
CALCUTTA, INDIA

RECEIVED JUNE 4, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF UTAH]

# 3,4-Dihydro-1,3,2H-Benzoxazines. Reaction of *p*-Substituted Phenols with N,N-Dimethylolamines

BY W. J. BURKE

Major attention in reactions involving phenol and formaldehyde has quite naturally been directed toward polymeric products in view of their wide industrial application. The marked reactivity of the intermediates involved, however, indicates the desirability of investigating further the possibility of isolating well defined monomeric compounds from such systems.

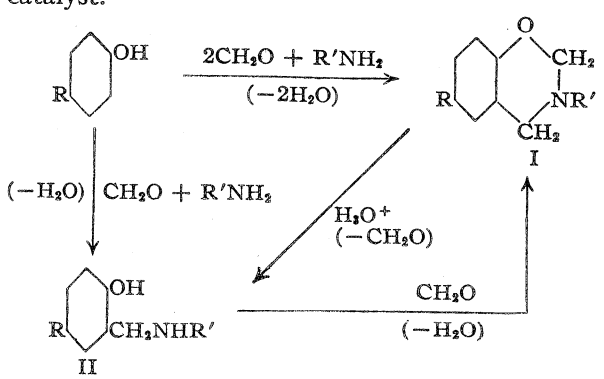
Interaction of secondary aliphatic amines and formaldehyde with phenols has been shown by Caldwell and Thompson,[1] and by Bruson and MacMullen[2] to result in the introduction of one or more dialkylaminomethyl substituents in positions ortho or para to the hydroxyl group. The reaction involved is shown as

$$C_6H_5OH + CH_2O + R_2NH \longrightarrow HOC_6H_4CH_2NR_2$$

Although generally considered to be a Mannich type of condensation, this and similar reactions involving the interaction of a secondary amine and formaldehyde with a compound containing active hydrogen were studied by others[3,4] several years before the initial related work of Mannich.[5]

Analogous studies involving primary rather than secondary aliphatic amines appear to have been limited to the use of 2-aminoethanol.[6] Reaction of equimolar quantities of this amine with formaldehyde and certain *o*- or *p*-substituted phenols resulted in crystalline compounds having *o*- or *p*-beta-hydroxyethylaminomethyl groups. Other phenols, such as the three cresols, gave resins containing nitrogen or sirups which could not be purified. The condensation of selected phenols and formaldehyde with sodium sulfanilate and related aminoaromatic sulfonic acid salts has also been reported[7] but the exact composition of the products was not determined.

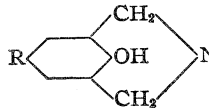
The present work has been concerned with the reaction of *p*-substituted phenols with formaldehyde and primary amines in a molar ratio of 1:2:1, respectively. This procedure led to the formation in good yield of 3,4-dihydro-3,6-disubstituted-1,3-2H-benzoxazines (I), a new series of compounds.[8] In an alternate method, equimolar quantities of the *p*-substituted phenol, formaldehyde, and primary amine reacted to give as an intermediate an *o*-alkylaminomethyl-*p*-substituted phenol (II). Conversion of II to I took place readily by treatment with formaldehyde in the presence of a basic catalyst.




(1) Caldwell and Thompson, THIS JOURNAL, **61**, 765 (1939).
(2) Bruson and MacMullen, *ibid.*, **63**, 270 (1941).
(3) Bayer and Co., German Patent 92,309 (1897).
(4) Einhorn, Bischkopff and Szelinski, *Ann.*, **343**, 223 (1905).
(5) Mannich and Krosche, *Arch. Pharm.*, **250**, 647 (1912).
(6) Bruson, THIS JOURNAL, **58**, 1741 (1936).
(7) Bruson, U. S. Patent 2,112,434 (1938).
(8) The nomenclature employed in this paper follows that kindly suggested by Dr. Leonard T. Capell of *Chemical Abstracts*.

For values for R and R′, see Table I.

Inasmuch as N-methylolamines are capable of attacking *p*-substituted phenols at the free ortho positions[1,2] the possibility of the alternate structure III




III

isomeric with I, might be considered. Study of the hydrolysis of the products in the presence of aqueous acid showed that one mole of formaldehyde was readily eliminated with the formation of a compound identical with the corresponding *p*-substituted-*o*-alkylaminomethylphenol II, prepared by an independent synthesis. This behavior is in accord with a 3,4-dihydro-1,3-2H-benzoxazine structure, which contains the labile —O—$CH_2$—N< group capable of releasing formaldehyde under the mild hydrolytic conditions used. Essentially complete recovery (95%) of starting material when 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine was treated with acetic anhydride in pyridine is also compatible with the formula assigned.

In the synthesis of 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines, the primary amine and formaldehyde were first condensed to the N,N-dimethylolamine, which was then allowed to react with the *p*-substituted phenol. As a means of obtaining homogeneous reaction media it was found convenient to employ dioxane as solvent. When the reagents were heated under gentle reflux the condensation took place readily and was essentially complete within fifteen minutes in certain instances. Methyl-, cyclohexyl- and benzylamines were used as examples of aliphatic, alicyclic and aralkyl primary amines in condensations with formaldehyde and a variety of *p*-substituted phenols. A summary of the products prepared is given in Table I. Both aqueous formaldehyde and paraformaldehyde were employed satisfactorily. The 3,4-dihydro-1,3,2H-benzoxazines were quite stable toward hot aqueous alkali and formed hydrochlorides readily.

Condensation of benzylamine with 2,6-dimethylol-4-methylphenol might be expected to lead to a compound of the type III. When these two reagents were heated together, however, little or no monomeric condensate appeared to have formed since the major portion (86%) of the dimethylolphenol was recovered. This behavior is in contrast to the related reactions in which a combination of either dimethylolurea and a primary amine or urea and a dimethylolamine readily resulted in the formation of a tetrahydro-5-substituted-2(1)*s*-triazone.[9]

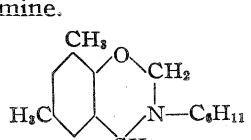
TABLE I

3,4-DIHYDRO-3,6-DISUBSTITUTED-1,3,2H-BENZOXAZINES FROM *p*-SUBSTITUTED PHENOLS AND N,N-DIMETHYLOLAMINES

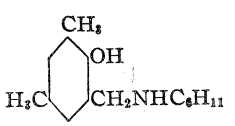
| Y of *p*-$YC_6H_4OH$ | Primary amine | Yield, % | M. p.,[a] °C. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | Benzyl | 79 | 71[b] | $C_{16}H_{17}NO$ | 80.30 | 80.18 | 7.16 | 7.41 | 5.85 | 6.20 |
| $C(CH_3)_3$ | Cyclohexyl | 92 | 94[c] | $C_{18}H_{27}NO$ | 79.07 | 79.11 | 9.96 | 9.70 | 5.12 | 5.06 |
| $C_6H_5$ | Cyclohexyl | 68 | 72[d] | $C_{20}H_{23}NO$ | ... | ... | .. | .. | 4.77 | 4.80 |
| $NHCOCH_3$ | Methyl | 63 | 145[e] | $C_{11}H_{14}N_2O_2$ | 64.06 | 64.15 | 6.84 | 6.54 | .. | .. |
| $NHCOCH_3$ | Benzyl | 61 | 168[e] | $C_{17}H_{18}N_2O_2$[f] | ... | ... | .. | .. | 9.92 | 9.98 |
| Br | Cyclohexyl | 54 | 92[e] | $C_{14}H_{18}NOBr$ | ... | ... | .. | .. | 4.73 | 4.63 |

[a] Uncorrected. [b] Recrystallized from methanol. [c] Recrystallized from 95% ethanol. [d] Recrystallized from ethyl acetate–methanol (1:1, by vol.). [e] Recrystallized from ethyl acetate–ethanol (95:5, by vol.). [f] This compound was prepared by Mr. Carl Weatherbee.

With a view to obtaining additional information regarding structure, 2,4-dimethylphenol was treated with formaldehyde and cyclohexylamine in a 1:2:1 molar ratio, respectively. The condensation resulted in the elimination of two molecules of water indicating the formation of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine (IV), since only a single ortho position was available for reaction. Upon hydrolysis of IV in aqueous acid, formaldehyde was evolved with the formation of V, which was also synthesized by the condensation of equimolar quantities of 2,4-dimethylphenol, formaldehyde, and cyclohexylamine.




IV




V

The heterocyclic products from *p*-substituted phenols accordingly behave as 3,4-dihydro-1,3,-2H-benzoxazines upon hydrolysis.

**Acknowledgment.**—The assistance given by the Research Corporation in the form of a Frederick Gardener Cottrell Research Grant is gratefully acknowledged.

## Experimental

**3,4-Dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine.**—The preparation of this compound by the two procedures given below indicates the general methods used in the synthesis of the 3,4-dihydro-1,3,2H-benzoxazines.

**Procedure A.**—Cyclohexylamine (39.6 g., 0.4 mole) was added portionwise with cooling to 200 ml. of dioxane containing 60 ml. of aqueous 37% formaldehyde (0.8 mole). After addition of 60 g. of *p*-*t*-butylphenol (0.4 mole), the mixture was heated under reflux for two hours. Upon cooling to room temperature, a crystalline solid (85 g.) separated. The product was recrystallized

(9) Burke, THIS JOURNAL, 69, 2136 (1947).

from 95% ethanol; m.p. 94°, yield 78%. The product was insoluble in water, 10% aqueous hydrochloric acid, and 10% aqueous potassium hydroxide but was soluble in acetic acid, benzene, and chloroform.

*Anal.* Calcd. for $C_{18}H_{27}NO$; C, 79.07; H, 9.96; N, 5.12. Found: C, 79.11; H, 9.70; N, 5.06.

**Procedure B.**—Paraformaldehyde (6 g., 0.2 mole) was dissolved in 8 ml. of warm methanol containing 0.1 g. of potassium hydroxide. The solution was cooled during the portionwise addition of 9.9 g. of cyclohexylamine (0.1 mole). After addition of 15 g. *p-t*-butylphenol (0.1 mole), the resulting solution was heated under reflux for fifteen minutes. Upon cooling the reaction mixture solidified. Recrystallization from 95% ethanol yielded 23 g. of product; m.p., 94°. An additional 2 g. was obtained from the mother liquor; yield 92%. A mixed m.p. determination with the product prepared by procedure A showed no depression.

In order to determine the effect of acetylating conditions on the product, the following experiment was carried out. A solution of 2.73 g. of the product (0.01 mole) in 10 ml. of pyridine and 6.1 g. of acetic anhydride (0.06 mole) was heated on a boiling water-bath for one and a half hours. The reaction mixture was poured into crushed ice and the resulting solid (2.6 g. or 95% recovery) removed by filtration. The product was recrystallized from ethanol; m.p. 94°. A mixed m.p. determination with starting material showed no depression.

**2-Cyclohexylaminomethyl-4-*t*-butylphenol.**—To 30 ml. of dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) was added 9.9 g. of cyclohexylamine (0.1 mole) with sufficient cooling to keep the temperature below 25°. After addition of 15 g. of *p-t*-butylphenol (0.1 mole) in 20 ml. dioxane with agitation, the resulting solution was heated under gentle reflux for one hour. A sticky mass of crystals was obtained upon removal of dioxane and water at room temperature. The product was recrystallized from ethanol; m.p. 112°; yield, 17 g. (65%).

*Anal.* Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 78.00; H, 10.01.

**Hydrolysis of 3,4-Dihydro-3-cyclohexyl-6-*t*-butyl-1,3,-2H-benzoxazine.**—To 2.73 g. of 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine (0.01 mole) was added 10 ml. of 95% ethanol and 5 ml. of aqueous hydrochloric acid (0.11 mole). The resulting solution was heated in a 50 ml. modified Claisen flask and 20 ml. of ethanol–water (1:1, by vol.) added during the course of the distillation. The distillate was collected in 25 ml. of water. The distillation was interrupted after a solid began to precipitate out and the volume of the residue was about 10 ml. Ethanol (20 ml.) was added and the resulting solution was removed from the flask. Addition of 6.1 ml. of 10% alcoholic potassium hydroxide (0.11 mole) to the solution resulted in the immediate formation of a precipitate. The product was washed thoroughly with water and recrystallized from ethanol; m.p. 112°; yield 2.2 g. (84%). A mixed melting point determination with 2-cyclohexylaminomethyl-4-*t*-butylphenol showed no depression.

Treatment of a portion of the distillate with 2,4-dinitrophenylhydrazine gave a yellow crystalline product, which was recrystallized from ethanol; m.p. 166°. A mixed m.p. determination with a specimen of the 2,4-dinitrophenylhydrazone of formaldehyde showed no depression.

**Reaction of 2-Cyclohexylaminomethyl-4-*t*-butylphenol with Formaldehyde.**—To 0.6 g. of paraformaldehyde (0.02 mole) dissolved in 10 ml. of methanol containing 0.05 g. of potassium hydroxide was added 2.61 g. of 2-cyclohexylaminomethyl-4-*t*-butylphenol (0.01 mole). Most of the phenol went into solution but within a minute the reaction mixture became a solid mass. Methanol (35 ml.) was added and the resulting solution heated under reflux for one and a half hours. Upon addition of 4 ml. of water and cooling, a white crystalline product (2.6 g.) separated out. The product was recrystallized from ethanol; m.p., 94°; yield 95%. A mixed m.p. determination with 3,4-dihydro-3-cyclohexyl-6-*t*-butyl-1,3,2H-benzoxazine, prepared as described above, showed no depression.

**3,4-Dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine.**—To 19.8 g. of cyclohexylamine (0.2 mole) in 100 ml. of dioxane was added 30 ml. of 37% aqueous formaldehyde (0.4 mole) with cooling. After addition of 22.4 g. of 2,4-dimethylphenol (0.2 mole), the resulting solution was heated under reflux for one and a half hours. A light brown liquid (46 g.) was obtained by removal of solvent under reduced pressure. Distillation of the product gave a light-yellow oil; b.p. 140–142° at 0.3 mm., yield 81%.

*Anal.* Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.01; H, 9.22.

In another run carried out under analogous conditions, the crude oil was dissolved in ethanol and an equivalent quantity of concentrated aqueous hydrochloric acid added with cooling. The product was isolated as the white crystalline hydrochloride; m.p. 192–195° (dec.); yield 80%.

*Anal.* Calcd. for $C_{16}H_{24}NOCl$: neut. equiv., 282. Found: neut. equiv., 280.

A mixed m.p. determination with the hydrochloride prepared from the distilled oil showed no depression. Treatment of the hydrochloride with an equivalent quantity of 10% alcoholic potassium hydroxide yielded the free base as a light-yellow oil. The free base was insoluble in water and aqueous 10% potassium hydroxide and was readily soluble in benzene, acetic acid, and chloroform.

**Hydrolysis of 3,4-Dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine Hydrochloride.**—A solution of 2.82 g. of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride in 25 ml. of water was heated in a distilling flask. An additional 25 ml. of water was added during the course of the distillation, which was continued until about 10 ml. of liquid remained. Removal of water yielded 2.6 g. of a crystalline product, which was recrystallized from water and then from ethanol; m.p. 214–215°, yield 96%.

*Anal.* Calcd. for $C_{15}H_{24}NOCl$; neut. equiv., 270. Found: neut. equiv., 268.

The presence of formaldehyde in the distillate was confirmed by the preparation of a 2,4-dinitrophenylhydrazone; m.p., 166°. A mixed melting point determination with the 2,4-dinitrophenylhydrazone of formaldehyde showed no depression.

To 1.0 g. (0.037 mole) of the above 2-cyclohexylaminomethyl-4,6-dimethylphenol hydrochloride in 15 ml. of ethanol was added 2.1 ml. of 10% alcoholic potassium hydroxide (0.037 mole). The precipitate of potassium chloride was removed by filtration and water added to the filtrate to incipient opalescence. Upon cooling, the crystalline free base (0.65 g.) was obtained; m.p. 51°, yield 68%.

*Anal.* Calcd. for: $C_{15}H_{23}NO$: C, 77.20; H, 9.93. Found: C, 77.36; H, 9.98.

**Direct Synthesis of 2-Cyclohexylaminomethyl-4,6-dimethylphenol.**—To 40 ml. of dioxane containing 7.5 ml. of 37% aqueous formaldehyde (0.1 mole) and 9.9 g. of cyclohexylamine (0.1 mole) was added 11.2 g. of 2,4-dimethylphenol (0.1 mole). The reaction mixture was heated under reflux for two hours. The solvent was removed under reduced pressure and the resulting solid recrystallized from ethanol; m.p. 51°, yield 8.5 g. (36%). A mixed m.p. determination with the free base obtained indirectly through hydrolysis of 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride showed no depression.

**Reaction of 2-Cyclohexylaminomethyl-4,6-dimethylphenol with Formaldehyde.**—To a solution of 0.6 g. of paraformaldehyde (0.02 mole) in 16 ml. of methanol containing 0.05 g. of potassium hydroxide was added 2.33 g. (0.01 mole) of 2-cyclohexylaminomethyl-4,6-dimethylphenol. The reaction mixture was refluxed for one and a half hours and then cooled in ice and water. Addition of 0.87 ml. of concentrated hydrochloric acid (0.01 mole) in 3 ml. of methanol resulted in the formation of a white crystalline product (1.8 g.) which was removed by filtra-

tion, and washed with cold water and then acetone; m.p. 192–195° (dec.). An additional 0.4 g. was obtained from the mother liquor: yield, 78%. A mixed m.p. determination with 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride showed no depression.

**Treatment of 2,6-Dimethylol-4-methylphenol with Benzylamine.**—A solution containing 3.36 g. of 2,6-dimethylol-4-methylphenol[10] (0.02 mole), 2.14 g. of benzylamine (0.02 mole) and 5 ml. of benzene was heated under reflux for three hours. Upon cooling and filtering 2.4 g. of solid was obtained, which after crystallization from ethanol melted at 131–132°. Admixture of 2,6-dimethylol-4-methylphenol with either the crude or recrystallized product did not result in a depression of the m. p. of the latter products. An additional 0.4 g. of the same material was obtained from the filtrate; recovery, 86%.

(10) This compound (m. p. 132–133°) was prepared by the procedure of Ullman and Brittner, *Ber.*, **42**, 2539 (1909). These authors recorded a m. p. of 135°.

## Summary

1. Reaction of *p*-substituted phenols with formaldehyde and primary aliphatic amines in a molar ratio 1:2:1, respectively, resulted in the formation of a new series of compounds, the 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines.

2. An alternate synthesis for the above compounds involving condensation of formaldehyde with *o*-alkylaminomethylphenols was reported.

SALT LAKE CITY, UTAH RECEIVED OCTOBER 1, 1948

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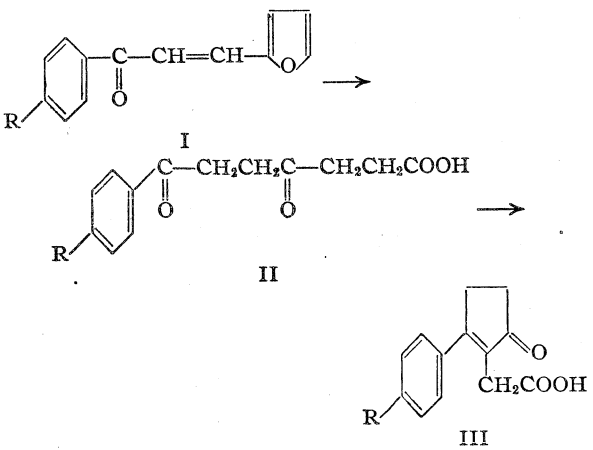
[CONTRIBUTION FROM THE CHARLOTTE DRAKE CARDEZA FOUNDATION, JEFFERSON MEDICAL COLLEGE]

# Some Aryl Substituted Cyclopentenones: A New Synthesis of the Cyclopentenophenanthrene Structure

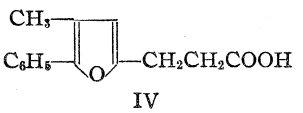
BY D. L. TURNER

The 3-(β-naphthyl)-2-cyclopenten-1-one-2-acetic acid of Robinson[1] has been found to produce myeloid hyperplasia when injected into guinea-pigs in large doses (100 mg.).[2] This observation led us to prepare a series of similar compounds for biological testing.

The desired compounds were made by the general methods of Robinson, and Kehrer and Igler,[3] from the furfurylidene ketones I (Table I) by way of the phenacyl levulinic acids II (Table II). The cyclopentenones III are formed by the alkaline catalyzed ring closure of the diketo-acids (Table III).




Anomalous behavior was shown by furfurylidene propiophenone; on acid hydrolysis, this substance took up the elements of one molecule of water only, and the product contained no carbonyl group. This substance is evidently 3-methyl-2-phenylfuran-5-propionic acid IV; its

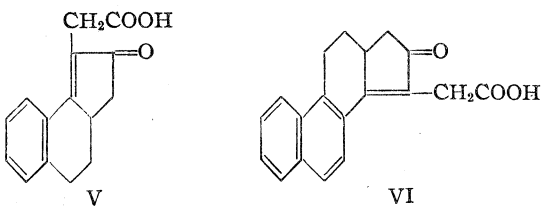



IV

absorption spectrum coincides almost exactly with that of 2-phenylfuran-5-propionic acid[4a] (Fig. 1). Robinson[1] has suggested that an intermediate naphthylfuranpropionic acid was formed in the hydrolysis of furfurylidene-2-acetylnaphthalene.

A similar furan had been isolated previously by Blicke[4b] from the hydrolysis of furfurylideneacetophenone.

The present work provides an easy preparation for the ring systems V and VI, available from α-tetralone and 1-keto-1,2,3,4-tetrahydrophenanthrene, respectively. Similar compounds, lacking




V VI

the acetic acid side-chains, have been made by Wilds,[5,6] who has studed their absorption spectra.[7] The absorption spectrum of the methyl ester of VI was found to be almost identical with that of Wilds' analogous substance (Fig. 2); slight discrepancies were found at low wave lengths where carboxyl group absorption might be expected to make a difference.

(1) Robinson, *J. Chem. Soc.*, 1390 (1938).
(2) Turner and Miller, unpublished.
(3) Kehrer and Igler, *Ber.*, **32**, 1178 (1899); **34**, 1263 (1901).
(4) (a) Robinson and Todd, *J. Chem. Soc.*, 1743 (1939); (b) Blicke, Warzynski, Faust and Gearien, THIS JOURNAL, **66**, 1675 (1944).
(5) Wilds, *ibid.*, **64**, 1421 (1942).
(6) Wilds and Johnson, *ibid.*, **68**, 86 (1946).
(7) Wilds, *et al.*, *ibid.*, **69**, 1985 (1947).

TABLE I

FURFURYLIDENE KETONES

| Substituted acetophenones | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| -*p*-ethyl- | *n*-Pentane | 61 | 51–52 | $C_{15}H_{14}O_2$ | 79.6 | 79.7 | 6.2 | 6.2 |
| -*p*-isopropyl- | *n*-Pentane | 75 | 63–64 | $C_{16}H_{16}O_2$ | 80.0 | 80.0 | 6.7 | 6.8 |
| -*p*-*s*-amyl- | | 79 | Liquid[a] | $C_{18}H_{20}O_2$ | 80.6 | 80.7 | 7.5 | 7.5 |
| -*p*-phenyl- | EtOH + MeOH | 81 | 137–139 | $C_{19}H_{14}O_2$ | 83.2 | 82.9 | 5.1 | 5.1 |
| -*m*-nitro- | Ethanol | 68 | 100–101 | $C_{13}H_9NO_4$ | 64.2 | 64.2 | 3.7 | 3.9 |
| *p*-Cyclohexyl- | Ethanol | 95 | 119–120 | $C_{19}H_{20}O_2$ | 81.4 | 81.6 | 7.2 | 7.3 |
| **Other ketones** | | | | | | | | |
| Propiophenone | *n*-Pentane | 83 | 58–59 | $C_{14}H_{12}O_2$ | 79.2 | 79.2 | 5.7 | 5.8 |
| 4-Methoxy-1-acetylnaphthalene | Methanol | 84 | 80–82 | $C_{13}H_{14}O_3$ | 77.7 | 77.7 | 5.1 | 5.3 |
| 1-Keto-1,2,3,4-tetrahydrophenanthrene | Ethanol | 99 | 119–120 | $C_{19}H_{14}O_2$ | 83.2 | 83.0 | 5.1 | 5.2 |

[a] B. p. 185° (3 mm.); 201° (5 mm.); $n^{25}D$ 1.6731.

TABLE II

ARYL DIKETO ACIDS

| Phenacyl levulinic acids | Method[b] | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| *p*-Methyl[a] | K. I. | Benzene | 61 | 112–113 | $C_{14}H_{16}O_4$ | 67.7 | 67.7 | 6.5 | 6.6 |
| *p*-Ethyl- | R. | $CCl_4$ | 60 | 104–105 | $C_{15}H_{18}O_4$ | 68.7 | 68.8 | 6.9 | 7.0 |
| *p*-Isopropyl- | R. | $CCl_4$ | 50 | 85–87 | $C_{16}H_{20}O_4$ | 69.5 | 69.4 | 7.3 | 7.3 |
| *p*-Phenyl- | R. | Acetone | 20 | 184–186 | $C_{19}H_{18}O_4$ | 73.5 | 73.2 | 5.8 | 5.9 |
| *p*-Cyclohexyl- | R. | $CCl_4$ | 32 | 125–127 | $C_{19}H_{24}O_4$ | 72.1 | 71.9 | 7.6 | 7.6 |
| **Other acids** | | | | | | | | | |
| γ-Keto-δ-(1-keto-1,2,3,4-tetrahydro-2-naphthyl)-valeric acid[c] | K. I. | $CCl_4$ | 16 | 103–104 | $C_{15}H_{16}O_4$ | 69.2 | 69.1 | 6.2 | 6.3 |
| γ-Keto-δ-(1-keto-1,2,3,4-tetrahydro-2-phenanthryl)-valeric acid | R. | Bz-$CHCl_3$ | 53 | 181–182 | $C_{19}H_{18}O_4$ | 73.5 | 73.7 | 5.8 | 5.8 |

[a] From furfurylidene methyl *p*-tolyl ketone. The furfurylidene ketone has been described by Kostanecki and Podrajansky, *Ber.*, 29, 2248 (1896), and by Maxim and Angelesco, *Bull. soc. chim.*, [4] 51, 1365 (1932). [b] R. = Robinson method; K. I. = Kehrer and Igler method. [c] From furfurylidene α-tetralone (Peak, Robinson and Walker, *J. Chem. Soc.*, 752 (1936)).

TABLE III

CYCLOPENTENONES

| Substituted 2-cyclopenten-1-one-2-acetic acids | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| 3-*p*-Tolyl- | Benzene | 98 | 162–163[d] | $C_{14}H_{14}O_3$ | 73.0 | 73.3 | 6.1 | 6.2 |
| 3-*p*-Ethylphenyl- | Benzene | 100 | 175–176 | $C_{15}H_{16}O_3$ | 73.7 | 73.7 | 6.6 | 6.6 |
| 3-*p*-Isopropylphenyl- | Benzene | 98 | 164–166 | $C_{16}H_{18}O_3$ | 74.4 | 74.5 | 7.0 | 7.0 |
| 3-*p*-*s*-Amylphenyl-[e] | Bz-cyclohex. | | 113–114 | $C_{18}H_{22}O_3$ | 75.5 | 75.6 | 7.7 | 7.9 |
| 3-*p*-Biphenylyl- | Benzene | 50 | 206–207 | $C_{19}H_{16}O_3$ | 78.1 | 77.8 | 5.5 | 5.5 |
| 3-*p*-Cyclohexylphenyl- | Benzene | 75 | 188–189 | $C_{19}H_{22}O_3$ | 76.8 | 76.8 | 7.4 | 7.5 |
| 3-*p*-Methoxyphenyl-[a,b] | Ether | 99 | 132–133 | $C_{14}H_{14}O_4$ | 68.3 | 68.4 | 5.7 | 5.8 |
| 3-*p*-Methoxyphenylmethyl ester[c] | Ether | | 87– 89 | $C_{15}H_{16}O_4$ | 69.2 | 69.3 | 6.2 | 6.2 |
| 3-(4-Methoxy-1-naphthyl)-[f] | Acetone | | 183 | $C_{18}H_{16}O_4$ | 73.0 | 72.9 | 5.4 | 5.5 |
| **Fused ring compounds** | | | | | | | | |
| 3,3a,4,5-Tetrahydro-2H-benz(*e*)-inden-2-one-1-acetic acid | Benzene | 35 | 177–178 | $C_{15}H_{14}O_3$ | 74.4 | 74.7 | 5.8 | 5.9 |
| 11,12,13,17-Tetrahydro-16H-cyclopenta(a)phenanthren-16-one-15-acetic acid | Benzene | 40 | 221–223 | $C_{19}H_{16}O_3$ | 78.1 | 77.9 | 5.5 | 5.7 |
| Methyl ester of preceding[c] | Ethanol | | 127–128 | $C_{20}H_{18}O_3$ | 78.4 | 78.3 | 5.9 | 6.0 |

[a] By hydrolysis of ester. [b] 7-*p*-Methoxyphenyl-4,7-diketoheptanoic acid has been made by Robinson. Furfurylidene *p*-methoxyacetophenone is described by Maxim and Angelesco, *Bull. soc. chim.*, [5] 1, 1128 (1934), as well as by Robinson.[4] [c] By esterification with diazomethane. [d] M. p. rose from 153–155° after drying *in vacuo* at 100°. [e] Semicarbazone from ethanol, m. p. 204° (dec). *Anal.* Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.4; H, 7.3. Found: C, 66.7; H, 7.5. [f] Semicarbazone from ethanol, m. p. 217° (dec). *Anal.* Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.6; H, 5.4. Found: C, 64.4; H, 5.7.

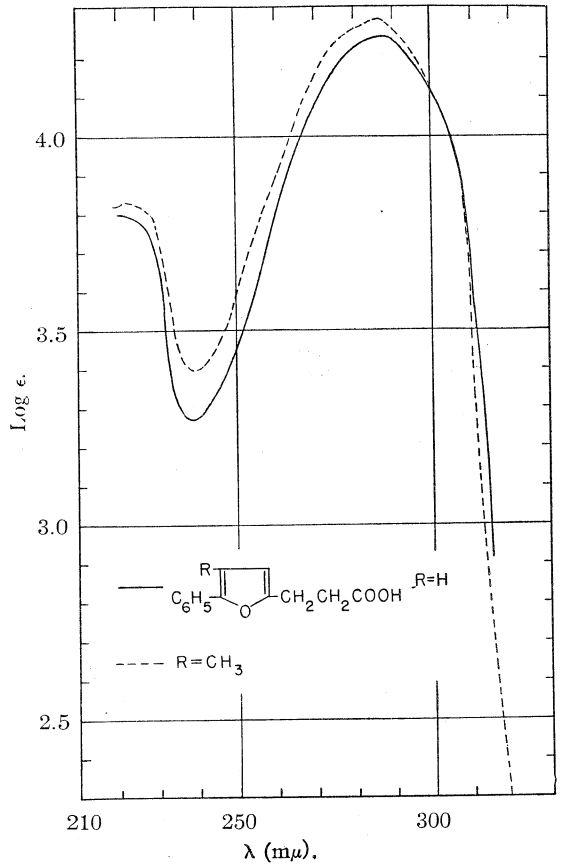



Fig. 1.—Spectra of phenylfurans.

Finally, we describe the preparation of 1-keto-1,-2,3,4,9,10-hexahydrophenanthrene by the method devised by Bachmann, Kushner and Stevenson[8] for the 7-methoxy derivative of this ketone. Since the yield was poor, we did not attempt to convert this ketone to the cyclopentenone. The 7-methoxy group facilitates the two ring closures of this synthetic method. Bachmann and Wendler,[9] and Johnson, Johnson and Petersen[10] have described alternative routes to 1-keto-1,2,3,4,9,10-hexahydrophenanthrene.

This investigation was aided by a grant from the American Cancer Society.

## Experimental[11]

The substituted acetophenones, not commercially available, were made by the general method of "Organic Syntheses."[12] Their properties agreed with those described in the literature.[13] The 1-keto-1,2,3,4-tetrahydrophenanthrene was prepared by the usual methods[14] from β-(1-naphthoyl)-propionic acid. However, the initial acid was made by the method of Lontz,[15] which does not seem to be widely known.

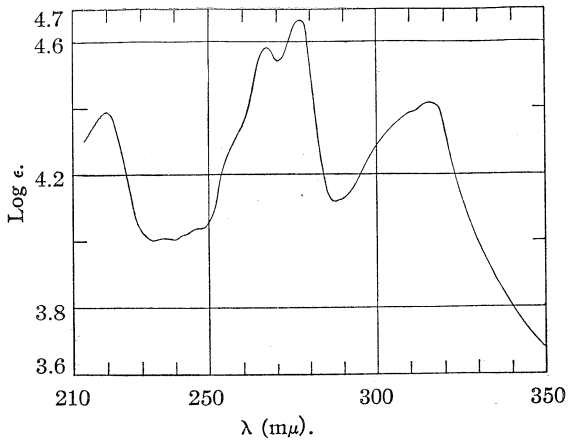



Fig. 2.—Spectrum of methyl 11,12,13,17-tetrahydro-16H-cyclopentaphenanthren-16-one-15-acetate.

**4-Methoxy-1-acetylnaphthalene.**—The methyl ether of α-naphthol (0.5 mole), acetic anhydride (0.5 mole), and iodine (10 g.) were heated together in an oil-bath at 160° for two hours, under a reflux condenser. The mixture was diluted with water and extracted with benzene. The benzene solution was washed with 5% sodium hydroxide, and then with 10% sodium bisulfite solution, then dried and distilled.[16] The product had b.p. 165° (2 mm.). Recrystallization from ether gave 47 g. (53% yield), m.p. 69–71°.[17]

**Furfurylidene Ketones.**—An equimolecular quantity of freshly distilled furfural was added to a solution of 100 g. of ketone in 100 ml. of ethanol. To the mixture was added 10 ml. 45% (by weight) of potassium hydroxide. The quantity of solvent was increased when the ketone was insoluble. The furfurylidene derivatives from *p*-ethyl- and *p*-isopropylacetophenone, and that from propiophenone, were obtained crystalline by diluting the reaction product with water and extracting with chloroform. The chloroform solution was washed with water, dried, and distilled. The residue could then be crystallized from *n*-pentane. Like chalcones, the furfurylidene ketones undergo photochemical alteration on standing.

**Diketo Acids.**—The Robinson[1] method indicated in Table II differs from that of Kehrer and Igler[3] by the addition of acetic acid to the hydrolysis mixture.[18]

**3-Methyl-2-phenylfuran-5-propionic Acid.**—The usual acid hydrolysis method of Robinson applied to furfurylidene propiophenone gave a 10% yield of this material in three extractions. The only other product was the usual residue of black tar. Recrystallized from benzene, the crystalline product from the acid hydrolysis mixture had m.p. 139–140°. Treated with boiling potassium hydroxide solution, under the conditions[1] for the preparation of the cyclopentenones (Table III), it was unaltered. It did not react with reagents for the carbonyl group.

*Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.7; H, 6.3.

**Cyclopentenones.**—These were obtained by the method of Robinson,[1] except as noted below.

(8) Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

(9) Bachmann and Wendler, *ibid.*, **68**, 2580 (1946).

(10) Johnson, Johnson and Petersen, *ibid.* **68**, 1926 (1946).

(11) The m. p. determinations of this paper were taken with Anschütz thermometers, but are otherwise uncorrected.

(12) Blatt (ed.), "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 3.

(13) *p-s*-Amylacetophenone is described by Hennion, THIS JOURNAL, **64**, 2421 (1942); *p*-cyclohexylacetophenone by Mayes and Turner, *J. Chem. Soc.*, 500 (1929). The others can be found in "Beilstein."

(14) Drake and McVey, *J. Org. Chem.*, **4**, 464 (1939).

(15) Lontz, U. S. Patent 2,339,789 (1944).

(16) This preparation is based on a method described by Kosak and Hartough, THIS JOURNAL, **68**, 2639 (1946), and by Chodroff and Klein, *ibid.*, **70**, 1647 (1948).

(17) Gattermann, Erhardt and Maisch, *Ber.*, **23**, 1199 (1890), give m. p. 71–72°.

(18) The yields reported in Table II might be increased by more complete extraction of the diketo-acids.

**3-*p*-*s*-Amylphenyl-2-cyclopenten-1-one-2-acetic Acid.**—To 50 g. of furfurylidene *p*-*s*-amylacetophenone was added 500 ml. of ethanol and 125 ml. of concentrated hydrochloric acid. After refluxing for ten hours, the solvent was distilled and the residual tar was refluxed with a mixture of 250 ml. of acetic acid, 250 ml. of concentrated hydrochloric acid and 500 ml. of water for two hours. The mixture was cooled, diluted with water, and extracted with ether. The ethereal solution was washed with water until the acetic acid was removed, and then the acidic hydrolysis products were removed with 9% sodium bicarbonate solution. The alkaline solution was acidified and extracted with carbon tetrachloride. Evaporation of the solvent gave 31 g. of oil. This was heated to 95° for one hour in 3 liters of 2% potassium hydroxide solution. The solution was treated with "Nuchar," filtered, and acidified. The resulting oil was taken up in ether; evaporation of the ether and rubbing the residue in carbon tetrachloride–*n*-pentane induced crystallization. The crystalline product weighed 12 g.

**3-(4-Methoxy-1-naphthyl)-2-cyclopenten-1-one-2-acetic Acid.**—The diketo-acid intermediate was again an oil, obtained as described for the preceding preparation. This oil (from 140 g. of furfurylidene ketone) was remethylated by dissolving in a slight excess of 10% sodium hydroxide and stirring with dimethyl sulfate for three hours without heating. The product was diluted with 1500 ml. water and 100 ml. 45% potassium hydroxide was added; it was boiled for one hour, treated with "Nuchar" and acidified. The acid precipitated as an oil, which crystallized on standing overnight; yield 21 g. The yield in this preparation, and in the preceding, could be increased by repeating the original acid extraction from the hydrolysis of the furfurylidene ketones several times.

**γ-(2,2-Dicarboxy-1,2,3,4-tetrahydronaphthylidene-1)-butyric Acid.**—Ethyl β-phenethylmalonate[19,20] (b. p. 148–150° (3 mm.)) was converted to the sodium derivative and caused to react with the acid chloride of ethyl hydrogen glutarate as described by Bachmann, Kushner and Stevenson[8] in their preparation of ethyl 5-keto-6,6-dicarbethoxy-8-*m*-anisyloctanoate, quantities being altered in accordance with the difference in molecular weights. Volatile material was removed from the product up to 180° (2–3 mm.). The residue was not distilled but was used in crude form for cyclization.[21] To 7 g. residue was added 50 ml. commercial 66° Be. sulfuric acid, previously cooled to 0°. The temperature rose to 7°. The mixture was then allowed to stand in a refrigerator at −22° for twenty hours. It was poured into ice-water and extracted with ether. The ether was dried and distilled. The residue was refluxed for three hours with 30 ml. of 45% aqueous potassium hydroxide and 20 ml. methanol. The methanol was distilled and the residue was diluted with water, and extracted with ether. Evaporation of the ether gave an oil that crystallized on adding chloroform. The crystalline product, 710 mg., was recrystallized from chloroform; the substance decomposed at 182–183°.

*Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.2; H, 5.3. Found: C, 63.4; H, 5.2.

This ring closure could not be effected with 100% phosphoric acid.[8]

Bachmann's procedure for converting γ-(6-methoxy-2,2-dicarboxy-1,2,3,4-tetrahydronaphthylidene-1)-butyric acid to 7-methoxy-1-keto-1,2,3,4,9,10-hexahydrophenanthrene,[8] involving refluxing for one hour with hydrochloric acid in acetic acid, was applied to 2.6 g. of the above tricarboxylic acid. Instead of the expected hexahydrophenanthrene ketone, there was obtained only a trace of neutral material and 1.0 g. of an acid, m.p. 87–88°, which is evidently the γ-(3,4-dihydro-1-naphthyl)-butyric acid of Bachmann and Wendler.[9] The acid was crystallized from dilute acetic acid and then from carbon tetrachloride.

*Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.7; H, 7.5. Found: C, 77.5; H, 7.3.

This monocarboxylic acid (0.8 g.) was converted to 1-keto-1,2,3,4,9,10-hexahydrophenanthrene by the method used by Stork[22] for the corresponding methoxy acid. The semicarbazone, previously described by Johnson, Johnson and Petersen,[10] was obtained in a yield of 0.5 g. It decomposed at 253–254°.[23]

*Anal.* Calcd. for $C_{15}H_{17}N_3O$: C, 70.6; H, 6.7. Found: C, 70.5; H, 6.7.

**Absorption Spectra.**—Measurements were made with a Beckmann quartz spectrophotometer. Absolute ethanol was used as solvent for the cyclopentaphenanthrene compound and 95% ethanol for the furans. The three substances were crystallized three times from ether–pentane to remove possible benzene of crystallization; they were dried *in vacuo*. Measurements were taken at intervals of 1 mμ about the maxima and minima, and at intervals of 2 mμ at other places. The results are shown in Table IV and in Figs. 1 and 2.

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA

| Compound | Maxima λ (mμ) | Maxima log ε | Minima λ (mμ) | Minima log ε |
|---|---|---|---|---|
| Methyl-11,12,13,17-tetrahydro-16H-cyclopentaphenanthren-16-one-15-acetate | 220 | 4.39 | 228 | 4.08 |
| | 236 | 4.00 | | |
| | 267 | 4.58 | | |
| | 277 | 4.66 | 287 | 4.12 |
| | 316 | 4.41 | | |
| 11,12,13,17-Tetrahydro-16H-cyclopentaphenanthren-16-one (data of Wilds[7] for major maxima and minima) | 218.5 | 4.32 | 228 | 4.03 |
| | 266 | 4.56 | | |
| | 276 | 4.63 | | |
| | 316 | 4.47 | 267 | 4.12 |
| 5-Propionic acids- | | | | |
| 2-phenyl-3-methylfuran- | 287 | 4.30 | 239 | 3.40 |
| 2-Phenylfuran- | 287 | 4.26 | 238 | 3.27 |

**Biological Activity.**—Most of the substances described here were tested by Dr. F. R. Miller of this Laboratory and found to be inactive. The 3-*p*-tolyl-cyclopentenone-acetic acid is the only one that produces myeloid hyperplasia comparable to that produced by myelokentric acid.[24] This work will be reported elsewhere.

## Summary

1. A series of 3-substituted 2-cyclopenten-1-2-acetic acids has been prepared by the method of Robinson.

2. The method has been extended to cyclic ketones. This provides an easy synthesis of 11,12,13,17-tetrahydro-16H-cyclopentaphenanthren-16-one-15-acetic acid.

PHILADELPHIA, PA. RECEIVED AUGUST 26, 1948

(19) Fischer and Schmitz, *Ber.*, **39**, 2208 (1906).

(20) Rupe and Wolfsleben, *Ann.*, **395**, 111 (1913).

(21) *Cf.* Wilds and Johnson, THIS JOURNAL, **70**, 1166 (1948).

(22) Stork, *ibid.*, **69**, 2936 (1947).

(23) Johnson, Johnson and Petersen give m. p. 257–258° (dec.).

(24) "Approaches to Tumor Chemotherapy," A. A. A. S., Washington, D. C., 1947, pp. 64–76.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

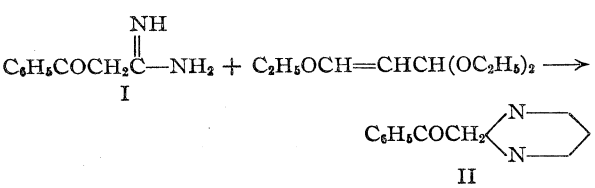
# Phenacylpyrimidines

BY BARBARA ROTH AND JAMES M. SMITH, JR.

A preceding paper[1] described a series of phenacylpyridines and -quinolines and their $\alpha$-amino derivatives, some of which showed moderate analgesic activity in preliminary tests on animals. It seemed of interest to investigate the corresponding phenacylpyrimidines, and therefore certain 2- and 5-phenacylpyrimidines have been prepared using benzoylacetamidine and $\alpha$-phenacylacetoacetic ester as intermediates. Phenacylpyrimidines previously reported in the literature include 1- and 5-derivatives obtained by treatment of a barbituric acid derivative with phenacyl bromide[2a] or alloxan with ethyl benzoylacetate.[2b]

Benzoylacetamidine (I) was prepared from benzoylacetonitrile through the imino ester hydrochloride. Haller[3] described the latter, which was treated with ammonia to obtain the free imino ester, but apparently no attempt was made to convert it to an amidine. Due to the presence of the benzoyl group, this amidine is unusual in regard to its stability and lack of strongly basic properties. The free amidine (I), rather than a hydrochloride, is the product isolated from the reaction of the imino ester hydrochloride with alcoholic ammonia. This can be recrystallized from water without decomposition.

To prepare 2-phenacylpyrimidine (II), benzoylacetamidine was condensed with $\beta$-ethoxyacrolein acetal. Condensation of I with acetylacetone

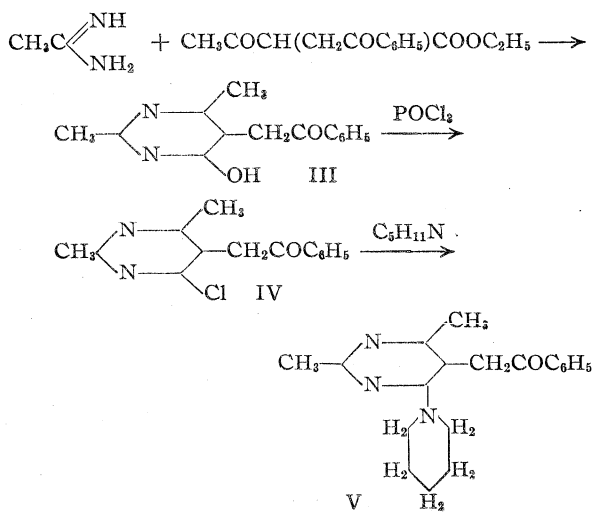


gave 4,6-dimethyl-2-phenacylpyrimidine, and with ethyl acetoacetate, 4-hydroxy-6-methyl-2-phenacylpyrimidine. These condensations were carried out by the method of Tuey[4] for the preparation of sulfadiazine from sulfaguanidine and $\beta$-ethoxyacrolein acetal.

Since it was found that phenacylpyridines and -quinolines brominated very readily on the methylene group, yielding $\alpha$-bromo derivatives which reacted readily with amines,[1] similar bromination reactions were carried out with 2-phenacylpyrimidine. A monobromo derivative was thereby formed which was very stable and had the properties expected for 5-bromo-2-phenacylpyrimidine, rather than an $\alpha$-bromo derivative. For example, it was unattacked by heating several hours with sodium hydroxide solution. It is not surprising that apparently a 5-bromopyrimidine was formed, since pyrimidines as a rule brominate very readily in this position. However, attempts to introduce a second atom of bromine in boiling glacial acetic acid were unsuccessful, even with the addition of acetic anhydride and benzoyl peroxide as catalysts, and in the presence of ultraviolet light.

As further evidence of the unreactivity of the methylene group of 2-phenacylpyrimidine, a Mannich condensation with formaldehyde and piperidine was attempted, to obtain 2-[$\alpha$-benzoyl-$\beta$-(1-piperidyl)-ethyl]-pyrimidine. However, under all conditions tried the starting material was recovered unchanged. Likewise, attempted nitrosation of the methylene group with butyl nitrite in alcoholic sodium methylate solution[5] was unsuccessful. Unreactivity of the keto group was also evidenced by lack of oxime formation by the usual methods.

For synthesizing 5-phenacylpyrimidines, $\alpha$-phenacylacetoacetic ester[6] was employed. Reaction with acetamidine in aqueous or alcoholic medium produced 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine (III). Chlorination of the latter proceeded in normal fashion with phosphorus oxychloride to yield the 6-chloro derivative (IV), which reacted readily with piperidine, giving 2,4-dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine (V). Compound III brominated readily in glacial acetic acid at 70°, but a mixture of products was obtained. These included the hydrobromide of the starting material and a dibrominated pyrimi-



(1) Smith, Stewart, Roth and Northey, THIS JOURNAL, **70**, 3997 (1948).

(2) (a) Keach and Hill, *ibid.*, **48**, 2743 (1926); Hultquist and Poe, *Ind. Eng. Chem., Anal. Ed.*, **7**, 398 (1935); Henze and Spurlock, THIS JOURNAL, **63**, 3360 (1941). (b) Kuhling, *Ber.*, **43**, 2406 (1910).

(3) Haller, *Bull. soc. chim.*, [2] **48**, 24 (1887).

(4) Tuey, British Patent 569,140, May 7, 1945.

(5) Meyer and Oelkers, *Ber.*, **21**, 1303 (1888).

(6) Paal, *ibid.*, **16**, 2866 (1883).

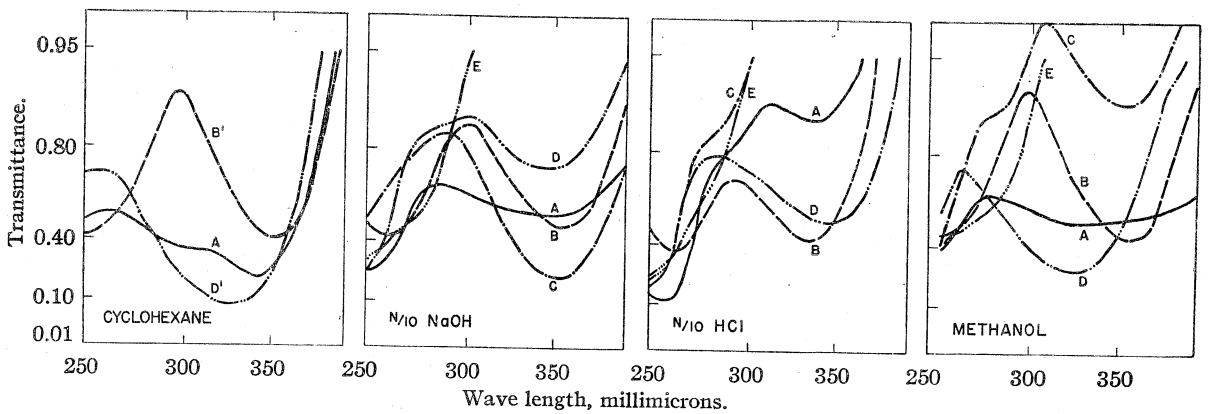



Fig. 1.—Ultraviolet absorption spectra[a] of 10 mg./l. solutions: A—, 2-phenacylpyridine; B– –, 2-phenacylpyrimidine hydrochloride; B'– –, 2-phenacylpyrimidine; C–·–, 4-phenacylpyridine hydrochloride; D–···–, 2-phenacyl-4,6-dimethylpyrimidine hydrochloride; D'–···–, 2-phenacyl-4,6-dimethylpyrimidine; E–···–, 2,4-dimethyl-5-phenacyl-6-hydroxypyrimidine hydrochloride.

[a] Data were obtained on a Beckman quartz spectrophotometer using 1-cm. cells. Readings were made at 5 mμ intervals except at points of inflection where they were made at 1 mμ intervals.

dine base. No monobrominated derivative was isolated from the mixture.

Pharmacological data on these compounds will be reported elsewhere.

In an effort to explain the difference in behavior of the 2-phenacylpyrimidines from the 2- and 4-phenacylpyridines and quinolines in regard to reactivity of the methylene group, a spectrophotometric study was carried out by Miss Ruth Abbott of this Laboratory on samples of 2- and 4-phenacylpyridine, 2-phenacylpyrimidine and its 4,6-dimethyl derivative, and 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine to see whether any differences in type of structure were indicated. While the data obtained do not definitely prove the structures of the phenacylpyrimidines, there is no indication that these structures are incorrect.

## Experimental[7,8]

**Benzoylacetamidine.**—Ten grams (0.069 mole) of benzoylacetonitrile[9] was dissolved in 50 ml. of dry benzene and 12.1 ml. (0.207 mole) of absolute alcohol added. The mixture was cooled to 0° and dry hydrogen chloride gas bubbled in until the mixture was saturated. It was kept at 0° over-night and then allowed to warm to room temperature, at which time only a small amount of crystalline material was present in the liquor. After two hours at room temperature, it had practically solidified. The product was filtered, washed with benzene, and dried in the vacuum desiccator; weight, 11.9 g. This was then mixed with 50 ml. of alcoholic ammonia, which had been saturated at 0°. The mixture stood for three days at room temperature, and was then filtered from ammonium chloride. The alcohol was distilled off, and ether added to the sirupy residue, resulting in the precipitation of 7 g. of benzoylacetamidine as a white solid. After two recrystallizations from water (1 g./20 ml.) the substance melted at 188–189°. It contained no halogen, and the *p*H of a saturated aqueous solution was 8.3. Upon warming with sodium hydroxide solution, ammonia was evolved.

*Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.6; H, 6.22; N, 17.3. Found: C, 66.1; H, 6.2; N, 16.7.

**2-Phenacylpyrimidine.**—A mixture of 16 g. (0.099 mole) of benzoylacetamidine, 17.8 g. (0.102 mole) of β-ethoxyacrolein acetal,[10] 38 ml. of amyl alcohol (b.p. 124–128°, from Pentasol) and 10 ml. of glacial acetic acid was refluxed for ten hours, and the ethyl acetate and amyl alcohol were then distilled off at atmospheric pressure. Upon cooling the residue, 10 g. of tan oily solid crystallized. After distillation of the mother liquor under vacuum to remove remaining solvents, and recrystallization of the dark residue from isopropyl acetate, an additional 2.1 g. of product was obtained. The resultant 12.1 g. was recrystallized from 65 ml. of isopropyl acetate, yielding 7.2 g. (49%) of yellow solid melting at 146–148°. Upon further recrystallization for analysis, the melting point was raised to 147.8–148.5°.

*Anal.* Calcd. for $C_{12}H_{10}N_2O$: C, 72.69; H, 5.09; N, 14.14. Found: C, 73.0; H, 5.3; N, 13.9.

An attempt to prepare an oxime by the usual method was unsuccessful.

**5-Bromo-2-phenacylpyrimidine.**—To 1.00 g. (0.005 mole) of 2-phenacylpyrimidine in 5 ml. of glacial acetic acid was added dropwise a solution of 0.808 g. (0.005 mole) of bromine in 2 ml. of glacial acetic acid at 20°. The bromine was taken up immediately. The mixture was poured into water, resulting in the precipitation of a yellow solid, which, upon recrystallization from alcohol, melted at 144.8–145.6°.

*Anal.* Calcd. for $C_{12}H_9BrN_2O$: C, 52.0; H, 3.28; Br, 28.9; N, 10.1. Found: C, 51.9; H, 3.4; Br, 28.8; N, 10.0.

The above reaction proceeded equally well in chloroform. The product was isolated by evaporating off the solvent and slurrying the resultant sirup in water, which resulted in the precipitation of the above-described 5-bromo-2-phenacylpyrimidine as a yellow solid. When the chloroform solution stood for some time, a small amount of light tan crystalline material separated which melted with decomposition at 246.5–249.0°. This was apparently the hydrobromide salt of the 5-bromo derivative, which completely hydrolyzed in water to the pyrimidine base.

When the above product was heated on the steam-bath for several hours in 5 *N* sodium hydroxide solution containing a little alcohol, the original material was recovered unchanged. Similarly, the bromo compound did not react with piperidine.

(7) All melting points are corrected.

(8) We are indebted to Mr. O. Sundberg and assistants for the microanalyses.

(9) Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932); Long, *ibid.*, **69** 990 (1947).

(10) Claisen, *Ber.*, **36**, 3670 (1903); Price and Moos, THIS JOURNAL, **67**, 207 (1945).

**Addition of Two Moles of Bromine to 2-Phenacylpyrimidine.**—A solution of 3.23 g. (0.02 mole) of bromine in 4 ml. of glacial acetic acid was added dropwise to a refluxing solution of 2 g. (0.01 mole) of 2-phenacylpyrimidine in 10 ml. of glacial acetic acid. At first the bromine was rapidly taken up, but the solution turned a dark red after approximately half had been added, and no more reaction appeared to take place. The mixture was refluxed for two hours after the addition was complete. The product was then cooled and poured into water. A quantitative yield of 5-bromo-2-phenacylpyrimidine was obtained. The reaction was repeated with the addition of 1 ml. of acetic anhydride and a few crystals of benzoyl peroxide. The same results were obtained, except for some darkening of the product in this case.

In another experiment, 1.2 g. (0.004 mole) of 5-bromo-2-phenacylpyrimidine was dissolved in 8 ml. of glacial acetic acid, and 0.5 ml. of acetic anhydride and a few crystals of benzoyl peroxide added. To this refluxing mixture was added dropwise a solution of 0.69 g. (0.004 mole) of bromine in 2 ml. of glacial acetic acid, in the presence of light from an ultraviolet lamp. The mixture became almost black, and some hydrogen bromide was given off. The only product which could be isolated from the black mixture was the original 5-bromo-2-phenacylpyrimidine.

**Attempted Mannich Reaction with 2-Phenacylpyrimidine.**—A mixture of 4.95 g. (0.025 mole) of 2-phenacylpyrimidine, 3.04 g. (0.025 mole) of piperidine hydrochloride, 1.13 g. (0.0375 mole) of paraformaldehyde, and 20 ml. of absolute alcohol was heated to refluxing for five hours. After the initial two hours an additional 0.75 g. of paraformaldehyde was added. Complete solution occurred. The mixture stood overnight at room temperature, and a precipitate of long yellow needles appeared. This proved to be 2-phenacylpyrimidine. Alcoholic hydrogen chloride was added to the solution until it was acid to congo red test paper. Another 0.75 g. of paraformaldehyde was added and the mixture refluxed for another twenty-six hours, small portions of additional paraformaldehyde being added from time to time. At the end of this time, the mixture was cooled and ether added, precipitating an oil which was taken up in water and neutralized with dilute sodium hydroxide solution. A yellow solid formed which after recrystallization from isopropyl acetate melted at 145.5–147.0° and showed no depression of the melting point with 2-phenacylpyrimidine.

**Attempted Nitrosation of 2-Phenacylpyrimidine.**—2-Phenacylpyrimidine (4.95 g., 0.025 mole) was slurried in 25 ml. of absolute alcohol, and a solution of 1.5 g. (0.028 mole) of sodium methylate in 10 ml. of absolute alcohol added. The solution was cooled to 0°, and 2.58 g. (0.025 mole) of freshly prepared butyl nitrite added dropwise. No change occurred in the appearance of the mixture, and no exothermic reaction took place. The mixture was stoppered and allowed to stand at room temperature for two days. The mixture was then cooled and the solid filtered off, washed with water and dried. The substance weighed 4.6 g., melted at 147.0–148.8° and showed no depression of melting point with 2-phenacylpyrimidine.

**4,6-Dimethyl-2-phenacylpyrimidine.**—A mixture of 10 g. (0.062 mole) of benzoylacetamidine, 6.2 g. (0.062 mole) of acetylacetone, 20 ml. of mixed amyl alcohols, and 6 ml. of glacial acetic acid was heated under reflux for twelve hours. The solvents were distilled off under vacuum, and the sirupy residue was washed with dilute sodium hydroxide solution and cold water, after which it slowly crystallized. Approximately 12.5 g. of crude 4,6-dimethyl-2-phenacylpyrimidine was obtained. This was purified by dissolving in hot 5 *N* hydrochloric acid, from which a yellow hydrochloride precipitated on cooling. Upon recrystallizing twice more from 5 *N* hydrochloric acid and twice from alcohol, with the aid of decolorizing charcoal, 8 g. of light yellow crystals was obtained which melted between 202–210°.

*Anal.* Calcd. for $C_{14}H_{14}N_2O \cdot HCl$: C, 64.0; H, 5.75; N, 10.7; Cl, 13.5. Found: C, 64.2; H, 5.64; N, 10.7; 13.6.

From the aqueous solution of the hydrochloride a light yellow base was precipitated on adding dilute sodium hydroxide solution. After drying in the vacuum desiccator, this melted at 74.0–75.5°.

*Anal.* Calcd. for $C_{14}H_{14}N_2O$: C, 74.3; H, 6.24; N, 12.4. Found: C, 74.4; H, 6.32; N, 12.3.

**4-Hydroxy-6-methyl-2-phenacylpyrimidine.**—This was prepared from benzoylacetamidine and ethyl acetoacetate in a fashion similar to the above, the product being purified by repeated reprecipitation from dilute sodium hydroxide solution. A white product was obtained which melted at 248.5–250.0°.

*Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.30; N, 12.3. Found: C, 68.6; H, 5.36; N, 12.2.

**2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine.**—A mixture of 515 g. (2.08 moles) of α-phenacylacetoacetic ester,[6] 197 g. (2.08 moles) of acetamidine hydrochloride, 84 g. (2.08 moles) of sodium hydroxide pellets dissolved in 830 ml. of water, and 100 ml. of 95% alcohol was stirred at room temperature for one-half hour, after which it was allowed to stand without stirring for two days. A thick crystalline mass formed, which was filtered off and washed well with water. This material, after drying at 50°, weighed 302 g., and contained considerable oily material. Upon recrystallization from 1100 ml. of 95% alcohol, a white crystalline product weighing 80 g. was obtained. This could be further purified by recrystallization from alcohol, benzene or isopropyl acetate, and then melted at 211–212°.

*Anal.* Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.83; N, 11.6. Found: C, 69.2; H, 5.8; N, 11.7.

The original mother liquor, upon standing two more days, deposited an additional 50 g. of somewhat oily crystalline product. After drying, this was dissolved in 250 ml. of absolute alcohol, and an excess of alcoholic hydrogen chloride added. Upon cooling, the hydrochloride precipitated as an almost white solid weighing 30 g. Upon two recrystallizations from 98% alcohol, with charcoal, the hydrochloride gradually sintered and melted with decomposition at 267–268°.

**4-Chloro-2,6-dimethyl-5-phenacylpyrimidine.**—A mixture of 106 g. of 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine and 265 ml. of phosphorus oxychloride was heated for one hour on the steam-bath. The excess phosphorus oxychloride was distilled off under vacuum, and the residue poured on ice and neutralized with sodium bicarbonate. The substance, which appeared tarry at first, solidified to a tan solid. After drying at 55°, the weight was 111 g. Upon recrystallization from 600 ml. of V.M. and P. naphtha, which served to separate it from some insoluble impurities, the yield was 82 g. or 72%. After two further recrystallizations with the aid of charcoal the melting point of the white product was 103.5–104.5°.

*Anal.* Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.5; H, 5.03; Cl, 13.6; N, 10.8. Found: C, 64.2; H, 5.0; Cl, 13.7; N, 10.8.

**2,4-Dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine.**—A mixture of 60 g. (0.23 mole) of 4-chloro-2,6-dimethyl-5-phenacylpyrimidine and 60 g. (0.70 mole) of piperidine was warmed on the steam-bath until an exothermic reaction commenced. Cooling was then necessary for a few minutes to keep the reaction under control, after which it was heated for an additional fifteen minutes on the steam-bath to complete the reaction. The mixture was then cooled, and sufficient benzene added to make a workable slurry. It was filtered from piperidine hydrochloride, and the benzene solution extracted with an excess of dilute hydrochloric acid, followed by clarification of the acid extracts and neutralization with ammonia. A gummy precipitate was formed which soon solidified. This was filtered off and dried at 45°; weight, 68.6 g. Upon recrystallization from 350 ml. of V.M. and P. naphtha with the aid of charcoal the white product weighed 55 g. (78% yield) and melted at 87–89°.

*Anal.* Calcd. for $C_{19}H_{23}N_3O$: C, 73.7; H, 7.50; N, 13.4. Found: C, 73.9; H, 7.7; N, 13.7.

The product was converted to the **hydrochloride** in absolute ether and recrystallized from alcohol–ether mixture. It then melted at 200–201°.

**Bromination of 2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine.**—2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine (1.00 g., 0.004 mole) was dissolved in 10 ml. of glacial acetic acid and a solution of 0.663 g. (0.004 m.) of bromine in 2 ml. of glacial acetic acid was added dropwise. No reaction occurred until the mixture was heated to 60–70°, when rapid decolorization took place. When a little more than half of the bromine had been added, white crystals began to separate, which redissolved for the most part by the time the remaining bromine had been added. The mixture was allowed to stand and cool for two hours, resulting in the slow formation of a white precipitate again. This was filtered, washed with ether, and dried; weight, 0.4 g. This proved to be a mixture consisting mainly of the hydrobromide of the starting material. On dissolving in water a small amount of insoluble material remained, which was removed by filtration. On neutralization of the filtrate with sodium bicarbonate, a white precipitate formed which, upon drying, melted at 207–209°, contained no halogen, and showed no depression of the melting point with the starting material. The acetic acid liquor yielded a white precipitate upon the addition of ether, but this became sirupy on all attempts at isolation. Upon pouring the acetic acid solution into water, a small amount of white precipitate formed; dry weight, 0.3 g. After purification by recrystallization from alcohol, the substance melted at 167–169°. Analysis indicated it to be a dibrominated base, which was not further identified.

*Anal.* Calcd. for $C_{14}H_{12}Br_2N_2O$: C, 42.0; H, 3.02; Br, 40.0; N, 7.01. Found C, 42.3; H, 2.97; Br, 40.1; N, 7.31.

## Summary

A series of 2- and 5-phenacylpyrimidines has been prepared for pharmacological testing purposes. Condensations of benzoylacetamidine, a new compound, with β-ethoxyacrolein acetal, acetylacetone and ethyl acetoacetate yielded 2-phenacylpyrimidine, 4,6-dimethyl-2-phenacylpyrimidine and 4-hydroxy-6-methyl-2-phenacylpyrimidine, respectively. Condensation of α-phenacylacetoacetic ester with acetamidine yielded 2,4-dimethyl-6-hydroxy-5-phenacylpyrimidine.

The methylene group of 2-phenacylpyrimidine has been shown to be unusually unreactive. Bromination of 2-phenacylpyrimidine produced the 5-bromo derivative only. Mannich and nitrosation reactions failed. The ketone did not yield an oxime.

2,4-Dimethyl-6-hydroxy-5-phenacylpyrimidine was chlorinated to yield the 6-chloro derivative, which reacted with piperidine to form 2,4-dimethyl-5-phenacyl-6-(1-piperidyl)-pyrimidine. Bromination reactions with the 6-hydroxy compound yielded mixtures, from which no monobrominated product was isolated.

BOUND BROOK, NEW JERSEY RECEIVED AUGUST 24, 1948

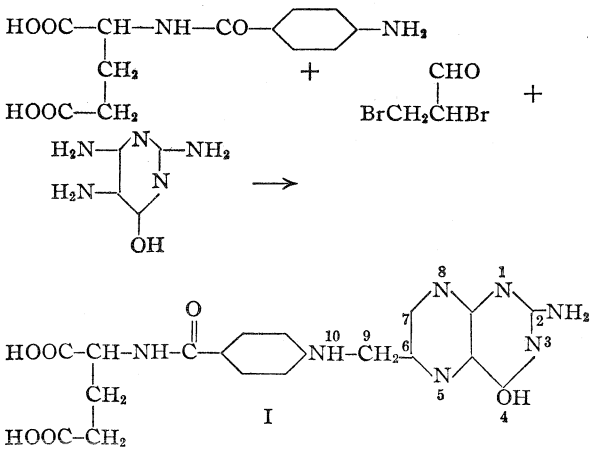
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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

# Analogs of Pteroylglutamic Acid. II. 9-Methylpteroylglutamic Acid and Derivatives

BY MARTIN E. HULTQUIST, JAMES M. SMITH, JR., DORIS R. SEEGER, DONNA B. COSULICH AND ERWIN KUH

Pteroylglutamic acid (I) was synthesized by Waller, *et al.*,[1] by the simultaneous reaction of 2,4,5-triamino-6-hydroxypyrimidine,[2] 2,3-dibromopropionaldehyde, and *p*-aminobenzoyl-*l*(+)-glutamic acid[3] in aqueous solution at *p*H 4.



I

(1) Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948); Angier, *et al.*, *Science*, **103**, 667 (1946).

(2) Traube, *Ber.*, **33**, 1371 (1900).

(3) Van der Scheer and Landsteiner, *J. Immunology*, **29**, 373 (1935).

This reaction has proved to be of wide application and a number of derivatives of I have been prepared by varying one or more of the three components.[4] Previous communications from this Laboratory have described $N^{10}$-alkyl[5] and 4-amino[6] analogs of pteroylglutamic acid. The present paper deals with a series of analogs in which a methyl group has been introduced on the methylene bridge in the 9-position.

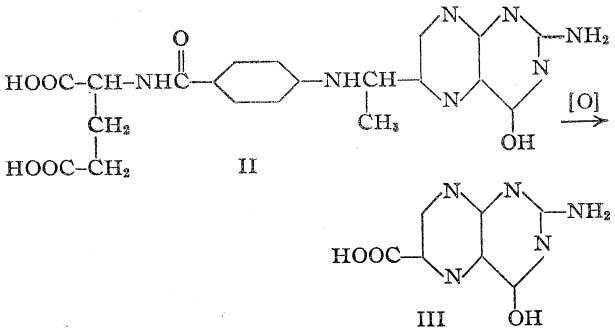
When 2,2,3-trichlorobutyraldehyde ("butyl chloral")[7] was reacted with 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid, there was formed N-[4-{[1-(2-amino-4-hydroxy-6-pteridyl)-ethyl]-amino}-benzoyl]-glutamic acid (II), hereafter designated as 9-methylpteroylglutamic acid.

(4) (a) Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947); (b) Hutchings, *et al.*, *ibid.*, **170**, 323 (1947); (c) Martin, Tolman and Moss, *Archives of Biochemistry*, **12**, 318 (1947); (d) Mowat, *et al.* THIS JOURNAL, **70**, 1096 (1948); (e) Boothe, *et al.*, *ibid.* **70**, 1099 (1948); (f) Smith, Cosulich, Hultquist and Seeger, *Trans. N. Y. Acad. Science*, [II] **10**, 82 (1948); (g) Gordon, *et al.*, THIS JOURNAL **70**, 878 (1948).

(5) Cosulich and Smith, *ibid.*, **70**, 1922 (1948).

(6) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947).

(7) Pinner, *Ann.*, **179**, 26 (1875). We are grateful to the Westvaco Chemical Corporation for a supply of butyl chloral.




Purification was accomplished by methods similar to those reported for pteroylglutamic acid.[1,4b,d,e,5] Also, it was found that recrystallization of the cyclohexylamine salt of II from aqueous butanol afforded a convenient method of obtaining an analytically pure material. Oxidation of II with hot alkaline permanganate gave solely 2-amino-4-hydroxypteridine-6-carboxylic acid (III).[8] This shows that the point of attachment of the side chain is in the 6-position on the pteridine ring.

9,10-Dimethylpteroic acid (IV) was prepared similarly, using *p*-methylaminobenzoic acid. Other variations in the starting materials resulted in 9,-

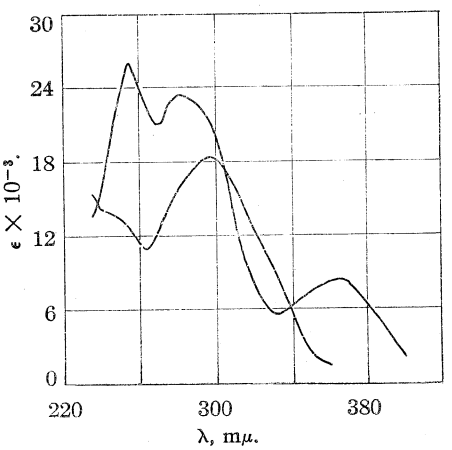



Fig. 1.—Ultraviolet absorption spectra of 9-methylpteroylglutamic acid (II)[a]; —, 0.1 *N* NaOH; – – – –, 0.1 *N* HCl.

[a] ε is the molecular extinction coefficient as defined by $I = I_0 10^{-\epsilon cl}$ where $c$ is the concentration in moles/liter and $l$ is the cell length in centimeters. Transmittancy ($I/I_0$) measurements of 10 mg./l. solutions were made in 1-cm. cells at 5 mμ intervals on a Model DU Beckman Spectrophotometer using a solvent filled cell in the reference position. Additional data were obtained at 2 mμ intervals at maxima, minima, and points of inflection.

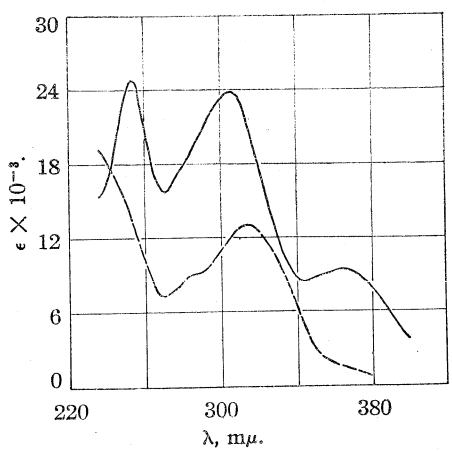



Fig. 2.—Ultraviolet absorption spectra of 9,10-dimethylpteroylglutamic acid (V)[a]; —, 0.1 *N* NaOH; – – – –, 0.1 *N* HCl.

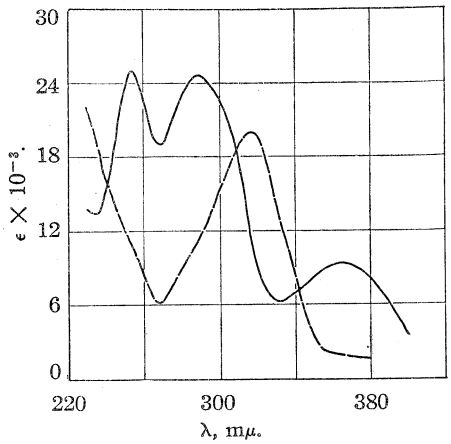



Fig. 3.—Ultraviolet absorption spectra of 9,10-dimethylpteroic acid (IV)[a]; —, 0.1 *N* NaOH; – – – –, 0.1 *N* HCl.

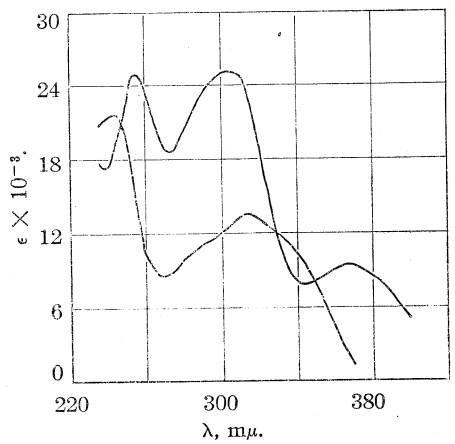
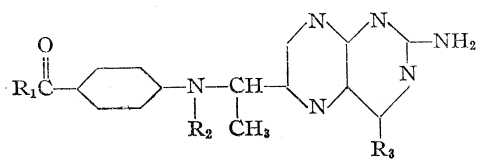



Fig. 4.—Ultraviolet absorption spectra of 4-amino-9,10-dimethylpteroylglutamic acid (VI)[a]: ——, 0.1 *N* NaOH; – – – –, 0.1 *N* HCl.



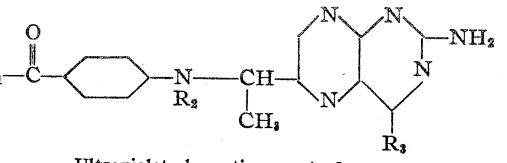

$R_1$ = OH; IV, $R_2$ = $CH_3$, $R_3$ = OH

$R_1$ = NHCH(COOH)
$CH_2CH_2COOH$; { V, $R_2$ = $CH_3$, $R_3$ = OH; VI, $R_2$ = $CH_3$, $R_3$ = $NH_2$

(8) Mowat, *et al.*, THIS JOURNAL, **70**, 14 (1948).

TABLE I

9-METHYLPTEROYLGLUTAMIC ACID AND DERIVATIVES



| $R_1$ | $R_2$ | $R_3$ | Ultraviolet absorption spectra[a] Maxima λ mμ 0.1 *N* NaOH | 0.1 *N* HCl | Antagonist activity[b] |
|---|---|---|---|---|---|
| -1(+)-glutamic acid | $-H$ | $-OH$ | 255 283 365 | 297 | 0.12 |
| -1(+)-glutamic acid | $-H$ | $-OH$ | | | 0.09[c] |
| $-OH$ | $-CH_3$ | $-OH$ | 253 288 365 | 317 | 1.12 |
| -1(+)-glutamic acid | $-CH_3$ | $-OH$ | 253 305 365 | 315 | 3.4 |
| -1(+)-glutamic acid | $-CH_3$ | $-NH_2$ | 255 306 369 | 244 316 | 1563.0 |
| $N^{10}$-Methylpteroylglutamic acid[5] | | | 255 302 368 | 307 | 100.0 |

[a] See footnote to Fig. 1. [b] An arbitrary value of 100 is assigned for the antagonist activity of $N^{10}$-methylpteroylglutamic acid, for half-maximum inhibition of the growth of *Streptococcus faecalis* R. The inhibition ratio for this compound is 2.0 at a concentration of pteroylglutamic acid of 0.1 microgram per 10 ml. (ref. 5). Values for other compounds are reported in terms of the standard. [c] Crude material.

10-dimethylpteroylglutamic acid (V), and 4-amino-9,10-dimethylpteroylglutamic acid (VI).

The biological properties of these compounds have been examined by Dr. E. L. R. Stokstad and Dr. B. L. Hutchings of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. The 9-methyl analogs are antagonists for pteroylglutamic acid in the growth of *Streptococcus faecalis* R., and also in certain animals. Details of this work will be reported elsewhere. The inhibition ratio of 9-methylpteroylglutamic acid for half-maximum growth of *S. faecalis* R is 2000 at a concentration of 0.01 microgram of pteroylglutamic acid per ml.

Table I summarizes the ultraviolet absorption data and relative antagonist activity of these analogs.

## Experimental

**9-Methylpteroylglutamic Acid (II).**—This compound was prepared from 2,4,5-triamino-6-hydroxypyrimidine hydrochloride,[2] 2,2,3-trichlorobutyraldehyde[7] and *p*-aminobenzoylglutamic acid,[3] under the conditions described by Waller, *et al.*, for the synthesis of pteroylglutamic acid[1]. A slurry of 20 g. of crude 9-methylpteroylglutamic acid and 8 g. of lime in 2000 ml. of water was heated at 80° for thirty minutes, clarified and washed with hot water. The filtrate was adjusted to *p*H 10.8 with aqueous zinc chloride, clarified, acidified to *p*H 3 and filtered. This cake was slurried in 2000 ml. of water, made alkaline with sodium hydroxide solution at 80° and then adjusted to *p*H 7 while cooling to 20°. After clarification, the filtrate was acidified to *p*H 3. The product was filtered and dissolved in 1000 ml. of water as the magnesium salt, treated with Darco G-60, clarified and reprecipitated at *p*H 3. The dry product weighed 2.2 g.; purity, 82.5%.

Further purification was accomplished by dissolving 1 g. of this material in 8 ml. of butanol, 2 ml. of water and 1 ml. of cyclohexylamine at 95°, and clarifying to remove some insoluble matter. After boiling to remove part of the water, there was gradually added 7.5 ml. of butanol and 3.5 ml. of cyclohexylamine. On stirring, there crystallized out the cyclohexylamine salt, which was filtered off at 20°. This was recrystallized again, using the above procedure, to give a light yellow, crystalline product.

*Anal.* Calcd. for $C_{32}H_{47}O_6N_9 \cdot 3H_2O$: C, 54.30; H, 7.55; N, 17.81. Found: C, 54.8; H, 7.55; N, 17.8.

The free acid was recovered from the cyclohexylamine salt by dissolving in water and acidifying to *p*H 3. It was dried at 100° (1 mm.) for seven hours.

*Anal.* Calcd. for $C_{20}H_{21}O_6N_7$: C, 52.74; H, 4.65; N, 21.53. Found: C, 52.9; H, 4.77; N, 21.5.

**Oxidation of II with Alkaline Permanganate.**—A solution of 0.2 g. of II in 60 ml. of *N* sodium hydroxide solution was treated with excess potassium permanganate for one and one-half hours at 95°. The permanganate color was then destroyed with a little sodium sulfite. The mixture was clarified, acidified to *p*H 3, cooled and filtered, yielding 0.075 g. of product which was identified as 2-amino-4-hydroxypteridine-6-carboxylic acid (III) by comparison with an authentic sample.[8]

Oxidation of the cyclohexylamine salt of II gave the same product in approximately the same yield.

**9,10-Dimethylpteroylglutamic Acid (V).**—This compound was synthesized by the method of Waller, *et al.*[1] using 2,4,5-triamino-6-hydroxypyrimidine, 2,2,3-trichlorobutyraldehyde, and *p*-methylaminobenzoylglutamic acid.[5] A mixture of 30 g. of the crude material, 9 g. of lime, and 2 l. of water was heated at 60° for forty minutes. After filtration with Hyflo-Supercel, the cake was washed with 750 ml. of water at 60°. The filtrate and wash were adjusted to *p*H 10.8–11.0 with 10% zinc chloride and then filtered free of precipitated material. The liquor was adjusted to *p*H 3–3.5 with dilute hydrochloric acid, cooled to 10°, and filtered. The cake was washed with water and then slurried in 1500 ml. of water and enough sodium hydroxide to give *p*H 11–12. After heating at 80° for ten minutes, the solution was adjusted to *p*H 7 while cooling to 20°, and filtered. The filtrate was treated with dilute hydrochloric acid to *p*H 3–3.5. The precipitate was filtered, reslurried in 1 l. of water containing enough magnesium carbonate to obtain about *p*H 9 at 80°, and filtered hot with 2 g. of charcoal. The filtrate at 80° was adjusted to *p*H 3–3.5 with hydrochloric acid and cooled to 10°. Orange microcrystalline material separated which was purified for analysis by repeating (at 1 g./l.) the last step twice more. On cooling to 10° after the second treatment, analytically pure yellow-orange microcrystalline material was isolated (see Table I for biological and ultraviolet absorption data). The analytical sample was dried at 100° and 2 mm. for five hours.

*Anal.* Calcd. for $C_{21}H_{27}N_7O_6 \cdot H_2O$: C, 51.7; H, 5.13; N, 20.13. Found: C, 51.4; H, 5.22; N, 19.8.

**Permanganate Oxidation of 9,10-Dimethylpteroylglutamic Acid (V).**—A solution of 0.5 g. of 9,10-dimethylpteroylglutamic acid in 166 ml. of N sodium hydroxide was treated at 80–90° with 5% potassium permanganate solution until the solution maintained a purple color. After adding sodium sulfite to destroy this color, manganese dioxide was filtered off and the filtrate adjusted to *p*H 3–3.5 with dilute hydrochloric acid. The precipitate,

isolated by filtering, washing with water and then acetone, and drying, was shown to be 2-amino-4-hydroxypteridine-6-carboxylic acid (III) by comparison of the ultraviolet absorption curve with that of an authentic sample.[8]

**9,10-Dimethylpteroic Acid (IV).**—This was prepared similarly to V above, except that *p*-methylaminobenzoic acid[6] was used (see Table I for ultraviolet absorption and biological data).

*Anal.* Calcd. for $C_{16}H_{16}N_6O_3 \cdot 0.5H_2O$: C, 55.1; H, 4.91; N, 24.1. Found: C, 54.7; H, 4.99; N, 24.0.

**N-[{N-[1-(2,4-Diamino-6-pteridyl)-ethyl]-N-methylamino}-benzoyl]-glutamic Acid, ("4-Amino-9,10-dimethylpteroylglutamic Acid") (VI).**—This compound was prepared by the method of Waller, *et al.*,[1] using 2,4,5,6-tetraminopyrimidine sulfate,[9] 2,2,3-trichlorobutyraldehyde and *p*-methylaminobenzoylglutamic acid.[5] A mixture of 31.6 g. of the crude, 9 g. of lime, and 2 l. of water was heated at 60° for forty minutes. After filtration, the cake was washed with 600 ml. of water at 60°. The combined filtrate and wash liquors were adjusted to *p*H 10.8–11.0 with 10% aqueous zinc chloride. The mixture was filtered, and the filtrate was adjusted to *p*H 3.5–4.0 with hydrochloric acid. After cooling to 5°, the precipitate was filtered, washed with water and slurried in 1500 ml. of water containing sodium hydroxide to give *p*H 11–11.5. After heating it at 60° for ten minutes, the *p*H of the solution was reduced to 7, while cooling the mixture to 20°, and filtered. The filtrate was adjusted to *p*H 3.5–4.0 with hydrochloric acid and cooled to 5°. After filtration, the cake was slurried in 1 l. of water containing enough lime to obtain *p*H 8.5–9 at 60° and filtered hot with 1.5 g. of charcoal. The filtrate was adjusted to *p*H 3.5–4.0 with hydrochloric acid and cooled to 0–5° overnight. The yellow-orange microcrystalline material which separated was isolated by filtration and was analytically pure. The biological and ultraviolet absorption data are shown in Table I.

*Anal.* Calcd. for $C_{21}H_{24}N_8O_5 \cdot 2H_2O$: C, 50.0; H, 5.55; N, 22.2. Found: C, 50.4; H, 5.42; N, 21.5.

**Acknowledgment.**—We are indebted to Mr. Richard L. Shepard for technical assistance in the preparation of certain of these substances, to Miss Ruth Abbott for the ultraviolet absorption data, and to Mr. O. Sundberg and coworkers for the microanalyses.

## Summary

N-[4-{[1-(2-Amino-4-hydroxy-6-pteridyl)-ethyl]-amino}-benzoyl]-glutamic acid (II), designated herein as 9-methylpteroylglutamic acid, has been synthesized and isolated in pure form. Corresponding analogs which have also been prepared are 9,10-dimethylpteroylglutamic acid (V), 4-amino-9,10-dimethylpteroylglutamic acid (VI), and 9,10-dimethylpteroic acid (IV).

These compounds exhibit antagonism for pteroylglutamic acid in the growth of *S. faecalis* R.

BOUND BROOK, NEW JERSEY
RECEIVED SEPTEMBER 27, 1948

(9) Traube, *Ber.*, **37**, 4545 (1904).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

# Mechanical Properties of Substances of High Molecular Weight. V. Rigidities of Polyisobutylene Solutions in Various Solvents[1]

BY J. N. ASHWORTH[2] AND JOHN D. FERRY

Many concentrated solutions of linear polymers behave as highly viscous liquids in steady flow, but possess solid-like rigidity in small oscillating deformations; transverse waves can be propagated in them at audio frequencies. From the wave length of these waves the rigidity can be calculated, and from the damping the mechanical loss, or the dynamic viscosity, can be derived. Measurements of this sort on solutions of polystyrene in xylene have been reported previously.[3]

In seeking to understand the mechanism of rigidity in polymer solutions, it is desirable to study a variety of molecular types. In this paper, measurements are reported for a non-polar polymer for which complications due to intermolecular forces should be at a minimum: polyisobutylene. As in the earlier work on polystyrene, the dependence of rigidity on frequency, concentration, and temperature has been studied. Also, four different solvents have been employed.

(1) Supported in part by the Research Committee of the Graduate School of the University of Wisconsin from funds supplied by the Wisconsin Alumni Research Foundation, and in part by a grant from Research Corporation.

(2) Present address: Rohm and Haas Co., Philadelphia, Pa.

(3) J. D. Ferry, THIS JOURNAL, **64**, 1323 (1942).

## Materials

The polyisobutylene was kindly furnished by Dr. John Rehner, Jr., of the Esso Laboratories. It was designated 303-92-1. From measurements of viscosities of dilute solutions in di-isobutylene, the intrinsic viscosity in this solvent at 20° was found to be 2.85 $(g./100\ cc.)^{-1}$, corresponding to a viscosity-average molecular weight of 1,200,000 on the basis of the interpolation equation of Flory.[4] Intrinsic viscosities in the solvents used for the rigidity studies were also determined at 20° and 30°; these are given in Table IV below. The details of the intrinsic viscosity measurements are presented elsewhere.[5]

In most cases, the polymer was used without purification. However, it contained a small amount of tiny fibrous foreign particles which, though negligible in quantity, were optically anisotropic and interfered somewhat with optical measurements of waves. Accordingly, a portion of the polymer was dissolved in toluene at a concentration of about five per cent., clarified by filtration through Whatman No. 4 filter paper on a

(4) P. J. Flory, *ibid.*, **65**, 372 (1943).

(5) J. N. Ashworth, Ph.D. Thesis, University of Wisconsin, 1948.

Buchner funnel, completely precipitated by methyl alcohol, and dried *in vacuo* at room temperature for twelve hours and at 60° for four hours. This preparation, hereafter referred to as clarified polymer, afforded the best measurements of damping.

The *n*-heptane was "99 mole per cent." sold by the Phillips Petroleum Corp. Xylene was obtained from Mallinckrodt and Merck, and chlorobenzene and isoöctane (2,2,4-trimethylpentane) from the Eastman Kodak Company. The solvents were used without further purification.

Preparation of concentrated solutions was expedited by rotating bottles containing polymer and solvent at about 12 revolutions per hour. Concentrations were determined by dry weight after heating samples *in vacuo* for twenty-four hours at 110°. Concentrations were expressed both as weight per cent. and as g./cc. The latter values were calculated assuming additivity of the volumes of polymer and solvent, taking the density of polymer as 0.91 and those of the solvents from the "International Critical Tables," and assuming that the thermal expansion coefficients of solutions were the same as those of the respective solvents.[3]

## Method

The apparatus and procedure were the same as previously described,[3,6] with some minor modifications. The Strobotron was mounted outside the air thermostat, and its illumination of the cell was improved by a reflector and a condensing lens. Photographic recording of the wave pattern was substituted for the former method of visual observation with horizontal and vertical micrometer adjustments. The rather faint pattern was satisfactorily photographed on Eastman Kodak Co. CTC plates or Contrast Process Panchromatic cut film, the latter affording a contrast between light and dark Babinet bands which was an improvement over visual observation.

The photographs of wave patterns were projected by an enlarger on cross-section paper, and the contours of the wavy Babinet bands were traced in pencil. An example is shown in Fig. 1. Similar projections of photographs of the undeviated Babinet bands, when superimposed, permitted measurements of the displacements from which damping data were calculated. The wave length was taken as the average of ten or more measured distances between successive maxima or minima on each photograph. There was no perceptible change in wave length with distance from the vibration source.

As in the previous studies on polystyrene, the damping was within experimental error exponential; a plot of ln $\delta$ ($\delta$ being the double refraction in the solution observed at the maxima and minima of the stroboscopically immobilized wave) against $x$, the distance from the vibrator plate, was a straight line.[7] The reciprocal slope of the line is $x_0$, the critical damping distance. Values of $\delta$ can be calculated from the equation[6] $\tan \delta = \tan \Delta \sin 2\alpha$, where $\Delta$ is the relative retardation corresponding the Babinet line displacement, and $\alpha$ is the angle between the axes of the Babinet and the polarizer. However, a simpler procedure was followed; since $\sin 2\alpha$ is small (in our case $\alpha = 2°14'$), $\tan \delta$ is nearly equal to $\delta$, and $\tan \Delta$ is proportional to $\delta$; it follows that the reciprocal slope of a plot of ln $\tan \Delta$ against $x$ is $x_0$, and the critical damping distance is obtained without calculating $\delta$ directly.

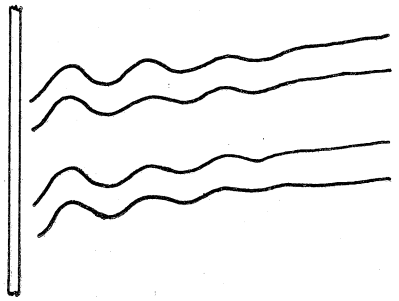


Fig. 1.—Tracing of wave pattern in 15.7% polyisobutylene in chlorobenzene, 17.1°, 400 cycles/sec. The vibrator plate is indicated at left.

The wave rigidity,[1] $\tilde{G}$, was calculated as $\lambda^2\nu^2\rho$, where $\lambda$ is the measured wave length, $\nu$ the frequency, and $\rho$ the density. The latter value was calculated assuming additivity of the volumes of polymer and solvent. The dimensionless damping index,[9] $\lambda/x_0$, was used to characterize the severity of the damping.

Different sizes of cells and vibrator plates were used in four combinations (Fig. 2). Comparisons of the same solutions with different cells and plates

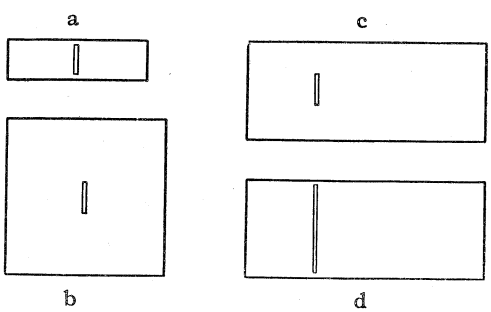



Fig. 2.—Cell-plate combinations (top view). Cell sizes: a, 1.0 × 3.5 cm.: b, 4.0 × 4.0 cm.; c and d, 2.5 × 6.0 cm. Plate widths: a, b, and c, 0.8 cm.; d, 2.5 cm.

(6) J. D. Ferry, *Rev. Sci. Instruments*, **12**, 79 (1941).

(7) The first maximum or minimum often deviated materially. This is to be expected from theoretical calculations[8] of wave propagation in which the finite dimensions of the cell are taken into account. The calculations show that the value of $x_0$ determined as outlined here is within a few per cent., and hence well within experimental error, of the value which would characterize the damping of a plane wave in a medium of infinite extent.[9]

(8) F. T. Adler, W. M. Sawyer and J. D. Ferry, unpublished work.

(9) J. D. Ferry, W. M. Sawyer and J. N. Ashworth, *J. Polymer Sci.*, **2**, 593 (1947).

revealed no differences in $\tilde{G}$ and $\lambda/x_0$ exceeding experimental scatter. Most measurements were made with combinations (c) and (d), which provided room for longer wave trains. The widest frequency range was achieved with combination (d). The cell used in (c) and (d) was of aluminum with glass windows cemented with litharge and glycerol.

In some cases the dynamic rigidity $G'$ and the dynamic viscosity $\eta'$, which are useful for comparison with results of other experimental methods and for theoretical interpretation, were calculated by the equations[9]

$$G' = \tilde{G}\frac{4\pi^2[4\pi^2 - (\lambda/x_0)^2]}{[4\pi^2 + (\lambda/x_0)^2]^2} \quad (1)$$

$$\eta' = \frac{\tilde{G}}{\omega}\frac{16\pi^3\lambda/x_0}{[4\pi^2 + (\lambda/x_0)^2]^2} \quad (2)$$

where $\omega$ is $2\pi$ times the frequency.

## Results

**Dispersion of Rigidity.**—In experiments where a frequency range of five or sixfold was achieved, a small increase in $\tilde{G}$ with increasing frequency was observed. Representative data for clarified polymer in chlorobenzene solutions are given in Table I (concentrations expressed in weight per cent). The dependence of $\tilde{G}$ on the frequency can be approximated by straight lines of equal slope (Fig. 3).

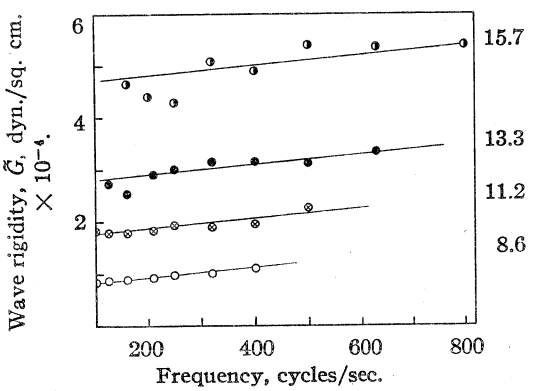



Fig. 3.—$\tilde{G}$ plotted against frequency for chlorobenzene solutions at 25°. Figures opposite the lines denote concentrations in weight per cent.

In other experiments, where the frequency range was limited to three or fourfold, the dispersion of $\tilde{G}$ was within experimental scatter (5 to 10%). It was, in any case, so small that the dispersion function appears to be essentially a plateau in the range from 100 to 1000 cycles/sec. for our solutions. Accordingly, to determine the dependence of $\tilde{G}$ on concentration and temperature, values measured at different frequencies were simply averaged.

**Dependence of Rigidity on Concentration and Temperature.**—Average values of $\tilde{G}$, together with the frequency range covered in each case, are given for solutions in *n*-heptane at different concentrations and temperatures in Table II. At constant weight concentration, the rigidity decreases somewhat with increasing temperature,

TABLE I

DISPERSION OF $\tilde{G}$ IN CHLOROBENZENE SOLUTIONS AT 25°

| Frequency, cycles/sec. | $\tilde{G}$, dyn/sq. cm., $\times 10^{-4}$ Concn. = 8.6% | 11.2% | 13.3% | 15.7% |
|---|---|---|---|---|
| 100 | .. | 1.82 | .. | .. |
| 110 | 0.85 | .. | .. | .. |
| 125 | .88 | 1.80 | 2.73 | .. |
| 160 | .89 | 1.80 | 2.54 | 4.67 |
| 200 | .. | .. | .. | 4.38 |
| 210 | .96 | 1.83 | 2.90 | .. |
| 250 | .99 | 1.93 | 3.00 | 4.31 |
| 320 | 1.00 | 1.89 | 3.15 | 5.11 |
| 400 | 1.12 | 1.93 | 3.16 | 4.90 |
| 500 | .. | 2.24 | 3.13 | 5.39 |
| 630 | .. | .. | 3.36 | 5.34 |
| 800 | .. | .. | .. | 5.41 |

TABLE II

$\tilde{G}$ OF *n*-HEPTANE SOLUTIONS

| Concn. polymer, % | Frequency range, cycles/sec. | Temp., °C. | $c$, g./cc. | $\tilde{G}$, dyn./sq. cm., $\times 10^{-4}$ | $\tilde{G}/c^2$ $\times 10^{-8}$ |
|---|---|---|---|---|---|
| 13.1 | 125–320 | −6.9 | 0.0955 | 0.66 | 7.5 |
| | | 1.3 | .0946 | .62 | 7.3 |
| | | 10.5 | .0935 | .59 | 7.2 |
| | | 18.5 | .0926 | .57 | 7.2 |
| | | 28.4 | .0916 | .57 | 7.4 |
| | | 35.2 | .0908 | .51 | 6.8 |
| | | | | Av. | 7.2 |
| 15.4 | 160–400 | 1.0 | 0.112 | 1.12 | 8.0 |
| | | 10.9 | .111 | 1.05 | 7.7 |
| | | 18.8 | .110 | 1.12 | 8.4 |
| | | 27.5 | .109 | 1.06 | 8.2 |
| | | 35.4 | .108 | 1.00 | 8.0 |
| | | | | Av. | 8.1 |
| 20.1 | 125–500 | −7.8 | 0.149 | 2.88 | 8.7 |
| | | 0.9 | .148 | 2.82 | 8.7 |
| | | 10.9 | .146 | 2.59 | 8.4 |
| | | 19.3 | .145 | 2.98 | 9.7 |
| | | 27.8 | .143 | 2.59 | 8.7 |
| | | 34.6 | .144 | 2.50 | 8.7 |
| | | | | Av. | 8.8 |
| 25.0 | 125–630 | −5.0 | 0.188 | 5.56 | 8.4 |
| | | 1.3 | .187 | 5.48 | 8.4 |
| | | 11.1 | .185 | 5.49 | 8.8 |
| | | 19.5 | .183 | 5.33 | 8.8 |
| | | 28.4 | .181 | 5.09 | 8.6 |
| | | 36.5 | .179 | 4.88 | 8.6 |
| | | | | Av. | 8.6 |
| 29.7 | 160–800 | −6.0 | 0.226 | 9.01 | 7.8 |
| | | 1.4 | .224 | 8.98 | 7.9 |
| | | 10.9 | .221 | 8.23 | 7.6 |
| | | 18.9 | .219 | 8.41 | 8.0 |
| | | 28.3 | .217 | 7.91 | 7.7 |
| | | | | Av. | 7.8 |
| | | | | Over-all average | 8.1 |

about 0.3% per degree. In the case of polystyrene–xylene solutions, where a somewhat more pronounced decrease was observed,[3] the temperature dependence of $\tilde{G}$ could be described by the relation $\tilde{G} = A_G e^{Q_G/RT}$, with $Q_G = 1500$ cal. The results of Table II can also be fitted by this relation, with $Q_G = 550$ cal. However, for polyisobutylene, the temperature dependence at constant weight concentration can be entirely attributed to the change in volume concentration due to thermal expansion; when rigidities are compared at constant *volume* concentration, the temperature dependence vanishes.

Proportionality of $\tilde{G}$ to the third power of $c$, the volume concentration (g./cc.) was anticipated from the behavior of polystyrene.[10] The last column of Table II shows that for polyisobutylene in *n*-heptane $\tilde{G}/c^3$ is constant for each solution over a temperature range from about −7 to 35°. The average values of $\tilde{G}/c^3$ for each solution are also close together, and no trend with increasing concentration is apparent.[12]

TABLE III

VALUES OF $\tilde{G}/c^3$ FOR SOLUTIONS IN XYLENE, ISOÖCTANE, AND CHLOROBENZENE

| Solvent | Concn., wt. % | $\tilde{G}/c^3 \times 10^{-6}$ | Av. |
|---|---|---|---|
| Xylene | 10.3[e] | 8.9 | |
| | 11.5[a] | 9.3 | |
| | 11.5[b] | 9.7 | |
| | 15.3[a] | 9.6 | |
| | 15.3[c] | 9.6 | |
| | 18.5[c] | 8.9 | |
| | 18.7[a,e] | 11.1 | |
| | 18.7[c,e] | 9.7 | 9.4 |
| | 18.7[d,e] | 11.1 | |
| | 24.5[c] | 8.6 | |
| | 25.1[c,e] | 9.1 | |
| | 25.3[a] | 9.5 | |
| | 28.7[c] | 7.9 | |
| | 33.5[c] | 7.9 | |
| Isoöctane | 10.7[d,f] | 12.2 | |
| | 15.4[c] | 9.0 | 10.1 |
| | 19.7[d] | 10.2 | |
| | 26.4[d,f] | 9.1 | |
| Chlorobenzene | 8.6[d,e,f] | 11.9 | |
| | 11.2[d,e,f] | 10.8 | 10.9 |
| | 13.3[d,e,f] | 10.2 | |
| | 15.7[d,e] | 10.5 | |

[a] Cell-plate combination a. [b] Cell-plate combination b. [c] Cell-plate combination c. [d] Cell-plate combination d. [e] Clarified polymer. [f] Measured at 25° only.

(10) Proportionality to $c^3$ was shown for the rigidity of polystyrene solutions after a calculated low-frequency component of rigidity had been subtracted from the measured values.[11] However, the low-frequency component was so small that the relation holds also for the total rigidity (see Fig. 7).

(11) J. D. Ferry, THIS JOURNAL, **64**, 1330 (1942).

(12) Since the frequency range represented by the average $\tilde{G}$ changes somewhat with concentration (Table II), this does not quite represent a test of the third power relation at constant frequency. Values interpolated from Fig. 3 at constant frequency and plotted logarithmically against log $c$ give slopes ranging from 2.7 to 3.0. However, these small differences are too close to experimental error to attempt to describe at present.

Data for the other solvents are given in detail in the thesis[5] on which this paper is based. In each case $\tilde{G}$ decreased about 0.3% per degree at constant weight concentration, but $\tilde{G}/c^3$ was independent of temperature and concentration.[13] The values of $\tilde{G}/c^3$ averaged at different temperatures for each solution are given in Table III.

In Table IV, the over-all averages of $\tilde{G}/c^3$ for the four solvents are correlated with the respective intrinsic viscosities at 20 and 30°. The intrinsic viscosities show that the solvents are arranged in the order of decreasing solvent power; the temperature dependence, which is probably significant only for chlorobenzene, also indicates that this is a somewhat poorer solvent than the others. The differences are on the whole slight, but it is clear that the order of decreasing intrinsic viscosity is the order of increasing rigidity.

TABLE IV

AVERAGE VALUES OF $\tilde{G}/c^3$ AND INTRINSIC VISCOSITIES

| Solvent | $\tilde{G}/c^3$, (dyn./sq. cm.) (g./cc.)$^{-3}$ $\times 10^{-6}$ | $[\eta]$, 20° | $[\eta]$, 30° |
|---|---|---|---|
| *n*-Heptane | 8.1 | 2.68 | 2.60 |
| Xylene | 9.4 | 2.63 | 2.67 |
| Isoöctane | 10.1 | 2.45 | 2.36 |
| Chlorobenzene | 10.9 | 2.15 | 2.35 |

**Damping.**—In almost all cases, the damping index, $\lambda/x_0$, varied within the rather narrow range from 0.6 to 1.2. Except in a few cases, the experimental scatter did not permit a reliable study of the dependence of damping index on concentration, temperature, or nature of solvent; as a first approximation, it was independent of all these variables.

With increasing frequency, $\lambda/x_0$ generally decreased. The best measurements, on chlorobenzene solutions, are given in Table V and plotted against the logarithm of the frequency in Fig. 4.

**Dynamic Rigidity and Viscosity.**—From the data in Tables I and V, the dynamic rigidity $G'$ and the dynamic viscosity $\eta'$ of the chlorobenzene

TABLE V

DAMPING INDICES IN CHLOROBENZENE AT 25°

| Frequency, cycles/sec. | Damping index, $\lambda/x_0$ Concn. = 11.2% | 13.3% | 15.7% |
|---|---|---|---|
| 125 | 1.14 | .. | .. |
| 160 | 0.97 | .. | .. |
| 200 | .. | .. | 1.20 |
| 210 | 1.00 | 0.96 | .. |
| 250 | 0.79 | .96 | 0.86 |
| 320 | .77 | .72 | .94 |
| 400 | .64 | .69 | .55 |
| 500 | .73 | .66 | .82 |
| 630 | .. | .70 | .74 |
| 800 | .. | .. | .64 |

(13) Since the thermal expansion coefficients of the solvents are all very nearly one-tenth per cent. per degree, $c^3$ decreases three-tenths per cent. per degree, accounting exactly for the observed decrease in rigidity.

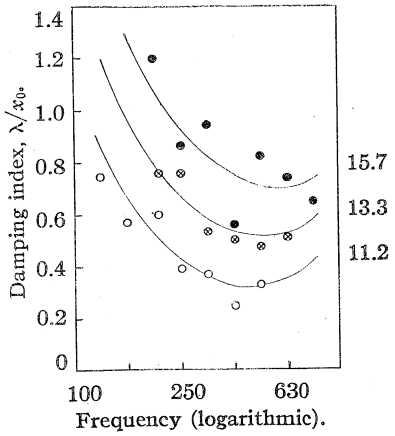



Fig. 4.—Damping indices for chlorobenzene solutions, plotted against the logarithm of the frequency. Figures opposite the curves denote concentrations in weight per cent. The ordinate scale refers to the 15.7% curve; the curves for 13.3% and 11.2% have been shifted downward 0.2 and 0.4 unit, respectively. The curves are calculated for retarded Maxwell elements, using the constants of Table VI.

solutions were calculated by equations (1) and (2), and they are plotted against the logarithm of the frequency in Figs. 5 and 6. The rigidity $G'$ is from three to ten per cent. smaller than $\tilde{G}$. The viscosity $\eta'$ is of the order of a few poises and falls off rapidly with increasing frequency; this is the usual behavior found for concentrated polymer solutions by direct measurements with transducer methods.[14] By contrast, the viscosity in steady flow of these solutions is of the order of hundreds to thousands of poises.

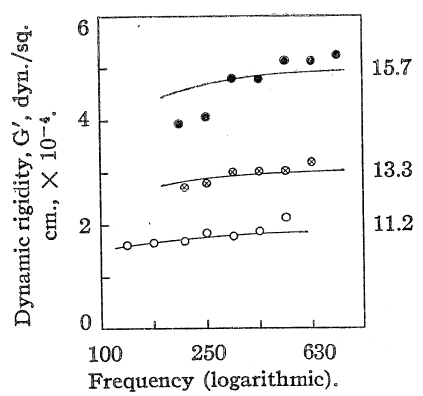



Fig. 5.—Dynamic rigidities of chlorobenzene solutions, plotted against the logarithm of the frequency. Figures opposite the curves denote concentrations in weight per cent. The curves are calculated for retarded Maxwell elements, using the constants of Table VI.

Since $G'$ never differs from $\tilde{G}$ by more than 10% in our experiments, the two rigidities can be taken as equivalent for some purposes, as in Fig. 7,

(14) T. L. Smith, J. D. Ferry and F. W. Schremp, *J. Appl. Physics*, in press.

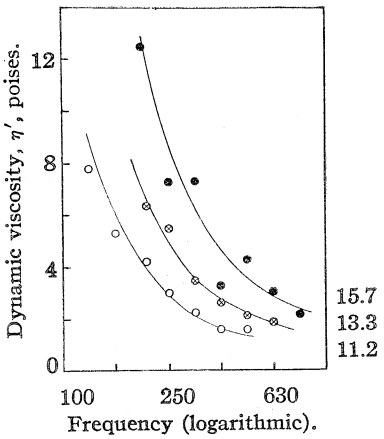



Fig. 6.—Dynamic viscosities of chlorobenzene solutions, plotted against the logarithm of the frequency. Figures opposite the curves denote concentrations in weight per cent. The curves are calculated for retarded Maxwell elements, using the constants of Table VI.

where $\tilde{G}$ values for solutions are compared with $G'$ for the undiluted polymer. In most cases the accuracy of $\lambda/x_0$ is insufficient for an adequate calculation of $\eta'$, although its order of magnitude can always be estimated from Eq. 2, since $\lambda/x_0$ almost never exceeds the range 0.6–1.2.

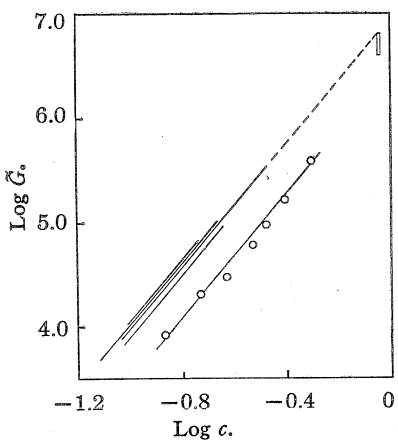



Fig. 7.—Log $\tilde{G}$ plotted against log $c$. Solid lines (drawn with slope of 3), in descending order: polyisobutylene in chlorobenzene, isoöctane, xylene, and heptane; polystyrene in xylene (points from ref. 3). Rectangle: $G'$ of pure polyisobutylene (ref. 16).

## Discussion

**Representation of Frequency Dependence by a Mechanical Model.**—A simple model which can imitate approximately the frequency dependence of mechanical properties of concentrated polymer solutions in the audio frequency range is a retarded Maxwell element,[9] with a viscous dashpot ($\eta_S$) in series with a parallel combination of spring ($G$) and dashpot ($\eta_P$). The three model constants are frequency-independent. In the range where $\omega\eta_S/G \sim 10$, when $\eta_P \ll \eta_S$, the

model gives the following dispersion behavior: both $\tilde{G}$ and $G'$ are represented by plateaus, almost equal to $G$, with a drop at lower frequencies, while the former rises at higher frequencies; $\eta'$ decreases with increasing frequency; and $\lambda/x_0$ goes through a minimum. The equations are given elsewhere,[9,15] together with illustrative graphs.

This behavior is qualitatively similar to the experimental dispersion shown in Figs. 3–6; and, for these chlorobenzene solutions, a fairly good quantitative fit is obtained, taking $\eta_P/\eta_S = 0.013$. The model constants chosen are given in Table VI, and the calculated curves are drawn in Figs. 4–6.

As would be expected from the fact that $G \cong G' \cong \tilde{G}$ in this frequency range, the frequency-independent rigidity $G$ is proportional to $c^3$. Both viscosities are proportional to $c^2$ in this case, so that the two relaxation times, $\tau_S = \eta_S/G$ and $\tau_P = \eta_P/G$, are inversely proportional to $c$. It should be noted that $\eta_S$ is smaller than the steady flow viscosity by a factor of about 0.03, so the utility of the model does not extend to zero frequency.

For most of the other solutions, experimental scatter does not permit model fitting. However, from the magnitudes of $\lambda/x_0$, it is clear that any application of a retarded Maxwell element would be restricted to $\eta_P/\eta_S$ ratios of the order of 0.01. For the xylene solutions, $\tau_S$ appeared to increase with increasing concentration.

TABLE VI

CONSTANTS OF RETARDED MAXWELL ELEMENTS DESCRIBING DISPERSION IN CHLOROBENZENE SOLUTIONS AT 25°

| Concn., g./cc. | $G \times 10^{-6}$, dyn/sq. cm. | $\eta_S$ poise | $\eta_P$ poise | $G/c^3 \times 10^{-6}$ | $\eta_S/c^2 \times 10^{-5}$ |
|---|---|---|---|---|---|
| 0.120 | 1.9 | 61 | 0.79 | 10.9 | 4.1 |
| .143 | 3.1 | 90 | 1.1 | 10.6 | 4.3 |
| .167 | 5.1 | 128 | 1.6 | 10.9 | 4.5 |

It is evident that important frequency-dependent phenomena must exist at lower frequencies than those employed here, since the rigidity must drop from the plateau exhibited in our frequency range to zero under constant stress.

**Dependence of Rigidity on Concentration.**—Pending measurements of dynamic rigidity at higher concentrations, which will require a different experimental method, it is of interest to extrapolate the $c^3$ relation to the pure polymer ($c$ = 0.91 g./cc.). Of course, the four solvents do not extrapolate into the same point, but the differences are small, as shown in Fig. 7; the value obtained is about $6 \times 10^6$ dyn./sq. cm. at 25°. This agrees quite well with measurements of $G'$ on the same sample of polymer by a twin transducer method,[16] which gave a range from 4 to $6 \times 10^6$ in the frequency range from 50 to 250 cycles/sec.

(15) J. D. Ferry, *J. Res. Nat. Bureau Standards*, **41**, 53 (1948).

(16) R. S. Marvin, E. R. Fitzgerald and J. D. Ferry, reported at the Los Angeles meeting of the Rubber Division of the American Chemical Society, July 22, 1948.

As a first approximation, apparently, all the solutions can be regarded as dilutions of the solid polymer, differing from it only in concentration and not fundamentally in structure.

The earlier data for polystyrene–xylene solutions[3] at 25° are also plotted in Fig. 7. In the concentration range studied, up to 52% polymer, the proportionality of $\tilde{G}$ to $c^3$ also holds; the rigidities are smaller than those of the polyisobutylene solutions by about a factor of three. The polystyrene rigidities, however, do not extrapolate into the rigidity of the pure polymer (about $5 \times 10^9$). This difference is undoubtedly associated with the fact that at 25° polyisobutylene is above, and polystyrene below, its brittle point. In the polystyrene–xylene system, the brittle transition must occur somewhere between 50 and 100% polymer at 25°.

**Origin of Rigidity.**—The rigidity observed in concentrated solutions of polyisobutylene and other polymers is no doubt due to storage of elastic energy in the deformation of long chain molecules. This could be accomplished by bending and stretching of bonds, or orientation entropy (rubber-like elasticity), or twist against the hindering potential opposing free rotation around bonds. For tension applied to the ends of an isolated contorted molecule, Kuhn[17] has shown that the contributions to deformation from bond bending and stretching are extremely small. In an analysis of the other two mechanisms, he finds that the molecular spring constant (force per unit extension) is inversely proportional to the number of bonds for orientation entropy, and inversely proportional to the square of this number for twist against the hindering potential.

To apply these considerations to a concentrated solution, we suppose the presence of a transitory network structure, whose net points are entanglements where two chains happen to be tightly kinked around each other. Then the molecular spring is not the entire molecule but the average strand between two points of entanglement. The number of entanglements should be proportional to the square of the volume concentration; if the strands are sufficiently short compared with the total molecular length so that free ends are negligible, the number of strands should also be proportional to the square of the concentration and their average length should be inversely proportional to the first power.

It follows[15] that the network rigidity should be proportional to the square of the volume concentration for rubber-like elasticity, but to the cube of the concentration for twisting against hindered rotation. The experimental concentration dependence thus corresponds to the latter mechanism.

On the basis of the network hypothesis, the temperature independence of $G/c^3$ would mean that in the polyisobutylene solutions the entangle-

(17) W. Kuhn, *Helv. Chim. Acta*, **29**, 609, 830, 1095 (1946).

ments are purely statistical, and not influenced by any perceptible energy differences. The similarity of the values in different solvents would have the same significance. The small differences which are observed could be attributed to differences in the entropy of entanglement, entanglements being slightly more probable in chlorobenzene, for example. A lower intrinsic viscosity, reflecting a greater tendency for the polymer chain to coil back on itself, should be associated with a greater entanglement probability[18] and hence a higher rigidity, in agreement with Table IV.

The network hypothesis predicts that the rigidity should be independent of molecular weight, provided the latter is high enough so that free ends outside entanglements can be neglected. Data are not yet available to test this conclusion.

From mechanical measurements at much higher frequencies on undiluted polyisobutylenes of low molecular weight, Mason and Baker[19] have also postulated an elastic mechanism involving twisting of the polymer chains.

**Interpretation of Model Constants.**—If $\tilde{G}$ (Table VI) represents the hindered rotation elasticity mechanism, $\eta_S$ could represent relaxation by rotation over the barriers or by slippage at entanglement points. Probably both mechanisms should occur, in different frequency ranges. According to Kuhn,[17] the former should be represented by a single relaxation time, directly proportional to the number of bonds involved; for the network, then, the relaxation time should be inversely proportional to concentration, and $\eta_S$ should be proportional to $c^2$. This appears to be the case for the chlorobenzene solutions. However, measurements should be extended to a broader frequency range before a detailed interpretation is attempted.

(18) A lower intrinsic viscosity means that in very dilute solution a smaller volume is pervaded by the average polymer coil. In concentrated solution, also, the volume pervaded is probably smaller. In concentrated solution, however, the domain of each coil is thoroughly interlaced by other molecules. The number of entanglements per cc. should be practically independent of the size of coil domain; but it should be markedly influenced by local chain configuration, back kinking giving rise to "snagging," and hence higher entanglement probability.

(19) W. P. Mason, W. O. Baker, H. J. McSkimin and J. H. Heiss, *Phys. Rev.*, **73**, 1074 (1948).

## Summary

1. The propagation of transverse waves in solutions of polyisobutylene ($\bar{M}_\eta$ = 1,200,000) in *n*-heptane, xylene, isoöctane, and chlorobenzene has been studied as a function of frequency, temperature, and concentration.

2. The rigidity $\tilde{G}$ increases only slightly with frequency in the range from 100 to 1000 cycles/sec.

3. At constant weight concentration, $\tilde{G}$ decreases slightly with increasing temperature; at constant volume concentration ($c$), $\tilde{G}$ is independent of temperature.

4. The rigidity is proportional to $c^3$; in the different solvents, the ratio $\tilde{G}/c^3$ increases slightly in the order named above, which is also the order of decreasing intrinsic viscosities (at 20°).

5. The damping index, $\lambda/x_0$, decreases with increasing frequency or passes through a minimum.

6. The dispersion of rigidity and damping in chlorobenzene solutions can be fitted by a retarded Maxwell element with a ratio of parallel to series viscosity of 0.013.

7. The concentration dependence of $\tilde{G}$ can be interpreted in terms of a transient network structure with storage of elastic energy by twist against potentials opposing free rotation about bonds in the chains.

MADISON, WISCONSIN RECEIVED AUGUST 30, 1948

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

# Variation of Monomer Pressure with Degree of Conversion in Emulsion Polymerization of Butadiene and of Butadiene–Styrene[1]

BY E. J. MEEHAN

## Introduction

During a polymerization reaction the pressure of the unpolymerized monomer decreases as the reaction proceeds to completion. The way in which the pressure changes with the degree of conversion of monomer to polymer depends upon the monomer and upon the nature of the polymerization system. Different relations between pressure and conversion are observed in a homogeneous system (solution or bulk polymerization) and in a heterogeneous system (emulsion polymerization).

Pressure measurements can yield certain information about the nature of the polymerization system. Thus in a homogeneous system pressure measurements gave directly the value of the monomer activity in the thermal polymerization of pure styrene.[1a] In the emulsion polymerization of a monomer which is only slightly soluble in water, the unreacted monomer is present as a separate (oil) phase during the earlier part of the reaction; in the latter part of the reaction the unre-

(1) This Investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(1a) Walling, Briggs and Mayo, THIS JOURNAL, **68**, 1145 (1946).

acted monomer is entirely dissolved in the polymer particles. The pressure of the system evidently indicates the exact point at which the separate monomer phase disappears. It was shown by W. B. Reynolds[2] that the pressure of butadiene remains constant and equal to the vapor pressure of pure butadiene during more than the first half of the emulsion polymerization of butadiene, corresponding to the presence of a separate phase of butadiene. The disappearance of this phase is made evident by an abrupt decrease of the pressure from that of pure butadiene. As another example the application to copolymerization studies may be mentioned. The pressure of a copolymerizing system is related to the composition of the copolymer which is formed. The pressure may increase, remain unchanged, or decrease during the first part of the reaction, depending on whether the copolymer contains less than, the same amount as, or more than, the relative amount of the more volatile monomer present at the beginning of the reaction.

It is possible to give a simple interpretation of the data of a copolymerizing system only so long as the oil phase is present. After this phase has disappeared one is dealing with a solution of excess of monomers in a suspension of polymer. If the monomer–polymer system were ideal in the sense that the partial pressure of the monomer would be proportional to the mole fraction of the monomer, there would be no significant decrease in pressure until the consumption of monomer had become substantially complete. Thus in the conversion of a monomer of molecular weight 100 into a polymer of number-average molecular weight 40,000, the mole fraction of unreacted monomer in the monomer–polymer system is 0.99 at 80% conversion and is 0.80 at 99% conversion. Actually a marked decrease in pressure occurs at conversions smaller than 80%, because polymer–solvent systems do not follow Raoult's law; the entropy of mixing is very different from the entropy of mixing given by classical thermodynamics.

In this paper data are given showing the dependence of pressure upon conversion in the emulsion polymerization of butadiene and of butadiene–styrene mixtures. The points of principal interest were the disappearance of the monomer phase in both cases and the connection with copolymer composition in the latter case. A discussion of data obtained after the disappearance of the oil phase is not given at the present time.

## Experimental

### A. Preparation of Polymerization Charges

The following formula was used in the preparation of the charges: temperature, 50 or 30°

| Ingredient | Parts by weight |
|---|---|
| Monomer(s)[a] | 100 |
| Water | 180 |
| Soap | Variable[b] |
| Potassium persulfate | 0.3 |
| *n*-Dodecylmercaptan | 0.5 |

[a] Either butadiene or butadiene (75)–styrene (25). [b] Usually 5; otherwise varied from 10 to 5/8.

The sources and purities of the various ingredients were the same as in previous investigations.[3] The charges were prepared either in 4-ounce glass bottles with metal screwcaps lined with self-sealing gasket material obtained from Dr. E. A. Willson of the B. F. Goodrich Company, or in a special metal reaction vessel described in a later section.

### B. Pressure Measurements

1. **Use of Pressure Gages.**—Some measurements were made using ordinary pressure gages by the method described by Harrison and Meincke.[4] The charges were prepared in glass bottles, and the pressure was measured by removing the bottle from the 50° thermostat and inserting through the self-sealing gasket a pressure gage equipped with a hypodermic needle. To minimize loss of butadiene from the bottle during this operation, the gage was maintained at a temperature of about 51° and the pressure in the gage was maintained at a pressure approximately equal to or greater than that expected in the bottle. The precision of these pressure measurements is about 2 pounds per square inch.

2. **Manometric Measurements.**—Houston and Briggs at Goodrich[5] constructed a mercury manometer of sufficient height to permit measurement on butadiene-containing systems at 50°, and determined pressure–conversion relations for a number of comonomer systems. A mercury manometer of similar dimensions was constructed in this Laboratory and used in connection with a completely closed polymerization system. The polymerizations were carried out in a chromium plated vessel with a capacity of about 100 ml. The vessel, subjected to horizontal agitation, was connected to the manometer system by means of a flexible brass helix leading to an iron vessel which served as mercury reservoir for the open-end manometer. Both helix and reservoir were immersed in the thermostat; this prevented the distillation of butadiene from the reaction vessel at 50° into the manometer. Since the mercury well was about one meter above the lowest point of the manometer it was possible to read pressures lower than atmospheric pressure.

In use, the polymerization vessel was filled with the ingredients of the charge and sealed. It was connected to the helix after the helix and the air space in the mercury well had been pumped out and flushed with butadiene several times to remove the last trace of oxygen. The pressure was read to the nearest millimeter during the desired period of time. At the end of the experiment hydroquinone was injected and the conversion was determined by the usual method of total solids. The pressures reported correspond to mm. at room temperature rather than at 0°. The over-all accuracy of the measurements was estimated to be better than 0.5%.

## Results

A. **Monomers and Monomer Mixtures.**—Accurate values of the vapor pressure and other thermal properties of pure 1,3-butadiene have been given by the Bureau of Standards.[6] The vapor pressure found at 50° was 4264 mm. (corrected to a column of mercury at 0°), and the rate of change of vapor pressure with temperature at 50° was 112 mm. per degree (calculated from the empirical pressure–temperature equation).

(2) W. B. Reynolds, private communication, March, 1944.

(3) E. J. Meehan, *J. Polymer Science*, **1**, 175 (1946).

(4) S. A. Harrison and E. R. Meincke, *Anal. Chem.*, **20**, 47 (1948).

(5) R. J. Houston and R. A. Briggs, private communication, Nov. 1, 1945.

(6) R. B. Scott, C. H. Meyers, R. D. Rands, Jr., F. G. Brickwedde and N. Bekkedahl, *J. Res. Nat. Bur. Standards*, **35**, 39 (1945).

The vapor pressure of butadiene at 50° was found in this research to be 4.27 meters with an average deviation of about 0.01 meter. This value agrees well with that of the Bureau of Standards; the precision of 0.01 meter indicates that the temperature was controlled within about 0.1°. Accurate values of the vapor pressure of styrene have been given by Pitzer, Guttman and Westrum[7] who found the vapor pressure at 50° to be 24.23 mm. mercury. The vapor pressure of styrene has been measured also by Patnode and Schreiber.[8] From the empirical equation given by these authors, one calculates that at 50°, $p = 24.4$ mm.

Known mixtures of butadiene and styrene of mole fraction of butadiene ranging from 1.000 to 0.278 were prepared in the metal vessel by adding a known amount of styrene by pipet, followed by the addition of slightly more than the desired weight of butadiene, which had been liquefied in Dry Ice–acetone. The excess of butadiene was allowed to evaporate until the desired weight was present, and the vessel was then quickly sealed. (The amount of styrene which evaporates with the excess of butadiene is negligibly small.) The observed pressures of the mixtures were found to agree within experimental error with the values calculated from the pressures of the pure monomers on the assumption that they form an ideal solution.

## B. Vapor Pressure of Polymerizing Systems

**1. Pressure Variation During the Emulsion Polymerization of Butadiene.**—It was shown already by Reynolds[2] that the pressure remained constant during the first (approximately) 60% conversion in the emulsion polymerization of butadiene. The experiments described now were directed to establish whether or not the conversion at which the butadiene pressure first becomes less than the pressure of pure butadiene depends on the amount of soap initially present in the charge. Charges were prepared according to the previously quoted recipe with the amount of soap varied from 10 ("2 soap") to $^5/_8$ ("$^1/_8$ soap"). The results of the pressure and conversion determinations are given in Table I.

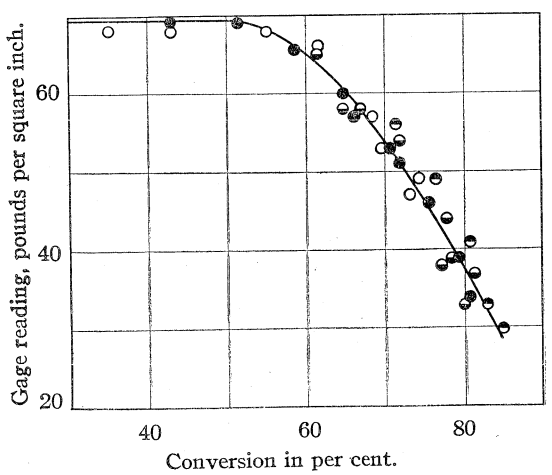



Fig. 1.—Emulsion polymerization of butadiene at 50°: ●, 2X soap; ◒, 1X soap; ◓, $^1/_4$X soap; ○, $^1/_8$X soap.

TABLE I

RELATION BETWEEN PRESSURE AND CONVERSION IN THE EMULSION POLYMERIZATION OF BUTADIENE AT 50°: 100 BUTADIENE, 180 WATER, 0.5 DDM, 0.3 PERSULFATE, AND S. F. FLAKES AS INDICATED

| Time in hr. | Gage pressure, pounds per sq. in. | Conv., % | Gage pressure, pounds per sq. in. | Conv., % |
|---|---|---|---|---|
| | A. 2 Soap | | | |
| 6 | .. | .. | 69 | 45.4 |
| 7 | .. | .. | 69 | 51.9 |
| 8 | .. | .. | 66 | 58.4 |
| 9 | 57 | 65.9 | 60 | 64.7 |
| 10 | 51 | 71.7 | 53 | 70.4 |
| 11 | 46 | 75.4 | .. | .. |
| 12 | 39 | 79.3 | .. | .. |
| 13 | 34 | 80.5 | .. | .. |
| | B. 1 Soap | | | |
| 13 | 64 | .. | .. | .. |
| 13.5 | .. | .. | 65 | 61.6 |
| 14 | 64 | .. | .. | .. |
| 15 | 62 | .. | 58 | 66.8 |
| 16 | 58 | 64.6 | 54 | 71.6 |
| 17 | 53 | 69.5 | 49 | .. |
| 18 | .. | | 44 | 77.7 |
| 18.25 | 47 | .. | .. | .. |
| 19 | .. | .. | 39 | 78.7 |
| 20 | 38 | 77.1 | 37 | 81.1 |
| 21 | 33 | 80 | | |
| | C. $^1/_4$ Soap | | | |
| 10 | 68 | .. | | |
| 15 | 68 | .. | | |
| 22 | 56 | 71.3 | | |
| 24 | 48 | 76.4 | | |
| 26 | 41 | 80.7 | | |
| 28 | 33 | 83.0 | | |
| 30 | 30 | 85.1 | | |
| | D. $^1/_8$ Soap | | | |
| 26 | 68 | .. | | |
| 31 | 68 | 55.1 | | |
| 33 | 66 | 61.5 | | |
| 35 | 57 | 68.3 | | |
| 37 | 49 | 74.2 | | |

The data of Table I are plotted as Fig. 1. It appears that the butadiene pressure first decreases at about 52% conversion, regardless of the amount of soap (from 2× to $^5/_8$×) initially present in the charge. The size of the polymer particles in the latex is changed greatly as the soap content is varied sixteen-fold. Thus it appears that the amount of butadiene which can dissolve in the polymer particles is determined only by the amount

(7) K. S. Pitzer, L. Guttman and E. F. Westrum, Jr., THIS JOURNAL, **68**, 2209 (1946).

(8) W. Patnode and W. J. Schreiber, *ibid.*, **61**, 3449 (1939).

of polymer and not by the size of the polymer particles.

This conclusion depends upon the assumption that an equilibrium value of the solubility is attained and maintained during the reaction. This was proved to be so in the following way. In several experiments the polymerization was halted (short-stopped) at various conversions greater and smaller than 52%, by the injection of hydroquinone. The pressure subsequently did not change upon continued rotation at 50° for twenty-four hours.

In a similar way (pressure gage technique) the pressure was determined during the emulsion polymerization of butadiene at 30°. It was found that the pressure drop occurred at the same conversion (52%) as at 50°, thus indicating that the solubility of butadiene in polybutadiene is not markedly temperature-dependent.

A few experiments were made with the accurate manometric technique with polybutadiene at 50° to verify the conclusions reached above on the basis of the gage measurements. In polymerizations with 1× and with 1/4× the ordinary amount of soap (5 parts per 100 parts monomers), it was found that the pressure drop occurred between 51–52% conversion.

**2. Variation of Pressure in the Emulsion Copolymerization of Butadiene–Styrene.**—The composition of the copolymer formed in the emulsion copolymerization of butadiene–styrene varies during the reaction.[9] The polymer initially formed contains relatively more butadiene than is present in the charge, so that the proportion of butadiene in the residual monomers decreases during the reaction. This causes a continual decrease in the pressure of the system apart from the relatively abrupt decrease which is observed when the separate phase of residual monomers disappears.

The variation of pressure with conversion up to about 60% conversion was determined accurately in two separate experiments for the previously-quoted mixture with 75 parts of butadiene, 25 parts of styrene and 5 parts of soap. The experiments were made by observing the pressure as a a function of time, and determining the conversion at the end of the experiment. The conversion at a given time could be calculated since it had been established that the rate of conversion in this recipe is constant up to more than 60% conversion. It was not attempted to adjust the weight of butadiene added to the reaction vessel to exactly the correct figure; moreover, some butadiene is lost in the operation of flushing out the manometer system to remove air. For these reasons the initial pressures observed in the experiments did not correspond exactly to that expected for a mixture containing 75.0% butadiene. Therefore all the observed pressures (after subtraction of 92 mm., corresponding to the vapor pressure of water at 50°) were corrected to an initial butadiene content of 75.0%, by multiplying all the values by the ratio of the theoretical initial pressure to the observed initial pressure. The data, corrected as described above, are given in Table II and Fig. 2.

(9) E. J. Meehan, *J. Polymer Science*, **1**, 318 (1946).

TABLE II

VARIATION OF MONOMER PRESSURE WITH CONVERSION IN THE EMULSION COPOLYMERIZATION OF BUTADIENE (75)–STYRENE (25) AT 50°

| Experiment A | | Experiment B | |
|---|---|---|---|
| Conversion, % | Pressure,[a] mm. | Conversion, % | Pressure,[a] mm. |
| 0 | 3650 | 0 | 3650 |
| 7.9 | 3641 | 3.5 | 3646 |
| 9.1 | 3641 | 6.9 | 3641 |
| 13.8 | 3637 | 13.8 | 3636 |
| 24.3 | 3620 | 25.9 | 3616 |
| 39.5 | 3586 | 34.6 | 3590 |
| 45.9 | 3546 | 41.6 | 3565 |
| 47.1 | 3527 | 48.4 | 3521 |
| 48.8 | 3506 | 50.4 | 3494 |
| 50.6 | 3487 | 50.9 | 3491 |
| 51.8 | 3464 | 51.6 | 3480 |
| 52.9 | 3431 | 55.1 | 3414 |
| 53.6 | 3424 | 57.0 | 3393 |
| 54.1 | 3406 | 62.6 | 3213 |
| | | 63.1 | 3199 |

[a] Adjusted to the theoretical initial pressure of 3650 mm. Hg.

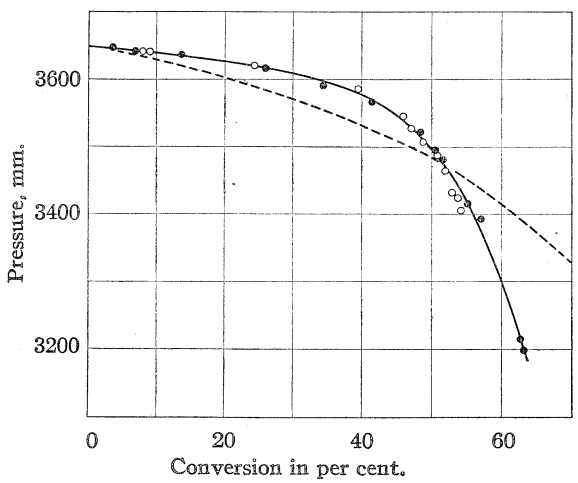



Fig. 2.—Pressure–conversion curve: emulsion polymerization of butadiene (75)–styrene (25), 50°.

Since the composition of the copolymer is known as a function of conversion[9] it is possible to calculate the composition of the total residual monomers at any conversion. Thus if a copolymer containing 19.2% styrene is formed at 50% conversion from a mixture which contained originally 75% butadiene, the residual monomers evidently contain 69.2% butadiene. This calculation does not give any information about the composition of the oil phase, since the residual monomers are in part dissolved in the polymer. So if the two monomers are dissolved to different extents in the

polymer, the distribution would result in a difference in the composition of the monomer mixture in the two phases.

If it is assumed (the correctness of the assumption can be checked immediately) that the composition of the free monomer phase is the same as that of the total monomer mixture, the dependence of pressure upon conversion can be calculated solely from the copolymer composition and the vapor pressures of the pure monomers, since the monomers form an ideal solution. The values so calculated are compared with the observed values in Fig. 2.

From Fig. 2 it is seen that up to about 50% conversion the observed and calculated pressures are in excellent agreement, the maximum deviation being less than 1.3%. The observed pressure becomes markedly less than the calculated value around 52% conversion, which indicates that it is at, or somewhere before, this conversion that the monomer phase disappears by solution in the polymer.

The point at which the monomer phase disappears also was determined approximately by visual examination of non-polymerizing systems. A quantity of "stripped" GR-S latex (*i. e.*, latex from which nearly all the unreacted monomers had been removed) of 69.3% conversion was obtained through the courtesy of Mr. W. K. Taft of the Government Rubber Pilot Plant in Akron, Ohio. To a definite amount of this latex of known polymer content, was added, in an ordinary polymerization bottle, such an amount of butadiene and styrene that the mixture polymer—monomer would correspond to 45, 50, 55 or 60% conversion. (For example, to prepare a latex corresponding to 55% conversion, 45 g. of mixed monomers was added to a quantity of latex which contained 55 g. of polymer.) The composition of the monomer mixture added to the latex was calculated by stoichiometry from the composition of the copolymer.[9] These polymer–monomer mixtures were then shaken at 50° and examined carefully and independently by a number of observers. A layer or droplets of residual monomers could be seen in the charges corresponding to 45 and 50% conversion, but not in those of 55 and 60% conversion. This is in agreement with the inference from the pressure measurements. It is of interest to note also, that there appeared to be a pronounced decrease in the viscosity of the latex upon the complete solution of the residual monomers. The charges corresponding to 45 and 50% conversion were noticeably more viscous than those of 55 and 60% conversion.

The agreement of observed and calculated values below 52% conversion shows that the assumption made in the calculation is essentially correct, which means that the monomers dissolve in the polymer particles in almost the same proportions that they are present in the total monomer mixture.

The conclusion that the composition of the monomer layer is not changed much by distribution with the polymer particles could be checked by direct experiments on non-polymerizing systems. (The measurements were not made with the accurate manometric method, but with the pressure gage-injection method.) To the stripped latex previously referred to, were added various amounts of different monomer mixtures, the amounts being chosen so that some undissolved monomer was present (*i. e.*, equivalent conversion less than 50%). It was found that the pressure of the monomer–polymer mixture was the same (within the limits of experimental uncertainty, 1–2%) as the pressure of the monomer mixture alone. This proves in a direct way, that there is little change in the composition of a butadiene–styrene mixture on dissolving in polymer.

Measurements of precision greater than 1% reveal a difference in the composition as a result of the distribution of the monomers between the phases. Consider the situation at exactly 40% conversion. The copolymer contains 18.7% styrene,[9] which corresponds to 70.8% butadiene in the total residual monomers. If the free monomer phase had this composition the hydrocarbon pressure would be 3527 mm. The actual pressure is 3576 mm. which corresponds to 72.5% butadiene in the monomer phase. Therefore the oil phase is slightly richer in butadiene than would correspond to the composition of the entire mixture, which means that relatively more styrene than butadiene is dissolved in the polymer particles.

If the solubility of butadiene in the copolymer were known, the amount of each monomer which is dissolved in the copolymer could be calculated since the compositions of the total monomer mixture and of the separate monomer phase are known. As an approximation, the solubility of butadiene in the copolymer may be taken equal to the solubility in polybutadiene, which is known from the observed pressure drop to be about 48/52 or 0.92 g. of monomer per g. of polymer. With this assumption, it may be calculated that at 40% conversion, 87% of the residual butadiene and 88% of the residual styrene are dissolved in the polymer, and at 20% conversion, about 32% of the residual butadiene and 37% of the residual styrene are dissolved. It should be emphasized that these calculated values are of only an approximate nature.

I wish to thank Dr. I. M. Kolthoff for many discussions and suggestions.

## Summary

The pressure of the residual monomer(s) has been measured during the emulsion polymerization of butadiene and of butadiene–styrene mixtures. During the emulsion polymerization of butadiene the monomer pressure is constant and equal to that of pure butadiene as long as a separate phase of undissolved butadiene is present.

The first drop in pressure corresponds to the disappearance of the phase of residual monomer by solution in the polymer. This occurs at about 52% conversion corresponding to a "solubility" of 0.92 g. of butadiene per g. of polybutadiene. This solubility is approximately the same at 30 and at 50°, and is unaffected by a sixteen-fold variation in the amount of soap used in preparing the emulsion charges. Equilibrium as regards distribution of monomer between the oil phase and the polymer phase appears to be maintained during the polymerization at 50°.

During the emulsion copolymerization of butadiene–styrene, the pressure changes continuously from the start of the reaction because of the change in the composition of the copolymer which is formed. At about 50–52% conversion a fairly abrupt drop in pressure occurs corresponding to the solution of excess monomers. The composition of the oil phase corresponds closely to the composition of the total residual monomers, which indicates that only a small change in composition of a butadiene–styrene mixture results from its distribution between the polymer and the oil phase.

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 16, 1948

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[CONTRIBUTION FROM HOWARD UNIVERSITY]

# Absorption Spectra of Azines and Dianils[1]

BY LLOYD N. FERGUSON AND THOMAS C. GOODWIN[2]

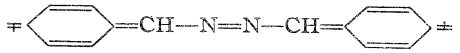
The order of increasing chromophoric power of the common chromophores was early recognized to be

C=C C=N C=O N=N C=S

This order has been attributed by several persons[3,4,5,6,6a] to the relative amounts of strain[7] within the double bonds. Other factors being equal, with increasing strain within the bond there results a less stable ground state, causing a smaller difference in the potential energies of the ground and first excited states and, hence, an absorption of light of longer wave length.

What appears to be at first glance an anomaly to this generalization is the fact that azines, which contain two stronger chromophores than a polyene hydrocarbon containing the same number of double bonds, absorb light of shorter wave length than the latter compounds. For instance, Lewis and Calvin[3] have pointed out that benzalazine, $C_6H_5CH{=}N{-}N{=}CHC_6H_5$, ($\lambda_{max.}$ = 301 mμ) absorbs light at shorter wave lengths than does 1,4-diphenylbutadiene, $C_6H_5CH{=}CH{-}CH{=}CHC_6H_5$ ($\lambda_{max.}$ = 334 mμ), and Blout and Fields[8] have reported that polyene azines of the generic formula $CH_3(CH{=}CH)_nCH{=}N{-}N{=}CH(CH{=}CH)_nCH_3$ have maximum absorption bands at shorter wave lengths than do the corresponding aliphatic polyene hydrocarbons with the same number of double bonds.

Lewis and Calvin have explained this on the basis of the "strain" theory by saying that due to the highly strained N=N bond in one of the predominant excited states of benzalazine



the potential energy of the excited state is raised. Although the ground state of the azine may lie above that of the diene, there is a larger difference between the energies of the first excited state and the ground state for the azine to the extent that it absorbs at shorter wave lengths. Blout and Fields have offered a different explanation. Their concept is to place greater emphasis on the contribution of forms Ib and Ic than on Ia to the resonance of the azines which, they believe, favors absorption at shorter wave lengths.[9]

$CH_3{-}CH{=}CH{-}CH{=}N{-}N{=}CH{-}CH{=}CH{-}CH_3$ I

$CH_3{-}\overset{\mp}{C}H{-}CH{=}CH{-}N{=}N{-}CH{=}CH{-}\overset{\pm}{C}H{-}CH_3$ Ia

$CH_3{-}\overset{+}{C}H{-}CH{=}CH{-}\overset{-}{N}{-}N{=}CH{-}CH{=}CH{-}CH_3$ Ib

$CH_3{-}CH{=}CH{-}CH{=}\overset{-}{N}{-}\overset{+}{N}{-}CH{=}CH{-}CH_3$ Ic

When the three compounds, glyoxaldianil ($C_6H_5N{=}CH{-}CH{=}NC_6H_5$), diphenylbutadiene and benzalazine are considered from Lewis' and Calvin's viewpoint, one may expect the dianil to absorb at longer wave lengths than the diene because, first, the dianil possesses two stronger chromophores and, second, the resonance of structures IIa, IIb and IIc for the dianil makes a greater contribution to the excited state than does the resonance of the corresponding ionic forms of the hydrocarbon.

(1) Data presented before the Organic Division of the American Chemical Society, Sept., 1947.

(2) Present address: Duriron Co., Dayton, Ohio.

(3) G. N. Lewis and M. Calvin, *Chem. Reviews*, **25**, 273 (1939).

(4) S. Dutt, *J. Chem. Soc.*, 1171 (1926).

(5) A. A. Kharkharov, *Chem. Abstracts*, **34**, 4065 (1940).

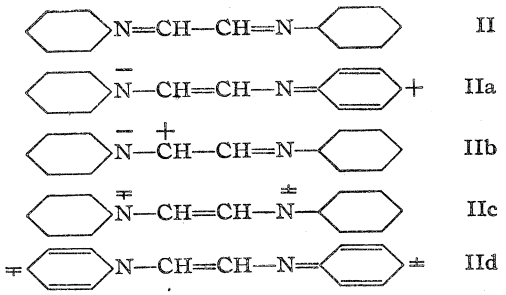
(6) L. N. Ferguson, *Chem. Reviews*, in press.

(6a) S. H. Lee and F. A. Matsen, Paper number 33 presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at Portland, Ore., September 14, 1948.

(7) The word "Strain" is used as a mechanical way of referring to the relative potential energy of a particular structure.

(8) E. R. Blout and M. Fields, THIS JOURNAL, **70** 189 (1948).

(9) The author is of the opinion that due to the greater electronegativity of nitrogen over carbon, the forms Ib and Ic do make a contribution to the resonance of the azines but this only tends to lower the potential energy of the excited states and would lead to absorption at longer wave lengths than the azines might have if these ionic forms were not possible contributors. This contribution, however, is too small to outweigh the opposite effect caused by the strain in the N=N bond.




Hence, one may anticipate the decreasing order of the chromophoric power of these three classes of compounds to be dianil, butadiene, azine. To verify this hypothesis, a number of dianils and azines were prepared and studied spectroscopically. These compounds are listed in Table I, together with their $\lambda_{max.}$ and $\epsilon_{max.}$, and their spectra are drawn in Figs. one to seven.

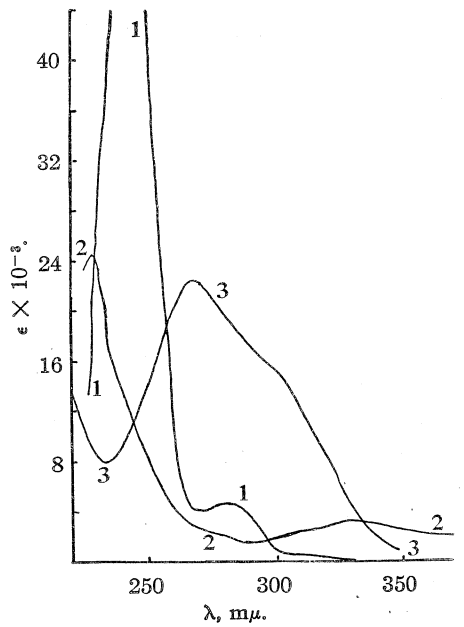



Fig. 1.—Absorption spectra of: di-(acetophenonal)-ethylenediamine, 1; diacetyldianil, 2; acetophenonazine, 3.

From the spectra it can be seen that the decreasing order of the longest wave length of absorption for compounds 10, 10a and 10b is in the order dianil, diene, azine. In addition, the dianils 5a and 6a have maximum absorption bands at longer wave lengths than do the corresponding azines 5 and 6. The hypsochromic shift in going from 8 to 8a cannot be explained satisfactorily. Unfortunately, all attempts to isolate the parent compound glyoxal dianil, $C_6H_5N{=}CH{-}CH{=}NC_6H_5$, were unsuccessful.

Upon looking at compounds 7 with 7a, 2 with 2a and 9 with 9a it is noted that there results a large difference between the maxima of the dianils and the azines when the hydrogen atoms on the methine carbon atoms have been replaced by

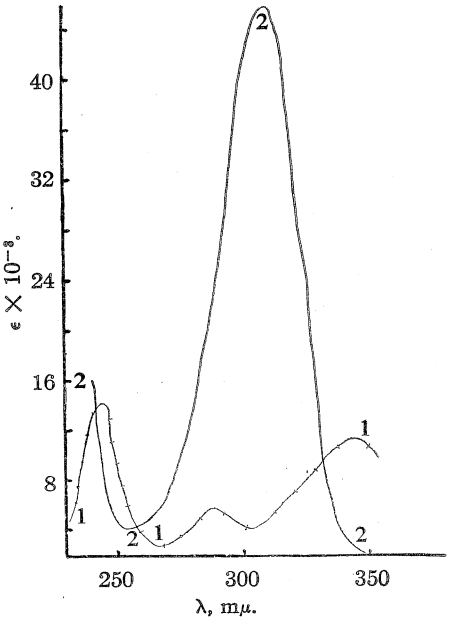



Fig. 2.—Absorption spectra of: glyoxaldi-(*p*-hydroxyanil), 1; *p*-hydroxybenzalazine, 2 (from reference in footnote a to Table I).

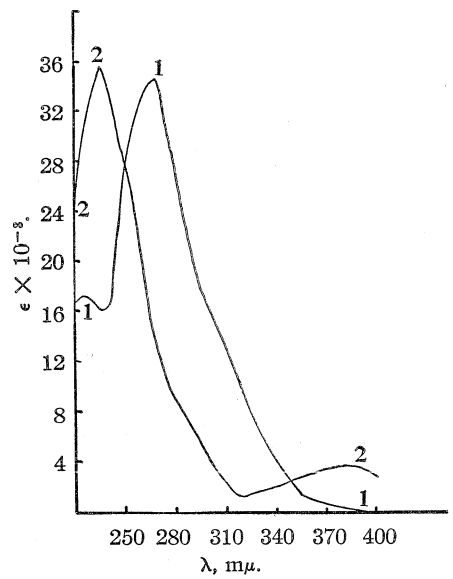
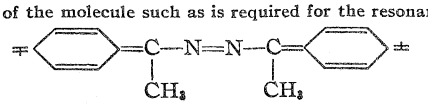



Fig. 3.—Absorption spectra of: *m*-nitroacetophenonazine, 1; diacetyldi-(*m*-nitroanil), 2.

methyl groups. This perhaps is due to three factors: 1, the absence of the highly strained N=N bond in the excited state; 2, a hypsochromic effect in the ketazines due to steric hindrance,[10] and 3,

(10) Spacial interference of the methyl groups prevent the coplanarity of the molecule such as is required for the resonant forms




This has been pointed out by Blout, Eager and Gofstein (THIS JOURNAL, **68**, 1983 (1946)) for a number of ketazines and is further observed for the pairs of compounds 6 with 7 and 8 with 9.

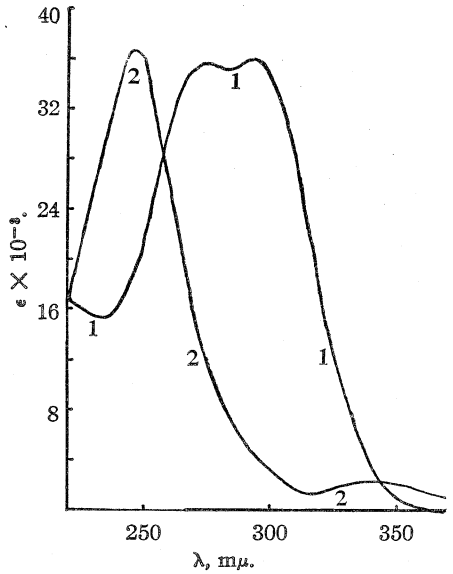



Fig. 4.—Absorption spectra of: *m*-nitrobenzalazine, 1 (from unpublished work by Ferguson and Branch); glyoxaldi-(-*m*-nitroanil), 2.

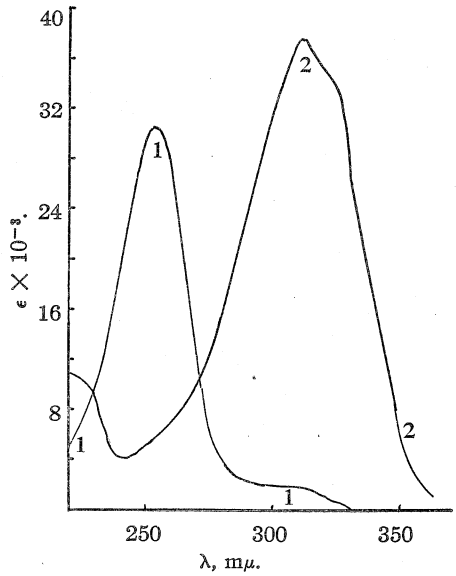



Fig. 6.—Absorption spectra of: glyoxaldi-(*p*-bromoanil), 1; *p*-bromobenzalazine, 2.

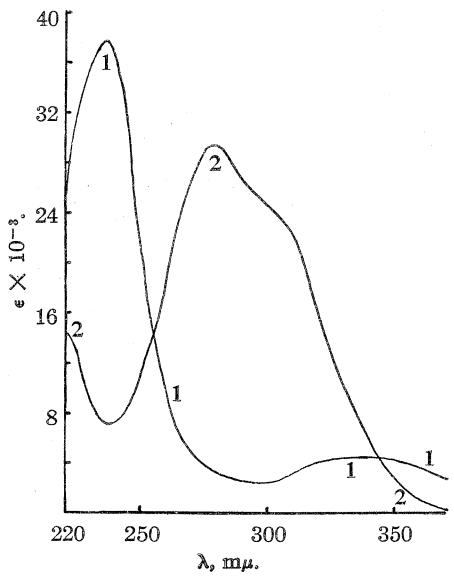



Fig. 5.—Absorption spectra of: diacetyldi-(*p*-bromoanil), 1; *p*-bromoacetophenonazine, 2.

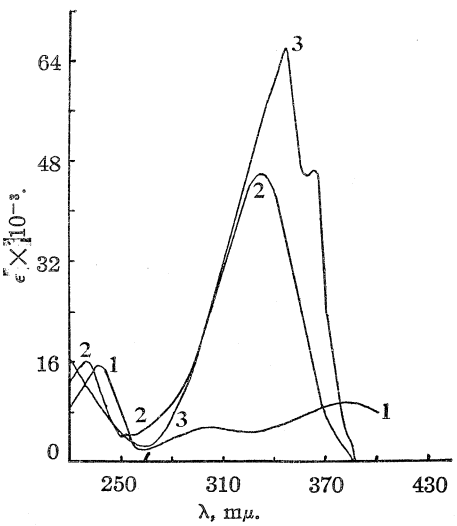



Fig. 7.—Absorption of: 1, glyoxaldi-(*p*-methoxyanil); 2, *p*-methoxybenzalazine; 3, 1,4-di-(*p*-methoxyphenyl)-butadiene-1.

a bathochromic effect by the methyl groups on the N=C—C=N system as observed when comparing the compounds 8a with 9a and 6a with 7a. This is the usual bathochromic effect of alkyl groups on a conjugated double bond which has been attributed to hyperconjugation.[11] This auxochromic effect by methyl groups is also revealed by the pair of compounds 3 and 4 where the steric factor, found in ketazines is absent.

Other points to be noted about the spectra are: 1, the large decrease in $\epsilon_{max.}$ in going from the C=N—N=C to the N=C—C=N system, 2, the close similarity of the absorption bands for the pairs of compounds 5 with 10 and 5a with 10a indicates the absence of association of the hydroxy compounds through hydrogen bonds, 3, the "insulation" effect, illustrated by comparing compound 1 and 3, is masked when comparing compound 2 with 4 because of the hypsochromic steric effect of the methyl groups in 2.

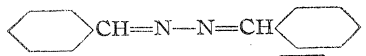
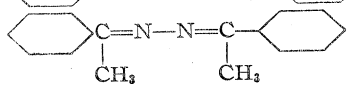
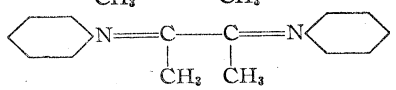
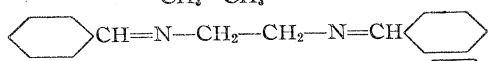
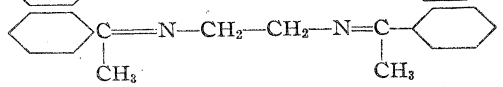
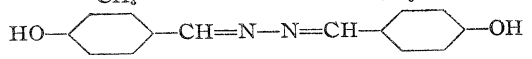
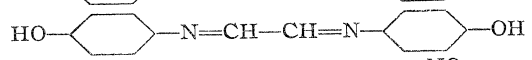
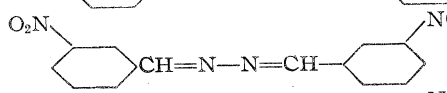
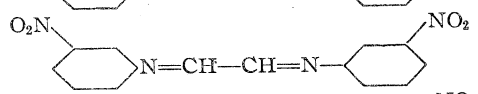
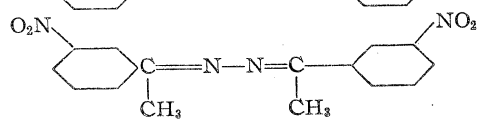
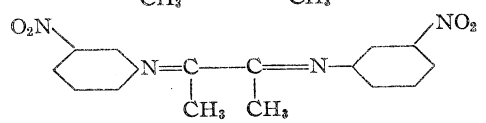
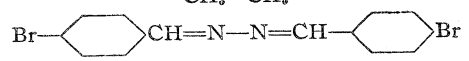
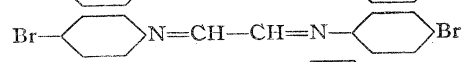
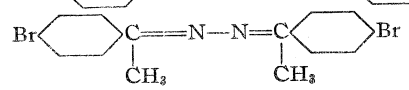
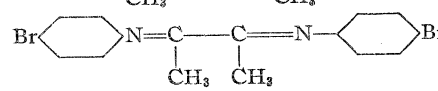
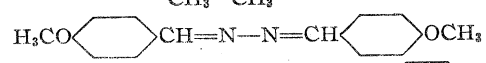
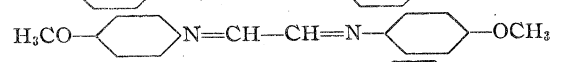
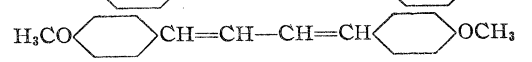
(11) R. S. Mulliken, *J. Chem. Phys.*, **7**, 339 (1939).

## Experimental

The compounds studied were prepared by one of four general procedures, which were: A, Mix the amine and carbonyl compound in 50 to 70% alcohol, warm a short period on the steam-bath and cool over a period of several hours. B, Identical to A except that 2 *N* acetic acid was the solvent. C, Identical to A except that $H_2O$ was the solvent. D, Dissolve glyoxal bisulfite in 2 *N* acetic acid

TABLE I

WAVE LENGTHS AND MOLECULAR EXTINCTION COEFFICIENTS OF THE MAXIMUM ABSORPTION BANDS OF SOME AZINES AND DIANILS

| | Compound | $\lambda_{max.}$, mμ | $\epsilon_{max.}$ | $\lambda'_{max.}$, mμ | $\epsilon'_{max.}$ | $\lambda''_{max.}$, mμ | $\epsilon''_{max.}$ |
|---|---|---|---|---|---|---|---|
| 1 |  | 301.1[a] | 38,000 | 213 | 17,000 | | |
| 2 |  | 267.5 | 22,500 | | | | |
| 2a |  | 331 | 2,875 | 228 | 24,600 | | |
| 3 |  | 247[a] | 29,800 | | | | |
| 4 |  | 280 | 4,360 | 243 | 49,900 | | |
| 5 |  | 333[a] | 46,000 | 228.5 | 18,000 | | |
| 5a |  | 388 | 9,740 | 301 | 5,780 | 236 | 14,150 |
| 6 |  | 294[b] | 36,200 | 225 | 17,000 | | |
| 6a |  | 333 | 2,080 | 245 | 36,800 | | |
| 7 |  | 266 | 34,900 | 225 | 17,450 | | |
| 7a |  | 375 | 3,460 | 234 | 35,750 | | |
| 8 |  | 311.5 | 37,800 | 221 | 13,400 | | |
| 8a |  | 299–302[c] | 1,830 | 254 | 30,600 | | |
| 9 |  | 279 | 29,300 | | | | |
| 9a |  | 336 | 4,560 | 236 | 37,550 | | |
| 10 |  | 331 | 45,900 | 229 | 16,260 | | |
| 10a |  | 382 | 9,470 | 300 | 5,810 | 236 | 15,410 |
| 10b |  | 363 | 46,600 | 345 | 66,000 | | |

[a] Values for these compounds taken from Ferguson and Branch, THIS JOURNAL, 66, 1467 (1944). [b] Value from unpublished work of L. N. Ferguson and G. E. K. Branch. [c] Shoulder.

and the amine in an equal volume of alcohol, mix and heat on the steam-bath for about half an hour and cool over a period of several hours. Ninety-five per cent. ethanol was always the solvent for recrystallization unless otherwise specified.

The absorption measurements were made using a Beckman Photoelectric Quartz Spectrophotometer, Model DU, with 1-cm. square, fused silica absorption cells. Ninety-five per cent. ethanol served as the solvent. The absorption by compounds 2a, 5a, and 10a was found to slowly increase during the measurement of their spectra, this increase being more marked in the regions of maximum absorption.

**Acetophenonazine,** $[C_6H_5(CH_3)C{=}N{-}]_2$.—By procedure A or B: m.p. obs. 120–121°; lit. 121° (Blout, Eager and Gofstein, ref. 10).

***p*-Bromoacetophenonazine,** $[p\text{-}BrC_6H_4(CH_3)C{=}N{-}]_2$. —By procedure A: m.p. obs. 159–160°. *Anal.* Calcd. for $C_{16}H_{14}N_2Br_2$: C, 48.8; H, 3.55. Found: C, 48.9; H, 3.76.

***m*-Nitro-acetophenonazine,** $[m\text{-}O_2N{-}C_6H_4(CH_3)C{=}N]_2$.—By procedure A: m.p. obs. 197–198°; lit. 194–195°. Knöpfer, *Monatsh.* **30**, 36(1909).

**Diacetyldianil,** $[C_6H_5N{=}(CH_3)C{-}]_2$.—By procedures A or B; Procedure C not successful: m.p. obs. 136–137°;

lit. 139–140°; H. von Pechmann, *Ber.*, **21**, 1415 (1888); Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

**Diacetyldi-(*m*-nitroanil)**, $[m\text{-}O_2NC_6H_4N{=}(CH_3)C{-}]_2$.—By procedure B: Procedure A not successful: m.p. obs. 112–113°. *Anal.* Calcd. for $C_{16}H_{14}O_4N_4$: N, 17.2. Found: N, 17.2.

**Diacetyldi-(*p*-bromanil)**, $[p\text{-}BrC_6H_4N{=}(CH_3)C{-}]_2$.—By procedure A: m.p. 181.5–182.5°; lit. 182–183°, Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

**Glyoxaldianil**, $[C_6H_5N{=}CH{-}]_2$.—Procedure A gave resins from which crystalline products could not be obtained. Procedures B, C, and D gave non-recrystallizable amorphous powders with m.p.'s 80–81°, 105–110° and 125–126°, respectively. Its synthesis was abandoned.

**Glyoxaldi-(*p*-bromanil)**, $[p\text{-}BrC_6H_4N{=}CH{-}]_2$.—By procedures A or D: m.p. obs. 181–181.5°; *Anal.* Calcd. for $C_{14}H_{12}N_2Br_2$: C, 45.7; H, 3.26. Found: C, 44.3; H, 2.97.

**Glyoxaldi-(*p*-methoxyanil)**, $[p\text{-}CH_3OC_6H_4N{=}CH{-}]_2$.—By procedures A and B: m.p. obs. 155°; lit. 158°, Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

**Glyoxaldi-(*p*-hydroxyanil)**, $[p\text{-}HOC_6H_4N{=}CH{-}]_2$.—By procedure A: m.p. obs. 190–191°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.0; H, 5.0. Found: C, 70.2; H, 6.0.

**Glyoxaldi-(*m*-nitroanil)**, $[m\text{-}O_2NC_6H_4N{=}CH]_2$.—By procedure D: m.p. obs. 202–203°. *Anal.* Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.4; H, 3.46. Found: C, 55.86; H, 3.74.

**1,4-Di-(*p*-methoxyphenyl-butadiene-1,3**, $[p\text{-}CH_3OC_6H_4{-}CH{=}CH{-}]_2$.—Prepared according to some unpublished work by Fieser and Potter. Mixed one half mole of freshly distilled anisaldehyde, one-fourth mole of succinic acid, and one-half mole of litharge in 150 cc. of acetic anhydride, and heated on a hot-plate under a reflux condenser for five hours. Then was added 200 cc. of 80% HOAc, the soln. cooled overnight, and the crystals filtered and recrystallized from *n*-propanol; colorless crystals, m.p. 222.5–223.5°.

**4,4-Dibromobenzaldazin**, $[p\text{-}BrC_6H_4CH{=}N{-}]_2$.—By procedure A: m.p. obs. 223.5°–224.5°, lit. 221; L. Gattermann, *Ann.*, **393**, 223(1912).

**4,4-Dimethoxybenzaldazin**, $[p\text{-}CH_3OC_6H_4CH{=}N{-}]_2$.—By procedure A: m.p. obs. 167–168°; lit. 168°; G. Knöpfer, *loc. cit.*

**Di(acetophenonal)-ethylenediamine**, $[C_6H_5(CH_3)C{=}N\text{-}CH_2{-}]_2$.—By procedure A: (drop HOAc added); white crystals from ligroin, m.p. 110–111°; *Anal.* Calcd. for $C_{18}H_{20}N_2$: N, 10.6. Found: N, 10.3.

**Acknowledgment.**—The authors are indebted to Mr. Theodore Austin, instructor of chemistry in Howard University, for drawing the spectra.

## Summary

The order of chromophoric power for the systems dianil, diene, and azine is discussed and illustrated to be decreasing in the order named. A bathochromic effect by substituting methyl groups upon the methine carbon atoms of the dianil system is noted.

HOWARD UNIVERSITY
WASHINGTON 1, D. C.

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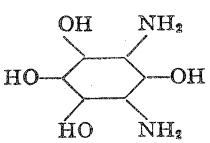
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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

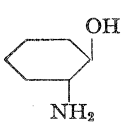
# Stereochemistry of Cyclic Amino-alcohols. Inversion, Retention and Participation[1]

BY G. E. MCCASLAND,[2] R. K. CLARK, JR.,[3] AND HERBERT E. CARTER

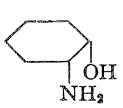
The isolation of streptamine (I),[4] one of the three major degradation products of streptomycin, has stimulated interest in the stereochemistry of polysubstituted alicyclic compounds, and of cyclic aminoalcohols in particular. Streptamine is one of the twenty possible diastereoisomeric forms of 1,3-diamino-2,4,5,6-tetrahydroxycyclohexane. Of these forms, eight are *meso* and twelve racemic, and the recent synthesis[5] of streptamine from glucosamine indicates that "natural" streptamine is the all-*trans*, *meso* form. In support of stereochemical studies on streptamine, model compounds of simpler structure were investigated.




I




II




III

For this purpose the 2-aminocyclohexanols were selected.

Both the *cis* and *trans* forms of 2-aminocyclohexanol lack a plane of symmetry and hence are theoretically resolvable. Thus the configurations cannot be established by resolution of the *trans* isomer, as with the diol or diamine. Experimentally, two racemic forms of 2-aminocyclohexanol are known. The first, isomer "A," melts at 68°; the second, isomer "B," melts at 72°. The melting points of a number of derivatives of "A" and "B" are given in Table I.

Isomer "A" was first prepared in 1905 by Brunel[6a] by the amination of cyclohexene oxide, and also can be obtained by the amination of cyclohexene halohydrin,[6b] or by the reduction of 2-hydroxycyclohexanone oxime.[6c] The preparation of the "B" isomer was first described in a 1936 patent,[7] and few details regarding it have been published. An alternate preparation of the "B" isomer (N-benzoyl), by the tosylation and detosylation of the "A" N-benzoyl derivative, is described below.

(1) The authors wish to thank the Abbott Laboratories; Eli Lilly and Company; Parke, Davis and Company; and The Upjohn Company for a generous grant in support of this work.

(2) Present address: Chemistry Department, University of Toronto.

(3) Present address: Abbott Laboratories, North Chicago.

(4) H. E. Carter, *et al.*, *Science*, **103**, 53 (1946).

(5) Wolfrom and Olin, Abstracts, Chicago Meeting, A.C.S., April, 1948, p. 5Q.

(6) (a) Brunel, *Ann. chim.*, [8] **6**, 253 (1905); (b) Osterberg and Kendall, THIS JOURNAL, **42**, 2616 (1920); (c) Wilson and Read, *J. Chem. Soc.*, 1269 (1935).

(7) *Chem. Abs.*, **32**, 7055 (1938); *Chem. Zentr.*, **108**, I, 2260 (1937).

Table I

Melting Points of *trans* and *cis* *d,l*-2-Aminocyclohexanol Derivatives

| Derivative | "A" (*trans?*) | "B" (*cis?*) |
|---|---|---|
| Free aminoalcohol | 68 | 72 |
| Hydrochloride | 175 | 185 |
| N-Acetyl | 127 | 147 |
| O,N-Diacetyl | 126 | ... |
| N-Benzoyl | 169 | 193[a] |
| O,N-Dibenzoyl | 215 | 153[a] |
| N-Benzoyl-O-acetyl | 144 | 193[a] |
| O-Benzoyl-N-acetyl | 199 | ... |
| N-Benzoyl-O-*p*-toluenesulfonyl | 114[a] | 165[a] |
| α-Naphthylthiourea | 172[a,b] | 150[a,b] |
| N-Benzylidene | 90–92[a,b] | ... |

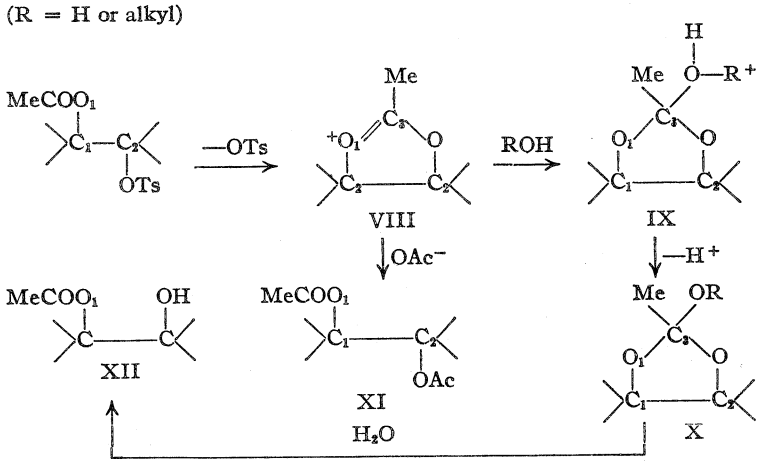
[a] Not previously reported. [b] To be described in a subsequent publication.

Isomer "A" is listed as "*cis*" in Beilstein,[8] on the basis of Brunel's designation. Certain later authors[9] favored the *trans* configuration for "A." It is now known that the oxide ring normally is opened in the *trans* manner. For this reason, and on the basis of the results described below, the "A" isomer will be designated as *trans*.

Chart I

Mechanism of Detosylations

(R = H or alkyl)




For benzamidotosylate, replace —O—by —NH— and Me by phenyl

Although direct physical methods, such as X-ray diffraction and dipole moment, may be the most powerful approach to such questions of molecular geometry, their application at present involves well-known difficulties, which need not be considered here. An alternate approach involves a study of the inversions or retentions at each step in the formation or reactions of the aminocyclohexanols. A functional group on a neighboring carbon atom can alter the normal steric result of a displacement on carbon from inversion to retention, or *vice versa*, and the extensive recent development[10] of theories to explain this "participation" furnishes an indispensable guide to such steric studies.

The formation of *trans*-2-aminocyclohexanol by amination of either cyclohexene oxide or the *trans* halohydrin in aqueous or alcoholic ammonia is to be expected on the basis of present knowledge concerning the formation and opening of oxide rings. Supporting evidence on this point was afforded by the reaction of cyclohexene oxide with potassium amide in anhydrous liquid ammonia. In this case the high concentration of the powerfully nucleophilic amide ion should make a *trans* ring-opening more certain. From this reaction only the "A" isomer (*trans*) was obtained; the yield, however, was small.[11]

## Tosylation and Detosylation

In 1942 Winstein, Hess and Buckles[12] conducted a series of experiments on the detosylation of *d,l-trans*-2-acetoxycyclohexyl-*p*-toluenesulfonate. The results obtained by these authors, and the mechanism proposed by them are shown in Chart I. Departure of tosylate ion yields the charged cyclic intermediate VIII, with inversion. In *dry* acetic acid–sodium acetate, the acetate ion attacks carbon atom $C_2$, with inversion, giving *trans*-diacetate XI (over-all *retention*). In *wet* acetic acid–sodium acetate, or in dry ethanol, the water or ethanol reacts more rapidly than acetate ion, to give the conjugate acid IX of the ortho ester X, which opens with retention to give the *cis*-acetoxyalcohol XII (over-all *inversion*).

It seemed probable to us that a *trans* acylamino group would participate in such detosylation reactions in the same manner as an acyloxy group. A comparison of the stereochemical behavior of the acylamino and acyloxy compounds might then provide evidence testing the validity of the *trans* assignment of configuration to "A" 2-aminocyclohexanol.

Accordingly, we prepared the N-benzoyl-O-*p*-toluenesulfonyl derivative of the "A" form of *d,l*-2-aminocyclohexanol, and solvolyzed it under Winstein's three conditions: (1) sodium acetate in dry acetic acid, (2) sodium acetate in acetic acid with a small amount of added water, (3) sodium acetate in absolute ethanol.

The results were completely analogous with those obtained by Winstein, *et al.*, for their *trans*-acyloxytosylate. In dry acetic acid the product we obtained was the "A" benzamidoacetate with

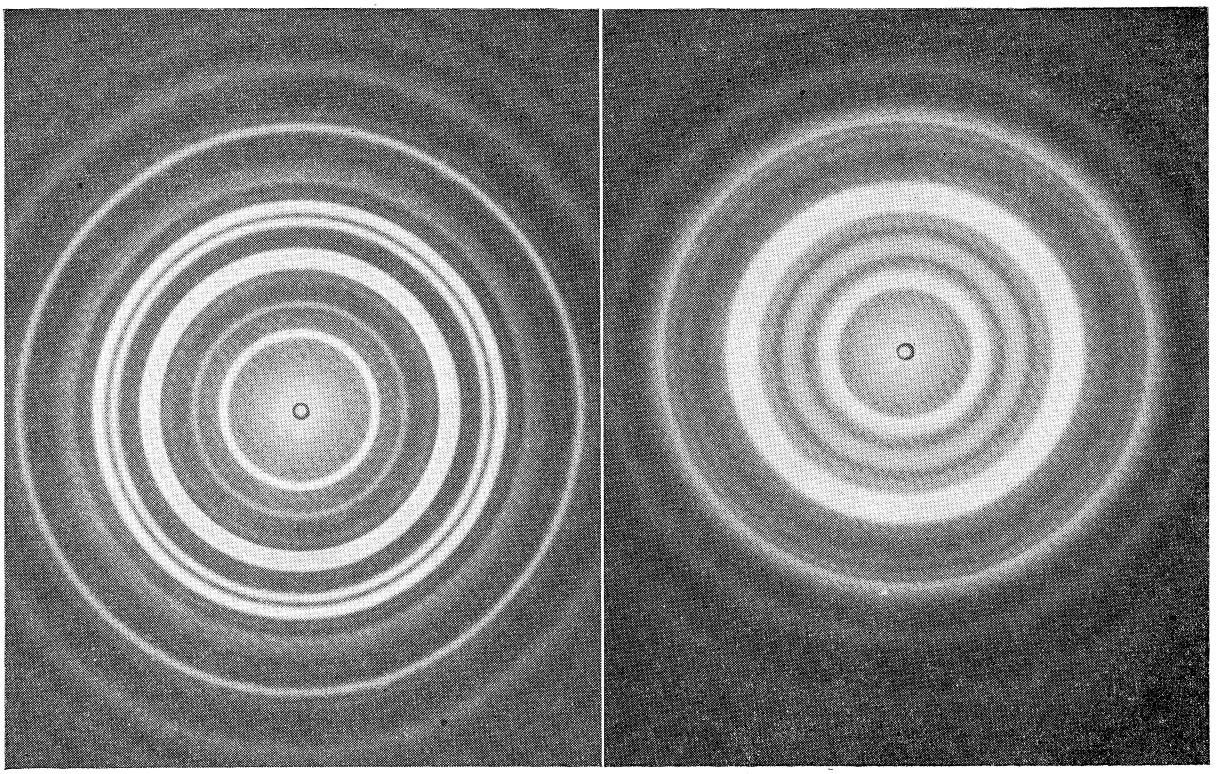
(8) Beilstein, 4th edition, Vol. XIII, p. 348.

(9) (a) Godchot and Mousseron, *Compt. rend.*, **194**, 981 (1932); (b) **198**, 2000 (1934); (c) Birckenbach, *et al.*, *Ber.*, **64**, 961, 1076 (1931); **66**, 1571 (1933).

(10) Winstein and co-workers, This Journal, **70**, 812–846 (1948), and previous publications.

(11) The low yield with amide ion in ammonia recalls the well-known inertness of the oxide ring to hydroxide in water.

(12) Winstein, *et al.*, This Journal, **64**, 2796 (1942); **70**, 812 (1948); *cf.* Criegee and Stanger, *Ber.*, **69B**, 2753 (1926).



*cis*, m. p. 147°. *trans*, m. p. 127°.

Fig. 1.—X-Ray powder spectra of *d,l*-2-acetaminocyclohexanols.

retention. In wet acetic acid, or in (dry) ethanol, the product was the "B" benzamidoalcohol with inversion.

The mechanism as modified by us for the benzamido compound is also given by Chart I if Me is replaced by phenyl and —$O_1$— by —NH—. Intermediate (X) in the acyloxy detosylation would be an ortho-ester; in the acylamino detosylation it would be a 2-hydroxy-2-phenyloxazolidine. While we have no direct evidence on the formation of the postulated intermediates, the striking parallelism between the results on acylamino- and acyloxytosylates strongly suggests a common mechanism. And it indicates that the "A" amino-alcohol, like the diol, has the *trans* configuration.[13]

## Chlorination and Dechlorination

The treatment of a secondary alcohol with phosphorus pentachloride commonly gives the alkyl chloride with inversion. In the case of *trans*-2-aminocyclohexanol hydrochloride the normal displacement of hydroxyl by chlorine might be expected to result, since participation by the neighboring positively charge ammonium ion seems improbable.

Experimentally the reaction of *trans*-2-aminocyclohexanol hydrochloride with phosphorus pentachloride gives a high yield of a 2-chlorocyclohexylamine hydrochloride which there is good reason to regard as *cis*. Attempts to dechlorinate this compound with silver oxide were unsuccessful; only starting material could be isolated (as the N-benzoyl derivative) from the reaction mixture. The chloride and its N-benzoyl derivative failed to react appreciably even when boiled for twenty-one hours with an acetic acid solution of silver acetate.

These results are quite in accord with the findings of Winstein and co-workers[13] who reported that *cis* isomers of 2-substituted cyclohexyl chlorides show a remarkable inertness. Likewise, Leffler and Adams[14] reported that *cis*-2-*p*-nitrobenzoylaminocyclohexyl chloride was highly inert (to alkali).

**X-Ray Powder Spectra.**—The X-ray spectra were observed on powdered samples of *trans* and *cis*-*d,l*-2-acetaminocyclohexanol. The results are shown in Fig. 1 and are presented merely for purposes of identification.

## Experimental[15,16]

**Preparation of *trans*-2-Aminocyclohexanol Derivatives** *d,l-trans*-**2-Aminocyclohexanol.**—(a) The amination pro-

(13) *dl-cis*-2-Acetoxycyclohexyltosylate reacts with dry acetic acid–acetate with inversion (Winstein, *et al.* THIS JOURNAL, **70**, 816 (1948)).

(14) Leffler and Adams, *ibid.*, **59**, 2256 (1937).

(15) Microanalyses by Clark Microanalytical Laboratory, Urbana, unless otherwise credited. Semi-micro Kjeldahl analyses by Dr. Robert S. Pogrund.

(16) All melting and boiling points are corrected.

cedure of Wilson and Read[6c] was found most convenient. Redistilled, colorless *d,l-trans*-2-chlorocyclohexanol (du Pont), b.p. 92–97° (33 mm.) was used. The product, colorless stout needles, m.p. 68°, b.p. 102–107° (9 mm.), darkens on prolonged standing in air, and is best stored *in vacuo*, or in the form of its hydrochloride. Solubility of the free aminoalcohol in benzene is about 8 g./100 ml. solvent.

*Anal.* Calcd. for $C_6H_{13}NO$ (115.17): N, 12.17. Found: N, 12.22.

(b) To regenerate the aminoalcohol from its hydrochloride, the latter was neutralized with an equivalent amount of 0.3 *N* ethanolic sodium hydroxide. After one-half hour at 0°, sodium chloride was filtered off, and the filtrate vacuum distilled to dryness, giving colorless needles, m. p. 68–69°.

*d,l-trans*-2-**Aminocyclohexanol Hydrochloride.**—Evaporation of a solution of the aminoalcohol in excess hydrochloric acid gave the hydrochloride,[6a] colorless prisms, m. p. 176–177° (without decomposition). The hydrochloride can be recrystallized from absolute alcohol–benzene (1:2).

**Amination with Potassium Amide–Liquid Ammonia.**—To a solution of one gram of potassium metal in 100 ml. of anhydrous liquid ammonia was added 5.0 g. of cyclohexene oxide,[17] and an iron nail as catalyst. This mixture was kept overnight at −33°. Ethanol was then added to destroy potassium amide, most of the ammonia was boiled off and the residual solution neutralized with hydrochloric acid. Inorganic matter was filtered off, and the filtrate vacuum distilled to dryness. The residue was again taken up in a little ethanol, filtered and distilled. Finally, the residue was taken up in aqueous 6 *N* hydrochloric acid, and the solution distilled to dryness, giving 0.14 g. of colorless crystals, m.p. 176–178°. A mixed m. p. with the *trans* hydrochloride was not depressed.

*Anal.* Calcd. for $C_6H_{14}NOCl$ (151.64): N, 9.24. Found: N, 9.30 (Kjeldahl).

Liquid ammonia alone failed to react with the oxide.

*d,l-trans*-2-**Acetaminocyclohexyl Acetate.**—The procedure of Raiford and Mortensen[18] was used. Recrystallization of the product from benzene–ligroin (1:1) yielded long, colorless needles, m. p. 117–119°.

*Anal.* Calcd. for $C_{10}H_{17}NO_3$ (199.25): N, 7.03. Found: N, 7.05 (Kjeldahl).

*d,l-trans*-2-**Acetaminocyclohexanol.**—This compound[18] is best prepared by hydrolysis of the diacetyl derivative. Titrations of samples from the reaction mixture with standard acid showed that the hydrolysis in 1 *N* sodium hydroxide at 25° is complete in thirty minutes or less. Recrystallization of the product from benzene gives short colorless needles, m. p. 126–127°.

*Anal.* Calcd. for $C_8H_{15}NO_2$ (157.21): N, 8.91. Found: N, 8.78 (Kjeldahl).

*d,l-trans*-2-**Benzoylaminocyclohexanol.**—The general method of Leffler and Adams[14] gave a 95% yield of crude product, colorless needles, m. p. 175–176°, which did not need recrystallization.

*d,l-trans*-2-**Benzoylaminocyclohexyl Benzoate.**—The procedure of Raiford[18] and Mortensen was used. The product melted at 215–216°.

*Anal.* Calcd. for $C_{20}H_{21}O_3N$ (323.38). N, 4.33; sapon. equiv., 323.4. Found: N, 4.69; sapon. equiv. 313.

## Preparation of *cis*-2-Aminocyclohexanol Derivatives

**2-Acetaminophenol.**—The method of Lumière and Barbier[19] was used. The alkaline solution of 2-aminophenol should be filtered (Super-Cel) to remove insoluble impurities. Recrystallization of the product from ethanol (Norit) gives colorless leaflets, m. p. 206–207°.

**2-Acetaminophenyl Acetate.**—The method of Meldola, *et al.*,[20] was found more satisfactory than others. The product was recrystallized from water, giving colorless needles, m. p. 74–77°. Further recrystallizations from either water or benzene–ligroin gave a maximum m. p. of 75–77°, which is that reported for the sesquihydrate.[20]

*d,l-cis*-2-**Acetaminocyclohexanol.**—A 22-g. portion of 2-acetaminophenol in 150 ml. of absolute ethanol was hydrogenated with Raney nickel catalyst at 100 atm. and 180°. The theoretical uptake of hydrogen was reached in four to six hours. The catalyst was removed by filtration, and the colorless or red filtrate concentrated in vacuum to a thick sirup, which crystallized on mixing with 100 ml. of acetone. Filtration and drying gave 2.5 g. (11%) of *d,l-cis*-2-acetaminocyclohexanol,[7] as colorless prisms, m. p. 146–147°. On recrystallization from acetone the m. p. was unchanged.

Fractional crystallization of the mother liquor, using various solvents, failed to yield any additional *cis* product, nor was it possible to isolate in a pure form any of the *trans* isomer, which is presumably present.

With the specially active nickel catalyst of Pavlic and Adkins,[21] the hydrogenation proceeded at 150°, but the yield was even lower.

When (dry, acid-free) ethyl acetate was used as hydrogenation solvent (to prevent alcoholysis), the yield was only 5%.

When diacetyl-2-aminophenol was hydrogenated, in ethanol, extensive alcoholysis occurred, and a very small yield of *cis*-2-acetaminocyclohexanol was obtained.

Hydrogenation of 2-acetaminophenol with platinum oxide catalyst gave an unpurifiable product.

*d,l-cis*-2-**Aminocyclohexanol Hydrochloride.**—A solution of 1.0 g. of the acetamino compound in excess of 6 *N* hydrochloric acid was refluxed for two hours, and distilled in vacuum to dryness. The residue was washed with a little acetone, giving 0.9 g. (94%) of colorless crystals,[7] m. p. 189–190°, with decomposition.

**Attempted Preparation of** *d,l-cis*-2-**Acetaminocyclohexyl Acetate.**—Application of the method used for the *trans* compound, and of other methods, failed to yield any crystalline product, possibly due to oxazoline formation.

*d,l-cis*-2-**Aminocyclohexanol.**—Treatment of the *cis* hydrochloride by the same procedure described for the *trans* isomer gives the free aminoalcohol,[7] colorless crystals, m. p. 72–73°.

*d,l-cis*-2-**Benzoylaminocyclohexanol.**—(a) Treatment of the aminoalcohol hydrochloride by the general procedure of Leffler and Adams[14] gave an 86% yield of crude product, colorless leaflets melting sharply at 189–190°, which did not need recrystallization. (b) This compound can be obtained by detosylation of the *trans* tosylate (see below).

*d,l-cis*-2-**Benzoylaminocyclohexyl Benzoate.**—Treatment of 150 mg. of the aminoalcohol hydrochloride by the Schotten–Baumann procedure, followed by benzoylation in hot pyridine, gave a product which crystallized from ethanol as colorless crystals, m. p. 152–154°.

*Anal.* Calcd. for $C_{20}H_{21}NO_3$ (323.38): N, 4.33; sapon. equiv. (O-benzoyl), 323.4. Found: N, 4.42 (Kjeldahl); sapon. equiv., 342.

## Inversion and Retention in Detosylation Reactions

**Preparation of** *d,l-trans*-2-**Benzoylaminocyclohexyl-***p*-**toluenesulfonate.**—To the benzamidoalcohol (4.4 g.) suspended in 10 ml. dry pyridine at 0° was added 4.3 g. of *p*-toluenesylfonyl chloride, and the clear yellow solution allowed to stand at 25° for twenty-four hours. The mixture was chilled to 0° and 10 ml. of 6 *N* hydrochloric acid and 20 ml. of water (both ice-cold) were successively added. The precipitate was filtered off, washed repeatedly with water and dried. The crude product (3.5 g.) was recrystallized from 15 ml. of 60–70% ethanol, giving 1.3 g. (18%) of colorless needles, m. p. 111–112°. A sample recrystallized again, for analysis, melted at 113–114°.

(17) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 185.

(18) Raiford and Mortensen, This Journal, **50**, 1201 (1928). (The m. p. of *d,l-trans*-2-acetaminocyclohexanol was incorrectly reported as 315° instead of 127°.)

(19) Lumière and Barbier, *Bull. soc. chim.*, [3] **33**, 784 (1905).

(20) Meldola, *et al.*, *J. Chem. Soc.*, **69**, 1323 (1896).

(21) Pavlic and Adkins, This Journal, **68**, 1471 (1946).

*Anal.* Calcd. for $C_{20}H_{23}O_4NS$ (373.45): C, 64.32; H, 6.21; N, 3.75. Found: C, 64.23; H, 5.91; N, 3.75.

The use of ethanol probably lowers the yield by detosylation, but no other satisfactory method of purification has been found.

**Inversion of Configuration with Wet Acetic Acid–Sodium Acetate: Formation of *d,l-cis*-2-Benzoylaminocyclohexanol.**—A mixture of 0.95 ml. of acetic acid (m. p. 16°), 0.05 ml. of water, 0.1 g. of fused sodium acetate, and 300 mg. of the *trans*-benzamidotosylate was refluxed four hours. After cooling, 10 ml. of water was added, and solid sodium carbonate added gradually until *p*H 8. The mixture was extracted with two 20-ml. portions of ether. The dried ether extract on evaporation gave an oily solid residue, which was washed with benzene–ligroin, yielding 25 mg. of colorless crystals, m. p. 179–182°. From the benzene–ligroin filtrate was obtained 15 mg. more material, of m. p. 186–188°; total yield[22] 40 mg. (22%). The product was recrystallized for analysis from benzene–ligroin, giving colorless plates, m. p. 192–193°.

*Anal.* Calcd. for $C_{12}H_{17}O_2N$ (219.28): N, 6.39. Found: N, 6.44.

**Retention of Configuration with Dry Acetic Acid–Sodium Acetate: Formation of *d,l-trans*-2-Benzoylaminocyclohexyl Acetate.**—An anhydrous acetic acid solution was prepared by refluxing 9.5 ml. of glacial acetic acid (m. p. 16°) with 0.53 ml. of acetic anhydride and 1.0 g. of fused sodium acetate. A 1.0-ml. aliquot of the resulting solution was added to 300 mg. of the *trans*-benzamidotosylate, and the mixture refluxed for four hours, with exclusion of moisture. After cooling, the reaction mixture was diluted with 4 ml. of water, causing the separation of 170 mg. (dry weight) of precipitate, m. p. 115–130°. The material was recrystallized from 50% ethanol, giving 80 mg. (38%)[22] of *trans*-2-benzoylaminocyclohexyl acetate,[18] colorless plates, m. p. 135–139°. A final recrystallization raised the m. p. to 143–144°.

**Inversion of Configuration with (Dry) Ethanol–Sodium Acetate: Formation of *d,l-cis*-2-Benzoylaminocyclohexanol.**—A mixture of 300 mg. of *trans*-benzamidotosylate, 280 mg. of fused sodium acetate, and 4.3 ml. of absolute ethanol was refluxed for forty-nine hours. After a few hours, crystals (sodium *p*-toluenesulfonate?) separated from the solution. After cooling, the filtered solution was evaporated to dryness, 1–2 ml. of water added, and the precipitate filtered off and washed with 2–3 ml. of water. The residue, after drying, was a crystalline powder, weight 157 mg., m. p. about 175°. Recrystallization from ethyl acetate gave 95 mg. (54%)[22] of *d,l-cis*-2-benzoylaminocyclohexanol, colorless plates, m. p. 184–186°.

**Preparation of *d,l-cis*-2-Benzoylaminocyclohexyl *p*-Toluenesulfonate.**—A 373-mg. portion of the *cis*-benzamidoalcohol was suspended in 1.0 ml. of dry pyridine. With ice-cooling, 350 mg. of *p*-toluenesulfonyl chloride was added, and the mixture left at 25° for fifty hours. At 0° there was successively added 2–3 ml. of water, 1.0 ml. of 6 *N* hydrochloric acid, and again 2–3 ml. of water. The precipitate was filtered off, washed well with water, and dried *in vacuo*. The colorless crystalline solid so obtained weighed 339 mg. and melted at 145–175°.

Between crossed Nicol prisms the crystals appeared as colorless needles, with a smaller amount of colored leaflets. By successive crystallizations from dilute ethanol or absolute methanol, an analytic sample of m. p. 163–165° was obtained which appeared nearly homogeneous (needles) under the polarizing microscope. The yield at this stage was very small, however, and has not yet been improved.

*Anal.* Calcd. for $C_{20}H_{23}O_4NS$ (373.45): C, 64.32; H, 6.21; N, 3.75. Found: C, 64.36; H, 6.20; N, 3.66.

### Chlorination and Dechlorination

***d,l-cis*-2-Chlorocyclohexylamine Hydrochloride.**—A 6.0-g. portion of the *trans* aminoalcohol hydrochloride was treated with 11.9 g. of finely powdered phosphorus pentachloride in 100 ml. of dry benzene at 10°, and the mixture stirred for two hours at 25°. The product was collected on a sintered glass filter and washed repeatedly with dry carbon tetrachloride. After drying, the product[6b] weighed 5.0 g., m. p. 179–181°, with decomposition. The product was recrystallized from benzene–alcohol (5:1) yielding 3.5 g. of colorless needles, m. p. 185–186°, with decomposition. A mixed m. p. with the starting material was depressed to 143–153°.

The free chloro-amine was obtained by neutralizing the hydrochloride with concentrated aqueous alkali at 0° in the presence of ether. The crude liquid chloro-amine obtained by evaporating the dried ether extract was used directly for further operations.

***d,l-cis*-2-Benzoylaminocyclohexyl Chloride.**—A 0.4-g. portion of the chloro-amine hydrochloride was treated by the Schotten–Baumann procedure at 0–10° with 2.0 equivalents of benzoyl chloride, and 4.0 equivalents of 1 *N* aqueous sodium hydroxide. The precipitate was washed with water, and recrystallized from ethanol, yielding 0.3 g. of colorless rectangular leaflets, m. p. 153–154°. A sample recrystallized again, for analysis, showed no change in m. p.

*Anal.* Calcd. for $C_{13}H_{16}NOCl$ (237.73): C, 65.68; H, 6.79; Cl, 14.92. Found: C, 66.27; H, 7.15; Cl, 15.12.

A mixed m. p. with the dibenzoyl derivative (m. p. 153°) was depressed. The compound gave a positive Beilstein test for halogen, but was totally inert to hot alcoholic silver nitrate, and when it was boiled for twenty-one hours with silver acetate–acetic acid, hardly any silver chloride was formed.

**Reaction of the *cis*-Chloro-amine with Silver Oxide or Carbonate.**—Silver nitrate solution was treated with excess sodium carbonate solution, and the precipitate was washed, and suspended in water. To an excess of the resulting suspension the *d,l*-chloro-amine (or its hydrochloride) was added in portions. (If added all at once, a gummy ball forms.) The mixture was stirred at 40° for two hours. The product was mainly unchanged starting material, even when the temperature was increased from 40 to 70°, or the reaction time increased, or sodium hydroxide used in place of sodium carbonate. This was verified by benzoylation of the product, giving a 54% yield of *d,l-cis*-2-benzoylaminocyclohexyl chloride, m. p. 150–153°; mixed m. p. with an authentic sample not depressed. (A mixed m. p. with the dibenzoyl derivative was depressed.) These results indicate that the *d,l*-chloro-amine very largely fails to react under these conditions.

### X-Ray Power Spectra

Patterns on powdered samples of *trans*- and *cis*-*d,l*-2-acetaminocyclohexanol were obtained using a flat cassette at 5 cm. from the sample and copper K$\alpha$ radiation. The results are shown as positive prints in Fig. 1.[23]

## Summary

1. Detosylation of *d,l-trans*-2-benzoylaminocyclohexyl-*p*-toluenesulfonate in dry acetic acid–sodium acetate gives the benzamidoacetate with retention. The reaction in wet acetic acid or (dry) ethanol gives the benzamidoalcohol with inversion. Thus, a neighboring acylamino group can participate in the same manner as a neighboring acyloxy group to determine the steric result of a detosylation reaction.

2. The steric results are consistent with the viewpoint that the 2-aminocyclohexanol of m. p. 68°, originally designated as *cis*, is actually the *trans* isomer.

3. The *cis* and *trans* forms of *d,l*-2-aminoc

(22) It is reasonable to expect that the amount of each detosylation product actually present in its reaction mixture may be considerably greater than the reported yield based on material actually isolated and purified.

(23) We are indebted to Dr. R. T. Miller and Dr. N. N. J of the Northern Regional Research Laboratory, Peoria, f observations.

hexanol have been characterized by the preparation of various new derivatives and by X-ray powder spectra.

4. The chloro-amine obtained by phosphorus pentachloride treatment of *d,l-trans*-2-aminocyclohexanol hydrochloride has a very inert halogen characteristic of its *cis* structure.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Sulfur-containing Amines. VI.[1] Antispasmodics

BY GEORGE M. FOHLEN,[2] WOLFGANG HUBER,[3] S. C. LASKOWSKI AND R. O. CLINTON

In previous communications[4,5] from these laboratories there have been described a number of sulfur-containing amines, which are of pharmacological interest as ester and amide precursors in local anesthetic types[1] and as side chains in antimalarial types.[6] In the present work we have extended the investigation to include derivatives of the sulfur-containing amines with a number of disubstituted acetic acid types, with the expectation that the sulfide linkage might provide favorable toxicity indices.[1]

The acids used were of the type which previous investigators have shown to form spasmolytically active esters, *viz.*: diphenylacetic, benzilic, fluorene-9-carboxylic, dibenzylacetic, α-cyclohexylphenylacetic and 9,10-dihydroanthracene-9-carboxylic acids.

The esters were prepared by either of two general methods. The first of these, reaction of an acid chloride with the alcohol or amine in cold benzene, is the preferable method. As has been previously indicated,[1] the reaction of the sulfur-containing amines with an acid chloride must be carefully controlled to avoid decomposition of the heat-labile sulfur compound. Only in two cases were satisfactorily stable hydrochlorides isolated; in general it was found preferable to isolate the free bases and convert them to the citrate salts.

The second method of preparing the basic esters utilized transesterification, in the presence of sodium alkoxide as catalyst. This method gave excellent results with both methyl benzilate[7] and methyl fluorene-9-carboxylate.

In Table I there are listed the esters prepared from straight and branched chain sulfur-containing amino alcohols. In addition, there was prepared one ester of an alcohol containing two sulfide linkages and a single example of an amide. These compounds, with other examples, are described in the experimental section.

(1) Paper V: Clinton, Salvador, Laskowski and Suter, THIS JOURNAL, **70**, 950 (1948).

(2) Present address: Barrett Division, Allied Chemical and Dye Corp., Philadelphia 6, Pennsylvania.

(3) Present address: Electronized Chemicals Corporation, New York, N. Y.

(4) Clinton, Suter, Laskowski, Jackman and Huber, THIS JOURNAL, **67**, 594 (1945).

(5) Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

(6) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945); **68**, 322 (1946).

(7) *Cf.* Holmes, U. S. Patent 2,399,736.

This series of compounds has been tested for antispasmodic activity *in vitro* against barium chloride and acetylcholine-induced spasms on rabbit intestinal strips and against histamine-induced spasms on strips of guinea pig ileum.[8] None of the compounds exhibited a high degree of activity against the acetylcholine-induced spasms. The activity against histamine-induced spasms was considerably less than that of papaverine, with the exception of 3-(3-(1-piperidyl)propylmercapto)-2-propyl fluorene-9-carboxylate citrate which was of the same order of magnitude. The compounds did not differ greatly in their musculotropic activity, *i. e.*, against barium chloride-induced spasms, all being equal to or slightly more active than papaverine.

## Experimental[9]

The following examples will serve to illustrate the various procedures used. The yields of the compounds varied from 24 to 87%, the lower yields being chiefly ascribable to isolation difficulties.

**2-(2-Diethylaminoethylmercapto)-ethyl Diphenylacetate Hydrochloride.**—To an ice-cooled solution of 13.0 g. of diphenylacetyl chloride in 100 ml. of dry benzene was added during a five-minute period, with shaking, a cold solution of 10.0 g. of 2-(2-diethylaminoethylmercapto)-ethanol[4] in 50 ml. of dry benzene. The clear solution was warmed for fifteen minutes on the steam-bath and then cooled. Five hundred milliliters of Skellysolve A was then added; the precipitated oil crystallized on cooling and scratching. After three recrystallizations from ethyl acetate there was obtained 15.8 g. (67%) of large white prisms.

With the other sulfur-containing amines it was necessary to convert the oily or low-melting hydrochlorides to the free bases by means of ethyl acetate–ammonia, and thence to the citrate through the use of citric acid monohydrate in acetone or absolute alcohol solution.

**3-(2-Diethylaminoethylmercapto)-propyl Benzilate Citrate.**—A mixture of 5 g. of methyl benzilate, 4 g. of 3-(2-diethylaminoethylmercapto)-propanol,[4] and 0.15 g. of sodium metal in 50 ml. of Skellysolve E was refluxed under a pressure of about 30 mm. for four hours. An equal volume of benzene was then added and the mixture was washed several times with water and dried. The oily residue remaining after removal of the solvents *in vacuo* was taken up in dry acetone and treated with a solution of 4.2 g. of citric acid monohydrate in acetone. The white crystalline product was then repeatedly recrystallized from acetone.

(8) We are indebted to Dr. T. J. Becker (deceased) and his staff for the pharmacological testing of these compounds. A more detailed report of these tests will be published elsewhere.

(9) All melting points are uncorrected. We are indebted to Mr. Morris E. Auerbach and his staff for the analyses.

TABLE I

BASIC ESTERS OF DISUBSTITUTED ACETIC ACIDS[a]

| Acid, RCOO– | *m* | *n* | R′ | Yield, % | M. p., °C.[b] | Formula | Analyses, % Nitrogen Calcd. | Nitrogen Found | Sulfur Calcd. | Sulfur Found |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $RCOO(CH_2)_mS(CH_2)_nNR'_2$ | | | | | | |
| Diphenylacetic | 2 | 2 | $(CH_3)_2$ | 45 | 73–75 | $C_{26}H_{33}NO_9S$ | 2.62 | 2.64 | 5.98 | 5.96 |
| Diphenylacetic | 2 | 2 | $(C_2H_5)_2$ | 69 | 94–95[c] | $C_{22}H_{30}ClNO_2S$ | 3.43 | 3.37 | [d] | [d] |
| Diphenylacetic | 3 | 2 | $(C_2H_5)_2$ | 87 | 112.5–113.0 | $C_{29}H_{39}NO_9S$ | 2.42 | 2.39 | [e] | [e] |
| Benzilic | 3 | 2 | $(C_2H_5)_2$ | 51 | 69–74 | $C_{29}H_{39}NO_{10}S$ | 2.36 | 2.44 | [f] | [f] |
| Fluorene-9-carboxylic | 2 | 2 | $(C_2H_5)_2$ | 54 | 95–97 | $C_{28}H_{35}NO_9S$ | 2.49 | 2.50 | 5.69 | 5.62 |
| Fluorene-9-carboxylic | 3 | 2 | $(CH_3)_2$ | 61 | 78–80 | $C_{27}H_{33}NO_9S$ | 2.48 | 2.60 | 5.86 | 5.56 |
| Dibenzylacetic | 2 | 2 | $(C_2H_5)_2$ | 71 | 95–101 | $C_{30}H_{41}NO_9S$ | 2.38 | 2.59 | [g] | [g] |
| Dibenzylacetic | 2 | 3 | $C_5H_{10}$[h] | 51 | 67–70 | $C_{32}H_{43}NO_9S$ | 2.28 | 2.24 | 5.20 | 5.11 |
| Dibenzylacetic | 2 | 3 | $(C_2H_5)_2$ | 40 | 94–97 | $C_{31}H_{43}NO_9S$ | 2.32 | 2.40 | 5.29 | 5.46 |
| α-Cyclohexylphenylacetic | 2 | 2 | $(C_2H_5)_2$ | 85 | 102–106 | $C_{28}H_{43}NO_9S$ | 2.46 | 2.63 | 5.63 | 5.30 |
| α-Cyclohexylphenylacetic | 3 | 2 | $(C_2H_5)_2$ | 64 | 105–109 | $C_{29}H_{45}NO_9S$ | 2.40 | 2.58 | 5.49 | 5.49 |
| 9,10-Dihydroanthracene-9-carboxylic | 2 | 2 | $(C_2H_5)_2$ | 33 | 137.0–137.5[c] | $C_{23}H_{30}ClNO_2S$ | 3.35 | 3.36 | 7.64 | 7.67 |
| | | | | $RCOOCH(CH_3)CH_2S(CH_2)_nNR'_2$ | | | | | | |
| Diphenylacetic | .. | 2 | $(CH_3)_2$ | 30 | 65–70 | $C_{27}H_{35}NO_9S$ | 2.56 | 2.58 | 5.84 | 6.02 |
| Fluorene-9-carboxylic | .. | 3 | $C_5H_{10}$[h] | 41 | 71–73 | $C_{31}H_{39}NO_9S$ | 2.33 | 2.37 | 5.32 | 5.15 |
| α-Cyclohexylphenylacetic | .. | 3 | $(C_2H_5)_2$ | 24 | 110–114 | $C_{30}H_{47}NO_9S$ | 2.40 | 2.47 | 5.49 | 5.40 |

[a] The esters are listed as the citrate salts, unless otherwise specified. [b] The melting points are uncorrected. The citrate salts melted in all cases with effervescence. [c] Hydrochloride. [d] Calcd.: C, 64.76; H, 7.41. Found: C, 64.55; H, 7.73. [e] Calcd.: C, 60.29; H, 6.80. Found: C, 60.22; H, 6.93. [f] Calcd.: C, 58.67; H, 6.62. Found: C, 58.62; H, 7.19. [g] Calcd.: C, 60.89; H, 6.98. Found: C, 60.84; H, 6.59. [h] 1-Piperidyl.

**2-(2-(2-Diethylaminoethylmercapto)-ethylmercapto)-ethyl Diphenylacetate Citrate.**—The condensation of 2-(2-(2-diethylaminoethylmercapto)-ethylmercapto)-ethanol[4] with diphenylacetyl chloride, and conversion of the isolated free base to the citrate was carried out as described previously. The **citrate monohydrate** formed waxy white crystals from acetone, m.p. 87–89°.

*Anal.* Calcd. for $C_{24}H_{33}NO_2S_2.C_6H_8O_7.H_2O$: C, 56.13; H, 6.75; N, 2.19. Found: C, 55.80; H, 6.46; N, 2.30.

**N-(2-(2-Diethylaminoethylmercapto)-ethyl) Diphenylacetamide.**—To a mixture of 17.6 g. of 2-(2-diethylaminoethylmercapto)-ethylamine,[4] 12.6 g. of sodium bicarbonate, and 80 ml. of water was added a solution of 27.6 g. of diphenylacetyl chloride in 100 ml. of chloroform, with vigorous stirring, during a period of forty-five minutes. The mixture was stirred for an additional hour; the chloroform layer was separated, washed with dilute sodium hydroxide solution and water and dried over anhydrous potassium carbonate. Concentration of the chloroform solution *in vacuo* yielded a viscous colorless oil which readily crystallized. Two recrystallizations from ethyl acetate–Skellysolve A gave 24.5 g. (62%) of product as white leaflets, m.p. 55.8–57.0°.

*Anal.* Calcd. for $C_{22}H_{30}N_2OS$: C, 71.31; H, 8.16. Found: C, 71.55; H, 7.64.

The **citrate** was prepared in absolute alcohol–ethyl acetate mixture: white rosettes, m.p. 80°.

*Anal.* Calcd. for $C_{22}H_{30}N_2OS.C_6H_8O_7$: citric acid, 34. Found: citric acid, 33.

## Summary

Fifteen esters of certain sulfur-containing amines with disubstituted acetic acids have been prepared for testing as antispasmodics. One related amide and an ester of a basic alcohol containing two sulfide linkages have also been prepared. No high degree of spasmolytic activity has been found in this series.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 30, 1948

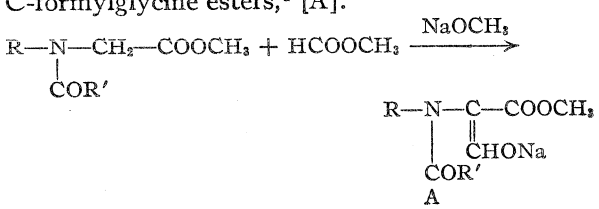
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Studies on Imidazoles. II. The Synthesis of 5-Imidazolecarboxylates from Glycine and Substituted Glycine Esters

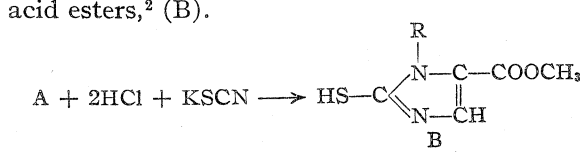
BY REUBEN G. JONES

A number of biologically important derivatives of imidazole including histamine, histidine, methylhistidine and pilocarpine have substituents attached to the 4- or 5-position of the imidazole ring. Although methods of synthesizing these compounds have been rather thoroughly investigated, the methods generally involve many tedious steps and low yields. Therefore, it was of interest to investigate more simple and direct ways of preparing imidazoles with suitable substituents in the 4(or 5)- and 1,5-positions.

This paper describes the synthesis of 5-imidazolecarboxylates from glycine and N-substituted glycine derivatives. It is known that N-acylated glycine esters may be formylated by the Claisen method to give the sodium enolate salts of N-acyl-C-formylglycine esters,[1] [A].



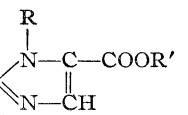
It has now been found that the sodium enolate salts (A) may be treated with acid and thiocyanate to yield 2-mercapto-5-imidazolecarboxylic acid esters,[2] (B).



This reaction takes place smoothly when the acyl group (—COR′) of A is formyl or acetyl but not when the acyl group is benzoyl. It was surprising to find that a pre-hydrolysis of A to form the intermediate, $RNHCH(CHO)COOCH_3$, was unnecessary. The reactions were best carried out by adding acid and thiocyanate simultaneously to a water or water–alcohol solution of A and heating. Under these conditions the N-acyl group appeared to be rapidly cleaved. A number of 2-mercapto-5-imidazolecarboxylates prepared in this way are presented in Table I.

TABLE I

2-MERCAPTO-5-IMIDAZOLECARBOXYLATES[2]



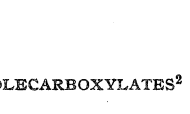
| R | R′ | Empirical formula | Yield, %[a] | M.p., °C. | Analyses,[b] % (C and H or N) Calcd. | Found |
|---|---|---|---|---|---|---|
| H | $CH_3$ | $C_5H_6N_2O_2S$ | 50 | 190–191 (dec.) | 17.70 | 17.24 |
| H | $C_2H_5$ | $C_6H_8N_2O_2S$ | 50–60 | 184 | 41.84, 4.68 | 42.03, 4.99 |
| $CH_3$ | $CH_3$ | $C_6H_8N_2O_2S$ | 72–77 | 193–194 | 16.27 | 16.43 |
| $(CH_3)_2CH$ | $CH_3$ | $C_8H_{12}N_2O_2S$ | 93 | 148–149 | 13.99 | 13.61 |
| $C_6H_{11}$[c] | $CH_3$ | $C_{11}H_{16}N_2O_2S$ | 90 | 171–172 | 11.66 | 11.56 |
| $C_6H_5CH_2$ | $CH_3$ | $C_{12}H_{12}N_2O_2S$ | 97 | 174–175[d] | 58.04, 4.87 | 58.00, 4.88 |
| $C_6H_5$ | $CH_3$ | $C_{11}H_{10}N_2O_2S$ | 86 | 224–225 (dec.) | 11.95 | 11.96 |
| $C_6H_5$ | $C_2H_5$ | $C_{12}H_{12}N_2O_2S$ | 91 | 188–190 | 11.28 | 11.43 |

[a] Yields are based on the N-formylglycine esters (Table III) as starting materials. [b] Analytical samples were recrystallized from water or alcohol. [c] Cyclohexyl. [d] A second crystalline modification of this compound was also obtained which melted at 146–147°. When this melt was seeded with the higher melting form, it resolidified and then melted again at 174–175°.

The mercaptoimidazoles of Table I were oxidized by the well-known nitric acid method[3] to form the imidazoles listed in Table II. This nitric acid oxidation was modified in that lower tempera-

TABLE II

5-IMIDAZOLECARBOXYLATES[2]



| R | R′ | Empirical formula | Yield, % | M.p., °C. | Nitrogen analyses,[a] % Calcd. | Found |
|---|---|---|---|---|---|---|
| H | $C_2H_5$ | $C_6H_8N_2O_2$[b] | 80–86 | 157–158 | 20.00[c] | 19.70 |
| $CH_3$ | $CH_3$ | $C_6H_8N_2O_2$ | 82–86 | 56–57[d] | 20.00 | 19.81 |
| $(CH_3)_2CH$ | $CH_3$ | $C_8H_{12}N_2O_2$ | 72 | liquid[e] | 16.66 | 16.34 |
| $C_6H_{11}$[f] | $CH_3$ | $C_{11}H_{16}N_2O_2$ | 97 | 90–91 | 13.45 | 13.57 |
| $C_6H_5CH_2$ | $CH_3$ | $C_{12}H_{12}N_2O_2$ | 83 | 63–64 | [g] | |
| $C_6H_5$ | $C_2H_5$ | $C_{11}H_{10}N_2O_2$ | 98 | 80–81 | 12.96 | 13.21 |

[a] Samples for analyses were recrystallized from water and/or alcohol. [b] Previously prepared by a different method, see ref. 8. [c] *Anal.* Calcd.: C, 51.42; H, 5.75. Found: C, 51.47; H, 5.53. [d] B. p. 115° (8 mm.). [e] B. p. 129–131° (13 mm.). [f] Cyclohexyl. [g] Analyzed as the nitrate, see Experimental.

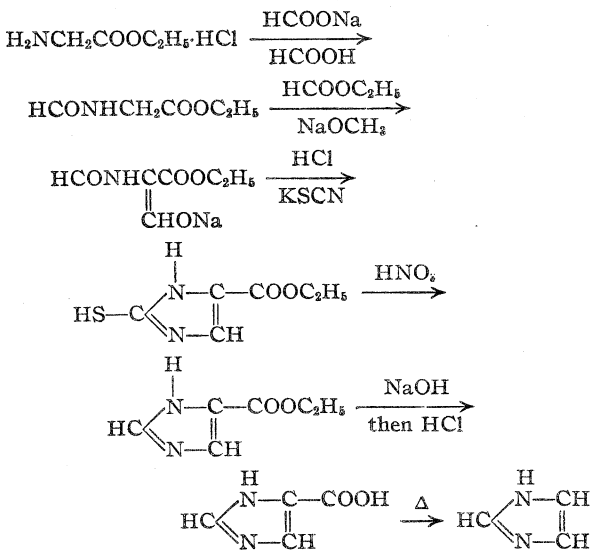
(1) Erlenmeyer and Stoop, *Ann.*, **337**, 236 (1904).

(2) When the substituent, R, is hydrogen the compound must be designated as a 4(or 5)-imidazolecarboxylate.

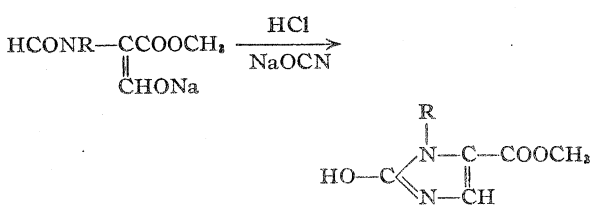
(3) Marckwald, *Ber.* **25**, 2354 (1892); Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

tures and more concentrated nitric acid were used. It was observed that the oxidation of mercaptoimidazoles even in hot nitric acid did not take place unless oxides of nitrogen were present. However, by adding a little sodium nitrite to initiate the oxidation, it was possible to carry out the reaction at 25 or 30°, and under these conditions there was no significant hydrolysis of the ester groups.

Starting with the readily available glycine ethyl ester hydrochloride, the present imidazole synthesis constitutes an excellent method for the preparation of imidazole itself. By the following sequence of reactions, imidazole has been obtained in over-all yields of 35 to 40%



The condensation of the sodium enolate salts A with cyanate took place less satisfactorily than with thiocyanate, and only moderate yields of 1-substituted-2-hydroxy-5-imidazolecarboxylates were obtained.



It has been found that the carbalkoxy groups in imidazoles such as those of Table II can be readily converted to aldehyde, ketone, hydroxymethyl and other groups valuable for the synthesis of important imidazole derivatives. This work will be the subject of a separate publication.

**Acknowledgment.**—The writer expresses his appreciation to William L. Brown and Howard L. Hunter for the microanalyses reported herein, and to Keith C. McLaughlin for valuable assistance.

## Experimental

**N-Formyl-N-substituted-glycine Esters.**—These compounds, listed in Table III, were prepared from the appropriate amine hydrochlorides by the method[4] illustrated in the following typical example.

A mixture of 272 g. (2.0 moles) of cyclohexylamine hydrochloride, 250 ml. of 40% formalin, and 100 ml. of water, in a flask provided with a stirrer, was cooled in an ice-bath, and with continuous stirring a cold concentrated, aqueous solution of 130 g. (2.0 moles) of potassium cyanide was added in portions over a period of two hours. The temperature was held below 10°, and a little solid carbon dioxide was added from time to time to maintain a carbon dioxide atmosphere. The mixture was stirred for one additional hour and then extracted with two 500-ml. portions of ether. After drying the solution over calcium oxide, the ether was removed by gentle warming, finally under vacuum. The crude cyclohexylaminoacetonitrile was dissolved in 2.5 l. of dry methanol which had been saturated in the cold with hydrogen chloride. This solution was allowed to stand overnight at room temperature and then heated under reflux for four hours. The ammonium chloride which had separated was removed by filtration. The filtrate was evaporated on the steam-bath under vacuum to a volume of about 800 ml. and again filtered through a pad of filter cell. Evaporation of this filtrate under vacuum left a residue of 340 g. of crude N-cyclohexylglycine methyl ester hydrochloride.

The crude ester hydrochloride was dissolved by warming in 250 ml. of 98% formic acid. To this solution was added a hot solution of 150 g. of sodium formate in 200 ml. of 98% formic acid. After the mixture had stood for one hour, the precipitated sodium chloride was removed by filtration through a layer of filter-cel, and 450 ml. of acetic anhydride was added in portions. When the vigorous reaction had subsided the mixture was heated on the steam-bath for one-half hour and then evaporated under vacuum to remove the formic and acetic acids. The residual liquid was taken into 1 l. of acetone whereupon a quantity of sodium chloride separated. The solution was filtered, the acetone distilled and, finally, the residual material was distilled under vacuum to yield pure N-formyl-N-cyclohexylglycine methyl ester as a colorless somewhat viscous liquid.

In the same way, N-formylglycine ethyl ester and methyl ester were prepared from glycine ethyl ester and methyl ester hydrochlorides respectively; and the N-formyl-N-

TABLE III

N-FORMYLGLYCINE ESTERS $HCON(R)CH_2COOCH_3$

| R | Empirical formula | Yield,[a] % | B. p., °C. (1.5 mm.) | $n^{25}D$ | Nitrogen, analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| H | $C_4H_7NO_3$ | 86[b] | 110–112 | 1.4555 | 11.96 | 11.31 |
| $CH_3$ | $C_5H_9NO_3$ | 39 | 97–100[c] | 1.4473 | 10.69 | 10.34 |
| $(CH_3)_2CH$ | $C_7H_{13}NO_3$ | 22 | 91–92 | 1.4503 | 8.80 | 8.67 |
| $C_6H_{11}$[d] | $C_{10}H_{17}NO_3$ | 40 | 138–140 | 1.4808 | 7.05 | 7.35 |
| $C_6H_5CH_2$ | $C_{11}H_{13}NO_3$ | 39 | 144–145 | 1.5296 | 6.76 | 6.83 |
| $C_6H_5$ | $C_{10}H_{11}NO_3$[5] | 76[e] | 140–142 | | | |

[a] Yields are for the over-all process and are based on the amine hydrochloride used. [b] This yield is based on glycine methyl ester hydrochloride. The corresponding N-formylglycine ethyl ester, b. p. 110° (1 mm.) was prepared in 92% yield from glycine ethyl ester hydrochloride. [c] This boiling point is at 4 mm. pressure. The compound was first prepared by Dr. Q. F. Soper. [d] Cyclohexyl. [e] This yield is based on N-phenylglycine methyl ester hydrochloride. The corresponding N-formyl-N-phenylglycine ethyl ester,[5] b. p. 157–159° (7 mm.), was obtained in 90% yield from N-phenylglycine ethyl ester.

(4) The preparation of the substituted glycine ester hydrochlorides from amine hydrochlorides, formaldehyde and cyanide reported here is a modification of Staudt's method for the synthesis of sarcosine: see Staudt, *Z. physiol. Chem.*, **146**, 286 (1925).

phenylglycine ethyl and methyl esters[5] were prepared from the corresponding ethyl and methyl ester hydrochlorides of N-phenylglycine.

**Condensation of N-Formylglycine Esters with Methyl Formate.**—One example will suffice to illustrate the method by which the N-formylglycine esters of Table III were condensed with methyl formate.

In a three-necked flask provided with a stirrer and thermometer was placed 106 g. (0.67 mole) of N-formyl-N-isopropylglycine methyl ester and 120 g. (2.0 mole) of dry methyl formate. The flask was surrounded with an ice-bath and, with continuous stirring, a suspension of 40 g. (0.74 mole) of sodium methoxide[6] in 150 ml. of dry benzene was added in five portions during a period of one-half to one hour. The temperature of the reaction mixture was maintained below 15°, and stirring was continued for one hour after all of the sodium methoxide had been added. The mixture was then placed in the refrigerator and allowed to stand for twenty-four hours.

If it was desired to isolate the sodium enolate salt, dry ether was added to the reaction mixture, and the solid was collected on a filter, washed with dry ether and dried in vacuum.

**2-Mercapto-5-imidazolecarboxylates.**—The following example of the preparation of ethyl 2-mercapto 4(or 5)-imidazolecarboxylate shows the method by which the compounds of Table I were prepared.

The reaction mixture of 411 g. (3.12 moles) of N-formylglycine ethyl ester, 700 g. of ethyl formate, 700 ml. of benzene and 183 g. (3.4 moles) of sodium methoxide, carried out as described above, was shaken with 1 l. of water. When all solid had dissolved, the aqueous solution was separated, cooled in an ice-bath and stirred while 565 ml. (6.8 moles) of 12 *N* hydrochloric acid was added slowly. To the resulting solution was added 350 g. (3.6 moles) of crystalline potassium thiocyanate. The mixture was warmed on the steam-bath at 50–70° for two hours, allowed to stand overnight and finally cooled in an ice-bath. The crystalline ethyl 2-mercapto-4(or 5)-imidazolecarboxylate was collected on a filter, washed with a little water and air dried. The yield was 304 g. Yields for a number of experiments varied from 50 to 60% based on N-formylglycine ethyl ester.

N-Acetylglycine ethyl ester[7] (58 g., 0.4 mole) was condensed with 100 ml. of ethyl formate and 24 g. (0.44 mole) of sodium methoxide in 115 ml. of benzene by the procedure described above. The mixture was extracted with 200 ml. of water, 42 g. of potassium thiocyanate and 75 ml. of 12 *N* hydrochloric acid were added to the aqueous solution, and it was heated on the steam-bath for two hours. There was thus obtained 31 g. (43% yield) of ethyl 2-mercapto-4(or 5)-imidazolecarboxylate, identified by melting point and mixed melting point.

N-Benzoyl-C-formylglycine ethyl ester, when treated with thiocyanate under the same conditions as described above for the formyl and acetyl analogs, gave no imidazole compound.

The reactions of thiocyanate with the formyl-N-cyclohexyl, N-benzyl and N-phenylglycine derivatives were carried out in 50% alcohol. In most cases, after acidifying the sodium enolate solutions with two equivalents of hydrochloric acid it was not necessary to immediately add the thiocyanate. For example, 25.7 g. (0.10 mole) of the dry sodium enolate salt of N-formyl-N-benzyl-C-formylglycine methyl ester was dissolved in 100 ml. of 50% alcohol and 19 ml. (0.23 mole) of 12 *N* hydrochloric acid was added. After standing for twenty hours at room temperature, 15 g. (0.155 mole) of potassium thiocyanate was added and the mixture was heated on the steam-bath until most of the alcohol had evaporated. The methyl 1-benzyl-2-mercapto-5-imidazolecarboxylate was collected by filtration, washed with water and air dried. The yield was 24.0 g. (97%). A similar experiment, in which the thiocyanate was added immediately after the hydrochloric acid, yielded 90% of the desired imidazole.

In the case of N-formyl-N-phenyl-C-formylglycine esters it was necessary to add the thiocyanate simultaneously with the acid in order to get a good yield of the mercaptoimidazole. When acidified solutions were allowed to stand without the addition of thiocyanate a sparingly soluble crystalline substance was deposited, the nature of which has not as yet been determined. For example, from 24.3 g. (0.10 mole) of the sodium enolate salt of N-formyl-N-phenyl-C-formylglycine methyl ester and 19 ml. of 12 *N* hydrochloric acid in 100 ml. of 50% alcohol, there was obtained, after twelve hours, 12 g. of crystalline precipitate, m. p. 145–146° (from alcohol).

*Anal.* Found: C, 66.53; H, 5.79; N, 5.79.

**Oxidation of 2-Mercapto-5-imidazolecarboxylates. 5-Imidazolecarboxylates.**—A solution of 330 ml. of concentrated nitric acid in 950 ml. of water in a large beaker was mechanically stirred, and 2 g. of sodium nitrite was added. The beaker was then surrounded with an ice-bath, and with continuous stirring 300 g. (1.75 mole) of crude methyl 1-methyl-2-mercapto-5-imidazolecarboxylate was added portionwise at such a rate that the temperature of the mixture remained at about 25–35°. After all material had been added the solution was stirred for about ten minutes or until the evolution of nitrogen oxides had completely stopped. An excess of solid sodium carbonate was added carefully and with stirring. The mixture was extracted with four 200-ml. portions of chloroform; the extract was dried, the chloroform removed and the residual liquid distilled in vacuum. The distillate immediately crystallized.

By the same method the other compounds listed in Table II were prepared from the corresponding 2-mercapto compounds. The 1-isopropyl compound was purified by distillation. The 1-cyclohexyl and 1-phenyl compounds separated as crystalline solids and were purified by recrystallization from chloroform–petroleum ether.

Methyl 1-benzyl-5-imidazolecarboxylate separated from the oxidation mixture as the nitrate which did not decompose in the presence of cold excess sodium carbonate. A sample was recrystallized from alcohol; m. p. 170–171°.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2 \cdot HNO_3$: C, 51.60; H, 4.76; N, 15.04. Found: C, 51.72; H, 4.52; N, 14.89.

The nitrate was boiled with sodium carbonate solution to liberate methyl 1-benzyl-5-imidazolecarboxylate.

The solution resulting from the oxidation of ethyl 2-mercapto-4(or 5)-imidazolecarboxylate was made basic with ammonium hydroxide (instead of sodium carbonate), chilled to 10° and the precipitated product collected and air dried.

**Imidazole-4(or 5)-carboxylic Acid.**[8]—Into 500 ml. of 6 *N* sodium hydroxide solution was stirred 250 g. (1.78 moles) of ethyl 4(or 5)-imidazolecarboxylate. The resulting solution was heated on the steam-bath for three hours and then cooled and acidified to *p*H 2.0 with concentrated hydrochloric acid. After standing for two hours the mixture was chilled to 0° and the white crystalline solid was collected on a filter. The product was stirred to a paste with 250 ml. of cold distilled water, filtered and washed on the filter with 200 ml. of alcohol followed by 200 ml. of ether. The yield of air dried product was 180 g. (84%); m.p. 271° (dec.) (lit.[8] 275°).

*Anal.* Calcd. for $C_4H_4N_2O_2$: N, 25.00. Found: N, 24.75.

**Imidazole.**—In a 200-ml. round-bottom flask carrying an eighteen-inch Vigreux column and a condenser set for distillation was placed 50 g. (0.45 mole) of 4(or 5)-imidazolecarboxylic acid. The flask was heated with a small flame and decarboxylation took place smoothly. The product was distilled under vacuum to yield 28.5 g. (94%) of pure imidazole, m.p. 90°.

**1-Phenyl-2-mercapto-5-imidazolecarboxylic Acid.**—A solution of 5 g. (0.02 mole) of ethyl 1-phenyl-2-mer-

(5) Paal and Otten, *Ber.*, **23**, 2587 (1890).

(6) Commercial sodium methoxide of good quality was satisfactory.

(7) Curtius, *Ber.*, **17**, 1663 (1884); *J. prakt. Chem.*, [2] **94**, 116 (1915).

(8) Pyman, *J. Chem. Soc.*, **109**, 186 (1916).

capto-5-imidazolecarboxylate in 12 ml. of 6 *N* sodium hydroxide solution was allowed to stand for forty-eight hours. The solution was acidified with acetic acid but nothing precipitated; therefore, hydrochloric acid was added whereupon a white precipitate of the desired acid seperated. The yield was 4.2 g. (95%). A sample was recrystallized from water for analysis; m.p. 198–200° (dec.).

*Anal.* Calcd. for $C_{10}H_8N_2O_2S$: N, 12.72. Found: N, 12.71.

**1-Methyl-2-mercapto-5-imidazolecarboxylic Acid.**—This was prepared from the methyl ester in the same way as described above for the corresponding phenyl compound m.p. 207–208°.

*Anal.* Calcd. for $C_5H_6N_2O_2S$: N, 17.71. Found: N, 17.55.

**N-Formyl-C-formylglycine Ethyl Ester.**—The dry sodium enolate salt from the condensation of 1.5 mole of N-formylglycine ethyl ester with ethyl formate was ground to a fine powder and added in one portion with stirring to a freshly prepared mixture of 135 ml. of 12 *N* hydrochloric acid and 200 g. of cracked-ice. As soon as all the salt had dissolved the solution was extracted with twenty 100-ml. portions of chloroform. The chloroform solution was dried with magnesium sulfate and evaporated in vacuum leaving 177 g. of crystalline residue. This was taken up in 1500 ml. of dry ether. The solution was decanted from a little insoluble gum, dried with magnesium sulfate, filtered and evaporated leaving 147 g. (62% yield) of white crystalline solid; m.p. 68–69°.

*Anal.* Calcd. for $C_6H_9NO_4$: C, 45.27; H, 5.70; N, 8.80. Found: C, 45.38; H, 6.32; N, 9.07.

The compound appeared to be somewhat hygroscopic; it was very soluble in alcohol or water, and slowly underwent decomposition at room temperature but could be kept for reasonably long periods of time at ice-box temperatures.

The corresponding methyl ester was also isolated but in lower yield because it was more water soluble and consequently more difficult to extract with chloroform. It was stable and not hygroscopic; m.p. 108–109°.

*Anal.* Calcd. for $C_5H_7NO_4$: N, 9.65. Found: N, 9.78.

**1-Substituted-2-hydroxy-5-imidazolecarboxylates.**—A solution of 20.9 g. (0.10 mole) of the sodium enolate salt of N-formyl-N-isopropyl-C-formylglycine methyl ester in 100 ml. of water was treated with 19 ml. of 12 *N* hydrochloric acid. The solution was allowed to stand for four hours then 9 g. of sodium cyanate was added. Effervescence took place. Gradually, a white crystalline precipitate of methyl 1-isopropyl-2-hydroxy-5-imidazolecarboxylate separated. After seven days the yield was 6.0 g. (32%). An analytical sample was recrystallized from alcohol; m.p. 174–175°.

*Anal.* Calcd. for $C_8H_{12}N_2O_3$: N, 15.21. Found: N, 14.87.

Methyl 1-cyclohexyl-2-hydroxy-5-imidazolecarboxylate was obtained in 22% yield from the sodium enolate salt of N-formyl-N-cyclohexyl-C-formylglycine methyl ester. It melted at 230–232°.

*Anal.* Calcd. for $C_{11}H_{16}N_2O_3$: N, 12.50. Found: N, 12.61.

Methyl 1-benzyl-2-hydroxy-5-imidazolecarboxylate was obtained in 8.6% yield from the sodium enolate salt of N-formyl-N-benzyl-C-formyglycine methyl ester. It melted at 160–161°.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.07. Found: N, 12.20.

Ethyl 2-hydroxy-4-(or 5)-imidazolecarboxylate, obtained in 14% yield from the sodium enolate salt of N-formyl-C-formylglycine ethyl ester melted at 243–245°.

*Anal.* Calcd. for $C_6H_8N_2O_3$: N, 17.95. Found: N, 18.46.

## Summary

A method for the preparation of 1-substituted-5-imidazolecarboxylates and 4(or 5)-imidazolecarboxylates from glycine derivatives is described. This method has also been shown to be a convenient synthesis of imidazole.

INDIANAPOLIS, INDIANA RECEIVED SEPTEMBER 24, 1948

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PENNSYLVANIA]

# Preparation of N-Alkyl Acrylamides and Methacrylamides by Pyrolysis of the Corresponding Acetoxy Amides

BY WILLIAM P. RATCHFORD, J. H. LENGEL AND C. H. FISHER

In a previous paper[2] it was shown that N,N-dimethylacrylamide (II) and acetic acid are obtained in high yields in the thermal decomposition of N,N-dimethyl-α-acetoxypropionamide (I). The present paper describes the preparation of certain acrylamides and methacrylamides (IV) by pyrolysis of appropriate acetoxy amides, and outlines some of the limitations of this method of making unsaturated amides.

$$\underset{\text{I}}{CH_3COOCH(CH_3)CON(CH_3)_2} \xrightarrow{520^\circ} \underset{\text{II}}{CH_2{=}CHCON(CH_3)_2} + CH_3COOH \quad (1)$$

$$\underset{\text{III}}{CH_3COOC(CH_3)_2CONHCH_3} \longrightarrow \underset{\text{IV}}{CH_2{=}C(CH_3)CONHCH_3} + CH_3COOH \quad (2)$$

N-Methyllactamide and N-methyl-α-hydroxyisobutyramide were made conveniently by allowing methyl lactate and methyl-α-hydroxyisobutyrate, respectively, to stand with methylamine at room temperature. N,N-Diethyllactamide, N,N-dibutyllactamide, and N,N-dimethylhydroxyisobutyramide could not be prepared satisfactorily by this method because of excessively low reaction rates. Diethylamine reacted slowly with polyactic acid[3] and with the methyl ester of polyactic acid, a moderate yield of N,N-diethyllactamide being obtained.

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Ratchford and Fisher, THIS JOURNAL, **69**, 1911 (1947).

(3) Filachione and Fisher, *Ind. Eng. Chem.*, **36**, 223 (1944).

TABLE I

PROPERTIES OF N-SUBSTITUTED AMIDES

| Amide | M. p., °C. | Boiling point °C. | Mm. | $d^{20}_4$ | $n^{20}D$ | $M^{20}D$ Calcd.[a] | $M^{20}D$ Obs. | C, % Calcd. | C, % Found | H, % Calcd. | H, % Found | N, % Calcd. | N, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Me lact- | 71.5–72 | 104 | 1.2 | ..... | ..... | ... | ... | 46.8 | 46.6 | 8.9 | 8.8 | 13.6 | 13.6 |
| Di-Et lact- | ..... | 115–117 | 12 | 0.9901 | 1.4540 | 39.65 | 39.66 | 58.2 | 57.9[g] | .. | .. | 9.7 | 9.7 |
| Me α-hydroxyisobutyr- | 72.5–73 | 118–120[b] | 0.2 | ..... | ..... | ... | ... | 51.3 | 51.2 | 9.5 | 9.5 | 12.0 | 11.8 |
| Me acetoxypropion- | 53.5–54 | 116.5–117.5[b] | 0.4 | ..... | ..... | ... | ... | 49.6 | 50.0 | 7.6 | 7.6 | 9.6 | 9.6[h] |
| Di-Et acetoxypropion- | ..... | 76.5–78[b] | 0.5 | 1.0212 | 1.4480 | 49.02 | 49.07 | 57.7 | 57.7[g] | .. | .. | 7.5 | 7.4[i] |
| Di-Bu acetoxypropion- | ..... | 106[b] | 0.6 | 0.9654 | 1.4505 | 67.49 | 67.85 | 64.2 | 64.2 | 10.4 | 10.3 | 5.8 | 5.8 |
| Me acetoxyisobutyr- | 70–73 | 88–89[b] | 0.4 | ..... | ..... | ... | ... | 52.8 | 52.9[g] | .. | .. | 8.8 | 8.8[j] |
| Di-Me acetoxyisobutyr- | 36.5–37.5 | 73.5[b] | 0.2 | ..... | 1.4520[c] | ... | ... | .. | ... | .. | .. | 8.1 | 8.3 |
| Di-Et acryl- | ..... | 95[d] | 19 | 0.9256 | 1.4672 | 37.66 | 38.06 | 66.1 | 65.9[g] | .. | .. | 11.0 | 11.2 |
| Me methacryl- | ..... | 108–110[e] | 10 | 0.9963 | 1.4700 | 28.69 | 27.76 | .. | ... | .. | .. | .. | ... |
| Di-Me methacryl- | ..... | 66–67[f] | 10 | 0.9272[f] | 1.4594[f] | 33.04 | 33.39 | .. | ... | .. | .. | 12.4 | 12.8 |

[a] For the atomic refraction of N in the disubstituted compounds the value 2.49 was used (reference 16 (a)); for the monosubstituted compounds, 2.76 (D'Alelio and Reid, THIS JOURNAL, 59, 109 (1937)), and for the other atoms the values of Eisenlohr (Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1739). [b] These measurements are subject to the errors encountered in distillations in the usual laboratory equipment (Hickman, *J. Phys. Chem.*, **34**, 627 (1930)). [c] For the supercooled liquid. [d] Jacobson and Mighton (U. S. Patent 2,311,548, Feb. 16, 1943) give the b. p. 93° (19 mm.). [e] Jacobson and Mighton, *ibid.*, give the b. p. 100° (10 mm.). [f] For a sample synthesized from methacrylic anhydride and dimethylamine. [g] Found by wet oxidation. [h] Sapon. equiv., calcd. 145.2, found: 144.4. [i] Sapon. equiv., calcd. 187.2, found 184.6. [j] Sapon. equiv., calcd. 159.2, found 160.5.

Probably the low reactivity of diethylamine (and the moderately high reactivities[4] of both piperidine and morpholine) toward methyl lactate can be explained on the basis of steric effects of the type discussed by Brown.[5] In a study of the addition compounds of reference acids and diethylamine,[5] Brown concluded that the configuration of diethylamine limits association with a highly hindered reference acid. If the plausible assumption is made that aminolysis occurs *via* the same mechanism as ammonolysis,[6] it is possible to consider the amide ion (or amine) the base and methyl lactate the reference acid (with association occurring between the carbonyl carbon atom and the nitrogen atom), and apply the steric theory of Brown to explain the observed phenomena.

N-Methylacetoxypropionamide, N-methylacetoxyisobutyramide (III) and N,N-diethylacetoxypropionamide were prepared by treatment of the corresponding lactamide or hydroxyisobutyramide with acetic anhydride. N,N-Diethylacetoxypropionamide, N,N-dibutylacetoxypropionamide and N,N-dimethylacetoxyisobutyramide (Table I) were made by the reaction of the proper dialkylamine with α-acetoxypropionyl chloride or α-acetoxyisobutyryl chloride.

The lower acetoxy amides of the present work were similar to N,N-dimethylacetoxypropionamide,[2] in that the amide, but not the acetoxy groups, were resistant to saponification (Table I).

N,N-Diethylacrylamide and acetic acid were the principal products of the thermal decomposition (500 to 550°) of N,N-diethylacetoxypropionamide, and therefore the pyrolysis method is suitable for the preparation of both N,N-dimethyl- and N,N-diethylacrylamide. A brief study of the pyrolysis of N-methyl- and N,N-dibutylacetoxypropionamide, however, indicated that the pyrolysis of α-acetoxy-propionamides is less satisfactory for producing N-monoalkylacrylamides or the higher N,N-dialkylacrylamides.

As pointed out earlier,[2] the pyrolysis behavior of N,N-dimethylacetoxypropionamide resembles that of its oxygen analog, methyl acetoxypropionate, in that acetic acid and an acrylic acid derivative are the principal products. The thermal decomposition of the N,N-diethyl amide, however, was distinctly different from that of ethyl acetoxypropionate, which yielded ethylene instead of ethyl acrylate as a major decomposition product.[7]

The pyrolysis behavior of N-methylacetoxypropionamide was similar to that of alkyl lactates[8] and α-acetoxypropionic acid[8] in that acrylic acid or its derivatives were formed in low yield. The common feature of alkyl lactates, acetoxypropionic acid, and N-methylacetoxypropionamide is the presence of hydrogen attached to oxygen or nitrogen, and therefore it appears that lactic acid derivatives having an O- or N-hydrogen (and perhaps S-hydrogen) are unsuitable for pyrolytic conversion into the corresponding acrylic acid derivatives.

It has been postulated[9] that the normal thermal decomposition of acetates (equation 3, X = H or alkyl) involves the transient formation and subsequent decomposition of a ring such as V into an olefinic product (VI) and acetic acid. When the acetate (or other ester) contains —COOH or —CONHR as substituents (that is, X = carboxyl or amide groups), the formation of rings[10] such

(4) Ratchford and Fisher, "Preparation of N-Substituted Lactamides," presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September 18, 1947.

(5) Brown and Taylor, THIS JOURNAL, **69**, 1332 (1947); Spitzer and Pitzer, *ibid.*, **70**, 1261 (1948).

(6) Hammett "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 359; Gordon, Miller and Day, THIS JOURNAL, **70**, 1946 (1948).

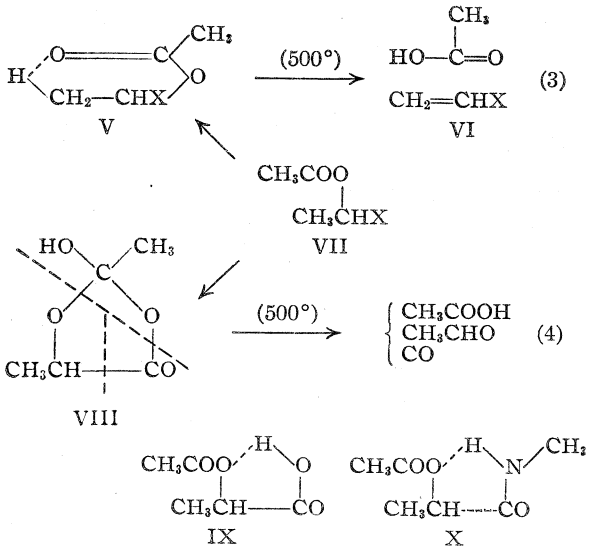
(7) Burns, Jones and Ritchie, *J. Chem. Soc.*, 400, 1054 (1935); Rehberg and Fisher, THIS JOURNAL, **67**, 56 (1945).

(8) Hurd, "Pyrolysis of Carbon Compounds," ACS Monograph 50, Reinhold Publishing Corp., New York, N. Y., 1929, pp. 426, 535.

(9) Hurd and Blunck, THIS JOURNAL, **60**, 2419 (1938).

(10) Somewhat similar rings have been proposed as the intermediates in several reactions (Arnold, "Stereochemistry of Five- and Six-membered Rings," presented before the Tenth National Organic Chemistry Symposium, American Chemical Society, Boston, Mass., June 12–14, 1947).

as VIII, IX, or X might take preference over that of the usual or normal intermediate (V). Scission of the bonds as shown in equation 4 might be responsible for decomposition into acetic acid, acetaldehyde and carbon monoxide, the products actually formed when α-acetoxypropionic acid is pyrolyzed.[8]




Both N-methyl-(IV) and N,N-dimethylmethacrylamide were obtained satisfactorily by pyrolyzing the corresponding α-acetoxyisobutyramides. These results suggest that α-acetoxyisobutyramides generally decompose more readily than α-acetoxypropionamides into the corresponding unsaturated amides. It has been demonstrated[11] that α-acetoxyisobutyrates decompose more readily than the corresponding α-acetoxypropionates into methacrylic or acrylic esters.

The success of the pyrolytic method for preparing these acrylamides and methacrylamides suggests that it may be useful in preparing certain crotonamides and amides of other unsaturated acids.

The pyrolysis of alkyl acetoxypropionates, which contain two ester groups, affords a comparison of the thermal stability of esters of acetic and α-acetoxypropionic acids.[7] Since N,N-diethylacetoxypropionamide contains both ester and amide groups, results obtained by pyrolyzing this compound may be used as a measure of the relative thermal stability of ester and amide groups; the formation of the acrylamide as the principal product indicates that the amide group is more stable.

**Acknowledgment.**—The authors gratefully acknowledge the assistance of C. O. Willits, Ruth W. Brand, Betty B. Linker and Pauline McDowell, who supplied most of the analytical data, and the interest and helpful suggestions of Allan R. Day.

(11) Filachione, Lengel and Fisher, THIS JOURNAL, **68**, 330 (1946).

## Experimental

**N,N-Diethyllactamide (Table I).**—When it was found that this lactamide was not obtained by the usual preparative method for lactamides,[2] other methods were tried. In the most successful experiment, 2 equivalents of polylactic acid (equiv. wt. 79) and excess diethylamine were circulated counter-currently through a heated tower[12] maintained at 175° and packed with 1/4-inch porcelain Berl saddles for five six-hour periods (1 pass per period). At the end of each period, the product from the tower was distilled to recover N,N-diethyllactamide; all other fractions, including the residue, were returned to the tower, and the process was repeated. At the end of successive periods, the total conversions to diethyllactamide were 18, 38, 53, 61 and finally 72%.

**N-Methyllactamide (Table I)** was obtained in 91% yield by distilling a mixture of 2 moles of methyl lactate, 2 moles of methylamine and 0.2 ml. of concentrated sulfuric acid that had been stored at room temperature for three weeks. The catalyst was neutralized with sodium acetate before distillation.

**N-Methyl-α-hydroxyisobutyramide** was obtained in 97% yield by distilling a mixture of 2 moles methyl hydroxyisobutyrate, 2 moles methylamine and 0.2 ml. concentrated sulfuric acid that had been stored at room temperature for two months (catalyst neutralized before distillation).

**Acetylation of N-Alkyllactamides.**—N-Methyllactamide and N,N-diethyllactamide were acetylated with acetic anhydride by the method used previously with N,N-dimethyllactamide,[2] high yields (98 and 95%) of the corresponding α-acetoxypropionamides being obtained.

**Reaction of α-Acetoxypropionyl Chloride with Amines.**—Acetoxypropionyl chloride (2.2 moles) was allowed to react with 2 moles of diethylamine. N,N-Diethyl-α-acetoxypropionamide was obtained in 66% yield by distillation of the reaction mixture. N,N-Dibutyl-α-acetoxypropionamide (69% yield) and N,N-dimethyl-α-acetoxyisobutyramide (78% yield) were made similarly from the appropriate acid chlorides and amines.

**N-Methyl-α-acetoxyisobutyramide** was prepared in 50% yield from N-methylhydroxyisobutyramide and 10% excess acetic anhydride, concentrated sulfuric acid being used as catalyst. After the catalyst had been neutralized and the acetic acid distilled, the acetoxy amide was collected at 118° (0.3 mm.). The low yield was due to the formation of viscous tacky fractions.

In determining the saponification equivalents[13] of Table I, a weighed sample was dissolved in 25 ml. of neutral ethanol cooled in ice-water, and titrated to determine free acidity, if any. Then 25 ml. of 0.2 *N* sodium hydroxide in ethanol was added. The weight of the sample was taken so that the alkali would be present in 50% excess of the ester group. The solution was refluxed on a steam-bath for one hour (air condenser), 50 ml. of distilled water was added, and refluxing was continued for another hour. At this point the condenser was rinsed, and excess alkali was back-titrated with 0.1 *N* hydrochloric acid, cresol red–thymol blue mixed indicator being used.

**Pyrolysis Experiments.**—Essentially the equipment and method described previously[14] were used. In some instances the acetoxy amide was dissolved in benzene prior to pyrolysis. The pyrolyzates were distilled (after a small amount of hydroquinone was added to prevent polymerization) to determine the nature and amounts of the products.

A solution consisting of 185.5 g. of N-methylacetoxypropionamide and 138.5 g. of benzene was pyrolyzed at 524° at a rate of 0.6 mole per hour of the amide (contact time, 2.9 sec., for the tube within 15° of 524°). The recovery of liquid products (1 g. of which neutralized 3.59 ml. *N* NaOH) was 97.2%. The following products were obtained on distillation (yields are expressed as per cent. of moles of acetoxy amide pyrolyzed): acetic acid, 87%,

(12) Filachione, Lengel and Fisher, *Ind. Eng. Chem.*, **37**, 388 (1945).

(13) We are indebted to C. O. Willits and his associates for his method and the saponification equivalents.

(14) Fein, Ratchford and Fisher, THIS JOURNAL, **66**, 1201 (1944).

TABLE II

PYROLYSIS OF N-ALKYL ACETOXY AMIDES

| Expt. | Amide pyrolyzed | G. | Temp., °C. | Contact time, sec. | Pyrolysis rate, mole/hr. | Liquid pyrolyzate % | Liquid pyrolyzate *N* NaOH to neutralize 1 g., ml. | Acetoxy amide recovered, % | Yield, % Alkyl acryl amide | Yield, % Acetic acid Titration | Yield, % Acetic acid Distillation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Di-Et-acetoxypropionamide | 110 | 506 | 2.5 | 0.452 | 96 | 3.16 | 28 | 77[a] | 79 | 40 |
| 2 | Di-Et-acetoxypropionamide | 169.5 | 520 | 1.7 | .548 | 97 | 4.69 | 17 | 75[a] | 86 | 77 |
| 3 | Di-Et-acetoxypropionamide | 255 | 523 | 4.5 | .296 | 96 | 4.83 | 0 | 66[b] | 87 | 56 |
| 4 | Di-Et-acetoxypropionamide | 257 | 520 | 1.6 | .55 | 98.5 | 3.95 | 16 | 72[a] | 87 | 78 |
| 5 | Di-*n*-Bu-acetoxypropionamide | 49 | 507 | 2.7 | .546 | 100 | 2.10 | [c] | 31[d] | 50 | 34 |
| 6 | Me-acetoxyisobutyramide | 95[e] | 476 | 1.2 | .842 | 100 | 2.12 | 9 | 65 | 76 | 64 |
| 7 | Di-Me-acetoxyisobutyramide | 71[f] | 480 | 1.7 | .877 | 99 | 2.62 | 0 | 87[a] | 95 | 59 |

[a] Corrected for acidic material, principally acetic acid, present. [b] Acid-free material. [c] Not definitely identified. [d] Crude, but polymerizable, material. [e] A solution of 95 g. of amide and 81 g. of benzene was pyrolyzed. [f] A solution of 71 g. of amide and 81 g. of benzene was pyrolyzed.

and water, 30–44%. A fraction of impure N-methylacrylamide was obtained (approximately 30% yield). The contents of the trap (cooled with solid carbon dioxide) had an aldehyde odor; treatment with 2,4-dinitrophenylhydrazine gave a compound identified as the acetaldehyde derivative: m.p., 165.5–166, mixed m. p., 165°.

*Anal.* Calcd. for $C_8H_8O_4N_4$: N, 25.0; C, 42.9; H, 3.6. Found: N, 24.6; C, 42.9; H, 3.8. The results of other pyrolysis experiments are given in Table II.

When the pyrolyzates of N,N-diethylacetoxypropionamide were distilled, it was found that the acrylamide fractions contained acetic acid (compare yields of acetic acid in Table II found by titration and distillation). In experiment 3 the crude acrylamide fractions were treated with aqueous sodium carbonate and extracted with ether. The ether extract was distilled, yielding an acid-free distillate having physical constants identical with those of the acrylamide made from acrylyl chloride and diethylamine. In experiment 4 the crude acrylamide fractions (containing 6% acetic acid) were redistilled, yielding the acrylamide containing 2.4% acid. In experiment 2 the crude diethylacrylamide fractions (with 7% acid) were redistilled to give the acrylamide with 0.9% acid; the yield of this material was 54% (based on acetoxy amide destroyed). In this experiment analysis of the gaseous products showed yields of 12, 5 and 2% for carbon monoxide, unsaturates and saturates, respectively.

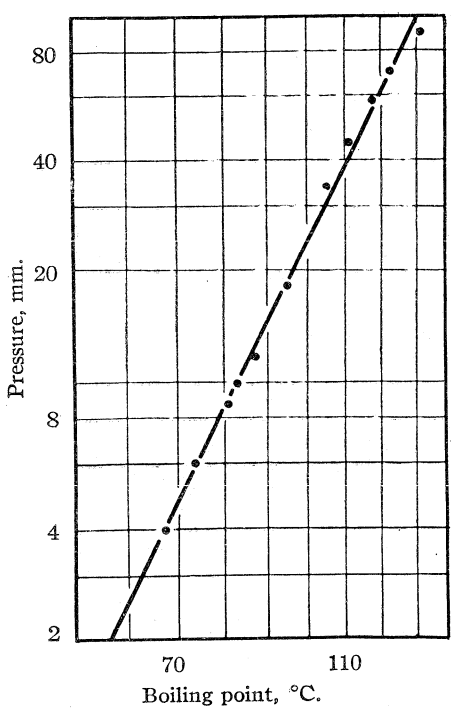



Fig. 1.—Boiling points of N,N-diethyl acrylamide.

Figure 1 shows a boiling point curve for N,N-diethylacrylamide.

When the pyrolyzate of N,N-dimethylacetoxyisobutyramide was distilled, 96% of all the acid charged was recovered in the distillate fractions; of the acid distilled, 24% was collected in the "N,N-dimethylmethacrylamide fractions." The latter distilled at 69–71° (10 mm.), but the acid content ranged from 18 to 6%, and $n^{20}D$ from 1.4481 to 1.4558. The acid content of the combined fractions was 13%. When heptane (in excess of that required for the reported heptane–acetic acid azeotrope[15]) was added to the combined fractions and the mixture carefully distilled, 96% of the acid charged was recovered; of this, 67% appeared in the "methacrylamide fractions," which distilled at 70° (10 mm.). The individual fractions showed acid contents from 15.6 to 5.2%; $n^{20}D$ ranged from 1.4498 to 1.4568.

Thus N,N-dimethylmethacrylamide strongly resembles N,N-dimethacrylamide in distilling with acetic acid.[2] Other N,N-disubstituted amides have been reported to form maximum boiling azeotropes with acetic acid.[16] The relatively large affinity of the N,N-dialkyl amides for acetic acid might be due to the increased electron density around the nitrogen caused by the presence of two electron-releasing alkyl groups. Possibly steric factors[5] are responsible for the fact that the N,N-diethyl amides have less attraction for acetic acid than the N,N-dimethyl amides. The N-methylacrylamide and N-methylmethacrylamide fractions were essentially acid-free.

**Polymeric Acrylamides.**—N,N-diethylacrylamide was polymerized in mass and in water solution, benzoyl peroxide and ammonium persulfate, respectively, being used as initiators.

Polymeric N,N-diethylacrylamide was moderately hard and transparent. It resembled polymeric N,N-dimethylacrylamide in appearance, but was much different in solubility characteristics. The polymeric N,N-diethylamide dissolved readily in benzene, toluene and acetone, and swelled in water, chloroform and carbon tetrachloride. A polymer prepared by polymerizing an aqueous solution of N,N-diethylacrylamide was more soluble in cold water than in hot water. It precipitated from hot water as a soft tacky mass.

A sample of impure N-methylacrylamide on storage in a refrigerator at about 5° darkened and polymerized slowly to a viscous tacky mass that was soluble in water but insoluble in chloroform, benzene, toluene, carbon tetrachloride, acetone, ethyl acetate and heptane.

(15) L. H. Horsley, *Anal. Chem.*, **19**, 508 (1947).

(16) (a) Ruhoff and Reid, THIS JOURNAL, **59**, 401 (1937); (b) Hanford and Stevenson, U. S. Patent 2,231,905 (Feb. 18, 1941).

## Summary

The pyrolysis method used previously to transform the acetyl derivatives of N,N-dimethyllactamide into N,N-dimethylacrylamide was applied to the preparation of other N-alkyl acrylamides and methacrylamides. N,N-Diethylacrylamide was obtained in good yield by the thermal decomposition of N,N-diethyl-α-acetoxypropionamide, but pyrolysis of N-methyl- and N,N-di-*n*-butyl-acetoxypropionamide was less satisfactory for the preparation of the corresponding acrylamides.

N-Methyl- and N,N-dimethylmethacrylamides were made successfully by pyrolyzing the corresponding N-alkyl α-acetoxyisobutyramides. Apparently methacrylamides can be made more readily than acrylamides by the pyrolysis method.


PHILADELPHIA 18, PENNSYLVANIA

RECEIVED AUGUST 13, 1948

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[CONTRIBUTION NO. 249 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

# Preparation and Properties of N-Methylol, N-Alkoxymethyl and N-Alkylthiomethyl Polyamides

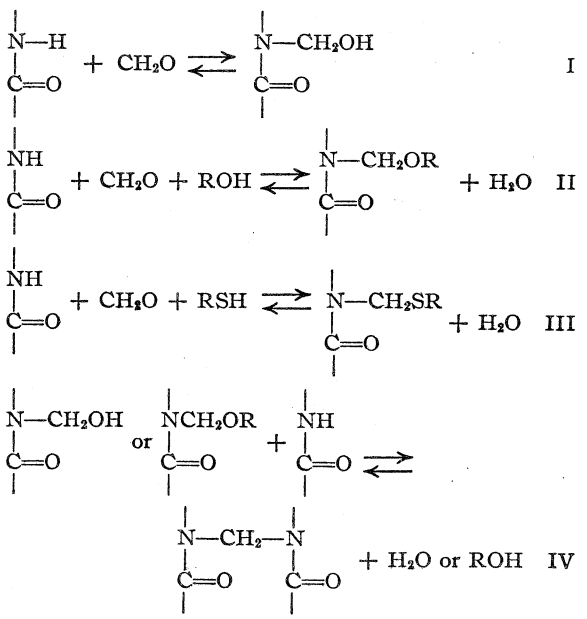
BY THEODORE L. CAIRNS, HENRY D. FOSTER, ARTHUR W. LARCHAR, ALLAN K. SCHNEIDER AND RICHARD S. SCHREIBER

The preparation and properties of high molecular weight, linear polyamides derived from amino acids and from diamine-dibasic acid salts have been studied in detail by Carothers.[1] There has, however, been no report of the chemical reactions which these polymers undergo. Other workers refer to the treatment of polyamides with formaldehyde to give slight modification[2,4] but the preparation of well-defined chemical entities is not described. This work was undertaken to explore the possible reactions of the high molecular weight polyamides and to study the properties of the derivatives obtained.

The starting materials for this investigation were polyhexamethyleneadipamide and polyhexamethylenesebacamide.[3] Both of these polymers are high melting solids which show appreciable solubility, without degradation of molecular weight, only in formic acid, phenol, sulfuric acid and solutions of salts such as calcium chloride in methanol. These two polymers are both sensitive to degradation by hydrolysis, alcoholysis, and ammonolysis at elevated temperatures. From consideration of these facts it is evident that the variety of experimental conditions which may be imposed upon these polyamides during a study of their chemical reactions is severely limited.

## Preparation

It has been found that these polyamides react with formaldehyde to yield an N-methylol derivative or with formaldehyde in the presence of alcohols or mercaptans to yield N-alkoxymethyl (II), and N-alkylthiomethyl (III) derivatives. In addition, a fourth product, probably having the crosslinked methylene structure (IV) has been obtained.[4,5] These reactions are represented in the following equations where the polyamide chain is indicated simply by the amide group.




The formation of the N-methylol polyamides (I) is brought about in the presence of acids or bases while the formation of II, III and IV is catalyzed by acids but not by bases. The same situation holds also for the reverse reaction: the methylol groups are readily removed by acids or bases

(1) (a) H. Mark, "High Polymers," Vol. I, "The Collected Papers of Wallace H. Carothers on High Polymeric Substances," Interscience Publishers, Inc., New York, N. Y., 1940; (b) Coffman, Berchet, Peterson and Spanagel, *J. Polymer Sci.*, **2**, 306 (1947).

(2) (a) Coffman, U. S. Patent 2,177,637 (1939); (b) Fraenkel-Conrat, Cooper and Olcott, THIS JOURNAL, **67**, 950 (1945); (c) McCreath, U. S. Patent 2,425,334 (1947).

(3) For convenience these polymers will be referred to as 66 and 610, respectively. The first number refers to the number of carbon atoms in the diamine used and the second to the number of carbon atoms in the dibasic acid.

(4) See also Hopff, Weickmann and Ufer, U. S. Patent 2,288,279 (1942).

(5) The following U. S. Patents are related to the work described here: Cairns, 2,393,972 (1946); Cairns, 2,430,860, (1947); Charch, 2,430,910 (1947); Foster and Larchar, 2,430,923 (1947).

while the alkoxymethyl and alkylthiomethyl groups and the methylene crosslinks are stable to bases but hydrolyzed easily in the presence of acids. Such behavior is also found with comparable derivatives of monomeric amides and with the formals which are analogs of the substituted amides under consideration here. It is also of interest that mild heat alone causes reversal of eqn. I but not of II or IV.

The N-methylol polyamides (I) may be prepared by the action of aqueous formaldehyde on solutions of 66 in formic acid at temperatures around 60°. In this case the conditions of reaction must be very carefully controlled in order to prevent the formation of the crosslinked structure (IV). This cross-linking manifests itself by a very rapid increase in the viscosity of the solution. In many cases the reaction mixture may change from a smooth solution of moderate viscosity to a tough, intractable, rubbery gel in a few seconds. A more controllable and satisfactory method for the preparation of N-methylol polyamides consists in treatment with formaldehyde in the presence of an inert medium (such as chloroform, dimethylformamide, dioxane or toluene) and a basic catalyst (potassium carbonate) at 120 to 150°. The use of pyridine as an inert medium is advantageous since it also serves as a basic catalyst.

The N-alkoxymethyl and N-alkylthiomethyl polyamides are prepared readily by the action of a solution of formaldehyde in an alcohol or mercaptan on a polyamide dissolved in formic acid at 60°. Prevention of cross-linking is, in these cases, accomplished by using an excess of alcohol or mercaptan. A second method for the preparation of N-alkoxymethyl derivatives involves the treatment of a solid polyamide with an alcohol–formaldehyde solution at temperatures up to 150° in the presence of catalytic quantities of acid. It has been demonstrated that the use of this method at elevated temperatures brings about some reduction in the average molecular weight of the polymer. The products obtained by this method are still true high polymers and exhibit the properties of high strength, elongation and flexibility, and show viscosity effects common to all soluble, high molecular weight, linear polymers.

## Degree of Substitution

The parent polyamides used in this study ranged in molecular weight up to perhaps 50,000 and were usually about 15,000 to 25,000. For 66 a molecular weight of 22,600 corresponds to a chain having 200 amide groups or 100 repeating units. In the preparation of the derivatives described here it was found possible to effect reaction with practically all of the amide groups under special conditions but major attention has been devoted to products having up to 50% amide substitution. Large excesses of formaldehyde and other reagents are usually required to bring about high degrees of substitution. Thus alkoxymethyl polyamides are prepared using about 7.5 moles of formaldehyde and 10 to 15 moles of alcohol per unit molecular weight of polyamide,[6] and of these quantities only about 0.5 to 1 mole of formaldehyde and alcohol appear as part of the final product. All the reactions under consideration here, with the possible exception of the formation of I, involve water as one of the products and it is therefore not surprising that addition of water to any reaction mixture results in a lowering of the degree of substitution. For example, under certain conditions a reaction mixture based on 1 unit mole of 66, 7.5 moles of paraformaldehyde, 11 moles of methanol and 0.4 mole of water yields a N-methoxymethyl-66 of about 45% amide substitution, and a similar mixture containing 4.0 moles of water gives a product of about 31% substitution. The second important factor governing the degree of substitution is the relative amounts of formaldehyde and polyamide used. Increasing the amount of formaldehyde increases the degree of substitution.

## Proof of Structure

The structure assigned to these derivatives is based first of all on the method of formation. Further it has been found that acid hydrolysis of a N-methoxymethyl-66 gives rise to formaldehyde in quantities which roughly balance the calculated values based on the methoxyl content of the same polymer as determined by the standard Zeisel method. The differences found between formaldehyde and methoxyl content usually indicate excess of formaldehyde over the calculated quantities. These observations point strongly toward the existence of groups of the structure $\begin{matrix} \\ \text{N}\text{–}(\text{CH}_2\text{O})_x\text{R} \\ \\ \text{C}{=}\text{O} \\ \end{matrix}$. Additional evidence supporting the N-alkoxymethyl structure is found in the fact that polyamides prepared from dibasic acids and N,N′-dialkylated diamines (such as N,N′-dimethylhexamethylenediamine) are apparently unaffected by treatment with formaldehyde. Finally, comparison of the infrared absorption spectra of 66 and N-methoxymethyl-66 indicates a definite reduction in the intensity of certain NH absorption bands in the case of the substituted derivative.[7] Unequivocal evidence to show that these products are not oxygen alkylated derivatives of the structure $\begin{matrix} \text{N} \\ \| \\ \text{C}\text{—}\text{OCH}_2\text{OR} \end{matrix}$ has not been obtained.

## Physical Properties

The parent polymers from which the alkoxymethyl derivatives are obtained by chemical reaction are hard, high-melting materials of consid-

(6) "Unit molecular weight" is the molecular weight of the recurring unit in the polymer. In the case of 66 this unit is $\text{HN}(\text{CH}_2)_6\text{NH}\text{—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—}(\text{CH}_2)_4\text{—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—}$.

(7) We are indebted to Dr. J. R. Downing for this observation.

erable strength and are capable of being oriented by the process of "drawing." These polymers are also "crystalline" as evidenced by their opacity when allowed to cool slowly from the melt and the typical sharp patterns obtained by X-ray diffraction of unoriented materials as well as the well-defined fiber pattern shown by oriented products. Most of these properties are almost certainly the manifestation of two structural features of these polyamides: first, they have uniform chains which can pack well into a crystal unit; and second, there is abundant opportunity for the formation of hydrogen bonds between chains which would result in very high interchain forces. The conversion of 66 into a N-alkoxymethyl-66 involves the replacement of some of the amide hydrogens by the $CH_2OR$ group. The removal of the amide hydrogens reduces the opportunity for interchain hydrogen bonds, and the introduction of the large $-CH_2OR$ group makes it less probable that the polymer chains can pack well into a crystal unit. The properties of the alkoxymethyl polyamides in comparison with the unsubstituted polymers from which they are derived are best interpreted in the light of these two structural characteristics.

The properties of 66 and the corresponding N-alkoxymethyl derivatives of two different degrees of substitution are listed in Table I.

TABLE I

PHYSICAL PROPERTIES OF POLYAMIDES

| | 66 | N-Methoxymethyl-66 35% Amide subst. | N-Methoxymethyl-66 50% Amide subst. |
|---|---|---|---|
| Max. concn. in hot 80% ethanol | None | About 40% | >60% |
| Melting point, °C. | 264 | 150–160° | 100–110 |
| Modulus of stiffness in 1000's lb./sq. in. | 290 | 14.2 | 3.0 |
| Recovery from 100% stretch, % | 30–35 | 70–80 | 90–95 |
| Tensile strength, lb./sq. in. | 8000–10,000 | 4500–6000 | 2000–3000 |

The solubility of the parent 66 and 610 is limited to mineral acids, strong organic acids, phenols and solutions of calcium chloride in methanol. The alkoxymethyl derivatives are soluble in all these solvents and also dissolve readily in the lower alcohols and mixtures of these alcohols with water or chloroform. Methanol and ethanol containing 15 to 30% water are excellent solvents for these polyamides and are much better than the alcohols alone. As the degree of amide substitution increases the solubility in alcohol increases and the stability of solutions toward gelation also increases. The stability of solutions of N-methoxymethyl-66 in aqueous alcohol shows a sharp increase around 30–35% amide substitution. It is interesting to note that Baker and Fuller[8] found that the related N-methyl polyamides also showed greatly increased solubility at about the same point. Most of these alkoxymethyl polyamides are insoluble in hydrocarbons, chlorinated hydrocarbons, esters and ketones. Certain unusual effects were noted in connection with the precipitation of N-methoxymethyl-66 from its alcohol solutions. Addition of acetone causes separation of the polymer from its alcohol solution, and the amount of acetone required to cause precipitation is directly related to the amide subsitution. The amount of acetone required, however, is independent of the *concentration* of polymer in the alcohol solution. In effect, a given polymer shows solubility in a critical acetone/alcohol ratio which is a function of the amide substitution. Addition of water to an alcohol solution of these polymers also causes precipitation but in this case the amount of water is independent of the *degree of amide substitution* and depends solely on the chemical structure of the base polyamide and the substituent group.[9] Thus, each of these polymer derivatives may be characterized by a simple test which has roughly the same utility as the melting point of a monomeric compound. These relationships, particularly the acetone precipitation, are also affected to a minor extent by the degree of polymerization. Specific examples of these data are shown in Table II.

TABLE II

PRECIPITATION OF N-ALKOXYMETHYL POLYAMIDES FROM SOLUTION

| Polymer | % Methoxyl | Volume of solvent to initiate precipitation, ml. (a) Acetone | (b) Water |
|---|---|---|---|
| N-Methoxymethyl-66 | 7.21 | 48 | 23.5 |
| | 9.72 | 66 | 22.8 |
| | 9.94 | 81 | 23.3 |
| N-Methoxymethyl-610 | 7.86 | 43 | 7.0 |
| | 8.03 | 53 | 7.1 |
| | 9.23 | 96 | 7.4 |
| | 9.81 | 128 | 7.5 |
| N-*n*-Propoxymethyl-66 | .. | 140 | 13.4 |
| N-Isobutoxymethyl-66 | .. | 105 | 11.0 |
| N-Isobutoxymethyl-610 | .. | 350 | 1.0 |

[a] Acetone added to refluxing, stirred solution of 1.0 g. of polymer in 20 ml. 80% ethanol in case of N-isobutoxymethyl-610 and products based on 66. The other polymers from 610 were measured at concentration of 0.5 g. in 12 ml. of 80% ethanol. [b] Water added to refluxing, stirred solution of 0.5 g. of polymer in 25 ml. of methanol in all cases.

The melting points of the N-substituted polymers decrease as the degree of substitution increases. In the case of N-methoxymethyl-66 the melting point changes from 264° for zero substitution to about 100° at 50% and finally to room temperature and lower at 70 to 80% substitution. The lowering of melting point as the amide hydrogen is replaced has been noted with other series of polyamides.[8,10]

The modulus of stiffness and of stretching also decreases rapidly as amide substitution increases. At about 50% substitution, products approaching

(8) Baker and Fuller, THIS JOURNAL, 65, 1120 (1943).

(9) C. S. Marvel, Office of Publication Board, Report PB 11193, discusses analogous effects in the precipitation of rubber from solution.

(10) Salisbury, U. S. Patent 2,351,074 (1944).

rubber and synthetic elastomers in this respect are obtained. The tensile strength decreases as substitution increases while the total elongation at break remains roughly constant.

One of the most striking changes in physical properties which accompanies substitution on the amide nitrogen is the increase in recovery from stretching. Unsubstituted 66 or 610 when stretched undergoes a deformation ("drawing" orientation—see ref. 1) which is not recovered when the stress is released unless the temperature is raised to a very high value. In the case of the alkoxymethyl polyamides the tendency to recover from stretching at room temperature is pronounced and at 45 to 50% substitution, rapid recoveries of 90–95% from elongations up to 500% of the original length are realized.

## Experimental[11]

**N-Methylol-66 (I).—(a) In Acidic Medium.**—A solution of 60 g. of 66 (0.265 unit mole) in 210 g. of 90% formic acid (sp. gr. 1.20) was prepared by stirring the mixture at 60° for one to two hours. Prolonged exposure of the polyamide to warm formic acid should be avoided since gradual hydrolysis of amide linkages occurs under these conditions. To this solution was added a solution of 60 g. (2 moles) paraformaldehyde in 110 ml. of water, also at about 60°, over a period of eight minutes. Care must be taken at the beginning of the addition since a too rapid rate at first will cause separation of the 66. Twelve minutes later 50 ml. of 60° water was added and after a total time, from the beginning of the aldehyde addition, of thirty-five minutes, the solution was poured into a mixture of 500 ml. of water and 500 ml. of acetone. To the resulting slightly turbid solution, 1500 ml. of water was added over a period of forty minutes causing the N-methylol-66 to separate as a granular powder. This product was washed by reslurrying several times with water, then with aqueous ammonia, water and finally acetone.

*Anal.*[12] Found $CH_2O$, 5.9. This corresponds to substitution of 23% of the amide groups with $CH_2OH$ groups.

Use of commercial formalin in the above procedure yields an N-methylol polyamide which also contains a few per cent. of methoxymethyl groups derived from the methanol present in the commercial product.

**(b) In Basic Medium.**—A mixture of 100 g. of 66 (pulverized to about 20-mesh size) 100 g. of paraformaldehyde and 300 g. of pyridine was charged into a 1-liter stainless steel tube which was mounted in a device for rocking and heating the tube. The mixture was heated to 130–135°, held at this temperature for thirty minutes and then cooled rapidly to room temperature. The resulting sirupy solution was filtered to remove a small amount of unchanged 66 and foreign material and then poured into a large volume of water. The polymer separated as a soft slime and was freed of solvent and formaldehyde by mechanical working (rubber rolls or dough mixer) in a stream of cold water. The product was air dried in the form of thin sheets. *Anal.* Found $CH_2O$, 12.6. This corresponds to substitution of 55% of the amide groups with methylol groups.

**N-Methoxymethyl-66 (II). (a) Preparation by Solution Method.**—A solution of 60 g. of 66 in 180 g. of 90% formic acid was prepared by stirring at 60°. To this was added a solution of 60 g. paraformaldehyde in 60 g. methanol[13] also heated to 60°. The rate of addition was very slow during the first minute in order not to precipitate any of the 66 and then was increased so that it was complete at the end of three minutes. Ten minutes after the aldehyde addition was begun,[14] 60 g. of methanol was added rapidly and the reaction allowed to proceed for a total of thirty minutes. The solution was then poured into 1700 ml. of equal parts (by volume) of acetone–water, and aqueous ammonia was added gradually. The addition of the ammonia caused the N-methoxymethyl-66 to separate as fine white granules. *Anal.* Found: $CH_3O$ (Zeisel), 7.13; $CH_2O$ by sulfite method,[12] 1.4. These values correspond to a total amide substitution of methoxymethyl and methylol groups of 36%.[15]

A procedure analogous to that described above but using an anhydrous formic acid/acetic acid mixture (prepared by addition of sufficient acetic anhydride to 90% formic acid to combine with the water present) yielded a higher substituted product. *Anal.* Found: $CH_3O$ (Zeisel), 9.94; $CH_2O$ by sulfite method, 0.30. The combined total amide substitution corresponding to these analyses is 46%.

**(b) Preparation by "Direct" Method.**—In a 1-gallon nickel-lined autoclave equipped with an efficient anchor type agitator and an overhead discharge line was placed 1000 g. of 66 (pulverized to pass a 16-mesh screen), 1000 g. of paraformaldehyde, 30 g. of water and 1500 g. of methanol. This mixture was heated to 139°, and a solution of 20 ml. of 85% phosphoric acid in 50 g. of methanol was forced in by means of nitrogen pressure. The reaction mixture was maintained between 139 and 140° for eight minutes and then discharged very rapidly (forty to fifty seconds) through the overhead pipe into a solution of 1600 ml. of methanol, 400 ml. of water and sufficient ammonia to neutralize the phosphoric acid catalyst. The resulting solution was freed of foreign material and a trace of unchanged 66 granules by filtration using a diatomaceous earth filter-aid, and the clear filtrate poured into water. The polymer was freed of solvent and aldehyde by working in a stream of water in a mixer. Finally treatment with 1% sodium hydroxide at 40° for fifteen minutes served to remove N-methylol substitution, and also caused the polymer to break up into fine granules. In most runs about 980 g. of polymer was obtained but there were, of course, high losses involved in the use of an autoclave with an overhead discharge line. *Anal.* Found $CH_3O$ (Zeisel), 10.53; amide substitution based on $CH_3O$, 45%. A procedure analogous to the above, using 300 g. of water in the reaction mixture, yielded a *lower substituted product*. *Anal.* Found $CH_3O$, 7.8; amide substitution based on $CH_3O$, 31%.

This direct synthesis of N-alkoxymethyl polyamides has been found to be of wide applicability. The optimum temperature generally varies for each polyamide–alcohol combination. For example, N-methoxymethyl-610 is best prepared at 130–133°, while a copolymer such as 66/610/

(11) We are indebted to Drs. J. W. Stillman and A. H. Halè of these Laboratories under whose supervision many of the analyses reported here were carried out.

(12) The analysis for $CH_2O$ derived from N-methylol groups was carried out by treating a solution of the polyamide in 70% aqueous alcohol with sodium sulfite and titrating the liberated alkali with standard acid.

(13) Such solutions are best prepared by warming a suspension of paraformaldehyde in methanol to 60° and then adding a trace of solid sodium or potassium hydroxide. Under these conditions most samples of paraformaldehyde dissolve very rapidly to give perfectly clear solutions. Such a solution undoubtedly contains a large proportion of the aldehyde and methanol in the form of the hemiacetal, $CH_3OCH_2OH$.

(14) The time at which this second quantity of methanol is added is an important factor in determining the total degree of substitution. The longer this time interval, the higher will be the degree of substitution. This is believed to be due to the effect of the water formed by the esterification of the formic acid by the methanol.

(15) Calculation of degree of amide substitution.—Equations have been derived which permit analyses to be simply converted to the per cent. of amide groups substituted. For N-methoxymethyl-66

$$Z - 0.014\,ZP = 3.65\,P$$

Where $Z$ = % of amide groups substituted, and
$P$ = % methoxyl

Similar relationships may be derived for any combination of substituent groups and kinds of analyses.

6,[16] which is soluble in methanol, may be converted to an alkoxymethyl derivative at temperatures around 50°. Higher alcohols require higher temperatures than does methanol; *n*-butyl alcohol reacts smoothly at 150°.

**N-Ethylthiomethyl-66.**—A solution of 60 g. of 66 (0.265 unit mole) in 150 ml. of 90% formic acid was prepared at room temperature. A solution of formaldehyde in ethyl mercaptan was prepared by the gradual addition of paraformaldehyde (60 g., 2 moles) to 120 g. (1.93 moles) of well cooled ethyl mercaptan containing a trace of sodium hydroxide. This solution was added to the 66 solution at room temperature. After one hour, during which time the temperature rose to 40° and the solution separated into two phases, 1200 ml. of acetone was added slowly to yield a homogeneous solution. Addition of aqueous ammonia to this solution caused the polymer to separate as white granules. This product was found to dissolve readily in warm ethanol. *Anal.* Found: S, 7.39; amide substitution based on sulfur content, 31%.

(16) This copolymer is prepared from 40 parts hexamethylenediammonium adipate, 40 parts hexamethylenediammonium sebacate, and 30 parts caprolactam. For details see Brubaker, Hanford and Wiley, U. S. Patent 2,285,009 (1942).

## Summary

The preparation and properties of representative examples of N-methylol, N-alkoxymethyl and N-alkylthiomethyl polyamides by the treatment of linear polyamides with formaldehyde in the presence of acids of bases, or with formaldehyde and alcohols or mercaptans in the presence of acids, respectively, have been described.

WILMINGTON, DELAWARE RECEIVED JULY 20, 1948

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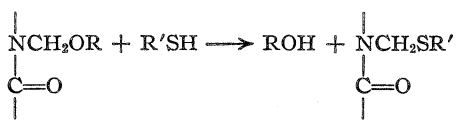
[CONTRIBUTION NO. 250 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & COMPANY]

# The Reactions of N-Alkoxymethyl Polyamides

BY THEODORE L. CAIRNS, HUGH W. GRAY, ALLAN K. SCHNEIDER AND RICHARD S. SCHREIBER

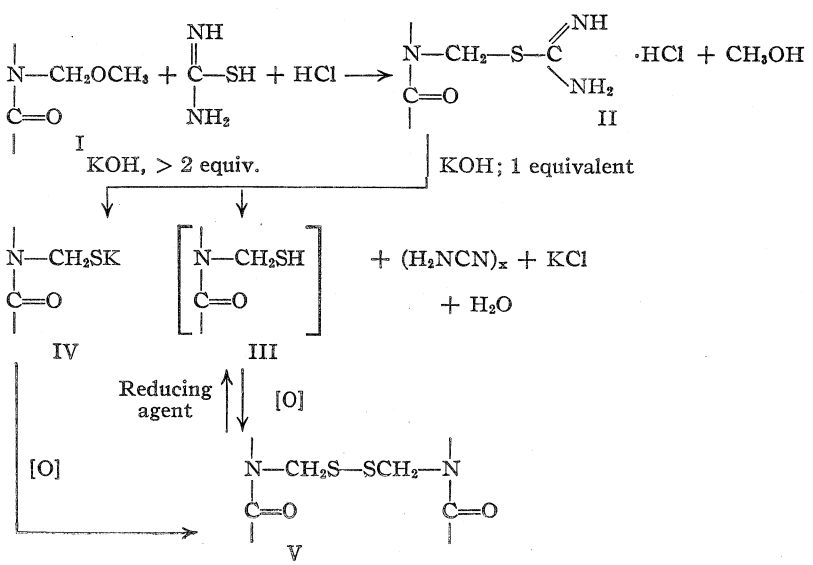
The previous paper has described the preparation and properties of the N-alkoxymethyl polyamides.[1] This report[2] is concerned with the chemical changes which these polymers undergo.

It has been found that the N-alkoxymethyl polyamides condense with compounds containing the thiol group to yield the corresponding N-alkylthiomethyl polyamides according to the equation



The reaction proceeds at room temperature in the presence of strong acids, such as hydrochloric acid, without the necessity of using large excesses of the mercaptan. In this respect it is greatly superior to the method for the preparation of these sulfur derivatives which was described earlier,[1] and permits the preparation of polyamide derivatives from difficultly available mercaptans such as octadecylmercaptan, 1-thiosorbitol and N,N′-diethyl-β-mercaptoethylamine.

An analogous product may be derived by condensation with thiourea. If one equivalent of concentrated hydrochloric acid is added to a methanol solution of N-methoxymethyl-66 and thiourea (1 mole thiourea per mole of methoxymethyl group) the polymer is very rapidly converted to a water-soluble form. The addition of sufficient alkali to neutralize the hydrochloric acid causes the solution to be converted into a rubbery gel, while the addition of about 2.2 equivalents of alkali for each equivalent of acid produces no apparent change in viscosity and the polymer remains water-soluble. Addition of oxidizing agents (*e. g.*, hydrogen peroxide) to this alkaline solution results in immediate gelation or, in the case of very dilute solutions, precipitation of the polymer. These observations may be explained as the result of a series of reactions represented by the following equations.

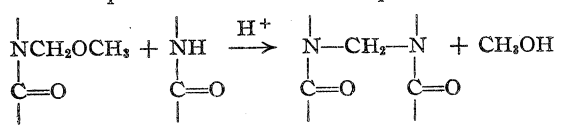



(1) Cairns, Foster, Larchar, Schneider and Schreiber, THIS JOURNAL, 71, 651 (1949).

(2) Cairns, U. S. Patent 2,430,859 (1947), and 2,430,860 (1947), are related to this work.

Treatment of I with thiourea and acid yields first, the S-alkyl isothiourea salt II, which is water-soluble. Action of an equivalent amount of alkali on this salt results in the formation of the N-mercaptomethyl polyamide III. This first step has an analogy in the reaction of monomeric N-methylol amides[3] while the formation of II is analogous to the well-known method for the preparation of mercaptans from the S-alkyl isothioureas.[4] The N-mercaptomethyl polyamide is very sensitive to oxidation and in the presence of atmospheric oxygen yields the cross-linked polymeric structure V which causes gelation of the solution. Addition of excess alkali to II forms the potassium salt of the mercaptomethyl polyamide (IV). This product is water soluble and is much less readily oxidized by air than is the free mercaptan III but yields the same product (V) when treated with oxidizing agents such as hydrogen peroxide or iodine. The potassium salt (IV) may be isolated as such and, if stored under nitrogen, remains water soluble for several days at least. Neutralization of a solution of II with sodium acetate results in the formation of an insoluble, sulfur-free product, which is probably the original unsubstituted polyamide. This series of reactions presents a useful route for the preparation of high polymers having a controllable number of cross-linkages between chains.

The action of aqueous acid on the alkoxymethyl polyamides results in hydrolysis of the substituent group with the regeneration of the unsubstituted amide group and is, in fact, the reversal of the synthetic method used for the preparation of these polymers. When heated with acid, in the absence of water or any solvent, an interchain condensation takes place as shown in the equation

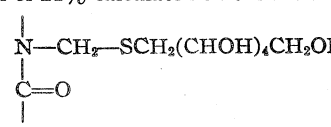


The evidence in support of this reaction is a decrease in methoxyl content and conversion of the original alkoxymethyl polyamide into an insoluble and infusible form. Insolubility and infusibility are the prime criteria of a three-dimensional, cross-linked polymer. Conditions under which the hydrolytic regeneration of the polyamide and the acid catalyzed cross-linking may be carried out are given in the experimental section.

## Experimental[5]

**N-Alkylthiomethyl Polyamides. (a) Reaction with Octadecyl Mercaptan.**—A solution of 20 g. of N-methoxymethyl-66 (% $CH_3O$ = 9.72) and 19 g. of crude octadecyl mercaptan in 100 ml. of absolute alcohol was prepared at 60–65°. The mercaptan mixture contained about 85% octadecyl mercaptan (0.066 mole). A solution of 1 ml. of concentrated hydrochloric acid in a few milliliters of absolute alcohol was added and after two hours at 60° the polymer was precipitated as a granular powder by the addition of acetone. After thorough washing with acetone the polymer was dried in air and finally over phosphorus pentoxide. *Anal.* Found: S, 3.72, 3.87; $CH_3O$, 1.20, 1.16. This octadecylthiomethyl derivative was found to have greatly reduced affinity for water as evidenced by the fact that it was not completely soluble in 80% aqueous ethanol but was readily soluble in absolute alcohol, whereas the original N-methoxymethyl-66 was more soluble in 80% alcohol than in absolute alcohol.

**(b) Reaction with 1-Thiosorbitol.**—A solution of 25 g. of N-methoxymethyl-66 (% $CH_3O$ = 11.5) and 32 g. of 1-thiosorbitol (0.16 mole) was prepared in 100 ml. of 80% aqueous methanol at 50°. A mixture of 1 ml. concentrated hydrochloric acid in about 5 ml. of methanol was added and the solution heated at 50° for two hours and then allowed to stand at room temperature for sixteen hours. Alcoholic alkali was added to neutralize the acid, and the polymer was precipitated as a soft plastic mass by pouring the solution into a large volume of water. The polymer was freed of impurities by working with water and was dried in the form of a thin film. *Anal.* Found: S, 6.42. The sulfur content corresponded to an amide substitution of 21% calculated on the basis of the formula



The introduction of large amounts of the hydrophilic thiosorbityl radical resulted in a polymer of greatly increased affinity for water. The product described above was found to be completely soluble in 30% ethanol–70% water (by volume) while the original N-methoxymethyl-66 did not dissolve in any alcohol–water mixture containing more than 50% water.

**N-Mercaptomethyl-66. (a) Reaction of N-Methoxymethyl-66 with Thiourea.**—A solution of 30 g. of N-methoxymethyl-66 (% $CH_3O$ = 9.72) and 6.0 g. of thiourea (0.079 mole) was prepared by stirring with 70 g. of aqueous methanol (80% methanol by volume) at 55–60° for about one hour. This solution was cooled to 30–35° and 6.35 ml. of concentrated hydrochloric acid (0.079 mole) in 15 ml. methanol was added. After about one minute a drop of this solution added to water gave no precipitate. After three minutes a solution of 0.84 g. potassium hydroxide (0.158 mole) in 10 ml. of water and 25 ml. of methanol was added. During the next few seconds the solution changed in color from pale yellow to pink and set to a transparent tough rubbery gel (V).

If the neutralization with potassium hydroxide was carried out in the presence of hydrogen sulfide, gelation did not take place. Further, addition of more than 2.0 moles of alkali per mole of acid used did not cause gelation of the solution, while any quantity less than 2.0 moles resulted in immediate gelation.

**(b) Isolation of the Disulfide of N-Mercaptomethyl-66 (V).**—A solution of 120 g. of N-methoxymethyl-66 (% $CH_3O$ = 6.46) and 36 g. of thiourea (0.47 mole) was prepared in 500 ml. of aqueous methanol (80% methanol by volume) at 60° and then cooled to room temperature. To this was added 36 ml. of concentrated hydrochloric acid (0.40 mole) in 50 ml. of methanol. After fifteen minutes this solution was poured into a mixture of 60 g. of potassium hydroxide (1.06 moles) dissolved in 25 ml. of water and 150 ml. of methanol with vigorous agitation. The precipitate which formed was separated by pressure filtration and the clear yellow, viscous filtrate was stored in an atmosphere of nitrogen.

A portion of this filtrate was diluted with a large volume of water and an excess of 3% hydrogen peroxide added. This caused the precipitation of a white curdy product—the disulfide of N-mercaptomethyl-66 (V). This polymer was washed free of all traces of alkali with water, finally

(3) (a) Albrecht, Frei and Sallman, *Helv. Chim. Acta*, 233E (1941); (b) Austin and Frank, U. S. Patent 2,323,111 (1943).

(4) "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., p. 345.

(5) We are indebted to Dr. J. W. Stillman and Dr. A. H. Hale of these Laboratories under whose supervision the analyses reported here were carried out.

washed with acetone and dried first in air and then in vacuum over phosphorus pentoxide. *Anal.* Found: S, 4.90; $CH_3O$, 3.08; ash (calcd. as $K_2SO_4$), 0.31. This disulfide was insoluble in hot aqueous ethanol and treatment with an excess of a mercaptan caused reduction to a soluble form. Addition of lead acetate to an aqueous solution of the potassium salt of N-mercaptomethyl-66 described above caused formation of a yellow precipitate.

**Hydrolysis of N-Methoxymethyl-66 by Aqueous Acid.**—The hydrolysis of the methoxymethyl group to $CH_3OH$, $CH_2O$ and the unsubstituted amide group may be carried out in a controllable fashion and thus is an additional method for obtaining any given degree of methoxyl content.

Small strips of film (0.002″ thick) of N-methoxymethyl-66 were suspended in a solution of 10 ml. of concentrated hydrochloric acid in one liter of water at 50° for various lengths of time. The strips were removed, washed thoroughly in water, soaked in aqueous ammonia, washed in water and finally dried in vacuum over phosphorus pentoxide.

| Time in acid solution, minutes | $CH_3O$, % |
|---|---|
| 0 | 7.13 |
| 1 | 6.61 |
| 2 | 5.41 |
| 3 | 4.57 |
| 4 | 2.77 |

**Acid Cross-linking of N-Methoxymethyl-66.**—A 20% solution of N-methoxymethyl-66 in methanol–water (80% methanol by weight) was prepared by stirring under reflux at 60°. To this was added maleic acid (1% based on the polymer) and the mixture stirred for thirty minutes to dissolve the acid. This solution was filtered under pressure, allowed to stand two hours at 60° to permit the air bubbles to rise out of the solution and was then cast into films on glass plates. The solvent was allowed to evaporate at room temperature for about twenty hours.

The pliable, transparent film prepared in this manner analyzed for 8.53% methoxyl. Baking this film (on the glass plate) for six hours at 60° gave a product of 6.94% methoxyl content; one hour at 100° gave a product of 6.31% methoxyl content. Both these baked films were found to be insoluble (although highly swollen) in hot 80% methanol, and they did not melt at any temperature but charred gradually about 295°. A film of the same N-methoxymethyl-66 prepared in a similar manner but without added acid melted at about 155° and was readily soluble in hot aqueous methanol even after baking for one hour at 100°.

## Summary

The conversion of N-alkoxymethyl polyamides to alkylthiomethyl and mercaptomethyl polyamides by treatment with mercaptans or thiourea in the presence of strong acids has been described.

WILMINGTON, DELAWARE RECEIVED JULY 20, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Perylene, a By-product from Some 1-Naphthyl-metallic Compounds

BY HENRY GILMAN AND CECIL G. BRANNEN

Incidental to the preparation of some substituted silanes using 1-naphthyllithium, perylene was isolated from several different mixtures. Mr. L. Miller[1] isolated this hydrocarbon from the reaction between 1-naphthyllithium and silicon tetrachloride, while we have found it in some reactions of 1-naphthyllithium with ethyl silicate and hexachlorodisilane, as well as with silicon tetrachloride.

In order to determine if a silicon compound is essential for the formation of perylene, 1-naphthyllithium was made from 1-bromonaphthalene of the highest purity available, hydrolyzed, and the residue examined chromatographically. Pure perylene in a yield of 3% was isolated from the mixture.

There is no evidence in the literature that 1,8-dibromonaphthalene is formed during the bromination of naphthalene and even if traces are formed, it is improbable that perylene in the yield of 3% could have come from that source. To reduce further the possibility that perylene might have resulted from a dibromo isomer, 1-naphthyllithium was prepared from the halide obtained from a Sandmeyer reaction and the mixture examined as before. A 2.8% yield of perylene was found.

Among the mechanisms by which perylene might be produced in this reaction are: (1) the formation and disproportionation of free radicals, followed by coupling; and (2) a ring closure, by dehydrogenation, of an intermediary biaryl, 1,1′-binaphthyl. Free radical formation and disproportionation have been advanced by several investigators,[2] and in this case the mechanism may be as shown by the following set of reactions

$$1\text{-}C_{10}H_7Br + Li \longrightarrow 1\text{-}C_{10}H_7^- + LiBr \quad (1)$$

$$2\ 1\text{-}C_{10}H_7^- \longrightarrow 1,1'\text{-}C_{10}H_7\text{-}C_{10}H_7 \quad (2)$$

$$2\ 1\text{-}C_{10}H_7^- \longrightarrow \text{(I)} + C_{10}H_8 \quad (3)$$

(I)

$$2\ (I) \longrightarrow \text{(II)} \quad (4)$$

(II)

Some organometallic compounds are known to effect dehydrogenation[3] and such dehydrogenation

(1) Unpublished studies, Iowa State College.

(2) (a) Gilman and St. John, THIS JOURNAL, **52**, 5017 (1930) (b) Kharasch and Fields, *ibid.*, **63**, 2316 (1941). (c) Wuis and Mulder, *Rec. trav. chim.*, **57**, 1385 (1938); Nauta and Mulder, *ibid.*, **58** 1062 (1939); Gomberg and Bachmann, THIS JOURNAL, **52**, 245 5 (1930); Blicke and Powers, *ibid.*, **51**, 3378 (1929); Bachmann and Clarke, *ibid.*, **49**, 2089 (1927). For a discussion with leading references, see Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 540.

(3) Gilman and Bradley, THIS JOURNAL, **60**, 2333 (1938).

may lead to cyclization.[4] This may be represented by the equation

$$1,1'\text{-}C_{10}H_7\text{-}C_{10}H_7 \xrightarrow{1\text{-}C_{10}H_7Li} \text{(II)} \quad (5)$$

To check the validity of equation (5), pure 1,1'-binaphthyl was refluxed for several days with phenyllithium and the mixture was examined for perylene. The fluorescent material was separated from the bulk of binaphthyl by chromatographic purification and was shown to contain perylene by the characteristic absorption bands at 410 and 435 mμ. Similar results were obtained using *p*-dimethylaminophenyllithium instead of phenyllithium.

The formation of perylene is not peculiar to the lithium compound since traces were found in the products resulting from the hydrolysis of the Grignard reagent, 1-naphthylmagnesium bromide.

**Acknowledgment.**—The authors thank William Meikle for assistance.

## Experimental

All identifications (other than those by absorption curves) were made by mixed m.p. The petroleum ether used as solvent had a b.p. of 90–115°. The perylene used was made by three methods: (1) from naphthalene[5a]; (2) from 1-bromonaphthalene[5b]; and (3) from β-dinaphthol.[5c] The m.p.'s and mixed m.p.'s of all combinations of the samples were 268–269° (cor.).

**Perylene from the Hydrolysis of 1-Naphthyllithium.**—One hundred grams (0.48 mole) of 1-bromonaphthalene ($n^{20}D$ 1.6578, sp. gr. $1.481^{20}/_{20}$) was added with stirring to 7.0 g. (1.0 g. atom) of lithium in 500 ml. of ether in an atmosphere of nitrogen, and refluxed one hour. The yield,

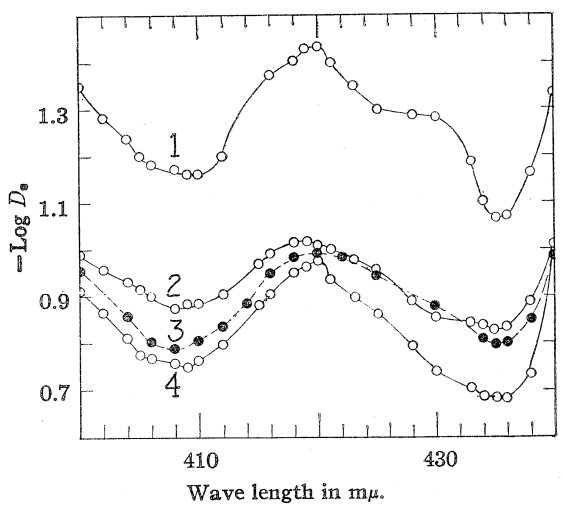



Fig. 1.—Ultraviolet absorption spectra in alcohol: (1) perylene ($1.4 \times 10^{-8}$ *M*); fluorescent material from (2) reaction of 1,1'-binaphthyl with *p*-dimethylaminophenyllithium, (3) prepn. of 1-naphthylmagnesium bromide, and (4) reaction of 1,1'-binaphthyl with phenyllithium. Measurements were made with a Beckman Spectrophotometer (Model DU).

as determined by acid titration,[6] was 96%. The ether solution was hydrolyzed with cracked ice, washed with water, steam distilled, and the resulting dark red solid residue, 11.8 g., dried *in vacuo* for forty-eight hours. After extraction in a Soxhlet for three days with petroleum ether, the 0.9 g. of insoluble residue, m.p. 190–260°, was discarded and the solution was diluted to 1 l. with pure solvent and examined chromatographically.

A 40-ml. portion of the petroleum ether extract was diluted to 250 ml., poured through a 15 × 150 cm. column of alumina[7] and observed with ultraviolet light. After development with, first, 1 l. of pure solvent and, second, 1 l. of 10% benzene–petroleum ether, the solvents were separately evaporated, giving 79 mg. (3.1%) of crude perylene, m.p. 261–264°, from the first filtrate, and a few crystals (not weighed) of 1,1'-binaphthyl, m.p. 155–156°, from the benzene–petroleum ether filtrate. Several other zones developed in the column, but they were not investigated.

The same procedure was followed using 1-bromonaphthalene prepared[8] by a Sandmeyer reaction from purified 1-naphthylamine. The yield of perylene in this experiment was 2.8%.

Perylene (mixed m.p.) was also obtained by the action of lithium metal on 1,1'-binaphthyl.

**1,1'-Binaphthyl and Phenyllithium.**—Ten grams of 1,1'-binaphthyl,[9] m.p. 155–156°, and 0.3 mole of phenyllithium in ether were refluxed under nitrogen for fifty-two hours and then poured onto cracked ice. The ether layer was washed with water and the solvent removed. The residue was dissolved in dry petroleum ether and the resulting yellow solution poured through an alumina column. The blue fluorescent zone was cut off, eluted, dried overnight at 130° and the adsorbed material was dissolved in 200 ml. of 95% ethanol. The absorption curve of the solution is shown in Fig. 1.

The authors are grateful to Dr. Robert R. Sealock for assistance.

**1,1'-Binaphthyl and *p*-Dimethylaminophenyllithium.**—Five grams (0.02 mole) of 1,1'-binaphthyl, m.p. 156°, added to 0.2 mole of *p*-dimethylaminophenyllithium in 250 ml. of ether, was refluxed for fourteen hours and then poured onto cracked ice. The ether solution was thoroughly washed with hydrochloric acid and water, dried with sodium sulfate, and concentrated. The residue was dissolved in 1 l. of petroleum ether and chromatographed. After two passes through a 15 × 150 cm. alumina column, 4.8 g. (96%) of the 1,1'-binaphthyl was recovered from the filtrate, while a bright blue fluorescent zone developed on the column. The blue zone was eluted with ether, the solvent removed, and the residue was dried and dissolved in 200 ml. of 95% ethanol. The absorption spectrum is shown in Fig. 1.

**Perylene from the Hydrolysis of 1-Naphthylmagnesium Bromide.**—Forty-one and four-tenths grams (0.2 mole) of 1-bromonaphthalene was added to 5.0 g. (0.21 g. atom) of magnesium in ether under the usual conditions to give a 96% yield of the Grignard reagent. The ether solution was carbonated by pouring upon crushed Dry Ice, extracted with 20% sodium hydroxide, washed with water and the solvent removed. The residue was dissolved in petroleum ether and chromatographed. The filtrate contained 2.1 g. (0.008 mole) of 1,1'-binaphthyl, m.p. 156°, while the column contained a blue fluorescent zone. The blue zone was cut off and eluted with ether, the solvent removed, and the residue dried. Substantial evidence that the residue contained perylene was obtained by comparison of the ultraviolet spectrum of the ethanol solution of this residue with that of an authentic sample of perylene in ethanol; see Fig. 1.

(4) Fuchs and Grosz, *Ber.*, **63**, 1009 (1930).

(5) (a) Scholl, Seer and Weitzenbock, *Ber.*, **43**, 2203 (1910); (b) Weitzenbock and Seer, *Ber.*, **46**, 1996 (1913); (c) Brass and Tengler, *ibid.*, **64B**, 1648 (1931).

(6) Gilman, Wilkinson, Fishel and Meyers, THIS JOURNAL, **45**, 150 (1923).

(7) Fisher Scientific Co., 80–200 mesh.

(8) Prepared by Mr. R. Brennan of this Laboratory.

(9) Prepared by the method of Krizewsky and Turner, *J. Chem. Soc.*, **115**, 559 (1919), from the Grignard reagent and cupric chloride and purified chromatographically on alumina from petroleum ether.

**1-Naphthyllithium and Silicon Compounds.**—Perylene was isolated from several mixtures resulting from the separate treatment of silicon tetrachloride, ethyl silicate and hexachlorodisilane with 1-naphthyllithium. In all cases the 1-napthyllithium was made in the conventional manner from the bromide and lithium.

A typical run is described. 1-Naphthyllithium (0.26 mole) in 400 ml. of ether was added to 17.9 g. (0.086 mole) of ethyl silicate and refluxed overnight. The ether was replaced with benzene, the solution filtered and the filtrate was concentrated to about 50 ml. and allowed to crystallize. The yellow solid, m.p. 190–210°, after two crystallizations from benzene melted at 268–269° and showed no depression of m.p. when mixed with perylene. The yield from this run was 2.1%.

Similar runs using silicon tetrachloride gave yields of perylene from 1.2 to 2.6%, and with hexachlorodisilane, 2.2 and 2.4%. The evidence is, therefore, that the silicon compounds play no significant part in the formation of perylene.

## Summary

The hydrocarbon, perylene, has been isolated from several reaction mixtures involving 1-naphthyllithium and 1-naphthylmagnesium bromide. The formation of perylene from the 1-naphthyl-metallic compounds may be due in part to a free radical mechanism and also to a cyclodehydrogenation of 1,1′-binaphthyl by means of organolithium compounds. Experiments are presented in support of this latter mechanism.

AMES, IOWA RECEIVED AUGUST 23, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Characterization of Sulfonic, Sulfinic, Phosphonic and Some Other Acids as Thallous Salts

BY HENRY GILMAN AND R. K. ABBOTT, JR.[1]

It has been suggested[2] that thallous sulfonates may be reagents of choice in the characterization of some sulfonic acids. Several advantages of the thallous salts as derivatives of the sulfonic acids were detailed in a previous contribution.[2] The present report extends the scope of the reaction to other types of acids, and also further defines certain limitations in the usefulness of the reaction.

Although the thallous arylsulfonates meet the requirements for good derivatives, the thallous alkylsulfonates appear to be less satisfactory derivatives.

The arylsulfinic acids appear to be conveniently characterized as thallous salts.

The aromatic thiols give excellent derivatives, but the aliphatic thiols give salts having insufficiently sharp melting points. Moreover, the thallous mercaptides are evidently unstable, decomposing on standing in the dark in tightly stoppered vials. However, the quantitative formation of the highly colored thallous mercaptides suggests their use as extremely sensitive qualitative tests for the detection of mercaptans.

Both arylphosphonic acids and arylphosphinic acids are readily characterized by this method. Either the mono- or the di-thallous salts of the phosphonic acids provide derivatives with good melting points.

Nitromethane and nitroethane readily form monothallous salts, but only the latter has a definite decomposition point.

2,4,6-Trinitrobenzoic acid gives a crystalline monothallous salt, melting with decomposition at 160–163°, which decarboxylates smoothly in boiling pyridine solution giving 1,3,5-trinitrobenzene and thallous oxalate. Thallous 2,4,6-trinitrobenzoate reacts further with a second equivalent of thallous hydroxide giving a blood-red complex of uncertain composition. 1,3,5-Trinitrobenzene was found likewise to react with one, two and three equivalents of thallous hydroxide giving complexes of rather indefinite composition which explode on heating.

Thallium trichloride reacts with sodium *p*-toluenesulfinate and with *p*-toluenesulfinic acid to give thallium dichloride *p*-toluenesulfinate.

$$p\text{-}CH_3C_6H_4SO_2Na + TlCl_3 \longrightarrow p\text{-}CH_3C_6H_4SO_2TlCl_2 + NaCl$$

However, the interesting observation was made that this compound did not eliminate sulfur dioxide with the formation of a carbon–metal linkage, as has been observed with some related mercury compounds.[3]

## Experimental

Two general procedures have been mentioned[2] for the preparation of thallous sulfonates. These procedures were used for the thallous salts described in Table I. The most important point in their preparation is the recrystallization solvent. In most cases it was desirable to evaporate the solution of salt almost to dryness and then recrystallize the salt from ethanol–water mixtures since most of them are very soluble in water and much less soluble in ethanol.

**Thallium Dichloride *p*-Toluenesulfinate.**—On mixing 0.1 mole each of sodium *p*-toluenesulfinate and thallium trichloride dissolved in a minimum of water, there was an immediate precipitate accompanied by an odor of *p*-toluenesulfonyl chloride. The precipitate was filtered, washed, and dried giving 36 g. (84%) of the salt, which melted at 203–205° (dec.).

*Anal.* Calcd. for $C_7H_7O_2Cl_2STl$: Tl, 47.4. Found: Tl, 47.6.

**2,4,6-Trinitrobenzoic Acid and Two Equivalents of Thallous Hydroxide.**—In order to determine whether the red precipitate transitorily encountered in the preparation

(1) Present address: General Electric, S. A., Caixa Postal 109, Rio de Janeiro, Brazil.

(2) Gilman and Abbott, THIS JOURNAL, 65, 123 (1943).

(3) Peters, *Ber.*, 38, 2567 (1905); Kharasch, THIS JOURNAL, 43, 610 (1921); London, *J. Chem. Soc.*, 823 (1932).

TABLE I

THALLOUS SULFONATES, SULFINATE, PHOSPHONATES, ETC.

| Thallous salt | M. p., °C.[a] | Yield, % | Formula | Tl analyses, % Calcd. | Found |
|---|---|---|---|---|---|
| Benzenesulfonate | 185–187 | 94 | $C_6H_5O_3STl$ | 56.5 | 56.3 |
| β-Naphthalenesulfonate | 234–236 | 92 | $C_{10}H_7O_3STl$ | 49.7 | 49.5 |
| Dodecylsulfonate[b] | 143–144 | 53 | $C_{12}H_{25}O_3STl$ | 45.1 | 44.6 |
| *p*-Toluenesulfinate | 154–156 | 89 | $C_7H_7O_2STl$ | 56.7 | 56.3 |
| Phenylphosphonate (mono) | 200–201 | 86 | $C_6H_6O_3PTl$ | 56.5 | 56.3 |
| Phenylphosphonate (di)[c] | 317–320 | 79 | $C_6H_5O_3PTl$ | 72.5 | 72.3 |
| Diphenylphosphinate[d] | 203–205 | 82 | $C_{12}H_{10}O_2PTl$ | 48.5 | 48.3 |
| Nitromethane | Dec. | 85 | $CH_2O_2NTl$ | 76.8 | 76.6 |
| Nitroethane[e] | 80–82 (dec.) | 81 | $C_2H_4O_2NTl$ | 73.4 | 73.2 |
| Methylmercaptide[f] | 136–140 (dec.) | 100 | $CH_3STl$ | 80.9 | 80.5 |
| Ethylmercaptide | Dec. | 100 | $C_2H_5STl$ | 76.8 | 76.4 |
| *n*-Butylmercaptide | 84–90 | 100 | $C_4H_9STl$ | 69.4 | 69.1 |
| Thiophenolate | 258–260 | 99 | $C_6H_5STl$ | 65.2 | 65.0 |
| *p*-Thiocresolate | 178–180 | 99 | $C_7H_7STl$ | 62.3 | 62.0 |
| Thio-β-naphtholate | 165–168 | 97 | $C_{10}H_7STl$ | 56.2 | 55.9 |
| 2,4,6-Trinitrobenzoate | 160–163 | 93 | $C_7H_2O_8N_3Tl$ | 44.3 | 44.1 |

[a] All melting points were taken on a Fisher–Johns type block, uncorrected. [b] The melting point of this compound was not sharp. After two recrystallizations from 95% ethanol, the crystals sintered at 125° before melting at 143–145°. [c] This compound showed a transition point at 260° when examined under a hot-stage microscope, melting and immediately resolidifying. The compound then melted to a clear phase at 317–320°. [d] A mixed melting point with monothallous phenylphosphonate was depressed to 140–150°. [e] This salt appeared to be extremely resistant to detonation by mechanical shock. [f] The canary yellow precipitate of thallous mercaptide obtained with the volatile aliphatic mercaptans is so delicate a test that the vapor present in the air was sufficient to give a precipitate with solutions of thallous hydroxide three or four feet distant. The mercaptides and thiophenolates were obtained from absolute methanol or ethanol solutions.

of thallous 2,4,6-trinitrobenzoate actually contained more than one equivalent of thallium, 0.02 mole of 1.04 *N* thallous hydroxide[2] was added to 0.01 mole of 2,4,6-trinitrobenzoic acid in 75 ml. of methanol. A heavy red precipitate formed after the addition of the first equivalent of base. After prolonged shaking, filtering, and drying, 5.6 g. of product was obtained. The compound exploded on heating. Analysis showed that nearly two atoms of thallium were present in the molecule, but no satisfactory agreement for any definite compound was indicated.

*Anal.* Calcd. for $C_7H_2O_8N_3Tl_2$: Tl, 61.7. Found: Tl, 59.4.

**1,3,5-Trinitrobenzene and Thallous Hydroxide.**—Equivalent amounts of 1,3,5-trinitrobenzene and thallous hydroxide were reacted in a manner similar to the previous experiment. The red precipitate did not melt but exploded on heating.

*Anal.* Calcd. for $C_6H_4O_7N_3Tl$: Tl, 46.9. Found: Tl, 41.1.

The products of reaction of trinitrobenzene with two and three equivalents of thallous hydroxide, respectively, likewise showed approximate but not stoichiometric amounts of thallium to be present.

*Anal.* Calcd. for $C_6H_5O_8N_3Tl_2$: Tl, 62.5. Found: Tl, 56.8. Calcd. for $C_6H_6O_9N_3Tl_3$: Tl, 70.0. Found: Tl, 62.5.

**Decarboxylation of Thallous 2,4,6-Trinitrobenzoate.**—A suspension of 0.01 mole of this salt in 25 ml. of pyridine was boiled until a microcrystalline precipitate was deposited, during which time the color of the solution changed from an intense green to a pale brown. On filtering off the precipitate and diluting the clear filtrate, 1.4 g. (67%) of 1,3,5-trinitrobenzene was obtained melting at 120–122°.

The crystalline precipitate was found to contain all the thallium of the original thallous 2,4,6-trinitrobenzoate in the monovalent state. It was soluble in hot water, insoluble in cold water and hot pyridine, and nitrogen-free, melting at 320° with decomposition.

*Anal.* Calcd. for $C_2O_4Tl_2$: Tl, 82.5. Found: Tl, 82.7.

Although thallous oxalate has been reported,[4] no record could be found of its melting or decomposition point. An authentic sample was prepared. It was found to melt at 315–320° with decomposition and to be identical with that obtained on pyrolysis of thallous 2,4,6-trinitrobenzoate in solubility, analysis and pyrolytic behavior.

**Acknowledgment.**—The authors are grateful to Dr. H. Smith Broadbent for valuable assistance.

## Summary

The thallous salts have been found to be well crystallized and easily prepared derivatives of the arylsulfonic, sulfinic, phosphonic and phosphinic acids, as well as for the thiophenols. However, they are of limited use for alkylsulfonic acids and of little value for mercaptans and the simple nitroalkanes.

Thallous 2,4,6-trinitrobenzoate, which also melts sharply, is pyrolyzed smoothly to 1,3,5-trinitrobenzene and thallous oxalate.

2,4,6-Trinitrobenzoic acid and 1,3,5-trinitrobenzene unite with more than one equivalent of thallous hydroxide giving red insoluble complexes.

AMES, IOWA RECEIVED SEPTEMBER 30, 1948

(4) Kuflmann, *Compt. rend.*, **55**, 607 (1862); Carstanjen, *J. prakt. Chem.*, **102**, 129 (1867); Lamy and des Cloizeaux, *Ann. chim. phys.*, **17**, 335 (1869).

[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

# β-Propiolactone. VI. Reactions with Phenols, Thiophenols and their Salts[1]

BY T. L. GRESHAM, J. E. JANSEN, F. W. SHAVER, R. A. BANKERT, W. L. BEEARS AND MARIE G. PRENDERGAST

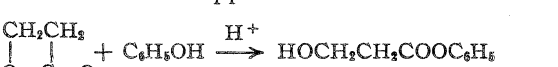
β-Propiolactone (I) and phenol react slowly at room temperature to give β-phenoxypropionic acid (II) and a small amount of a polymer of I. At higher temperatures (above 150°) the polymerization[2] becomes the major reaction. Except for the rate these results are similar to those ob-



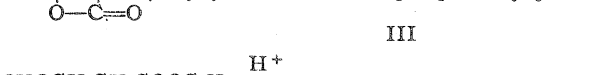
I II

served in the reaction between alcohols[3] and I. The polymers were separated from the phenoxy acids by alkaline saponification but it was necessary to avoid an excess of alkali; otherwise the phenoxy acids were cleaved to phenol and hydracrylic acid. Nuclear substituents had marked effects on the yields of β-phenoxypropionic acids (Table II). These products result from ring opening of I at the alkyl–oxygen link.

In the presence of catalytic amounts of sulfuric acid a striking change in the reaction of I with phenol occurs. Phenyl hydracrylate (III) is formed rapidly in high yield. This product must arise from ring opening of I at the acyl–oxygen linkage and it is somewhat surprising that none of II is formed. This appears to be in direct con-



III



IV

trast to the acid catalyzed reactions of I with alcohols[3] since the hydracrylate does not result from the polymers of I and phenol. The polymerization of I occurs to only a small extent.

The primary product (III) undergoes a self-alcoholysis to give phenyl β-(β-hydroxypropionoxy)-propionate (IV). This reaction continues at the expense of III beyond the few minutes required for complete reaction of I with phenol and it is possible to minimize it only to a small extent by increasing the excess of phenol or by reducing the acid catalyst concentration. The reaction also occurs to a similar extent with III and sulfuric acid in phenol solution.

Nuclear substituents have little or no effect on the yields of phenyl hydracrylates (Table I) as judged by the combined yields of phenyl hydracrylates and phenyl β-(β-hydroxypropionoxy)-propionates. The amount of self-alcoholysis tended to increase with increasing acid strength of the phenol.

The lactone and sodium phenoxide in water solution gave rise to sodium β-phenoxypropionate (V) in low yield. Hydrolysis to sodium hydracrylate (VI) accounts for most of I and variations in time, temperature, concentration and excess sodium phenoxide had only minor effects on the yields of V. In these reactions cleavage of the lactone ring occurred at the alkyl–oxygen link as in the salt reactions.[4]

Using the optimum conditions found for the reaction of I with sodium phenoxide, large variations in the yields of β-phenoxypropionates were observed with nuclear substituted phenols. The



V



VI

effects of substituents (Table II) differ from those reported for similar reactions of phenoxides with alkyl halides[5] and ethylene oxide.[6]

β-Propiolactone reacts much more rapidly with thiophenol than it does with phenol and the yield of β-thiophenoxypropionic acid is higher. With aqueous sodium thiophenoxide the yield of sodium β-thiophenoxypropionate is nearly quantitative.

## Experimental

**Materials.**—The phenols were Eastman Kodak Company chemicals or equivalent grade. They were redistilled before use. The β-propiolactone was similar to that described in the first paper[1] of this series.

**Reaction of β-Propiolactone with Phenol. A. Non-Catalyzed. β-Phenoxypropionic Acid. (II).**—A solution of one mole (72 g.) of β-propiolactone and three moles (282 g.) of phenol was kept at 100° for six hours with stirring. The unreacted lactone and most of the excess phenol was distilled at 20 mm. until the flask temperature was 140°. An ether solution of the distillation residue was extracted with three 300-ml. portions of saturated sodium bicarbonate solution. Evaporation of the extracted ether solution left a small residue of phenol. The combined sodium bicarbonate extract was boiled to hydrolyze the polymer until the volume was 500 ml. On cooling and acidifying with concentrated hydrochloric acid, pure β-phenoxypropionic acid was deposited. After standing overnight, the precipitate was filtered with suction, washed with water and dried at room temperature. The colorless product melted at 94–95°; yield 24.8 g., 14.8%; (18 hr. reaction time; yield 42.5 g., 24%).

(1) Presented in part at the 113th meeting of the American Chemical Society, Chicago, Illinois, April 22, 1948.

(2) Gresham, Jansen and Shaver, THIS JOURNAL, **70**, 998 (1948).

(3) Gresham, Jansen, Shaver, Gregory and Beears, *ibid.*, **70**, 1004 (1948).

(4) Gresham, Jansen, Shaver and Gregory, *ibid.*, **70**, 999 (1948).

(5) Boyd and Marle, *J. Chem. Soc.*, 2117 (1914).

(6) Goldsworthy, *ibid.*, 1234 (1926).

TABLE I

PHENYL HYDRACRYLATES

| Phenol substituent | Yield,[a] % | B. p. °C. | Mm. | $n^{20}D$ | $d^{20}_4$ | Sapon. equiv.[b] Calcd. | Found | Carbon, %[c] Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 39.8 | 90–92 | 0.2 | 1.5200 | 1.1596 | 166.0 | 166.5 | 65.06 | 65.09 | 6.07 | 5.94 |
| *o*-$CH_3$ | 37.8 | 83–84 | .1 | 1.5170 | 1.1307 | 180.0 | 182 | 66.67 | 66.17 | 6.72 | 6.74 |
| *m*-$CH_3$ | 41.3 | 84–85 | .1 | 1.5178 | 1.1300 | 180.0 | 182 | 66.67 | 66.13 | 6.72 | 6.78 |
| *p*-$CH_3$[d] | 46.5 | 84–85 | .1 | 1.5170 | 1.1315 | 180.0 | 182 | 66.67 | 66.17 | 6.72 | 6.71 |
| *o*-Cl | 22.4 | 80–82 | .1 | 1.5283 | 1.2620 | 200.5 | 197 | 53.87 | 55.37 | 4.52 | 4.91 |
| *p*-Cl | 32.7 | 93–94 | .1 | 1.5332 | 1.2860 | 200.5 | 208 | 53.87 | 53.54 | 4.52 | 4.63 |
| *o*-$OCH_3$ | 19.0 | 101–105 | .05 | 1.5220 | 1.1750 | 196.0 | 188 | 61.21 | 62.44 | 6.17 | 6.46 |
| *p*-$OCH_3$[e] | 35.1 | 104–105 | .05 | .... | .... | 196.0 | 190 | 61.21 | 60.73 | 6.17 | 6.15 |

[a] Recrystallized from carbon tetrachloride, m. p. 27–28°. [b] Saponification equivalents for some compounds are in poor agreement with that calculated due to instability and interference of colored decomposition products in determining end-points. [c] Analysis for carbon is in poor agreement with that calculated, except for the unsubstituted ester, due to impurities which appear to be mostly the phenyl β-(β-hydroxypropionoxy)-propionates. Repeated attempts to purify these compounds were not successful due to the great ease with which they underwent a self-alcoholysis under distillation conditions. [d] M. p. 42–43°. [e] The yield of polymer-free residue assumed to be dimeric self-alcoholysis products were: *o*-$CH_3$, 31.8; *m*-$CH_3$, 34.2; *p*-$CH_3$, 38.2; *o*-$OCH_3$, 38.0; *p*-$OCH_3$, 44.8; *o*-Cl, 59.4; *p*-Cl, 51.4.

*Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07; neut. equiv., 166. Found: C, 65.13; H, 6.14; neut. equiv., 169.5.

**Stability of β-Phenoxypropionic Acid in Alkaline Solution.**—A suspension of 10 g. (0.06 mole) of phenoxypropionic acid (m.p. 94–95°) in 200 ml. of water containing 2.48 g. (0.06 mole) of 97% sodium hydroxide was boiled under a reflux condenser for thirty minutes. Solution was complete at the boiling point. The solution was cooled, acidified with concentrated hydrochloric acid and after standing three hours was filtered from the β-phenoxypropionic acid. The solid acid was washed with water and dried at room temperature; wt. 9.5 g.; 95% recovery. The loss is mostly due to water solubility.

A similar experiment but using 4.96 g. (0.12 mole) of 97% sodium hydroxide gave a recovery of 7 g. (70%) of β-phenoxypropionic acid. Continued boiling of a similar solution for five hours resulted in the recovery of 0.5 g. (5%) of the phenoxy acid and 3.5 g. of phenol (62%).

**B. Acid Catalyzed. Phenyl Hydracrylate (III) and Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).**—β-Propiolactone (one mole, 72 g.) was added over a period of fifteen minutes to phenol (3 moles, 282 g.) containing 0.5 g. of sulfuric acid. The reaction was stirred and held at 46–50° by means of an ice-bath. After twenty minutes the catalyst was neutralized with an equivalent of sodium methoxide and most of the excess phenol removed at reduced pressure until the flask temperature was 100° at 1 mm. The residue was taken up in 400 ml. of ether and the solution filtered from a small amount (7 g.) of polymer, extracted with 100 ml. of saturated sodium bicarbonate, washed twice with water, dried over anhydrous sodium sulfate and evaporated. The residue was distilled at 0.2 mm. and phenyl hydracrylate (66 g., 39.8%) was collected as a colorless oil at 90–92° leaving a residue (88 g., 37%) of phenyl β-(β-hydroxypropionoxy)-propionate. Acidification of the sodium bicarbonate extract with concentrated hydrochloric acid gave no insoluble material, showing no phenoxy acid was formed. Physical and analytical data are shown in Table I.

Increase in time of reaction to six hours gave a reduction (18%) of III and an increase (15%) of IV. Doubling the number of moles of phenol in the reaction mixture gave an increase (10%) of III and a decrease (4%) of IV.

**Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).**—Distillation of combined residues (270 g.) from reactions carried out as in B above in a short-path still at 0.001 mm. gave 226 g. of product which was collected at a film temperature of 90–97°; $n^{20}D$ 1.5100; $d^{20}_4$ 1.2036.

*Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88; sapon. equiv., 119; acetyl value, 7.2; mol. wt., 238. Found: C, 61.13; H, 6.13; sapon. equiv., 122; acetyl value, 7.3; mol. wt. (cryoscopic in benzene), 230. It appears from these data that the product contained phenyl hydracrylate as an impurity.

The phenyl urethan derivative was recrystallized from chloroform from which it separated as small prisms; m. p. 97–98°.

*Anal.* Calcd. for $C_{19}H_{19}O_6N$: N, 3.92. Found: N, 3.85.

**Self-Alcoholysis of Phenyl Hydracrylate. Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).**—A solution of 166 g. (1 mole) of phenyl hydracrylate, 1 g. of sulfuric acid, and 470 g. (5 moles) of phenol was stirred and held at 46° for six hours. The reaction mixture, after treatment as in B above, gave 488 g. phenol, 70 g. (42% recovery) of phenyl hydracrylate, and 44 g. (37%) of phenyl β-(β-hydroxypropionoxy)-propionate, $n^{20}D$, 1.5070. The phenyl urethan derivative melted at 97–98° after recrystallization from chloroform. The mixture melting point with the phenyl urethan above was not depressed.

**The Reaction of β-Propiolactone (I) with Sodium Phenoxides. General Procedure.**—β-Propiolactone (0.5 mole) was added over an eight-minute period to a solution of 0.5 mole of sodium hydroxide and 0.5 mole of the phenol in 200 ml. of water at 100° with stirring. The heat of reaction held the temperature during the addition of I and heat was then supplied to maintain the temperature for a total time of fifteen minutes. The solution was cooled to 30° with an ice-bath, and acidified with 50 ml. of concentrated hydrochloric acid. The colorless oil which separated was extracted with three 200-ml. portions of ether. The combined ether extract was shaken twice with 300-ml. portions of saturated sodium bicarbonate. The solids, which precipitated on acidification of the alkaline solution, were filtered, washed with water, dried and recrystallized from benzene–hexane. The yields, physical and analytical data for the β-phenoxypropionic acids are given in Table II.

**β-Thiophenoxypropionic Acid.**[7]—One mole (72 g.) of I was added dropwise (fifteen minutes) to 110 g. (1 mole) of thiophenol at 100–110° with stirring. After an additional hour the mixture was distilled at 5 mm. to give a crude fraction, b.p. 145–175°, of β-thiophenoxypropionic acid which solidified on cooling. This was crystallized from ether–petroleum ether. It formed small flat plates, m.p. 57–58°; yield 89 g. (49%).

*Anal.* Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.21; H, 5.56; S, 17.68.

**Sodium β-Thiophenoxypropionate.**—One mole (72 g.) of I was added slowly to a stirred mixture of 41.7 g. (1 mole) of 97% sodium hydroxide and 110 g. (1 mole) of thiophenol in 200 ml. of water. The temperature was held at 10° during the addition and at room temperature

(7) Krollpfeiffer and Schultze, *Ber.*, **56B**, 1821 (1923).

TABLE II

$RR'C_6H_5OCH_2CH_2COOH$

| RR' | Yield, % Phenol[g] | Yield, % Sodium phenoxide[a] | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|
| H | 14.8 | 18.1[b] | 94–95 | 65.06 | 65.13 | 6.07 | 6.14 |
| *o*-CHO | .. | 32.0 | 113–114 | 61.85 | 61.87 | 5.19 | 5.27 |
| *p*-CHO | .. | 54.8 | 127–128 | 61.85 | 61.84 | 5.19 | 5.24 |
| *o*-$NO_2$[c] | 0.2 | 32.2 | 117–118 | 51.19 | 51.36 | 4.29 | 4.37 |
| *m*-$NO_2$[c] | 3.7 | 45.1 | 111–112 | 51.19 | 51.33 | 4.29 | 4.38 |
| *p*-$NO_2$[c] | 0.2 | 51.2 | 114–115 | 51.19 | 51.28 | 4.29 | 4.36 |
| *o*-Cl[d] | 0.4 | 49.9 | 112–113 | 53.87 | 53.99 | 4.52 | 4.55 |
| *m*-Cl[d] | 1.5 | 36.2 | 82–83 | 53.87 | 53.95 | 4.52 | 4.55 |
| *p*-Cl[d] | 4.5 | 28.9 | 134–135 | 53.87 | 54.00 | 4.52 | 4.53 |
| 2,4-di-Cl | .. | 51.4 | 91–92 | 45.98 | 46.11 | 3.43 | 3.45 |
| *o*-Br[e] | .. | 52.2 | 109–110 | 44.10 | 44.15 | 3.70 | 3.72 |
| *p*-Br[e] | .. | 29.9 | 142–143 | 44.10 | 44.17 | 3.70 | 3.76 |
| *o*-$OCH_3$ | 0.8 | 20.2 | 127–128 | 61.21 | 61.38 | 6.17 | 6.18 |
| *m*-$OCH_3$ | 3.9 | 24.0 | 81–82 | 61.21 | 61.22 | 6.17 | 6.13 |
| *p*-$OCH_3$ | 11.6 | 11.5 | 106–107 | 61.21 | 61.35 | 6.17 | 6.16 |
| *o*-$C_6H_5$ | .. | 12.5 | 93–94 | 74.36 | 74.47 | 5.83 | 5.95 |
| *m*-$C_6H_5$ | .. | 19.0 | 136–137 | 74.36 | 74.42 | 5.83 | 5.89 |
| *p*-$C_6H_5$ | .. | 3.0 | 168–169 | 74.36 | 74.46 | 5.83 | 5.89 |
| *o*-$CH_3$[f] | 3.3 | 12.9 | 91–92 | 66.65 | 66.69 | 6.71 | 6.73 |
| *m*-$CH_3$[f] | 4.4 | 16.8 | 104–105 | 66.65 | 66.72 | 6.71 | 6.76 |
| *p*-$CH_3$[f] | 14.4 | 14.7 | 144–145 | 66.65 | 66.64 | 6.71 | 6.74 |
| 3,5-di-$CH_3$ | .. | 16.2 | 86–87 | 68.02 | 68.06 | 7.27 | 7.25 |
| *o*-$C_6H_{11}$ | .. | 3.4 | 89–90 | 72.55 | 72.59 | 8.12 | 8.16 |
| *p*-$C_6H_{11}$ | .. | 11.6 | 115–116 | 72.55 | 72.67 | 8.12 | 8.12 |
| *p*-*t*-$C_4H_9$ | .. | 12.9 | 93–94 | 70.24 | 70.26 | 8.16 | 8.14 |
| *p*-$CH_2C_6H_5$ | .. | 14.4 | 133–134 | 74.98 | 75.07 | 6.29 | 6.31 |
| *p*-$OCH_2C_6H_5$ | .. | 13.1 | 147–148 | 70.57 | 70.52 | 5.92 | 5.89 |
| 2-$OCH_3$-4-$C_3H_3$ | .. | 20.8 | 97–98 | 66.08 | 66.08 | 6.83 | 6.79 |
| 2-*i*-$C_3H_7$-5-$CH_3$ | .. | 4.4 | 93–94 | 70.24 | 70.28 | 8.16 | 8.15 |

[a] % yields are for purified products. [b] Less than 1 g. of β-phenoxypropionic acid was lost due to water solubility when it was carried through the work-up procedure. Other reaction conditions and results were: The yield was not changed with increased time. The yield was lower (7.8%) at 50° in one hour and with less time it was still lower. Greater dilution (300 ml. water) gave decreased yield (16.9%). Increase in the ratio of sodium phenoxide to lactone (2:1) did not change the yield. [c] *Anal.* Calcd. for $C_9H_9O_5N$: N, 6.63. Found: N, *o*-, 6.62; *m*-, 6.57; *p*-, 6.59. [d] *Anal.* Calcd. for $C_9H_9O_3Cl$: Cl, 17.67. Found: Cl, *o*-, 17.60; *m*-, 17.67; *p*-, 17.59. [e] *Anal.* Calcd. for $C_9H_9O_3Br$: Br, 32.61. Found: Br, *o*-, 32.58; *p*-, 32.73. [f] Sodium phenoxide reactions at lower temperatures (30°) for one hour gave the following % yields with the cresols: *o*-, 5.0%; *m*-, 7.0%; *p*-, 5.8%. Although the yields of β-cresoxypropionic acids are lower, the ratio of yields is similar to that at 100°. [g] A above; six hours, 100°.

for an additional hour. The crystals which separated after acidification with 100 ml. of concentrated hydrochloric acid were filtered, washed with water, dried and recrystallized from ether–petroleum ether, m.p. 57–58°; yield, 166 g. (91%). The mixture melting point with the above sample was not depressed.

## Summary

β-Propiolactone reacts with phenol to give β-phenoxypropionic acid. In the presence of acid catalysts phenyl hydracrylate is formed. It reacts with sodium phenoxide to give sodium β-phenoxypropionate. The effects of nuclear substituents on these reactions are described. Thiophenol and its sodium salt react more rapidly but give similar products in higher yields.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Carbon Alkylations with 1-Methylgramine and its Methiodide[1]

BY H. R. SNYDER AND ERNEST L. ELIEL[2]

In previous papers,[3] alkylations of sodium cyanide and acetamidocyanoacetic ester with the methiodide (I) of 1-methylgramine (II) have been described. These alkylations, which proceed much more readily than corresponding reactions of quaternary salts of benzyldimethylamine,[4,5] undoubtedly occur by a substitution mechanism. However, their existence does not constitute proof that the Mannich base itself (II), as well as the quaternary ammonium salt (I), is capable of reacting by any mechanism other than the elimination-addition scheme[3a] proposed for gramine.

Further experiments have now been undertaken to elucidate this point. The alkylation reactions of the methiodide (I) have been extended to ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate, and tricarbethoxymethane, all of which were alkylated in the form of the sodium salts. The intermediate esters were not isolated but were hydrolyzed to the substituted malonic acid (III). Decarboxylation of this acid, either thermally or in refluxing pyridine,[6] yielded 1-methylindole-3(β)-propionic acid (IV). In view of the allylic rearrangement observed in the alkylation of sodium cyanide with the salt (I),[3b] an unequivocal proof of the structure of IV was considered necessary. The structure was proved by a Curtius degradation *via* the methyl ester, hydrazide, and azide of IV; the azide was subjected to rearrangement in dry xylene, and the resulting isocyanate was converted directly into N-phthalyl-1-methyltryptamine by baking it with phthalic anhydride. The phthalimide thus obtained was identical with an authentic specimen. The possibility still exists that in

(1) Presented in part before the Organic Division of the American Chemical Society at the Chicago meeting in April, 1948.

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(3) (a) Snyder and Eliel, THIS JOURNAL, **70**, 1703 (1948); (b) **70**, 1857 (1948); (c) **70**, 3855 (1948).

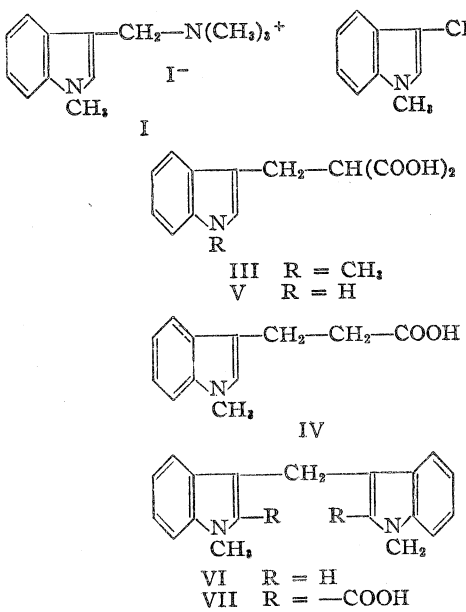
(4) von Meyer, *Abhandl. math.-phys. Klasse sächs. Akad. Wiss.*, **31**, 179 (1908); *Chem. Zentr.*, **80**, II, 1800 (1909).

(5) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

(6) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2609 (1942).

the alkylations with ethyl malonate and ethyl cyanoacetate small amounts of rearrangement products accompanying the major product (III) may have escaped detection, but in the other two alkylations the crude product (III) had essentially the same melting point as an analytically pure specimen, indicating that it was quite homogeneous.

Alkylations by 1-methylgramine (II) itself were found to proceed with ethyl cyanoacetate, ethyl acetamidomalonate, and tricarbethoxymethane. From an attempted alkylation of sodium cyanide in refluxing aqueous alcohol no neutral products could be obtained; 92% of the base (II) was recovered. Gramine under the same conditions yields indole-3-acetamide and indole-3-acetic acid.[7] The alkylation products from ethyl cyanoacetate and tricarbethoxymethane were identified by hydrolysis to the malonic acid (III). The product from ethyl acetamidomalonate was identified by hydrolysis and decarboxylation to N-acetyl-1-methyltryptophan.[3c] Some of the alkylation reactions were carried out in the presence of a trace of the sodium salt of the active methylene compound, and some without any added base. In one case (cyanoacetic ester) in which the reaction was carried out both with and without the sodium salt, it was noted that the presence of the sodium salt retards the speed of the reaction considerably and seems to have no appreciable effect on the yield of the alkylation product. Thus there seems to be some indication that the alkylation reaction is acid-base catalyzed.




Even with tricarbethoxymethane, which gave the highest yield of alkylation product, the overall yield of IV was only about 25%, while in a comparison experiment with gramine, skatylmalonic acid (V) was obtained in a yield of 67%. The yields from the other two alkylations were of the order of 15% and compare very unfavorably with the yields of the corresponding alkylation products from gramine.[5,8] Any explanation of the mechanism of the alkylation reaction must take this difference into account, but the fact that 1-methylgramine does act as an alkylating agent suggests that the elimination-addition mechanism[3a] is not *necessarily* the path of alkylations with Mannich bases of the gramine type.

The reactions of ethyl cyanoacetate and ethyl acetamidomalonate with II produced as a by-product (12–15% yield) a crystalline substance, the analysis of which indicated that it might be 1,1′-dimethyl-3,3′-diindolylmethane (VI). That the by-product is VI was proved by an unequivocal synthesis from $\alpha,\alpha'$-diketopimelic acid and *unsym*-methylphenylhydrazine; treatment of the dihydrazone of the diketo acid with hydrochloric acid (Fischer synthesis) yielded the dicarboxylic acid (VII) which was decarboxylated to VI in refluxing quinoline. A simpler, but less unequivocal synthesis of VI consists in the condensation of methylindole and formalin in the presence of acetic acid, which yields over 90% of VI.[9] The formation of VI from 1-methylgramine (II) involves a reversal of the Mannich reaction. Similar reactions are known in the case of phenolic Mannich bases, which undergo self-alkylation when treated with boiling dilute sodium hydroxide.[10] The self-alkylation of 1-methylgramine, however, does not seem to be brought about by base alone. The base II was recovered to the extent of 70% or more after prolonged heating at 225° in the presence of sodium methoxide and metallic sodium with or without the addition of an equal weight of 1-methylindole, and none of the condensation product VI could be isolated from these reactions. However, methylgramine *acetate* yielded 66% of the coupling product (VI) when refluxed in aqueous solution for one hour. Thus the self-condensation of 1-methylgramine appears to be acid-base catalyzed. Similar self-alkylations of other indole derivatives of the Mannich base type have been reported in the literature.[11]

Methylgramine methiodide (I) also underwent self-alkylation to VI when refluxed with aqueous sodium hydroxide or sodium acetate. In this case the formation of formaldehyde was demonstrated by its odor and by conversion to its methone derivative. Two experiments were devised to obtain evidence as to whether self-alkylation consists in a reverse Mannich reaction of part of the methiodide

(7) Snyder and Pilgrim, *ibid.*, **70**, 3770 (1948); Salzer, "Verfahren zur Darstellung substitutierter Essigsaueren," Department of Commerce, U. S. Publication Board PB 706.

(8) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945).

(9) 1-Methylindole reacts with benzaldehyde at 100° in the presence of catalytic amounts of zinc chloride; the product is assumed to be 1,1′-dimethyl-3,3′-diindolylphenylmethane, but its structure has not been proved [Fischer, *Ber.*, **19**, 2988 (1886); *Ann.*, **242**, 372 (1887)].

(10) Auwers and Dombrowski, *Ann.*, **344**, 280 (1906).

(11) Passerini, *et al.*, *Gazz. chim. ital.*, **63**, 138 (1933); **65**, 933 (1935); Neri, *ibid.*, **64**, 420 (1934).

(I) followed by alkylation of the methylindole so formed by more of the quaternary salt (I), or whether two molecules of the methiodide couple and subsequently lose the elements of formaldehyde and trimethylamine. In one experiment a mixture of the quaternary salt (I), water, and sodium hydroxide was steam distilled in the hope of removing methylindole before it had an opportunity to react. However, no methylindole was found in the steam distillate. In another experiment, the methiodide (I), methylindole, and sodium hydroxide were refluxed in aqueous alcohol. The high yield of the product VI (98% of practically pure material if calculated on the basis of the methiodide alone) and the low recovery of methylindole make it almost certain that part of the methylindole was alkylated, but the evidence is not quite conclusive.

When the methiodide or the hydrochloride of 1-methylgramine was refluxed with water alone, an oily product soon separated and solidified on cooling; the solution contained free formaldehyde, as shown by the methone test. However, no homogeneous indole derivative could be isolated from this reaction.

## Experimental[12,13]

**Reaction of Methylgramine Methiodide (I) with Sodiomalonic Ester.**—Sodium (0.23 g., 0.01 atom) was dissolved in 8 g. of ethyl malonate at 80° in a two-necked flask equipped with a stirrer and an air-cooled condenser protected by a soda-lime tube. Three and three-tenths grams of I (0.01 mole) was added, the temperature was raised to 130–140°, and the mixture was stirred for ten hours. Trimethylamine was given off. At the end of the reaction period gas evolution had practically ceased. Stirring was continued for two hours at 140–150°. A solution of 10 g. of potassium hydroxide in 100 ml. of 80% ethanol was then added and the solution was refluxed for four and one-half hours. Fifty milliliters of water was added and most of the alcohol was distilled. The residual solution was decanted from some resin, boiled with Norite, filtered, and acidified with hydrochloric acid. An oily precipitate, which solidified on standing in the ice box overnight, was obtained. It was collected and dissolved in sodium bicarbonate solution and the solution was boiled with Norite, filtered with suction, acidified, and chilled as before. The brown solid (III) was collected, washed with water and dried; wt. 0.55 g. (22%), m. p. 165.5–167.5° (dec.). Repeated washings with chloroform and recrystallization from ethyl acetate–petroleum ether (b. p. 30–60°) raised the melting point to 172.5–173° (dec.).

*Anal.* Calcd. for $C_{13}H_{13}O_4N$: C, 63.14; H, 5.30. Found: C, 63.29, 63.55; H, ——, 5.48.

When absolute ethanol was employed as a solvent in the alkylation, the yield of III was essentially the same but the product was less pure.

**Reaction of Methylgramine Methiodide (I) with Sodiocyanoacetic Ester.**—Sodium (0.34 g., 0.015 atom) was dissolved in 8.4 g. (0.075 mole) of ethyl cyanoacetate. Five grams (0.015 mole) of I was added and the suspension was stirred at 125° for twelve hours. A solution of 15 g. of potassium hydroxide in 75 ml. of 80% ethanol was added and the mixture was refluxed for eleven hours. It was worked up as described for the reaction with sodiomalonic ester. The product was partly crystalline and partly resinous. The crystals weighed 0.65 g. (17.5%) and melted at 159–160° (dec.); two recrystallizations raised the melting point to 170–171° (dec.) and the mixed melting point with the product from malonic ester was 172–172.5° (dec.). The resinous part crystallized after several weeks and melted at 135–145° (dec.), weight 1.7 g.

**Reaction of Methylgramine Methiodide (I) with Ethyl Cyanomalonate Sodium Salt.**—A solution of 3.3 g. of I (0.01 mole) and 2.1 g. (0.01 mole) of ethyl cyanomalonate sodium salt[14] in 20 ml. of water was refluxed for one hour. There was a vigorous evolution of trimethylamine, and a viscous oil separated. The aqueous layer was decanted, filtered from a little solid material, and extracted with ether. The ether extract, the solid collected and the oily residue were combined and the ether was removed in a current of air. The residue was refluxed for six hours with 25 ml. of 10% aqueous sodium hydroxide solution. The solution was cooled, decanted from some resinous material, boiled with Norite, filtered with suction and acidified with hydrochloric acid. A crystalline precipitate appeared. The solution was chilled, and the precipitate was collected, washed with ice water and dried. There was obtained 1.25 g. (51%) of a light pink powder of m. p. 172–173° (dec.); the mixed melting point with III was 172–173° (dec.).

The use of absolute alcohol as a solvent in this alkylation did not affect the yield and quality of the product.

**Reaction of Methylgramine Methiodide (I) with Tricarbethoxymethane Sodium Salt.**—To a solution of 0.23 g. (0.01 atom) of sodium in 30 ml. of absolute alcohol were added 4.65 g. (0.02 mole) of tricarbethoxymethane[15] and 3.3 g. (0.01 mole) of I. The mixture was refluxed for one and one-half hours while a current of nitrogen was passed over it. There was a vigorous evolution of trimethylamine. Ten milliliters of 40% aqueous sodium hydroxide was added, followed, after ten minutes, by 10 ml. of water, while refluxing was continued. Trimethylamine evolution resumed for a short time. After two and one-fourth hours heating was discontinued, and the solution was concentrated *in vacuo*, extracted twice with ether, acidified with concentrated hydrochloric acid and chilled. Brown crystals separated. They were collected and dissolved in 15 ml. of a saturated solution of sodium carbonate and 25 ml. of water. The solution was boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid, and chilled. After having been thoroughly washed with ice water and dried, the light pink crystals (III) weighed 1.55 g. (62.5%), m. p. and mixed m. p. 171–172° (dec.).

When the alkylation was carried out in aqueous medium, the yield was only 34.5%.

**Decarboxylation of III.**—(a) Thermal: Fairly pure III of m. p. 165.5–167.5 (0.550 g.) was heated in an oil-bath at 180–190° until gas evolution ceased (about five minutes). The product was distilled in a short-path apparatus at 0.4 mm., bath temperature 150°. The yield of IV was 0.300–0.325 g. (67–72%), m. p. 123–125°. Recrystallization from benzene gave white platelets, m. p. 125.5–126°.

*Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.28; H, 6.65; N, 6.95.

When impure III (melting point around 140°) was decarboxylated, pure IV was obtained by sublimation, but the yield dropped to 38%.

(b) In Pyridine: Two grams of pure III was refluxed for twenty minutes in 20 ml. of pyridine. The pyridine was distilled *in vacuo*, and 20 ml. of 1:4 hydrochloric acid was added to the residue, which then crystallized promptly. The crystals were collected, washed with water, and dried; weight 1.47–1.56 g. (89.5–94.5%), m. p. 120.5–123.5°. Recrystallization from benzene raised the melting point to 124–126°.

**Curtius Degradation of IV.**—(a) Methyl Ester of IV: To 0.624 g. of IV dissolved in 30 ml. of ether was added an

(12) All melting points are corrected.

(13) Microanalyses by Miss Emily Davis, Mrs. Jane Wood and Mr. Howard Clark.

(14) Haller, *Ann. chim.*, [6] **16**, 426 (1889). The authors are indebted to Mr. George Segre of the division of chemical engineering for a sample of this compound.

(15) Lund and Voigt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 594.

ethereal solution of diazomethane prepared from 2 g. of nitrosomethylurea.[16] There was an immediate evolution of nitrogen. The solution was allowed to stand for two hours, then a solution of glacial acetic acid in ether was added dropwise until the excess diazomethane was destroyed, as shown by decolorization of the solution. The ethereal solution was extracted twice with small portions of 10% sodium carbonate solution, which were then extracted with about 50 ml. of ether in a second separatory funnel. The ethereal solutions were washed with water, combined, dried over sodium sulfate and distilled. A viscous oil resulted which would not crystallize. It was distilled in a two-bulb microdistillation apparatus at 0.25 mm., bath temperature 180–190°, to yield 0.58 g. (83.5%) of a light yellow oil.

The picrate crystallized in dark red needles from methanol, melting point 98–99°.

*Anal.* Calcd. for $C_{19}H_{18}O_9N_4$: C, 51.12; H, 4.06. Found: C, 51.25; H, 4.33.

(b) Hydrazide of IV: A solution of 0.40 g. of the above ester in 4 ml. of methanol was refluxed for twenty hours with 0.75 ml. of 85% hydrazine. On concentration of the solution the hydrazide crystallized. It was collected, washed with aqueous methanol and dried. The yield was 0.32 g. (80%), m. p. 135.5–136.5°. Recrystallization of a sample from benzene containing a little absolute ethanol yielded fine white needles of melting point 136.5–137.5°.

*Anal.* Calcd. for $C_{12}H_{15}N_3O$: C, 66.32; H, 6.97. Found: C, 66.28; H, 6.81.

**(c) N-Phthalyl-1-methyltryptamine.**—Two milliliters of a solution of 0.6 ml. of concentrated hydrochloric acid in 10 ml. of water was cooled to 10° and there was added to it, in succession, 0.175 g. of the above hydrazide, 2 ml. of ether, and 0.2 ml. of a 37.5% solution of sodium nitrite in water. After thorough shaking, the layers were separated, and the aqueous layer was twice more extracted with small portions of ether. The ether layers were washed with sodium bicarbonate solution followed by water; they were then combined and dried over calcium chloride. Five milliliters of xylene was added and the ether and part of the xylene were distilled *in vacuo*. The xylene solution was then refluxed for a short time, 0.2 g. of phthalic anhydride was added, and refluxing was continued for a total of two hours. The xylene was distilled and the residue was heated to 240°. It was then allowed to cool somewhat and 3 ml. of ethanol was added. The tan crystals which appeared when the solution was cooled weighed 0.050 g. After one recrystallization the derivative melted at 172–175°. Two further recrystallizations from the same solvent raised the melting point to 174.5–176.5°. The mixed melting point with an authentic sample of the phthalimide[3a] of melting point 176.5–177° was 176–176.5°. The two samples were indistinguishable under the microscope and their infrared spectra were essentially identical.[17]

**Reaction of 1-Methylgramine (II) with Cyanoacetic Ester.**—In the presence of sodium: To a solution of 3.8 g. (0.02 mole) of 1-methylgramine in 6.8 g. (0.06 mole) of ethyl cyanoacetate 25 mg. of sodium was added and the mixture was heated at 150° for twenty-four hours in a flask equipped with a short air condenser. Additional 25-mg. portions of sodium were added at the end of five and eighteen hours. A basic gas was evolved. When the gas evolution had ceased at the end of twenty-four hours, the reaction mixture was cooled and 50 ml. of 1 *N* hydrochloric acid was added. The mixture was extracted twice with 70-ml. portions of ether. No unchanged methylgramine was recovered when the aqueous layer was made alkaline. The ether layers were washed twice with water, combined, dried over sodium sulfate, and the solvent was distilled. The residue was hydrolyzed by refluxing overnight with a solution of 10 g. of potassium hydroxide in 50 ml. of 80% ethanol. Forty milliliters of water was then added and most of the ethanol was distilled. The residue was extracted with ether, boiled with Norite, filtered with suction, acidified with hydrochloric acid and chilled. The acid was partly resinous and partly crystalline. The crystals were collected, washed, and dried; weight 0.2 g., m. p. 164.5–165.5° (dec.). Three recrystallizations raised the melting point to 171.5–172° (dec.); the mixed melting point with III was 172–172.5 (dec.). Decarboxylation of the acid yielded IV, identified by melting point and mixed melting point. The resinous part crystallized after standing in the ice box for several weeks; weight 1.3 g., m. p. 139.5–147.5° (dec.). The over-all yield of very impure material was 1.5 g. (30%), which corresponds to about 15% of pure material, as shown by the fact that the low-melting material gave a 38% yield of IV upon decarboxylation.

The ether solution containing the unsaponifiable reaction products was distilled to give a brown residue, which recrystallized on standing. Recrystallization from 95% ethanol yielded 0.3 g. of crystals of melting point 92–96°. Four more recrystallizations from 95% ethanol (Norite was used in the second) gave pure 1,1′-dimethyl-3,3′-diindolylmethane (VI) melting at 109.5–111.5°.

*Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.16; H, 6.61; N, 10.21. Found: C, 83.06, 83.06; H, 6.60, 6.75; N, 10.31, 10.19.

The dipicrate was obtained by dissolving the parent substance in benzene, adding an excess of a saturated solution of picric acid in benzene, allowing the solution to evaporate, and digesting the residue with absolute ethanol to remove excess picric acid. The material was recrystallized from benzene–petroleum ether (b. p. 30–60) as dark red crystals melting at 112–113°.

*Anal.* Calcd. for $C_{31}H_{24}N_8O_{14}$: C, 50.81; H, 3.30. Found: C, 51.05; H, 3.43.

Without sodium: A solution of 3.8 g. (0.02 mole) of II and 3 g. (0.03 mole) of methyl cyanoacetate was heated at 135–150° for two hours. There was a very vigorous evolution of a basic gas, which practically ceased at the end of one and one-half hours. The reaction product was hydrolyzed by refluxing it overnight with a solution of 6 g. of potassium hydroxide in 50 ml. of water. The solution was cooled, decanted from undissolved material, extracted with ether, boiled with Norite, filtered with suction and acidified. A dark oil separated which solidified on standing in the ice box for several days. It was collected, washed with water and dissolved in acetone (there was no acetone-insoluble material). The acetone was distilled and the residue was decarboxylated by heating it at 180–190° until no more gas was given off. The decarboxylated acid was evaporatively distilled at 0.1 mm., bath temperature 135–205°. There was obtained 1.24 g. of crystals of m. p. 101–115°. Recrystallization from benzene yielded 0.71 g. (17.5%) of IV, m. p. and mixed m. p. 124.5–126°. No further amount of pure material could be recovered from the mother liquors.

The neutral residue of the saponification was taken up in ethyl acetate and added to the ether extract of the alkaline saponification mixture. The combined solutions were dried over sodium sulfate and concentrated. The addition of alcohol to the concentrate yielded 0.225 g. of crystals (VI); m. p. 106.5–110.5°; there was no depression in melting point when the crystals were mixed with the analytical sample obtained as described above. The mother liquors yielded a second crop weighing 0.035 g. of m. p. 105.5–109°; total yield 0.260 g. (9.5%).

**Reaction of 1-Methylgramine (II) with Acetamidomalonic Ester.**—A solution of 3.8 g. (0.02 mole) of II, 8.7 g. (0.04 mole) of ethyl acetamidomalonate and *ca.* 25 mg. of sodium was heated under nitrogen for twenty-four hours at 115–120° and for fifteen hours at 140–145° in a flask equipped with a short air condenser. A basic gas was evolved. The solution was cooled and the resulting syrup was taken up in 60 ml. of ether and extracted with 1 *N* hydrochloric acid. When the aqueous extract was made alkaline, no methylgramine was liberated. The

(16) Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 166.

(17) The authors are indebted to Mrs. Agatha Johnson for the absorption studies.

ether solution was washed with water, dried over sodium sulfate, and concentrated. The residual amber sirup could not be crystallized. It was hydrolyzed by refluxing for three hours with 7 g. of potassium hydroxide in 7 ml. of water and 63 ml. of 95% ethanol. Thirty-five milliliters of water was added and most of the ethanol was distilled. The aqueous solution was extracted twice with 50-ml. portions of ether, boiled with Norite, filtered with suction, acidified with hydrochloric acid and chilled. A partly crystalline and partly resinous precipitate resulted. The crystalline material (presumably the alkylated acetamidomalonic acid) was collected, washed, and dried; it weighed 0.23 g. (3.8%). It was recrystallized once from absolute ethanol–acetone–benzene–petroleum ether and melted at 110.5–111.5° (dec.); it was not further purified.

When 40 mg. of this material was refluxed with *ca.* 3 ml. of water for four hours, white crystals of melting point 171–172° separated on cooling. The mixed melting point with N-acetyl-1-methyltryptophan[30] was 171–172.5°.

The resinous part of the malonic acid was collected by decantation and washed with water. It was refluxed with water for three and one-half hours and filtered to remove some resin. On cooling, the filtrate deposited tan crystals which were collected and dried; weight 0.40 g. (7.7%), m. p. 166.5°. Recrystallization from acetone–benzene (Norite) raised the melting point to 169–171°; the mixed melting point with N-acetyl-1-methylptryptophan was 169.5–171°.

The ether solution containing the unsaponifiable reaction products was concentrated and the residue was crystallized from 95% ethanol (Norite) to yield 0.25 g. of crystals (VI) of melting point 107.5–111° and 0.15 g. of impure material. Recrystallization from petroleum ether (b. p. 60–90°) raised the melting point to 108.5–111°. The mixed melting point with the neutral material obtained from the ethyl cyanoacetate reaction was 108.5–111°.

An attempt was made to condense II with acetamidomalonic ester in boiling xylene in the presence of sodium hydroxide,[8] but no crystalline materials could be obtained from the condensation under these conditions.

**Reaction of 1-Methylgramine (II) with Tricarbethoxymethane.**—A solution of 3.8 g. (0.02 mole) of II in 10.8 g. (0.05 mole) of tricarbethoxymethane[14] was heated under nitrogen at 160–170° for three hours. A basic gas was evolved. A solution of 20 g. of potassium hydroxide in 20 ml. of water and 160 ml. of 95% ethanol was added and the mixture was refluxed for six hours. One hundred and sixty milliliters of water was added and most of the ethanol was distilled. The solution was cooled, extracted with ether, boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid, and allowed to stand in the ice box for five days. The precipitate was partly crystalline and partly resinous. The crystals were collected, washed and dried; weight 0.51 g., m. p. and mixed m. p. (with III) 165.5–168° (dec.). Much of the non-crystalline portion dissolved in acetone, leaving 0.30 g. of crystals, apparently the mono-potassium salt, which melted around 250° after darkening around 200°. The crystals were dissolved in water (in which they were readily soluble) and hydrochloric acid was added to the solution. There was obtained 0.22 g. of crystals of melting point 173–175° (dec.); mixed m. p. with III 171–172° (dec.). The total yield of III was 0.73 g. (15%).

The acetone wash was concentrated, and the resinous residue was decarboxylated at 180–190° and sublimed at 0.1 mm. The sublimate was dissolved in sodium carbonate solution; the solution was extracted twice with ether, boiled with Norite, filtered, acidified, and chilled. It yielded 0.34 g. (8.5%) of crystals of IV; melting point and mixed melting point 122.5–124.5°.

**Attempted Reaction of 1-Methylgramine (II) with Sodium Cyanide.**—A solution of 3.8 g. of II and 5 g. of sodium cyanide in 10 ml. of water and 40 ml. of 95% ethanol was refluxed for eighty-four hours. Part of the ethanol was distilled, 50 ml. of water was added, and the emulsion was twice extracted with 100-ml. portions of ether.

The aqueous portion was boiled with Norite, filtered, and acidified with concentrated hydrochloric acid (hood!). There was no separation of organic material.

The ether layers were washed once with water, extracted with three 25-ml. portions of 1 *N* hydrochloric acid, washed with water, dried, and distilled. The residue weighed less than 0.1 g.

The acid layer was made alkaline with 10% sodium hydroxide, and extracted twice with 50-ml. portions of ether. After having been dried, the ether was distilled from 3.5 g. of 1-methylgramine (92% recovery) identified by its picrate (melting point 145.5–146°, mixed melting point 145.5–146.5°).

**Reaction of Gramine with Tricarbethoxymethane.**—A solution of 3.5 g. (0.02 mole) of gramine in 10.8 g. (0.05 mole) of tricarbethoxymethane[14] was heated under nitrogen at 115–120° for an hour and at 125–130° for an hour. There was a vigorous evolution of a basic gas, which ceased at the end of the heating period. Hydrolysis was effected by refluxing the product for six hours with a solution of 20 g. of potassium hydroxide in 20 ml. of water and 160 ml. of 95% ethanol. One hundred and forty milliliters of water was added and most of the ethanol was distilled. The solution was filtered, extracted with ether, boiled with Norite, filtered with suction and acidified with concentrated hydrochloric acid. After one week in the ice box the solution had deposited crystals which were collected, washed with ice water and dried; weight 1.26 g., m. p. 165.5–167.5° (dec.). Concentration of the mother liquors in a current of air led to the separation of a second crop; weight 1.79 g., m. p. 160–163° (dec.). The total yield was 3.05 g. (67%). Recrystallization from water (Norite) raised the melting point to 175.5–177° (dec.) [(lit.[5] 178° (dec.); lit.[18] 188–189° (dec.)].

Decarboxylation in Pyridine: The above acid (V) (0.60 g.) was decarboxylated in exactly the same manner as described for the acid III. There was obtained 0.38 g. (78%) of indole-3($\beta$)-propionic acid, m. p. 129.5–132.5°. Recrystallization from water raised the melting point to 133–134° (lit.[5] 132–133°, lit.[18,19] 134°).

**1,1′-Dimethyl-2,2′-dicarboxy-3,3′-diindolylmethane (VII).**—Methylenebisoxalacetic ester was obtained from oxalacetic ester and formaldehyde by the method of Blaise and Gault.[20] To convert it into $\alpha,\alpha'$-diketopimelic acid, 28 g. of the hydrate of methylenebisoxalacetic ester, 28 ml. of water and 12 ml. of concentrated hydrochloric acid were refluxed until the solution had become homogeneous (one hour). The solution was neutralized with 10% aqueous sodium hydroxide and then acidified slightly with a few drops of glacial acetic acid. The addition of 6 ml. of *unsym*-methylphenylhydrazine in 25 ml. of water containing sufficient glacial acetic acid to make a homogeneous solution caused the separation of a dark oil. The mixture was allowed to stand for two hours, the aqueous phase was decanted, and the residue was washed once with water by decantation. The water layers were extracted with ether, and the ether layer was combined with the water-insoluble oil. The ether was removed in a current of air, and the residue was swirled on the steam-bath with 45 ml. of water and 15 ml. of concentrated hydrochloric acid until it had solidified and then for five minutes longer. The suspension was chilled and the solid was collected. It was then dissolved in a slight excess of 5% aqueous sodium hydroxide. The aqueous solution was extracted with ether, boiled with Norite, filtered with suction, acidified with concentrated hydrochloric acid and chilled. Slightly tan crystals separated. They were collected, washed with ice-water and dried; weight 2.5 g. (40%), m. p. 202–203.5° (dec.). Four recrystallizations from acetone–alcohol raised the melting point to 227–228° (dec.).

*Anal.* Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.58; H, 5.01; N, 7.73. Found: C, 69.71; H, 5.30; N, 7.92.

**1,1′-Dimethyl-3,3′-diindolylmethane (VI).**—From VII: A solution of 0.250 g. of VII (m. p. 226–227°) in 2.5

(18) Maurer and Moser, *Z. physiol. Chem.*, **161**, 131 (1926).

(19) Ellinger, *Ber.*, **38**, 2884 (1915).

(20) Blaise and Gault, *Bull. soc. chim.*, [4] **1**, 78 (1907).

ml. of distilled quinoline was refluxed for ten minutes. It was cooled and taken up in *ca.* 25 ml. of ether. The ether solution was washed five times with 10-ml. portions of 1 *N* hydrochloric acid, five times with 5-ml. portions of 2.5% sodium hydroxide and twice with water. It was dried over sodium sulfate, the solvent was distilled, and the residue was crystallized from 95% ethanol. There was obtained 0.045 g. (20%) of white crystals; melting point 107.5–110°. Recrystallization from 95% ethanol raised the melting point to 109.5–111.5°. The mixed melting point with the material obtained in the alkylation reactions (described above) was the same, and the two samples had the same crystalline aspect under the microscope.

1,1′-Dimethyl-3,3′-diindolylmethane is very sensitive to both air and acids. When exposed to the atmosphere it turns pink. Ordinary Darco could not be used to decolorize solutions of VI, as it turns them bright red. Ammonia washed Darco was found satisfactory for decolorization purposes.

**From Methylindole.**—To 1 ml. (1.07 g.) of methylindole dissolved in 2 ml. of glacial acetic acid, 1 ml. of 40% aqueous formalin was added, and the reagents were mixed by shaking. The mixture warmed up and after a few minutes became heterogeneous and crystallized in part. The crystals were collected, and the non-crystalline, viscous portion was treated with a mixture of 95% ethanol and ethyl acetate, whereupon it also crystallized. The combined crystals were washed with 95% ethanol and dried. By reworking the mother liquors a total yield of 1.05 g. (94%) of VI of melting point 100.5–108.5° was obtained. Two recrystallizations from 95% ethanol (with ammonia-washed Darco in the first) raised the melting point to 108.5–110.5°. The mixed melting point with samples obtained by other methods (see above) was the same.

**From I.**—(a) A solution of 3.3 g. of I and 5 g. of the trihydrate of sodium acetate in 25 ml. of water was refluxed for three hours. Trimethylamine was evolved. The emulsion was cooled and extracted with ether. The ether layer was dried and concentrated and the residual oil was crystallized from 95% ethanol containing a little ethyl acetate. The crystals were collected, washed with 95% ethanol and dried; weight 1.19 g. (87%), m. p. 93–105.5°. Recrystallization from ether–petroleum ether (b. p. 30–60°) followed by two recrystallizations from 95% ethanol raised the melting point to 108.5–111.5°. There was no depression of melting point on admixture with samples of VI obtained by other methods.

Formaldehyde was identified in the aqueous layer by its odor and by the melting point of its methone derivative obtained by adding an alcoholic solution of methone to the aqueous layer; melting point and mixed melting point 190.5–191.5°.

(b) A solution of 3.3 g. of I and 1.5 ml. of 40% aqueous sodium hydroxide in 18.5 ml. of water was steam distilled for one hour. The distillate did not have the odor of methylindole. It was extracted with ether, and the ether was dried over sodium sulfate and distilled. There was a small amount of viscous residue which had none of the properties of 1-methylindole.

The residue, which contained a water-insoluble oil, was extracted with ethyl acetate. The ethyl acetate solution was concentrated by evaporation until crystals began to form; 95% ethanol was then added, and the mixture was chilled. The crystals were collected, washed with cold 95% ethanol, and dried; weight 0.87 g. (63.5%), m. p. 107.5–110°.

(c) A solution of 3.30 g. (0.01 mole) of I, 1.31 g. (0.01 mole) of 1-methylindole and 1.5 ml. of 40% aqueous sodium hydroxide in 7.5 ml. of water and 17.5 ml. of 95% ethanol was refluxed for six hours. The mixture was then steam distilled until the odor of methylindole in the residue was very faint. The distillate was extracted with ether and the ether was dried and distilled. The residue, after brief drying at 100° and 15 mm. pressure, weighed 0.64 g. It was distilled at 15 mm., air-bath 140–160°. The distillate was somewhat impure 1-methylindole ($n^{20}D$ 1.6029, melting point of crude picrate[21] 135.5–138.5°) and weighed 0.53 g. (40.5% recovery). There was a distillation residue of 0.06 g.

The residue of the steam distillation was extracted with ethyl acetate and worked up as described before; yield 1.34 g. of VI (98% if based on I alone), m. p. 107–110°. When the experiment was repeated, the yield was 1.28 g. of material of melting point 108.5–110.5° and 0.08 g. of melting point 102.5–107.5°.

When the alcoholic mother liquor was evaporated to dryness, and the residue was dried *in vacuo* (15 mm.) at 100°, 0.81 g. of a viscous oil remained. This oil was only very slightly soluble in cold 95% ethanol and could therefore not have contained much 1-methylindole.

(d) A solution of 1.12 g. (0.005 mole) of methylgramine hydrochloride[22] and 0.68 g. (0.005 mole) of sodium acetate trihydrate in 10 ml. of water was refluxed for one hour. The resulting mixture had a strong formaldehyde odor and contained an oil which crystallized on cooling. The solid was extracted with ethyl acetate, and the ethyl acetate extract was dried over sodium sulfate and evaporated in a current of nitrogen. The concentrate crystallized. Ethanol was added to it and the crystals were collected, washed with 95% ethanol and dried; weight 0.45 g. (66%), melting point and mixed melting point with samples obtained by other routes, 110–112°.

When the aqueous layer of the reaction mixture was made alkaline, some unchanged methylgramine separated and a basic gas (presumably dimethylamine) was liberated.

When a solution of 0.6 g. of methylgramine and 0.44 g. of sodium acetate trihydrate in 10 ml. of 50% ethanol was refluxed for one hour, there was no noticeable evolution of formaldehyde or dimethylamine, and no neutral material was formed. Methylgramine (77%, isolated as the hydrochloride) was recovered.

**Behavior of Methylgramine Methiodide and of Methylgramine Hydrochloride in Boiling Water.**—One gram of I was refluxed for one hour with 10 ml. of water. An oil separated and solidified on cooling. It was collected and dried; weight 0.35 g., m. p. 77–99°. Attempts to obtain a homogeneous substance from this material failed. The water solution contained formaldehyde, identified by its methone derivative, melting point and mixed melting point 188.5–190.5°.

The hydrochloride of II under the same conditions yielded an intractable white solid of melting point 50–90°. The water solution contained formaldehyde, identified by its odor and methone derivative. When it was made alkaline, a basic gas of ammoniacal odor (presumably dimethylamine) was given off.

**Thermal Stability of Gramine and of 1-Methylgramine.** When gramine was heated above its melting point, dimethylamine was evolved copiously and a brown resin resulted.

Heating of 1-methylgramine (1 g.) in the presence of small amounts of sodium methoxide and metallic sodium at 150–155° for four hours, then at 215–225° for nine hours, and finally at 160° for twelve hours, yielded an oil which was almost entirely soluble in 1 *N* hydrochloric acid. Extraction of the acid solution with ether yielded only a trace of neutral material. When the acid solution was made alkaline and extracted with ether, there was recovered 0.7 g. (70%) of 1-methylgramine, identified by its picrate, melting point 138.5–143.5° and after recrystallization 144–145.5°.

**Attempted Reaction of 1-Methylgramine (II) with 1-Methylindole.**—One gram of II, 1 g. of 1-methylindole and a trace of sodium methoxide were heated for four hours at 150–155°, for nine hours at 215–225° and then for twelve hours at 160°. The oil was cooled and dissolved in ether. The ether solution was exhaustively ex-

(21) The melting point of the picrate of 1-methylindole recorded in the literature is 150°, but we have never obtained specimens melting higher than 143.5–144.5° from pure 1-methylindole.

(22) For details of the preparation of this hydrochloride see Snyder and Eliel, THIS JOURNAL, **70**, 4233 (1948).

tracted with 1 *N* hydrochloric acid. The neutral products, obtained by distillation of the ether, weighed 0.77 g., were entirely soluble in cold petroleum ether, and yielded a picrate of melting point 141.5–143.5°, indicating that the material was practically pure 1-methylindole. The alkaline fraction, recovered by making the acid extract alkaline and extracting with ether, weighed 0.90 g. (90% recovery) and yielded a picrate of melting point 135.5–137.5°. Two recrystallizations from 95% ethanol raised the melting point to 140–141.5°; mixed melting point with the picrate of II, 144–145.5°.

## Summary

The sodium salts of ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate and tricarbethoxymethane have been alkylated with 1-methylgramine methiodide. The highest yield (62.5%) of the substituted malonic acid was obtained by saponifying the alkylation product of tricarbethoxymethane. Decarboxylation of the substituted malonic acid in refluxing pyridine gave a 90% yield of 1-methylindole-3(β)-propionic acid, whose structure was proved by a Curtius degradation.

Ethyl cyanoacetate, ethyl acetamidomalonate, and tricarbethoxymethane have been alkylated with 1-methylgramine. The yields of alkylation products are consistently lower than in the case of corresponding alkylations with gramine.

As a by-product in the alkylations with 1-methylgramine, 1,1′-dimethyl-3,3′-diindolylmethane was obtained. The structure of this product has been proved by unequivocal synthesis. The same product was obtained from methylindole and formaldehyde in the presence of acetic acid, from 1-methylgramine methiodide and aqueous sodium hydroxide or sodium acetate, and from 1-methylgramine hydrochloride and aqueous sodium acetate.

1-Methylgramine was found to be much more stable to heat than gramine.

URBANA, ILLINOIS RECEIVED AUGUST 19, 1948

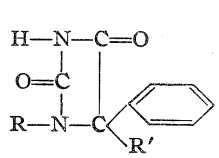
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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO., DETROIT, MICHIGAN]

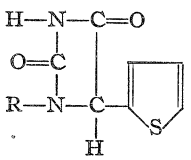
# The Preparation of 1-R-5-(2-Thienyl)-hydantoins

BY LOREN M. LONG, C. A. MILLER AND GRAHAM CHEN

We have reported the synthesis and pharmacological activity of a series of 1-R-5-R′-5-phenylhydantoins[1] which may be represented by formula I. As reported in that paper, the more effective compounds in regard to protection against electrically induced convulsions are those in which R represents a short chain hydrocarbon group while R′ represents hydrogen.



I



II

Although our evidence to date does not indicate that the mere substitution of the 2-thienyl group for the phenyl group in physiologically active compounds is likely to lead to derivatives of greatly increased activity, the comparison of such related series is of interest and is sometimes necessary for patent purposes. For these reasons we decided to prepare the 2-thienyl derivatives represented by formula II in which R represents an alkyl, alkenyl, cycloalkyl or aralkyl group.

The only series of thiophene-containing hydantoins previously reported was prepared by Spurlock.[2] This series consists of 5-R-5-(2-thienyl)-hydantoins where R may be an alkyl or a phenyl group. Careful studies[3] recently made employing the electroshock method with cats have indicated that at best these derivatives are equal in activity to the corresponding phenyl compounds and that as a rule they are inferior. Final proof of relative therapeutic effectiveness, however, must await clinical studies.

The compounds summarized in Table I were prepared by the general method outlined in the earlier paper.[1] 2-Thiophenealdehyde was treated with an amine and the resulting thenylidene R-amine was converted to the corresponding aminonitrile by the addition of hydrogen cyanide. Treatment with cyanic acid yields the desired hydantoin. The various intermediates were not isolated. As indicated in Table I, in most instances the yields were inferior to those obtained with benzaldehyde. No attempt was made to improve the method, as sufficient material for testing was obtained in each case.

**Pharmacology.**—Most of the compounds herein reported have been tested both for inhibition of electrically induced convulsions in cats and metrazol-induced convulsions in rats. The activities listed in Table I indicate that the lower members of the series are the more effective anticonvulsants. This is in accord with the results obtained with the corresponding phenyl derivatives reported in the earlier publication.[1]

In each case, those compounds exhibiting an activity of 4+ when administered to cats in doses of 100 mg./kg. showed a lower activity at 50 mg./kg. Thus, no member of the series is as active as Dilantin.[4]

(1) Long, Miller and Troutman, THIS JOURNAL, **70**, 900 (1948).

(2) Spurlock, U. S. Patent 2,366,221.

(3) Chen and Ensor, unpublished data.

(4) Dilantin, registered trade-mark of Parke, Davis & Co. for 5,5-diphenylhydantoin.

TABLE I

1-R-5-(2-THIENYL)-HYDANTOINS

| R | M. p., °C. | Yield, % | Formula | Nitrogen, % Calcd. | Found | Activity: Electro-shock[a] | Activity: Metrazol[b] |
|---|---|---|---|---|---|---|---|
| Methyl | 163–164 | 38 | $C_8H_8N_2O_2S$ | 14.28 | 14.29 | + | 4+/250 mg. |
| Ethyl | 163–165 | 49 | $C_9H_{10}N_2O_2S$ | 13.33 | 13.37 | 4+ | 3+/50 mg. |
| Propyl | 109–110 | 47 | $C_{10}H_{12}N_2O_2S$ | 12.49 | 12.68 | 4+ | 3+/125 mg. |
| Isopropyl | 173–174 | 28 | $C_{10}H_{12}N_2O_2S$ | 12.49 | 12.47 | 2+ | 4+/250 mg. |
| Allyl | 105–106 | 48 | $C_{10}H_{10}N_2O_2S$ | 12.61 | 12.38 | 4+ | 4+/125 mg. |
| Butyl | 123–125 | 47 | $C_{11}H_{14}N_2O_2S$ | 11.76 | 12.01 | + | 4+/250 mg. |
| *s*-Butyl | 148–150 | 7 | $C_{11}H_{14}N_2O_2S$ | 11.76 | 12.14 | | |
| 1-Methylbutyl | 136–137 | 14 | $C_{12}H_{16}N_2O_2S$ | 11.11 | 11.14 | | +/250 mg. |
| Cyclohexyl | 181–183 | 2 | $C_{13}H_{16}N_2O_2S$ | 10.60 | 10.60 | | |
| Benzyl | 191–193 | 35 | $C_{14}H_{12}N_2O_2S$ | 10.29 | 10.29 | + | 4+/500 mg. |
| Phenethyl | 156–157 | 61 | $C_{15}H_{14}N_2O_2S$ | 9.79 | 9.75 | + | 3+/250 mg. |

[a] These results were obtained with an oral dose of 100 mg. for each compound. For a discussion of the method see Putnam and Merritt, *Science*, 85, 525 (1937). [b] An activity of 4+ means that five out of five rats are completely protected against a convulsive dose of metrazol.

Although the activity against metrazol is obtained without evidence of depression, doses at higher levels than those given in Table I induce appreciable hypnosis. Such hypnotic activity is an undesirable characteristic when possessed by potential anticonvulsant compounds.

## Experimental

**Material.**—The 2-thiophenealdehyde employed in the preparation of all of the compounds listed in Table I was obtained from Arapahoe Chemicals, Inc. It was used without further purification. The various amines were supplied by Eastman Kodak Co. or by Sharples Chemicals Inc.

**1-Propyl-5-(2-thienyl)-hydantoin.**—Except for minor details the preparation of this compound is typical of the series. Aqueous solutions of methylamine and ethylamine were used in preparing the first two members of the series while anhydrous amines were added to aqueous mixtures of 2-thiophenealdehyde in all other preparations. The precipitation of 1-methyl-5-(2-thienyl)-hydantoin from aqueous alkali is best carried out by the addition of hydrochloric acid while carbon dioxide, either gaseous or solid, is completely satisfactory for precipitating the remaining members of the series.

To a mixture of 33.6 g. (0.3 mole) of 2-thiophenealdehyde and 30 ml. of water in a small flask fitted with a mechanical stirrer, a reflux condenser and a dropping funnel was added 18.9 g. (0.32 mole) of propylamine over a period of fifteen minutes. The mixture became quite warm. Stirring was continued for one hour and then the flask was immersed in an ice-bath.

In another flask, equipped with a stirrer and a thermometer, 125 ml. of 80% aqueous acetic acid was cooled to 0°. With slow stirring 22.8 g. (0.35 mole) of potassium cyanide was added in portions so that the temperature remained below 8°. When the addition was complete, stirring was continued until the temperature was 0°.

The cold solution was stirred while the mixture of thenylidene propylamine and water was added at a fairly rapid rate. The temperature remained below 5°. When the addition was complete, the mixture was allowed to cool to −5°. At this point 27 g. (0.32 mole) of potassium cyanate was added rapidly. There was a slight rise in temperature. The mixture was stirred for one-half hour while being cooled and then for an additional half hour at room temperature.

The mixture was again cooled to 0° and 100 ml. of concentrated hydrochloric acid was added dropwise, the temperature remaining below 15°. Stirring was continued for one-half hour followed by heating on a steam-bath for another half hour. The hot mixture was poured into 300 g. of chipped ice. A thick yellow liquid precipitated which solidified after several minutes. The solid product was filtered off and purified by solution in 300 ml. of 5% aqueous sodium hydroxide, charcoaling and reprecipitation with carbon dioxide. Recrystallization from benzene and ligroin resulted in only a slight increase in melting point.

**Acknowledgment.**—The authors wish to thank Mr. A. W. Spang for the analytical data recorded in Table I and Mr. Charles R. Ensor and Mrs. Isobel G. Clarke for technical assistance in determining the anti-convulsant activity of the compounds reported herein.

## Summary

A series of 1-R-5-(2-thienyl)-hydantoins has been prepared and tested for anticonvulsant activity. Those derivatives containing not more than three carbon atoms in the 1-substituent are the more active members of the series against electrically induced and metrazol-induced convulsions.

DETROIT, MICH. RECEIVED SEPTEMBER 27, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

# The Influence of N-Methylation upon the Electrical Conductivity of Dodecylammonium Chloride

BY A. W. RALSTON, F. K. BROOME AND H. J. HARWOOD

The substitution of the hydrogens of ammonia by alkyl groups is attended by an increase in basicity,[1] and Hall and Sprinkle[2] have shown that the introduction of one alkyl group into ammonia brings about a decided increase in basicity, a second alkyl group results in only a slight, further increase, whereas a third alkyl group produces a slight drop in basicity. The ionization constants of the tertiary amines are therefore comparable to those of the primary amines and are appreciably lower than those of the secondary amines. The long-chain, symmetrical secondary amines have been reported[3] to have much higher ionization constants than the primary amines, the values observed being essentially independent of the lengths of the hydrocarbon chains. The introduction of a fourth alkyl, or other hydrocarbon radical, into the amine molecule, with the formation of the quaternary ammonium compounds is accompanied by a profound change in the chemical and physical properties.[4] Certain of the quaternary ammonium bases, for example, tetramethylammonium hydroxide, are among the strongest bases known. In view of these facts we have undertaken a critical study of the effects of methylation upon the physical properties of dodecylammonium chloride and have studied the solubilities in water and in a number of organic solvents and also the electrical conductivities of aqueous solutions of dodecyl-, methyldodecyl-, dimethyldodecyl-, and trimethyldodecylammonium chlorides. This present paper reports the electrical conductivities of aqueous solutions of these compounds and compares their tendency toward colloid formation as portrayed by their conductivities. To our knowledge, no such studies have been previously made upon a comparable series of compounds.

## Experimental

**Preparation of Methyldodecylammonium Chloride.**—Dodecyl chloride was prepared from dodecyl alcohol (f.p. 24.0°) by treatment with gaseous hydrogen chloride using zinc chloride as the catalyst. Methylamine was purified as the benzal derivative. The reaction of the dodecyl chloride (331 g., 1.62 moles) with 458 g. of an ethanol solution containing 218 g. (7.04 moles) of methylamine was accomplished by heating the reactants in an autoclave at 125° for eight hours. After addition of 60 g. of sodium hydroxide, the excess methylamine was removed by distillation and the methyldodecylamine extracted with Skellysolve B and dried over potassium carbonate. Distillation through a Vigreux column yielded 258 g. (80%) of methyldodecylamine, b.p. 80–85° (0.4 mm.) and 56 g. (19%) of methyldidodecylamine, b.p. 180–185° (0.4 mm.). Purification of the methyldodecylamine was accomplished by fractionation through a Stedman-packed column. A fraction of the methyldodecylamine (f. p. 16.5°) was converted to the hydrochloride by treating its benzene solution with gaseous hydrogen chloride. The salt was recrystallized from benzene containing a little methanol.

*Anal.* Calcd.: N, 5.94. Found: N, 5.99.

**Preparation of Dimethyldodecylammonium Chloride.**—Dimethyldodecylamine was prepared in the manner previously described.[5] A fraction was converted to the hydrochloride by treatment of its ether solution with gaseous hydrogen chloride. The salt was recrystallized from ethyl acetate.

*Anal.* Calcd.: N, 5.61. Found: N, 5.68.

The conductivities were determined in the manner and with the equipment previously described.[6]

## Results and Discussion

The equivalent conductivities at 30° plotted against $\sqrt{N_V}$ of aqueous solutions of dodecyl-, methyldodecyl-, dimethyldodecyl- and trimethyldodecylammonium chlorides are shown in Fig. 1. The values for dodecylammonium chloride have been taken from a recent publication.[7] The

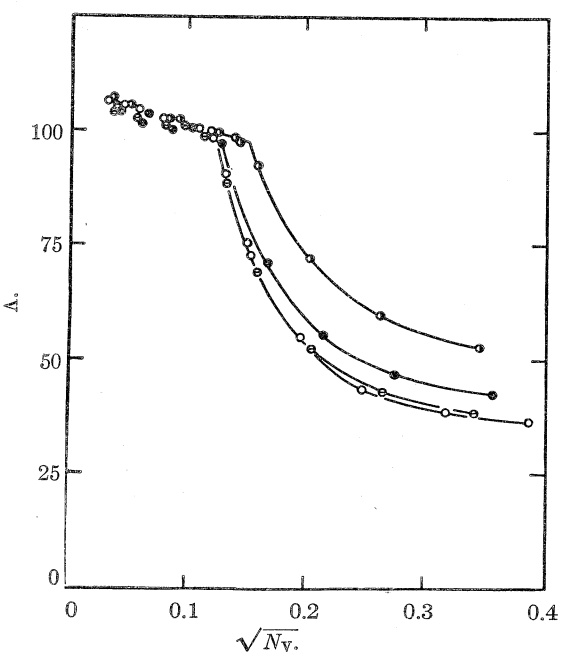



Fig. 1.—Equivalent conductivities of dodecylammonium chloride and N-methyl derivatives at 30°: ○, dodecylammonium chloride; ⊖, methyldodecylammonium chloride; ●, dimethyldodecylammonium chloride; ◑, trimethyldodecylammonium chloride.

(1) Bredig, *Z. physik. Chem.*, **13**, 191 (1894).
(2) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).
(3) Hoerr, McCorkle and Ralston, *ibid.*, **63**, 328 (1943).
(4) Flürscheim, *J. Chem. Soc.*, **95**, 718 (1909).
(5) Reck, Harwood and Ralston, *J. Org. Chem.*, **12**, 517 (1947).
(6) Ralston, Hoerr and Hoffman, THIS JOURNAL, **64**, 97 (1942).
(7) Ralston and Eggenberger, *ibid.*, **70**, 436 (1948).

curves show that the conductivities of dodecyl- and methyldodecylammonium chlorides are almost identical, indicating that the transition from the primary to the secondary amine salt is not accompanied by a significant change in solution behavior. The tertiary amine salt, dimethyldodecylammonium chloride, has a somewhat higher concentration at the critical point and a higher equivalent conductivity at concentrations beyond the critical point. A much larger difference is encountered in going from the tertiary amine hydrochloride to the quaternary ammonium chloride. Trimethyldodecylammonium chloride has a significantly higher critical concentration and a much higher equivalent conductivity beyond this point. The values of $\Lambda_0$, $\Lambda_c$, $\sqrt{N_c}$, and $N_c$ for these four salts are shown in Table I.

TABLE I

| Compound, chloride | $\Lambda_0$ | $\Lambda_c$ | $\sqrt{N_c}$ | $N_c$ |
|---|---|---|---|---|
| Dodecylammonium | 108.5 | 100.0 | 0.121 | 0.0146 |
| Methyldodecylammonium | 107.9 | 99.1 | .121 | .0146 |
| Dimethyldodecylammonium | 109.2 | 98.1 | .127 | .0161 |
| Trimethyldodecylammonium | 109.8 | 97.8 | .151 | .0228 |

These values together with the curves in Fig. 1 show that for this series of salts the greatest change in conductivity behavior occurs in going from the tertiary amine salt to the quaternary ammonium salt. The colloidal state, as evidenced by the values of $N_c$, is assumed at the same concentration for the salts of the primary and secondary amines, at a somewhat higher concentration for the tertiary amine salt and at a materially higher concentration for the quaternary ammonium salt. The values of $\Lambda_c$ undergo a progressive, small decrease in going from the primary to the quaternary ammonium salt. The conductivities of these four salts at concentrations lower than the critical concentration are not significantly different as shown by the small differences in the values of $\Lambda_0$.

## Summary

1. The equivalent conductivities of aqueous solutions of dodecyl-, methyldodecyl-, dimethyldodecyl-, and trimethyldodecylammonium chlorides have been determined.

2. The greatest difference in these values is observed in going from dimethyldodecylammonium chloride to trimethyldodecylammonium chloride.

CHICAGO, ILLINOIS RECEIVED OCTOBER 1, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

# The Electrical Conductivities of Tris-(hydroxyalkyl)-alkylammonium Chlorides

BY A. W. RALSTON, D. N. EGGENBERGER AND H. J. HARWOOD

The substitution of short-chain hydroxyalkyl groups for methyl groups in trimethylalkylammonium chlorides renders the long-chain cations more hydrophilic and should result in a modification of the colloidal properties portrayed by the electrical conductivities of aqueous solutions. In contrast to this expectation, it recently has been shown[1] that the progressive substitution of 2-hydroxyethyl groups for methyl groups in trimethylhexadecylammonium chloride does not bring about a significant change in either the equivalent conductivity or the concentration at the critical point. Substitution of one of the methyl groups in trimethylhexadecylammonium chloride by a 2,3-dihydroxypropyl group is likewise not attended by a noticeable change in the critical concentration. The critical concentration of trimethyldodecylammonium chloride is materially greater than that of trimethylhexadecylammonium chloride, thus manifesting that the colloidal state is not so readily assumed with the former salt as with the latter. As a consequence, the incorporation of hydroxyalkyl groups into a trimethyldodecylammonium salt should have a greater relative effect upon its colloidal properties than a similar incorporation into a trimethylhexadecylammonium salt. The present paper discusses the effect of the substitution of the methyl groups in trimethyldodecylammonium chloride by hydroxyethyl and 2,3-dihydroxypropyl groups and compares these effects with similar substitutions in the hexadecyl homolog.

(1) Ralston, Eggenberger, Harwood and Du Brow, THIS JOURNAL, **69**, 2095 (1947).

## Experimental

**Preparation of tris-(2,3-Dihydroxypropyl)-dodecylammonium Chloride.**—To a solution of 38 g. of sodium hydroxide in 400 cc. of ethanol was added 80 g. of dodecylamine (f. p. 28.2°). The solution was cooled to 15° and to it was added 120 g. of glycerol 1-chlorohydrin. The reaction which occurred was accompanied by an appreciable rise in temperature. After standing overnight the sodium chloride was filtered off and the ethanol distilled, the last traces of solvent being removed under reduced pressure. Without purification, the bis-(2,3-dihydroxypropyl)-dodecylamine was treated with 47.8 g. of glycerol 1-chlorohydrin and the mixture heated on the steam-bath at 100° for sixteen hours. Attempts to purify the product by crystallization from a number of solvents were unsuccessful. Some purification was achieved by dissolving the quaternary ammonium salt in ethyl acetate (700 cc.) containing methanol (35 cc.) and cooling the solution to −10°. The upper layer was decanted and the process repeated. After removal of the solvent under reduced pres-

sure the product was dried *in vacuo* over calcium chloride. The tris-(2,3-dihydroxypropyl)-dodecylammonium chloride was obtained as a sticky, plastic mass. A purity of 95% was indicated by titration with standard sodium dodecyl sulfate using dichlorofluorescein as indicator.

**Preparation of tris-(2,3-Dihydroxypropyl)-hexadecylammonium Chloride.**—This compound was prepared from hexadecylamine according to the above procedure. It was obtained as a plastic mass with an indicated purity of 100%.

**Preparation of tris-(2-Hydroxyethyl)-dodecylammonium Chloride.**—This was prepared from dodecylamine and ethylene chlorohydrin in a manner similar to that described above. The product was a white, crystalline solid which was somewhat hygroscopic. The indicated purity was 100%.

The electrical conductivities of solutions of the quaternary ammonium salts were determined in the manner and with the equipment previously described.[2]

## Results and Discussion

The equivalent conductivities plotted against $\sqrt{N_v}$ of dodecyltrimethylammonium chloride, tris-(2-hydroxyethyl)-dodecylammonium chloride, and tris-(2,3-dihydroxypropyl)-dodecylammonium chloride are shown in Fig. 1. Substitution of the three methyl groups of trimethyldodecylammonium chloride by hydroxyethyl groups enhances the colloidal properties as evidenced by the decrease in the critical concentration. The equivalent conductivity of tris-(2-hydroxyethyl)-dodecylammonium chloride is higher than that of trimethyldodecylammonium chloride at concentrations below the critical point; however, it is significantly lower at the higher concentrations. The difference in these curves may be explained on the basis of a greater tendency toward solubilization of the tris-(2-hydroxyethyl)-dodecylammonium chloride. Substitution of the three methyl groups by 2,3-dihydroxypropyl groups brings about a profound change in the nature of the conductance curve. Tris-(2,3-dihydroxypropyl)-dodecylammonium chloride shows a greatly decreased conductivity over the entire concentration range investigated, the curve having little similarity to those of typical colloidal electrolytes. The incorporation of the six hydroxyl groups into the molecule is therefore attended by a decided modification of the colloidal behavior as evidenced by the absence of a well-defined critical point.

Figure 2, which compares the equivalent conductivities of trimethylhexadecylammonium chloride and tris-(2,3-dihydroxypropyl)-hexadecylammonium chloride, shows that both these compounds function as typical cationic electrolytes. This behavior is in sharp contrast to that of the dodecyl homologs and indicates that the paraffin nature of the hexadecylammonium ion is not decidedly modified by the introduction of three 2,3-dihydroxypropyl groups.

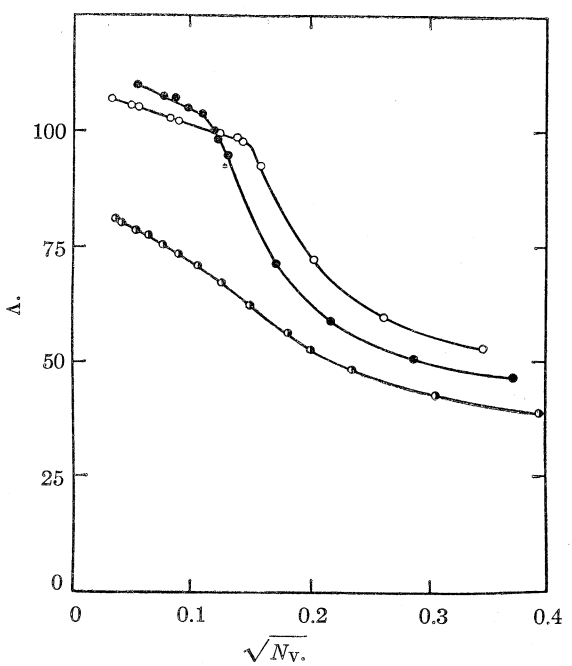



Fig. 1.—Equivalent conductivities of hydroxyalkyldodecylammonium chlorides at 30°: O, dodecyltrimethylammonium chloride; ●, tris-(2-hydroxyethyl)-dodecylammonium chloride; ◑, tris-(2,3-dihydroxypropyl)-dodecylammonium chloride.

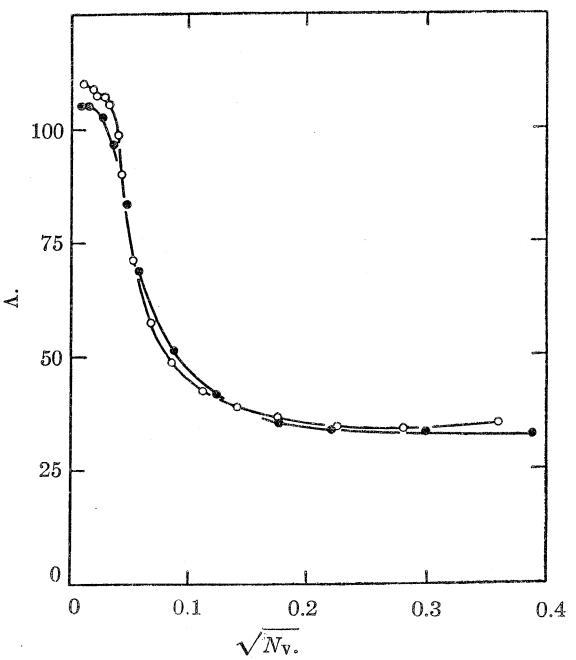



Fig. 2.—Equivalent conductivities of hexadecyltrimethylammonium chloride and tris-(2,3-dihydroxypropyl)-hexadecylammonium chloride at 30°: O, hexadecyltrimethylammonium chloride; ●, tris-(2,3-dihydroxypropyl)-hexadecylammonium chloride.

## Summary

1. The equivalent conductivities of trimethyldodecyl-, tris-(2-hydroxyethyl)-dodecyl-, tris-(2,3-dihydroxypropyl)-dodecyl-, trimethylhexadecyl-

(2) Ralston, Hoerr and Hoffman, *ibid.*, **64**, 97 (1942).

and tris-(2,3-dihydroxypropy)-hexadecylammonium chlorides have been compared.

2. The substitution of hydroxyethyl groups for methyl groups in trimethyldodecylammonium chloride does not greatly modify the colloidal properties; however, the substitution of 2,3-dihydroxypropyl groups results in a decided modification. A similar substitution in trimethylhexadecylammonium chloride is without a significant effect.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

# The Dissociation Constants of Some Mono-substituted Benzeneseleninic Acids[1]

BY JAMES D. McCULLOUGH AND EDWIN S. GOULD

## Introduction

The benzeneseleninic acids are white crystalline solids analogous to benzenesulfinic acids in the sulfur series. They are weak acids of strengths comparable to that of acetic acid. A series of thirteen of these compounds has been prepared, six members of which have not been previously described in the literature. Acidic dissociation constants were determined by titration of approximately 0.005*F* solutions of the acids with standard (0.1*N*) carbonate-free sodium hydroxide using a model H Beckman *p*H meter. The dissociation constants thus obtained have been correlated with the Hammett $\rho$–$\sigma$ treatment[2] and a $\rho$ value for the ionic dissociation observed. The effects of small temperature changes on the dissociation constants have been noted for a number of the acids and have been found to be similarly small.

## Experimental

I. **Syntheses.**—The seleninic acids were prepared from the corresponding diselenides through oxidation with concentrated hydrogen peroxide.

$$R_2Se_2 + 3H_2O_2 = 2RSeO_2H + 2H_2O \qquad (1)$$

A. **Preparation of Diselenides.**—The diselenides were prepared by the two methods described by Campbell and McCullough.[3] The numbers in Table I refer to the numbering of the methods used by those authors.

B. **Oxidation of Diselenides.**—Two methods were employed depending on whether the diselenide was liquid or solid.

1. **Solid Diselenides.**—Ten grams of the diselenide was added to 10 ml. of 1,4-dioxane and the mixture warmed to about 60° to dissolve as much solid as possible. It was then cooled to below 5° and C. P. concentrated hydrogen peroxide (20–28%) was added dropwise, stirring the mixture and cooling externally to keep the temperature under 10°. After addition of a threefold excess of peroxide, fifteen grams of ice was added and the resulting solid (which was almost white) was filtered off and washed with 10 ml. of ice water.

2. **Liquid Diselenides.**—Ten grams of the diselenide was dissolved in 15 ml. of diethyl ether. Concentrated hydrogen peroxide was added dropwise; but after each five or six drops, the solution was swirled vigorously over a warm water-bath at 45° to ensure as complete a reaction as possible. If the temperature of the mixture rose above 38°, it was cooled to below 34°, ether being added from time to time to replace that lost by evaporation. After addition of a threefold excess of peroxide, the ether was stripped off at room temperature with a water pump, leaving a mixture of white seleninic acid and orange oil impurities.

If the amount of orange oil was excessive, 30 cc. of 6*N* ammonia was added to the residue, dissolving the acid. The solution was washed twice with 20-ml. portions of ether, removing a large part of the orange residue. The aqueous layer was acidified with dilute sulfuric acid, and an excess of potassium iodide was added along with an additional 15 ml. of ether to reduce the acid back to the original diselenide. The mixture was shaken thoroughly, and just enough sodium thiosulfate solution was added to reduce the $I_3^-$ formed. The ether layer, containing the diselenide, was separated, washed twice with dilute sodium hydroxide, twice with distilled water, and reoxidized with hydrogen peroxide as before.

C. **Purification Method.**—One of two methods was used, depending upon the solubility in water of the seleninic acid involved.

1. **Slightly Soluble Acids.**—A ten per cent. excess of 15*N* ammonia was added to the solid acid, and the solution was stirred until no white solid remained. The solution was filtered, decolorized twice with Norite, and the acid reprecipitated by slow addition of C. P. 6 *N* hydrochloric acid. The solid was washed with ice water, dissolved in a minimum volume of methanol, and the methanolic solution added dropwise to boiling water until cloudiness formed. At that point, 25% more boiling water was added, the solution filtered hot, decolorized if necessary, then cooled rapidly with scratching to 0°. After thirty minutes, the crystallized acid was filtered off and recrystallized as before, this time cooling very slowly. The crystals, usually needles, were filtered off, dried in a vacuum desiccator over calcium chloride for two days, and a preliminary melting point taken. If the melting point was above 120°, the acid was dried in an oven for an hour at 90°. If the melting point was below 120°, the solid was kept in the vacuum desiccator for three additional days. Difficulty was encountered in removing the last traces of water from the solid; for if it were dried too persistently, the product turned pink, indicating decomposition. For this reason, the equivalent weights of some of the acids were as much as 1% low while some were 3 or 4% high. This difficulty should not, however, affect the accuracy of the dissociation constants.

2. **Soluble Acids.**—If the acid was quite soluble in cool water, treatment with ammonia was omitted, the crude product dissolved directly in a minimum quantity of hot (but not boiling) water (80°), the solution filtered hot, decolorized with norite until a pale yellow, and the acid reprecipitated by cooling. A second recrystallization was then made. The drying procedure was that described above.

D. **Special Method.**—*m*-Nitrobenzeneseleninic acid was prepared by nitration of benzeneseleninic acid nitrate as described by Friend.[4] The procedure was modified by

(1) Based on research carried out under Task Order I of Contract N6onr-275, between the Office of Naval Research and the University of California, Los Angeles. Presented at the Chicago meetings of the American Chemical Society, April, 1948.

(2) Louis P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1941.

(3) Tod W. Campbell and James D. McCullough, THIS JOURNAL, 67, 1965 (1945).

(4) Friend, "Text-book of Inorganic Chemistry," Vol. XI, Charles Griffin and Company, Ltd., London, 1937, p. 48.

TABLE I

IONIZATION CONSTANTS FOR SUBSTITUTED BENZENESELENINIC ACIDS

| | Substituent | Preparation D | O | P | M. p., °C. | $pK_{25°}$ | $n$ | Mean dev. | $\sigma$ | Equivalent weight Theor. | Acid | Ox. × 3[5] | Se, % Theor. | Anal.[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | None | 2 | 1 | 2 | 121 | 4.79 | 4 | 0.03 | 0.00 | 189.2 | 188.2 | 189.8 | 41.7 | 41.7 |
| 2 | *p*-$CH_3$ | 2 | 1 | 1 | 170 | 4.88 | 3 | .05 | − .170 | 203.2 | 206.3 | | | |
| 3 | *m*-$CH_3$ | 1 | 2 | 2 | 121 dec. | 4.80 | 3 | .03 | − .069 | 203.2 | 208.2 | | | |
| 4 | **p*-F | 1 | 2 | 2 | 132–140 dec. | 4.50 | 2 | .005 | .062 | 207.2 | 205.3 | 206 | 38.1 | 38.8 |
| 5 | **m*-F | 1 | 2 | 2 | 115–124 dec. | 4.34 | 2 | .003 | .337 | 207.2 | 212.2 | 209 | 38.1 | 38.5 |
| 6 | *p*-Cl | 2 | 1 | 1 | 170–185 | 4.48 | 3 | .006 | .227 | 223.7 | 229.3 | | | |
| 7 | *m*-Cl | 1 | 1 | 1 | 145–147 dec. | 4.47 | 3 | .06 | .373 | 223.7 | 224.3 | 223 | | |
| 8 | *p*-Br | 2 | 1 | 1 | 177–181 | 4.50 | 3 | .03 | .232 | 268.1 | 269.7 | 268 | | |
| 9 | **m*-Br | 1 | 1 | 1 | 157–159 | 4.43 | 3 | .01 | .391 | 268.1 | 269.5 | 270 | | |
| 10 | **p*-$CH_3O$ | 1 | 2 | 2 | 101 | 5.05 | 2 | .01 | − .268 | 219.2 | 219.4 | | | |
| 11 | **m*-$CH_3O$ | 1 | 2 | 2 | 118 | 4.65 | 2 | .01 | .115 | 219.2 | 220.0 | 220 | 36.1 | 35.6 |
| 12 | *m*-$NO_2$ | | | 2 | 152 | 4.07 | 2 | .02 | .710 | 234.2 | 236.3 | 235 | | |
| 13 | **o*-$C_6H_5$ | 2 | 2 | 2 | 89 | 4.67 | 1 | ... | None | 263.2 | 263.0 | 264 | 30.0 | 29.7 |

* Denotes new compound. D, denotes method of preparation of diselenide. O, denotes oxidation method. P, denotes purification method. $n$, denotes the number of determinations. $\sigma$, denotes Hammett's substituent constant.

reducing the heating time to thirty minutes and by diluting the starting material with an equal weight of concentrated nitric acid. The product is white, not yellow, as reported by Friend. (It is possible that the di-nitro compound is described.)

### II. Physical Measurements

A half-millimole sample of acid was weighed into a 250-ml. beaker and dissolved in 100 ml. of distilled water previously boiled twenty minutes to remove carbon dioxide. The titration was made with standard, approximately 0.1 *N* carbonate-free sodium hydroxide delivered from a 10-ml. buret. The solution was stirred and protected from carbon dioxide during the titration. Readings were taken with a Beckman Model H *p*H meter at the start and after each milliliter of base added. In the region of the end-point the *p*H value was read at each drop. The temperature of the solution was noted during each titration. The equivalence point was assumed to be at a *p*H value of 8.0 and the *p*H at half-neutralization was obtained either by interpolation or graphically. Complete titration curves were prepared for a number of the acids and with the remainder, readings were taken only in the vicinities of the half-neutralization and the equivalence points. In order to get an approximate evaluation of the temperature coefficients of the dissociation constants, the *p*H at half-neutralization was determined at both 25 and 35° for five of the acids.

## Results and Discussion

A typical titration curve, that for the *p*-methoxy acid, is shown in Fig. 1. A summary of results is shown in Table I. The melting points are in some cases rather sharp while in others a decomposition takes place which appears to involve a loss of water to give the anhydride. Further heating then causes the anhydride to melt. This behavior is noted for some acids in the table. The rather large discrepancies between the observed and theoretical equivalent weights is probably due to the difficulty of drying the acids without decomposition as previously noted. The tendency toward high experimental values is probably due to incomplete drying. This should not affect the accuracy of the *pK* values determined.

(5) McCullough, Campbell and Krilanovich, *Anal. Chem.*, **18**, 638 (1946).

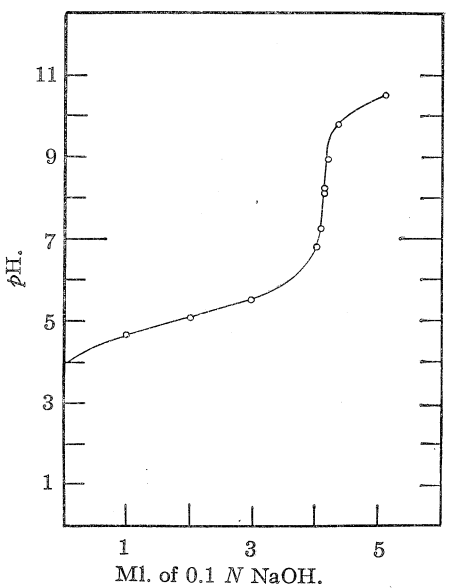



Fig. 1.—Titration curve for *p*-methoxybenzeneselenic acid.

In calculating the *pK* values from the *p*H at half-neutralization, correction was made for the activity coefficient of the acid anion. This was done as follows

$$K = \frac{a_{H^+}a_{X^-}}{a_{HX}} = \frac{a_{H^+}C_{X^-}\gamma_{\pm}}{C_{HX}\gamma_{HX}} \quad (1)$$

Since the activity coefficient of the un-ionized acid is practically unity, we have

$$-\log K = -\log a_{H^+} - \log \frac{C_{X^-}}{C_{HX}} - \log \gamma_{\pm} \quad (2)$$

or

$$pK = pH - \log \frac{C_{X^-}}{C_{HX}} - \log \gamma_{\pm} \quad (3)$$

At the half-neutralization point

$$C_{X^-} = C_{HX} \quad (4)$$

so that

$$pK = (p\mathrm{H})_{1/2} - \log \gamma_{\pm} \quad (5)$$

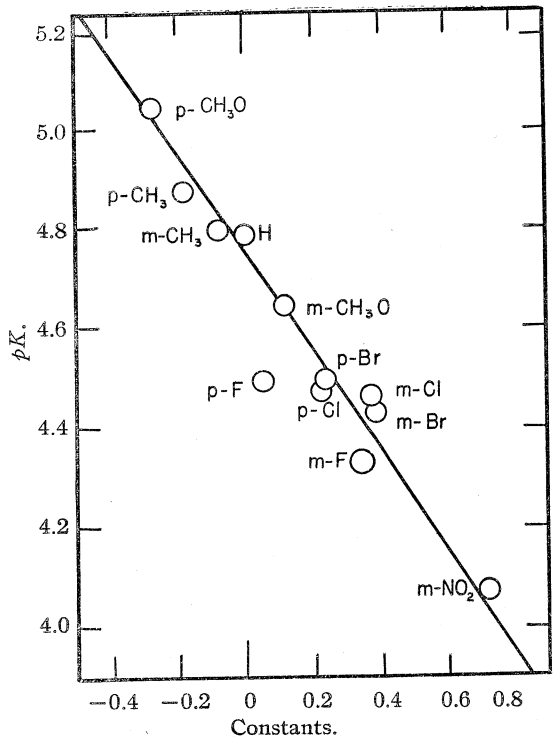



Fig. 2.—Plot of $pK$ *vs.* Hammett's substituent constants.

Since

$$-\log \gamma_{\pm} = 0.505 Z_a^2 \sqrt{\mu} \quad (6)$$

this term has the value 0.025 under our experimental conditions, which leads to

$$pK = (p\mathrm{H})_{1/2} + 0.025 \quad (7)$$

A plot of the $pK$ values at 25° is made against Hammett's substituent constants ($\sigma$ values) in Fig. 2 and it is seen that a good approximation to a straight line results. The best straight line through the points has a slope of 1.0 which indicates that the ionization constants of the benzeneseleninic acids have the same susceptibility toward substituents as do the benzoic acids which were the source of the $\sigma$ values.

The $pK$ values of the benzeneseleninic acids are rather insensitive to changes of temperature. The five acids investigated were the parent acid, *p*-$CH_3$, *m*-$CH_3$, *p*-Cl and *m*-Cl. In all cases the $pK$ increased approximately 0.02 unit per 10° rise in temperature in the range 25–40°.

## Summary

1. Thirteen benzeneseleninic acids have been prepared, six of which are new. Methods of preparation are described.

2. The ionization constants (as $pK$) of these acids have been determined by potentiometric titration using a Beckman $p$H meter. The $pK$ values thus found are a linear function of Hammett's $\sigma$ values.

3. Approximate temperature coefficients of the $pK$ values have been noted for five of the acids.

RECEIVED NOVEMBER 9, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

# The Surface Tension of Aqueous Sulfuric Acid Solutions at 25°

BY R. M. SUGGITT, P. M. AZIZ AND F. E. W. WETMORE

**Introduction.**—In this Laboratory we required values of the surface tension of sulfuric acid solutions at 25° up to the concentration corresponding to maximum conductivity. Morgan and Davis[1] reported values obtained by the drop-weight method; later Harkins and Brown[2] showed that certain corrections must be applied in using this method, but until now the corrected values have not been reported. More recently Sabinina and Terpugow[3] presented data obtained by the method of capillary rise, but gave no experimental details and reported no values for solutions less than 23% by weight acid.

The differential maximum bubble pressure technique described by Sugden[4] was chosen for our measurements, not only because it involves bubble formation which parallels the experimental arrangement for which we required the data, but also because choice of this technique would afford comparison of data obtained by three different methods.

(1) Morgan and Davis, THIS JOURNAL, **38**, 555 (1916).
(2) Harkins and Brown, *ibid.*, **41**, 499 (1919).
(3) Sabinina and Terpugow, *Z. physik. Chem.*, **A173**, 237 (1935).
(4) Sugden, "The Parachor and Valency," George Routledge and Sons, London, 1930, p. 208.

## Experimental

The solutions were made from C. P. sulfuric acid and twice-distilled water. The individual solutions were standardized by precipitation of barium sulfate and by titration against freshly prepared sodium carbonate.

The apparatus, as shown in Fig. 1, consisted of a pressure generator G and reservoir R (20 liters) connected to the bubble-forming tubes immersed in the liquid, and a sensitive manometer M attached as closely as possible to the tubes. The pressure generator consisted simply of a fine oil stream admitted to a bottle at controlled rate; thus the head required to form bubbles could be maintained at any slow rate of air flow to the tubes. The reservoir minimized pressure fluctuations during the measurements. A connection C to the compressed air line served for setting the initial pressure roughly. The manometer was a water-filled 6 mm. i.d. U-tube enclosed in a thermally lagged box. A glass scale ruled at 0.5 mm.

intervals was set directly behind the U-tube; at the front a vertical square bar carried two vertically adjustable channels in which were set micrometer telescopes on ground slides for forward adjustment. The liquid level was determined by focussing a telescope on the meniscus and reading the micrometer graticule; the telescope was then run forward to bring the glass scale into focus and readings on the graticule taken for the nearest scale lines above and below the meniscus reading. By interpolation the meniscus level was referred to the glass scale. Readings of level difference could be made to 0.001 mm., an order of magnitude better than required.

Precision-bore Pyrex tubing was used for the bubble-forming tubes. The ends to be immersed were ground normal to the bore with very fine carborundum on a rotating linen disc; during this grinding the possibility of crushing or flaring of the bore was avoided by filling the end of the tube with deKhotinsky cement. The chipped edges left from the manufacturer's grinding were thus removed until microscopic examination showed a sharply circular bore. The outside diameter of both tubes was about 6 mm., the internal diameters, respectively, 0.227 and 0.454 mm., as measured with a microscope and graticule and with the ratio confirmed by the data obtained for water. The manufacture of precision-bore tubing in recent years has made possible the happy choice of tubes with bore ratio 2:1. The tubes were held in universally adjustable supports mounted in a framework which in turn was attached to a large cylindrical post with a clamping sleeve. By means of this arrangement the tubes were set vertically parallel; later they could be removed from liquid and reimmersed without change of slant or relative height. The small difference in level of the tips of the two tubes was determined with a micrometer telescope by measurement of the distance from each tip to the surface of a pool of mercury. The difference was confirmed during the runs. The liquid under test was maintained at 25.00 ± 0.02° with a conventional thermostat T. The temperature was determined with a thermometer calibrated by comparison with a platinum resistance thermometer.

With sufficiently slow formation of bubbles the maximum bubble pressure is independent of the rate of formation. Following preliminary tests the rate was set at one bubble every seven seconds (not critical). The pressure reading of the manometer slowly rose as the bubble nucleus expanded, dropping suddenly when the bubble exceeded the critical size; the maximum pressure was recorded. Every determination on a solution was preceded by one on water. Only with meticulously cleaned tubes could the readings be duplicated from one day to another.

## Experimental Results

In Table I are recorded duplicate readings of pressure differences found for the two tubes, in terms of the solution at 25° as the manometric liquid. With the exception of one number patently in error, no readings were found outside the limits of the duplicates shown. Values of the surface tension $\gamma$ were calculated through the method of successive approximation recommended by Sugden and the average value for each solution is recorded in Table 1. These values are based on

TABLE I

SURFACE TENSION OF AQUEOUS SULFURIC ACID AT 25°

| Acid, % | Press. diff. in mm. | | $\gamma$ | $\Delta$ |
|---|---|---|---|---|
| 4.11 | 63.24 | 63.24 | 72.21 | 0.24 |
| 8.26 | 61.85 | 61.83 | 72.55 | 0.58 |
| 12.18 | 60.48 | 60.46 | 72.80 | 0.83 |
| 17.66 | 58.86 | 58.84 | 73.36 | 1.39 |
| 21.88 | 57.66 | 57.66 | 73.91 | 1.94 |
| 29.07 | 55.66 | 55.65 | 74.80 | 2.83 |
| 33.63 | 54.42 | 54.43 | 75.29 | 3.32 |

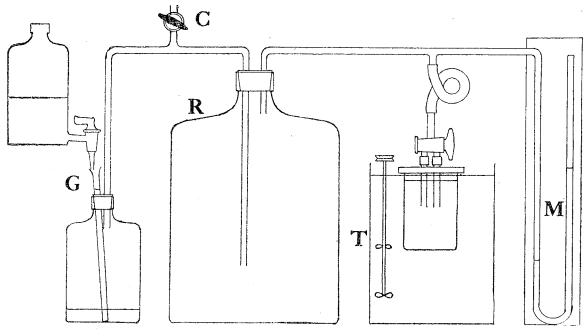



Fig. 1.—Experimental arrangement.

the assumption that the surface tension of water at 25°, $\gamma_0$, is 71.97 dynes/cm.[5] The increment of the surface tension of a solution over that of pure water, $\Delta = \gamma - \gamma_0$, is given as the more suitable recording of the data, since it is independent of small variations in $\gamma_0$ and will serve at any later time for calculating $\gamma$ by adding it to the then acceptable value of $\gamma_0$.

**Correction of the Data of Morgan and Davis.**—The values reported by Morgan and Davis were calculated from the formula $\gamma' = 936.0\ w$ (Eqn. 1), in which $\gamma'$ is the uncorrected surface tension, 936.0 a quantity dependent on the radius of their tube, but not, by their assumption, on the composition of the liquid, and $w$ is the average drop-weight in grams. Harkins and Brown suggested the form $\gamma = w\phi/r$ (Eqn. 2), in which $\gamma$ is the corrected surface tension, $r$ the radius of the tube, and $\phi$ is an empirical term depending on $r$ and the cube root of the volume, $v$, of one drop. The value of $v$ can be determined from the density of the liquid and the value of $w$ calculated through Eqn. 1. It so happens that $\phi$ can be expressed as a linear function of the variable $r/v^{1/3}$ over a range sufficient for the calculations here: $\phi = A + Br/v^{1/3}$ (Eqn. 3), *e. g.*, for $r/v^{1/3} = 0.61$ to 0.64, $A = 207.6$ and $B = 70$. Thus $r$ can be calculated by substituting in

TABLE II

SURFACE TENSION OF AQUEOUS SULFURIC ACID, CORRECTED DATA OF MORGAN AND DAVIS

| | $\Delta$ | | | |
|---|---|---|---|---|
| Acid, % | 0° | 30° | 50° | 25° (calcd.) |
| 4.67 | −0.23 | 0.24 | 0.45 | 0.17 |
| 8.93 | −0.17 | 0.49 | 0.83 | 0.39 |
| 16.40 | 0.42 | 1.21 | 1.67 | 1.09 |
| 22.73 | 0.98 | 2.08 | 2.63 | 1.92 |
| 28.18 | 1.60 | 2.68 | 3.45 | 2.49 |
| 32.90 | 2.06 | 3.28 | 4.26 | 3.06 |
| 37.05 | 2.28 | 3.75 | 4.81 | 3.50 |
| 40.71 | 2.41 | 4.13 | 5.31 | 3.84 |
| 45.46 | 2.47 | 4.41 | 5.74 | 4.08 |
| 49.51 | 2.03 | 4.39 | 5.88 | 4.01 |

(5) "International Critical Tables," Vol. IV, p. 447. In a recent private communication Professor F. E. Bartell of the University of Michigan has kindly offered the value 72.00 at 25° as part of a corrected series to be published by him shortly. This corrected value will be useful in obtaining $\gamma$ more accurately, but its use does not change the values of $\Delta$ cited here.

Eqn. 2 an acceptable value of $\gamma$ and in Eqn. 2 and 3 the values of $v$ and $w$ found as shown above. The data of Morgan and Davis for water and the more acceptable values of $\gamma_0$[5] give $r$ at 0, 30 and 50° as 0.2687, 0.2686 and 0.2685 cm., respectively; one would expect a small opposite thermal variation. The effective radius was taken as 0.2686 cm. and through Eqn. 1, 2 and 3 values of $\gamma$ were calculated from the data of Morgan and Davis. In Table II are shown the corrected values of $\Delta$, along with values for 25° obtained by parabolic interpolation of these data for 0, 30 and 50°.

**Comparison of Data.**—Table III shows the data of Sabinina and Terpugow for 10, 20, 30, 40 and 50°, as well as values for 25° obtained by graphical interpolation rather than the linear interpolation they used.

In Fig. 2 the data for 25° from the three experimental methods are compared. The line has been drawn to give a minimum square deviation of the points, without weighting. The circles have radius equal to 0.07 unit, or about 0.1% of $\gamma$. In Table IV are given the values of $\Delta$ corresponding to the mean curve of Fig. 2. Over the range 0 to 35% acid the points show an average vertical deviation of 0.07 unit, or 0.1% of $\gamma$. It is quite apparent that the data from the work of Morgan and Davis lie consistently below the other two sets; a part of this difference may have arisen in the parabolic interpolation, but undoubtedly a part is due to difference in the experimental method used.

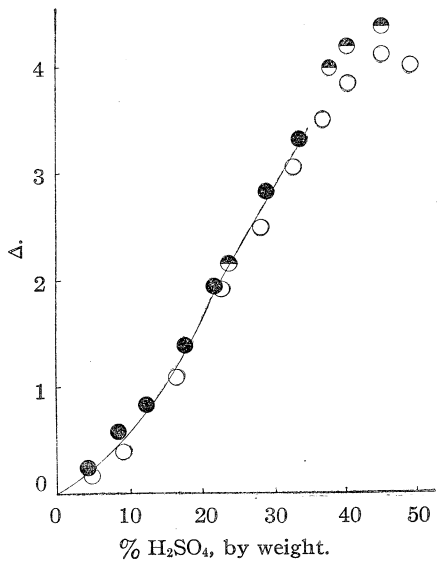



Fig. 2.—Surface tension of sulfuric acid at 25°: ○, Morgan and Davis; ◓, Sabinina and Terpugow; ●, Suggitt, Aziz and Wetmore.

TABLE III

SURFACE TENSION OF AQUEOUS SULFURIC ACID, DATA OF SABININA AND TERPUGOW

| | Δ | | | | | |
|---|---|---|---|---|---|---|
| Acid, % | 10° | 20° | 30° | 40° | 50° | 25° (calcd.) |
| 23.80 | 1.56 | 1.90 | 2.45 | 3.08 | 3.75 | 2.16 |
| 38.00 | 3.09 | 3.66 | 4.33 | 5.00 | 5.75 | 3.99 |
| 40.61 | 3.24 | 3.88 | 4.53 | 5.36 | 6.10 | 4.19 |
| 45.43 | 3.39 | 4.04 | 4.75 | 5.68 | 6.53 | 4.38 |

TABLE IV

SURFACE TENSION OF AQUEOUS SULFURIC ACID AT 25°, MEAN VALUES

| Acid, % | 5 | 10 | 15 | 20 | 25 | 30 | 35 |
|---|---|---|---|---|---|---|---|
| Δ | 0.24 | 0.58 | 1.02 | 1.63 | 2.27 | 2.85 | 3.42 |

## Summary

1. The surface tension of aqueous sulfuric acid at 25° has been determined over the range 0 to 33% acid by means of the differential maximum bubble pressure method.

2. The data of Morgan and Davis obtained by the drop-weight method have been recalculated in accordance with the corrections of Harkins and Brown.

3. Surface tension values obtained by three different methods have been compared.

TORONTO, CANADA RECEIVED MAY 24, 1948

[CONTRIBUTION FROM UNIVERSITY OF MISSOURI, SCHOOL OF MINES, DEPARTMENT OF METALLURGY]

# The Sodium Tungsten Bronzes. I. Chemical Properties and Structure

BY M. E. STRAUMANIS

## Introduction

The tungsten bronzes were discovered by F. Wöhler in 1824.[1] Since they have metallic properties, the name "tungsten bronzes" was applied, although they are neither alloys nor intermetallic compounds.

Later the "bronzes" were investigated by Brunner,[2] Spitzin[3] and others. W. F. de Jong found that the bronzes have the perovskite ($CaTiO_3$) type of structure and that the formula of the yellow bronze must be $NaWO_3$.[4] G. Hägg confirmed this statement and showed (1) that tungsten in the yellow bronze is pentavalent, (2) that sodium metatungstate and tungstic oxide form solid solutions with lattice contraction and change of color (from yellow through red and violet to dark blue) and (3) that the bronzes are very good electric conductors.[5]

The intention of this present work is to describe the still unknown qualities of tungsten bronzes and to find the end of the solid solution series.

## Preparation of the Bronzes

Because of the limited amount of the required high purity starting material (sodium tungstate, tungsten and tungstic oxide) available, the quantities of the bronzes obtained were insufficient for precise chemical analyses. In fact, chemical analyses are not necessary because the absorption of tungstic oxide by the bronze is accompanied by shrinkage of its lattice. This property was used to determine the composition of the resulting bronzes. The lattice constants were found by the powder method, applying the author's technique.[6] Although the work was not done in thermostats, the precision was sufficient to determine the tungstic oxide content of the bronzes with an accuracy of 0.1% by weight. The presence of other reaction products in the samples has also been confirmed by X-rays.

The purest yellow bronzes (without any excess tungstic oxide) have the highest lattice constants and they must be prepared first. It can be shown that these compounds become brighter when treated with sodium vapor. The reduction was carried out in small iron tubes (0.5 × 2 cm.); on the bottom of the tube there was a piece of sodium approximately 1 mm. in diameter; the rest of the tube was filled with bronze (*e. g.*, the blue); the tube was closed loosely with an iron stopper and then slipped into a slightly larger tube of "supremax" or quartz glass, which finally was evacuated, annealed and sealed off. On heating in a furnace at 700–800° the reaction was completed in half an hour. The reaction began at about 400°. The sodium vapor reacted to produce sodium tungstate and tungsten in the iron tube. On the top of these products were grains of yellow bronze, followed by grains of darker colored bronze. Powder diagrams of the bright yellow grains showed that the highest lattice constants obtained by Hägg[5] ($a$ = 3.850 kX) could be attained easily and even surpassed (see Table I).

TABLE I

HIGHEST LATTICE CONSTANTS OF THE YELLOW BRONZE, AFTER TREATMENT WITH LITHIUM OR SODIUM VAPOR, OR TUNGSTEN POWDER (UNDER FUSED $NaWO_4$)

| Sample | Reductant | $a$ in kX | Color |
|---|---|---|---|
| 81 | Li | 3.8479 | Golden |
| 76 | Na | 3.8479 | yellow |
| 183 | W | 3.8494 | Brighter golden yellow |
| 62 | Na | 3.8502 | Bright |
| 69 | Na | 3.8504 | yellow |
| 70 | Na | 3.8504 | Bright |
| 61 | Na | 3.8508 | yellow |
| 182 | W | 3.8520 | Bright |
| 182a | W | 3.8518 | yellow |

In the presence of tungsten under molten sodium tungstate the reaction evidently comes to equilibrium and an essentially purer bronze results. It is probable that sample 182 contains only a very small excess of $WO_3$.

This sample was prepared according to the reaction

$$3Na_2WO_4 + 2WO_3 + W = 6NaWO_3$$[7]

The best results were obtained when the reaction took place under a cover of excess sodium tungstate:

| | |
|---|---|
| W | 0.60 g. |
| $WO_3$ | 1.52 |
| $Na_2WO_4$ | 2.88 + 3 g. (anhydrous) |
| | 8.0 g. |

The dry mixture was slowly heated in vacuum up to 950° and then during the course of four hours uniformly cooled down to 700°. Then the current was turned off. The bronze crystals were completely under solid sodium tungstate, which could be removed with boiling water. On the sur-

(1) Wöhler, *Pogg. Ann.*, **2**, 350 (1824).

(2) Brunner, "Beitrage zur Kenntnis der Wolframbronzen," dissertation, Zürich, 1903.

(3) Spitzin, *Z. anorg. allgem. Chem.*, **148**, 69 (1925); Spitzin and Kaschtanoff, *ibid.*, **157**, 141 (1926); *Z. anal. Chem.*, **75**, 440 (1928).

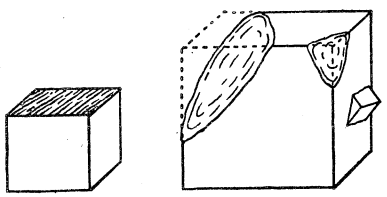
(4) de Jong, *Z. Krist.*, **81**, 314 (1932); de Jong and Stek, *ibid.*, **83**, 496 (1932). See also Glemser and Sauter, *Z. anorg. allgem. Chem.*, **252**, 156, 159 (1943).

(5) Hägg, *Z. physik. Chem.*, **B29**, 192 (1935).

(6) Straumanis and Ievinš, "Die Präzisionsbestimmung von Gitterkonstanten nach der asymmetrischen Methode," Springer, Berlin, 1940; Edwards, Ann Arbor, Mich., 1948.

(7) Worked out by Dr. G. Münch in the Institute for Metal Chemistry in Marburg.

face of the very nice cubic crystals of bronze, there still adhered sodium tungstate and fine tungsten powder (greenish appearance). These were easily removed with warm sodium hydroxide solution containing some sodium peroxide. Of course, the crystals then appeared slightly corroded (Fig. 1a). At higher temperatures larger crystals are obtained, but they were defective as evidently the bronze begins to decompose at 1000° (Fig. 1b). The sodium tungstate in excess obviously furthers the growth of the crystals; the bronze does not dissolve in it even at higher temperatures.



a b

Fig. 1.—Crystal diagrams: a, cubic crystal slightly stripped; b, a larger and defective crystal with intergrowth.

For preparation of any deeper colored bronze the exact stoichiometric reaction (in vacuum, one-half—one hour, 700–800°) $NaWO_3 + xWO_3 \rightarrow$ deeper colored bronze was used.

**Properties of Pure $NaWO_3$.**—A sketch of two crystals is shown (Fig. 1). The crystals are shiny, brittle and have weak cleavage parallel to 100. The cleavage planes also have a strong metallic luster.[8] The crystals are good electric conductors. The conductivity ($\sim$ 400 $\Omega^{-1}$/cm.$^{-1}$) is comparable with that of graphite.[9]

Under oxygen-free water the compound keeps its luster for several months and no appreciable solubility was detected. However, dissolution was observed in oxygen-rich water

$$2NaWO_3 + {}^1/_2O_2 \longrightarrow Na_2W_2O_7 \text{ (very slowly)}$$

The presence of $Na_2W_2O_7$ was proven beyond doubt by power photographs. An addition of hydrogen peroxide considerably increased the velocity of the reaction.

Strong bases dissolve sodium metatungstate only in the presence of oxidizing agents

$$2NaWO_3 + 2NaOH + {}^1/_2\,O_2 \text{ (air)} \longrightarrow 2Na_2WO_4 + H_2O \text{ (very slowly)}$$

$$2NaWO_3 + Na_2O_2 \longrightarrow 2Na_2WO_4 \text{ (quickly)}$$

The deeper colored bronzes dissolve in bases more readily the more tungstic oxide the compounds contain. The reaction is retarded by the pentavalent tungsten, it must be first oxidized to soluble tungstates.

The high resistance of sodium metatungstate to acids can be explained by the development of insoluble surface films containing tungstic acid. A mixture of nitric and hydrofluoric acids destroys the yellow bronze rather quickly. A greenish precipitate results which sometimes turns yellow (tungstic acid) and sometimes white.

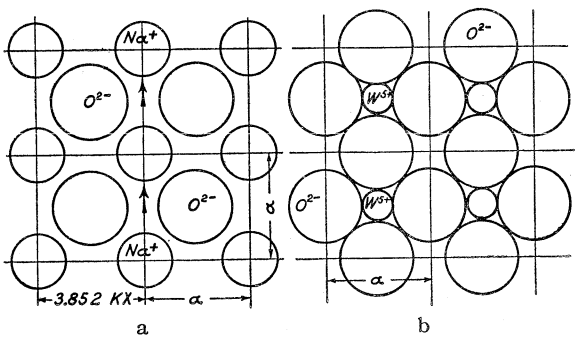
The phenomena observed during heating of the bronze can be explained as follows: In the bronze crystals there is an equilibrium that is in accordance with the statements of Hägg[5] on the structure of $NaWO_3$

$$Na^+W^{V}O_3 \rightleftharpoons W^{VI}O_3 + Na^0 \qquad (1)$$

A rise in temperature promotes this oxidation–reduction reaction to the right. Sodium ion acts as oxidizing agent, converting $W^{5+}$ into $W^{6+}$

$$W^{V}O^-_3 \longrightarrow W^{VI}O_3 + e$$
$$Na^+ + e \longrightarrow Na^0 \qquad (2)$$

The electron has only to pass from $W^{5+}$ to sodium ion and the reaction is finished. The bronze must therefore have good electric conductivity[10] and the sodium ion must be very mobile. The mobility of sodium ion follows also from the structure of sodium metatungstate (see Fig. 2).




a b

Fig. 2.—Structure of $NaWO_3$ (according to Hägg), showing positions: $Na^+$ 000, $W^{5+}$ $\frac{111}{222}$, $3O^{2-}$ $\frac{11}{22}0$, $\frac{1}{2}0\frac{1}{2}$, $0\frac{11}{22}$; a, first layer; b, second layer; the third is identical with the first.

The sodium ion squeezes from one 000-site to another, especially at higher temperatures. If tungstic oxide is only slightly in excess there will be many empty 000-sites in the crystals.

On heating the yellow bronze in air, it begins to cake and turns blue-black. According to (1), sodium oxidizes on the surface and the tungstic oxide distributes in the crystal

$$NaWO_3 + xWO_3 = NaWO_3(W^{VI}O_3)_x \qquad (3)$$
deeper colored bronze

Simultaneously on the surface occurs

$$2NaWO_3 + {}^1/_2O_2 \longrightarrow Na_2W_2O_7, \text{ and}$$
$$Na_2O + WO_3 \longrightarrow Na_2WO_4 \qquad (4)$$

On heating sodium metatungstate above 700–800° *in vacuo*, reaction (1) becomes noticeable and the sodium vapor reduces the sodium metatungstate. Tungsten, sodium tungstate and some not

(8) The polished, ground crystal is reddish and becomes yellow after few days. Moisture instantly causes the yellow color; however, it disappears soon.

(9) See the article of Straumanis and Dravnieks, THIS JOURNAL, **71**, 683 (1949).

(10) Friedrich, *Z. Physik*, **31**, 813 (1925); **34**, 637 (1925); see also Meyer, *Z. Elektrochem.*, **50**, 274 (1944).

yet identified products result. The latter cause the caking of the sodium metatungstate crystals (m. p. of sodium tungstate is $\sim$ 700°). A part of the sodium vapor reacts with the glass or porcelain; the color of the resulting bronze then becomes deeper.

These reduction reactions can be completely suppressed, if there is present in the tube a sodium acceptor (*e. g.*, iodine in an evacuated tube at 700° *ca.* one hour)

$$\begin{aligned} NaWO_3 &\rightleftarrows Na + WO_3 \\ Na + I &\longrightarrow NaI \\ NaWO_3 + xWO_3 &\longrightarrow NaW^{V}O_3(W^{VI}O_3)_x \end{aligned} \qquad (5)$$

With the help of iodine the sodium of the sodium metatungstate can be extracted almost completely; a few tenths of one per cent. remain in the resulting tungstic oxide which is then green.

A very good sodium acceptor is tungstic oxide itself (700°, vacuum); the bronze reacting according to (2) and (3) and the tungstic oxide with sodium according to (1), from right to left. A homogeneous composition finally results. The sodium metatungstate extracts the tungstic oxide even from a ($Na_2WO_4$ + $WO_3$)–melt.[11]

It follows from this that a deeper colored bronze must absorb the sodium from a brighter one until the sodium pressure is equal. Even 1-mm. crystals of the yellow bronze, embedded in an excess of the red bronze and heated under vacuum become red or in a similar fashion blue if embedded in a blue bronze (this corresponds to "mimicry" in the living world). However, they do not lose their single crystal properties.

By increasing the sodium vapor pressure, reaction (1) can be directed from right to left, the vacant 000-sites will be filled while the corresponding amount of W(VI) passes into W(V) and the bronze becomes brighter (Table I).

**The Solubility Limit of Tungstic Oxide in Sodium Metatungstate.**—For determination of this limit the reaction (3) and the reaction

$$NaWO_3 + xI \rightleftarrows Na_{(1-x)}(W^{V}O_3)_{1-x}(W^{VI}O_3)_x + xNaI \quad (x < 1) \qquad (6)$$

were used. All experiments were carried out at 800° in evacuated fused tubes. The results are summarized in Fig. 3. Between 27 and 30% tungstic oxide there is a transition zone; the red bronze absorbs tungstic oxide without changing the lattice. This phenomenon was proven by repeated experiments on different samples. Thus the succeeding violet and blue bronzes must have a slightly different structure although the difference is not visible from the X-ray diagram.[12] At the above-mentioned point the bronzes have the highest electric conductivity.[9]

The lattice contraction follows from the fact that the W(VI) has a smaller ionic radius than W(V). The deviation of the measured lattice constants from the calculated points is shown in Table II.

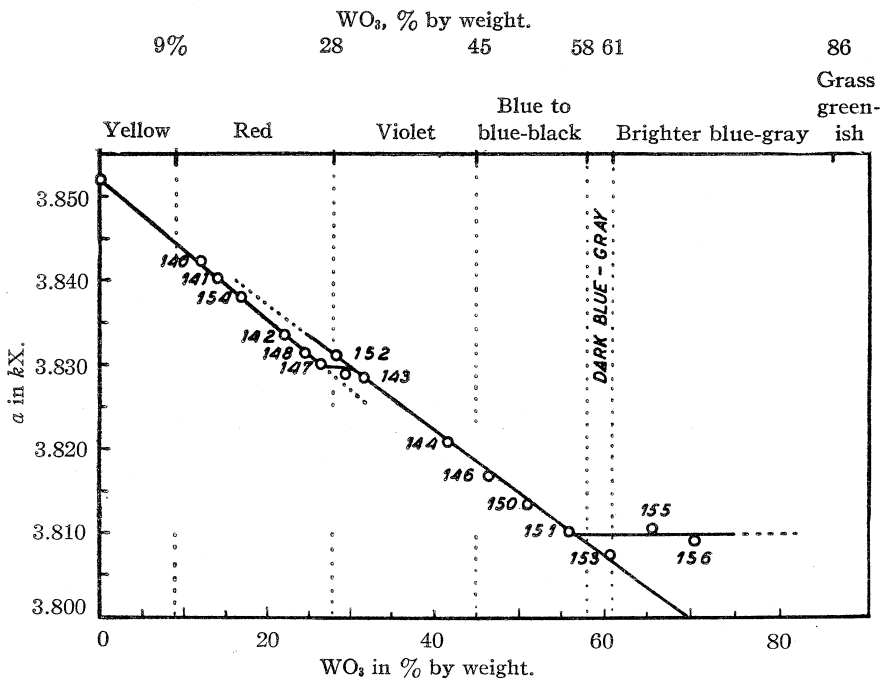



Fig. 3.—The solubility of tungstic oxide in cubic sodium metatungstate is between 56–57% by weight of tungstic oxide, using reaction (3) and 800°.

Up to 52% tungstic oxide the lines are sharp, then the background begins to darken. At 57% tungstic oxide new lines appear. The limit is between 56 and 57% tungstic oxide (at 800°, rapid cooling, see Fig. 3). The cubic bronze cannot absorb more than 57% tungstic oxide without changing its structure. This statement is only partially correct as it depends on the method of preparing the tungstic oxide rich sample.

If the sodium is extracted from the sodium metatungstate using reaction (6), one can obtain compounds with considerably higher tungstic oxide content without breaking down the old cubic lattice:

(11) If the yellow bronze and tungstic oxide in two adjacent dishes are heated under vacuum, the tungstic oxide becomes blue, violet or even red, because the bronze evaporates sodium and the tungstic oxide absorbes it readily.

(12) See v. Laue, "Röntgenstrahl-Interferenzen," Leipzig, 1940, p. 179b, or 1948, p. 193.

$$(W^{V}O_6)^{7-} \rightleftharpoons (W^{VI}O_6)^{6-} + e$$
$$e + Na \longrightarrow Na$$

and outside of the crystals

$$Na + I \longrightarrow NaI$$

The old structure remains in perfect order (sharp lines); only the lattice shrinks, while in the first case (reaction 3), a new lattice must be built up from the triclinic tungstic oxide. Extracting the sodium with iodine, a sample with a lattice constant $a$ = 3.7913 kX, corresponding to 81.9% tungstic oxide, was obtained. However, weak new lines were already on the film.

TABLE II

THE DEVIATION OF THE MEASURED POINTS FROM LINEARITY

The first 6 points: $a = 3.8519 - 0.000829.WO_3\%$; the last 7 points: $a = 3.8519 - 0.000743.WO_3\%$.

| No. | Wt. $WO_3$, % | $a$ meas. in kX | $a$ calcd. in kX | Diff. | Diff. in % |
|---|---|---|---|---|---|
| 140 | 12.08 | 3.8422 | 3.8419 | +0.0003 | +0.0078 |
| 141 | 13.96 | 3.8403 | 3.8403 | ± .0000 | ± .000 |
| 154 | 16.88 | 3.8380 | 3.8379 | + .0001 | + .0026 |
| 142 | 21.88 | 3.8335 | 3.8338 | − .0003 | − .0078 |
| 148 | 24.5 | 3.8312 | 3.8314 | − .0002 | − .0026 |
| 147 | 26.48 | 3.8303 | 3.8300 | + .0003 | + .0078 |
| 152 | 28.42 | 3.8311 | 3.8308 | + .0003 | + .0078 |
| 143 | 31.60 | 3.8285 | 3.8284 | + .0001 | + .0026 |
| 144 | 41.90 | 3.8208 | 3.8208 | ± .0000 | ± .000 |
| 146 | 46.5 | 3.8167 | 3.8174 | − .0007 | − .018 |
| 150 | 51.0 | 3.8134 | 3.8140 | − .0006 | − .016 |
| 151 | 56.0 | 3.8103 | 3.8103 | ± .0000 | ± .000 |
| 153 | 60.8 | 3.8075 | 3.8068 | + .0007 | + .018 |

The change in color of the samples with the contraction of the lattice (increasing tungstic oxide content) can also be seen from Fig. 3. Of course, the change is not sudden but gradual.

## The Nature of the Cubic Bronzes

From the description given it is evident that all the cubic tungsten bronzes from yellow to dark blue belong to the same series of anionic substitutional mixed crystals: the complexes $(W^{V}O_6)^{7-}$ of the sodium metatungstate are replaced at random by the slightly smaller $(W^{VI}O_6)^{6-}$ complexes (the corners of the octahedra are common); the sodium sites remain open. The ready replacement can be explained by the statement of Brakken that in tungstic oxide the $(W^{VI}O_6)^{6-}$ complexes are already present.[13]

The formation of solid solutions is therefore possible, even if the components belong to different crystal systems (here cubic and triclinic). The conditions are: (1) the dimensions of the replaceable structure units cannot differ more than 5% in any direction[14] and (2) the sum of the charges must be zero. This occurs frequently when the components have a similar chemical formula and a similar lattice structure with similar lattice constants (Grimm).

The samples of the bronzes also confirm the rule that compounds containing an element in two valencies are intensely colored.

**Compounds with a Higher Tungstic Oxide Content.**—Extracting sodium from the blue bronze (~ 80% tungstic oxide) by help of iodine, gives a blue-greenish sample that begins to sublime at 850°. In the sample there are thin, long, blue needles with a greenish lustre. Rotating crystal diagrams showed that these belong to the previously described tetragonal bronze (lattice constants: $a$ = 12.47 kX; $c$ = 3.819; $c/a$ = 0.306).[15] This diagram is similar to that of the cubic blue bronze.

With further loss of sodium (or tungstic oxide absorption) the samples become brighter and more greenish. The tetragonal cell contracts and new lines appear. At 92–96.4% tungstic oxide by weight a greenish-gray sample results. The diagrams have very many sharp lines and have a certain similarity with the tetragonal bronzes.

When the sodium is extracted still more, olive-green samples, brighter than the above-mentioned, can be obtained. The X-ray films are very rich with lines and show transition to the pure tungstic oxide patterns. In the region of 96.4–98.2% tungstic oxide the diagram of pure tungstic oxide can clearly be observed.

If the bronze contains more than 98.6% tungstic oxide, the powder photographs cannot be distinguished from pure tungstic oxide but the lines are, strange to say, sharper than the lines of the pure compound. Samples up to 99.3% tungstic oxide were prepared; their color is bright greenish-gray, they sublime to form thick, very brittle, slightly translucent crystals (not needles).

There are also some other compounds in the reaction tubes, especially when they are heated above 1000°. Even traces of sodium metatungstate give the tungstic oxide a greenish color.

**Acknowledgment.**—This work was carried out in the Institute for Metal Chemistry of Marburg (Germany). I am very grateful to the Director of that Institute, Geheimrat Professor Dr. R. Schenck, for the opportunity of working there for three years and for his considerate attitude and help. Likewise I am much indebted to the Director of the Mineralogical Institute of the University of Marburg, Professor Dr. F. Laves. I thank sincerely Dr. A. W. Schlechten and Professor A. Legsdin, School of Mines in Rolla, for correcting the English of my papers.

## Summary

It has been proven that the sodium tungsten

(13) Brakken, *Z. Krist.*, **78**, 487 (1931): tungstic oxide consists of octahedra also (with common oxygen corners). But these are oblique, because the symmetry of the lattice is triclinic or pseudo rhombic. The oblique octahedra evidently change into regular when absorbed by the bronze.

(14) Straumanis and Stahl, *Z. physik. Chem.*, **194**, 130 (1944).

(15) de Jong and Stek, ref. 4, found $a$ = 17.5 Å. (in the direction of the diagonal of the base 12.4Å); $c$ = 3.8; $c/a$ = 0.217. Hägg, ref. 5, found $a$ = 12.13 and $c$ = 3.77 Å.

bronzes ($NaWO_3$) can lose sodium according to the reversible reaction $NaW^{V}O_3 \rightleftarrows Na^0 + W^{VI}O_3$.

The tungstic oxide dissolves in the remaining sample with formation of anionic substitutional solid solutions. The cubic bronzes can contain up to 80% tungstic oxide. The lattice constants *versus* tungstic oxide-content are shown in Fig. 3.

The properties of pure sodium metatungstate and those of the solid solutions are described. The tetragonal blue bronzes contain 80–90% tungstic oxide. Their color is more greenish. Compounds with 92–96.4% tungstic oxide were green. For samples with still higher tungstic oxide concentration see above.

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# The Sodium Tungsten Bronzes. II. The Electrical Conductivity of the Bronzes

BY M. E. STRAUMANIS[1] AND A. DRAVNIEKS[2]

**Introduction.**—The high electrical conductivity of tungsten bronzes was reported first by Hägg[3] who observed a large increase in conductivity with increase in temperature. He suggested that the increase was the result of progressive sintering.

More recent investigations made by the authors, however, show that the conductivity effect is much more complex in nature. The purpose of the present paper is to establish the factors responsible for these changes in conductivity.

**The General Behavior of Sintered Yellow Bronzes.**—The specimens were prepared from either a pure yellow powder of sodium tungsten bronze or from a corresponding mixture of tungsten powder, tungsten trioxide and sodium tungstate (composition given on page 684). The powder was pressed into small cylinders by means of a steel pellet press and the specimens were then sintered at 700–750° in high vacuum for one to two hours and cooled under vacuum. The specimens were 10–15 mm. long, about 6 mm. in diameter, hard and brittle. The color was yellow to orange. The ends of the specimens were ground parallel, polished and coated with graphite. To measure the electrical resistance, the specimens were fastened in a jig (Fig. 2b) supplied with suitable leads. The resistance was measured with a good technical ohmmeter.

Generally, the resistance of freshly prepared specimens was 0.2–0.6 ohm, depending on the composition. However, the resistance increased continuously,[4] reaching values of 10,000 ohms and even higher (Fig. 1). The reproducibility of the resistance *vs.* time curves was poor. Sections of the curve can be described by an equation of the form

$$r = r_0 (1 + \alpha\sqrt{t})$$

where $r_0$ = initial resistance, $t$ = time and $\alpha$ = coefficient which changes slowly with time. The weight of a specimen increased by 0.08–0.2% during a run.

(1) University of Missouri, School of Mines & Metallurgy, Department of Metallurgy, Rolla, Mo.

(2) Illinois Institute of Technology, Chemistry Department, Corrosion Research Laboratory.

(3) Hägg, *Z. physik. Chem.*, **B29**, 201 (1935).

(4) Observed first by Dr. G. Münch, State Institute of Metal Chemistry, Marburg a. Lahn.

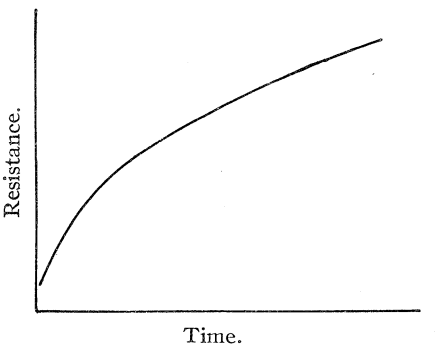



Fig. 1.—Increase of electrical resistance with time of a briquette of yellow bronze exposed to air.

The resistance of a specimen did not change when it was kept in vacuum, or in hydrogen, nitrogen, hydrogen sulfide, dry oxygen or pure water vapor, or when the specimen was protected from air by rubber tubing. When the atmospheric air was admitted, the resistance started to increase immediately. A particularly rapid and irregular increase in resistance was caused by oxygen saturated with moisture or moist air. The change due to moist air is shown in Table I.

TABLE I

RESISTANCE CHANGES OF TWO SPECIMENS OF BRONZE SPECIMEN $B_2$ IS YELLOW BRONZE, 10.3% $WO_3$; SPECIMEN $F_1$ IS RED-BROWN BRONZE, 12% $WO_3$; AIR SATURATED WITH WATER VAPOR AT 20°

| Specimen $B_2$ | | | Specimen $F_1$ | |
|---|---|---|---|---|
| Time, min. | Resistance, ohm | Remarks | Time, min. | Resistance, ohm |
| 0 | 0.45 | High | 0 | 0.54 |
| 90 | .46 | vacuum | 60 | .55 |
| 100 | .62 | Water | 70 | .58 |
| 120 | .67 | vapor | 210 | .64 |
| 130 | .70 | pure | 245 | .68 |
| 140 | 6.3 | Air | 250 | 3.3 |
| 150 | 23.0 | and | 260 | 18 |
| 160 | 55 | water | 270 | 53 |
| 170 | 101 | vapor | 280 | 115 |
| 180 | 160 | | 290 | 220 |
| 330 | 620 | | 300 | 330 |
| 360 | 640 | | 320 | 600 |
| | | | 350 | 1100 |

At resistances over 1000 ohms polarization effects were observed. This polarization was never observed when only small amounts of moisture were allowed to make contact with the specimens.

The lost conductivity can be easily restored to an appreciable extent by drying the specimen over phosphorus pentoxide or by placing it in a vacuum; *e. g.*

| | | |
|---|---|---|
| 50 ohms | (moist air) | 120 ohms |
| 120 hms | ($P_2O_5$) | 60 ohms |
| 60 ohms | (moist air) | 850 ohms |
| 850 ohms | ($P_2O_5$) | 200 ohms |

Full restoration is achieved only by sintering the sample in vacuum. Mild warming in air restores the conductivity in part, but the resistance increases again upon cooling, since renewed adsorption of oxygen and water vapor takes place. Table II shows the course of an experiment in air and in vacuum.

TABLE II

THE DECREASE OF RESISTANCE OF A SPECIMEN OF YELLOW BRONZE IN AIR AND IN VACUUM AT ELEVATED TEMPERATURES

| In air | | | In vacuum | | | |
|---|---|---|---|---|---|---|
| Time, min. | Temp., °C. | Resistance, ohm | Time, min. | Temp., °C. | Resistance, ohm | Press., mm. |
| 0 | 22 | >12000 | 0 | 20 | 12000 | 0 |
| 25 | 70 | 9200 | 20 | 280 | 2000 | 0 |
| 38 | 80 | 1090 | 30 | 290 | 620 | 0.2 (?) |
| 50 | 90 | 450 | 40 | 310 | 390 | 0.2 |
| 65 | 100 | 120 | 80 | 390 | 36 | 0.2 |
| 100 | 105 | 56 | 90 | 410 | 13 | 0.2 |
| 153 | 105 | 41 | 110 | 550 | 1.9 | 0.2 |
| 161 | 100 | 41 | 170 | 580 | 1.2 | 1.5 |
| 178 | 90 | 44 | 200 | 680 | 1.0 | 2.0 |
| 181 | 80 | 45 | 215 | 730 | 0.9 | 2.2 |
| 184 | 72 | 46 | 230 | 790 | 0.82 | 2.5 |
| 186 | 65 | 47 | 240 | 800 | 0.78 | 2.5 |

The pressure developed in vacuum is due to adsorbed gases evolved from the specimen.

The conductivity can also be restored if the specimen is heated by passing a strong electric current through it.

Consequently, it may be stated that the increase in resistance of sintered porous specimens of tungsten bronzes is caused by the simultaneous adsorption of oxygen and water vapor. The presence of both is necessary.

The small amounts of adsorbed oxygen and moisture (several tenths of a per cent.) causing the changes and easy desorption indicate that the formation of sodium tungstate is not the process responsible for the effects described. However, it is known that the conductivity of pure elements can be appreciably decreased by intercrystalline layers of poorly conducting surfaces. A typical example is boron.[5]

Sodium bronze ($NaWO_3$) decomposes at high temperatures; tungsten, sodium tungstate and other compounds are formed.[6] Sodium tungstate acts as an intercrystalline cement holding the grains of pure bronze (see sintering, page 686). But only the metallic tungsten could be expected to form unstable, poorly conducting adsorption compounds with water and oxygen.[7]

Investigations on very pure tungsten bronzes were conducted to eliminate the effects caused by the intercrystalline substance.

**The Conductivity of Pure Sodium Tungsten Bronzes.**—The apparatus as shown in Figs. 2a and b was employed to measure the conductivity, temperature coefficients and change of conductivity under the influence of different agents. The specimen was placed in the glass tube between the two well-fitted steel pistons of the jig (Fig. 2b). The screw was tightened until the measured resistance attained a constant value. Then the jig was placed in the apparatus shown in Fig. 2a. The resistance of the leads was subtracted from the total measured resistance. The device could also be employed for measuring the resistance of powders.

The procedure used for removing the tungsten and sodium tungstate particles from the specimens is described in the previous article.

The data measured on powders of two tungsten bronzes are shown in Table III.

TABLE III

THE SPECIFIC RESISTANCES ($\sigma$) AND CONDUCTIVITIES ($\kappa$) OF THE TWO PUREST SODIUM TUNGSTEN BRONZES IN VACUUM AT DIFFERENT TEMPERATURES, IN WATER VAPOR, AND IN WATER VAPOR WITH AIR

| $NaWO_3$, almost 100%, fine crystalline | | | | $NaWO_3 \cdot WO_3$ (11.6% $WO_3$), reddish, coarsely crystalline | | | |
|---|---|---|---|---|---|---|---|
| Time, min. | Temp., °C. | $\sigma$ ohm. | $\kappa$ $ohm^{-1}$ | Time, min. | Temp., °C. | $\sigma$ ohm. | $\kappa$ $ohm^{-1}$ |
| 0 | 450 | 0.0059 | 170 | 0 | 450 | 0.036 | 28 |
| 20 | 300 | .0029 | 350 | 25 | 400 | .033 | 30 |
| 65 | 20 | .0029 | 350 | 30 | 350 | .031 | 32 |
| Water vapor, 14 mm. | | | | 35 | 300 | .02 | 50 |
| 80 | 20 | .0029 | 350 | 90 | 20 | .0026 | 385 |
| 110 | 20 | .0029 | 350 | 1290 | 20 | .0026 | 385 |
| Air admitted, 90 mm. | | | | Water vapor with air | | | |
| 140 | 20 | .0029 | 350 | 1310 | 20 | .0026 | 385 |
| | | | | 1390 | 20 | .0026 | 385 |

The agreement in values obtained at 20° (350–385 $ohm^{-1}$) is satisfactory in view of the low reproducibility of such measurements.

The measurements on pressed and sintered specimens of yellow bronze are shown in Table IV. They possess lower conductivity, and the conductivity does not change in dry air, but decreases rapidly in moist air.

The negative temperature coefficient indicates a metallic (electronic) type of conductivity.[8]

The fact that some authors[8] have found a positive temperature coefficient of conductivity may be explained by the presence of moisture and oxy-

(5) Henninger, *Ann. Physik*, **28**, 245 (1937).

(6) Straumanis, THIS JOURNAL, **71**, 679 (1949).

(7) If tungsten is replaced by metallic silver (mixture of silver $Na_2WO_4$ and $NaWO_3$) no change in resistance could be observed (see p. 686).

(8) Meyer, *Z. Elektrochem.*, **50**, 276 (1944).

TABLE IV

THE SPECIFIC RESISTANCES ($\sigma$) AND CONDUCTIVITIES ($\kappa$) OF TWO SINTERED BRONZE SPECIMENS OF DIFFERENT COMPOSITION IN VACUUM, HYDROGEN AND DRY AIR AT DIFFERENT TEMPERATURES

| Specimen A with 4.4% $WO_3$ | | | | Specimen $C_2$ with 10.6% $WO_3$ | | | |
|---|---|---|---|---|---|---|---|
| Time, min. | Temp., °C. | $\sigma$, ohm. | $\kappa$, $ohm^{-1}$ | Time, min. | Temp., °C. | $\sigma$, ohm. | $\kappa$, $ohm^{-1}$ |
| 0 | 18 | 0.18[a] | 5.6 | 0 | 20 | 0.21[a] | 4.8 |
| 30 | 250 | .13[a] | 7.7 | 40 | 400 | .12[a] | 8.3 |
| 40 | 350 | .03[a] | 33 | 50 | 450 | .08[a] | 12.5 |
| 80 | 430 | .024[a] | 42 | 60 | 470 | .053[a] | 18.8 |
| Hydrogen admitted | | | | 75 | 475 | .044[a] | 23 |
| 130 | 430 | .018 | 55 | 95 | 485 | .04[a] | 25 |
| 185 | 430 | .013 | 77 | 105 | 400 | .028 | 36 |
| Hydrogen exhausted, vacuum | | | | 115 | 300 | .02 | 50 |
| 200 | 300 | .013 | 77 | 130 | 200 | .017 | 59 |
| 210 | 200 | .011 | 91 | 155 | 20 | .015 | 67 |
| 225 | 50 | .0098 | 102 | 195 | 20 | .015 | 67 |
| 2800 | 15 | .0072 | 139 | Dry air admitted | | | |
| 2860 | 15 | .0072 | 139 | 285 | 20 | .015 | 67 |
| | | | | 2835 | 20 | .015 | 67 |

[a] The specimens contained adsorbed oxygen and water vapor.

gen in the nitrogen employed to blanket the specimens in earlier work. The present paper shows that water and oxygen are again adsorbed upon lowering the temperature. In this way a positive temperature coefficient is obtained due to reaction which is not germane to pure $NaWO_3$ (bronze) or to $NaWO_3$ containing tungsten trioxide.

The conductivities and temperature coefficients of bronzes with higher tungsten trioxide content are shown in Table V.

TABLE V

THE CONDUCTIVITIES AND TEMPERATURE COEFFICIENTS OF CONDUCTIVITY OF SODIUM–TUNGSTEN BRONZES WITH HIGHER TUNGSTEN TRIOXIDE CONTENT (ALL SOLID SOLUTIONS)

| Specimen | $WO_3$, % | $\kappa$ in $ohm^{-1}$ at °C. 20 | 400 | 430 | 450 | 500 | $\frac{1}{\kappa_0} \times \frac{d\kappa}{dT} \times 10^3$ |
|---|---|---|---|---|---|---|---|
| III | 0 | 350 | .. | .. | 170 | .. | −1.2 |
| A | 4.4 | 189 | 73 | .. | ... | .. | −1.6 |
| A | 4.4 | 139[a] | .. | 77 | ... | .. | −1.1 |
| $E_1$ | 7.9 | 51[a] | 38 | .. | ... | .. | −0.67 |
| $E_2$ | 7.9 | 26 | 16 | .. | ... | .. | −1.0 |
| $_1E_2$ | 10.3 | 44 | .. | 13 | ... | .. | −1.7 |
| $B_2$ | 10.3 | 44 | .. | .. | ... | 10 | −1.6 |
| $C_2$ | 10.6 | 99 | 14[c] | .. | ... | .. | −2.6 |
| $C_2$ | 10.6 | 67 | .. | .. | ... | 25[d] | −1.3 |
| $F_1$ | 12.0 | 21[b] | 19 | .. | ... | .. | −0.25 |

[a] 15°. [b] 25°. [c] 350°. [d] 485°.

Here large differences in conductivity of different specimens were observed, even in parallel experiments. Generally, the conductivity decreases with increasing tungsten trioxide content. The temperature coefficient is negative throughout and its values lie within 1:10 ratio.

The specimens with still higher tungsten trioxide content are very brittle and collapse under pressure applied in the jig. Since for specimens with more than 35% tungsten trioxide the resistance was not affected by moist air, a simpler apparatus was employed.

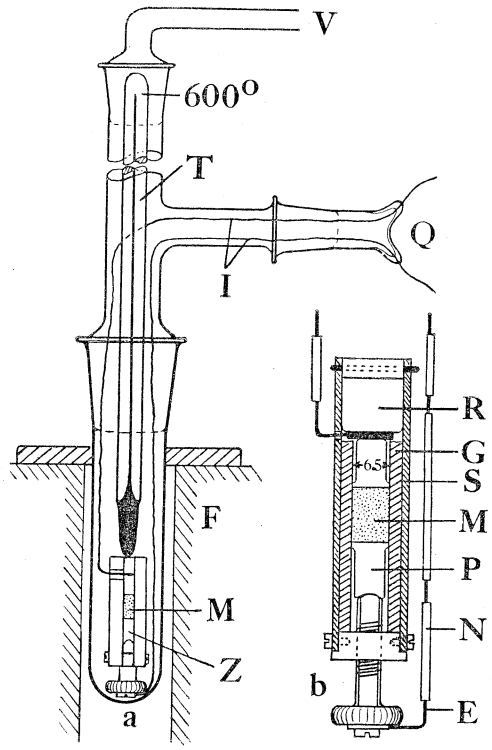



Fig. 2,—Apparatus for the measurement of resistance of sintered samples or powders in vacuum or in the presence of different gases at different temperatures: a, the complete apparatus; b, the jig; E, lead; F, furnace; G, glass tube; I, insulated leads; M, specimen; N, insulation; P, steel piston; Q, to ohmmeter; R, porcelain; S, slitted iron tube; T, thermometer; V, to vacuum pump; Z, slit.

TABLE VI

THE SPECIFIC RESISTANCE OF SODIUM TUNGSTEN BRONZES WITH HIGH TUNGSTEN TRIOXIDE CONTENT. THE COLORS OF BRONZES, SEE PAGE 683, ROOM TEMPERATURE

| Specimen | $WO_3$, % | $\sigma$, ohm | Specimen | $WO_3$, % | $\sigma$, ohm |
|---|---|---|---|---|---|
| $G_1$ | 38.8 | 0.00166 | 116 | 93.6 | 980 |
| 146 | 46.5 | 52 | 117 | 94.8 | 360 |
| 150 | 51 | 135 | 118 | 95.6 | 155 |
| 155 | 65 | 3.2 | 120 | 96.9 | 8300 |
| 104 | 69.6 | 4.5 | 121 | 97.3 | 2800 |
| 156 | 70 | 6.3 | 122 | 97.8 | 16300 |
| 105 | 73 | 67 | 123 | 98.2 | 13700 |
| 107 | 79 | 65 | 125 | 98.9 | 29000 |
| 109 | 86.5 | 23 | 126 | 99.1 | 31500 |
| 114 | 91 | 24 | 127 | 99.3 | 17000 |
| 115 | 92 | 70 | $WO_3$[a] | 100 | 200000 |

[a] Heated in vacuum at 920°

The violet specimen $G_1$ with 38.8% tungsten trioxide had the highest conductivity in the whole

series, 600 ohm$^{-1}$.[9] With higher tungsten trioxide contents the resistance increases rapidly but the results fluctuate. The addition of small amounts of $NaWO_3$ decreases the resistance of tungsten trioxide very effectively. Tungsten trioxide is a semiconductor of the excess type.[10,11,12]

**Reasons for Resistance Changes in Sintered Specimens.**—The measurements reported above demonstrate that the pure sodium tungsten bronzes possess constant conductivity at constant temperature. Therefore, the changes in resistance of sintered specimens of bronze are caused by an intercrystalline phenomenon and due to an intercrystalline substance.

If the metallic tungsten is assumed to take part in the effect, the behavior of a mixture of tungsten and sodium tungstate should be similar to that of the bronze specimens. Accordingly, an identical study was made with specimens of a tungstate and tungsten powder mixtures. These were pressed in the same way as the bronze specimens, with subsequent heating at 600° in vacuum. The resistances were as shown in Table VII.

TABLE VII

SPECIFIC RESISTANCE OF $Na_2WO_4$ WITH DIFFERENT AMOUNTS OF TUNGSTEN ADDED

| Wt. % W | 13 | 20 | 30 | 40 | 50 | 55 |
|---|---|---|---|---|---|---|
| Resist. ohm | 17000 | 12000 | 11400 | 334 | 0.29 | 0.067 |

The specimen with 50% tungsten was dark gray and its behavior studied in the apparatus of Fig. 2. The resistance in atmospheric air began to increase during the first day. The specimen showed the same behavior as the bronzes. At very high moisture contents the specimen became white and the changes in resistance were then irreversible, apparently due to the formation of sodium tungstate from the tungsten.

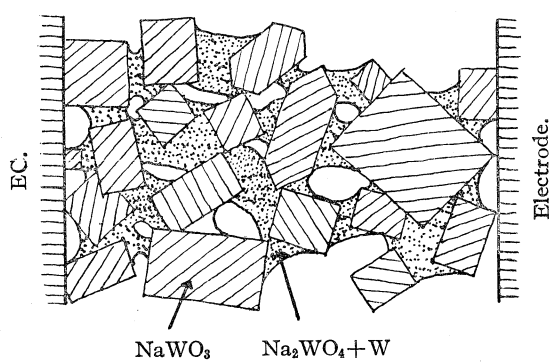



Fig. 3.—Structure of a sintered sodium tungsten bronze specimen: sodium tungstate cements the bronze grains, the black dots represent tungsten, the pores are white. The bronze crystals are shown smaller than they actually are in comparison with the intercrystalline tungstate–tungsten mass.

Similar specimens prepared from sodium tungstate with 30% silver powder added had 0.32 ohm resistance, but this value did not change in moist air. No changes of resistance were observed in pressed tungsten powders.

Consequently, it may be concluded that the resistance changes of sintered bronzes are caused by elementary tungsten in combination with sodium tungstate or similar products. The presence of elementary tungsten in sintered bronzes was also detected by X-ray diffraction patterns. Free tungsten and sodium tungstate are not found if the bronze specimens contain more than about 35% tungsten trioxide. Such specimens are therefore brittle and insensitive to moist air.

**The Structure of Sintered Bronze Specimens.**—The schematic structure of sintered specimens is suggested by the foregoing observations as shown in Fig. 3.

The conductivity of the aggregate is caused by tungsten particles which form conducting bridges in the mass of sodium tungstate. The latter also cements the grains of the bronze. In moist air the formation of adsorption compounds begins on the surface of the tungsten particles with a simultaneous binding of oxygen and water. As a result many bridges are ruptured and the resistance of the whole aggregate increases. The diffusion of moist oxygen proceeds deeper and deeper through the pores. Upon placing in vacuum or heating, the adsorption compound is decomposed and the conductivity improves. However, not all of the interrupted bridges can be regenerated. In many places the reaction may proceed to form sodium tungstate, a non-conductor. Also, $NaWO_3$ is slowly oxidized to tungstate. The volume increases and cracks are formed. The degree of destruction depends upon the duration of contact with moist oxygen and the amount of moisture. The regeneration is not complete in vacuum or by gentle heating as sodium tungstate does not decompose and is not reduced at low temperatures in hydrogen. Upon heating to 700° in vacuum the bronze decomposes partly to tungsten and sodium tungstate and new tungsten bridges are formed. In this way the effects observed concerning the conductivity behavior of tungsten bronzes are easily and completely explained.

**Adsorption Compound on the Surface of Tunsgten.**—The concept of the adsorption compound which is used as an explanation for the change of the conductivity of a tungsten–tungstate mass needs further elaboration. Although it is well known that at high temperatures tungsten easily forms oxide films,[13,14,15] this does not occur under ordinary conditions. The surface of a tungsten grain is probably in a particularly active state, as a result of being embedded in the sodium tung-

(9) Perhaps the bronzes of transition composition, THIS JOURNAL, **71**, 679 (1949), possess still higher conductivity.

(10) Friedrich, *Z. Physik*, **31**, 813 (1925).

(11) Friedrich, *ibid.*, **34**, 637 (1925).

(12) Meyer, *ibid.*, **85**, 278 (1933).

(13) Langmuir, *Physik Z.*, **15**, 529 (1914).

(14) Kingsdom, *Phys. Rev.*, **24**, 510 (1924).

(15) Donal, *ibid.*, **36**, 1172 (1930).

state.[16] In this active state tungsten is able to react with oxygen and water forming an unstable adsorption compound. This view is supported by the following experiment: The purest yellow bronze was mixed with anhydrous sodium tungstate and tungsten powder and pressed. Specimens of this mixture behaved in the same way as the sintered bronze specimens.

**Acknowledgment.**—The above-mentioned work was performed in the State Institute for Metal Chemistry, Marburg a. d. Lahn, Germany. One of the authors (A. Dravnieks) would like to extend his gratitude to Dr. R. Schenck, director, for permission to use the Institute facilities for this investigation.

## Summary

The specific conductivity of pure yellow sodium tungsten bronze is about 400 $ohm^{-1}$ and the temperature coefficient is negative. The conductivity is electronic.

The temperature coefficient is definitely negative also for bronzes with up to 20% of tungsten trioxide (in solid solution). The highest specific conductivity (600 $ohm^{-1}$) is shown by the violet bronze with 38.8% of tungsten trioxide. At higher trioxide contents the resistance of the powder increases.

In the preparation of sintered specimens of sodium tungsten bronzes the $NaWO_3$ decomposes partly upon heating in vacuum, and tungsten, sodium tungstate and similar products are formed. These products cement the powder to a hard, brittle, porous specimen. Tungsten particles form conducting bridges between the crystals of actual bronze. The bridges are interrupted reversibly to some extent by moist oxygen. In this way the peculiar electrical behavior of sintered specimens can be completely explained.

Specimens with more than 35% of trioxide do not contain any free tungsten; therefore, the increase in resistance in moist air does not occur.

(16) Anhydrous sodium tungstate is quasicubic and the lattice constant is ~5.57 kX.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE ARGONNE NATIONAL LABORATORY]

# The Oxidation States of Neptunium in Aqueous Solution[1,2]

BY J. C. HINDMAN, L. B. MAGNUSSON[3] AND T. J. LACHAPELLE[3a]

The preliminary investigation in 1940 by the discoverers of element 93 (neptunium), McMillan and Abelson,[4] led these authors to the conclusion that there were lower and upper oxidation states of neptunium analogous to the +4 and +6 oxidation states of uranium. These and other experiments,[5] including those by Voigt, Sleight, Hein and Wright,[6] which suggested the possible existence of a +5 oxidation state, were performed by tracer methods using the 2.3 day beta emitting isotope $Np^{239}$. By use of the long-lived alpha emitting $Np^{237}$ discovered in 1942 by Wahl and Seaborg,[7] it is possible to study neptunium with weighable amounts of material and in July, 1944, Magnusson and LaChapelle[8] succeeded in isolating the first pure compounds of neptunium using as the source of the $Np^{237}$ uranium irradiated with cyclotron neutrons. At this time these investigators definitely established the existence of the +4 and +6 oxidation states by the preparation of microgram quantities of the solid compounds, neptunium(IV) dioxide, $NpO_2$, and sodium neptunium(VI) dioxytriacetate, $Na_2NpO_2(OOCCH_3)_3$. Zachariasen[9] was able to show by X-ray diffraction studies that these compounds were isomorphous with the analogous compounds of uranium and plutonium.

The isolation and purification of milligram quanties of $Np^{237}$ made possible a more extensive investigation of the chemistry of this element. The first few milligrams were isolated as the result of special runs in the chemical extraction plant of the Clinton Laboratories (now the Oak Ridge National Laboratory) in Tennessee. The $Np^{237}$ from this source was concentrated and isolated in pure form by a group from the Metallurgical Laboratory. This group was headed by J. J. Katz and consisted of Magnusson, LaChapelle, J. R. Gilbreath and W. C. Beard. Larger quanti-

(1) This work was carried out during 1945 at the Metallurgical Laboratory of the University of Chicago under Contract No. W-7401-eng-37.

(2) Presented in part before the Division of Physical and Inorganic Chemistry at the Chicago Meeting of the American Chemical Society in April, 1948.

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(3a) Present address: Department of Chemistry, University of California at Los Angeles, Los Angeles, California.

(4) E. M. McMillan and P. H. Abelson, *Phys. Rev.*, **57**, 1185 (1940).

(5) G. T. Seaborg and A. C. Wahl, THIS JOURNAL, **70**, 1128 (1948).

(6) A. F. Voigt, N. R. Sleight, R. E. Hein and J. M. Wright, Manhattan Project report CN-1979, Oct. 10, 1944. To appear as paper No. 15.9 of Vol. 14B, Plutonium Project Record of the National Nuclear Energy Series.

(7) G. T. Seaborg and A. C. Wahl, to be published as paper No. 1.5, Vol. 14B, Plutonium Project Record of the National Nuclear Energy Series, *Phys. Rev.*, **73**, 940 (1948) (written on April 14, 1942).

(8) L. B. Magnusson and T. J. LaChapelle, Manhattan Project CN-2088, Sept. 1, 1944, THIS JOURNAL, **70**, 3534 (1948).

(9) W. H. Zachariasen, Manhattan Project report CN-2091, Sept. 4 (1944). To appear as papers Nos. 20.7, 20.8, Plutonium Project Record of the National Nuclear Energy Series; Symposium on Chemistry of Transuranium Elements, 1948 Spring Meeting, Am. Chem. Soc., Chicago, Ill., *Phys. Rev.*, **73**, 1104 (1948).

ties were obtained during 1945 as the by-product of the operation of the plutonium project plant at the Hanford Engineer Works in the State of Washington. This latter material was isolated as the result of a process designed for the recovery of neptunium at the Hanford Engineer Works by a group at the Metallurgical Laboratory under the direction of F. W. Albaugh and R. C. Thompson.

The initial objective of the work with pure neptunium was the identification of the oxidation states in aqueous solution. In the first part of this paper experiments are described which demonstrate the existence of the +4, +5 and +6 oxidation states of neptunium in solutions of perchloric, hydrochloric and sulfuric acids. That neptunium(III) could exist in aqueous solution was first shown polarographically by Watters.[10]

In the second part of the paper are described experiments on which are based a scheme of oxidation potentials relating the +3, +4, +5 and +6 oxidation states in hydrochloric acid solution.

## 1. The +4, +5 and +6 Oxidation States of Neptunium

It was expected that the various oxidation states of neptunium like those of uranium and plutonium would have highly characteristic absorption spectra in solution. After establishing the identity of a single oxidation state, one should then be able to titrate the neptunium solution spectrophotometrically with oxidizing or reducing agents and thus to determine the oxidation numbers of any higher or lower states produced.

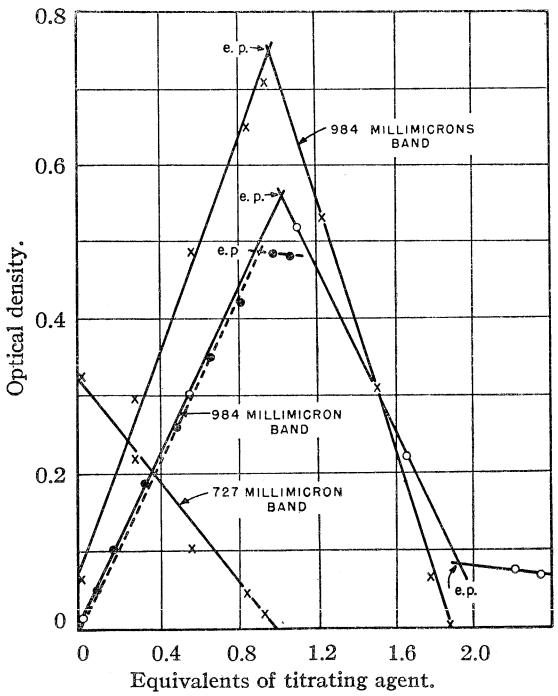



Fig. 1.—Titration of neptunium with oxidizing and reducing agents: ●, reduction of Np(VI) by Sn(II) in 1.0 *M* HCl; ×, oxidation of Np(IV) by Ce(IV) in 0.5 *M* $H_2SO_4$; O, reduction of Np(VI) by Fe(II) in 0.5 *M* $H_2SO_4$.

(10) J. I. Watters, Manhattan Project memorandum MUC-JIW-53, Feb. 8, 1945.

### Experimental

The absorption spectrum measurements were made with a Beckman quartz spectrophotometer. The instrument was operated, in general, at a slit width of 0.01 to 0.02 millimeter. Readings were made at 2 millimicron intervals in the spectral region from 350 to 600 millimicrons, at 2.5 millimicron intervals in the region from 600 to 1000 millimicrons, and at 5 millimicron intervals above 1000 millimicrons except in the vicinity of absorption bands where readings at 1 millimicron intervals were made. In the case of very sharp absorption bands the peak maximum was located by slowly rotating the wave length drum and finding the point of maximum deflection of the galvanometer. Special adapters were made so that Corex absorption cells of 1.000 ± 0.002 cm. and 0.500 ± 0.002 cm. could be used with samples of 1.1 and 0.5 milliliter of solution, respectively.

The first preparation for spectrophotometric examination was made by heating 1.16 mg. of dry, olive-green neptunium hydroxide (later identified as neptunium(IV) hydroxide) in 52 microliters of 9.40 molar perchloric acid. After several hours heating in a water-bath, dilution with water produced a clear, pale green solution, 1.0 molar in perchloric acid. The spectrum of this solution was marked by three sharp, strong absorption bands, at 723, 964 and 984 millimicrons. Later experiments showed this solution contained a mixture of oxidation states.

An excess of argentic oxide was added to the green solution, which turned nearly colorless with a faint pink cast. The strong, sharp absorption bands associated with the initial spectrum had disappeared. A dark brown "hydroxide" was precipitated from the solution by the addition of a slight excess of ammonia. This hydroxide was dissolved in warm 10 molar hydrochloric acid and the solution was diluted to 0.5 molar acid, becoming a yellow green in color. The spectrum was very similar to that of the perchloric acid solution after the argentic oxidation. The spectral identity was taken as evidence that the same oxidation state existed in both solutions.

The first production of a lower oxidation state was carried out by adding small aliquots of Sn(II) to the oxidized neptunium chloride solution. It was found that addition of stannous chloride caused the appearance of an absorption band at 984 millimicrons which increased in optical density until the amount of stannous chloride added was roughly equivalent to one-half mole per mole of neptunium. Further addition of stannous chloride produced only a slight reduction in peak height. A more precise duplication of this titration is illustrated in Fig. 1. An interesting phenomenon observed in the titration was the small growth of the 723 millimicron peak observed in the original perchloric acid solution. The peak disappeared rather quickly.

A neptunium fluoride precipitate (tentatively identified as $KNpF_5$ or $K_2NpF_6$) was made from the above solution by saturating the solution with sulfur dioxide, then making the solution one molar in potassium fluoride and four molar in hydrofluoric acid. This green precipitate was fumed to dryness with sulfuric acid yielding bright green crystals. An absorption spectrum of the solution produced when the crystals were dissolved in 0.5 molar sulfuric acid showed two prominent peaks at 727 and 971 millimicrons analogous to the peaks at 723 and 964 millimicrons observed in the original neptunium solution in perchloric acid.

Oxidation of the neptunium sulfate solution was carried out by adding aliquots of 0.069 molar Ce(IV) in 0.5 molar sulfuric acid. A peak at 984 millimicrons, corresponding to the peak produced by reduction of an oxidized solution with Sn(II), reached its maximum height when the mole ratio of added Ce(IV) to Np was approximately one. An additional equivalent of Ce(IV) reduced the peak to zero

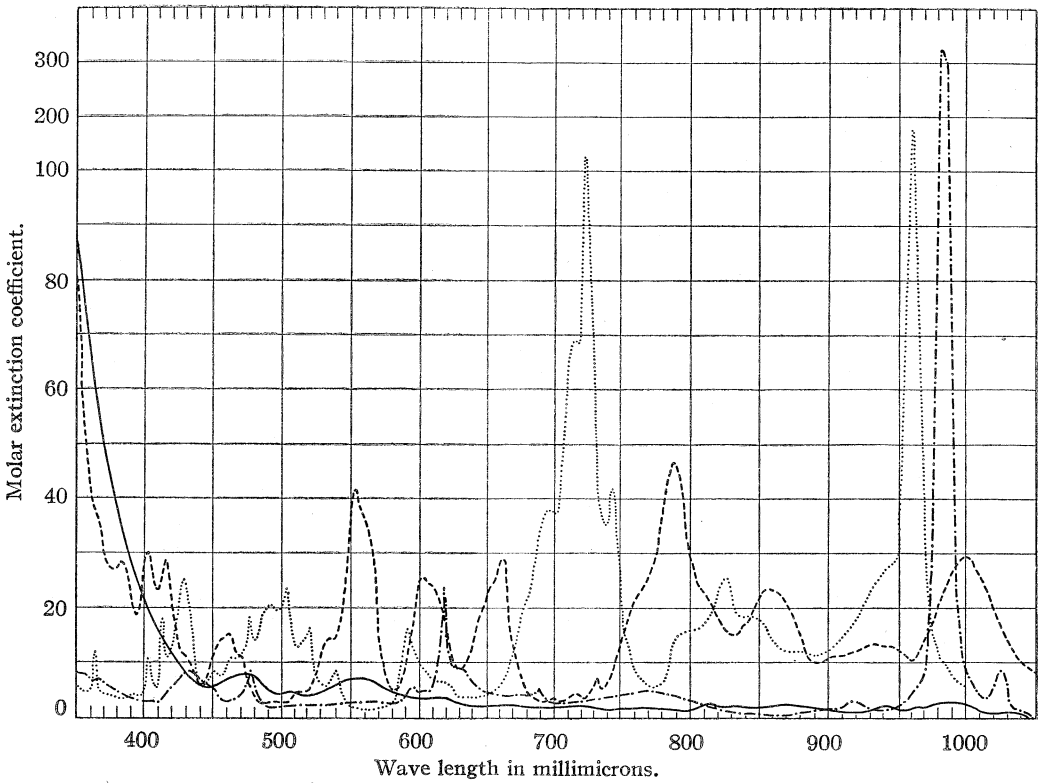



Fig. 2.—Absorption spectra of neptunium ions in aqueous solution: ---, Np(III) in 1.0 *M* HCl; . . ., Np(IV) in 1.0 *M* HCl; -·-, Np(V) in 1.0 *M* HCl; —, Np(VI) in 1.0 *M* $HClO_4$.

optical density (Fig. 1). The spectrum of the latter solution was similar to that of the oxidized perchloric and hydrochloric acid solutions.

A six microliter sample (10 micrograms of neptunium) was removed from the ceric oxidized solution and precipitated in a capillary by making the solution four molar in sodium ion and two molar in acetate ion. An X-ray diffraction pattern of the precipitate was found by Zachariasen[9] to be identical with that of the salt he had previously identified as sodium neptunyl acetate, $NaNpO_2(OOCCH_3)_3$. On the basis of this evidence, it was concluded that the highest oxidation state obtained was +6. The oxidation numbers of the other two states are, therefore, +4 and +5. Data on the stoichiometric reduction of Np(VI) in 0.5 molar sulfuric acid by ferrous ion are also given in Fig. 1.

## Discussion

Differences in absorption spectra have led to the identification of three oxidation states of neptunium in aqueous solution. The lowest state obtained is characterized by two strong, sharp absorption bands at 723 and 964 millimicrons in chloride or perchlorate solution. Figure 2 shows the spectrum of Np(IV) in 1.0 *M* hydrochloric acid solution. These bands are shifted to 727 and 971 millimicrons in 0.5 molar sulfuric acid solution. This shift is presumably caused by complex ion formation involving neptunium(IV) and sulfate ions. The next higher oxidation state, which differs in oxidation number by one unit from both the lowest state and highest state obtained as determined by stepwise spectrophotometric titration with oxidizing or reducing agents, has a spectrum characterized by a sharp, strong band at 984 millimicrons in perchlorate, chloride or sulfate solutions. Figure 2 shows the spectrum of the +5 oxidation state in 1.0 molar hydrochloric acid solution. Isolation of the salt $NaNpO_2(OOCCH_3)_3$ from the solution of highest oxidation number has been used to identify this state as the +6 oxidation state. The oxidation numbers of the other two states are +4 and +5. The spectrum of the +6 state shown in Fig. 2 has no marked absorption bands in the visible region of the spectrum. The spectrum of the +6 perchlorate is given rather than the chloride because of the difficulty in correcting the chloride spectrum for the presence of chlorine.

## 2. The Oxidation Potentials of Neptunium Couples

**The Np(III)–Np(IV) Potential.**—A preliminary attempt to prepare Np(III) by reduction of Np(IV) in 1.0 molar hydrochloric acid at a platinum cathode was unsuccessful, leading to the conclusion that the potential for the Np(III)–Np(IV) couple was more positive than zero. It has been found, however, that the failure to obtain Np(III) may be attributed to the extremely rapid oxidation of Np(III) in the presence of air. Watters[10] showed with the polarograph that Np(III) could be formed in solution; and, although the Np(III)–Np(IV) couple ap-

peared to be irreversible at the dropping mercury electrode, Watters[10] estimated the formal oxidation potential of the couple in 0.25 molar sulfuric acid to be approximately +0.1 volt. Further experiments by the authors revealed that Np(III) could be obtained in fair yield in hydrochloric acid by reduction of Np(IV) with a mercury pool cathode and that Np(III) is stable with respect to oxidation by hydrogen ion in one molar hydrochloric acid.

## Experimental

Gross neptunium concentrations were determined by radiometric assay. Assays of concentrations of the individual oxidation states were made spectrophotometrically. All potential measurements were made at 25 ± 1°, using a Rubicon precision potentiometer and galvanometer of 0.003 microampere per mm. sensitivity.

The micro-scale reduction cell employed for the preparation of Np(III) consisted of a 1-cm. corex spectrophotometer absorption cell with air-tight connections. Details of its construction are given elsewhere.[11] The complete electrolytic apparatus was mounted in a cell holder for convenient transfer to the Beckman spectrophotometer.

1.5 ml. of 0.00752 molar Np(IV) solution in 1.63 molar hydrochloric acid was placed in the cell and the cork sealed with ceresin wax. Oxygen was removed by bubbling pure nitrogen, saturated with water vapor, through the solution for ten minutes before the electrolysis. The solution was reduced by electrolyzing with a current density of *ca.* 8 milliamperes/sq. cm. Nitrogen was continuously bubbled through to stir the solution and to assist in maintaining an oxygen-free atmosphere. The reduction was stopped periodically and the nitrogen inlet and vent disconnected and sealed to permit insertion of the holder into the spectrophotometer. The extent of reduction was determined by observing the decrease in the 723 millimicron absorption band of Np(IV). The change in hydrochloric acid concentration was computed from the total number of coulombs passed through the cell. The solution was electrolyzed for a total of 1278 milliampere-minutes, resulting in a reduction of the hydrochloric acid concentration to 0.96 molar (no volume change perceptible). The optical density of the 723 millimicron band had been reduced to 16% of the value before electrolysis. The nitrogen inlet and vent were sealed and the complete absorption spectrum of the solution was measured over the range 350–1050 millimicrons. Over a period of two hours during the measurement of the absorption spectrum the optical density at 723 millimicrons increased by only 1% of the peak value.

A few bubbles of air were blown through the solution. Alternate measurements of the optical density of the 723 millimicron absorption band and the e.m.f. of the neptunium cell were made. The e.m.f. measurements were made using the $Hg^0$ cathode as the indicator electrode and a saturated potassium chloride–calomel electrode as the reference electrode. The 723 millimicron absorption band optical density was observed to increase steadily over a period of five hours to the maximum value observed in the pure Np(IV) solution before the electrolysis. The measured potentials were very stable, shifting slowly to less positive values as the oxidation proceeded. At the completion of the experiment radiometric assays showed the concentration of the neptunium to be the same as before the electrolysis.

## Results

The color of the Np(III) solution was pale purple, similar to that of U(III) and Pu(III). From a plot of the complete absorption spectrum measured immediately after the electrolysis, the amount of Np(IV) present in the solution was estimated by a series of approximations. It was concluded that the Np(IV) had been approximately 87% reduced to Np(III). The Np(III) absorption spectrum reproduced in Fig. 2 was obtained by correcting the observed spectrum for the Np(IV) contribution.

The optical density of the solution at the times of e. m. f. measurements was obtained by interpolation from a density–time plot. The Np(III) and Np(IV) concentrations were derived from the equation

$$D - E_{III}C/E_{IV} - E_{III} = C_{IV} \qquad (1)$$

where $C$ = total neptunium concentration in moles liter$^{-1}$; $D$ = measured optical density at 723 millimicrons; $E_{III}$ = molar extinction coefficient of Np(III) at 723 millimicrons; $E_{IV}$ = molar extinction coefficient of Np(IV) at 723 millimicrons; $C_{III}$ = concentration of Np(III) in moles liter$^{-1}$; $C_{IV}$ = concentration of Np(IV) in moles liter$^{-1}$.

The molar extinction coefficients, $E_{III}$ and $E_{IV}$, were evaluated as follows: The measured optical density of the Np(IV) 723 millimicron band has been found from independent measurements to conform to Beer's law over the range of concentrations of Np(IV) in this experiment, the molar extinction coefficient being equal to 126.[12] A value for the molar extinction coefficient, $E_{III}$, of 4.2 was obtained by subtracting the estimated peak height at 723 millimicrons contributed by Np(IV) in a complete spectrum measured after reduction. Concentrations of Np(III) and Np(IV) at the times of e. m. f. measurement were calculated directly from the interpolated density at 723 millimicrons using equation 1. The formal potential, $E_f$, of the Np(III)–Np(IV) couple was calculated by the use of equation 2.

$$E_f = -E_{measured} + E^0(Hg\text{–}HgCl) + 0.05914 \log (C_{IV}/C_{III}) \qquad (2)$$

The $E^0$ of the saturated calomel reference electrode was taken as −0.245 volt. The formal potential as defined by equation 2 is the potential of the Np(III)–Np(IV) couple in 1 molar hydrochloric acid at equal concentrations of Np(III) and Np(IV).

Although the precision of the measurements is higher, the measured potentials are not considered to be more accurate than ±0.005 volt. On this basis the potential of the couple

$$Np(III) \rightleftharpoons Np(IV) + e^- \qquad (3)$$

is −0.137 ± 0.005 volt.

**The Np(IV)–Np(V) Potential.**—The potential of a bright platinum electrode inserted in a solution containing Np(IV) and Np(V) in one molar hydrochloric acid drifts to less positive values with no indication of approaching constancy

(11) L. B. Magnusson, T. J. LaChapelle and J. C. Hindman, to be published as paper No. 15.3, Vol. 14B, Plutonium Project Record of the National Nuclear Energy Series.

(12) J. C. Hindman, L. B. Magnusson and T. J. LaChapelle, paper to appear as No. 15.2 of Vol. 14B, Plutonium Project Record of the National Nuclear Energy Series.

TABLE I

THE FORMAL OXIDATION POTENTIAL OF THE Np(III)–Np(IV) + $e^-$ COUPLE IN 1.0 MOLAR HYDROCHLORIC ACID

| Optical density at 723 millimicrons | Np(IV) moles/liter × $10^3$ | Np(IV)/Np(III) | $E_{meas.}$ volt | $E_f$, volt |
|---|---|---|---|---|
| 0.157 | 1.03 | 0.162 | 0.154 | −0.138 |
| .184 | 1.26 | .205 | .146 | − .140 |
| .236 | 1.68 | .293 | .140 | − .136 |
| .266 | 1.93 | .352 | .136 | − .136 |
| .274 | 2.00 | .370 | .135 | − .136 |
| .315 | 2.33 | .459 | .128 | − .137 |
| .334 | 2.49 | .506 | .126 | − .136 |
| .360 | 2.70 | .574 | .123 | − .136 |
| .387 | 2.92 | .651 | .121 | − .135 |
| .438 | 3.34 | .821 | .115 | − .135 |
| .487 | 3.75 | 1.02 | .108 | − .136 |
| .589 | 4.58 | 1.62 | .096 | − .137 |
| .639 | 4.99 | 2.06 | .089 | − .137 |
| .661 | 5.17 | 2.31 | .083 | − .140 |
| .707 | 5.55 | 2.98 | .080 | − .137 |
| .743 | 5.85 | 3.75 | .074 | − .137 |
| .781 | 6.16 | 4.92 | .065 | − .139 |
| .812 | 6.41 | 6.41 | .060 | − .137 |
| .814 | 6.43 | 6.56 | .058 | − .138 |
| .817 | 6.46 | 6.87 | .056 | − .139 |
| .849 | 6.72 | 9.75 | .049 | − .138 |
| .852 | 6.74 | 10.05 | .047 | − .139 |
| .856 | 6.78 | 10.8 | .045 | − .139 |

within a period of several hours. For this reason, an indirect method was used to obtain the potential of this couple. Preliminary experiments showed that the reduction of Np(V) by Fe(II) was not quantitative in one molar hydrochloric acid. Estimates of the potential were therefore obtained from measurements on solutions containing Np(V), Np(IV), Fe(III) and Fe(II) in equilibrium.

## Experimental

In the first experiment, 2.0 ml. of a 0.0042 molar Np(VI) solution in 1.00 molar hydrochloric acid was titrated with a 1.00 molar Fe(II) solution in 1.00 molar hydrochloric acid. The Fe(II) solution was prepared by dissolving a weighed quantity of $Fe^0$ in hydrochloric acid. The reduction was followed spectrophotometrically. Although the reduction of the Np(VI) to Np(V) was instantaneous the further reduction to Np(IV) took approximately eighty minutes to reach equilibrium after each addition of Fe(II). The concentration of Np(IV) was calculated from the optical density of the 723 millimicron band and the concentration of the Np(V) by difference. The electrode system used consisted of a bright platinum indicator electrode and a $Ag^0$–AgCl reference electrode.

TABLE II

POTENTIAL MEASUREMENTS ON Np(IV)–Np(V) COUPLE IN 1.00 *M* HCl (0.00423 *M* Np; $t$ = 25°)

| Np(V)/Np(IV) | $E$ obs., volt | $E_f$, volt |
|---|---|---|
| 5.04 | 0.530 | −0.734 |
| 2.01 | .510 | − .737 |
| 0.790 | .487 | − .738 |
| 0.447 | .471 | − .732 |
| 0.0944 | .440 | − .746 |
| | Av. | −0.737 |

TABLE III

POTENTIAL MEASUREMENTS ON Np(IV)–Np(V) COUPLE IN 1.00 *M* HCl ($t$ = 25°)

| Np, mole/liter | Np(V)/Np(IV) | $E$ obs., volt | $E_f$, volt |
|---|---|---|---|
| 0.00366 | 0.167 | 0.453 | −0.739 |
| .00366 | .0388 | .423 | − .750 |
| .00274 | .676 | .491 | − .746 |
| .00274 | .129 | .430 | − .727 |
| .00396 | .247 | .474 | − .737 |
| .00396 | .0883 | .436 | − .725 |
| | | Av. | −0.737 |

In two additional experiments, potential measurements were taken at two ratios of Np(IV) to Np(V).

## Calculations and Results

The formal oxidation potential of the Np(IV)–Np(V) couple was calculated from the equation

$$E_f = -E_{measured} + E_{Ag^0-AgCl} + 0.05914 \log a_{Cl^-} + 0.05914 \log \frac{C_V}{C_{IV}} \quad (4)$$

In this equation $C_V$ and $C_{IV}$ represent the molar concentrations of Np(V) and Np(IV), respectively. The $E$ value of the $Ag^0$–AgCl electrode is taken as −0.222 volt and the value of $a_{Cl^-}$ as 0.84 (the mean activity of a one molar hydrochloric acid solution).

The data are summarized in Tables II and III. The accuracy of the measurements is not considered to be greater than ±10 millivolts. The potential of the couple

$$Np(IV) \longrightarrow Np(V) + e^- \quad (5)$$

is −0.74 ± 0.01 volt in one molar hydrochloric acid at 25°.

**The Formal Potential of the Np(V)–Np(VI) Couple.**—The couple was measured in 1.00 molar hydrochloric acid solution during the course of a stannous ion reduction of Np(VI).

## Experimental

The cell consisted of a bright platinum wire indicator electrode and a silver–silver chloride reference electrode. The neptunium was reduced by adding an aliquot of 0.05 molar stannous chloride in 1.0 molar hydrochloric acid and measuring the potential after equilibrium was established as judged by a constant optical density for the 984 millimicron Np(V) absorption band. Reduction of Np(VI) by chloride caused a slow falling off of the measured potential so the first reading obtained upon inserting the electrode was taken as most nearly representing the true potential.

## Calculations and Results

The formal potential of the Np(V)–Np(VI) couple in 1.00 molar hydrochloric acid was calculated in two ways from the data obtained. The first method involved the determination of the Np(V) concentration spectrophotometrically and

the concentration of the Np(VI) by difference. Observation has shown that the Np(V) band at 984 millimicrons does not obey Beer's law. Since accurate calibration curves were not available the spectrophotometric densities were disregarded except for determination of equilibrium after each addition of stannous chloride. The amount of Np(VI) in the solution was obtained by subtraction according to the reaction equivalence

$$2Np(VI) + Sn(II) \rightleftarrows 2Np(V) + Sn(IV) \quad (6)$$

This method of calculation gave more consistent results. The potentials were calculated by an equation analogous to equation 4. The data are summarized in Table IV.

TABLE IV

FORMAL OXIDATION POTENTIALS FOR THE Np(V)–Np(VI) COUPLE in 1 *M* HCl, 0.00556 *M* Np; $t = 25°$

| $\frac{NpVI}{NpV}$ | $E_{meas.}$, volt | $E_f$, volt |
|---|---|---|
| 1.90 | 0.912 | −1.135 |
| 1.50 | .904 | −1.134 |
| 1.21 | .900 | −1.135 |
| 0.771 | .891 | −1.138 |
| .487 | .875 | −1.134 |
| .281 | .863 | −1.136 |
| .130 | .842 | −1.135 |

Although it is believed that the cell behaved reversibly, two complicating factors reduced the precision of measurement: (1) Np(VI) is slowly reduced by chloride in the presence of platinum, and (2) the reduction of Np(VI) by Sn(II) is rather slow, so that attainment of equilibrium is somewhat uncertain. The formal oxidation potential for the reaction

$$Np(V) \rightleftarrows Np(VI) + e^- \quad (7)$$

is $-1.14 \pm 0.02$ volt in one molar hydrochloric acid at 25°.

## Discussion

Although the oxidation potentials of the couples given in this paper are not thermodynamic $E^0$ values, they are nevertheless quite useful in predicting the stabilities of the different oxidation states and their probable reactions with various oxidizing and reducing agents.

Direct observation of the stabilities of the various oxidation states is in agreement with what would be expected on the basis of the reported oxidation potentials. Np(III) in one molar hydrochloric acid is extremely unstable to air oxidation and can be maintained in solution only by using precautionary measures to exclude oxygen. Both the +4 and +5 states have been found to be stable in one molar hydrochloric acid over periods of days. From the potential of the couple of −0.74 v., air oxidation of Np(IV) to Np(V) can occur, although the reaction is slow. Np(V) solutions exhibit the expected stability in one molar hydrochloric acid solution. Np(VI) is not stable in hot one molar hydrochloric acid, being slowly reduced to Np(V). Although the reaction with cold hydrochloric acid is very slow at room temperatures, contact with platinum catalyzes the reduction in some manner so that Np(V) is produced at an appreciable rate at the platinum surface. Np(III) undoubtedly cannot be maintained in a nitrate solution, and Np(IV) is slowly oxidized to Np(V) in nitric acid. Np(V) solutions have been prepared in one molar nitric acid with no evidence of disproportionation into Np(IV) and Np(VI). It is expected that the Np(IV)–Np(V) potential in one molar nitric acid is close to that in hydrochloric acid.

Np(V) disproportionates to a considerable extent in one molar sulfuric acid because of preferential complexing of Np(IV) and Np(VI) by the sulfate ion. In high concentration of sulfuric acid, Np(V) would be unstable since, in addition to the sulfate effect, the disproportionation reaction probably has a hydrogen ion dependence.

Considerable evidence has been accumulated to show that the ions of the +3, +4, +5 and +6 oxidation states of neptunium, like those of the corresponding oxidation states of the elements uranium and plutonium, are $Np^{+3}$, $Np^{+4}$, $NpO_2^+$ and $NpO_2^{++}$ in molar acid solution in the absence of complexing agents. Details of this evidence will appear in subsequent publications.

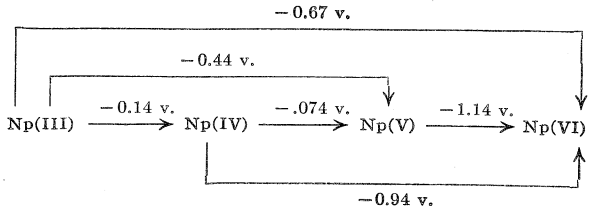
The reversibility of the Np(III)–Np(IV) and the Np(V)–Np(VI) couples is probably connected with the fact that only electron transfers are involved, whereas the irreversibility of the Np(IV)–Np(V) couple would appear to arise from the fact that oxygen transfer must also occur, a process which would appear to be slow at a noble metal electrode. The sluggishness of reactions involving the oxidation of Np(IV) or the reduction of Np(V), as by ferrous ion or stannous ion, would also presumably be attributable to the slowness of the oxygen transfer process.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. G. T. Seaborg for his stimulating interest and advice during the course of this research. The authors also wish to acknowledge the many helpful suggestions made by Dr. B. B. Cunningham.

## Summary

Spectrophotometric titrations of neptunium solutions with oxidizing and reducing agents have been used, together with the isolation of the salt $NaNpO_2(OOCCH_3)_3$ from the solution of the highest oxidation state obtained, to establish the existence of the +4, +5 and +6 states of neptunium. In contrast to both uranium and plutonium, the +5 state of neptunium has been found to be quite stable in acid solution.

The formal oxidation potentials for the various neptunium couples have been measured in one molar hydrochloric acid. These may be represented schematically as follows:




The Np(III)–Np(IV) and Np(V)–Np(VI) couples have been found to behave reversibly while the Np(IV)–Np(V) couple is irreversible. In the latter case measurements of the potential in a system in equilibrium with Fe(II) and Fe(III) have been used to obtain the value of the couple.

RECEIVED SEPTEMBER 20, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Supported Oxides of Manganese[1]

BY P. W. SELWOOD, T. E. MOORE,[2] MARYLINN ELLIS AND KATHRYN WETHINGTON

The applicability of the susceptibility isotherm method has already been described for supported oxides of chromium, and of copper. The present paper describes exploratory studies on the use of the method for supported oxides of manganese. Similar papers on nickel and on iron and other elements will shortly be forthcoming from this Laboratory.[3]

## Experimental Part

X-Ray, magnetic susceptibility and surface area studies were made by standard methods previously described.[3]

One of the objectives of all this work is the relation of inorganic structure to catalyst activity. The various supported oxide systems are, therefore, referred to as catalysts, even though their applicability as catalysts may not be obvious.

**Preparation of Catalysts.**—Manganese oxides supported on alumina were prepared as follows: a water solution made from recrystallized manganous nitrate was impregnated in excess on γ-alumina. The area of the alumina was about 200 m.$^2$ g.$^{-1}$ (BET nitrogen). The susceptibility of the alumina was $-0.3 \times 10^{-6}$ and was independent of temperature. The impregnated alumina was filtered with suction, then dried and heated to 150–160° for forty-eight hours under slightly reduced pressure. The product was removed, ground, screened and reheated for twenty-four hours at 200°. This procedure would normally be expected to yield a layer of manganese dioxide in the *pyrolusite* structure covering the alumina. A series of catalysts was prepared in this way. Variations in manganese content was obtained by changing the concentration of the impregnating solution. Manganese concentrations ran from about 1 to over 20%. The color of all the finished catalysts ranged from pale tan to black. Analytical and other data are given below.

Prolonged heating of manganese dioxide results in the quantitative formation of the sesquioxide in the *bixbyite* structure. Some of the catalysts described above were subjected to thermal decomposition at 600°. The properties of this series are also described below.

During the course of this work it became obvious that manganese oxides supported on high-area *rutile* would be an interesting system for study. Considerable difficulty was experienced in obtaining this support, but finally a laboratory prepared sample was obtained from the National Lead Company, Titanium Division. This titania was all in the *rutile* structure, had a surface area of about 129 m.$^2$ g.$^{-1}$ (BET nitrogen), and had a susceptibility of $-0.3 \times 10^{-6}$, which was substantially independent of temperature.

A series of supported manganese catalysts was prepared on the titania by procedures identical with those described for the alumina support, except that heating was not carried over 200°. Somewhat more concentrated impregnating solutions were found to be required to obtain equivalent concentrations of manganese on titania as compared with alumina.

One catalyst was made containing rhenium supported on alumina. γ-Alumina was impregnated with a hot saturated solution of potassium perrhenate. The mixture was kept hot for twenty minutes, then filtered and dried at 110°. The sample was then ignited in vacuum to 350°. After magnetic and other measurements had been made the sample was further heated in hydrogen at 350° for twenty-four hours. Before reduction the sample was white, and afterward gray. A few miscellaneous preparations are briefly indicated below.

**Analytical Procedures.**—The analytical data required were (1) manganese, and (2) "active" oxygen. For the manganese determination the sample was dissolved in sulfuric acid containing ferrous sulfate. The manganese was then oxidized with sodium bismuthate in nitric acid. The resulting permanganate was titrated with ferrous sulfate.

(1) This paper describes, in part, work performed under contract with the Squier Signal Laboratory, Signal Corps Engineering Laboratories, as part of their program for the improvement of dry cells.

(2) Present address: Department of Chemistry, Oklahoma A. and M. College, Stillwater, Oklahoma.

(3) This is the fifth paper on the susceptibility isotherm from this Laboratory. The third and fourth appeared in THIS JOURNAL, **70**, 2145, 2271 (1948).

For "active" oxygen a known excess of standard ferrous ammonium sulfate was employed in dissolution of the sample. The excess was then titrated with standard permanganate.

The titania-supported samples were very slow to dissolve. In fact, direct solution in sulfuric acid probably would not have been possible had not the original ignition temperature been kept down to 200°. Fortunately, higher ignition temperatures were not necessary.

The single sample of supported rhenium on alumina was analyzed by the nitron acetate method.[4]

## Results

The first series to be considered is that in which manganous nitrate is impregnated on γ-alumina and then ignited at not over 200°. The results are presented in Table I. Following plans used previously we give the weight per cent. of manganese in each sample, and the magnetic susceptibility per gram of sample at three temperatures. Directly below each measured susceptibility there is given the calculated susceptibility per gram of manganese in each corresponding sample. Thus the first catalyst sample had a susceptibility at 25° of $13.8 \times 10^{-6}$ per gram of sample. This sample contained 23.4% of manganese, and the susceptibility per gram of manganese is then $60.4 \times 10^{-6}$.

Table II shows similar data for the same system ignited at 600°, and Table III gives the corresponding data for the manganese oxide supported on high-area *rutile*.

TABLE I

SUSCEPTIBILITY OF MANGANESE OXIDE ON ALUMINA, IGNITED AT 200°

| Wt. % manganese | Susceptibilities × $10^6$ 83°K. | 195°K. | 298°K. |
|---|---|---|---|
| 63.1 (crystalline *pyrolusite*) | 44 | 31 | 27 |
| | 69.8 | 49.1 | 42.8 |
| 23.4 | 27.5 | 16.8 | 13.8 |
| | 119 | 73.2 | 60.4 |
| 20.8 | 21.6 | 14.9 | 12.1 |
| | 105 | 73.2 | 59.7 |
| 19.8 | 20.4 | 14.0 | 11.2 |
| | 105 | 72.3 | 58.1 |
| 16.1 | 17.2 | 11.5 | 9.1 |
| | 109 | 73.1 | 58.5 |
| 11.9 | 10.1 | 7.6 | 6.0 |
| | 87.4 | 66.5 | 52.9 |
| 10.0 | 7.9 (102°K.) | 6.2 (186°K.) | 5.1 |
| | 82.0 | 65.0 | 54.1 |
| 8.5 | 6.8 | 5.1 | 4.1 |
| | 84.8 | 64.8 | 52.9 |
| 8.5 | 6.4 (102°K.) | 5.7 (186°K.) | 4.2 |
| | 80.0 | 71.7 | 54.2 |
| 8.3 | 6.1 (102°K.) | 5.1 (186°K.) | 4.1 |
| | 78.3 | 66.3 | 54.2 |
| 4.6 | 6.6 | 3.5 | 2.7 |
| | 152 | 84.8 | 67.3 |
| 3.1 | 5.4 | 3.5 | 2.6 |
| | 187 | 126 | 96.7 |
| 3.0 | 4.1 | 2.4 | 1.7 |
| | 150 | 93.3 | 70.0 |
| 2.4 | 8.1 | 3.7 | 2.7 |
| | 355 | 171 | 129 |
| 1.8 | 6.3 | 2.6 | 1.9 |
| | 371 | 167 | 128 |
| 1.3 | 4.8 | 2.2 | 1.3 |
| | 400 | 200 | 131 |
| 1.0 | 5.0 | 2.2 | 1.3 |
| | 540 | 260 | 170 |
| 0.6 | 2.6 | 1.0 | 0.6 |
| | 500 | 235 | 167 |

TABLE II

SUSCEPTIBILITY OF MANGANESE OXIDE ON ALUMINA, IGNITED AT 600°

| Wt. % manganese | Susceptibilities × $10^6$ 83°K. | 195°K. | 298°K. |
|---|---|---|---|
| 26.3 | 66.7 | 45.7 | 34.0 |
| | 255 | 175 | 131 |
| 18.5 | 47.1 | 30.7 | 23.9 |
| | 255 | 168 | 131 |
| 16.6[a] | 39.2 | 28.7 | 19.1 |
| | 238 | 175 | 118 |
| 8.9 | 23.6 | 15.9 | 11.2 |
| | 269 | 182 | 129 |
| 6.1[a] | 18.8 | 10.3 | 7.1 |
| | 315 | 175 | 123 |
| 4.4 | 15.2 | 8.8 | 5.9 |
| | 353 | 209 | 143 |
| 4.0[a] | 14.9 | 8.0 | 4.8 |
| | 383 | 200 | 130 |
| 3.0 | 13.1 | 6.5 | 4.5 |
| | 447 | 231 | 160 |
| 2.7[a] | 12.8 | 5.3 | 3.4 |
| | 489 | 211 | 141 |
| 1.8 | 8.0 | 3.9 | 2.4 |
| | 462 | 240 | 156 |
| 1.1[a] | 7.6 | 2.7 | 1.6 |
| | 727 | 282 | 182 |
| 1.0 | 4.6 | 2.1 | 1.2 |
| | 492 | 251 | 160 |

[a] Sample was prepared by direct decomposition of manganous nitrate on alumina at 600°. The other samples were derived from those of Table I by further heat treatment at 600°. There does not seem to be any difference in the two preparations.

The remaining experimental and derived data are more conveniently shown graphically. Figure 1 shows susceptibility isotherms for the three states of supported manganese, namely, low-temperature ignition on alumina, high-temperature ignition on alumina, and ignition on *rutile*.

Figures 2, 3 and 4 show, respectively, the concentration of manganese plotted against magnetic moment for each of the three series. The magnetic moment is given in Bohr magnetons as calculated from the usual formula $\mu = 2.84\sqrt{\chi_M(T + \Delta)}$. On the same graphs there are

(4) Furman, "Scott's Standard Methods of Chemical Analysis," 5th ed., D. Van Nostrand Co., Inc., New York, N. Y., 1939, p. 771.

TABLE III

SUSCEPTIBILITY OF MANGANESE OXIDE ON *Rutile*

| Wt. % manganese | Susceptibilities × $10^6$ 102°K.[a] | 186°K. | 298°K. |
|---|---|---|---|
| 18.8 | 15.1 | 12.7 | 10.2 |
| | 78.7 | 66.5 | 53.8 |
| 12.5 | 12.4 | 9.8 | 7.5 |
| | 96.8 | 76.7 | 59.2 |
| 7.9 | 9.7 | 7.1 | 5.7 |
| | 119 | 87.4 | 71.0 |
| 3.9 | 6.7 | 4.7 | 3.5 |
| | 167 | 115 | 87.2 |
| 3.1 | 6.1 | ... | 2.9 |
| | 194 | ... | 90.4 |
| 1.3 | 4.1 | 2.7 | 1.7 |
| | 292 | 192 | 123 |

[a] Note different temperatures caused by rebuilding of apparatus.

shown the apparent valences of the manganese obtained from the chemical analyses according to the following procedure: total gram-atoms of oxygen in a sample is equal to the sum of gram-atoms of active plus inactive oxygen, and this is equal to the sum of gram-atoms of active oxygen plus manganese. The valence of manganese is twice the gram-atoms of total oxygen per gram-atom of manganese.

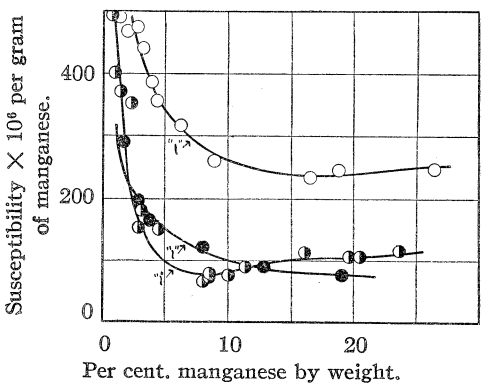



Fig. 1.—Susceptibility isotherms for supported manganese oxides at −171°: O, high ignition on $Al_2O_3$; ◑, low ignition on $Al_2O_3$; ●, $MnO_2$ on $TiO_2$.

Figure 5 shows percentage of manganese plotted against the Weiss constant ($\Delta$) for all three series of catalysts.

The single sample of supported rhenium on γ-alumina contained 4.8 per cent. of rhenium. The magnetic susceptibility before reduction was 0.3 × $10^{-6}$, and after reduction it was −0.1 × $10^{-6}$. Supported rhenium obviously does not show the magnetic dispersion effect.

## Discussion of Results

Supported manganese shows the same magnetic dispersion effect first reported for chromium and now shown to apply to nearly all paramagnetic ions except molybdenum and rhenium. The effect will, for obvious reasons, probably not be found in the paramagnetic rare earths. Its failure to appear in molybdenum and rhenium is probably due to covalent bonds between adjacent positive ions.

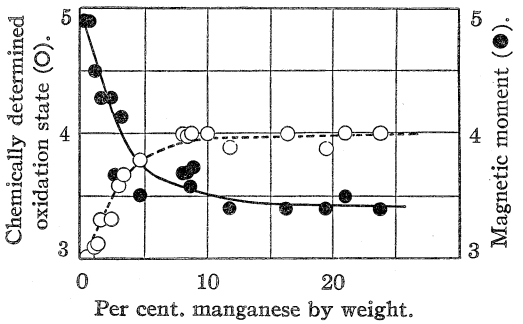



Fig. 2.—Oxidation state (O), and magnetic moment (●) for low-ignition series on alumina.

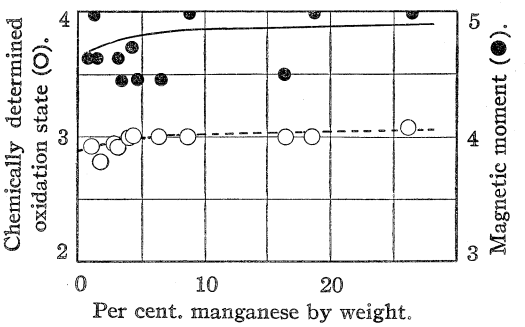



Fig. 3.—Oxidation state (O), and magnetic moment (●) for high-ignition series on alumina.

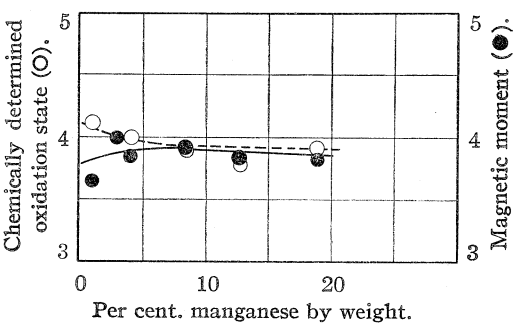



Fig. 4.—Oxidation state (O), and magnetic moment (●) for series on *rutile*.

The general shape of the susceptibility isotherm for supported manganese is the same as for the chromia–alumina system, except that the low-ignition series on alumina shows a very much sharper point "*l*" than anything heretofore observed. It is more convenient to discuss the high-ignition series on alumina first.

It would be expected that ignition of manganous nitrate at 600° would result in the formation of reasonably pure $Mn_2O_3$. The magnetic moment in the supported series ignited at this temperature is shown to be very close to the theoretical spin-only moment (4.9) for manganese in the plus three oxidation state. The conclusion that man-

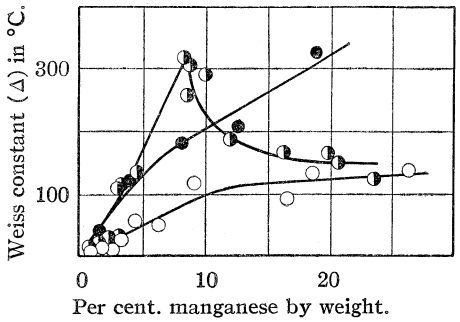



Fig. 5.—Weiss constants as a function of concentration: ○, high-ignition on $Al_2O_3$; ◑, low-ignition on $Al_2O_3$; ●, $MnO_2$ on $TiO_2$.

ganese has a valence of three throughout this series is amply verified by direct chemical analysis for total manganese and for active oxygen.

The shape of the susceptibility isotherm in this series is, therefore, in no way connected with changing oxidation state, and must be attributed to changing environment. The large change of the Weiss constant with manganese concentration is evidence that the number of nearest manganese neighbors possessed by each manganese ion changes rapidly at the lower manganese concentrations. Following the argument previously presented for chromium, with which this series is closely parallel, we conclude that the manganese ions are aggregated in microcrystals of $Mn_2O_3$, and that much of the alumina surface remains bare. Our conclusion is, again, that as at point "*l*" the manganese oxide layers are only three or four atoms thick. This general pattern seems to be the commonest susceptibility isotherm encountered.

The situation with respect to low temperature ignition of manganous nitrate on alumina is very different. Ignition at 200° would normally yield *pyrolusite*. The actual result, however, is that while the manganese clearly has an oxidation state of plus four at high concentrations, the oxidation state is definitely three at low concentrations. This result is shown both by the chemical analysis and by the magnetic moment, which are in excellent agreement with each other. (The theoretical spin-only moment for $Mn^{+4}$ is 3.87). Simultaneous with this change in oxidation state, the Weiss constant shows an astonishing maximum in the neighborhood of 8% manganese.

We shall first consider the surprising change in oxidation state from four to three as the manganese concentration is lowered. It is well known that the $Mn^{+3}$ ion has approximately the same radius as the $Al^{+3}$ ion, and also that the $\gamma$-form of $Mn_2O_3$ is isomorphous with $\gamma$-$Al_2O_3$. It is suggested that the crystal lattice of the alumina exerts an inductive action on the manganese sufficient to cause a change of valence. It might be said that the manganese oxide attempts to imitate the crystal structure of the support, even to the extent of changing oxidation state. The effect described is somewhat related to the phenomenon of oriented overgrowth, and is reminiscent of a current theory of nucleoprotein synthesis.[5]

This effect apparently is of fairly general occurrence with transition group ions, provided the proper charge and radius may be assumed without too much difficulty. The effect does not occur with copper or silver supported on alumina, but it does occur with nickel on alumina and on *rutile*. It occurs with iron on *rutile* as will be described in forthcoming papers, and it occurs with manganese on *rutile* as shown in the results given in this paper. The effect may be expected to have a number of applications in the field of promoters, catalysts in general, corrosion, coprecipitation, crystallography and in the preparation of unique oxidizing agents.

It remains to explain the peculiar Weiss constant found in this series. It seems probable that the layers of manganese atoms in actual contact with alumina always are subject to the inductive action of the alumina and consequently always have the manganese in the plus three oxidation state. When large amounts of manganese are present these surface layers are negligible in their percentage contribution to the magnetic susceptibility. But as the concentration of manganese goes down the relative importance of the layers next to the alumina progressively increases until they ultimately account, at the limit, for all the manganese present.

Hence, according to this picture, the apparent change of oxidation state in the manganese is not so much an actual change in valence as a change in the ratio of manganese touching alumina and hence in the +3 state, to manganese merely touching manganese and hence reverting to the normal +4 state.

If the degree of exchange interaction in *bixbyite* were greater than that in *pyrolusite*, then the anomalous Weiss constants obtained would be easily explained. Actually the Weiss constants for supported +3 manganese are consistently lower than those for +4 manganese. This is clearly shown in Fig. 5. In order to further establish this point some Mn(III) on alumina was prepared by hydrogen reduction at 200° rather than by thermal decomposition at 600°. This also showed a lower Weiss constant than the +4 state.

In seeking an explanation of the anomalous Weiss constants in the $MnO_2/Al_2O_3$ series consideration was given to the fact that many solids show a variety of peculiar properties when metal ions of differing charges occupy adjacent positions in the lattice. It was thought that possibly the exchange interaction would increase if a +3 Mn ion were adjacent to a +4 ion, and that the large increase of the Weiss constant might be a measure of the number of manganese ions in this peculiar

(5) A preliminary communication concerning this effect of valence inductivity was given in THIS JOURNAL, **70**, 883 (1948).

condition, namely, of being adjacent to manganese ions of different charge.

A further experiment was performed for the purpose of testing this idea. The experiment has some unusual features and will be described.

**Slow Reduction of $MnO_2/Al_2O_3$.**—A catalyst containing 20% manganese, substantially all in the +4 state, on alumina was slowly reduced in hydrogen at 180°. The reduction to the +3 state at this temperature took several weeks. At frequent intervals the sample was cooled, removed, and its susceptibility was determined. Figure 6 shows the Weiss constant of this sample plotted as a function of oxidation state.

In this experiment it was hoped that there would be produced a detectable proportion of +3 and +4 manganese ions in adjacent positions. The experiment is obviously one of some difficulty because of the tendency for heterogeneous reactions to proceed from discrete spots so that +3, +4 ion groups may occur only instantaneously at the reaction boundary. Furthermore, there is no reason to expect a maximum number of such groups at the point of 50% conversion from +4 to +3 manganese.

Under these circumstances the results are very gratifying. It is clearly shown that during the course of reduction the Weiss constant rises, but that when reduction is complete the Weiss constant is lower for the supported +3 state than for the +4 state. The erratic changes observed for the Weiss constant are not experimental error, but are probably a measure of the fluctuating proportion of +3, +4 ion groups present at the various stages of reduction.

The success of this experiment supports the view expressed concerning the anomalous Weiss constants found in this system.

The peculiar susceptibility isotherm found for the low-ignition manganese on alumina series is thus seen to be due to a combination of two changes both of which lead to greatly increased susceptibility at low manganese concentrations. These two changes are a change of oxidation state, and a change of environment. While both changes lead to an increase of susceptibility, the changing oxidation state alone at first produces an increase of the Weiss constant, but the increasing dispersion ultimately reduces the Weiss constant to zero. This is the first example we have encountered where the shape of the susceptibility isotherm is determined both by an oxidation state change and an environmental change.

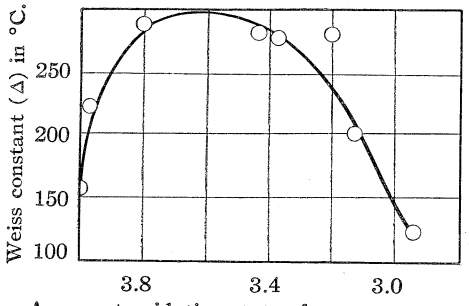



Fig. 6.—Weiss constants as a function of oxidation state during slow reduction of $MnO_2$ to $Mn_2O_?$.

The idea of supporting manganese on *rutile* was suggested by the considerations described above. It was clear that if our interpretation were correct then manganese on high-area *rutile* ought to yield all the manganese in the oxidation state of plus four. This proved to be the case and the susceptibility isotherm is a typical example of the type in which the whole change is due to change of environment and not to change of oxidation state. Titania seems to be the only diamagnetic solid isomorphous and approximately isometric with *pyrolusite*, of reasonable stability, and capable of being prepared in a high-area form.

It may be objected that manganous nitrate would give Mn(IV) even if ignited on low-area *rutile*. This is, of course, correct, but in that case the normal dispersion effect would be absent, the susceptibility of the manganese would be independent of concentration and the situation would resemble that previously reported for chromia supported on low-area corundum.

## Summary

The susceptibility isotherm method has been extended to supported manganese. It has been found that in favorable cases supported transition group oxides may imitate the crystal structure of the support even to the extent of changing oxidation state.

EVANSTON, ILLINOIS RECEIVED AUGUST 9, 1948

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

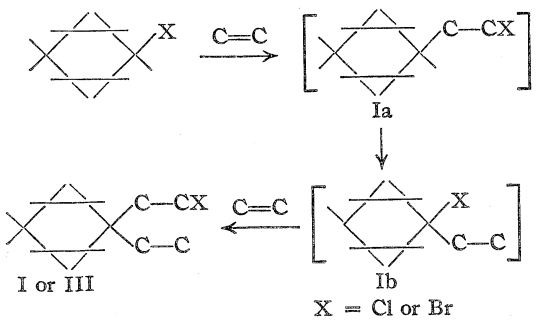
# Condensation of Saturated Halides with Unsaturated Compounds. V. Condensation of Cycloalkyl Halides with Ethylene and with Vinyl Halides

BY LOUIS SCHMERLING

The condensation of alkyl chlorides and bromides with olefins,[1] cycloölefins[2] and haloölefins[3] in the presence of metal halide catalysts was described in previous papers in this series. Examples of the reaction of cycloalkyl chlorides and bromides with ethylene and chloroethylene are given in the present communication (Table I).

The condensation of the tertiary chloride, 1-chloro-1-methylcyclohexane, with ethylene in the presence of aluminum chloride or ferric chloride yielded 1-(2-chloroethyl)-1-methylcyclohexane (II), the product of the addition of the chlorine atom and the 1-methylcyclohexyl group to the double bond of the olefin. Hydrolysis of the chloride yielded an alcohol, presumably 2-(1-methylcyclohexyl)-ethanol.

When the secondary chloride, chlorocyclohexane, was condensed with ethylene, the product was not the expected (2-chloroethyl)-cyclohexane (Ia) but rather 1-(2-chloroethyl)-1-ethylcyclohexane (I) formation of which involved the reaction of two molecular proportions of ethylene




The primary compound, Ia, contains a tertiary carbon atom and readily isomerizes to the tertiary chloride, Ib, which is more reactive than the original secondary chloride and rapidly condenses with ethylene to yield I. Since I does not contain a tertiary carbon atom, it undergoes no further reaction and is, therefore, the principal condensation product. The plausibility of this mechanism and of the structure assigned to the product was indicated by the fact that I was also obtained by the reaction of synthetic 1-chloro-1-ethylcyclohexane (Ib) with ethylene in the presence of aluminum chloride at −10 to 0°.

In a similar manner, the reaction of bromocyclohexane with ethylene in the presence of aluminum chloride produced 1-(2-bromoethyl)-1-ethylcyclohexane (III). That the bromo and chloro compounds had the same carbon skeleton was shown by converting them to the same derivative. Furthermore, condensation of (2-bromoethyl)-cyclohexane (Ia) with ethylene also yielded 1-(2-bromoethyl)-1-ethylcyclohexane, thus furnishing additional evidence in support of the mechanism.

The behavior of the secondary cycloalkyl halides is analogous to that of the secondary alkyl chloride, *s*-butyl chloride, which yielded 1-chloro-3-methyl-3-ethylpentane rather than 1-chloro-3-methylpentane when condensed with ethylene in the presence of aluminum chloride.[1]

The reaction of the halocyclohexanes with ethylene offers a means of synthesizing 1-alkyl-1-ethylcyclohexanes. Thus, reduction of 1-(2-bromoethyl)-1-ethylcyclohexane (III) yielded 1,1-diethylcyclohexane which had not been reported previously.

Condensation of vinyl chloride with chlorocyclohexane, 1-chloro-1-methylcyclohexane, and 1-chloro-1-methylcyclopentane, yielded, respectively, (2,2-dichloroethyl)-cyclohexane, 1-(2,2-dichloroethyl)-1-methylcyclohexane, and 1-(2,2-dichloroethyl)-1-methylcyclopentane. The structure of the (2,2-dichloroethyl)-cyclohexane was proved by hydrolyzing it to cyclohexaneacetaldehyde; that of the 1-(2,2-dichloroethyl)-1-methylcyclohexane was supported by its hydrolysis to an aldehyde identical with that obtained by oxidation of the alcohol prepared via the condensation of 1-chloro-1-methylcyclohexane with ethylene.

(2,2-Dibromoethyl)-cyclohexane was obtained by the reaction of bromocyclohexane with vinyl bromide in the presence of aluminum chloride.

## Experimental

**Procedures.**—The experimental procedures will be summarized very briefly since they were similar to those previously described for the analogous reactions of alkyl halides with ethylene[1] and with haloölefins.[2]

In Method A, ethylene was bubbled through a stirred mixture (cooled to about −60°) of the cycloalkyl halide, *n*-pentane diluent (if used) and the catalyst. The temperature of the mixture was permitted to rise until absorption of the olefin began and was then maintained at about that point for the duration of the experiment.

In Method B, the mixture of reactants (other than ethylene) and catalyst in a glass liner (cooled to about −78°) was sealed into an Ipatieff-type rotating autoclave which was then rotated at room temperature for four hours. When ethylene was used, it was charged to a pressure of 30 atmospheres.

In Method T, the mixture of reactants and catalyst in a large test-tube was shaken manually while the temperature rose gradually from −60° to the temperature of incipient reaction, indicated by the evolution of tiny bubbles of gas. The test-tube was intermittently cooled and warmed until there was little sign of reaction at a temperature at least 10° higher than the original reaction temperature. This method was admittedly crude and was not expected to give the highest possible yields of products;

(1) L. Schmerling, THIS JOURNAL, **67**, 1152 (1945).
(2) L. Schmerling, *ibid.*, **69**, 1121 (1947).
(3) L. Schmerling, *ibid.*, **68**, 1650, 1655 (1946).

TABLE I

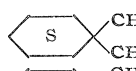
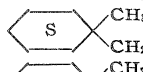
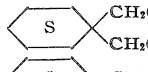
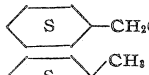
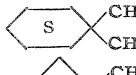
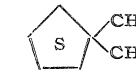
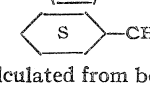
CONDENSATION OF CYCLOALKYL HALIDES WITH ETHYLENE AND VINYL HALIDES

| Method | Reactants: RX[a] | Reactants: G. | Reactants: Unsatd. cpd., g. | Catalyst MX | Catalyst G. | Temp., °C. | Duration, hr. | Condensation prod.: Compd. | Condensation prod.: G. | Condensation prod.: % | Higher boiling prod., g. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | With ethylene | | | | | | |
| A | $C_6Cl$ | 50 | 13[b] | $AlCl_3$ | 6 | −12 to − 8 | 0.5 | I | 8 | 10 | 9 |
| A | $MeC_6Cl$ | 31[c] | 15[b] | $AlCl_3$ | 3 | −30 to −25 | 1.0 | II | 16 | 43 | 12 |
| B | $MeC_6Cl$ | 25 | 10[b] | $AlCl_3$ | 3 | 25 | 4[d] | II | 9 | 30 | 17 |
| B | $MeC_6Cl$ | 15 | 1[b] | $FeCl_3$ | 3 | 25 | 4[d] | II | 2 | 11 | 2 |
| A | $EtC_6Cl$ | 31[c] | 19[b] | $AlCl_3$ | 5 | −10 to 0 | 1.5 | I | 11 | 30 | 5 |
| A | $C_6Br$ | 150[c] | 84[b] | $AlCl_3$ | 10 | −20 to −10 | 1.2 | III | 65 | 32 | 68 |
| A | ....[h] | 153[c] | 21[b] | $AlBr_3$ | 4 | 0 to 20 | 3.0 | III | 17 | 10 | 19 |
| | | | | | With vinyl chloride | | | | | | |
| T | $C_6Cl$ | 120 | 58 | $AlCl_3$ | 5 | −15 to 35[e] | ..[e] | IV | 65 | 38 | 32 |
| B | $C_6Cl$ | 50 | 25 | $FeCl_3$ | 5 | 23 | 4[d] | IV | 5 | 7 | 3 |
| T | $MeC_6Cl$ | 33 | 16 | $AlCl_3$ | 1 | −10 to 20 | 0.2 | V | 11 | 23 | 2 |
| T | $MeC_6Cl$ | 50 | 25 | $AlCl_3$ | 3 | −10 to 0 | 1.0 | V | 38 | 52 | 9 |
| T | $MeC_5Cl$ | 16 | 9 | $AlCl_3$ | 1 | 0 to 5 | 0.1 | VI | 5 | 20 | 3 |
| | | | | | With vinyl bromide[f] | | | | | | |
| T | $C_6Br$ | 82 | 53 | $AlCl_3$ | 1 | ...[g] | ..[g] | VII | 24 | 18 | 17 |

[a] $C_6Cl$ and $C_6Br$ = cyclohexyl chloride and bromide, respectively. $MeC_6Cl$ = 1-chloro-1-methylcyclohexane. $EtC_6Cl$ = 1-chloro-1-ethylcyclohexane. $MeC_5Cl$ = 1-chloro-1-methylcyclopentane. [b] Determined by gain in weight of reaction mixture; includes dissolved gas. [c] *n*-Pentane (50 g.) used as diluent. [d] Time during which autoclave was rotated; it was permitted to set at room temperature overnight before it was opened. [e] The reaction mixture was warmed during eight minutes, with intermittent shaking, from −78 to −12°. There was a sudden rise in temperature to 35° even though the reaction tube was immersed in a Dry Ice–acetone-bath. After two minutes at 35–30°, the mixture cooled to −40°. The total reaction time was eleven minutes. [f] Obtained from Westvaco Chlorine Products Corp. [g] The mixture of reactants and catalyst was allowed to warm up from −78 to −40° during six minutes; most of the catalyst dissolved. There was a sudden reaction, the temperature rose to 50° in ten seconds and half of the mixture was blown from the reaction tube. The remaining 67 g. was a deep red solution. The yield shown is that of the product actually isolated. [h] (2-Bromoethyl)-cyclohexane.

TABLE II

PROPERTIES OF THE HALOALKYLCYCLOALKANE PRODUCTS

| Compd. | Formula | B. p., °C. | B. p., Mm. | B. p. at 760 mm., °C.[a] | $n^{20}D$ | $d^{20}_4$ | Mol. ref. Calcd. | Mol. ref. Obs. | Analyses[b]: Calcd. C | Calcd. H | Calcd. X | Found C | Found H | Found X |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I |  | 77–78 | 3 | 229–230 | 1.4750 | 0.9595 | 51.0 | 51.20 | ... | ... | 20.31 | ... | ... | 20.29 |
| II |  | 59–60 | 4 | 202–203 | 1.4702 | 0.9626 | 46.4 | 46.5 | 67.25 | 10.67 | 22.08 | 67.20 | 10.75 | 22.27 |
| III |  | 86–86 | 3 | 239–240 | 1.4945 | 1.1854 | 53.9 | 53.9 | 54.78 | 8.74 | 36.48 | 55.13 | 8.68 | 36.24 |
| IV |  | 87–87 | 9 | 214–214 | 1.4815 | 1.1002 | 46.7 | 46.8 | 53.03 | 7.79 | ... | 53.41 | 7.92 | ... |
| V |  | 79–80 | 3 | 228–229 | 1.4858 | 1.0941 | 51.3 | 51.1 | 55.37 | 8.27 | 36.36 | 55.22 | 7.98 | 36.50 |
| VI |  | 86–87 | 11 | 206–208 | 1.4780 | .... | 46.7 | ... | 53.03 | 7.79 | 39.18 | 52.89 | 7.84 | 39.22 |
| VII |  | 100–101 | 4 | 252–253 | 1.5270 | 1.5729 | 52.6 | 52.8 | 35.30 | 5.93 | 58.77 | 35.95 | 5.29 | 58.54 |

[a] Calculated from boiling point under reduced pressure using nomograph prepared for hydrocarbon conversions. This was found to give accurate results for halogenated derivatives. [b] Microanalyses by Dr. T. S. Ma, then at the University of Chicago, and by Mr. C. W. Beazley, Micro-Tech Laboratories, Skokie, Illinois.

it had the advantage that the experiments could be carried out quickly.

**Materials.**—The chloro- and bromocyclohexane were Eastman Kodak Co. products. Vinyl chloride and (2-bromoethyl)-cyclohexane were obtained from The Dow Chemical Company; vinyl bromide, from Westvaco Chlorine Products Corp. The 1-chloro-1-methyl-cyclohexane was prepared in 35% yield by a modification of the method described by Bartlett, Condon and Schneider[4]; an equimolar mixture of methylcyclohexane and *t*-butyl chloride was stirred for one hour with 2% by weight of aluminum chloride at −25 to −10°. The 1-chloro-1-methylcyclopentane and the 1-chloro-1-ethylcyclohexane

(4) P. D. Bartlett, F. E. Condon and A. Schneider, THIS JOURNAL, **66**, 1534 (1944).

were each obtained in 20% yield in analogous manner. The former boiled at 79–81° at 197 mm. (120–122° at 760 mm.); $n^{20}D$ 1.4452. The latter boiled at 51–53° at 5.5 mm. (183–185° at 760 mm.); $n^{20}D$ 1.4590.

### Characterization of the Products

**1-(2-Chloroethyl)-1-ethylcyclohexane (I).**—The product prepared by the condensation of chlorocyclohexane with ethylene had the same boiling point and refractive index as that obtained by the reaction of 1-chloro-1-ethylcyclohexane with ethylene; the infrared spectra[5] showed that the two were identical (Fig. 1). Furthermore, both were converted to the same anilide, β-(1-ethylcyclohexyl)-propionanilide, by the reaction of the Grignard reagents with phenyl isocyanate[6]; m. p. and "mixed" m. p., 90–91°.

*Anal.* Calcd. for $C_{17}H_{25}ON$: N, 5.40. Found: N, 5.21.

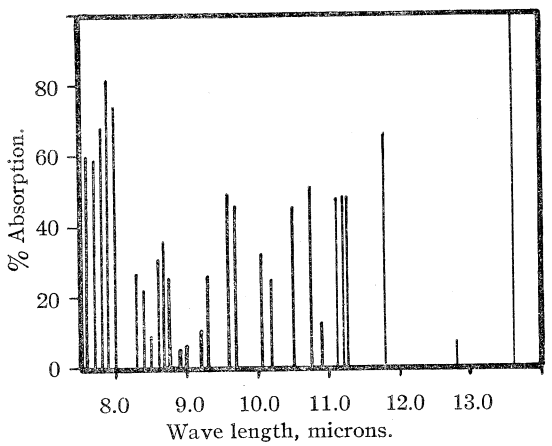



Fig. 1.—Infrared absorption spectrum of 1-(2-chloroethyl)-1-ethylcyclohexane.

**1-(2-Bromoethyl)-1-ethylcyclohexane (III).**—Both preparations of this compound (*i. e.*, the products of the reaction of ethylene with bromocyclohexane and with (2-bromoethyl)-cyclohexane) yielded the same anilide as did the corresponding chloride (I); m. p. and "mixed" m. p., 90–91°.

The bromide was converted to a new hydrocarbon, 1,1-diethylcyclohexane, by heating a solution of 20 g. (0.09 mole) of the compound in 50 cc. of propanol under reflux for eight hours with 9 g. of zinc granules (which had been pretreated by stirring with a solution of 1 g. of cupric chloride in 30 cc. of water and then washing with ethanol). There was recovered 10 g. (0.07 mole) of liquid boiling at 173–174°; $n^{20}D$ 1.4502.

*Anal.* Calcd. for $C_{10}H_{20}$: C, 85.62, H, 14.38. Found: C, 85.78; H, 14.20.

**1-(2-Chloroethyl)-1-methylcyclohexane (II).**—This compound was converted to the corresponding carbinol by heating 8 g. (0.05 mole) with a suspension of 3 g. of magnesium oxide in 110 g. of water in a sealed tube at 225° for four hours. There was obtained 3.5 g. (0.02 mole) of 2-(1-methylcyclohexyl)-ethanol, b. p. 82° at 3 mm.; $n^{20}D$ 1.4686.

*Anal.* Calcd. for $C_9H_{18}O$: C, 75.98; H, 12.76. Found: C, 76.17; H, 12.49.

The 3,5-dinitrobenzoate derivative of the alcohol melted at 95°.

*Anal.* Calcd. for $C_{16}H_{20}N_2O_6$: N, 8.33. Found: N, 8.38.

The α-naphthylamine addition compound of the 3,5-dinitrobenzoate melted at 107°.

The alcohol was oxidized by the repeated insertion of a hot, partially oxidized copper wire spiral (heated in flame) in the boiling liquid (0.5 cc.) and its vapor. The product yielded a 2,4-dinitrophenylhydrazone, m. p. 84–85°. There was no depression of the melting point when this derivative was mixed with the analogous derivative prepared, as shown below, from the aldehyde obtained by hydrolyzing 1-(2,2-dichloroethyl)-1-methylcyclohexane (V).

**(2,2-Dichloroethyl)-cyclohexane (IV).**—A mixture of 13 g. (0.07 mole) of the dichloride, 4 g. (0.1 mole) of magnesium oxide and 100 g. of water in a sealed tube was heated at 250° for four hours. There was obtained 5 g. (0.04 mole) of cyclohexaneacetaldehyde, b. p. 36–37° at 3 mm. (178–179° at atmospheric pressure); $n^{20}D$ 1.4668. The aldehyde yielded a 2,4-dinitrophenylhydrazone, m. p. 114°.

*Anal.* Calcd. for $C_{14}H_{18}O_4N_4$: N, 18.29. Found: N, 18.08.

The melting point of the semicarbazone of the aldehyde depended on the temperature at which the sample tube was inserted in the bath. It ranged from 155–156.5° (insertion at 145°) to 159° (insertion at 158°).

*Anal.* Calcd. for $C_9H_7ON_3$: N, 22.93. Found: N, 22.50.

Various melting points are reported in the literature for the semicarbazone of cyclohexaneacetaldehyde: 132–134°,[7] 153°,[8] 162°[9] and 171–172°.[10]

**1-(2,2-Dichloroethyl)-1-methylcyclohexane (V).**—When 21 g. (0.11 mole) of this dichloride was heated at 225° with 4.5 g. (0.1 mole) of magnesium oxide and 100 cc. of water, there was obtained 9 g. (0.06 mole) of aldehyde, presumably 1-methylcyclohexaneacetaldehyde, b. p. 78–80° at 12 mm.; $n^{20}D$ 1.4728. The analytical data indicated that the aldehyde was impure, a possible contaminant being 1-(2-chlorovinyl)-1-methylcyclohexane. No attempt was made to purify the product.

*Anal.* Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 71.18; H, 10.03.

The semicarbazone and 2,4-dinitrophenylhydrazone derivatives prepared from the impure aldehyde melted at 177–178° and 84–85°, respectively. The latter derivative did not depress the melting point of the analogous derivative of the aldehyde obtained by oxidizing the alcohol prepared by hydrolyzing 1-(2-chloroethyl)-1-methylcyclohexane (II). This may be taken as mutual confirmation of the structures assigned to compounds II and V.

*Anal.* Calcd. for $C_{10}H_{19}ON_3$ (semicarbazone): N, 21.30. Found: N, 20.82.

*Anal.* Calcd. for $C_{15}H_{20}O_4N_4$ (dinitrophenylhydrazone): N, 17.49. Found: N, 17.12.

**Acknowledgment.**—The author wishes to thank Mr. E. E. Meisinger for assistance with part of this work.

## Summary

Condensation of the tertiary chlorides, 1-chloro-1-methylcyclohexane and 1-chloro-1-ethylcyclohexane, with ethylene in the presence of aluminum chloride results in the formation of 1-(2-chloroethyl)-1-methylcyclohexane and 1-(2-chloroethyl)-1-ethylcyclohexane, respectively.

Condensation of the secondary cyclohexyl hal-

(5) The author is indebted to Dr. W. S. Gallaway, Physics Division, Universal Oil Products Company, for the infrared absorption analysis. For a description of the procedure used see THIS JOURNAL, **69**, 1124 (1947).

(6) A. M. Schwartz and J. R. Johnson, *ibid.*, **53**, 1063 (1931); see also, H. W. Underwood, Jr., and J. C. Gale, *ibid.*, **56**, 2117 (1934).

(7) (a) O. Wallach, *Ann.*, **359**, 313 (1908); (b) E. Venus-Danilova, *Ber.*, **61**, 1954 (1928).

(8) A. Skita, *ibid.*, **48**, 1694 (1915).

(9) F. Sigmund, *Monatsh.*, **49**, 271 (1928).

(10) H. Rupe, W. Messner and E. Kambli, *Helv. Chim. Acta*, **11**, 449 (1928).

ides, chlorocyclohexane or bromocyclohexane, with ethylene yields the 1-(2-haloethyl)-1-ethylcyclohexanes, the reaction proceeding via the isomerization and subsequent condensation (with a second molecule of ethylene) of the primary product, (2-haloethyl)-cyclohexane.

(2,2-Dihaloethyl)-cycloalkanes are obtained by the reaction of vinyl chloride (or bromide) with chlorocyclohexane (or bromocyclohexane), 1-chloro-1-methylcyclohexane, and 1-chloro-1-methylcyclopentane.

A number of apparently new products including 1,1-diethylcyclohexane, 2-(1-methylcyclohexyl)-ethanol and crystalline derivatives, and 1-methylcyclohexaneacetyldehyde and crystalline derivatives have been prepared during the characterization of the condensation products.

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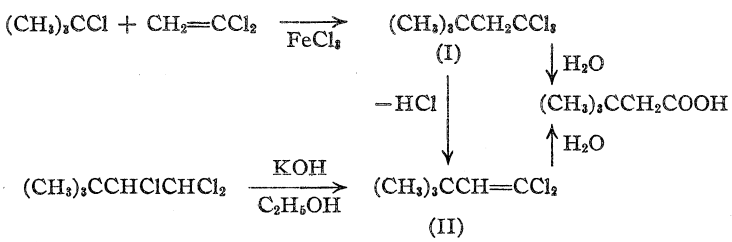
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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

# Condensation of Saturated Halides with Unsaturated Compounds. VI. Condensation of Alkyl and Cycloalkyl Chlorides with Vinylidene Chloride[1]

BY LOUIS SCHMERLING

The condensation of alkyl chlorides with 1,1-dichloroethylene (*i. e.*, vinylidene chloride) in the presence of metal halide catalysts offers a convenient means for preparing 1,1,1-trichloroalkanes and 1,1-dichloro-1-alkenes. Thus, for example, the ferric chloride catalyzed reaction of *t*-butyl chloride with the dichloroethylene yields both 1,1,1-trichloro-3,3-dimethylbutane (I) and its dehydrochlorination product, 1,1-dichloro-3,3-dimethyl-1-butene (II), the relative amounts of the two products depending on the reaction conditions.




When the temperature was kept at −10 to +10° (chiefly at −10 to 0°), a 65% yield of I and a 13% yield of II were obtained. At a somewhat higher temperature (8–23°) the yields were reversed, a 60% yield of II and a 14% yield of I being obtained.

It is interesting to note that no carbon skeletal rearrangement accompanied the formation of the dichlorohexene by the dehydrochlorination of the 1,1,1-trichloro-3,3-dimethylbutane. Confirmation of the structures of the two products is found in the fact that each yielded *t*-butylacetic acid when heated with water at 275°. The dichloride was shown to be identical with that obtained by the reaction of 1,1,2-trichloro-3,3-dimethylbutane with alcoholic potash.

The reaction of isopropyl chloride with vinylidene chloride at 0–25° in the presence of aluminum chloride resulted in a 30% yield of 1,1-dichloro-3-methyl-1-butene. The primary product, 1,1,1-trichloro-3-methylbutane was obtained in low yield only; the major portion underwent dehydrochlorination to the dichloropentene, the hydrogen chloride adding to the vinylidene chloride to form 1,1,1-trichloroethane which was also obtained in 30% yield. The structure of the 1,1-dichloro-3-methyl-1-butene was indicated by the fact that it was identical with the product of the the dehydrochlorination of 1,1,2-trichloro-3-methylbutane.

The reaction of vinylidene chloride with cyclohexyl chloride in the presence of aluminum chloride proceeded in a similar manner to that with isopropyl chloride. The principal product (30–50% yield) was the dichloroölefin, 1,1-dichloro-2-cyclohexylethylene, rather than the saturated trichloride, 1,1,1-trichloro-2-cyclohexylethane. 1,1,1-Trichloroethane was again obtained as by-product in yield corresponding to the hydrogen chloride evolved during the conversion of the intermediate trichlorocyclohexylethane to the dichlorocyclohexylethylene. Hydrolysis of the dichloride yielded cyclohexaneacetic acid.

## Experimental

**Procedures.**—The procedures were similar to those previously described for the condensation of alkyl halides with haloölefins.[2] In Method T, the mixture of reactants and catalyst in a large test-tube was shaken intermittently at the temperature range shown in the table. In Method S, the mixture of reactants was gradually added to a stirred mixture of the catalyst and *n*-pentane diluent.

### Identification of Products.

**1,1,1-Trichloro-3,3-dimethylbutane (I).**—A sealed tube containing 12.5 g. of the trichloride and 150 cc. of water was heated at 275° for four hours in a rotating autoclave. There was obtained 5.5 g. of organic acid, b. p. 182–183°; $n^{20}D$ 1.4153. It crystallized when cooled to 0°. Its *p*-phenylphenacyl ester melted at 92°. *t*-Butylacetic acid boils at 183°, melts at 6° and yields a *p*-phenylphenacyl ester[3] melting at 92°.

(1) Preceding paper in this series, THIS JOURNAL, **71**, 698 (1949).

(2) L. Schmerling, *ibid.*, **68**, 1650 (1946).

(3) F. Wrede and A. Rothhaas, *Ber.*, **67**, 739 (1934).

TABLE I

CONDENSATION OF SATURATED CHLORIDES WITH VINYLIDENE CHLORIDE

| Method | Reactants: Satd. RCl | Chloride, g. | $CH_2=CCl_2$,[a] g. | Catalyst MX | G. | Temp., °C. | Duration, hr. | Chief products: Compd. | G. | % | Higher boiling prod., g. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T | *t*-BuCl | 98 | 93 | $FeCl_3$ | 2 | −10 to 10 | 0.8 | I | 119 | 65 | |
| | | | | | | | | II | 19 | 13 | 1 |
| T | *t*-BuCl | 47 | 40 | $FeCl_3$ | 1 | 8 to 23[b] | 0.5 | I | 11 | 14 | |
| | | | | | | | | II | 38 | 60 | 1 |
| S | *i*-PrCl | 95 | 117 | $AlCl_3$ | 9[c] | 1 to 20[c] | 3.0 | III | 51 | 30 | |
| | | | | | | | | V | 48 | 30 | 15 |
| T | *c*-$C_6H_{11}Cl$ | 67 | 50 | $AlCl_3$ | 2 | ...[d] | ..[d] | IV | 45 | 48 | |
| | | | | | | | | V | 21 | 30 | 11 |
| S | *c*-$C_6H_{11}Cl$ | 140 | 114 | $AlCl_3$ | 6 | 0 to 20 | 1.5 | IV | 64 | 30 | |
| | | | | | | | | V | 48 | 30 | 21 |

[a] Obtained from The Dow Chemical Co., redistilled immediately before use. [b] The catalyst was added to the mixture of reactants cooled to 8° by immersion in an ice–water-bath. The temperature rose to 23° and then dropped to 10° in two minutes. It was permitted to set at about this temperature for twenty minutes more, after which it was washed, dried and distilled. [c] The mixture of reactants was added during one and one-half hours to a stirred suspension of 4 g. of aluminum chloride in 62 g. of *n*-pentane at 1–3°. Additional catalyst (5 g.) was added and the temperature was permitted to rise (stirring continued) to 20° during the next one and one-half hours. [d] The catalyst was added to the mixture of reactants at −70° and the temperature was permitted to rise. A sudden reaction occurred at −20°; the temperature rose to 35° for a moment and then dropped to −10° when immersed in the bath at −78°. The total reaction time was three to four minutes.

TABLE II

PROPERTIES OF THE POLYCHLORO PRODUCTS

| Compd. | Formula | B. p., °C. | B. p., Mm. | B. p., at 760 mm., °C.[a] | $n^{20}D$ | $d^{20}_4$ | Mol. ref. Calcd. | Mol. ref. Obs. | Analyses[b], %: Calcd. C | Calcd. H | Calcd. Cl | Found C | Found H | Found Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $(CH_3)_2CCH_2CCl_2$ | 64–65 | 18 | 166–167 | 1.4608 | 1.1644 | 44.6 | 44.6 | 38.00 | 5.85 | 56.15 | 38.26 | 6.03 | 55.75 |
| II | $(CH_3)_2CCH{=}CCl_2$ | 55–56 | 39 | 138–139 | 1.4537 | 1.0588 | 39.2 | 39.1 | 47.06 | 6.59 | 46.35 | 46.90 | 6.71 | 46.20 |
| III | $(CH_3)_2CHCH{=}CCl_2$ | 50–51 | 71 | 118–119 | 1.4454 | 1.0686 | 34.6 | 34.6 | 43.19 | 5.80 | 51.01 | 43.21 | 5.84 | 50.92 |
| IV | *c*-$C_6H_{11}CH{=}CCl_2$ | 95–96 | 19 | 204–205 | 1.4948 | 1.1236 | 46.3 | 46.4 | 53.63 | 6.76 | 39.61 | 53.86 | 7.11 | 39.35 |
| V | $CH_2CCl_2$ | ... | .. | 73–74 | 1.4375 | | | | | | | | | |

[a] Calculated from boiling point under reduced pressure using nomograph prepared for hydrocarbon conversions. This was found to give accurate results for halogenated hydrocarbons. [b] Microanalyses by Mr. C. W. Beazley, Micro-Tech Laboratories, Skokie, Illinois.

**1,1-Dichloro-3,3-dimethyl-1-butene (II).**—The hydrolysis of 12 g. of this dichloride was carried out using the same procedure as was used for the trichloride. The sealed tube broke during the heating. The product which was recovered from the autoclave was made alkaline and ether extracted. About 5 g. of unreacted dichloride was recovered from the ether. Acidification of the alkaline solution yielded 1.5 g. of organic acid, m. p. 0–5°, the *p*-phenylphenacyl ester of which melted at 92°. There was no depression of the melting point of this ester when it was mixed with the corresponding derivative of the acid derived from 1,1,1-trichloro-2,2-dimethylbutane.

Further evidence in support of the structure assigned to dichlorodimethylbutene was obtained by showing that the same compound was obtained by the dehydrochlorination of 1,1,2-trichloro-3,3-dimethylbutane (prepared by the condensation of *t*-butyl chloride with *cis*-dichloroethylene[4]). Fifteen grams (0.08 mole) of the trichloride was added to a solution of 10 g. (0.18 mole) of potassium hydroxide in 40 cc. of ethanol. The temperature rose to 45° and potassium chloride began to precipitate out. The mixture was permitted to set overnight, the potassium chloride (6 g., 0.08 mole) was filtered off, and the filtrate was washed, dried and distilled. There was obtained 6.0 g. (0.04 mole) of product boiling at 55° at 40 mm. (138°

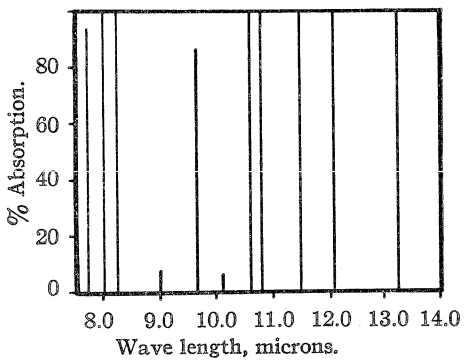



Fig. 1.—Infrared absorption spectrum of 1,1-dichloro-3,3-dimethyl-1-butene.

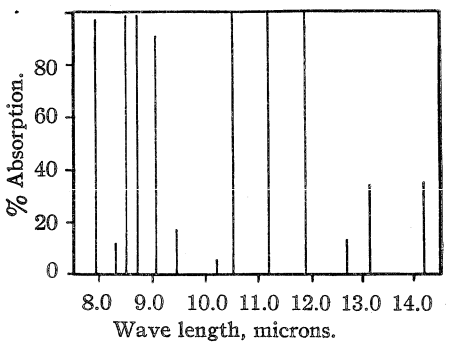



Fig. 2.—Infrared absorption spectrum of 1,1-dichloro-3-methyl-1-butene.

(4) L. Schmerling, THIS JOURNAL, 68, 1655 (1946).

at 760 mm.); $n^{20}D$ 1.4530. The infrared absorption spectrum[5] of this product was identical with that of II (Fig. 1).

**1,1-Dichloro-3-methyl-1-butene (III).**—The infrared spectrum of this compound was identical with that of the product obtained by the dehydrochlorination of 1,1,2-trichloro-3-methylbutane, the condensation product of isopropyl chloride and *cis*-dichloroethylene[4] (Fig. 2). The dehydrochlorination of 17 g. (0.10 mole) of the trichloride by the procedure described above for the dehydrochlorination of 1,1,2-trichloro-3,3-dimethylbutane yielded 6 g. (0.08 mole) of potassium chloride and 6.5 g. (0.05 mole) of product boiling at 115–116° at atmospheric pressure; $n^{20}D$ 1.4460.

**1,1-Dichloro-2-cyclohexylethylene (IV).**—Hydrolysis of 10 g. of this compound by heating with 100 g. of water at 275° for four hours yielded 5 g. of an organic acid boiling at 244–247° and melting at 28–29°. It yielded an amide melting at 166–167°. The reported[6] properties of cyclohexaneacetic acid are: b. p. 245–247°; m. p. ranging from 27 to 32–33°; amide, m. p. 168°, 171–172° (cor.).

(5) The author is indebted to Dr. W. S. Gallaway, Physics Department, Universal Oil Products Company, for the infrared absorption analyses reported in this paper. For a description of the procedure used, see THIS JOURNAL, **69**, 1124 (1947).

(6) Beilstein, 4th ed., Vol. IX, p. 14.

**Acknowledgment.**—The author wishes to thank Mr. J. P. West for assistance in this work.

## Summary

The condensation of *t*-butyl chloride with vinylidene chloride in the presence of ferric chloride yields a mixture of 1,1,1-trichloro-3,3-dimethylbutane and 1,1-dichloro-3,3-dimethyl-1-butene, the relative amounts of the two products depending chiefly on the reaction temperature.

The aluminum chloride catalyzed condensation of the secondary chlorides, isopropyl chloride and cyclohexyl chloride, with vinylidene chloride yields as major products the unsaturated dichlorides, 1,1-dichloro-3-methyl-1-butene and 1,1-dichloro-2-cyclohexylethylene respectively. 1,1,1-Trichloroethane, formed by the hydrochlorination of vinylidene chloride is a by-product in both cases.

RIVERSIDE, ILL. RECEIVED JULY 22, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ST. VINCENT COLLEGE]

# Furfuryl and Thenylalkylamines from Schiff Bases[1,2]

BY BERTIN L. EMLING, J. E. BEATTY AND J. R. STEVENS

A number of secondary amines have been prepared[3] by the action of organomagnesium halides on Schiff bases. However, since none of the furfurylideneamines or thenylideneamines have as yet been utilized in this type of reaction, it was decided to investigate their behavior. Six isomeric alkylfurfurylamines have been prepared as represented by the equations

$$C_4H_3OCHO + H_2N{-}R' \xrightarrow{(-H_2O)}$$

$$C_4H_3O{-}CH{=}N{-}R' + RMgBr \xrightarrow[C_4H_3OCH(R){-}NHR']{\text{(hydrolysis)}} \quad (1)$$

One thenylamine, $C_4H_3S{-}CH(C_2H_5){-}NH(C_4H_9)$, was also prepared from thenylidenebutylamine and ethylmagnesium bromide. The Schiff bases prepared and used in the syntheses are listed in Table I. The methyl- and ethylfurfurylideneamines were prepared by Schwabbauer[4] who lists only their boiling points. The remaining Schiff bases are not described in the literature. Table II lists the furfurylamines, synthesized from the Schiff bases, and their α-naphthylurea derivatives. The ureas were prepared from the amines and α-naphthyl isocyanate.

(1) Presented before the Organic Division at the 114th meeting of the American Chemical Society, Washington, D. C., Aug. 30–Sept. 3, 1948.

(2) The authors wish to acknowledge the assistance of John Heid, Harvey Patterson, Glenn Johnson, Ernest Goral, Thomas Solomon and Walter Hubis in some of the experimental work.

(3) (a) Campbell, *et al.*, THIS JOURNAL, **70**, 3868 (1948); (b) Moffett and Hoehn, *ibid.*, **69**, 1792 (1947); (c) Gilman, Kirby and Kinney, *ibid*, **51**, 2252 (1929).

(4) Schwabbauer, *Ber.*, **35**, 410–415 (1902).

TABLE I

N-ALKYLFURFURYLIDENEAMINES

| Amine | B. p., °C. | Mm. | Yield, % | $n^{20}D$ | $d^{20}_4$ | N Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| Methyl | 53 | 16 | 85 | 1.5269 | 1.025 | 12.8 | 12.6 |
| Ethyl | 67 | 18 | 86 | 1.5170 | 0.988 | 11.4 | 11.2 |
| Propyl | 87–88 | 21 | 90 | 1.5105 | 0.967 | 10.2 | 10.1 |
| Butyl | 90 | 13 | 90 | 1.5057 | 0.950 | 9.26 | 9.21 |
| Amyl | 104–105 | 10 | 85 | 1.5024 | 0.940 | 8.48 | 8.35 |
| Butyl[a] | 112–113 | 13 | 90 | 1.5459[b] | 0.990[b] | 12.0 | 11.9[c] |

[a] Thenylideneamine. [b] $n^{25}D$ and $d^{25}_4$. [c] *Anal.* Calcd. for $C_9H_{13}S$: S, 19.2. Found: S, 19.1.

Gilman, Kirby and Kinney[3c] reported a case of 1,4-addition to benzophenone anil under reaction conditions involving high temperature and a long period of heating. While we were of the opinion that 1,2-addition to the carbon–nitrogen structure took place under the mild conditions used in our reactions we desired to prove this. For this purpose one of the furfurylamines was synthesized from furan

$$C_4H_4O + (C_2H_5CO)_2O \xrightarrow{ZnCl_2}$$

$$C_4H_3O{-}COC_2H_5 \xrightarrow{NH_2OH}$$

$$C_4H_3O{-}C(NOH)C_2H_5 \xrightarrow[C_2H_5OH]{Na}$$

$$C_4H_3O{-}CH(NH_2)C_2H_5 + C_4H_9I \xrightarrow[C_4H_3O{-}C(H)(NHC_4H_9)(CH_2CH_3)]{\text{xylene}} \quad (I)$$

The amine, I, was not isolated but reacted in ligroin with α-naphthyl isocyanate to give the corresponding urea, 1-butyl-1-(α-ethylfuryl)-3-(α-naphthyl)-urea.

TABLE II

N-ALKYL-(α-ALKYLFURFURYL)-AMINES, $C_4H_3O$—CH(R)—NHR′

| Amine R | Amine R′ | B. p. °C. | Yield,[a] Mm. | Yield,[a] % | $n^{20}D$ | $d^{20}_4$ | N Analyses, % Calcd. | N Analyses, % Found | α-Naphthyl ureas[b] M. p.,[c] °C. | α-Naphthyl ureas[b] N Analyses, % Calcd. | α-Naphthyl ureas[b] N Analyses, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $n$-$C_5H_{11}$ | 102–103 | 15 | 36 | 1.4681 | 0.913 | 7.73 | 7.74 | 83 | 8.00 | 7.98 |
| $C_2H_5$ | $n$-$C_4H_9$ | 108–109 | 25 | 60 | 1.4635 | .907 | 7.73 | 7.58 | 76–77 | 8.00 | 7.99 |
| $n$-$C_3H_7$ | $n$-$C_3H_7$ | 107–108 | 24 | 47 | 1.4634 | .904 | 7.73 | 7.72 | 87 | 8.00 | 7.94 |
| $n$-$C_4H_9$ | $C_2H_5$ | 105.5–106.5 | 23 | 47 | 1.4636 | .909 | 7.73 | 7.80 | 119–119.5 | 8.00 | 8.05 |
| $n$-$C_5H_{11}$ | $CH_3$ | 75–76 | 3 | 52 | 1.4649 | .913 | 7.73 | 7.77 | 121 | 8.00 | 8.07 |
| iso-$C_5H_{11}$ | $CH_3$ | 67.5–68.5 | 4 | 55 | 1.4644 | .913 | 7.73 | 7.66 | 149 | 8.00 | 7.97 |
| $C_2H_5$ | $n$-$C_4H_9$[d] | 84 | 3 | 60 | 1.5172[e] | .961[e] | 7.14 | 7.07[f] | | | |

[a] Based on Schiff base. [b] Yields based on the isocyanate were all about 90%. [c] All melting points are corrected. [d] Thenylamine, $C_4H_3SCH(C_2H_5)NH(C_4H_9)$. [e] $n^{25}D$ and $d^{25}_4$. [f] *Anal.* Calcd. for $C_{11}H_{19}NS$: S, 16.25. Found: S, 16.18.

This proof of the 1,2-addition was further substantiated by oxidizing two of the furfurylamines, *i. e.*, N-butyl-α-ethyl and N-*n*-amyl-α-methyl, with potassium ferricyanide[5] to 2-furoic acid. N-Butyl-(α-ethylthenyl)-amine was also oxidized with alkaline potassium permanganate to 2-thiophenecarboxylic acid.

## Experimental

**Reagents.**—The chemicals used in all syntheses were reagent grade with the exception of furan which was kindly supplied by the Electrochemicals Department, E. I. du Pont de Nemours and Co.

**Furfurylidenebutylamine.**—All of the Schiff bases were prepared by essentially the same procedure.[6] The yields were uniformly 85% or better. Only the preparation of furfurylidenebutylamine will be outlined here. Freshly distilled furfural (96 g., 1 mole) was added dropwise with stirring to 88 g. (1.2 moles) of butylamine, kept at 15–20°, and the mixture was then stirred at room temperature for thirty minutes. Solid sodium hydroxide was added with cooling to saturate the aqueous layer, the mixture was extracted with ether and the ether extract dried over potassium hydroxide and distilled. The yield was 136 g., 90%.

**N-Butyl-(α-ethylfurfuryl)-amine.**—This procedure is typical. To the ethylmagnesium bromide obtained from 54.5 g. (0.5 mole) of ethyl bromide and 13 g. of magnesium turnings was added with cooling 68 g. (0.45 mole) of furfurylidenebutylamine dissolved in 70 ml. of ether. After refluxing for two hours the mixture was poured onto 300 g. of ice and then made acidic with hydrochloric acid. The ether layer was separated and the water layer after washing with an additional 75 ml. of ether was made basic with sodium hydroxide and steam distilled. The distillate was extracted with ether, dried over anhydrous magnesium sulfate and distilled; yield 49 g., 60%.

**α-Naphthylureas.**—These were prepared according to the procedure described by French and Wirtel[7] except that the amine was added to the α-naphthyl isocyanate in a 2:1 molar ratio. When no excess of amine was employed a glass resulted which was extremely difficult to crystallize. The urea of N-butyl-(α-ethylthenyl)-amine could not be crystallized. All of the ureas were recrystallized from ligroin.

**Furyl Ethyl Ketone**[8].—Eighty-eight grams (1.3 moles) of furan, 338 g. (2.6 moles) of propionic anhydride and about 5 g. of freshly fused zinc chloride were placed in a 1-liter 3-neck flask and stirred under anhydrous conditions for one hour and then at room temperature for two hours when 450 ml. of water was added. After stirring for an additional hour, potassium hydroxide was added with cooling until alkaline. The organic layer was extracted with ether, dried over anhydrous magnesium sulfate and distilled from a Claisen flask at 77–77.5° at 17 mm.; yield 84 g., 52%. The product crystallized on standing; m. p. 28°. The semicarbazone melted at 187–189° agreeing closely with the value reported by Asahina and Murayama.[9]

**Furylethylketoxime.**—This was prepared by a standard procedure[10]; yield, 68%; m. p. 46–48°.

**Reduction of Furylethylketoxime.**—Four hundred and fifty grams of absolute alcohol was placed in a 1-liter round-bottom flask provided with a wide mouth Liebig condenser. To this was added 32 g. of furylethylketoxime and then 80 g. of sodium in small pieces as rapidly as was consistent with the boiling of the alcohol. After one hour undissolved sodium was removed and the mixture cooled in an ice-bath and acidified with dilute sulfuric acid. Then 700 ml. of water was added. The alcohol was removed under vacuum. The residue was made alkaline with solid potassium hydroxide and then extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and distilled; b. p. 63–65° at 7 mm.; yield, 10 g.; $n^{25}D$, 1.4673. The picrate of the amine melted at 168–173° with decomposition. Erlenmeyer and Simon[11] report a melting point of 168° but do not mention decomposition.

**1-Butyl-1-(α-ethylfurfuryl)-3-α-naphthylurea.**—In a 200-ml. round-bottom flask 20 ml. of technical xylene, 1.6 g. (0.013 mole) of (α-ethylfurfuryl)-amine and 4.2 g. (0.023 mole) of butyl iodide was refluxed gently for four hours. After cooling the xylene was extracted with 25 ml. of water. The water solution was made basic with sodium hydroxide and extracted with 6 ml. of ligroin. The ligroin solution was dried over sodium hydroxide and reacted with 2 ml. of α-naphthyl isocyanate dissolved in 2 ml. of ligroin. An oil precipitated. The ligroin was decanted and about 6 ml. more of ligroin was added to the oil and the mixture stirred. After the oil had separated the second ligroin solution was decanted. The residual oil solidified to a glass but could not be crystallized. Four drops of α-naphthyl isocyanate was now added to each of the decanted ligroin solutions and a precipitate formed in each. After combining the two precipitates and recrystallizing three times from ligroin the small quantity of crystals obtained melted at 76–77° (cor.) on a Fisher–Johns apparatus. Mixed m. p. with the urea prepared by means of the Grignard method was 76–77° (cor.). This was the only successful attempt at isolation of the pure urea. Other attempts under what appeared to be the same conditions failed.

**Oxidation of N-Butyl-(α-ethylfurfuryl)-amine.**—Two grams of the amine, 50 g. of potassium ferricyanide and 20 g. of potassium hydroxide were dissolved in 300 ml. of water and refluxed for two hours when 25 g. more of po-

(5) Brown, *Iowa State College J. Sci.*, **11**, 227–229 (1937).

(6) Campbell, Sommers and Campbell, THIS JOURNAL, **66**, 82–84 (1944).

(7) French and Wirtel, *ibid.*, **48**, 1736–1739 (1926).

(8) Hartough and Kosak, *ibid.*, **69**, 1012–1013 (1947).

(9) Asahina and Murayama, *Archiv. Pharm.*, **252**, 455 (1914); "Beilstein," 1st supplement, **17**, 157.

(10) Samuel M. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1946, p. 198.

(11) Erlenmeyer and Simon, *Helv. Chim. Acta*, **24**, 1210–1213 (1941).

tassium ferricyanide and 10 g. of potassium hydroxide were added and reflux continued for two more hours. Iron oxide was removed by filtering the hot mixture. The solution was then evaporated under 15 mm. pressure to one-half its original volume, cooled and filtered, made acidic with hydrochloric acid and extracted with ether. The ether was evaporated and the residue recrystallized from ligroin giving 0.02 g. of a solid; m. p. 130°; mixed m. p. with Eastman Kodak Co. white label furoic acid, 130°.

**Oxidation of N-Butyl-(α-ethylthenyl)-amine.**—To a solution of 8 g. of sodium hydroxide and 8.8 g. of potassium permanganate in 500 ml. of water was added slowly with stirring 1 g. of N-butyl-(α-ethylthenyl)-amine. After six hours the solution was filtered, evaporated to about 100 ml. and again filtered. The filtrate was washed with ether, made acidic with dilute hydrochloric acid and extracted with ether. Evaporation of the ether gave 0.55 g. of crystals; m. p. 126–126.5° after two recrystallizations from water.

Neutral equivalent: calcd. for 2-thiophenecarboxylic acid, 128.1; found, 128.8.

## Summary

1. Five furfurylideneamines, three of which are new, and one new thenylideneamine have been prepared.

2. Six new furfurylamines and one new thenylamine have been synthesized.

3. The structures of the furfurylamines and of the thenylamines have been shown to be most probably those which result from 1,2-addition of the alkylmagnesium halides to the carbon–nitrogen double bond of the Schiff bases.

LATROBE, PA. RECEIVED OCTOBER 11, 1948

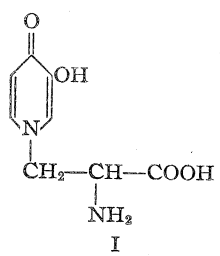
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Leucenol. VI. A Total Synthesis

BY ROGER ADAMS AND J. L. JOHNSON[1]

Leucenol, from *Leucaena glauca Bentham*, has been shown through degradation studies to have formula I.[2] During the investigation of leucenol



I

in this Laboratory, a variation in the melting point and rotation was frequently observed, which appeared to be dependent on the method of extraction and purification. Experiments have now been completed which permit a clarification of this variability. As obtained directly from the extract by the procedure used originally in this Laboratory or by the method of Kostermans,[3] leucenol had a rotation of −21° in water and a melting point of 228–229°. One recrystallization from water does not cause any essential change in these constants. Mascré[4] and Adams, *et al.*,[2a] reported optical inactivity for leucenol, Bickel and Wibaut[2c] reported −9°, while still others[2e,3,5] gave values of −21° or −22°. The rotation in 1% hydrochloric acid was found to be +10° as compared with Bickel and Wibaut's[2c] value of +6.7°. Mascré[4] and Adams, *et al.*,[2a] observed melting point values of 283–287° and 291°, the latter authors specifying a Maquenne block, but in open tubes previous investigators have given values of 226–227°,[2c] 228°,[5] and 231°.[5]

An explanation of these variations is found in the following observations. Samples of leucenol, after two or three crystallizations from water, were found to have rotations of −16 to −18°, although the melting points were about the same as before recrystallization. By boiling in water for forty-eight hours, the optical activity completely disappeared. The product had obviously racemized. When the racemic modification crystallized from a boiling aqueous solution as the water was evaporated to a volume below that of saturation of the compound, the product had a melting point of 235–236°. On the other hand, if a cold aqueous solution was permitted to evaporate, the product which was obtained had a melting point of 227–228°. By analysis, the former was shown to be anhydrous and the latter hydrated with one-half molecule of water. The anhydrous and hydrated forms are interconvertible by the treatment described. The hydrate does not lose its water even at 150°, and at 180° it decomposes. These two products have quite different infrared absorption spectra (Fig. 1). It is noteworthy that 3,4-dihydroxypyridine (3-hydroxy-4-pyridone) and α-amino-β-(N-4-pyridone)-propionic acid, of which leucenol is a derivative, hydrate and the infrared absorption spectra of the anhydrous and hydrated forms differ.[2b] Optically active leucenol does not form a hydrate under the conditions used for preparing the hydrated racemic modification. The facile

(1) From a thesis presented by J. L. Johnson to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1949.

(2) (a) Adams, Cristol, Anderson and Albert, THIS JOURNAL, **67**, 89 (1945); Adams and Jones, *ibid.*, **69**, 1803 (1947); Adams and Govindachari, *ibid.*, **69**, 1806 (1947); (b) Adams, Jones and Johnson, *ibid.*, **69**, 1810 (1947); (c) Bickel and Wibaut, *Rec. trav. chim.*, **65**, 65 (1946); Wibaut and Kleipool, *ibid.*, **66**, 24 (1947); Wibaut, *Helv. Chim. Acta*, **29**, 1669 (1946); (d) Bickel, THIS JOURNAL, **69**, 1801, 1805 (1947); (e) **70**, 326, 328 (1948).

(3) Kostermans, *Rec. trav. chim.*, **65**, 319 (1946).

(4) Mascré, *Compt. rend.*, **204**, 890 (1937).

(5) Renz, *Z. physiol. Chem.*, **244**, 153 (1936); Nienburg and Tauböck, *ibid.*, **250**, 80 (1937).

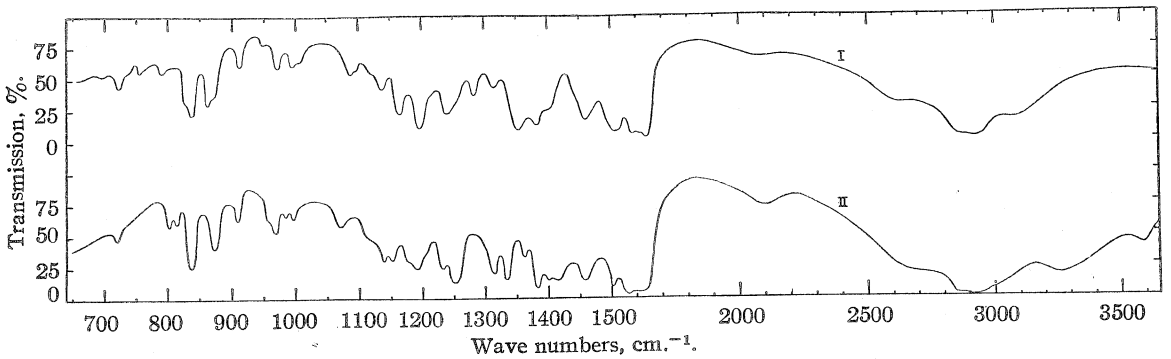
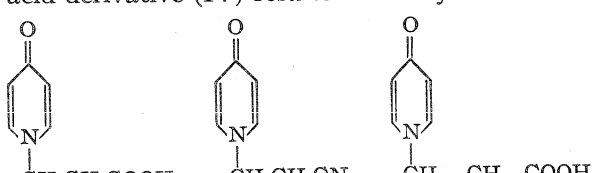



Fig. 1.—I, Anhydrous *dl*-leucenol; II, *dl*-leucenol hemihydrate. [The samples were prepared by grinding the crystalline compounds with paraffin oil to reduce light scattering. Absorptions due to the C–H frequencies of the paraffin oil occur at 2920, 2855, 1459 and 1378 cm.$^{-1}$, and mask the C–H frequencies of the compounds.]

racemization of the natural product is fortunate since it provides a compound with which a *dl* synthetic product may be compared.

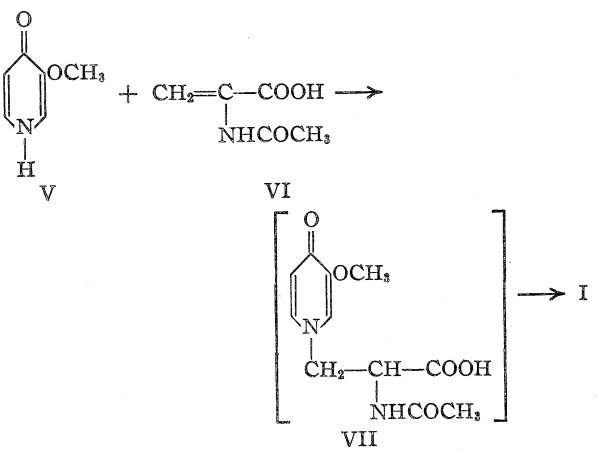
The initial approach to the synthesis involved a study of the conversion of γ-pyrone to the appropriate 4-pyridones by a reaction with primary amines. Ammonia and methylamine condense to give 4-pyridone and 1-methyl-4-pyridone, respectively.[6] β-Alanine was found to react similarly to give an 80% yield of 1-β-carboxyethyl-4-pyridone (II). β-Alanine ester did not react as smoothly and the primary condensation product could not be isolated in a pure state; however, on acid hydrolysis, an acid was obtained identical with that formed from β-alanine. The condensation of γ-pyrone with α,β-diaminopropionic acid or α-hydroxy-β-aminopropionic acid failed to give products from which pure compounds could be isolated.

Attention was next directed to reactions of 4-pyridone. Its condensation with β-bromopropionic acid was unsuccessful. On the other hand, it added to acrylonitrile with formation of 1-β-cyanoethyl-4-pyridone (III). Upon hydrolysis of this product, 1-β-carboxyethyl-4-pyridone (II) resulted which is the same compound as that derived from γ-pyrone and β-alanine. α-Acetamidoacrylic acid (VI) and 4-pyridone reacted in a similar manner, using dioxane as solvent. The product could not be isolated, but after hydrolysis with hydrochloric acid, the α-aminopropionic acid derivative (IV) resulted in low yield.




II III IV

The last reaction provided a possible route to the synthesis of the leucenol molecule through the use of 3-methoxy-4-pyridone (V) and α-acetamidoacrylic acid (VI). The condensation was effected merely by heating the two reactants together without catalyst at 90–100° in presence of dioxane. The reaction product (VII) did not crystallize and was therefore hydrolyzed directly with aqueous hydriodic acid in order to cleave the methoxyl group to hydroxyl and the acetamido group to the amine. After this was completed, the hydriodic acid was neutralized and the water removed. The by-products were extracted with




hot methanol and the residue crystallized by evaporating a water solution at room temperature. A 25.5% yield of *dl*-leucenol hemihydrate resulted. The *dl*-leucenol, anhydrous, was prepared by distilling off water from a saturated boiling solution and filtering the crystals from the hot solvent.

These products showed identical properties with those of racemized natural leucenol. The comparison was made of the melting points, infrared absorption spectra, and analyses of the hydrated and anhydrous forms. Melting points of mixtures of the synthetic and the racemic form from the natural product were not depressed. The color reactions with ferric chloride, ninhydrin, and Folin reagent were the same with synthetic *dl*-leucenol, racemized natural leucenol, and natural leucenol.

(6) Haitinger and Lieben, *Monatsh.*, **5**, 339 (1884); Meyer, *ibid.*, **26** 1311 (1905).

These experiments establish unequivocally the structure of leucenol as I.

The authors are indebted to Mrs. J. L. Johnson for the infrared analyses and their interpretation.

## Experimental

**Natural Leucenol.**—Crude leucenol obtained by the extraction procedure of Kostermans[3] was purified according to the method of Bickel and Wibaut.[2c] The product was obtained as white needles, m. p. 228–229° (cor.) with decomposition. The method of isolation previously used in this laboratory[2a] gives lower yields of leucenol having the same melting point and rotation.

*Anal.* Calcd. for $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.57; H, 4.98; N, 14.42.

*Rotation.* 0.049 g. made up to 25 ml. with water at 22° gave $\alpha_D$ −0.084°; *l*, 2; $[\alpha]^{22}D$ −21°. 0.096 g. made up to 10 ml. with 1% hydrochloric acid at 23° gave $\alpha_D$ 0.098; *l*, 1; $[\alpha]^{23}D$ +10°.

An attempt to form a hydrate in the same manner used for preparing *dl*-leucenol hemihydrate from *dl*-leucenol failed.

**Racemization of Natural Leucenol.**—A solution of 2.5 g. of natural leucenol, ($[\alpha]^{23}D$ −20°) in 250 ml. of water was heated under reflux for forty-eight hours. The volume of the solution was reduced to approximately 50 ml. by distilling off water at atmospheric pressure. The crystals, which separate during this procedure, were filtered while the mixture of crystals and solution was hot. Brownish needles of anhydrous *dl*-leucenol weighing 1.0 g. were thus obtained. Two recrystallizations, in which a saturated boiling aqueous solution was evaporated to a smaller volume and filtered while still hot, resulted in white needles, m. p. 235–236° (cor.) with decomposition. No rotation could be observed.

*Anal.* Calcd. for $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.57; H, 5.21; N, 14.32.

The procedure for forming the anhydrous *dl*-leucenol in a pure state is more reliable than merely cooling a boiling saturated solution which may result in anhydrous *dl*-leucenol contaminated with a small amount of the hydrate.

***dl*-Leucenol Hemihydrate.**—A solution of 0.25 g. of *dl*-leucenol, prepared from natural leucenol, in 30 ml. of water was evaporated to 15 ml. in a vacuum desiccator over phosphorus pentoxide. The hemihydrate separated in the form of white needles in a yield of 0.18 g. The product darkens at 215–226°, and melts at 227–228° (cor.) with decomposition.

*Anal.* Calcd. for $C_8H_{10}O_4N_2 \cdot {}^1/_2H_2O$: C, 46.46; H, 5.33; N, 13.55. Found: C, 46.42; H, 5.35; N, 13.44.

### 1-β-Carboxyethyl-4-pyridone

**A. From β-Alanine.**—A solution of 0.5 g. of γ-pyrone[7] and 0.5 g. of β-alanine in 3 ml. of water was sealed in a 14-mm. Pyrex glass tube, and the tube immersed in an oil-bath at 105° for four hours. The tube was cooled, opened, and the reaction mixture poured into 75 ml. of acetone. The yellow solid which separated was partially purified by dissolving it in 20 ml. of 90% methanol and adding acetone slowly to precipitate the product. Crystallization from water yielded white needles, m. p. 182.5–183.5° (cor.). The yield was 0.68 g. (81%).

*Anal.* Calcd. for $C_8H_9O_3N$: C, 57.47; H, 5.39. Found: C, 57.20; H, 5.49.

**B. From β-Alanine Methyl Ester.**—A solution of 1.1 g. of β-alanine methyl ester hydrochloride, in 30 ml. of ethanol was boiled with 2.2 g. of freshly prepared silver oxide for twenty minutes. The precipitated silver chloride and excess silver oxide were separated by filtration. The volume of the filtrate was increased to 50 ml., and 0.8 g. of γ-pyrone was added. The solution was evaporated to 10 ml., but no crystals separated from the yellow solution on standing overnight in a refrigerator. On evaporating the solution to dryness over phosphorus pentoxide in a vacuum desiccator a yellow oil was obtained.

This oil was dissolved in 10 ml. of 20% aqueous sulfuric acid, and the solution was heated under reflux for two hours. The hot solution was made basic by addition of barium hydroxide, and then acidic (*p*H 4) by addition of dilute sulfuric acid. The precipitated barium sulfate was separated by filtration, and the clear filtrate was evaporated to dryness yielding a glassy residue. The residue was extracted with four 10-ml. portions of warm 90% methanol. The methanol insoluble material was recrystallized from water to yield 0.3 g. of β-alanine; its identity was established by means of its infrared absorption spectrum. The methanol was evaporated to 10 ml., and acetone was added to precipitate 0.135 g. (10%) of 1-β-carboxyethyl-4-pyridone.

**Hydrolysis of 1-β-Cyanoethyl-4-pyridone to 1-β-Carboxyethyl-4-pyridone.**—The substituted propionitrile may be hydrolyzed to give an 80% yield of 1-β-carboxyethyl-4-pyridone; it is more convenient, however, to hydrolyze the cyanoethylation mixture directly.

The crude nitrile obtained from 2 g. of 4-pyridone was dissolved in 20 ml. of 30% aqueous sulfuric acid. The solution was heated under reflux for five hours. While still hot, it was made basic by addition of barium hydroxide, then acidic (*p*H 4) by addition of dilute sulfuric acid. The slurry was filtered to remove the precipitated barium sulfate. The filtrate was evaporated to dryness yielding a glassy yellow residue. The residue was dissolved in 100 ml. of 90% methanol, and the methanol allowed to evaporate off at room temperature. A powdery yellow product separated. After recrystallization from water 1.7 g. (50%) of white needles resulted, identical with the product obtained from the reaction of γ-pyrone with β-alanine.

**1-β-Cyanoethyl-4-pyridone.**—A mixture of 1.0 g. of 4-pyridone,[8] 0.85 g. of acrylonitrile, and approximately 10 mg. of sodium 4-pyridone was heated in an oil-bath at 60–65° for five hours. The solid dissolved slowly during the first three hours of heating. The yellow reaction mixture was warmed with 10 ml. of acetonitrile, the solution filtered to remove a small amount of gelatinous material, and the filtrate evaporated to approximately 3 ml. in a stream of filtered air. A yield of 1.2 g. of slightly yellow product was then obtained. Four recrystallizations from acetonitrile yielded a white product which after drying at 60° and 1 mm. pressure for five hours melted at 109–111° (cor.). The yield of dried product was 0.65 g. (42.5%).

*Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44. Found: C, 64.57; H, 5.59.

**α-Amino-β-(N-4-pyridone)-propionic Acid.**—A suspension of 1.0 g. of 4-pyridone and 1.45 g. of α-acetamidoacrylic acid[9] in 4 ml. of dioxane was heated in a metal-bath at 90–100° for four hours. The dioxane was evaporated off to yield a brown gum which failed to crystallize from ethanol or methanol. The impure α-acetamidopropionic acid derivative was dissolved in 15 ml. of concentrated hydrochloric acid, and the solution was heated under reflux for six hours. The excess hydrochloric acid and water were evaporated off, and the brown residue was dissolved in 5 ml. of concentrated aqueous ammonia. The ammonia and water were evaporated and the residue dried in a vacuum desiccator. The dry residue was washed with 200 ml. of boiling methanol in four portions. The methanol insoluble material, weighing 0.4 g. was recrystallized from 5 ml. of water to yield 0.25 g. (13%) of white needles, m. p. 178° (cor.) with decomposition. The product was a monohydrate. After heating at 100° and 1 mm. for thirty-six hours, the hydrate lost its water to yield the anhydrous amino acid. Slight decomposition occurred as judged by the sample becoming slightly yellow. The melting point of the anhydrous product was 170–172° (cor.) with decomposition. The anhydrous amino acid is extremely hygroscopic.

(7) Willstätter and Pummerer, *Ber.*, **37**, 3740 (1904); **38**, 1461 (1905).

(8) Arndt, *Ber.*, **63**, 593 (1930).

(9) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

*Anal.* Calcd. for (monohydrate) $C_8H_{10}O_3N_2 \cdot H_2O$: C, 48.01; H, 6.05; N, 14.02. Found: C, 48.14; H, 6.15; N, 14.12. Calcd. for (anhydrous) $C_8H_{10}O_3N_2$: C, 52.75; H, 5.53. Found: C, 52.43; H, 5.54.

Synthetic *dl*-Leucenol.—A suspension of 0.9 g. of 3-methoxy-4-pyridone[2d] and 0.95 g. of α-acetamidoacrylic acid in 5 ml. of dioxane was heated at 95–100° for five hours. The dioxane was removed in a stream of air during the last hour of heating. A solution of the brown reaction mixture in 20 ml. of aqueous hydriodic acid (sp. gr. 1.50) was heated under reflux for six hours. The water and excess acid were removed under reduced pressure, and the residue was allowed to stand overnight in a vacuum desiccator over solid potassium hydroxide. The dry residue was dissolved in 20 ml. of water, and the solution was filtered to remove a small amount of insoluble brownish material. The filtrate was made just acid to brom cresol green (*p*H range, 3.8–5.4) by addition of dilute potassium hydroxide solution. Most of the water was distilled off under reduced pressure, and the residue was dried in a vacuum desiccator. The dry residue was washed with 200 ml. of hot methanol in 20-ml. portions to remove the potassium iodide and by-products. The insoluble material weighed 425 mg. and was reddish-brown in color. One recrystallization carried out by evaporating a water solution of the product at room temperature gave pinkish needles, m. p. 225–227° (cor.) with decomposition, and having the infrared absorption spectrum of *dl*-leucenol hemihydrate (Fig. 1). The yield was 380 mg. (25.5%). Two more recrystallizations carried out in the same way gave a white product; it darkens at 215–226° and melts at 227–228° (cor.) with decomposition. The melting point of a mixture of this product with racemized natural leucenol hemihydrate showed no depression.

*Anal.* Calcd. for (hemihydrate) $C_8H_{10}O_4N_2 \cdot {}^1/_2H_2O$: C, 46.46; H, 5.33; N, 13.55. Found: C, 46.21; H, 5.60; N, 13.56.

A portion of the hemihydrate was dissolved in water and the solution boiled down until crystals separated. The hot solution was filtered to give anhydrous *dl*-leucenol, m. p. 235–236° (cor.) with decomposition. The melting point of a mixture of this product with anhydrous racemized natural leucenol showed no depression.

*Anal.* Calcd. for (anhydrous) $C_8H_{10}O_4N_2$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.47; H, 5.16; N, 14.24.

Condensation of 3-hydroxy-4-pyridone[2b] with α-acetamidoacrylic acid proceeded much less smoothly than the reaction described above. Only a 4% yield of *dl*-leucenol was obtained.

## Summary

1. Natural leucenol, which is levorotatory, is racemized when heated in aqueous solution for forty-eight hours.

2. The *dl*-leucenol has been synthesized by condensation of 3-methoxy-4-pyridone with α-acetamidoacrylic acid, and hydrolysis of the primary condensation product.

3. *dl*-Leucenol can be isolated in an anhydrous or a hydrated form.

URBANA, ILLINOIS RECEIVED DECEMBER 27, 1948

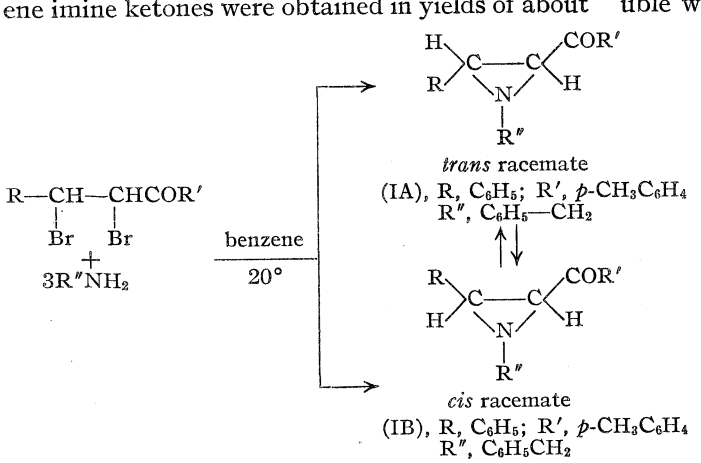
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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

# Ethylene Imine Ketones. IV.[1] Isomerism and Absorption Spectra[2]

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[3]

In previous investigations[1] of the reaction of primary amines with α,β-dibromoketones, ethylene imine ketones were obtained in yields of about 25%. The fact that diphenylethylenimine exists in *cis* and *trans* forms[4] suggests that these low yields may have been due to the formation of pairs of geometrical isomers, of which only the less soluble was isolated in each instance studied. It is also possible, of course, that products of other types, such as piperazines and α-imino ketones, are formed along with one or more forms of the ethylene imine ketones.




The reaction of benzylamine with α,β-dibromobenzyl-*p*-methylacetophenone[1] has now been found to give the isomeric products (IA) (29%) and (IB) (37%), when carried out in dry benzene solution at temperatures between 20 and 30°. No evidence for the formation of a piperazine was observed in these studies.

The low melting isomer (IB) was the more labile of the two. This compound partially decomposed and rearranged to the higher melting isomer (IA) when saturated petroleum ether solutions of it were exposed to sunlight at room temperature. An inspection of scale models for such ethylene imine ketone structures indicated that the racemate (IB) would be a more highly strained arrangement than (IA). Thus (IB) might be expected to undergo rearrangement, possibly through an enol form, to the less strained structure (IA). Acid and base catalyzed rearrange-

(1) For the previous paper in this series see Cromwell, THIS JOURNAL, **69**, 258 (1947).

(2) Presented before a session of the Division of Organic Chemistry, 113th Meeting of the American Chemical Society, Chicago, Illinois, April 20, 1948.

(3) Abstracted from the Ph.D. thesis (June, 1948); du Pont Fellow, 1946–1947.

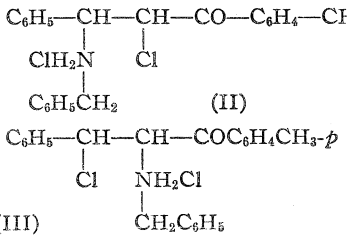
(4) Weissberger and Bach, *Ber.*, **64**, 1095 (1931).

ments of ethylene imine ketones are under investigation at present in this laboratory.

Hot aqueous hydrogen chloride reacted with the isomers, (IA) and (IB), to give mixed chloroamino ketone hydrochlorides. Analysis and iodine release studies[5] of these two products indicated them to be mixtures of the two probable ring cleavage products, α-chloro-β-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (II) and β-chloro-α-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (III).

Excess dry hydrogen chloride reacted with (IA) to give good yields of the hydrochloride (III). The *cis* racemate (IB) gave a mixed hydrochloride product (IV) with this same reagent. Iodine release studies indicated this latter substance (IV) to be made up of approximately 46% (II) and 54% (III).

The reaction with two equivalents of hydrogen chloride is characteristic of an ethylene imine. If either (IA) or (IB) had possessed the structure of a β-amino-α,β-unsaturated ketone, or an α-amino-α,β-unsaturated ketone, or an α-imino ketone, hot aqueous hydrogen chloride should have formed a 1,3-diketone or a 1,2-diketone, respectively.[6] The following paper in this series[7] reports a more detailed study of the cleavage of ethylene imine ketone rings by hydrogen chloride.



Ultraviolet absorption spectra studies (see Table I and Fig. 1) of (IA), (IB) and 1-benzyl-2-phenyl-3-benzoylethylenimine[8] revealed a strong fundamental absorption band in the region of 2400–2600 Å. A low intensity absorption near 3300 Å. was again observed.[9]

These ethylene imine ketones show absorption spectra very similar to those of the parent saturated ketones (see Fig. 2). The only important grouping, other than the benzene rings, affecting ultraviolet light absorption by (IA), (IB) and 1-benzyl-2-phenyl-3-benzoylethylenimine is the two-chromophore, arylcarbonyl structure. The related β-amino-α,β-unsaturated ketones have a strong fundamental absorption band near 3450 Å.[9,10] α-Amino-α,β-unsaturated ketones absorb strongly at 2800–2900 Å. and at 2500 Å., and mildly and generally from 3600 to 4000 Å.[9,10]

The maximum absorption band of the isomer (IB) was 30–80 Å. nearer the red, with a 2000–3000 greater extinction coefficient value, as compared with (IA). The more strained structure (IB) would be expected to absorb light of longer wave lengths.

The changes in the absorption spectra after sunlight irradiation of solutions of (IA) and (IB) are shown in Tables III and IV and in Fig. 3. Hexane solutions of (IA) or (IB) were stable when stored in the dark for several days. Solutions of (IA) were unaffected by sunlight irradiation. It was found that hexane solutions of (IB) underwent considerable change upon exposure to sunlight. A general broadening (90 Å.) of the maximum absorption band was observed for this latter substance. A freshly prepared 50-50 mixture of (IA) and (IB) showed a similar absorption curve. This is further evidence of the ability of (IB) to rearrange to (IA) under the influence of sunlight.

**Acknowledgment.**—The senior author appreciates a grant from the Research Council of the University of Nebraska which aided in the completion of this investigation.

## Experimental

**1-Benzyl-2-phenyl-3-*p*-toluylethylenimines (IA) and (IB).**—To a suspension of 60.0 g. (0.15 mole) of α,β-dibromobenzyl-*p*-methylacetophenone[11] in 150 ml. of benzene was added 50.0 g. (0.45 mole) of benzylamine. The mixture was kept cool (15°) and stirred one hour, stored in the dark at room temperature for twenty-four hours, then filtered to remove 55 g. of benzylamine hydrobromide (94%). The volume of the residual reaction solution was reduced about two-thirds by vacuum distillation and 100 ml. of petroleum ether added to give 15.5 g. (29% yield) of a colorless crystalline product, m. p. 113–114°. One recrystallization of this product (IA) from absolute alcohol, raised the m. p. to 120–121°, while further recrystallization often lowered it to 116–118°.[1]

Upon exposure to light these colorless crystals rapidly developed a deep pink color. When returned to a dark environment for several days, the crystals again became colorless. This same color change was observed with (IA) under a nitrogen atmosphere in a sealed quartz tube.

The benzene–petroleum ether filtrate from (IA) was evaporated and the residue mixed with 200 ml. of petroleum ether and cooled for two days in the ice chest. Filtration gave 25.0 g. (49% yield) of a colorless, fluffy solid, m.p. 70–85°. Recrystallization of this product from low-boiling petroleum ether gave 19 g. (37% yield) of a colorless, fluffy product, m. p. 70–74°. Upon exposure to light this product, (IB), slowly acquired a yellow tint. Extensive manipulation of (IB) in various solvents converted some of it to (IA). Exposure of saturated petroleum ether solutions of (IB) to direct sunlight caused the precipitation of small amounts of (IA).

*Anal.* Calcd. for $C_{23}H_{21}NO$: mol. wt., 327; C, 84.37; H, 6.47; N, 4.28. Found for (IA): mol. wt., 318; C, 84.73; H, 6.64; N, 4.20. Found for (IB): mol. wt., 337; C, 84.51; H, 6.24.

**Reaction of 1-Benzyl-2-phenyl-3-*p*-toluylethylenimines (IA) and (IB) with Hydrogen Chloride**

**1. With Aqueous Hydrogen Chloride.**—Mixtures of 16 ml. of 6 *N* hydrochloric acid with 2.0-g. samples of (IA) and (IB) were refluxed for two hours and then allowed to stand at room temperature for a day. The solid precipitates were filtered from the solutions and recrystallized once from boiling methanol.

(5) Cromwell and Wankel, THIS JOURNAL, **70**, 1320 (1948).

(6) For a review of the properties of such amino ketones, see Cromwell, *Chem. Rev.*, **38**, 83–137 (1946).

(7) Cromwell and Wankel, THIS JOURNAL, **71**, 711 (1949).

(8) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

(9) Cromwell and Johnson, *ibid.*, **65**, 316, 2481 (1943).

(10) Watson, M.S. Thesis, University of Nebraska, 1948.

(11) Weygand, *Ber.*, **35**, 1068 (1902).

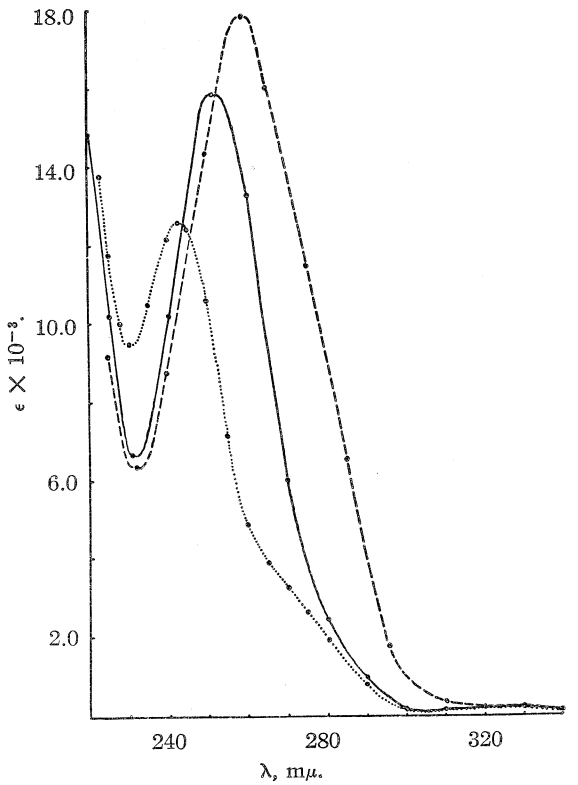



Fig. 1.—1-Benzyl-2-phenyl-3-benzoylethylenimine, .....; (IA), —; (IB), – – –.

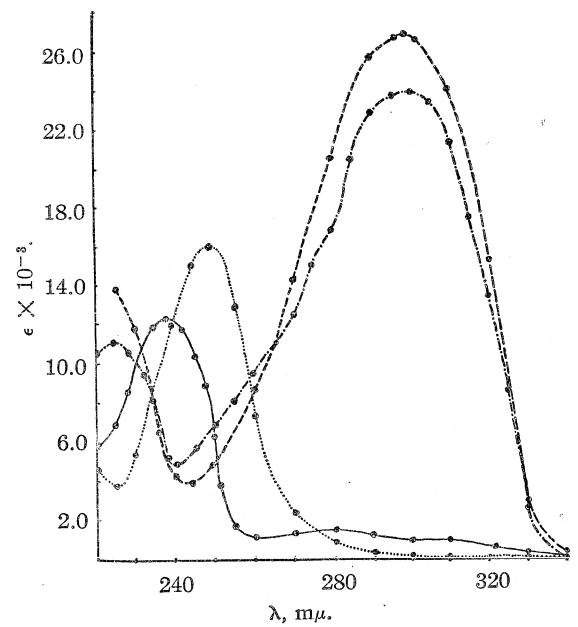



Fig. 2.—Benzal-*p*-methylacetophenone, – – –; benzalacetophenone, ·—·; benzyl-*p*-methylacetophenone, ....; benzylacetophenone, —.

(IA) gave 1.5 g., m. p. 161–162.5°; iodine release was 33% in fifteen minutes at 66°.

(IB) gave 1.94 g., m. p. 161–162°; iodine release was 20% in fifteen minutes at 66°.

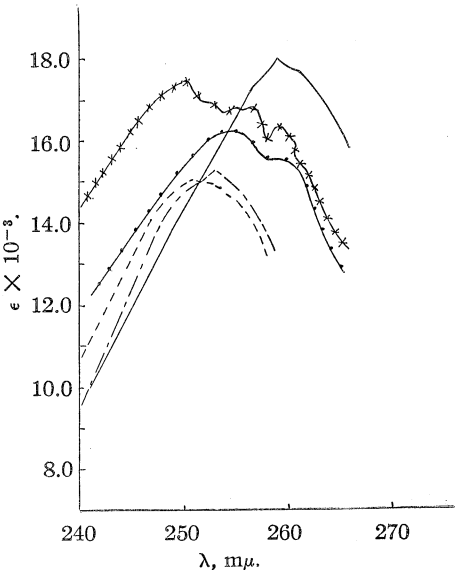



Fig. 3.—Absorption spectra in hexane of (IA): fresh solution, – – –; after two days in dark + two days in light, – – –; of (IB), fresh solution, —; after two days in dark + two days in light —×—×—; 50% (IA) + 50% (IB), fresh solution, —●—●—●—.

*Anal.* Calcd. for $C_{23}H_{23}NOCl_2$: Cl, 17.72. Found: for product from (IA), Cl, 17.80; for product from (IB), Cl, 17.91.

Mixtures of these two products showed m. p. 160–162°.

**2. With Excess Dry Hydrogen Chloride.**—Samples (2.0 g.) of (IA) and (IB) were dissolved in 10 ml. of acetone and the solutions cooled in an ice-bath. An excess of a saturated, dry, ether solution of hydrogen chloride was added, with stirring, in two minutes. After standing in the ice-chest for one day, the solutions were filtered.

(IA) gave 2.0 g. of a colorless crystalline product (III), m. p. 163–165°; recrystallized from methanol and ether, m. p. 167–170°; iodine release in thirty minutes at 66° was 0.0%.

(IB) gave 1.9 g. of colorless product (IV), m. p. 155–158°; recrystallized from methanol and ether, m. p. 161–165°; iodine release in fifteen minutes was 46.5% at 66°.

*Anal.* Calcd. for $C_{23}H_{23}NOCl_2$: C, 68.99; H, 5.79; N, 3.50; Cl, 17.72. Found for (III): C, 68.72; H, 5.79; N, 3.69; Cl, 17.48. Found for (IV): C, 68.79; H, 5.76; N, 3.57; Cl, 18.00.

**Absorption Spectra Studies of Ethylene Imine Ketones.**—These measurements were made with a Beckmann Model DU Photoelectric Quartz Spectrophotometer. At the sensitivity used, the maximum band width was one millimicron with an accuracy of 0.1% for the density measurements. The two solvents used were laboratory grade 95% ethyl alcohol and hexane-from-petroleum, purified by the procedure recommended by Weissberger.[12]

Using purified hexane, the ultraviolet absorption spectra of (IA), (IB), 1-benzyl-2-phenyl-3-benzoylethylenimine, benzal-*p*-methylacetophenone, benzylacetophenone, benzalacetophenone, and benzyl-*p*-methylacetophenone were observed. These studies were made within two hours of the time the solutions were prepared. The results are summarized in Table I, and the complete curves are shown in Fig. 1 and Fig. 2.

In Table II is given the summary of the results obtained when some of these compounds were studied in 95% alcohol solutions.

(12) Weissberger, "Physical Methods of Organic Chemistry," Vol. II, Interscience Publishers Inc., New York, 1946, p. 766; "Organic Solvents," the Clarendon Press, Oxford, 1935, p. 99.

TABLE I

ABSORPTION SPECTRA DATA OF SOME CHALCONE DERIVATIVES (IN HEXANE SOLUTION)

| Compound | Molar concn. × $10^5$ | Maxima λÅ. | Maxima ε × $10^{-3}$ | Minima λÅ. | Minima ε × $10^{-3}$ |
|---|---|---|---|---|---|
| (IA) m. p. 120–121° | 12.50 | 2510 | 15.90 | 2310 | 6.59 |
| | | 3150 | 0.19 | | |
| (IB) m. p. 71–72° | 11.15 | 2590 | 17.91 | 2320 | 6.46 |
| | | 3300 | 0.21 | | |
| 50% (IA) + 50% (IB) | 10.10 | 2555 | 16.25 | .. | .. |
| | | 2600 | 15.50 | | |
| 1-Benzyl-2-phenyl-3-benzoylethylenimine | 10.81 | 2430 | 12.62 | 2300 | 9.56 |
| | | 3250 | 0.16 | | |
| Benzyl-*p*-methylacetophenone | 11.90 | 2485 | 16.01 | 2250 | 3.93 |
| Benzal-*p*-methylacetophenone | 9.13 | 2990 | 26.86 | 2440 | 4.00 |
| Benzylacetophenone | 23.81 | 2380 | 12.40 | 2600 | 1.10 |
| | | 2800 | 1.50 | | |
| Benzalacetophenone | 14.50 | 2260 | 12.10 | 2410 | 4.85 |
| | | 2990 | 23.90 | | |

TABLE II

ABSORPTION SPECTRA DATA OF SOME CHALCONE DERIVATIVES (IN 95% ALCOHOL SOLUTION)

| Compound | Molar concn. × $10^4$ | Maxima λÅ. | Maxima ε × $10^{-3}$ | Minima λÅ. | Minima ε × $10^{-3}$ |
|---|---|---|---|---|---|
| (IA) m. p. 120–121° | 6.07 | 2595 | 17.0 | 2320 | 4.71 |
| (IB) m. p. 71–72° | 0.477 | 2620 | 18.3 | 2310 | 5.30 |
| (IB) (crude) m. p. 71–74° | 0.621 | 2620 | 18.3 | 2320 | 5.25 |
| Benzyl-*p*-methylacetophenone | 1.14 | 2540 | 15.2 | 2350 | 2.61 |
| Benzal-*p*-methylacetophenone | 1.08 | 3100 | 27.8 | 2480 | 3.39 |

**Effect of Time and Light Exposure on the Absorption Spectra of *cis* and *trans* Ethylene Imine Ketones (IB) and (IA).**—A 0.000117 to 0.000100 molar solution in hexane of each of the highly purified samples of (IA) and (IB) was prepared. These solutions were stored in new, volumetric flasks which had been bathed in concentrated sulfuric acid for several days, and then rinsed with distilled water and dried. These solutions were stored in the dark The ultraviolet spectra were examined periodically and little or no change observed. After two days the solutions were each divided into two portions, one portion of each being exposed to direct sunlight for about forty-eight hours. The remaining portions were again stored in the dark. No significant changes in the spectra of (IA) were observed with either portion. With (IB) the portion again stored in the dark showed no change, but that exposed to sunlight displayed approximately a 100 Å. shift in the wave length of the maximum absorption band and a general broadening of the band.

TABLE III

EFFECT OF LIGHT ON LOW MELTING 1-BENZYL-2-PHENYL-3-*p*-TOLUYLETHYLENE IMINE (IB)

| Storage time | | | | | | |
|---|---|---|---|---|---|---|
| Dark storage | 0 | 24 | 48 | 96 | 48 | |
| Light storage | 0 | 0 | 0 | 0 | 48 | |
| Total hours | 0 | 24 | 48 | 96 | 96 | |
| $\lambda_{max}$ Å. | 2590 | 2600 | 2600 | 2600 | 2500 | 2600 |
| $\epsilon_{max} \times 10^{-3}$ | 18.08 | 17.91 | 17.92 | 17.74 | 17.57 | 16.30 |

TABLE IV

EFFECT OF LIGHT ON HIGH MELTING 1-BENZYL-2-PHENYL-3-*p*-TOLUYLETHYLENE IMINE (IA)

| Storage time | | | | | |
|---|---|---|---|---|---|
| Dark storage | 0 | 24 | 48 | 96 | 48 |
| Light storage | 0 | 0 | 0 | 0 | 48 |
| Total hours | 0 | 24 | 48 | 96 | 96 |
| $\lambda_{max}$ Å. | 2530 | 2520–30 | 2520 | 2510–20 | 2510 |
| $\epsilon_{max} \times 10^{-3}$ | 15.24 | 15.27 | 15.27 | 15.25 | 15.15 |

In Table I and Fig. 3 are given the results of a study made with a freshly prepared 50–50 mixture of (IA) and (IB) in hexane solutions. These studies were made within two hours of the time the solution was prepared.

## Summary

*cis* and *trans* racemates of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine have been isolated from the reaction of benzylamine with α,β-dibromobenzyl-*p*-methylacetophenone. The physical properties, absorption spectra and behavior with hydrogen chloride are consistent with the configurations that have been assigned. The interconvertibility of these geometrical isomers has been studied.

LINCOLN, NEBRASKA RECEIVED JULY 27, 1948

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[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

# Ethylene Imine Ketones. V.[1] Reaction with Hydrogen Chloride[2]

BY NORMAN H. CROMWELL AND RONALD A. WANKEL[3]

Previous investigations of the reactions of ethylene imine ketones with hydrogen halides have shown that the ethylene imine ring cleaves in the two directions under various conditions.[1,4]

It was of interest to re-investigate the reaction of benzylamine with α,β-dibromobenzylacetophenone[5] in an attempt to account for a larger portion of the starting materials. A further aim of this investigation was a quantitative product study of the reaction of ethylene imine ketones with minimum amounts of hydrogen chloride.

We were unable to isolate a lower-melting, more soluble form of 1-benzyl-2-phenyl-3-benzoylethylenimine. However, when the filtrate from the isolation of the higher-melting, less soluble form of this compound (I) (m. p. 108°)[5] was treated with

(1) For paper IV see, Cromwell and Hoeksema, THIS JOURNAL, **71**, 708 (1949).

(2) Presented before a session of the Division of Organic Chemistry, 113th Meeting of the American Chemical Society, Chicago, Illinois, April 20, 1948.

(3) Abstracted from the Ph.D. thesis (1949); du Pont Fellow, 1947–1948.

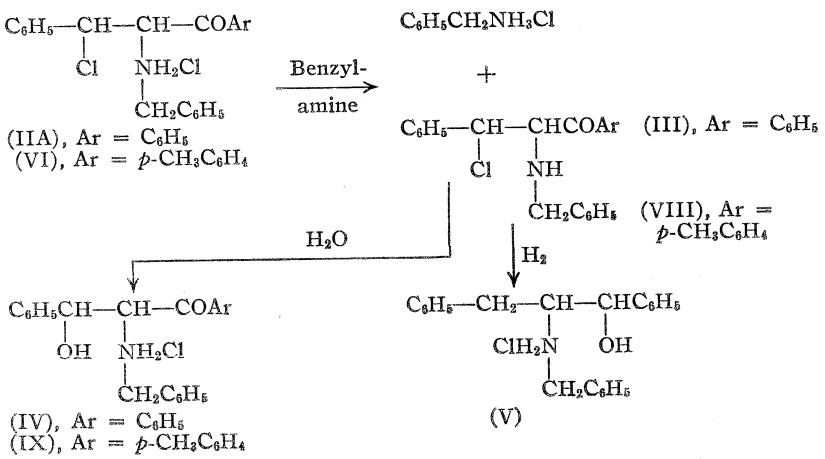
(4) Cromwell and Caughlan, THIS JOURNAL, **67**, 2235 (1945).

(5) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

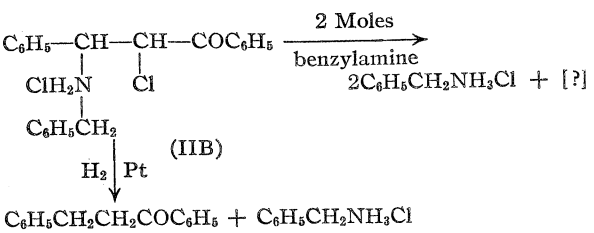
excess dry hydrogen chloride, most of the remaining starting materials were accounted for. A mixed dichloride product ($C_{22}H_{21}NOCl_2$) resulted which was separated by recrystallization into nearly equal amounts of β-chloro-α-benzylaminobenzylacetophenone hydrochloride (IIA) and α-chloro-β-benzylaminobenzylacetophenone hydrochloride (IIB). The isomer (IIA) had been obtained in a previous investigation of the reaction of ethylene imine ketone (I) with excess hydrogen chloride, and assigned this structure.[6]

The dichloride (IIB) reacted with dry, acidified acetone solutions of potassium iodide to release nearly one equivalent of iodine, while (IIA) gave almost no reaction under the same conditions.[6] Neither of these products showed any tendency to rearrange to the other on standing in either methyl alcohol or benzene saturated with dry hydrogen chloride.

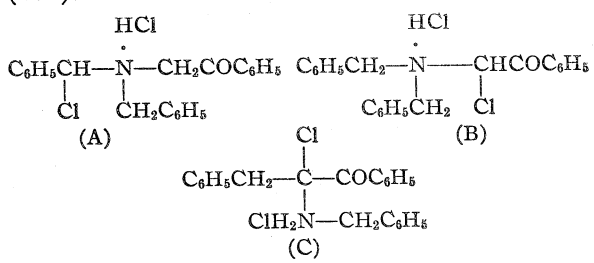
When (IIA) was warmed with a benzene solution of benzylamine the base (III), α-benzylamino-β-chlorobenzylacetophenone, resulted. Compound (III) was readily hydrolyzed by warm aqueous alcohol to α-benzylamino-β-hydroxybenzylacetophenone hydrochloride (IV). Catalytic hydrogenation converted (III) into the known[7] 2-benzylamino-1,3-diphenylpropanol-1 hydrochloride (V) (and picrate). This latter experiment seems to afford unequivocal proof for the structure assigned to (IIA).




When the dichloride (IIB) was treated with a warm benzene solution of benzylamine, two equivalents of benzylamine hydrochloride were formed. This indicated that the chlorine attached to carbon was more readily removed here than in (IIA). Catalytic hydrogenation of (IIB) gave a good yield of benzylacetophenone. The intermediate product in this latter reaction may have been β-benzylaminobenzylacetophenone. It has been reported previously, from this laboratory, that such β-amino ketones readily undergo beta elimination during catalytic hydrogenation.[8]




We believe the structure of (IIB) has been definitely established. Other structures, such as (A), (B) and (C), for these products (IIA) and (IIB), seem to have been eliminated. Moreover, it is not possible for (IIA) and (IIB) to be related as racemates of the same position isomer, (IIA) or (IIB).




The isomeric dichlorides (IIA) and (IIB) were also obtained from a quantitative experiment with pure 1-benzyl-2-phenyl-3-benzoylethylenimine (m. p. 108°) (I). When minimum amounts of dry hydrogen chloride were employed, the α-chloro ketone (IIB) was the major (73.5%) product, while (IIA) was formed in lesser amounts (26.5%). Addition of one equivalent of dry hydrogen chloride to a cold acetone–ether solution of (I) resulted in the primary precipitation of quite pure (IIB). From the filtrate of (IIB) some unchanged ethylene imine ketone (I) was isolated. Addition of a second calculated amount of dry hydrogen chloride to the filtrate of (I) caused the formation of a mixed dichloride. This latter product was separated into the two isomers, (IIA) and (IIB), by taking advantage of the expected differences in the basic strengths of the free bases of these two dichlorides.

Iodine release data showed the above dichloride to be approximately a 50-50 mixture of (IIA) and (IIB). This product was treated with one equivalent of benzylamine and the precipitated benzylamine hydrochloride filtered off. One-half of an equivalent of hydrogen chloride was added to precipitate (IIB), the hydrochloride of the stronger base. A second one-half equivalent of the same reagent then precipitated (IIA).

It has been reported[1] that excess amounts of

(6) Cromwell and Wankel, THIS JOURNAL, **70**, 1321 (1948).
(7) Wilson and Sun, *J. Chinese Chem. Soc.*, **2**, 243 (1935).
(8) Cromwell, Wiles and Schroeder, THIS JOURNAL, **64**, 2432 (1942).

dry hydrogen chloride reacted with *trans*-1-benzyl-2-phenyl-3-*p*-toluylethylenimine to give β-chloro-α-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (VI). The *cis* isomer gave a mixed dichloride which was indicated to contain approximately 54% of (VI) and 46% of α-chloro-β-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (VII).

Quantitative experiments using minimum amounts of dry hydrogen chloride, as with the ethylene imine ketone (I), have been carried out with these *cis* and *trans* isomers mentioned above. The *trans* isomer gave 78% of the α-chloro ketone (VII) and 22% of the β-chloro ketone (VI). The *cis* isomer gave 54% of (VII) and 46% of (VI). These relative percentage yields were approximated from iodine release studies with the chloride products. Figure 1 compares the rate of iodine release by relatively pure α-chloro ketone (VII) with that of a pure sample of (IIB).

From both of these hydrogen chloride cleavage experiments some ethylene imine ketone was recovered. It is significant that, from the experiment starting with the *cis* isomer, we isolated the *trans* ethylene imine ketone. This indicates that the rearrangement of the *cis* isomer to the *trans* isomer may be catalyzed by acid as well as by light.[1]

β-Chloro-α-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (VI) reacted with a warm benzene solution of excess benzylamine to lose only one equivalent of hydrogen chloride, and form the base (VIII). Warm, aqueous alcohol converted (VIII) to β-hydroxy-α-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (IX). Configuration studies of these dichlorides, including ring closure to the ethylene imine ketones by the α-chloro products, are being undertaken.

**Discussion of Hydrogen Chloride Reaction Mechanisms.**—It seems evident that the first product from the reaction of an ethylene imine ketone with hydrogen chloride is the simple salt (S). A hydrochloride of type (S) was isolated in a previous investigation.[5] The direction of the cleavage of the ethylene imine ring in the salt (S) is determined by the conditions of the experiment and the configuration of the original ethylene imine ketone. The results obtained from the quantitative dry hydrogen chloride experiments suggest several possible mechanisms that serve as a working hypothesis for the kinetic studies that are in progress.

### $S_N1$ and/or $S_N2$ Ring Cleavage Mechanism

If the mechanism is of an $S_N1$ type then the ring would be expected to open, mainly according to scheme [1] if the α-carbon has the greater electron density. For an $S_N2$ type of ring cleavage, scheme [2] would be the major reaction course if the β-carbon is the more electrophilic. It is to be recalled that the *trans* ethylene imine ketones gave, mainly, the α-chloro ketones with minimum amounts of hydrogen chloride. The *cis* form studied reacted much more rapidly to give only slightly more α-chloro ketone than β-chloro ketone, under these conditions. Excess chloride ion concentration should favor the $S_N2$ mechanism and course [2].

### Carbonyl Directed 1–4 Ring Cleavage Mechanism

Under the influence of excess hydrogen chloride the salt (S) might also be expected to undergo ring cleavage by way of a carbonyl directed 1,4-attack, as indicated above. An inspection of scale models indicates that with the *trans* structures transition complex (T) could form readily. In the *cis* form the aryl group on the β-carbon would be expected to repel the chlorine atom of the hydrogen chloride molecule to such an extent that a transition complex (T) would seem unlikely. It is to be recalled that excess dry hydrogen chloride converted the *trans* ethylene imine ketones almost entirely into β-chloro ketones. A similar experiment with the *cis* compound gave only slightly less α-chloro ketone than β-chloro ketone.

**Acknowledgment.**—The senior author appreciates a grant from the Research Council of the University of Nebraska which aided in the completion of this investigation.

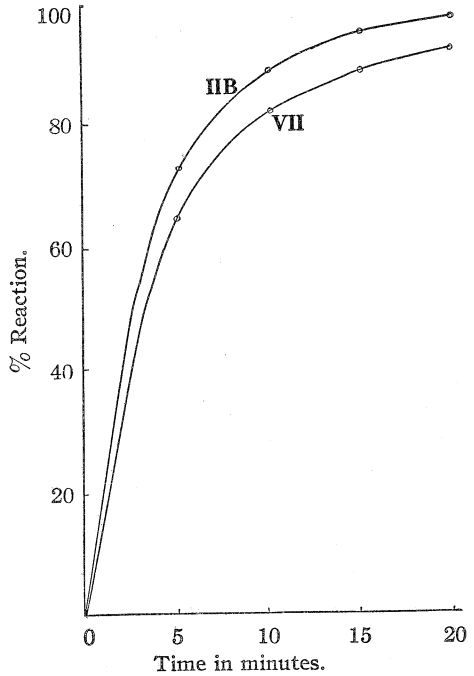



Fig. 1.—Rates of iodine release by α-chloro-β-aminoketones (IIB) and (VII) in a dry acetone–alcohol acidic solution of potassium iodide at 66°.

## Experimental

**Reaction of α,β-Dibromobenzylacetophenone with Benzylamine. Quantitative Studies.**—Following the directions outlined previously[1] for the preparation of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine, a 46% yield of 1-benzyl-2-phenyl-3-benzoylethylenimine, m. p. 108°[6] was obtained from α,β-dibromobenzylacetophenone. It was not possible to isolate a solid, low-melting isomer in this case. The reaction mixture filtrate was treated with an excess of an absolute alcohol solution of dry hydrogen chloride, to give as a first crop, colorless crystals, 24% yield, m. p. 159–164°. Two recrystallizations of this product from methyl alcohol and dry ether gave a 20% yield of (IIA), m. p. 164–166°. Iodine release[6] at 66° in thirty minutes was 6.4% for this product.

*Anal.* Calcd. for $C_{22}H_{21}NOCl_2$: Cl, 18.36. Found: Cl, 18.30.

The filtrate from (IIA) was treated with several times its volume of dry ether and cooled for two days to give a second crop of colorless crystals (20% yield), m. p. 149–150°, of (IIB); recrystallized from methyl alcohol and dry ether, m. p. 151–152°. (IIB) released 95.4% of one equivalent of iodine at 66° in fifteen minutes. See also Figure 1.

*Anal.* Calcd. for $C_{22}H_{21}NOCl_2$: Cl, 18.36. Found: Cl, 18.32. A 50-50 mixture of (IIA) and (IIB) showed a m. p. 150–159° and gave an iodine release value of 51% in either fifteen or thirty minutes.

In this experiment, 90% of the original α,β-dibromobenzylacetophenone was accounted for. Neither (IIA) nor (IIB) underwent any appreciable change on standing at room temperature in dry methyl alcohol solution for four days.

**α-Benzylamino-β-chlorobenzylacetophenone (III).**—A 5.0 g. (0.013 mole) sample of the hydrochloride (IIA) was mixed with 50 ml. of benzene and 1.39 g. (0.013 mole) of benzylamine, heated on the steam-bath for ten minutes, and then allowed to stand at room temperature for three hours. Dry ether was added and the colorless precipitate of benzylamine hydrochloride filtered off, wt. 1.85 g. (99% of one equivalent). The filtrate was evaporated under reduced pressure and petroleum ether added. Colorless crystals formed and were filtered off, wt. 3.0 g. (0.0086 mole, 66% yield), m. p. 92–93°; iodine release at 66° in thirty minutes was 3.0%.

*Anal.* Calcd. for $C_{22}H_{20}NOCl$: C, 75.52; H, 5.76. Found: C, 75.88; H, 5.84.

Compound (III) decomposed after standing at room temperature for twenty-four hours in a vacuum desiccator.

When the hydrochloride (IIB) was placed in benzene and treated with benzylamine, two equivalents of benzylamine hydrochloride were formed immediately. Evaporation of the benzene left an oil which solidified at −15° but which could not be resolved to a solid product at room temperature. This possibily was a low melting form of 1-benzyl-2-phenyl-3-benzoylethylenimine.

**α-Benzylamino-β-hydroxybenzylacetophenone Hydrochloride (IV).**—An attempted recrystallization of this product (III) from hot aqueous alcohol resulted in a hydrolysis, and precipitated a product no longer soluble in ether or acetone, m. p. 210° (IV).

*Anal.* Calcd. for $C_{22}H_{22}NO_2Cl$: C, 71.82; H, 6.03; N, 3.81. Found: C, 71.54; H, 6.20; N, 3.93.

A more extensive decomposition accompanied this hydrolysis as indicated by the presence of benzaldehyde.

**Hydrogenation of (III).**—A 2.0-g. sample of (III) was dissolved in 20 ml. of methanol and 0.5 g. of 10% palladium-on-charcoal catalyst added. This mixture was shaken for two hours with hydrogen at room temperature under a pressure of 38 lb. per sq. inch. The catalyst was filtered off and the methanol evaporated under reduced pressure. Addition of dry ether gave mixed hydrochlorides, wt. 1.0 g., m. p. 205–210°. This product was dissolved in water and the solution treated with dilute sodium hydroxide to give an oily precipitate which was extracted with ether. On passing dry hydrogen chloride into the dried ether solution, a colorless precipitate formed, m. p. 223–225°; recrystallized from alcohol and ether, m. p. 228–229°; wt. 0.7 g. (V).

*Anal.* Calcd. for $C_{22}H_{24}NOCl$: C, 74.66; H, 6.84; N, 3.96. Found: C, 74.36; H, 6.96; N, 3.78.

A sample of 2-benzylamino-1,3-diphenylpropanol-1 hydrochloride was prepared and found to have a m. p. of 228–229° instead of m. p. 220° as previously reported.[7] Several careful mixed m. p. and mixed freezing point experiments indicated this compound to be identical with (V). The picrate of the free base of (V) was prepared, m. p. 149–150°, and found to be identical with the authentic picrate of 2-benzylamino-1,3-diphenylpropanol-1.[7]

**Hydrogenation of (IIB).**—A 0.6 g. (0.00155 mole) sample of the hydrochloride (IIB) was dissolved in 20 ml. of absolute alcohol and 0.1 g. of platinum oxide catalyst added. The mixture was shaken for thirty minutes with hydrogen at room temperature under a pressure of 45 lb. per sq. inch. The catalyst was filtered off and the solvent evaporated under reduced pressure. Addition of dry ether gave 0.15 g. (0.00104 mole) of benzylamine hydrochloride. Evaporation of the ether filtrate gave 0.2 g. (0.00095 mole, 61% yield) of a colorless, crystalline product, m. p. 70°, identical with benzylacetophenone.

**Treatment of 1-Benzyl-2-phenyl-3-benzoylethylenimine with Minimum Amounts of Hydrogen Chloride.**—A 3.0-g. (0.00959 mole) sample of 1-benzyl-2-phenyl-3-benzoylethylenimine (m. p. 108°) was dissolved in 25 ml. of dry acetone and cooled in an ice-bath to 5°. A 25.1-ml. quantity of a 0.383 molar dry, hydrogen chloride-in-ether solution (0.0096 mole of HCl) was added slowly with stirring. A large amount of white precipitate formed immediately and remained for several hours (the ethylene imine ketone hydrochloride).[5] After standing at room temperature for one day, the solution had developed a pale-yellow color, the original precipitate had disappeared and a lesser amount of larger, colorless crystals appeared which were filtered off, m. p. 149°, wt. 1.0 g. (0.00259 mole, 27% yield). This product was identical in all respects with (IIB), giving an iodine release of 93.2% in fifteen minutes at 66°.

*Anal.* Calcd. for $C_{22}H_{21}NOCl_2$: C, 68.39; H, 5.48; N, 3.63. Found: C, 68.17; H, 5.71; N, 3.42.

Evaporation of the filtrate from (IIB) left a semi-solid residue which was recrystallized from a benzene–petroleum ether mixture to give 0.60 g. (0.00192 mole) of the starting ethylene imine ketone, m. p. 103–106°, identified by a mixed m. p. experiment and by its behavior in direct sunlight (turned pink).

Assuming that about 0.0044 mole of the chlorobenzylaminobenzylacetophenones remained in the filtrate from the recovery of the ethylene imine ketone, 11.5 ml. of the 0.383 molar dry, ether–hydrogen chloride solution (0.0044 mole of HCl) were added and the solution cooled in an ice-bath to give an immediate precipitation of a colorless product which was filtered off; wt. 1.5 g. (0.00389 mole); m. p. 141–145°; iodine release, 49.4% in fifteen minutes at 66°.

A separation of this mixed product melting at 141–145° was effected by a method based upon the differences in the basic strengths of α-chloro-β-benzylaminobenzylacetophenone and α-benzylamino-β-chlorobenzylacetophenone. A 0.70 g. (0.00182 mole) sample was mixed with 25 ml. of dry ether and treated with 0.20 g. (0.00187 mole) of benzylamine. After standing for fifteen hours in the ice chest the precipitated benzylamine hydrochloride was filtered off. The ether filtrate was then treated with 0.0009 mole of hydrogen chloride. After cooling at 0° for one day, a colorless product was filtered off, wt. 0.34 g. (0.00088 mole), m. p. 148–150°; iodine release at 66° in fifteen minutes was 77%. This was fairly pure (IIB). To the filtrate was now added a second 0.0009 molar quantity of hydrogen chloride. After standing for twenty-four hours, a second product was obtained, m. p. 161–162°, wt. 0.27 g. (0.0007 mole); iodine release at 66° in thirty minutes was 2.3%. This was fairly pure (IIA).

This entire experiment was repeated with the same results at each step, within 5–10%.

The chloride (IIA) was identical in all respects with the chloride obtained previously from the reaction of excess dry or aqueous hydrogen chloride and 1-benzyl-2-phenyl-3-benzoylethylenimine, and was assigned the structure β-chloro-α-benzylaminobenzylacetophenone hydrochloride.[4,6] Both (IIA) and (IIB) remained unchanged after standing for several days in a mixture of dry benzene and dry ether saturated with dry hydrogen chloride.

**Reaction of *cis* and *trans* 1-Benzyl-2-phenyl-3-*p*-toluylethylenimines with Minimum Amounts of Hydrogen Chloride.**—Following the procedure as outlined above for 1-benzyl-2-phenyl-3-benzoylethylenimine, the following results were obtained with these *cis* and *trans* isomeric ethylene imine ketones.[1]

**From 1.8 g. (0.0055 mole) of this *trans* isomer,** the first hydrochloride product (VII) weighed 0.5 g. (0.00125 mole), m. p. 155–161°; iodine release in fifteen minutes at 66° was 88.7% (see also Fig. 1). When recrystallized from methanol and ether, the melting point increased to 163–167°; but the iodine release value was practically unchanged. This sample (VII) was almost pure α-chloro-β-benzylaminobenzyl-*p*-methylacetophenone hydrochloride. Also obtained in the second step was 0.9 g. (0.00225 mole) of mixed hydrochlorides, m. p. 159–162°, which gave an iodine release of 65.4%. Evaporation of the residual mixture gave 0.35 g. (0.00107 mole) of unreacted ethylene imine ketone.

**From 2.0 g. (0.00612 mole) of the *cis* isomer,** the first hydrochloride product weighed 0.57 g. (0.00142 mole), m. p. 156–159°; iodine release for this product at 66° in fifteen minutes was 53.8%. Evaporation of the filtrate from this product gave 0.2 g. (0.00061 mole) of the *trans* instead of the *cis* ethylene imine ketone, as shown by a mixed m. p. and its light sensitivity. Treatment of the residual solution with more dry hydrogen chloride gave a second hydrochloride product, wt. 1.08 g. (0.0027 mole), m. p. 150–155°. Iodine release for this product in fifteen minutes at 66° was 54.2%.

Continuous fractional recrystallizations from ethanol and dry ether separated both of these products into nearly equal amounts of (VII) and β-chloro-α-benzylaminobenzyl-*p*-methylacetophenone hydrochloride (VI).

**β-Chloro-α-benzylaminobenzyl-*p*-methylacetophenone (VIII).**—Repeating the procedure outlined above for the preparation of (III), 2.0 g. of the hydrochloride (VI) gave 0.714 g. of benzylamine hydrochloride and 1.0 g. of (VIII); recrystallized from an ether–petroleum ether mixture, m. p. 105° (decomposed then resolidified).

*Anal.* Calcd. for $C_{23}H_{22}NOCl$: C, 75.93; H, 6.09; N, 3.85. Found: C, 76.11; H, 6.07; N, 4.10.

**β-Hydroxy-α-benzylaminobenzyl-*p*-methylacetophenone Hydrochloride (IX).**—Following the procedure outlined for the preparation of (IV), 0.4 g. of (VIII) gave 0.23 g. of (IX), recrystallized from methanol and ether, m. p. 208–210°.

*Anal.* Calcd. for $C_{23}H_{24}NO_2Cl$: C, 72.33; H, 6.34; N, 3.67. Found: C, 72.09; H, 6.52; N, 3.71.

## Summary

1. Excess amounts of dry hydrogen chloride react with the *trans* forms of ethylene imine ketones to give mainly the β-chloro-α-aminoketone hydrochlorides. Minimum amounts of this reagent convert these *trans* forms largely into the isomeric α-chloro-β-aminoketone hydrochlorides.

2. The *cis* form of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine reacts very rapidly with excess or minimum amounts of dry hydrogen chloride to give nearly equal amounts of the α-chloro and β-chloro ketones.

3. Structure proofs for the closely related α-chloro-β-aminoketones and β-chloro-α-aminoketones have been devised. Possible mechanisms to account for these different ring cleavages have been discussed.

LINCOLN, NEBRASKA RECEIVED JULY 27, 1948

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

# Ethylene Imine Ketones. VI.[1] Reactions with Phenylhydrazine[2]

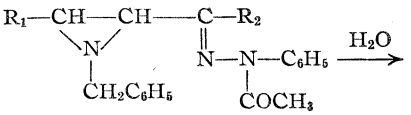
BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[3]

Continuing our comparative studies of the reactions of ethylene imine ketones with known reactions of epoxy ketones it was of interest to investigate the behavior of the former with phenylhydrazine. A similar study of the reaction of hydrazine with an epoxy ketone[4] has shown that the epoxide ring is opened to give an intermediate 4-hydroxypyrazoline which on heating loses water to yield the corresponding pyrazole.

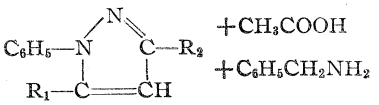
It was of considerable interest to compare the phenylhydrazine reactions of the *cis* and *trans* isomeric 1-benzyl-2-phenyl-3-*p*-toluylethylenimines, reported in a previous communication.[5]

With what may be presumed to be the *trans* forms in each case[1,5] 1-benzyl-2-phenyl-3-benzoylethylenimine,[6] 1-benzyl-2-*p*-tolyl-3-benzoylethylenimine,[7] and 1-benzyl-2-phenyl-3-*p*-toluylethylenimine,[5] each reacted with phenylhydrazine in glacial acetic acid to give the corresponding pyrazoles (I), (II) and (III) and the N-acetylphenylhydrazones of the ethylene imine ketones, (IV), (V) and (VI). The identities of the former were established by comparison with authentic samples synthesized by known methods.

The N-acetylphenylhydrazones (IV), (V) and (VI) have been assigned these structures because on hydrolysis they give the expected pyrazoles, and because they have absorption spectra, see Fig. 1, that are similar only to that of an N-acetylphenylhydrazone.[8]



(IV) $R_1$ and $R_2$ = $C_6H_5$
(V) $R_1$ = *p*-$CH_3C_6H_4$; $R_2$ = $C_6H_5$
(VI) $R_1$ = $C_6H_5$; $R_2$ = *p*-$CH_3C_6H_4$



(I) and (III)

Since it was possible that the general absorption spectra shown by these compounds (V) and (VI) were the result of pyrazole impurities in an acetylated pyrazoline of type (IX), study of the spectrum of a mixture of the pyrazole (III) and of the acetylated product (IX) was undertaken. As is indicated by Fig. 2, such an explanation of the general absorption shown by (VI) is unlikely.

Even with the mildest conditions the pyrazole resulted from the phenylhydrazine reactions with the *trans* form of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine. The mechanism of its formation probably involves the intermediate formation of the phenylhydrazone (A) which then undergoes an intramolecular ring opening and closure to form the 4-benzylaminopyrazoline (B). The configuration of (B) may be such that the benzylamino group on carbon atom-4 and the hydrogen on carbon-5 are on the same side of the pyrazoline ring. Compound (B) might then lose benzylamine readily by an intramolecular reaction as indicated to form the pyrazole.

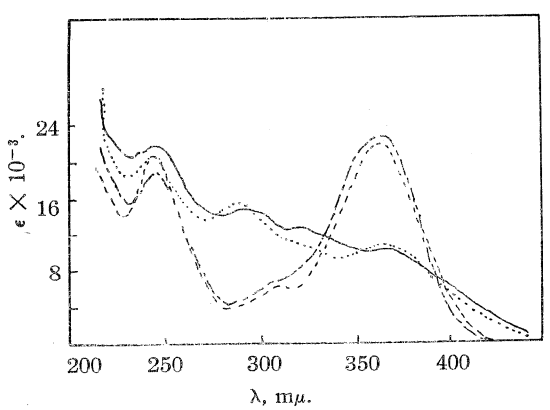



Fig. 1.—V, . . .; VI, —; VII, — —; IX, — — —.

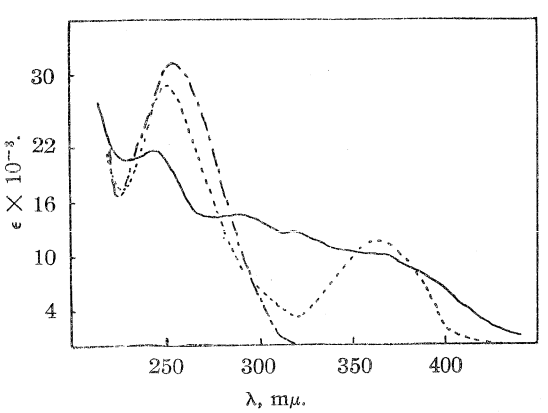



Fig. 2.—VI, —; III, — —; mixture of III and IX, — — —.

(1) For the previous paper in this series see Cromwell and Wankel, THIS JOURNAL, **71**, 711 (1949).

(2) Presented before a session of the Division of Organic Chemistry, 114th Meeting of the American Chemical Society, St. Louis, Mo., September 8, 1948.

(3) Abstracted from the thesis of Herman Hoeksema submitted to the Graduate College of the University of Nebraska in partial fulfillment of the requirements for the Ph.D. degree, June, 1948. American Chemical Society predoctoral research fellow, 1947–1948.

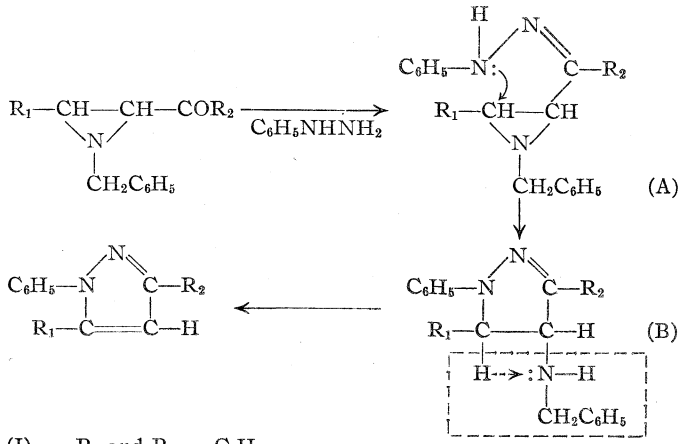
(4) Jorlander, *Ber.*, **49**, 2782 (1916).

(5) Cromwell and Hoeksema, THIS JOURNAL, **71**, 708 (1949).

(6) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

(7) Cromwell, *ibid.*, **69**, 258 (1947).

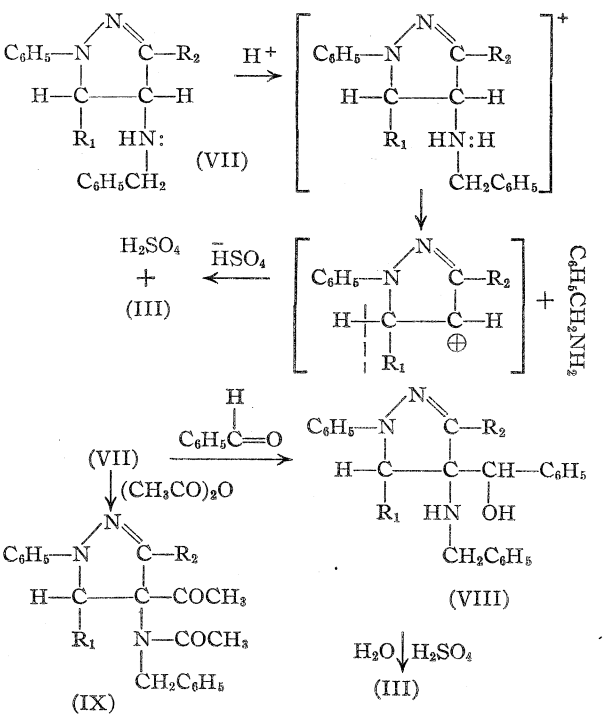
(8) Grammaticakis, *Bull. soc. chim.*, [5] **7**, 527 (1940).



(I) $R_1$ and $R_2$ = $C_6H_5$
(II) $R_2$ = $C_6H_5$, $R_1$ = $p$-$CH_3C_6H_4$
(III) $R_1$ = $C_6H_5$, $R_2$ = $p$-$CH_3C_6H_4$

The *cis* form (low melting) of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine[5] gave excellent yields of 1,5-diphenyl-3-*p*-tolyl-4-benzylaminopyrazoline (VII). Even in warm glacial acetic acid this *cis* isomer gave only (VII). The structure assigned to (VII) is consistent with the fact that it gives the standard tests for pyrazolines, that it shows the same blue fluorescence as the known parent 1,5-diphenyl-3-*p*-tolylpyrazoline,[9] and that it cannot be hydrogenated to yield aniline as would be expected with a phenylhydrazone. Moreover, in strong acid solution (VII) loses benzylamine to give the corresponding pyrazole (III).

The aminopyrazoline (VII) condensed with benzaldehyde to give a product whose properties indicate it probably has structure (VIII), and with acetic anhydride to give the diacetylated product which has been assigned the structure (IX). These are expected reactions, for the pyrazolines have active hydrogen in the 4-position.[10] Compound (VIII) was converted to pyrazole (III) on heating with dilute sulfuric acid. The properties of compounds of types (VIII) and (IX) are being studied further in an extended investigation. Studies of the absorption spectra of the diacetylated aminopyrazoline (IX) and of the benzaldehyde condensation product (VIII) indicated them to be similar to those of both the parent 1,5-diphenyl-3-*p*-tolylpyrazoline and the 4-benzylamino-1,5-diphenyl-3-*p*-tolylpyrazoline (VII) (see Figs. 1 and 3). It is to be observed that pyrazolines and phenylhydrazones have similar but not identical spectra, see Fig. 3.



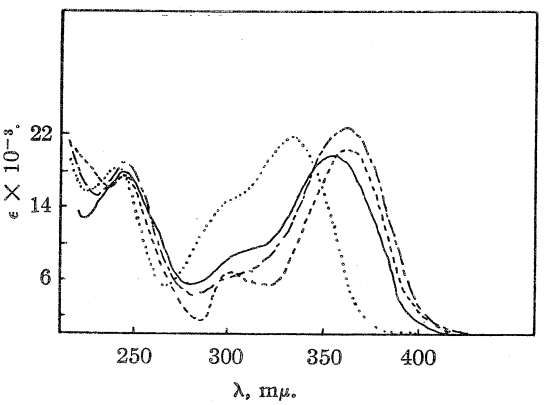



Fig. 3.—1,5-Diphenyl-3-*p*-tolylpyrazoline,—; VII, — –; VIII, – – –; X, ....

The formation of the aminopyrazoline (VII) from the *cis* isomer may be explained by the same mechanism as given above for the formation of (A) and (B) from the *trans* ethylene imine ketone. In the former case, however, the benzylamino group on carbon-4 and the hydrogen on carbon-5 might now be expected to turn up on opposite sides of the pyrazoline ring and intramolecular loss of benzylamine becomes less probable. Thus in neutral or basic media (VIII) is quite stable, but in acid solution, where solvolytic protons are available, (VII) can lose benzylamine to give the pyrazole by the mechanism shown later.

These considerations may suggest why 4-amino derivatives of 1,3,5-triarylpyrazolines have heretofore been unknown.

**Acknowledgment.**—The senior author appreciates a grant from the Research Council of the University of Nebraska which aided in the completion of this investigation.

(9) Raiford and Peterson, *J. Org. Chem.*, **1**, 544 (1937).

(10) Curtius and Wirsing, *J. prakt. Chem.*, [2] **50**, 531 (1894).

TABLE I

PHYSICAL AND ANALYTICAL PROPERTIES

| Pyrazoles | No. | M. p., °C. | Yield, % | Formula | Percentage composition Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| 1,3,5-Triphenyl- | (I) | 135 | 37 | $C_{21}H_{16}N_2$ | 85.10 | 5.44 | 9.46 | 85.32 | 5.57 | 9.51 |
| 1,3-Diphenyl-5-*p*-tolyl- | (II) | 119 | 46 | $C_{22}H_{18}N_2$ | 85.14 | 5.84 | 9.03 | 85.18 | 5.70 | 9.22 |
| 1,5-Diphenyl-3-*p*-tolyl- | (III) | 130 | 32 | $C_{22}H_{18}N_2$ | 85.14 | 5.84 | 9.03 | 85.40 | 5.75 | 9.02 |
| Acetylphenylhydrazones of | | | | | | | | | | |
| 1-Benzyl-2-phenyl-3-benzoylethylenimine | (IV) | 135–140 | 33 | $C_{30}H_{27}N_3O$ | 80.86 | 6.33 | 9.43 | 80.95 | 6.24 | 9.42 |
| 1-Benzyl-2-*p*-tolyl-3-benzoylethylenimine | (V) | 148 | 30 | $C_{31}H_{29}N_3O$ | ... | .. | 9.14 | ... | .. | 9.04 |
| 1-Benzyl-2-phenyl-3-*p*-toluylethylenimine | (VI) | 149 | 30 | $C_{31}H_{29}N_3O$ | 81.01 | 6.36 | 9.14 | 81.41 | 6.41 | 9.10 |
| 1,5-Diphenyl-3-*p*-tolylpyrazoline | | | | | | | | | | |
| 4-Benzylamino- | (VII) | 124 | 75 | $C_{29}H_{27}N_3$ | 83.41 | 6.52 | 10.07 | 83.60 | 6.60 | 10.14 |
| 4-Benzylamino-4-(phenylhydroxymethyl)- | (VIII) | 165–170 | 67 | $C_{36}H_{33}N_3O$ | 82.57 | 6.35 | 8.03 | 82.62 | 6.67 | 7.78 |
| 4-Acetobenzylamino-4-aceto- | (IX) | 91–96 | 75 | $C_{33}H_{31}N_3O_2$ | 79.01 | 6.23 | 8.38 | 78.87 | 6.55 | 8.26 |

## Experimental

**Reaction of Ethylene Imine Ketones (*trans* Isomers) with Phenylhydrazine in: (a) Glacial Acetic Acid.**—The ethylene imine ketone (2.1 g., 0.006 mole) was dissolved in 10 ml. of glacial acetic acid. One gram (0.009 mole) of phenylhydrazine was added and the solution warmed to 50° for a few minutes and then cooled to room temperature. After standing at room temperature for twenty-four hours the solution was cooled to 0° and the precipitated product removed by filtration and purified by recrystallization from benzene–alcohol mixtures to give the colorless pyrazole. The acetic acid filtrate was treated with an equal volume of water to give a yellow gummy precipitate which was recrystallized several times from benzene–absolute alcohol and benzene–petroleum ether mixtures to give the yellow N-acetylphenylhydrazones of the ethylene imine ketones.

In this way the pyrazole (I) and N-acetylphenylhydrazone (IV) were obtained from 1-benzyl-2-phenyl-3-benzoylethylenimine[6]; pyrazole (II) and N-acetylphenylhydrazone (V) from 1-benzyl-2-*p*-tolyl-3-benzoylethylenimine[7]; and pyrazole (III) and N-acetylphenylhydrazone (VI) from 1-benzyl-2-phenyl-3-*p*-toluylethylenimine (high m.p.)[5] (see Table I). A mixture of (V) and (VI) melted at 125–135°.

**(b) Pyridine Solution.**—A 35% yield of the pyrazole (III) resulted when the corresponding ethylene imine ketone (high melting) was mixed with one equivalent of glacial acetic acid and 2.5 equivalents of phenylhydrazine in pyridine solution at room temperature. No other products were isolated from this experiment.

**(c) Alcohol Solution.**—To a solution of 3.0 g. (0.009 mole) of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine (high m.p.) in 150 ml. of ethyl alcohol was added 1.0 g. (0.009 mole) of phenylhydrazine and 1.0 g. (0.017 mole) of glacial acetic acid. The solution stood at room temperature for four hours and in the ice chest for three days. The precipitated product was removed by filtration and recrystallized from alcohol, 1.1 g. (38% yield), m.p. 129.5°, mixed with (III), m.p. 129–130°. From the residual reaction mixture was recovered 0.1 g. of the unchanged starting ethylene imine ketone.

**Synthesis of Pyrazoles (I), (II) and (III).**—The pyrazoles (II) and (III) were prepared for the first time from the corresponding benzalacetophenone dibromides by the method outlined by Barnes[11] in 20–35% yields. These products melted the same as (II) and (III), respectively, and mixtures showed no depression of melting point. A mixture of (II) with (III), however, melted at 98–105°.

(11) Barnes and Dodson, THIS JOURNAL, 65, 1585 (1943).

The pyrazole (I), a known compound, was prepared according to the method of Wislicenus[12] in 50% yields and was identical with (I).

**Hydrolysis of the N-Acetylphenylhydrazones (IV) and (VI).**—One-gram samples of compounds (IV) and (VI), respectively, were mixed with 5 ml. of hot alcohol. These suspensions were poured into 25 ml. of boiling 20% sulfuric acid and the resulting mixtures refluxed for ten hours. The solutions were cooled and the colorless products filtered and recrystallized from alcohol. In this way 90–100% yields of the pyrazole (I) resulted from (IV), and the pyrazole (III) from (VI).

**Reaction of 1-Benzyl-2-phenyl-3-*p*-toluylethylenimine (*cis* Form) with Phenylhydrazine: (a) In Alcohol Solution.**—Nine grams (0.027 mole) of the low m.p. ethylene imine ketone was dissolved in 150 ml. of ethyl alcohol. To this solution were added 3.0 g. (0.027 mole) of phenylhydrazine and 3.0 g. (0.05 mole) of glacial acetic acid. As the solution stood at room temperature slow crystal growth was observed. After four hours the mixture was cooled to yield a pale-yellow product which was recrystallized twice from absolute alcohol to give colorless crystals of (VII). All solutions of this product displayed a blue fluorescence. It also gave the Knorr[13] and the Raiford[9] tests for pyrazolines. On refluxing a benzene solution of (VII) for three hours no change took place.

**(b) In Glacial Acetic Acid.**—A 2.1-g. (0.006 mole) sample of the ethylene imine ketone (m.p. 72–74°) was dissolved in 10 ml. of glacial acetic acid and 1.0 g. (0.009 mole) of phenylhydrazine added. The solution was heated to 50° for a few minutes, allowed to stand at room temperature for three hours and finally cooled in the ice chest for several days. No precipitation took place. On adding water to the reaction mixture a gummy product was obtained which, after recrystallization from alcohol, gave a 48% yield of a product identical in all respects with the aminopyrazoline (VII).

**Attempted Hydrogenations of the Aminopyrazoline (VII).**—The aminopyrazoline (VII) resisted hydrogenation and was recovered unchanged from reaction mixtures employing palladium on charcoal and hydrogen at 50 lb./sq. in. at 100°, or platinum oxide under similar conditions. Boiling sodium and alcohol solutions likewise did not change this product.

**Hydrolysis of the Aminopyrazoline (VII).**—A 3.0-g. sample of (VII) was warmed on a steam-bath for three and one-half hours with 50 ml. of 20% sulfuric acid. From the cooled solution was isolated 2.1 g. of a pyrazole identical with (III).

(12) Wislicenus, *et al.*, *Ann.*, **308**, 253 (1899).

(13) Knorr, *Ann.*, **238**, 200 (1887).

**Reaction of Benzaldehyde with the Aminopyrazoline (VII).**—Two grams (0.0048 mole) of (VII) was mixed with 3.1 g. (0.29 mole) of benzaldehyde, 5 ml. of ethyl alcohol and 1 ml. of glacial acetic acid and heated under reflux for eight hours. Cooling the reaction mixture gave a product which, after recrystallization from absolute alcohol and then a benzene–absolute alcohol mixture, was a pale-yellow crystalline material (VIII). Calcd. for $C_{36}H_{38}N_3O$: mol. wt., 523.6. Found: mol. wt., 510. When a sample of (VIII) was heated for five hours with 20% sulfuric acid, pyrazole (III) resulted in a 60% yield.

TABLE II

ABSORPTION SPECTRA OF PHENYLHYDRAZINE DERIVATIVES IN 95% ALCOHOL

| Derivative | Fig. no. | Molar concn. × $10^5$ | Maxima λ(mμ) | Maxima ε×$10^{-3}$ | Minima λ(mμ) | Minima ε×$10^{-3}$ |
|---|---|---|---|---|---|---|
| (V) | 1 | 14.3 | 360 | 10.7 | 335 | 9.09 |
| | | | 288 | 15.4 | 272 | 13.4 |
| | | | 244 | 20.3 | 231 | 18.2 |
| (VI) | 1,2 | 9.06 | 365 | 10.5 | 359 | 10.3 |
| | | | 324 | 12.8 | 313 | 12.5 |
| | | | 287 | 14.8 | 275 | 14.3 |
| | | | 245 | 21.8 | 230 | 20.5 |
| (VII) | 1,3 | 4.77 | 361 | 22.9 | 282 | 4.27 |
| | | | 245 | 18.9 | 230 | 15.1 |
| (IX) | 1 | 4.95 | 365 | 22.4 | 317 | 5.50 |
| | | | 312 | 6.28 | 284 | 3.87 |
| | | | 245 | 20.4 | 228 | 14.0 |
| (III) | 2 | 6.19 | 255 | 31.4 | 227 | 16.9 |
| Mixture of [a] (III) + (IX) | 2 | 4.65 | 365 | 11.5 | 320 | 3.08 |
| | | | 253 | 28.8 | 227 | 17.5 |
| (VIII) | 3 | 5.03 | 365 | 20.2 | 320 | 5.80 |
| | | | 308 | 6.32 | 284 | 3.50 |
| | | | 245 | 17.7 | 235 | 16.3 |
| 1,5-Diphenyl-[b] 3-*p*-tolyl-pyrazoline | 3 | 2.40 | 355 | 19.9 | 278 | 5.08 |
| | | | 242 | 17.9 | 223 | 12.7 |
| (X) | 3 | 5.93 | 333 | 21.9 | 267 | 5.32 |
| | | | 240 | 18.3 | 223 | 15.1 |

[a] A 1.93-mg. sample of (III) and 2.72 mg. of (IX) were dissolved in 200 ml. of 95% alcohol. The molar concn. of this solution was calculated assuming a molecular weight of 501.6 (value for (IX)). [b] Prepared according to the directions of Raiford and Peterson, ref. 9.

**Acetylation of Aminopyrazoline (VII).**—A 1.0-g. sample of (VII) was refluxed for two hours with 15 ml. of acetic anhydride. Most of the acetic anhydride was distilled under vacuum and the residue treated with sodium bicarbonate solution. The solid residue was recrystallized from benzene and petroleum ether and finally from 90% alcohol. The pale-yellow product was dried under vacuum at 80° for three hours to give (IX).

**Benzyl-*p*-methylacetophenone Phenylhydrazone (X).**—This phenylhydrazone (X) was prepared from benzyl-*p*-methylacetophenone in the usual way in 90% yields and recrystallized from ethyl alcohol, m.p. 77–79°. This compound decomposed to a tar after exposure to light and air for a few days.

*Anal.* Calcd. for $C_{22}H_{22}N_2$: N, 8.91. Found: N, 9.10, 8.94.

**Absorption Spectra Measurements.**—These measurements were made using a Beckman Model DU Photoelectric Quartz Spectrophotometer. At the sensitivity used, the maximum band width was one millimicron, with a rated accuracy of 0.1%. Pure 95% alcohol was used as a solvent medium since most of these compounds were not sufficiently soluble in a non-polar solvent such as heptane (see Figs. 1, 2 and 3, and Table II).

## Summary

1. *trans* Ethylene imine ketones react with phenylhydrazine to give the corresponding pyrazoles and N-acetylphenylhydrazones of the ethylene imine ketones.

2. *cis* Ethylene imine ketones give the intermediate 4-aminopyrazolines which are stable in neutral or basic solutions but lose benzylamine to give the pyrazole when a solvolytic proton becomes available in acid solutions.

3. The absorption spectra of these compounds have been compared to aid in the elucidation of their structures. The pyrazolines have similar but not identical spectra with those of related phenylhydrazones.

LINCOLN, NEBRASKA RECEIVED AUGUST 2, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, SOUTHWESTERN MEDICAL COLLEGE]

# 16-Substituted Steroids. VI. The Steric Structure of Steroidal 16,17-Ketols and 16,17-Glycols[1]

BY MAX N. HUFFMAN AND MARY HARRIET LOTT

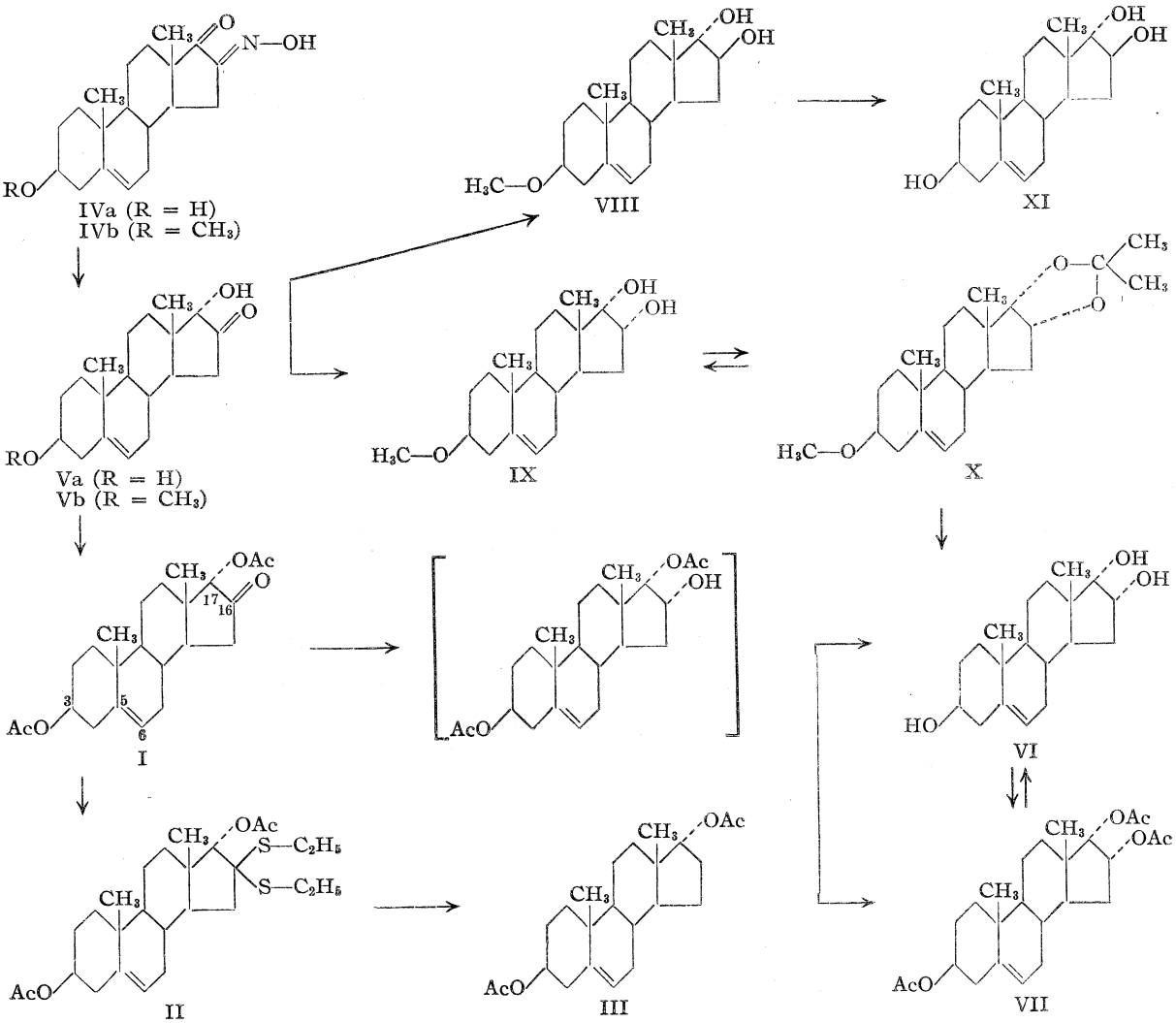
Stodola, Kendall and McKenzie[2,3] have shown that the zinc–acetic acid reduction of 16-oximino-17-ketosteroids followed by acetylation results in the formation of 16-keto-17-acetoxysteroids. The Stodola reduction of 16-oximinodehydroisoandrosterone, for instance, was found to give, after acetylation with acetic anhydride in pyridine, an androstenediolone diacetate in which the ketone group clearly occupied the $C_{16}$ position. We have confirmed this finding of Stodola and co-workers and furthermore shown that the acetoxyl at $C_{17}$ has the $\alpha$ spatial configuration. If the 3($\beta$),17-diacetoxy-16-keto-$\Delta^5$-androstene (I) of Stodola is treated with ethyl mercaptan in the presence of fused zinc chloride and anhydrous sodium sulfate[4] a crystalline diethyl thioacetal (II) is readily obtained in good yield. This thioacetal loses its mercaptyl residues on hydrogenolysis with modified Raney nickel, and there is obtained the known 3($\beta$),17($\alpha$)-diacetoxy-$\Delta^5$-androstene (III). Since in these reactions there can be no question of

(1) The announcement of the findings described in this publication was presented as a Communication by Huffman and Lott, THIS JOURNAL, 69, 1835 (1947).

(2) Stodola, Kendall and McKenzie, *J. Org. Chem.*, 6, 841 (1941).

(3) Stodola and Kendall, *ibid.*, 7, 336 (1942).

(4) Bernstein and Dorfman, THIS JOURNAL, 68, 1152 (1946).




keto–carbinol isomerization, it is certain that the original androstenediolone diacetate had its carbonyl at position 16 and its $C_{17}$ acetoxyl in the $\alpha$ spatial configuration.

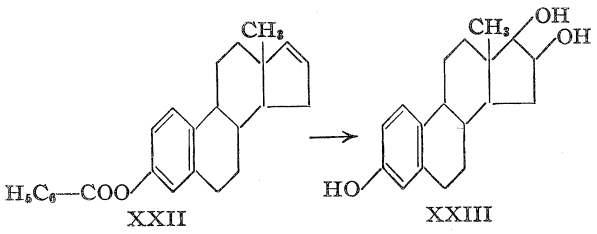
It seems clear that the method of carbonyl reduction by thioacetal hydrogenolysis (discovered by Wolfrom and Karabinos[5]) should find wide application in structural studies in the general group of vicinal ketols where the Clemmensen and Wolff-Kishner methods of reduction are decidedly unsuited.

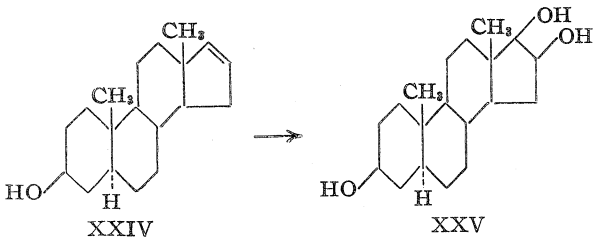
The Stodola reduction of 16-oximino-17-ketosteroids is peculiar in that there is produced, instead of the expected amine, a 16,17-ketol. We feel certain that such ketols are actually 16-keto-17($\alpha$)-hydroxysteroids and that no rearrangement occurs upon acetylation. The zinc–acetic acid reduction of 16-oximinodehydroisoandrosterone (IVa) gives an androstenediolone[6] (Va) which furnishes 3($\beta$),17($\alpha$)-diacetoxy-16-keto-$\Delta^5$-androstene (I) either upon long standing with acetic anhydride and pyridine or upon very rapid acetylation with acetic anhydride and phosphoric acid according to Ciusa and Sollazzo.[7] The yields are virtually identical in both methods of esterification. These facts suggest that no rearrangement of the ketol takes place during esterification. Furthermore, ketols prepared by Stodola reduction of 16-oximino-17-ketosteroids may be acetylated and the resulting acetate then saponified to produce the identical ketol which was originally esterified. For instance, 3-benzyloxy-17($\alpha$)-acetoxy-16-keto-$\Delta^{1,3,5}$-estratriene (XIVb) may be saponified to produce the same estradiolone-3-benzyl ether (XIIIb) from which the 17-acetoxy derivative was formed.

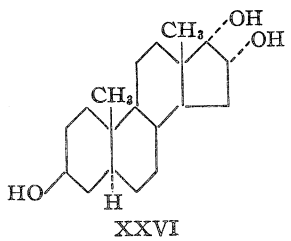
The most decisive evidence in regard to the structure of Stodola-prepared 16,17-ketols comes, in our opinion, from the studies on the oxidation products of these ketols resulting from lead tetraacetate cleavage of steroid Ring D. Baer[8,9] has

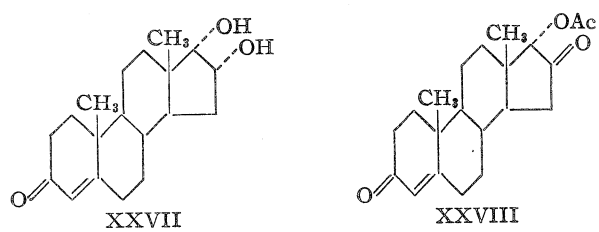
(5) Wolfrom and Karabinos, THIS JOURNAL, **66**, 909 (1944).
(6) Butenandt, Schmidt-Thomé and Weiss, *Ber.*, **72**, 417 (1939).
(7) Ciusa and Sollazzo, *Ann. chim. applicata*, **33**, 72 (1943).
(8) Baer, THIS JOURNAL, **62**, 1597 (1940).
(9) Baer, *ibid.*, **64**, 1416 (1942).

XVIII
XVII
XVI
XV
XIIIa (R = H)
XIIIb (R = CH2C6H5)
XIIIc (R = CH3)
XIVa (R = COCH3)
XIVb (R = CH2C6H5)
XIVc (R = CH3)
XIIa (R = H)
XIIb (R = CH2C6H5)
XIIc (R = CH3)
XIX
XX
XXI

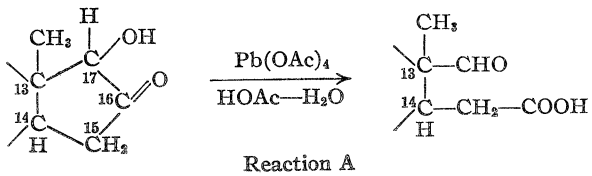


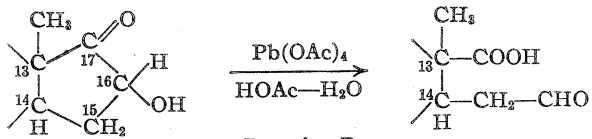




shown that vicinal ketols (both acyclic and cyclic) can be oxidized with lead tetra-acetate in aqueous acetic acid with rupture of the carbon to carbon bond between the functional groups to produce an aldehyde and a carboxylic acid. The aldehyde arises from the original carbinol carbon and the carboxylic acid from the original carbonyl carbon of the vicinal ketol so treated. After lead tetra-acetate cleavage of Ring D of Stodola-prepared 16,17-ketols it has been found that the carboxylic acid so produced is not the well-known tertiary one attached to steroid position $C_{13}$. If the 16,17-ketol (XIIIc) prepared by the zinc–acetic acid reduction of 3-methoxy-16-oximino-17-keto-$\Delta^{1,3,5}$-estratriene (XIIc) is treated briefly with lead tetra-acetate in aqueous acetic acid, there is obtained an aldehyde–acid (XV) which furnishes an easily crystallizable semicarbazone-acid (XVI). Treatment of this semicarbazone-acid with diazomethane destroys its acidic properties with formation of the methyl ester (XVII). This semicarbazone-methyl ester is readily saponified to regenerate the original semicarbazone-acid (XVI) under conditions which would not hydrolyze a carbomethoxy group at $C_{13}$. This finding seems interpretable only upon the basis that the original carbonyl on the intact Ring D occupied position 16, for had this carbonyl been at position 17, the carboxylic acid produced by lead tetra-acetate cleavage would have been attached to tertiary position 13 (Contrast Reaction A and Reaction B).




Reaction A




Reaction B

Furthermore, had the original estradiolone-3-methyl ether been a 16-hydroxy-17-ketosteroid, the aldehyde–acid produced on lead tetra-acetate cleavage (as in Reaction B) would have led to the same semicarbazone-methyl ester (XVIII) as that recently prepared by Miescher[10] and which melts at 212–213° (cor.). Our semicarbazone-methyl ester (XVII) decomposes at 166–167.5° (uncor.) with evolution of gas.

From the foregoing evidence, and from evidence shortly to be presented, we feel justified in stating that Stodola-prepared 16,17-ketols possess the structure of 16-keto-17($\alpha$)-hydroxysteroids. It is noteworthy that 16,17-diketosteroids likewise form 16-keto-17($\alpha$)-hydroxysteroids upon reduction with zinc or with titanium trichloride.[11,12]

Stodola, Kendall and McKenzie[2] found that catalytic reduction of 3($\beta$),17($\alpha$)-diacetoxy-16-keto-$\Delta^5$-androstene (I) in ethanol yielded, after further acetylation, the triacetate (VII) of the androstenetriol originally prepared by Butenandt.[6] We have repeated the experiment of Stodola, *et al.*, except that reduction with hydrogen and Raney nickel was effected in a medium of ethyl acetate–ethanol (2.5:1) in order to obviate any danger of saponification of the diacetate (I), the structure of which is now quite securely known. We likewise found that Butenandt's androstenetriol is formed (reduction of I followed by acetylation to give the triacetate VII). Now Butenandt[6] clearly showed that his androstenetriol (VI) possessed the $C_{16}$–OH and $C_{17}$–OH in *cis* relationship from the standpoint of geometric isomerism, and we have confirmed this point as will be seen later; there is, therefore, no doubt that Butenandt's triol is 3($\beta$),16($\alpha$),17($\alpha$)-trihydroxy-$\Delta^5$-androstene (VI).

If a 16-keto-17($\alpha$)-hydroxysteroid be reduced with 2% sodium amalgam in excess dilute ethanolic acetic acid (40°), there is produced a mixture of *cis*-oid and *trans*-oid 16,17-glycols. (At temperatures above 40° there is apparently produced relatively more of the *cis*-oid form.) Thus if 3($\beta$)-

(10) Heer and Mierscher, *Helv. Chim. Acta*, **29**, 1895 (1946).
(11) Huffman, *J. Biol. Chem.*, **167**, 273 (1947).
(12) Huffman and Lott, *ibid.*, **172**, 325 (1948).

methoxy-17($\alpha$)-hydroxy-16-keto-$\Delta^5$-androstene (Vb) is reduced with sodium amalgam as described, there is obtained a mixture of geometrically isomeric 16,17-glycols (VIII and IX). In this mixture the *trans*-oid component (VIII) is less soluble and may readily be obtained in pure form by repeated crystallization. The remaining isomer (IX) is obtained by transformation to the cyclic acetonide (X) and by purification in this form. Hydrolysis of this acetonide (X) followed by demethylation furnishes Butenandt's triol[6] (VI) —known with certainty to be 3($\beta$),16($\alpha$),17($\alpha$)-trihydroxy-$\Delta^5$-androstene. Demethylation of the *trans*-oid 3-ether (VIII) yields Hirschmann's triol[13] (XI) which must from the foregoing evidence be 3($\beta$),16($\beta$),17($\alpha$)-trihydroxy-$\Delta^5$-androstene as it is the only *trans*-oid glycol possible from the 16-keto-17($\alpha$)-hydroxy configuration. (At this point it should be carefully noted that proof of the $\alpha$ spatial configuration of the carbinol group in unesterified Stodola-prepared 16,17-ketols is now complete, for such a ketol has been shown to give rise to a known 16($\alpha$),17($\alpha$)-glycol).

Upon sodium amalgam reduction as just described, 3,17($\alpha$)-dihydroxy-16-keto-$\Delta^{1,3,5}$-estratriene (XIIIa) yields a mixture of geometrically isomeric 16,17-glycols (XIX and XX). If this mixture be treated briefly with anhydrous hydrogen chloride in absolute acetone, the *cis*-oid isomer (XX) reacts to furnish a cyclic acetal (XXI) whereas the *trans*-oid (XIX) does not. It was found that the acetal could be readily separated from the *trans*-oid glycol by partitioning between chloroform and 0.1 *N* sodium hydroxide, the free glycol passing to the alkaline phase and the acetal remaining in the chloroform. The *trans*-oid isomer (XIX), recovered from the alkali, proved to be the sex hormone estriol (theelol); and the acetal, after hydrolysis, furnished a substance (XX) identical with the estrogenic triol originally named isoestriol-A.[14] Estriol is, therefore, 3,16($\beta$),17($\alpha$) trihydroxy-$\Delta^{1,3,5}$-estratriene (XIX), and isoestriol-A is 3,16-($\alpha$),17($\alpha$)-trihydroxy-$\Delta^{1,3,5}$-estratriene (XX).

It is to be observed that catalytic hydrogenation[6,2,14] of a 16-keto-17($\alpha$)-hydroxysteroid has, so far, always given the 16($\alpha$),17($\alpha$)-glycol, whereas sodium amalgam reduction yields a mixture of 16($\beta$),17($\alpha$)- and 16($\alpha$),17($\alpha$)-glycols.

In 1945 Prelog, Ruzicka and Wieland[15] submitted 3-benzoxy-$\Delta^{1,3,5,16}$-estratetraene (XXII) to reaction with osmium tetroxide and obtained, after saponification, an isomer (XXIII) of estriol to which was assigned the structure 3,16($\alpha$),17($\alpha$)-trihydroxy-$\Delta^{1,3,5}$-estratriene. It is certain that this estriol possesses its $C_{16}$ and $C_{17}$ hydroxyl groups in *cis* arrangement as the latter groups were introduced by the known osmium tetroxide reaction; however, Prelog, Ruzicka, and Wieland assumed that the $C_{16}$–$C_{17}$ hydroxyl groups would form on the least sterically hindered side of the steroid skeleton (*i. e.*, opposite to the $C_{13}$–methyl group). For the same reasons, Ruzicka, Prelog and Wieland[16] assigned the structure 3($\beta$),16($\alpha$),-17($\alpha$)-trihydroxyandrostane to the triol (XXV) which results from the osmium tetroxide oxidation of 3($\beta$)-hydroxy-$\Delta^{16}$-androstene (XXIV).

Since we have already determined the structure of isoestriol-A as that of 3,16($\alpha$),17($\alpha$)-trihydroxy-$\Delta^{1,3,5}$-estratriene (XX), it follows that the isomeric estriol of Ruzicka, *et al.*, must be a 3,16($\beta$),-17($\beta$)-trihydroxy-$\Delta^{1,3,5}$-estratriene (XXIII) as it is not identical with isoestriol-A, yet must have the $C_{16}$–OH and $C_{17}$–OH in *cis* arrangement. For similar reasons the androstanetriol of Ruzicka, *et al.*,[16] must be 3($\beta$),16($\beta$),17($\beta$)-trihydroxyandrostane (XXV) since this compound is not identical with 3($\beta$),16($\alpha$),17($\alpha$)-trihydroxyandrostane (XXVI) prepared by hydrogenation of Butenandt's triol.

In Table I is presented a résumé of the steric structures of steroidal 16,17-ketols and 16,17-glycols. Only key compounds in these series are included, functional derivatives in general being omitted. While a certain amount of speculation has heretofore been advanced concerning the stereochemistry of these structures, the authors hope now to have placed this subject within the realm of rigorous organic chemistry.

## Experimental[17,18]

### PART I. Proof of Structure of 3($\beta$),17($\alpha$)-Diacetoxy-16-keto-$\Delta^5$-androstene (I)

**Preparation of the Diethyl Thioacetal of 3($\beta$),17($\alpha$)-Diacetoxy-16-keto-$\Delta^5$-androstene.**—3($\beta$),17($\alpha$)-Diacetoxy-16-keto-$\Delta^5$-androstene[2] (I), 0.25 g. (m.p. 124.5–125°), was mixed with 0.50 g. of anhydrous sodium sulfate and 0.25 g. of freshly fused zinc chloride and the whole at once covered with 10 cc. of ethyl mercaptan (Eastman Kodak Co. No. 958). The reaction flask was stoppered, its contents mixed until solution of the diacetate had become complete, and then placed in the ice box for seventy-two hours. The excess mercaptan was removed *in vacuo* at room temperature and the resulting solid residue taken up alternately in 1.0 *N* sodium hydroxide (200 cc.) and ethyl ether (200 cc.) containing a slight amount of pyridine. After the two phases had been shaken together and the alkali separated off, the ether was washed three times with water, dried over sodium sulfate, and evaporated at 50°. The almost colorless oil was crystallized in the ice box from aqueous acetone containing a trace of pyridine. A second crystallization from this medium gave 253 mg. of flakes melting at 136.5–138° (II). An analysis of this material, which contained a touch of yellow color, indicated that it was already substantially pure.

*Anal.* Calcd. for $C_{27}H_{42}O_4S_2$: S, 12.96. Found: S, 12.74, 12.68.

**Hydrogenolysis of 3($\beta$),17($\alpha$)-Diacetoxy-16-keto-$\Delta^5$-androstene Diethyl Thioacetal (II).**—Approximately 3 g. of modified Raney nickel catalyst in absolute ethanol was added to 0.21 g. of thioacetal (m.p. 136.5–138°), and after the addition of 30 cc. of dioxane, the mixture was heated for seven hours on the steam-bath (air condenser). After having been allowed to stand overnight at room tempera-

(13) Hirschmann, *J. Biol. Chem.*, **150**, 363 (1943).

(14) Huffman and Darby, THIS JOURNAL, **66**, 150 (1944).

(15) Prelog, Ruzicka and Wieland, *Helv. Chim. Acta*, **28**, 250 (1945).

(16) Ruzicka, Prelog and Wieland, *ibid.*, **28**, 1609 (1945).

(17) All melting points are uncorrected unless otherwise specified.

(18) All 16-keto-17-hydroxysteroids were prepared by zinc–acetic reduction of the corresponding 16-oximino-17-ketosteroid according to Stodola, *et al.*[2,3]

TABLE I

| Original name | Author | M. p., °C. |
|---|---|---|
| | Androgen Series | |
| Androstenediolone | Butenandt, Schmidt–Thomé and Weiss[a] | 197 |
| Androstenediolone diacetate | Butenandt, Schmidt–Thomé and Weiss[a] | 123 |
| | Stodola, Kendall and McKenzie[b] | 124–125 |
| 16-Ketotestosterone acetate | Stodola and Kendall[c] | 194–195 |
| Androstenetriol | Butenandt, Schmidt–Thomé and Weiss[a] | 273–275 |
| | Stodola, Kendall and McKenzie[b] | |
| 16-Oxytestosterone | Butenandt, Schmidt–Thomé and Weiss[a] | 172–173 |
| Urinary androstenetriol | Hirschmann[d] (isolation) | 266–270 cor. |
| | Huffman and Lott[e] | |
| "Androstan-triol-(3β,16α,17α)" | Ruzicka, Prelog and Wieland[f] | 265–266 cor. |
| Androstane-3(β),16(α),17(α)-triol | Huffman and Lott (this publication) | 251–253 |
| | Estrogen Series | |
| 16-Hydroxyestrone | Huffman[g] | 234–237 |
| 16-Oxyestrone methyl ether | Butenandt and Schäffler[h] | 169–169.5 cor. ? |
| | Huffman[i] | 167–168[j] |
| 16-Acetoxyestrone methyl ether | Butenandt and Schäffler[h] | 149 cor. ? |
| | Marrian[k] (isolation) | |
| Estriol (theelol) | Doisy, Thayer, Levin and Curtis[l] (isolation) | 280–282 cor. |
| | Huffman[i] | |
| | Butenandt and Schäffler[h] | |
| | | 267–269 |
| Isoestriol-A | Huffman and Darby[m] | 274–276[n] |
| "$\Delta^{1,3,5}$-Oestratrien-triol-(3,16α,17α)" | Prelog, Ruzicka and Wieland[o] | 236.5–237 cor. |

ture, the mixture was filtered free of catalyst and the filtrate distilled *in vacuo* to a volume of 5–10 cc. Addition of several volumes of water precipitated the hydrogenolysis product, which was filtered after several hours at 5°. The well-washed and dried crystals were dissolved in acetone, filtered from a slight amount of insoluble material, and the acetone evaporated to dryness. Solution was next effected in methanol and crystallization allowed to take place at 5°. The sequence of solution in acetone, filtration from insoluble residue, evaporation of filtrate, and recrystallization from methanol was repeated until no more matter insoluble in acetone was observed. Several further recrystallizations from methanol yielded finally 34 mg. of plates (III) melting at 157–158°. A mixed melting point test with authentic 3(β),17(α)-diacetoxy-$\Delta^5$-androstene[19] (m.p. 158–158.5°) supplied by Dr. Hans Hirschmann showed a melting point value of 157.5–158.5°.

*Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.92, 73.84; H, 9.11, 9.16.

From the methanolic mother liquors were recovered an additional 30 mg. of diacetate melting at 153–154.5°.

## PART II. Proof that Stodola-Prepared 16,17-Ketols Are 16-Keto-17(α)-hydroxysteroids.

**3(β),17(α)-Dihydroxy-16-keto-$\Delta^5$-androstene (Va).**—This material, prepared according to Stodola, Kendall and McKenzie,[2] was recrystallized once from aqueous acetic acid to give tiny leaves melting at 197–199°. Butenandt and co-workers,[6] who first prepared this androstenediolone (Va) by another method, reported a melting point of 197°.

**Acetylation of 3(β),17(α)-Dihydroxy-16-Keto-$\Delta^5$-androstene.**—Androstenediolone (400 mg., as above) (Va) was dissolved in 5 cc. of dry pyridine in the cold. Acetic anhydride (3 cc.) was then added, the phases mixed well and left to react for twenty-four hours at room temperature in a stoppered flask. The diacetate was then precipitated by the addition of 200 cc. of ice water, and, after three hours in the ice box, filtered and washed copiously with water. The diacetate, without drying, was dissolved in methanol and recrystallized from boiling aqueous methanol, final crystallization being allowed to take place overnight at 5°. After filtration and drying in the desiccator, the product was treated with charcoal in acetone and the solvent evaporated to leave a colorless oil. This oil was redissolved in 9.0 cc. of 95% ethanol and 3.0 cc. of water. After 24 hours at 5°, 332 mg. of silky needles (I) (desiccator dried) were obtained. These melted at 124.5–125°.

*Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.22, 71.28; H, 8.30, 8.37.

Another acetylation of androstenediolone (identical batch as above, m.p. 197–199°) was effected according to the method of Ciusa and Sollazzo.[7] Acetic anhydride (10 cc.) was added to 393 mg. of the ketol, and then 1.0 cc. of 90% phosphoric acid (Mallinckrodt) gradually added with continuous swirling. Solution of the steroid took place at once and much heat was evolved. The reaction flask was allowed to cool for thirty minutes with continuous swirling of its contents. Then 200 cc. of ice water was added and the isolation and purification of the diacetate were carried out exactly as in the case of the acetic anhydride–pyridine acetylation. There were obtained 313 mg. of silky needles (I) which melted at 124.5–125° either by themselves or after admixture with the diacetate obtained in the preceding paragraph. The yields by the pyridine method and the phosphoric acid method were thus 65 and 62%, respectively.

**Acetylation of 3-Benzyloxy-17(α)-hydroxy-16-keto-$\Delta^{1,3,5}$-estratriene (XIIIb) and Saponification of the 17-Acetoxy Derivative (XIVb).**—3-Benzyloxy-17(α)-hydroxy-16-keto-$\Delta^{1,3,5}$-estratriene (XIIIb) (m.p. 197–200°, with yellow color),[12] prepared as previously described,[12] (0.37 g.) was treated with pyridine (5 cc.) and acetic anhydride (3 cc.) as usual. The acetate, precipitated with ice water, was recrystallized from hot acetone–ethanol–water, final crystal formation being allowed to take place at 5°. The yield of felt-like needles (XIVb) was 0.38 g., melting at 140–141°. Further recrystallization of this acetate did not improve its melting point.

*Anal.* Calcd. for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23. Found: C, 77.50, 77.57; H, 7.23, 7.16.

3-Benzyloxy-17(α)-acetoxy-16-keto-$\Delta^{1,3,5}$-estratriene (125 mg., m.p. 140–141°) (XIVb) was saponified by re-

(19) Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935); Butenandt and Hanisch, *Ber.*, **68**, 1859 (1935).

TABLE I (*Continued*)

| Optical rotation | Steric structure | Formula |
|---|---|---|
| | 3(β),17(α)-Dihydroxy-16-keto-Δ⁵-androstene | Va |
| | 3(β),17(α)-Diacetoxy-16-keto-Δ⁵-androstene | I |
| $[\alpha]^{25}_{4561}$ −56° | 17(α)-Acetoxy-3,16-diketo-Δ⁴-androstene | XXVIII |
| | 3(β),16(α),17(α)-Trihydroxy-Δ⁵-androstene | VI |
| | 16(α),17(α)-Dihydroxy-3-keto-Δ⁴-androstene | XXVII |
| | 3(β),16(β),17(α)-Trihydroxy-Δ⁵-androstene | XI |
| $[\alpha]^{16}D$ −19 ± 4° | 3(β),16(β),17(β)-Trihydroxyandrostane | XXV |
| $[\alpha]^{26}D$ +18° | 3(β),16(α),17(α)-Trihydroxyandrostane | XXVI |
| $[\alpha]^{29.5}D$ −102° | 3,17(α)-Dihydroxy-16-keto-Δ¹,³,⁵-estratriene | XIIIa |
| | 3-Methoxy-17(α)-hydroxy-16-keto-Δ¹,³,⁵-estratriene | XIIIc |
| | 3-Methoxy-17(α)-acetoxy-16-keto-Δ¹,³,⁵-estratriene | XIVc |
| $[\alpha]^{27}D$ +61° | 3,16(β),17(α)-Trihydroxy-Δ¹,³,⁵-estratriene | XIX |
| $[\alpha]^{29.5}D$ +88° | 3,16(α),17(α)-Trihydroxy-Δ¹,³,⁵-estratriene | XX |
| $[\alpha]^{22}D$ +58 ± 5.5° | 3,16(β),17(β)-Trihydroxy-Δ¹,³,⁵-estratriene | XXIII |

[a] Butenandt, Schmidt-Thomé and Weiss, *Ber.*, **72**, 417 (1939). [b] Stodola, Kendall and McKenzie, *J. Org. Chem.*, **6**, 841 (1941). [c] Stodola and Kendall, *ibid.*, **6**, 837 (1941). [d] Hirschmann, *J. Biol. Chem.*, **150**, 363 (1943). [e] Huffman and Lott, *ibid.*, **172**, 789 (1948). [f] Ruzicka, Prelog and Wieland, *Helv. Chim. Acta*, **28**, 1609 (1945). [g] Huffman, THIS JOURNAL, **64**, 2235 (1942). [h] Butenandt and Schäffler, *Z. Naturforsch.*, **1**, 82 (1946). [i] Huffman, *J. Biol. Chem.*, **169**, 167 (1947). [j] It is not certain whether there exists a lower-melting crystalline modification (m. p. 162–163°) of this ketol [*cf.* Huffman, *ibid.*, **167**, 273 (1947).] [k] Marrian, *Biochem. J.*, **24**, 435 (1930). [l] Doisy, Thayer, Levin and Curtis, *Proc. Soc. Exp. Biol. Med.*, **28**, 88 (1930); Thayer, Levin and Doisy, *J. Biol. Chem.*, **91**, 655 (1931). [m] Huffman and Darby, THIS JOURNAL, **66**, 150 (1944). [n] Isoestriol-A in the form of tiny, flat needles melting at 274–276° has been obtained; it is possible that these represent a crystalline modification of the microscopic crystals melting at 267–269°. [o] Prelog, Ruzicka and Wieland, *Helv. Chim. Acta*, **28**, 250 (1945).

fluxing for one hour in 0.25*N* aqueous methanol. After the methanol had been largely removed by distillation on the steam-bath, the cooled mixture was taken up in ethyl ether, and the latter extracted well with alkali and then washed with water. Evaporation of the ether yielded a crystalline residue which was crystallized once from aqueous ethanol and once from absolute methanol to give 63 mg. of tiny needles (XIIIb) melting at 198.5–200.5°. This material showed no mixed melting point depression with authentic 3-benzyloxy-17(α)-hydroxy-16-keto-Δ¹,³,⁵-estratriene.[12]

**Acetylation of 3,17(α)-Dihydroxy-16-keto-Δ¹,³,⁵-estratriene (XIIIa) and Saponification of the 3,17-Diacetoxy Derivative (XIVa).**—This ketol, 302 mg. (m.p. 233–235°) (XIIIa) prepared from 16-oximinoestrone (XIIa) as previously described,[12] was acetylated with acetic anhydride (3 cc.) in pyridine (3 cc.) during forty-eight hours. The excess anhydride was decomposed with ice water and the diacetate taken up in benzene. The benzene phase was washed with dilute sulfuric acid, with bicarbonate, and washed finally with water. Evaporation of the benzene solution yielded a semicrystalline residue which was saponified without further purification. To effect saponification, the crude diacetate (XIVa) was dissolved in 24 cc. of hot methanol and, after cooling, 15 cc. of 1.5*N* potassium hydroxide added; the phases were mixed well and left in a stoppered flask for twenty-four hours at room temperature. The clear solution was diluted with water, acidified with hydrochloric acid and then extracted with ethyl ether. After having been washed with bicarbonate and water, the ethereal phase was evaporated, and the resulting crystalline residue was leached with cyclohexane, treated with charcoal, recrystallized once from aqueous methanol and finally recrystallized from 50% acetic acid to give 187 mg. of ketol (XIIIa) melting at 232–235°. A mixed melting point test performed with this material and authentic 3,17(α)-dihydroxy-16-keto-Δ¹,³,⁵-estratriene gave a value of 234–236°.

A 76-mg. portion of this ketol (187 mg. batch, m.p. 232–235°) gave upon oximation (120 mg. of hydroxylamine hydrochloride, 240 mg. of crystalline sodium acetate, 10 cc. of aqueous ethanol, two hour reflux) 70 mg. of **oxime** decomposing at 224–225°.[12]

**Lead Tetraacetate Cleavage of 3-Methoxy-17(α)-hydroxy-16-keto-Δ¹,³,⁵-estratriene (XIIIc).**—To 352 mg. of 3-methoxy-17(α)-hydroxy-16-keto-Δ¹,³,⁵-estratriene[19a] (m.p. 164–166°) (XIIIc) was added 18 cc. of 0.0705 molar lead tetraacetate in acetic acid. The steroid soon dissolved at room temperature, whereupon 4 cc. of 50% acetic acid was added. After the solution had been swirled continuously for thirty minutes, 200 cc. of 1% ethylene glycol in water was added. The cleaved steroid (XV) was allowed to crystallize at 5° for a day and then filtered, washed well with water, and dried *in vacuo* over sulfuric acid. Semicarbazone formation was effected without further purification.

**7-Methylmarrianolic Acid Hemialdehyde Semicarbazone (XVI).**—The crude aldehyde-acid (of the preceding paragraph) (XV) was dissolved in 40 cc. of methanol and to this solution were added 0.40 g. of semicarbazide hydrochloride and 0.56 g. of crystalline sodium acetate dissolved in 5 cc. of water. This mixture was warmed to dissolve all components and then distilled on the steam-bath during

(19a) Huffman, *J. Biol. Chem.*, **169**, 167 (1947).

thirty minutes until the volume had been reduced to 10 cc. Ice water (50 cc.) was added in one portion to insure precipitation of the semicarbazone-acid in a finely divided state. The mixture of crude semicarbazone-acid was transferred to a separatory funnel using 100 cc. of ethyl acetate, and after the addition of 40 cc. of 0.21*N* hydrochloric acid, partitioned well. After removal of the aqueous phase, the ethyl acetate phase was extracted briefly with 100 cc. of ice-cold 1.0*N* potassium hydroxide. Acidification (ice-bath) of the potassium hydroxide with 85% phosphoric acid (acid to congo red) re-precipitated the semicarbazone-acid which, after a day in the ice box, was filtered and washed copiously with water. The yield of nicely crystalline air-dried 7-methylmarrianolic acid hemialdehyde semicarbazone (XVI) was 316 mg. decomposing at 185–186° with evolution of gas. Recrystallization of a 50-mg. portion of this semicarbazone-acid from aqueous isopropyl alcohol gave 46 mg. decomposing at 188–189°. A second recrystallization from the same medium yielded 41 mg. decomposing at 192–193°; but, oddly, a third recrystallization gave 35 mg. decomposing at the original value of 185–186°. Analysis was performed upon the original 316-mg. batch (XVI).

*Anal.* Calcd. for $C_{20}H_{27}O_4N_3$: C, 64.32; H, 7.29; N, 11.25. Found: C, 64.17, 64.06; H, 7.33, 7.30; N, 11.10, 11.16.

**Esterification of 7-Methylmarrianolic Acid Hemialdehyde Semicarbazone (XVI).**—To a solution of 199 mg. of semicarbazone-acid (dec. 185–186°) (XVI) in 5 cc. absolute ethanol plus 5 cc. of ethyl acetate was added an excess of a concentrated ethereal solution of freshly prepared diazomethane. The yellow solution was then diluted with 100 cc. of ethyl ether and shaken well with 100 cc. of 1.0*N* hydrochloric acid. The ethereal phase was extracted twice with 100-cc. portions of 1.0 *N* potassium hydroxide and washed twice with 50-cc. portions of water. After the addition to the ether of 5 cc. of ethyl acetate and 5 cc. of absolute ethanol, the solution was distilled *in vacuo* at 50°. The nicely crystalline residue of methyl ester (dried *in vacuo* over sulfuric acid and potassium hydroxide) weighed 194 mg. It was recrystallized once from aqueous methanol (containing 1 drop of acetic acid) to give 184 mg. of material decomposing at 166.5–167.5° with evolution of gas. A second crystallization from absolute methanol gave 128 mg. of tiny needles (XVII) in rosettes which decomposed at 166–167.5° with evolution of gas.

*Anal.* Calcd. for $C_{21}H_{29}O_4N_3$: C, 65.09, H, 7.54; N, 10.85. Found: C, 64.99 64.91; H, 7.58, 7.53; N, 10.86, 10.95.

7-Methylmarrianolic acid hemialdehyde (*primary*) semicarbazone methyl ester (XVIII), prepared by Heer and Miescher,[10] melts at 212–213° (cor.), apparently with no decomposition.

**Saponification of 7-Methylmarrianolic Acid Hemialdehyde (tertiary) Semicarbazone Methyl Ester (XVII).**—To a solution of 90 mg. of semicarbazone-methyl ester (dec. 166–167.5°) in 6.0 cc. of methanol was added 2.0 cc. of aqueous potassium hydroxide (from a solution of 4.0 g. of potassium hydroxide in 20 cc. of water) and the mixture swirled continuously for thirty minutes at room temperature. The mixture was then heated for a few seconds on the steam-bath to redissolve a portion of ester which had crystallized from the medium, and the mixture then swirled at room temperature for another thirty minute interval. The mixture was again heated for a few seconds and swirled at room temperature during a third thirty minute interval, after which it was transferred to a separatory funnel using 50 cc. of 1.0 *N* potassium hydroxide, freed of a slight turbidity with 50 cc. of ethyl ether, and the alkaline layer carefully acidified (ice-bath) with 2.6 cc. of 85% phosphoric acid. The semicarbazone soon crystallized; and after a night in the ice box, it was filtered and washed well with water. The yield of white, granular crystals (XVI) was 59 mg. decomposing at 186–187° with evolution of gas. A mixed melting point, performed with this product and the original semicarbazone (dec. 185–186°), showed no depression.

According to Heer and Miescher,[10] the carbomethoxy group at $C_{13}$ is not saponified by refluxing for 2.5 hours in a solution of 4 g. of potassium hydroxide in 60 cc. of methanol and 20 cc. of water. Our semicarbazone-methyl ester actually may be saponified by refluxing in 0.4 molar potassium carbonate in aqueous methanol, although the heat promotes some destruction of the sensitive semicarbazone.

## PART III. Proof of Steric Structure of Steroidal 16,17-Glycols.

**Reduction of 3(β),17(α)-Diacetoxy-16-keto-Δ⁵-androstene (I) to the Glycol Stage.**—To a solution of 147 mg. of 3(β),17(α)-diacetoxy-16-keto-Δ⁵-androstene (m.p. 123–124°) (I) in 25 cc. of ethyl acetate contained in the Cheronis[20] semimicro hydrogenation apparatus was added 1 cc. of Raney nickel catalyst (completely free of alkali) and the latter rinsed down with 10 cc. of absolute ethanol. A stream of hydrogen was blown through the solution for eight hours at a bath temperature of 60–65°. The solution, freed of catalyst by filtration, was evaporated on the steam-bath, and the cooled semi-crystalline residue was acetylated with acetic anhydride (2 cc.) in dry pyridine (3 cc.) at room temperature for two days. The triacetate, obtained in the usual manner, was recrystallized once from aqueous methanol and four times from ethanol to give 30 mg. of plates (VII) melting sharply at 208–209°[21]; these showed no mixed melting point depression with a sample of androstenetriol triacetate (m.p. 206.5–208.5°) furnished by Dr. Stodola. The X-ray patterns of the Stodola triacetate and our triacetate are identical.[22]

*Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.27, 69.27; H, 8.40, 8.31.

An additional 23 mg. of crude triacetate was obtained from the mother liquors.

Stodola, Kendall, and McKenzie obtained their triacetate by acetylation of the product resulting from the four-hour hydrogenation of 3(β),17-(α)-diacetoxy-16-keto-Δ⁵-androstene (I) in alcohol using Raney nickel catalyst. A consideration of the parallel findings of Stodola, *et al.*,[2] and Butenandt, *et al.*,[6] in this series leaves no doubt that both groups were dealing with the same androstenetriol.

**3(β)-Methoxy-17(α)-hydroxy-16-keto-Δ⁵-androstene (Vb).**—Pure 3(β)-methoxy-16-oximino-17-keto-Δ⁵-androstene[23] (0.99 g.) (IVb) was reduced in the usual way with zinc in aqueous acetic acid (3.0 g. of zinc dust, 75 cc. of 50% acetic acid, one hour reflux) and the 16,17-ketol precipitated by dilution with water. Recrystallization from aqueous ethanol, aqueous methanol, and from aqueous acetone yielded 0.58 g. of ketol melting at 180–183° (with yellow turning).[12] Of this product 50 mg. was treated with charcoal and recrystallized from aqueous ethanol to give 43 mg. melting at 188–191° (Vb).

*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.45; H, 9.44.

**Sodium Amalgam Reduction of 3(β)-Methoxy-17(α)-hydroxy-16-keto-Δ⁵-androstene (Vb).**—3(β)-Methoxy-17(α)-hydroxy-16-keto-Δ⁵-androstene (1.22 g., m.p. 180–183°) (Vb) was dissolved in 150 cc. of 95% ethanol plus 15 cc. of acetic acid and reduced with 300 g. of 2% sodium amalgam, as previously described,[23] the temperature being carefully maintained at 40°, and 10 cc. of 50% acetic acid being added as soon as sodium acetate commenced to precipitate. The reaction mixture was distributed between ether (750 cc.) and water (600 cc.) and the ether further washed, once with 1.0 *N* sodium hydroxide and twice with water. Evaporation of the ether yielded a crystalline residue which was recrystallized twice from acetone–cyclohexane–Skellysolve B and once from aqueous ethanol to give 574 mg. of Hirschmann's triol methyl ether[23] (m.p. 195–196°) (VIII).

(20) Cheronis and Koeck, *J. Chem. Ed.*, **20**, 488 (1943).

(21) With Dr. Stodola's melting point apparatus these crystals melted at 213–214.5° (personal communication, Dr. Stodola).

(22) Personal communication, Dr. Stodola.

(23) Huffman and Lott, *J. Biol. Chem.*, **172**, 789 (1948).

The combined mother liquors were taken up in ether and the solution washed three times with water. The crystalline residue resulting from the evaporation of the ethereal phase was dissolved in 40 cc. of 75% propanol containing 0.40 g. of carboxymethoxylamine hemihydrochloride and 0.60 g. of potassium acetate. This mixture was refluxed for one hour and the ketonic fraction removed from the non-ketonic material in the usual way. There resulted 0.46 g. of crystalline non-ketones. The non-ketonic fraction was dissolved in 42 cc. of absolute acetone at room temperature and 6 cc. of acetone saturated with anhydrous hydrogen chloride added. The acetalizing medium was swirled continuously during fifteen minutes and then added in one portion to 300 cc. of ice-cold 3% potassium carbonate, and thorough mixing effected at once. After a day in the ice box, the precipitated acetonide was filtered, washed with water, and dried *in vacuo* to give 0.42 g. of material. This crude acetonide was recrystallized twice from aqueous methanol containing a trace of pyridine (treatment with charcoal). The yield of glistening plates was 265 mg. melting at 144–145.5°. Of this material 101 mg. was recrystallized from absolute methanol (trace of pyridine) to give 55 mg. of long, flat colorless needles (X) melting at 146.5–148°.

*Anal.*, Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.47, 76.56; H, 10.01 10.05.

**The Transformation of 3(β)-Methoxy-16(α),17(α)-dihydroxy-Δ⁵-androstene Acetonide (X) to 3(β),16(α),17(α)-Triacetoxy-Δ⁵-androstene (VII).**—To a solution of 0.34 g. of acetonide (m.p. 144–145.5°), prepared as above, in 50 cc. of ethanol was added 10 cc. of 1.2 molar phosphoric acid and the solution refluxed for thirty minutes and then left overnight at room temperature. The water-clear solution was distributed between ethyl ether and water, and the organic phase then washed with dilute sodium bicarbonate and with water. Evaporation of the ether gave a crystalline residue which was acetylated in pyridine (5 cc.) with acetic anhydride (3 cc.) in the usual manner. The diacetate, procured by precipitation with ice water, was dried thoroughly and then treated with 0.21 g. of *p*-toluenesulfonic acid monohydrate in 21 cc. of acetic anhydride for thirty minutes on the steam-bath by the method previously described.[18] The reaction mixture, after having been cooled in the ice-bath, was diluted with 100 cc. of ice water and then left for three days at 5°. The precipitated triacetate was recrystallized from ethanol to give 199 mg. of waxy plates melting at 204–206°. Another crystallization from 5 cc. of ethanol (ice box) gave 152 mg. melting at 207–208.5°. A third crystallization from 5 cc. of ethanol (ice box) yielded 119 mg. of plates (VII) melting at 208–209.5°. A mixed melting point test performed with androstenetriol triacetate furnished by Dr. Stodola gave no depression.

**The Sodium Amalgam Reduction of 3,17(α)-Dihydroxy-16-keto-Δ¹,³,⁵-estratriene (XIIIa).**—This 16,17-ketol (m.p. 232.5–234°) (XIIIa) was reduced with sodium amalgam in the manner previously described (0.44 g. of ketol in 50 cc. of ethanol plus 5 cc. of acetic acid, 100 g. of 2% sodium amalgam, finally 5 cc. of 50% acetic acid, temperature 40°). The supernatant fluid was decanted from the mercury and the latter rinsed twice with ethanol. To the combined alcoholic solutions was added 50 cc. of water and the diluted liquid distilled (steam-bath) until ebullition had nearly ceased. More water (50 cc.) was then added to the mixture, and after a day in the ice box, the glycols were filtered and dried at 90°. The yield of crystalline material was 0.36 g. Any trace of ketonic material was separated from this residue with carboxymethoxylamine in the fashion previously described (0.25 g. of carboxymethoxylamine hemihydrochloride, 0.50 g. of potassium acetate, 40 cc. of 75% propanol, 1.5 hours reflux).

**Separation of *cis*-oid and *trans*-oid 16,17-Glycols Formed by Sodium Amalgam Reduction of 3,17(α)-Dihydroxy-16-keto-Δ¹,³,⁵-estratriene (XIIIa).**—The crystalline non-ketonic fraction of the preceding section was dissolved in 35 cc. of absolute acetone and 5 cc. of acetone saturated with anhydrous hydrogen chloride added. After the acetalizing medium had been swirled continuously for eighteen minutes, 50 cc. of aqueous potassium carbonate (≈ 1.50 g. of potassium carbonate) was added in one portion, mixed at once, and then diluted to a volume of 400 cc. with water. After a day in the ice box the precipitated material was filtered, washed with water containing 0.5% pyridine, and then dried in the vacuum desiccator. The resulting 0.29 g. of dried material was dissolved in 300 cc. of chloroform and partitioned with 300 cc. of 0.1 *N* sodium hydroxide. The alkaline phase was separated and again washed with 300 cc. of chloroform. The sodium hydroxide fraction was then acidified with 3 cc. of concentrated hydrochloric acid and extracted with 400 cc. of ethyl ether. The ether was washed once with 200 cc. of water, and after the addition of a few drops of pyridine, evaporated to a white crystalline residue. This residue was recrystallized twice from acetone–cyclohexane–Skellysolve B, treated with charcoal, and then finally recrystallized from aqueous acetone. White microscopic crystals of estriol (theelol) (XIX) were obtained (85 mg.). These melted at 268–269.5° and showed no depression of melting point after admixture with authentic theelol supplied by Dr. D. W. MacCorquodale of The Abbott Laboratories. A mixed melting point test performed with authentic isoestriol-A gave a value of 251.5–256°.

Methylation of a portion of this 85-mg. batch of estriol gave **estriol methyl ether** (34 mg. of triol in 25 cc. of 0.5 *N* sodium hydroxide shaken one hour with 0.6 cc. of methyl sulfate). This derivative (13 mg.) melted at 158–161° and showed no mixed melting point depression with authentic theelol methyl ether.

Acetylation of another portion of this estriol (32 mg. in 1 cc. of pyridine and 1 cc. of acetic anhydride) gave a product (42 mg.) melting at 124.5–126°. **Estriol triacetate** melts at 126°.[24]

The 600 cc. of solution comprising the combined chloroform phases in the above separation was washed with water (350 cc.) and evaporated to dryness. There resulted an oily residue which was taken up in 50 cc. of ethanol, and after the addition of 10 cc. of 1.2 molar phosphoric acid, refluxed on the steam-bath for thirty minutes. To the hydrolysis medium was then added 25 cc. of water and boiling allowed to continue without the condenser until most of the ethanol had been removed. The mixture was then left overnight in the ice box and the precipitated material filtered, washed well with water, and dried in the oven (100°); yield, 0.12 g. of white crystals. These were treated with charcoal and recrystallized from aqueous methanol to give 94 mg. of small flat needles (XX) melting at 272–275°. A mixed melting point test performed with known isoestriol-A (m.p. 274–276°)[25] showed no depression.

**Isoestriol-A Acetonide (XXI).**—Isoestriol-A (91 mg., from the preceding experiment) (XX) was covered with 10 cc. of absolute acetone and then 1.5 cc. of acetone saturated with anhydrous hydrogen chloride added. The mixture was swirled for eight minutes, although solution was effected within one minute time. Then, in one portion, 10 cc. of aqueous potassium carbonate (≈ 0.45 g. of potassium carbonate) was added, mixed in at once, and then diluted to a volume of 50 cc. with water. After a day in the ice box, the precipitated acetonide was filtered and washed well with water containing a trace of pyridine. The air-dried product was recrystallized once from water–acetone–pyridine and once from water–methanol–pyridine to give 91 mg. of flakes which nearly melted at 98° but formed a liquid melt only at 182–184°. After several recrystallizations from water–methanol–pyridine it was finally learned that this compound actually possesses a double melting point. The final product (28 mg.) cleared almost completely at 103.5–104.5°, then solidified, and again melted sharply at 183.5–184.5° (XXI). Analysis indicates that it is hydrated with one molecule of water.

(24) Thayer, Levin and Doisy, *J. Biol. Chem.*, **91**, 655 (1931).

(25) Isoestriol-A in the form of tiny, flat needles melting at 274–276° has been obtained; it is possible that these represent a crystalline modification of the microscopic crystals melting at 267–269°.

*Anal.*, Calcd. for $C_{21}H_{28}O_3 \cdot H_2O$: C, 72.80; H, 8.73. Found: C, 72.77, 72.63; H, 8.69, 8.61.

**Attempted Acetonide Formation with Estriol-3-methyl Ether.**—Estriol-3-methyl ether (350 mg., m.p. 157–158°) was covered with 35 cc. of anhydrous acetone and treated with 5 cc. of 8% hydrogen chloride in absolute acetone as usual. After thirty minutes swirling, 50 cc. of aqueous potassium carbonate (≈ 1.5 g. of potassium carbonate) was added in one portion, mixed at once, and placed at 5°. After a day at 5°, the precipitated white plates were filtered, washed well with water (0.5% pyridine), and then dried in the oven. The recovery of estriol-3-methyl ether melting at 158–159.5° was 334 mg.

**3(β),16(α),17(α)-Trihydroxyandrostane (XXVI).**—Adams catalyst (0.10 g.) was suspended in 10 cc. of acetic acid and reduced with hydrogen; then 155 mg. of pure 3(β),16(α),17(α)-triacetoxy-$\Delta^5$-androstene (VII) in 25 cc. of absolute ethanol was added. Hydrogenation was carried out for thirty minutes at atmospheric pressure, the catalyst removed by filtration, and the solution of hydrogenated steroid evaporated *in vacuo*. Saponification of the crystalline residue was accomplished by refluxing for one hour in a solution of 20 cc. of 2 *N* sodium hydroxide and 60 cc. of ethanol. The neutral residue was recrystallized consecutively from aqueous ethanol, aqueous methanol, absolute acetone, aqueous methanol, absolute acetone, and from aqueous ethanol to give 64 mg. of triol melting at 251–253° (XXVI).

*Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.97, 73.87; H, 10.49, 10.41; $[\alpha]^{26}D$ + 18° ($c$ = 0.53 in 95% ethanol)[26].

**Acknowledgment.**—The authors wish to thank Dr. Frank Stodola for his aid in determining the identity of his and their samples of androstanetriol triacetate. They wish also to extend their appreciation to Dr. Hans Hirschmann for his sample of androstenediol diacetate and for determining the optical rotation of their androstane-3(β),16(α),17(α)-triol. To the United States Standard Products Company, who gave generous financial support to this project, the authors are greatly indebted. Micro-analyses were performed by Dr. E. W. D. Huffman, Denver.

## Summary

The 16,17-ketols resulting from the zinc–acetic acid reduction of 16-oximino-17-ketosteroids and 16,17-diketosteroids have been found to be 16-keto-17(α)-hydroxysteroids.

The steric structures of steroidal 16,17-glycols have been determined.

(26) This optical rotation was determined by Dr. Hans Hirschmann.

DALLAS, TEXAS RECEIVED JUNE 30, 1948

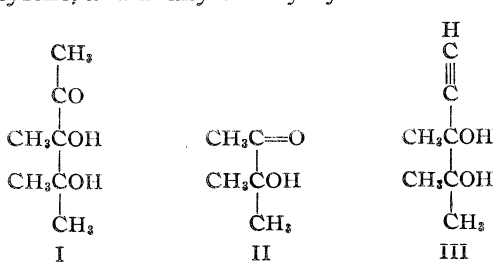
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# 2,3-Dimethyl-4-pentyne-2,3-diol as a Source of C-Methyl Sugars

BY CHARLES D. HURD AND JAMES MOFFAT

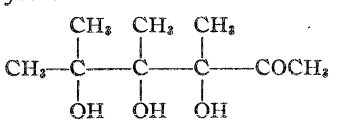
At the outset of this work it was planned to synthesize a monosaccharide whose alcohol groups were tertiary. 3,4-Dimethyl-3,4-dihydroxy-2-pentanone (I) was selected. Such a structure obviously may be regarded as 1,2,3,3-C-tetramethylglycerose. These steps were visualized in the synthesis: acetone to dimethylethynylcarbinol to 3-methyl-3-hydroxy-2-butanone (II) following known procedures, then to 2,3-dimethyl-4-pentyne-2,3-diol (III) by condensation with acetylene, and finally to I by hydration of III.




Steps through the synthesis of III were completed when the work was interrupted by war. Shortly thereafter, Favorskii and Onishchenko[1] announced their synthesis of both I and III, preparing III by pyrolysis of 2,3,6,7-tetramethyl-4-octyne-2,3,6,7-tetraol (IV), $CH_3(CMeOH)_2C{\equiv}C(CMeOH)_2CH_3$. IV was prepared by gradual addition of II into a mixture of potassium hydroxide and dry ether previously saturated with acetylene. They produced I by hydrating the triple bond of III with mercuric sulfate and dilute sulfuric acid.

We prepared III in about 90% yields directly from II by use of sodium acetylide with liquid ammonia as solvent. The acetic ester of III was prepared readily with ketene as the acetylating agent, whereas it could not be prepared with acetic anhydride and pyridine.

The present synthesis seems general. In other words, just as I is obtainable from II, a similar sequence of steps from I should give rise to a C-pentamethyltetrose:




## Experimental

Dimethylethynylcarbinol and 3-methyl-3-hydroxy-2-butanone (II) were made in accordance with previously established directions.[2] 2,3-Dimethyl-4-pentyne-2,3-diol (III) was synthesized from the latter as follows.

To 300 ml. of dry liquid ammonia at −78° in a protected 3-necked flask was added 10.3 g. of sodium. Dry

(1) A. E. Favorskii and A. S. Onishchenko, *J. Gen. Chem. (U. S. S. R.)*, **11**, 1111 (1941); *C. A.*, **37**, 3735 (1943).

(2) Hurd and McPhee, THIS JOURNAL, **69**, 239 (1947); **71**, 398 (1949).

acetylene gas was passed into the solution until the blue color of the solution was discharged, after which 21.3 g. of 3-methyl-3-hydroxy-2-butanone was added dropwise with stirring. After a reaction period of four hours, the processing steps included distilling off the ammonia, dissolving the residue in water, extracting the solution with ether, drying over potassium carbonate and distilling. The yield of product collected at 75–77° (6 mm.) was 22.9–24.3 g. (86–91%); $n^{25}D$ 1.4600; $d^{25}_4$ 1.001.

*Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.43. Found: C, 65.42; H, 9.11.

**Diacetate.**—A solution was prepared containing 5.5 g. of III, 20–25 g. of benzene, and two drops of sulfuric acid previously dissolved in ether. Ketene was passed into this solution for an hour at room temperature then for thirty minutes at 70–75°. Acidic impurities were removed by rinsing with sodium bicarbonate solution and with water. Then, after drying, the solvent was removed. Most of the product distilled at 120° (15 mm.); yield, 4.2 g. The thick, colorless distillate set to a crystalline mass within a few minutes; m. p. 54–56°. The crystals were very soluble in most organic solvents, including ligroin. The product is very volatile in steam.

Crystallization from solvents was not an easy matter. A 9:1 water–alcohol mixture maintained below 45° (to avoid liquefying the crystals) was the best solvent found. Purification is more readily achieved by sublimation. With conditions chosen at 130° and 40 mm. pure crystals were obtained melting at 55.0–55.5° (uncor.).

*Anal.* Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.62; H, 7.60.

**Acknowledgments.**—This investigation was supported by a grant during 1942 from the Graduate School of Northwestern University. Micro combustion analyses were performed by Dr. T. S. Ma. Assistance in the purification of the diacetate was given by Dr. Arthur Berger.

## Summary

3,4-Dimethyl-4-pentyne-2,3-diol and its diacetate are described. Attention is called to the fact that the hydration product of the former, namely, 3,4-dimethyl-3,4-dihydroxy-2-pentanone may be regarded as a monosaccharide composed of tertiary alcohol groups.

EVANSTON, ILLINOIS RECEIVED AUGUST 23, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

# Studies of Hemiacetal Formation in Alcohol–Aldehyde Systems. I. Cryoscopic Studies

BY F. E. MCKENNA,[1] H. V. TARTAR AND E. C. LINGAFELTER

The existence of an equimolar addition compound between an alcohol and an aldehyde was probably first mentioned by Jacobson.[1a] He considered the structure to be $CH_3CHOHOC_2H_5$ and called it an aldehyde alcoholate. Perkin[2] noted an initial decrease followed by a rapid increase in temperature when an aldehyde is mixed with an alcohol or water; this change was ascribed to a depolymerization of the alcohol or water followed by compound formation. The term hemiacetal came to be used for this type of supposed addition compound because of the purported relationship to the well-known acetal molecule.

Several more recent workers have investigated binary mixtures of aldehydes and alcohols for evidence on the existence of the hemiacetal. Wolf and Merkel[3] have confirmed Perkin's finding on the temperature changes when aldehydes and alcohols are mixed together. Curves representing density or index of refraction as a function of the composition presented by Adkins and Broderick[4] showed maxima at 50 mole per cent. Herold and Wolf[5] using absorption spectra measurements found maximum absorption with equimolar proportions, the band due to the carbonyl group being replaced by one characteristic of the ether-like linkage ascribed to the hemiacetal. They observed a time lag for this change of absorption which was attributed to the gradual establishment of a hemiacetal–alcohol–aldehyde equilibrium.

De Leeuw[6] determined the freezing point curve for the system acetaldehyde–ethanol. He found two maxima with aldehyde to alcohol ratios of 1:1 and 1:2. He also postulated that the latter compound in the presence of a dehydrating agent or of a catalyst could lose water to form the acetal.

Schimmel and Company[7] reported that mixtures of aliphatic alcohols and aldehydes (*n*-heptyl to *n*-undecyl) gave crystalline compounds of constant composition, 1:1. They were unable to prepare any derivatives of these substances because the reagents caused dissociation to aldehyde and alcohol.

The present results reported herein are from a cryoscopic investigation of the systems: *n*-heptanol–*n*-heptaldehyde, and methanol–propionaldehyde. Previously Schimmel and Company[7] had reported a melting point of 2° for the product obtained from an equimolar mixture of *n*-heptanol and *n*-heptaldehyde. The system methanol–propionaldehyde affords compounds with the smallest alkyl groups adapted to convenient investigation.

(1) Present address: Air Reduction Sales Co., Research Laboratories, Murray Hill, New Jersey.

(1a) Jacobson, *Ber.*, **4**, 215 (1871).

(2) Perkin, *J. Chem. Soc.*, **45**, 477 (1881); **51**, 826 (1887).

(3) Wolf and Merkel, *Z. physik. Chem.*, **187**, 61 (1940).

(4) Adkins and Broderick, THIS JOURNAL, **50**, 499 (1928).

(5) Herold and Wolf, *Z. physik. Chem.*, **2B**, 39 (1928); **12B**, 194 (1931); **16B**, 213 (1932); **18B**, 265 (1932); *Z. Elektrochem.*, **38**, 633 (1932); **39**, 566 (1933).

(6) De Leeuw, *Z. physik. Chem.*, **77**, 284 (1911).

(7) Schimmel and Co., *Ann. Reports*, p. 71 (1933).

## Experimental

**Purification of Materials.**—(a) **Propionaldehyde** was furnished by the Eastman Kodak Co. (White Label); boiling point range 47.8 to 50.5°. It was found that propionaldehyde cannot be kept pure in the presence of air. When distillation was attempted in air a yellow oily substance was produced. Qualitative tests with ammonium thiocyanate to which a crystal of ferrous (free of ferric) ammonium sulfate had been added showed that peroxides were formed and that this was accompanied by an increase in the refractive index from $n^{25}D$ 1.3601 to 1.3630 at room temperature. The rate of change was dependent upon the previous treatment (acidic or alkaline) of the Pyrex flasks even though followed by quite thorough rinsing with distilled water. Brühl[8] has reported the refractive index, $n^{20}D$ 1.3636.

Consequently all samples of propionaldehyde were purified by distillation under nitrogen and collected in glass containers which had been previously boiled out with water for twenty to thirty minutes and dried. The fraction boiling at 48.0 ± 0.05° (760 mm.) was used for all measurements. The refractive index was $n^{25}D$ 1.3601 and the freezing point −80.05°. Walden[9] has reported the freezing point to be −81°.

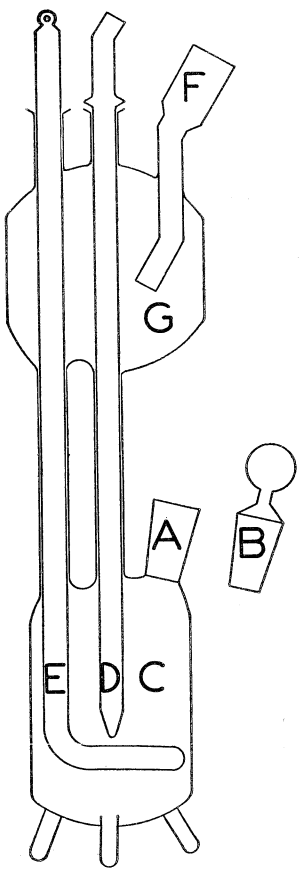


Fig. 1.—Cryostat.

Buckler[10] has stated that his samples of propionaldehyde polymerized spontaneously, even at low temperatures. Such behavior was not observed in this investigation.

(b) **Methanol.**—The material used was the fraction which distilled at 64.6 ± 0.05° (760 mm.). The fractionation was effected under nitrogen to prevent the formation of peroxides. The freezing point was found to be −98.02°. Previous investigators[11] have reported freezing points ranging from −97.0° to −98.54°, the average being −97.6°.

A transition temperature was found by Parks[12] to be −112° and by Kelley[13] −115.7° with supercooling as much as 25° obtainable. A transition temperature of −113.5° was observed with the methanol used in this investigation.

(c) ***n*-Heptanol.**—The *n*-heptanol distilled at 175.4 ± 0.05° (760 mm.) from the Eastman Kodak Co. product (White Label). This was further purified by fractionation under nitrogen; freezing point −34.03°. Deffet[14] reports: f. p., −34.1°; b. p. 176.35°.

(d) ***n*-Heptaldehyde.**—The *n*-heptaldehyde (Eastman White Label) distilled at 152.6 ± 0.05° (760 mm.). To prevent peroxide formation it was fractionated under nitrogen into previously boiled-out flasks. The freezing point was −43.71°. Deffet[14] reported f. p., −43.3°; b. p., 152.8°.

A slight charring of the residual liquid was observed during the fractionation (760 mm.) of both *n*-heptanol and *n*-heptaldehyde.

**Apparatus.**—The original plan was to construct the cryostat of a metal of high thermal conductivity. It was found that solutions of aldehydes and alcohols react with metals, in some cases forming crystalline compounds. Consequently the compounds were distilled in a nitrogen atmosphere directly into the glass cryostat. This apparatus is a modification of that described by Kanolt[15] and is shown in Fig. 1. The ground-glass joint A fits the adapter at the condenser. At other times this opening can be closed with the ground-glass stopper B. The liquids under investigation are contained in bulb C. The thermo-element tube D is removable. E is the stirrer. F is a small funnel for the addition of a small drop of liquid air to induce crystallization in case a solution should supercool. The bulb G permits the circulation of dry nitrogen around the stirrer and the thermo-element tubes to prevent the entry of moist air.

The distillation apparatus consisted of a 500-ml. distilling flask to the neck of which was attached a glass column, 25 cm. long, 1.3 cm. diam., packed with small glass helices. The outlet of the condenser was provided with a ground-glass joint to fit the inlet of the cryostat. A ground-glass cap with a sealed-in tube admitted a slow stream of purified nitrogen into the distilling flask.

The cryostat was placed in an unsilvered, one-liter Dewar flask. The gas pressure between the walls could be varied by means of a vacuum pump, thus allowing control of the rate of cooling or warming of the material in the cryostat. This Dewar, in turn, was contained in a five-liter, silvered, Dewar flask.

The refrigerant in the outer Dewar was liquid air, for the methanol–propionaldehyde system, and solid carbon dioxide in acetone, for the *n*-heptanol–*n*-heptaldehyde system. The cryostat was surrounded by a bath liquid (contained in the unsilvered Dewar) having the following composition by weight: 16.2% chloroform, 28.2% methylene chloride, 37.3% ethyl bromide and 18.3% trichloroethylene. This is similar to the bath liquid suggested by Kanolt[15] as not flammable and freezing around −150°.

**Temperature Measurements.**—The temperatures in the cryostat were measured with a two-junction copper–constantan thermo-element. This was constructed of Leeds and Northrup no. 38 copper and no. 30 constantan wire, which was free of inhomogeneities. The junctions were spot-welded. The thermo-element was given two coats of Bakelite varnish, then wrapped with silk binding tape and given an outer coat of Bakelite varnish. The element was placed in tube D of the cryostat and molten naphthalene poured around it to afford good heat transmission. The e. m. f. was measured with a Leeds and Northrup White Single Potentiometer of 10,000 microvolt range, and a Leeds and Northrup HS galvanometer. The thermo-element was calibrated at the temperatures of melting ice, melting mercury, subliming carbon dioxide and boiling oxygen.

**Procedure.**—The cryostat was steamed out for thirty minutes and dried. The weighed cryostat was attached to the distilling apparatus and a slow stream of nitrogen passed in to flush out the air. Then the components of the solution were distilled into the cryostat.

The unsilvered Dewar flask was evacuated to reduce heat transfer. The cryostat was immersed in the bath liquid and the cooling begun by admitting some gas to the space between the walls.

In determining melting points, a very small amount of refrigerant was kept in the outer Dewar to ensure slow heating not too far removed from equilibrium conditions.

(8) Brühl, *Ann.*, **200**, 139 (1880).

(9) Walden, *Z. physik. Chem.*, **55**, 220 (1899).

(10) Buckler, *J. Chem. Soc.*, 1036 (1937).

(11) Kelley, THIS JOURNAL, **51**, 180, 779, 1145 (1929); Keyes, *J. Math. Physics (MIT)*, **1**, 243 (1922); Joukovsky, *Bull. soc. chim. Belg.*, **43**, 397 (1934); Roper, THIS JOURNAL, **60**, 1693 (1938); Ross and Summerville, *J. Chem. Soc.*, 2770 (1926); Stull, THIS JOURNAL, **59**, 2726 (1937); Timmermans, *J. chim. phys.*, **27**, 401 (1930).

(12) Parks, THIS JOURNAL, **47**, 338 (1925).

(13) Kelley, *ibid.*, **51**, 180 (1929).

(14) Deffet, *Bull. soc. chim. Belg.*, **40**, 385 (1931).

(15) Kanolt, *U. S. Bur. Standards, Sci. Paper* No. 520.

Upon completion of the measurements on a given solution, the cryostat was removed from the bath, brought to room temperature and reweighed. In no case was any loss observed.

## Results

The freezing-point composition data for *n*-heptanol–*n*-heptaldehyde are presented in Table I and Fig. 2. The maximum at 2.25° for the solution with equimolar concentrations shows compound formation (hemiacetal) between one molecule of *n*-heptaldehyde and one molecule of *n*-heptanol.

TABLE I

FREEZING POINT–COMPOSITION DATA FOR THE SYSTEM: *n*-HEPTANOL–*n*-HEPTALDEHYDE

| Alcohol, mole fraction | Freezing point, °C. Primary | Eutectic | Alcohol, mole fraction | Freezing point, °C. Primary | Eutectic |
|---|---|---|---|---|---|
| 0.000 | −43.71 | ..... | 0.456 | + 1.57 | −58.44 |
| .037 | −46.11 | −58.92 | .489 | + 2.25 | ..... |
| .074 | −50.44 | −58.92 | .594 | + 0.47 | −50.02 |
| .108 | ..... | −58.92 | .662 | − 4.16 | ..... |
| .143 | −48.15 | −58.92 | .715 | −10.31 | ..... |
| .187 | −34.52 | −58.87 | .777 | −26.04 | ..... |
| .238 | −19.69 | −58.92 | .794 | −32.97 | −50.07 |
| .296 | − 7.85 | ..... | .829 | −44.92 | −50.13 |
| .353 | − 1.98 | ..... | .849 | −49.06 | −50.13 |
| .401 | + 0.33 | ..... | .877 | −45.27 | −50.13 |
| | | | 1.000 | −34.03 | ..... |

It was observed that a solid having a composition between that of A and of B could be superheated, the amount depending on the rate of warming. In some cases it was possible to superheat the solid to the melting temperature of the compound C.

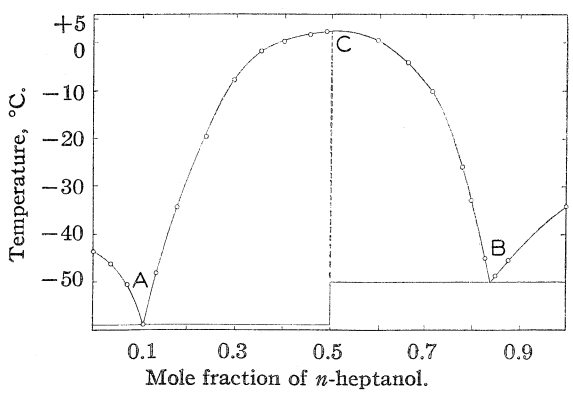



Fig. 2.—Freezing points for the *n*-heptanol–*n*-heptaldehyde system.

Also it was possible to produce a rather high degree of supercooling of some solutions with compositions intermediate between A and B. This was prevented by slow cooling, by seeding the solution with some of the solid or by dropping a small amount of liquid air onto the surface of the solution.

The freezing point–composition data for the methanol–propionaldehyde system are presented in Table II and Fig. 3. Here also a maximum, higher than the melting point of either component of the system, was found at −66.75° for equimolar concentrations of aldehyde and alcohol.

TABLE II

FREEZING POINT–COMPOSITION DATA FOR THE SYSTEM: METHANOL–PROPIONALDEHYDE

| Alcohol, mole fraction | Freezing point, °C. Primary | Eutectic | Transition, °C. |
|---|---|---|---|
| 0.000 | − 80.05 | ..... | |
| .094 | − 96.15 | −114.9 | |
| .151 | −112.2 | −114.9 | |
| .249 | − 91.17 | −114.9 | |
| .353 | − 74.84 | −114.9 | |
| .502 | − 66.75 | ..... | −117.3 |
| .606 | − 75.49 | −134.0 | −118.5 |
| .706 | −101.1 | −134.0 | −120.5 |
| .793 | −132.9 | −134.0 | ..... |
| .859 | −114.0 | −134.0 | −118.4 |
| .982 | − 99.53 | −134.0 | −114.3 |
| 1.000 | − 98.02 | ..... | −113.5 |

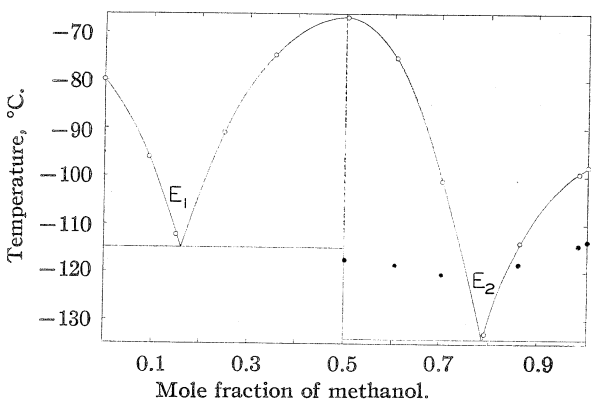



Fig. 3.—Freezing points and transition temperatures for the methanol–propionaldehyde system: O, freezing points; ●, transition temperature.

No superheating was observed in this system; the supercooling was also negligible. In a few instances the solution set to a jelly-like transparent solid but a slight movement of the stirrer caused the jelly-like material to become a crystalline solid.

The transition temperature of methanol was observed in all cases where the solid phase was the alcohol. A transition was also observed in compositions varying from eutectic $E_2$ and 50 mole per cent. methanol; the temperature varied from −113.5 to −120.5°.

The maximum in the curve for the *n*-heptanol–*n*-heptaldehyde system is broader and flatter than that for the methanol–propionaldehyde system. This indicates that the larger hemiacetal molecule is more dissociated than the smaller one. The fact that the system involving the smaller hemiacetal did not supercool or superheat to the extent of that with the larger hemiacetal, may indicate that equilibrium is reached more rapidly between the smaller alcohol and aldehyde molecules.

The solid which separated from a solution which was relatively rich in one of the components was finely divided; the solid formed from a solution of approximately equimolar proportions was in larger crystals.

## Summary

1. The effect of previous treatment of glass surfaces on the properties of propionaldehyde stored in glass vessels has been pointed out.

2. A cryostat has been constructed for use in cryoscopic investigations in solutions of alcohols and aldehydes.

3. The freezing point–composition relationships have been investigated for the systems: (a) *n*-heptanol–*n*-heptaldehyde and (b) methanol–propionaldehyde.

4. The results prove the formation of a compound (hemiacetal) between one molecule of an alcohol and one molecule of an aldehyde.

SEATTLE, WASHINGTON RECEIVED SEPTEMBER 30, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

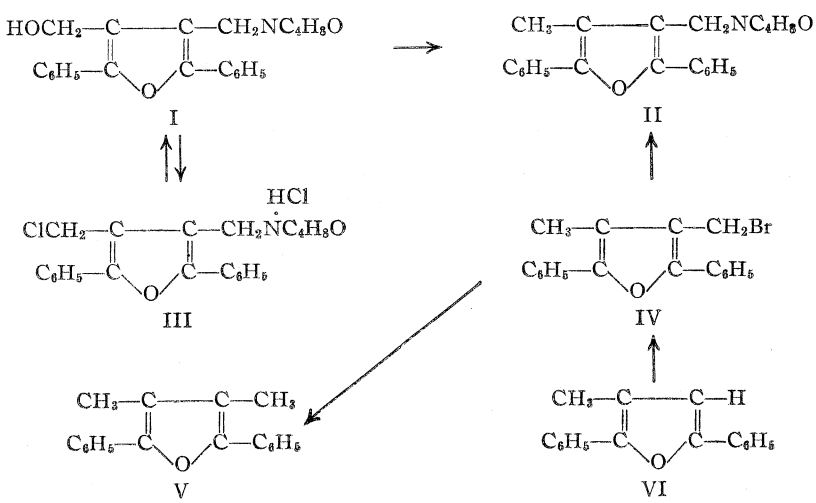
# 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran and Some Derivatives[1,2]

BY PHILIP S. BAILEY AND GENE NOWLIN

In an earlier paper[3] was described the isolation of 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I) from a Mannich reaction employing 1,2-dibenzoylethane, paraformaldehyde and morpholine hydrochloride in benzene solution. As stated there, the identity of I was not at first apparent. The present paper deals principally with reactions which led to its identification and some interesting reactions of its derivatives. Improvement in the yield of I is reported. The generality of the reaction leading to I has also been demonstrated by the fact that piperidine hydrochloride gives similar results.

Reduction of I by means of hydriodic acid or by stannous chloride gave II, the structure of which was established by synthesis from 3-methyl-2,5-diphenylfuran (VI). This consisted of the bromomethylation of VI to give IV, followed by treatment of IV with morpholine. Any possible doubt as to the course of the bromomethylation reaction was removed by the catalytic hydrogenolysis of IV to give known 3,4-dimethyl-2,5-diphenylfuran (V). Treatment of I with a chloroform solution of hydrogen chloride gave 3-(chloromethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran hydrochloride (III) which in turn was easily converted back to I. The chloromethyl compound (III) also was made by the chloromethylation of 3-(morpholinylmethyl)-2,5-diphenylfuran. These reactions confirm the structure assigned to I because of reactions reported earlier.[3,4]

The structures of the two products of the Mannich reaction using piperidine hydrochloride (2,5-diphenyl-3-[piperidylmethyl]-furan and 3-[hydroxymethyl]-2,5-diphenyl-4-[piperidylmethyl]-furan) were proven by characteristic syntheses starting from 3-(bromomethyl)-4-chloro-2,5-diphenylfuran, syntheses earlier carried out for the corresponding morpholine compounds.[4]




1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) was prepared by the characteristic nitric acid oxidation[5] of II and was found to give some interesting reactions. Reductive furanization of VII back to II, either directly or stepwise through VIII, establishes the structure of VII. When VII is treated with 6 *N* hydrochloric acid it dissolves, and when the resulting solution is neutralized with sodium carbonate, a product shown to be I crystallizes.

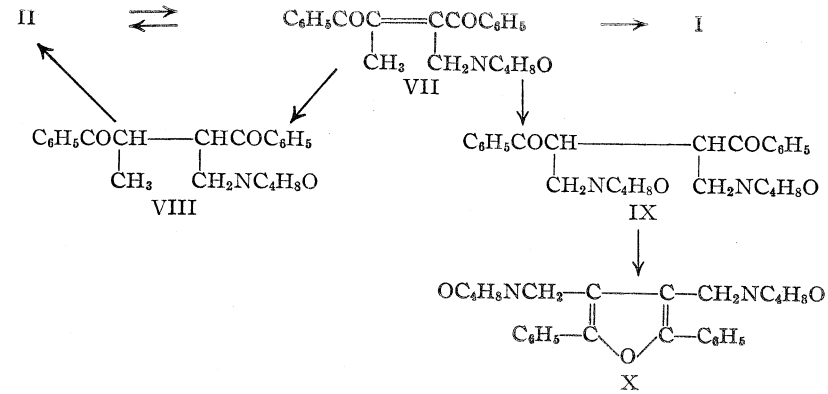
(1) Presented before the Southwest Regional Meeting of the American Chemical Society, Shreveport, Louisiana, December 10, 1948. A small portion was included in a paper presented at the Chicago meeting of the American Chemical Society, April, 1948.

(2) This work was partially supported by a University of Texas Research Institute grant, Project 70, and by a Frederick Gardner Cottrell grant from the Research Corporation, New York, N. Y.

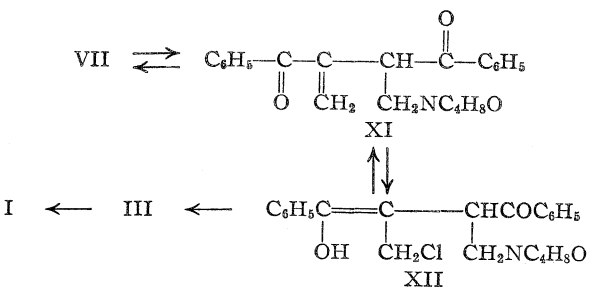
(3) Bailey and Lutz, THIS JOURNAL, **70**, 2412 (1948).

(4) Lutz and Bailey, *ibid.*, **68**, 2002 (1946).

(5) Lutz and Wilder, *ibid.*, **56**, 978 (1934).




This is a reaction similar to that between 1,2-dibenzoyl-1-methylethylene and amines, reported earlier.[6] Probably the reaction occurs through the steps shown below. It differs from the amine reaction[6] in that the acidic medium apparently favors cyclization of intermediate XII to a furan (III) rather than ketonization. It has been shown that III is easily hydrolyzed to I, simply upon treatment with sodium carbonate solution.




Treatment of VII with morpholine gave IX, a reaction completely analogous to the reaction of 1,2-dibenzoyl-1-methylethylene with amines.[6] The structure of IX was proven by cyclization to known X. In this connection it is interesting to note that in an earlier paper[4] the structure of the dihydrochloride of X (which analyzed for an extra molecule of water) was left in doubt as to whether it was an extraordinarily stable monohydrate of the furan, or whether it was a diketone, a dihydrochloride having the same structure as the dihydrochloride of the then unknown IX. The dihydrochlorides of X and IX have been shown to be definitely different, although difficulty was experienced in characterizing the salt of IX because of its great hygroscopic properties (the salt of X is not extremely hygroscopic). Upon neutralization, the dihydrochloride of IX gives back IX, not X; whereas the dihydrochloride in question (that of X) gives back X upon neutralization. Of course it is possible that the dihydrochlorides of IX and X are stereoisomers of one another, one a *meso* and the other a *dl*. However, if a ring opening did occur during the formation of a salt of X, the intermediate formed (probably a dienol) should fall into the more stable configuration of IX. Also the mechanism of formation of IX from VII should cause it to have the more stable configuration. Since the salts of IX and X are different, they must have different structures, and the dihydrochloride of X probably is only an unusually stable monohydrate.

(6) Lutz and Bailey, THIS JOURNAL, 67, 2229 (1945).

## Experimental[7]

**3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).**—A mixture of 48 g. of 1,2-dibenzoylethane, 48 g. of morpholine hydrochloride, 28 g. of paraformaldehyde, 2 ml. of concd. hydrochloric acid and 200 ml. of benzene was refluxed with efficient stirring for forty-eight hours, during which time 0.5 g. of paraformaldehyde was added every twelve hours. Two layers were present the entire time. The reaction mixture was worked up by the method described in another paper.[3] Thus was obtained 44.5 g. (65.5% yield) of the hydroxymethyl compound (I) which melted at 169–171°. In a number of different runs of this size the yields varied from 43 to 65%.

Where smaller runs were made, it was necessary to increase the ratio of benzene and hydrochloric acid to dibenzoylethane in order to maintain the above yields. For example, from a reaction mixture consisting of 4.8 g. of dibenzoylethane, 4.8 g. of morpholine hydrochloride, 2.9 g. of paraformaldehyde, 0.2 ml. of hydrochloric acid and 20 ml. of benzene, the yield of I was 7%, while from a similar reaction in which the volumes of benzene and hydrochloric acid were tripled, and everything else remained the same, the yield of I was 43%.

**3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) from 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I). A. By Hydriodic Acid Reduction.**—A mixture of 15 g. of I and 150 ml. of hydriodic acid (sp. gr., 1.7) was heated at 128° for twenty hours. The precipitate was filtered off and triturated with ethyl acetate; yield, 17.5 g. of brown crystals. A hot methanolic solution of the material was made slightly basic by the dropwise addition of 10% sodium hydroxide solution. After standing overnight the resulting mixture crystallized; 12.2 g. (86% yield), colorless crystals, m. p. 94–96°. Several recrystallizations from methanol raised the melting point to 95–96°.

*Anal.* Calcd. for $C_{22}H_{23}NO$: C, 79.25; H, 6.95. Found: C, 78.97; H, 6.81.

**B. Reduction with Stannous Chloride.**—A solution of 1 g. of I in 5 ml. of glacial acetic acid was added to a hot solution of 5 g. of stannous chloride in 7 ml. of glacial acetic acid and 5 ml. of hydrochloric acid. The resulting solution was refluxed for ten minutes, after which it was cooled and poured into 200 ml. of water, where crystallization occurred. Treatment of the resulting crystals (1.1 g.) with methanol and sodium hydroxide, as described in the preceding experiment, yielded 0.7 g. of colorless crystals (m. p. 94–96°); no depression was observed in a mixture melting point with the material obtained from the hydriodic acid reduction.

**3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) from 3-Methyl-2,5-diphenylfuran (VI). A. Bromethylation of VI to IV.** To a solution of 0.3 g. of paraformaldehyde in 3.2 g. of 30% hydrogen bromide–acetic acid reagent, was added a solution of 1.4 g. of VI in 5 ml. of glacial acetic acid. The resulting mixture was stirred at 15° for two hours. The precipitate, which started to form after ten minutes, was filtered off and washed with

(7) All melting points reported here are corrected. Some of the micro-analyses were performed by the Micro-Tech Laboratories of Skokie, Illinois.

cold acetic acid; 1.4 g., m. p. 81–83°. After several recrystallizations from ligroin (b. p. 90–105°) the melting point was 83–84°. The compound gave a positive Beilstein test.

*Anal.* Calcd. for $C_{18}H_{15}BrO$: C, 66.07; H, 4.62. Found: C, 66.05; H, 4.67.

Catalytic hydrogenolysis (Raney nickel) of a small sample of IV in the presence of an equivalent amount of potassium hydroxide in methanol solution yielded 3,4-dimethyl-2,5-diphenylfuran (V), which was identified by a mixture melting point with a known sample.[8]

**B. Treatment of IV with Morpholine.**—A solution of 1 g. of IV and 1 g. of morpholine in 30 ml. of dry ether was allowed to stand overnight, after which the morpholine hydrobromide was filtered off and the filtrate was washed, dried and evaporated. Crystallization of the residual oil from ethanol gave 1.0 g. of II (m. p. 95–96°) which showed no depression in a mixture melting point with the material from the reduction of I.

**3-(Chloromethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran Hydrochloride (III). A. From 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).**—A solution of 1 g. of I in 25 ml. of chloroform, saturated with hydrogen chloride, was set aside for two months, after which time it was evaporated. Several recrystallizations of the residue (1.3 g., m. p., 185–189°) from acetone raised the melting point to 232–233°[9].

*Anal.* Calcd. for $C_{22}H_{23}Cl_2NO_2$: C, 65.35; H, 5.73. Found: C, 65.52; H, 5.97.

**B. From 3-(Morpholinylmethyl)-2,5-diphenylfuran.**—Into a solution of 2 g. of 3-(morpholinylmethyl)-2,5-diphenylfuran hydrochloride and 0.2 g. of paraformaldehyde in 14 ml. of glacial acetic acid, was passed hydrogen chloride for twenty-four hours. The solution was evaporated under reduced pressure and the residue was recrystallized several times from acetone; yield 1.6 g., m. p. 231–233°, no depression in a mixture melting point with the material obtained in part (A).

In another run the reaction mixture was worked up by dilution with water and neutralization with sodium carbonate. The product was I. Also, when crystalline III was shaken with sodium carbonate solution and ether it was converted to I.

**The Mannich Reaction in Benzene Solution Using Piperidine Hydrochloride. A. 3-(Hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan.**—A reaction mixture consisting of 4.8 g. of 1,2-dibenzoylethane, 4.3 g. of piperidine hydrochloride, 3.0 g. of paraformaldehyde, 60 ml. of benzene and 0.6 ml. of concd. hydrochloric acid was refluxed with stirring for forty-eight hours, during which time 0.1 g. of paraformaldehyde was added every twelve hours. The mixture was treated with 50 ml. of 6 *N* hydrochloric acid and extracted with ether. When the hydrochloric acid layer was worked up as described in the morpholine experiment[3] there was obtained 3.0 g. (46% yield) of crystals which melted at 161–165°. Several recrystallizations from ethanol raised the melting point to 169–170°.

*Anal.* Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25. Found: C, 79.28; H, 7.36.

**B. 2,5-Diphenyl-3-(piperidylmethyl)-furan.**—When the above reaction was repeated and worked up in precisely the same way with the exception that only 30 ml. of benzene and 0.3 ml. of hydrochloric acid was used, there was obtained 4.7 g. of material (m. p., 201–205°) which did not dissolve in either the hydrochloric acid or the ether layer. From the hydrochloric acid layer was obtained 0.5 g. of 3-(hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan. The 4.7-g. batch of crystals was dissolved in hot water, the solution was neutralized with sodium carbonate, and the resulting mixture was extracted with ether. From the ether extract was obtained 2.5 g. of colorless crystals which after recrystallization from ethanol melted at 83–84°.

*Anal.* Calcd. for $C_{22}H_{23}NO$: C, 83.25; H, 7.30. Found: C, 83.13; H, 7.26.

**2,5-Diphenyl-3-(piperidylmethyl)-furan from 3-(Bromomethyl)-4-chloro-2,5-diphenylfuran. A. 3-Chloro-2,5-diphenyl-4-(piperidylmethyl)-furan.**—To a solution of 1 g. of 3-(bromomethyl)-4-chloro-2,5-diphenylfuran[4] in 20 ml. of ether was added 0.7 g. of piperidine. After twelve hours the reaction mixture was filtered and the filtrate was washed, dried and evaporated. Thus was obtained 0.9 g. of colorless crystals which melted at 76–77°, after purification by recrystallization from ethanol.

*Anal.* Calcd. for $C_{22}H_{22}ClNO$: C, 75.09; H, 6.30. Found: C, 75.00; H, 6.48.

**B. Catalytic Hydrogenolysis of 3-Chloro-2,5-diphenyl-4-(piperidylmethyl)-furan** (0.8 g.) was carried out in a solution also containing 0.13 g. of potassium hydroxide and 40 ml. of methanol. The catalyst was Raney nickel (0.2 g.); 59 ml. of hydrogen was absorbed, after which the mixture was filtered, the filtrate was evaporated, and the residue was crystallized from isopropyl alcohol. The product was 0.6 g. of 2,5-diphenyl-3-(piperidylmethyl)-furan (m. p. 83–85°; no depression in a mixture melting point with a sample obtained from the Mannich reaction).

**3-(Hydroxymethyl)-2,5-diphenyl-4-(piperidylmethyl)-furan from 2,5-Diphenyl-3-(piperidylmethyl)-furan.**—A solution of 0.6 g. of paraformaldehyde in 12 g. of 30% hydrogen bromide–acetic acid reagent was added to a solution of 2.5 g. of 2,5-diphenyl-3-(piperidylmethyl)-furan in 8 ml. of glacial acetic acid. After twelve hours the mixture was poured into 200 ml. of water. Neutralization with sodium carbonate gave an oil which crystallized when treated with ether. Recrystallization yielded 0.86 g. of colorless crystals which melted at 167–170° and showed no depression in a mixture melting point with the product obtained from the Mannich reaction.

**1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII).**—To a solution of 6 g. of 3-methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II) in 40 ml. of propionic acid, cooled to 0°, was added a cold solution of 12 ml. of nitric acid in 24 ml. of propionic acid. After twenty minutes the solution was poured into water and neutralized with sodium carbonate. The resulting mixture was extracted with ether and the ether extract was washed, dried and evaporated. Thus was obtained 6 g. of crude yellow crystals, which after several recrystallizations from ethanol melted at 104–105°.

*Anal.* Calcd. for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.64. Found: C, 75.86, 75.76; H, 6.50, 6.59.

Conversion to the picrate, by treating an ethanolic solution of VII with an ethanolic picric acid solution, gave a yellow solid which melted at 163–165° after several recrystallizations from an isopropyl alcohol–acetone mixture.

*Anal.* Calcd. for $C_{28}H_{26}N_4O_{10}$: C, 58.13; H, 4.53. Found: C, 58.10, 58 15; H, 4.42, 4.35.

**Reduction of 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII). A. To 3-Methyl-4-(morpholinylmethyl)-2,5-diphenylfuran (II).**—To a solution of 5 g. of stannous chloride, 5 ml. of hydrochloric acid and 7 ml. of acetic acid was added a solution of 0.6 g. of VII in 5 ml. of acetic acid. The mixture was heated over a steam-bath, with stirring, for five minutes, after which it was diluted with water and neutralized with sodium carbonate. Extraction with ether and evaporation of the ether extract gave an oil which was crystallized from ethanol (0.4 g., m.p. 99–100°) and identified as II by a mixture melting point with an authentic sample.

**B. To 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethane (VIII).**—A porcelain spatulaful of zinc dust was added to a solution of 2 g. of VII in 40 ml of glacial acetic acid. The reaction mixture was stirred and warmed over a steam-bath for nine minutes, after which it was filtered. The filtrate was neutralized with sodium carbonate and extracted with ether. Evaporation of the ether solution and crystallization of the residue from

(8) Lutz and Taylor, THIS JOURNAL, **55**, 1593 (1933).

(9) If the melting point tube is placed in a bath preheated to 200°, the compound immediately melts, then resolidifies and melts again at 232–233°.

ethanol gave 1.2 g. of colorless crystals which melted at 112–113°. The melting point did not change upon recrystallization.

*Anal.* Calcd. for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17. Found: C, 75.20; H, 7.39.

Furanization of VIII to II was accomplished by treating a solution of 1 g. of VIII in 5 ml. of acetic anhydride with 0.17 ml. of sulfuric acid (to bring about salt formation) followed by five drops excess. After twenty minutes the mixture was poured into water, where it was neutralized with sodium carbonate and extracted with ether. Evaporation of the ether extract and crystallization of the residue from ethanol gave colorless crystals (melting at 98–100°) which were shown to be II by a mixture melting point with an authentic sample.

**Conversion of 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) to 3-(Hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).**—Five-tenths gram of VII was dissolved in 100 ml. of 6 *N* hydrochloric acid and the solution was extracted with ether. Neutralization of the acid layer with sodium carbonate gave 0.48 g. of material which melted at 168–172° after recrystallization from ethanol; it showed no depression in a mixture melting point with known 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran (I).

**1,2-Dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX).**—A solution of 1 g. of 1,2-dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene (VII) in 10 ml. of morpholine was warmed at 75–80° for twenty-four hours. The solution was then poured into water and extracted with ether. Evaporation yielded 0.98 g. of crystals which melted at 135–140°. Several recrystallizations from ethanol raised the melting point to 141–142°. A mixture melting point with 3,4-di-(morpholinylmethyl)-2,5-diphenylfuran (X)[4] (m. p. 143–144°) was depressed to 125–131°.

*Anal.* Calcd. for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39. Found: C, 71.56; H, 7.55.

Treatment of this material with 6 *N* hydrochloric acid, followed by neutralization with sodium carbonate, produced no change.

**Conversion of 1,2-Dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX) to 3,4-Di-(morpholinylmethyl)-2,5-diphenylfuran (X).**—To a solution of 0.5 g. of IX in 5 ml. of acetyl chloride was added, dropwise, 0.53 ml. of concd. sulfuric acid. After twenty minutes the dark green solution was poured into water and the resulting solution was neutralized with sodium carbonate. Extraction with ether and evaporation of the ether extract gave 0.41 g. of crystals which melted at 115–122°. Several recrystallizations from ethanol raised the melting point to 143–144°. The material showed no depression in a mixture melting point with known 3,4-di-(morpholinylmethyl)-2,5-diphenylfuran (X),[4] but showed a twenty degree depression in a mixture melting point with starting material (IX).

**The Dihydrochloride of IX** was made by treating an ether solution of IX with excess ethereal hydrogen chloride. It proved to be difficult to purify because of its great hygroscopic properties; for this same reason, a carbon and hydrogen analysis was not made. Several recrystallizations from acetone by the addition of dry ether gave colorless crystals melting at 120–123°.

*Anal.* Calcd. for $C_{26}H_{34}Cl_2N_2O_4$: $Cl^-$, 13.92. Found: $Cl^-$, 13.75.

The dihydrochloride was converted back to IX by neutralizing an aqueous solution of it with sodium carbonate. The yield was 70% and the melting point after one recrystallization from ethanol was 139–141°. There was no depression in a mixture melting point with known 1,2-dibenzoyl-1,2-di-(morpholinylmethyl)-ethane (IX), but a twenty degree depression was observed with known X.

## Summary

A rigorous proof of structure for 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran is presented. 1,2-Dibenzoyl-1-methyl-2-(morpholinylmethyl)-ethylene has been made and found to undergo some interesting reactions. Treatment of the latter with hydrochloric acid, followed by neutralization with sodium carbonate, gives 3-(hydroxymethyl)-4-(morpholinylmethyl)-2,5-diphenylfuran, while treatment with morpholine gives 1,2-dibenzoyl-1,2-di-(morpholinylmethyl)-ethane. Mechanisms are discussed.

AUSTIN, TEXAS RECEIVED OCTOBER 15, 1948

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[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

# Hydrogenation Products from Furfuralacetofuran

BY KLIEM ALEXANDER AND GEORGE H. SMITH, JR.

The chalcone-like compound, furfuralacetofuran,[2] represents a little known type of furfural condensation product. It is readily obtainable by condensing furfural with 2-acetylfuran. The latter intermediate is conveniently available by the preparative procedure of Hartough and Kosak.[3] Total hydrogenation of furfural and difurfural ketone and aldehyde condensation products, in which all of the ethylenic, carbonyl and furyl groups were saturated, has been reported by several authors.[4,5] Intermediates prepared by selective hydrogenation of the alkene and carbonyl groups have, however, received much less attention. Adkins and associates[4,6] have shown that by suitable choice of catalyst and other reaction conditions, the alkene, carbonyl, and furan ring groups of β-furylacrolein can be selectively hydrogenated in that order. In this instance they also observed a complicating side reaction involving ring closure of an intermediate, probably β-furylpropionaldehyde, and leading to the bicyclic structure 1,9-dioxa-5-spirononane. More drastic conditions of hydrogenation gave various ring cleavage and other hydrogenolysis products.

In this study procedures were developed for the conversion of furfuralacetofuran (I) to 1,3-di-

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

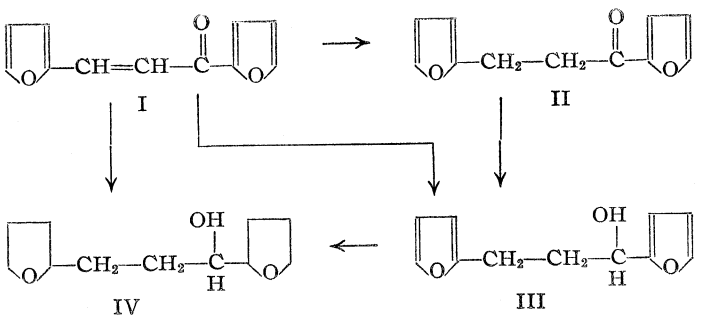
(2) Previously reported by Weygand and Strobelt, *Ber.*, **68**, 1839 (1935).

(3) H. D. Hartough and A. I. Kosak, THIS JOURNAL, **69**, 3093 (1947).

(4) H. Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937.

(5) A. Hinz, G. Meyer and G. Schücking, *Ber.*, **76B**, 676 (1943).

(6) (a) H. E. Burdick and H. Adkins, THIS JOURNAL, **56**, 438 (1934); (b) M. Farlow, H. E. Burdick and H. Adkins, *ibid.*, **56**, 2498 (1934).




furylpropanone-1 (II), 1,3-difurylpropanol-1 (III), and 1,3-ditetrahydrofurylpropanol-1 (IV). With the exception of II → III, which was not attempted, these are stepwise changes as indicated below. A number of trial reactions performed under varying conditions of temperature and catalyst choice served to show that I → IV occurs rapidly and nearly quantitatively with Raney nickel catalyst at temperatures up to 130°. Likewise I → III occurs very rapidly and almost quantitatively at 110–120° with copper–chromium oxide catalyst, the reaction stopping abruptly with the absorption of two moles of hydrogen. Attempts to go from I to III by use of a nickel on kieselguhr catalyst gave confusing results. Of the two moles of hydrogen that would be required for such a change (saturation of the alkene and carbonyl groups), a rapid absorption of about 1.3 moles, apparently, occurred at temperatures in the range 45–65°. At this point absorption became very slow but increased again to a moderate rate in the range 75–100° and continued at a smoothly decreasing rate to nearly complete saturation of the compound. The product, isolated on stopping the reaction when two moles of hydrogen had been absorbed, was a mixture still showing considerable reactivity toward carbonyl reagents.

Conversion of I to II, using nickel on kieselguhr catalyst, was not entirely satisfactory, since, as indicated above, processes other than the simple saturation of an ethylenic bond are evidently taking place during the first rapid absorption of hydrogen.

Consideration has been given to the possibility that cyclization products analogous to those reported by Adkins[6] and others,[5] may have been formed. Careful fractionation of the total reaction mixture resulting from the preparation of IV, however, failed to show any significant amounts of lower boiling components.

## Experimental[7]

**Catalysts and Apparatus.**—The copper–chromium oxide, Raney nickel, and nickel on kieselguhr catalysts employed were prepared according to the procedures of Adkins.[4] All hydrogenations were conducted in a rocker-type, high-pressure hydrogenation bomb assembly.

**2-Acetylfuran.**—The method of Hartough and Kosak[3] was employed. In agreement with their findings, orthophosphoric acid was the most generally satisfactory catalyst for the acetylation of furan. Yields as high as 77% were obtained from mixtures containing 68 g. (1 mole) of furan and 204 g. (2 moles) of acetic anhydride, to which was added 10 g. of sirupy phosphoric acid (85%). The reaction mixtures were stirred and maintained at 45–60° for one and one-half to two hours.

**Furfuralacetofuran (I).**—A mixture of water (300 cc.), 95% alcohol (225 cc.), 2-acetylfuran (110 g., 1 mole), and freshly distilled furfural (96 g., 1 mole) was placed in a flask provided with a stirrer and cooled to 5–10° by an ice-bath. To this, with stirring, was added a solution of 50 g. of sodium hydroxide in 150 cc. of water. The temperature rapidly increased to about 25° then gradually fell. When, after six to eight minutes, the temperature had fallen to 10–15°, the ice-bath was removed and stirring continued for three to four hours. The product separated as a crystalline yellow solid. The reaction mixture was cooled in an ice–salt mixture, filtered, and the product washed with water until free of alkali. Crystallization from an alcohol–water mixture, after treatment with activated carbon, gave 168 g. (89% yield) of furfuralacetofuran as pale yellow crystals. The m. p., 89–90°, agrees with that reported by Weygand and Strobelt.[2] *Anal.* Calcd. for $C_{11}H_8O_3$: C, 70.2; H, 4.28. Found: C, 70.3; H, 4.47. The compound is stable, showing no color or other changes on standing for several months.

**1,3-Difurylpropanone-1 (II).**—Furfuralacetofuran (94 g., 0.5 mole), dissolved in ethanol and the solution made up to a volume of 370 cc., was hydrogenated in the presence of 3 g. of nickel on kieselguhr catalyst at 45–65° (initial hydrogen pressure 1500 p. s. i.) until the pressure drop corresponded to approximately 0.5 mole of hydrogen absorption. This required twenty to thirty minutes. By stopping the reaction at this point 84 g. of a yellow-orange liquid, b. p. 104–110° (0.5 mm.); $n^{27}D$ 1.5400; $d^{27}_4$ 1.1642 was obtained. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.4; H, 5.29. Found: C, 69.1; H, 5.45. Further distillation indicated a mixture of products but failed to give appreciable separation of them. That the main product is 1,3-difurylpropanone-1 is indicated by the preparation of an oxime and a 2,4-dinitrophenylhydrazone in good yield.

Oxime: colorless needles, m. p. 83–84°. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: N, 6.83. Found: N, 6.82, 6.88.

2,4-Dinitrophenylhydrazone: fine, red needles from ethanol–ethyl acetate mixture, m. p. 157.5–159.5°; yield, 80–85%. *Anal.* Calcd. for $C_{17}H_{14}O_6N_4$: C, 55.2; H, 3.81; N, 15.13. Found: C, 55.15; H, 3.60; N, 15.18.

**1,3-Difurylpropanol-1 (III).**—Furfuralacetofuran (94 g., 0.5 mole), dissolved in absolute ethanol and the solution, made up to a volume of 370 cc., was hydrogenated in the presence of 4 g. of copper–chromium oxide catalyst. Absorption of hydrogen occurred very rapidly in the temperature range of 90–115° and at pressures of 300–1000 p. s. i. The reaction stopped abruptly when two moles of hydrogen per mole of furfuralacetofuran had been absorbed. Distillation of the product, after removal of catalyst and solvent, gave 87 g. (91% yield) of a nearly colorless liquid, b. p. 99–100° (0.25 mm.); $n^{25}D$ 1.5133; $d^{25}_4$ 1.1388. A sample of this product on further hydrogenation over Raney nickel gave IV in excellent yield. *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.29. Found: C, 67.4; H, 6.58. This compound formed a 3,5-dinitrobenzoate (colorless, needle crystals from ethanol), m. p. 93.5–94.5°. *Anal.* Calcd. for $C_{18}H_{14}O_8N_2$: C, 56.0; H, 3.65; N, 7.26. Found: C, 55.9; H, 3.48; N, 7.33.

**1,3-Ditetrahydrofurylpropanol-1 (IV).**—Furfuralacetofuran (62.7 g., 0.333 mole) in 220 cc. of ethanol was hydrogenated in the presence of 5 g. of Raney nickel catalyst at temperatures up to 130°. The initial hydrogen pressure was 1700 p. s. i. Absorption began just above room temperature and was essentially complete (6 moles of hydrogen per mole) in fifty minutes at 130°. Filtration from catalyst, followed by removal of solvent and distillation of the product at reduced pressure, gave 63.2 g. (95% yield)

(7) All analyses are micro determinations by C. H. Van Etten and Mary B. Wiele of this Laboratory.

of a colorless, somewhat viscous liquid, b. p. 108–112° (0.5 mm.); $n^{25}D$ 1.4727; $d^{25}_4$ 1.0617; $M_D$ calcd. 52.88; $M_D$ found, 53.41. It is miscible in all proportions with water and with all the common organic solvents. *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.05. Found: C, 65.8; H, 10.03.

A 100-g. sample of this product on vacuum fractionation through a Podbielniak semi-micro column was found, except for a 3.3 cc. fore-run, to be homogeneous as regards distillation constants and refractive index.

A liquid benzoate ester was obtained in approximately 70% yield when a 0.25-mole sample was refluxed with excess benzoic acid in dry toluene, with *p*-toluene-sulfonic acid as the catalyst, and the water removed by azeotropic distillation. Its constants were: b. p. 182–183° (0.5 mm.); $n^{25}D$ 1.5158; $d^{25}_4$ 1.1038. A sample of this ester, on alkaline hydrolysis, gave an approximately quantitative recovery of benzoic acid and an oil identical with the above 1,3-ditetrahydrofurylpropanol-1 as shown by density, refractive index, boiling point and solubility behavior. *Anal.* Calcd. for $C_{18}H_{24}O_4$: C, 71.0; H, 7.94; S. E. 304.4. Found: C, 71.0; H, 8.04; S. E., 288, 304, 292. With 3,5-dinitrobenzoyl chloride in pyridine solution, the alcohol formed a solid derivative, m. p. 93–94° from ethanol. *Anal.* Calcd. for $C_{18}H_{22}O_8N_2$: C, 54.9; H, 5.62; N, 7.10. Found: C, 54.7; H, 5.41; N, 7.18.

This 3,5-dinitrobenzoate ester was different from that of III above, and both of these were different from that of ethanol, as shown by mixed melting point determinations.

## Summary

1. Furfuralacetofuran has been obtained in about 90% yield by the alkali-catalyzed condensation of furfural with 2-acetylfuran.

2. Procedures are given for the catalytic hydrogenation of furfuralacetofuran to 1,3-difurylpropanone-1, 1,3-difurylpropanol-1, and 1,3-ditetrahydrofurylpropanol-1. Good yields of these were obtained. These hydrogenation products have been characterized by preparation of several derivatives.

PEORIA, ILLINOIS RECEIVED SEPTEMBER 23, 1948

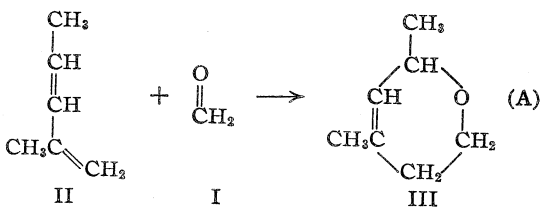
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[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

# A Diels–Alder Type Reaction with Formaldehyde

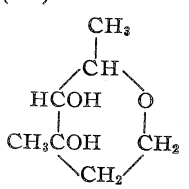
BY THOMAS L. GRESHAM AND THOMAS R. STEADMAN

We wish to report an unusual example of the Diels–Alder reaction,[1] in which formaldehyde (I) participates as a dienophile, reacting (A) with methylpentadiene[2] to yield 2,4-dimethyl-5,6-dihydro-1,2-pyran (III).



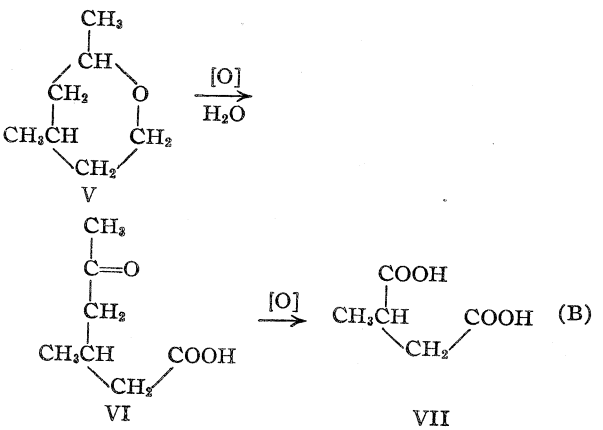
II I III (A)

A solid derivative for III was obtained by hydroxylation of the double bond with either potassium permanganate or *t*-butyl hydroperoxide,[3] yielding *cis*-3,4-dihydroxy-2,4-dimethyl-5,6-dihydro-1,2-pyran (IV).



IV

Hydrogenation of III proceeded readily with either Raney nickel or Adams catalyst, yielding 2,4-dimethyltetrahydropyran (V). Oxidation (B) of V with aqueous chromic acid gave 3-methyl-5-oxohexanoic acid (VI) and methylsuccinic acid (VII) confirming the structure (III) anticipated for the pyran from reaction A on the basis of the respective polarizations of the diene and I. The presence of the isomeric 3,5-dimethyltetrahydropyran should have led to the formation of $\alpha,\alpha'$-dimethylglutaric acid as well.



V VI VII (B)

In a recently issued patent[4] regarding the preparation of II from 2-methyl-2,4-pentanediol, the occurrence of 2,4,6-trimethyl-5,6-dihydro-1,2-pyran among the products was reported. This by-product was considered to have arisen by the reaction of acetaldehyde (formed from the glycol by dehydration and concomitant cleavage) with either an intermediate methylpentenol or II. It seems, therefore, quite probable that in general aldehydes will add to II to yield pyrans. Since we were unable to show that either butadiene or

(1) Norton, *Chem. Rev.*, **31**, 319 (1942).

(2) The methylpentadiene was a commercially available material obtained from the Shell Development Company, Emeryville, Calif., reported by them to consist of 85% 2-methylpentadiene-1,3 and 15% 4-methylpentadiene-1,3.

(3) Milas and Sussman, THIS JOURNAL, **59**, 2345 (1937); Milas and Harris, *ibid.*, **60**, 2434 (1938).

(4) Schelling and Anderson, U. S. Patent 2,422,802 (1947).

piperylene would react with I under conditions leading to pyran formation from I and II, we conclude that II is a very active diene in the Diels–Alder synthesis by reason of the favorable polarizing influence of the methyl groups.

## Experimental

**Formaldehyde and Methylpentadiene**—A mixture of 125 g. (1.5 moles) of methylpentadiene and 22.5 g. (0.75 mole) of α-polyoxymethylene was heated in a sealed, stainless steel pressure vessel at 185° for 6.5 hours with agitation. The cooled reaction mixture was dried over anhydrous magnesium sulfate and distilled from a Claisen flask. There was recovered 28 g. (22.5%) of methylpentadiene. A 51.6 g. yield (61.2% yield based on I) of the pyran was obtained: b. p. 125–130° (734 mm.). The properties of a purified sample were: b. p. 126–127° (740 mm.); $n^{30}D$ 1.4401, $d^{30}_4$ 0.877; $MR_D$, calcd. for III, 33.5, obs., 32.9. An examination of the infrared absorption spectrum[5] led to the conclusion that no impurity containing an hydroxyl group was present. From the reaction mixture there was also obtained 27 g. of methylpentadiene dimer, b. p. 110–114° (30 mm.), which accounted for a further 22% of the starting material.

*Anal.* Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.47, 74.60; H, 10.75, 10.65. Equivalent weight: calcd. for III, 56. Found[6]: 56.0, 57.5 (bromination with pyridine sulfate bromide); 58.3 (hydrogenation over Adams catalyst).

**Hydroxylation of III.**—To a well-stirred, cooled (15–20°) mixture of 600 ml. of water and 82.5 g. of III was added a solution of 233 g. of potassium permanganate in 3 l. of warm water over a period of three hours. After standing two days at room temperature the reaction mixture was filtered free of the precipitated manganese dioxide and the filtrate evaporated on a steam-bath to a volume of 250 ml. This concentrate was extracted continuously with ether overnight. The ether was distilled from the extract and the residual ether and water removed by distillation with carbon tetrachloride. On cooling, the carbon tetrachloride solution yielded 27.5 g. of crude glycol (IV) (25.6% yield). Recrystallization of crude IV from carbon tetrachloride yielded white crystals, m. p. 74.0–74.5°. On standing for a few days in a vial, the material was found to have changed in melting point: m. p. 90.0–90.5°. By heating this higher melting form for a few minutes above its melting point and allowing crystallization to take place spontaneously, it proved possible to secure the lower melting form.

*Anal.* Calcd. for $C_7H_{14}O_3$: C, 57.55; H, 9.58; mol. wt., 146.2. Found: C, 57.55, 57.40; H, 9.59, 9.62; mol. wt., 144, 141; equivalent weight (neutral sodium periodate), 148, 148.[7]

The same glycol (IV) was obtained by mixing 56 g. (0.5 mole) of III and 90 g. of *t*-butyl hydroperoxide dissolved in 270 g. of anhydrous *t*-butyl alcohol, with 5 ml. of 0.5% osmium tetroxide solution (in *t*-butyl alcohol) as catalyst. After standing six days at room temperature, the reaction mixture was distilled at atmospheric pressure to remove most of the *t*-butyl alcohol. At a pressure of 21 mm., IV distilled as a yellow oil, b. p. 120–130°, which partially solidified on seeding. A recrystallization from carbon tetrachloride gave 5.2 g. of slightly yellow crystals, which after two more recrystallizations melted at 89–91°. The melting point of a mixture with IV obtained by permanganate oxidation showed no depression.

**2,4-Dimethyltetrahydropyran (IV).**—In the reaction vessel of a Burgess–Parr hydrogenation apparatus was placed 56 g. of III and 13 g. of Raney nickel (moist with ethanol). The theoretically expected amount of hydrogen was absorbed during a period of three hours. Distillation of the filtered reaction mixture gave 47 g. of V, b. p. 116–121° (740 mm.). The infrared absorption curve[5] of the material showed the presence of a small amount of an hydroxyl containing material, arising presumably by hydrogenolysis. This impurity was removed by refluxing the product for two hours with 2 g. of sodium. A sample, distilled from sodium, b. p. 118–119°, had the following physical properties: $d^{25}_4$ 0.8422; $n^{25}D$ 1.4188; $MR_D$, calcd. for IV, 34.0, obs., 34.2.

*Anal.* Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.78, 73.80; H, 12.20, 12.25.

**Oxidation of 2,4-Dimethyltetrahydropyran.**—To a mixture of 149 g. of anhydrous sodium dichromate, 750 ml. of water and 224 g. of concentrated sulfuric acid was added 65 g. of V dropwise with good stirring, keeping the temperature of the reaction mixture between 30 and 40° with the aid of a cold-water-bath. When all the V had been added, the reaction mixture was warmed to 50° for one hour and then heated to the reflux temperature for thirty minutes. The unoxidized V was steam-distilled from the reaction mixture (23 g. recovered) and the residue continuously extracted with ether for sixteen hours. The dried extract was boiled down on a steam-bath, yielding a mixture of VI and VII. A portion of this mixture when treated with semicarbazide yielded a semicarbazone, m. p. 169.5–170.5°. This derivative of VI has been previously reported[8] as melting sharply at a temperature between 170° and 174°, depending on the rate of heating.

*Anal.* Calcd. for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88; neutral equivalent, 201.2. Found: C, 47.74, 47.80; H, 7.53, 7.45; N, 20.93, 20.85; neutral equivalent, 196, 198.

Distillation of the crude mixture of acids gave 9.5 g. of an oil, b. p. 137–142° (9 mm.), neutral equivalent 114.6, 114.1. Calcd. for VII, neutral equivalent 66; calcd. for VI, neutral equivalent 144. Therefore the mixture was 62% VI and 38% VII. On standing for two weeks a crystalline deposit of VII was observed in the distilled mixture of acids, m. p. 109–110° after one recrystallization from chloroform. A mixed melting point with a specimen of methylsuccinic acid obtained by hydrogenation of itaconic acid showed no depression.

*Anal.* Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10; neutral equivalent, 66.0; mol. wt., 132.1. Found: C, 45.54, 45.40; H, 6.22, 6.16; neutral equivalent, 67, mol. wt. (ebullioscopic, acetic acid), 130, 134.

## Summary

Formaldehyde reacts with 2-methylpentadiene-1,3 to yield 2,4-dimethyl-5,6-dihydro-1,2-pyran.

BRECKSVILLE, OHIO RECEIVED SEPTEMBER 13, 1948

(5) Data J. J. Shipman.

(6) Analysis by A. K. Kuder.

(7) Analysis by W. P. Tyler.

(8) Auwers and Peters, *Ber.*, **43**, 3091 (1910).

# NOTES

## A Method of Estimating and Minimizing the Error of Measurement of the Rate of a Radioactive Exchange Reaction

By Norman Davidson and John H. Sullivan

It has been explicitly pointed out by several authors that for a radio-active exchange reaction between two components in chemical equilibrium, the activity of either component varies in a simple exponential manner with time.[1,2] We present here, as a consequence of this analysis, a method for: (a) the estimation of the error, due to the error of radioassay, in the rate constant for the exchange reaction, as a function of the extent of exchange; (b) the selection of the optimum degree of exchange to minimize this error.[3]

For the case where the rate is measured by the decrease in the activity of the component that initially contained all the activity, the integrated rate expression is

$$\ln\left[\left(\frac{a}{b}+1\right)\frac{x}{c}-\frac{a}{b}\right]=-R(a,b)\,\frac{a+b}{ab}\,t \qquad (1)$$

In this relation: $a$ is concentration of component A that initially contained all the activity; $b$ is concentration of initially inactive component B; $c$ is initial activity of A; $x$ is activity of A at time $t$ and $R(a, b)$ is the rate of exchange.

For very short times of reaction $x$ will be almost the same as $c$ and the error in the rate large. For long times of reaction, the components will be almost in equilibrium with respect to the distribution of activity which will then change but little with time. It is often the case that the errors in $a$, $b$, $t$ are small compared to the errors of radioassay in $x$ and $c$. Set $z = x/c$ and $s = R((a + b)/ab)t$. The variable $s$ is dimensionless and proportional to two factors: (1) $Rt$, the total number of concentration units (*i. e.*, atoms/cc. or moles/liter) that have undergone mutual exchange, and (2) the term $(a + b)/ab$. (Displayed in the form $s = Rt/b + Rt/a$, it is evident that $s$ is the sum of the number of exchanges per atom of $a$, and the number of exchanges per atom of $b$). Then

$$-\frac{\mathrm{d}\ln s}{\mathrm{d}\ln z}=\frac{1+(a/b)\exp(s)}{s}=E(a/b,s) \qquad (2)$$

The relation $\sigma_s = |\mathrm{d}s/\mathrm{d}z|\sigma_z$ holds for the standard deviations, $\sigma_s$ and $\sigma_z$, of $s$ and $z$, because of the assumption that the error in $s$ is due entirely to the error in $z$.[4] Then

$$\frac{\sigma_s}{s}\times\frac{z}{\sigma_z}=-\frac{\mathrm{d}\ln s}{\mathrm{d}\ln z}=E(a/b,s) \qquad (3)$$

For $\sigma_z,(\sigma_z/z)^2 = (\sigma_x/x)^2 + (\sigma_c/c)^2$; the standard deviations of the activities may be due to statistical counting errors or may be manipulative errors determined by reproducibility tests. It is often the case that the fractional error in $x,(\sigma_x/x)$, is a constant; this is roughly true, for example, if the error is principally a counting error and one counts all samples to the same number of counts, or if the error is a manipulative error in preparing chemically identical samples for radioassay. For such cases, the minimum of $E$ locates the point for minimum error in $s$ (and hence in the rate function $R$). Knowing the value of $s$ corresponding to the minimum value of $E$ and using a preliminary value of $R$, the optimum $t$ may be chosen.

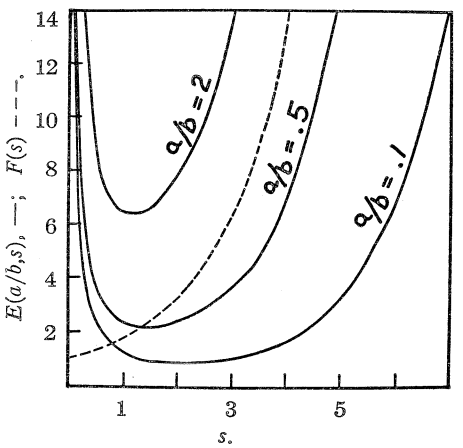



Fig. 1.—Error functions for exchange reactions.

The minimum of the error function, $E$, may be found by solution of the equation: $s - 1 = (b/a)\exp(-s)$. It will generally be more useful to construct a family of curves like those in the figure so that the error in $s$ will be known for any $s$ (or $z$). Estimates of the standard deviation in $s$ obtained in this way are useful, for example as weighting factors in averaging data or in least squares treatments of data on the variation of rate of exchange with temperature or ionic strength. For such applications, the function $E$ is useful even when the fractional error of radioassay is not constant. For these cases, knowing $\sigma_x$ as a function of $x$ and hence (for given $a$ and $b$) as a function of $s$, one could construct the function, $E(s)\sigma_x(s)/x(s)$, and thus select the point of minimum error. For the usual case where $\sigma_x/x$ does not change too rapidly with $x$, it may be sufficient to select by inspection a point in the region of the minimum of the $E(s)$ curve without making the more elaborate calculations required to select the optimum point.

(1) McKay, *Nature*, **142**, 997 (1938).

(2) Duffield and Calvin, This Journal, **68**, 557 (1946).

(3) Roseveare, *ibid.*, **53**, 1651 (1931), has applied similar arguments to the problem of estimating and minimizing the error in the rate constants for chemical reactions.

(4) See, for example, Margenau and Murphy, "The Mathematics of Physics and Chemistry," D. Van Nostrand Co., New York, N. Y., 1943. p. 498.

For the case where the rate of exchange is measured by the growth of activity, $y$, in B

$$y(t) = y(\infty)\ [1 - \exp(-s)] \quad (4)$$

$$\mathrm{d}\ln s/\mathrm{d}\ln(y/y(\infty)) = (\exp(s) - 1)/s = F(s) \quad (5)$$

The figure contains a plot of this function, too. In this case, of course, the fractional error in $y$ cannot possibly be constant as $y$ approaches zero; an estimate of $\sigma_y$ as a function of $y$ is needed for selecting an optimum reaction time or calculating the error of a particular determination.

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GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA RECEIVED AUGUST 9, 1948

## A Convenient Synthesis of N,N-Dimethyl-*p*-nitroaniline and N,N-Dimethyl-*o*-nitroaniline

BY TOD W. CAMPBELL

There are a number of methods in the literature for the preparation of N,N-dimethylnitroaniline[1]; but most of them are troublesome and result in low yields of a product which is usually of not too high purity. The methods in the literature[1g,i] which give acceptable or good yields involve a reaction in which a nitrohalobenzene is allowed to react with dimethylamine.

The author has found that this reaction is most conveniently brought about by refluxing a pyridine solution of nitrohalobenzene with a mixture of dimethylamine hydrochloride and sodium bicarbonate. The desired product is obtained in virtually quantitative yield; in the case of the para isomer, the product can be crystallized directly from the reaction solvent in a high state of purity. This procedure is therefore recommended for the preparation of these two substances.

### Experimental Part

***p*-Nitrodimethylaniline.**—A mixture of 42 g. of *p*-bromonitrobenzene, 300 cc. of pyridine, and 50 g. of sodium bicarbonate was placed in a 500-cc. round-bottom flask. To this mixture was added 30 g. of dimethylamine hydrochloride dissolved in about 10 cc. of warm water. The mixture was refluxed for ten hours. Mechanical stirring was not employed, since serious bumping did not occur. At the end of the reflux period, the hot solution was filtered free of inorganic salts, and the latter was extracted with 200 cc. of acetone, which was added to the pyridine solution. The mixed extracts were boiled, and water added to near the cloud point. On cooling, bright yellow needles of *p*-nitrodimethylaniline, 1–3 cm. in length, crystallized out. The melting point was observed to be 163.7–164.1° (lit. 163–166°) on a calibrated Anschütz thermometer in a Hershberg apparatus. The mother liquor on concentration to one third of its original volume gave an additional small yield of fine yellow needles, which had a melting point anywhere from 1–10 degrees low, for various experiments. One recrystallization from methanol raised the melting point to 163.5–164°. The over-all yield of pure product was 32.4–33.6 g. (94–97%).

***o*-Nitrodimethylaniline.**—The above procedure was employed to prepare the ortho substituted derivative. Ten grams of *o*-nitrochlorobenzene gave 8.9 g. (85%) of product; b. p. 149 at 20 mm.; $n^{25}D$ 1.6080.

*Anal.* Calcd. for $C_8H_{10}N_2O_2$; C, 57.81; H, 6.06. Found: C, 57.53; H, 6.21.

UNIVERSITY OF CALIFORNIA
LOS ANGELES 24, CALIF. RECEIVED AUGUST 19, 1948

(1) (a) Beilstein "Handbuch," Vol. XII, 690, 714, and first Supplement; (b) Le Fevre, *J. Chem. Soc.*, 147 (1930); (c) Davies, *Bull. soc. chim.*, [5] **2**, 295 (1935); (d) Donald and Reade, *J. Chem. Soc.*, 53 (1935); (e) Marsden and Sutton, *ibid.*, 599 (1936); (f) Shorygin, Topchier and Anan'ina, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 981 (1938); (g) Hodgson and Kershaw, *J. Chem. Soc.*, 280 (1930); (h) Evans and Williams, *ibid.*, 1199 (1939); (i) Senear, Rapport, Mead, Maynard and Koepfli, *J. Org. Chem.*, **11**, 378 (1946).

## Vapor Density of Diborane[1]

BY E. M. CARR, J. T. CLARKE AND H. L. JOHNSTON

In connection with the process of adding diborane to a calorimeter it was necessary to determine its density at 275.16°K. The diborane was obtained from the Naval Research Laboratory, subjected to a two-plate distillation and shown by the cryoscopic method to have a purity of 99.95 mole per cent. The diborane was introduced into an evacuated, weighed and calibrated 1-liter Pyrex bulb immersed in a constant temperature water-bath at 275.16°K. and constant to 0.01° C. during the measurement. The pressure was read on a 15 mm. i. d. manometer using a Gaertner cathetometer and a standard meter bar in an insulated case; the readings were converted to standard conditions and meniscus corrections made according to Cawood and Patterson.[2] The bulb was then reweighed (using a similar bulb as tare) on a Troemner 4-kg. balance. One bulb had 1/8 inch Pyrex helices with a surface area 16.0 times that of the interior part of the bulb added to it. Since all density measurements were made at approximately atmospheric pressure the amount of adsorption was assumed to be constant.

The results were used to calculate the density and the second virial coefficient $B$ in the equation

$$n - A = \frac{PV}{RT + PV}$$

where $A$ equals moles of diborane adsorbed on the surface of a 1-liter bulb and was found to have a value of $2.4 \times 10^{-5}$ mole. A summary of the data is

| Pressure, atm., $P$ | Temperature, °K., $T$ | Moles in gas phase, $n - A$ | Volume of bulb, ml., $V$ | Second virial coef. $B$ (ml.) 275.16° K. | Density g./l. 1 atm. 275.16°K. |
|---|---|---|---|---|---|
| 0.98832 | 275.20 | 0.048232 | 1090.2 | −247 | 1.2398 |
| .98201 | 275.14 | .047296 | 1076.4 | −233 | 1.2393 |
| .99445 | 275.16 | .048488 | 1090.2 | −223 | 1.2386 |
| .94553 | 275.16 | .046104 | 1090.2 | −234 | 1.2393 |
| .96219 | 275.17 | .046314 | 1076.4 | −227 | 1.2388 |
| .97098 | 275.15 | .046690 | 1076.4 | −199 | 1.2374 |
| | | Average | | −227 | 1.2389 |
| | | Av. deviation | | ±11 | ±0.0006 |

(1) This work was carried out under contract between the Office of Naval Research and The Ohio State University Research Foundation.

(2) Cawood and Patterson, *Trans. Faraday Soc.*, **29**, 514–523 (1933).

The value $B$ equals $-227$, determined experimentally agrees very well with the value $B$ equals $-240$ calculated from Berthelot's equation and the critical constants of A. E. Newkirk.[3]

(3) A. E. Newkirk, THIS JOURNAL, **70**, 1978 (1948).

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RECEIVED SEPTEMBER 13, 1948

## The Preparation of Xanthopterin

BY GERTRUDE B. ELION, AMOS E. LIGHT AND GEORGE H. HITCHINGS

The method of Totter[1] for the preparation of xanthopterin (2-amino-4,6-dihydroxypteridine) has several advantages with respect to the time involved, convenience and availability of starting materials, over those of Purrmann[2,3] and Koschara.[4] As will be shown, however, the product of this procedure is impure, as determined spectrographically. Moreover, such impure xanthopterin is shown to have a microbiological activity quite different from that of pure xanthopterin. The possibility exists that some of the reported biological activities of xanthopterin may be attributable to such impurities. This note describes modifications of the Totter procedure which result in their elimination.

### Experimental: Preparation of Xanthopterin

**Leucopterin.**—The leucopterin was prepared by the method of Purrmann.[5] On standing, after neutralization, the acid filtrate from the crystallization of leucopterin deposited a red precipitate which had microbiological activity (Precipitate A, Expt. 9, Table I).

**Dihydroxanthopterin.**—Leucopterin (6 g., 0.03 mole) was suspended in 40 ml. of water and 4% sodium amalgam (88 g., 0.153 mole) was added in small portions with stirring, the temperature being maintained below about 50°. On completion of the reduction the mixture was decanted from the mercury and chilled in an ice-bath. The sodium salt of dihydroxanthopterin precipitated in shiny crystals which were filtered off, washed with 5 ml. of ice water and dried *in vacuo* (3.73 g., 60%). A small additional quantity of dihydroxanthopterin (0.46 g.) was obtained by acidification of the mother liquors. The filtrate from this fraction, on standing several days, deposited a red precipitate which had purine-like activity (Precipitate B, Expt. 10, Table I).

The sodium dihydroxanthopterin (3.73 g.) was dissolved in 300 ml. of hot water, with the aid of a small quantity of sodium hydroxide solution, filtered and acidified with acetic acid. Dihydroxanthopterin monohydrate precipitated as pale yellow microcrystals (3.4 g.); *cf.* Hitchings and Elion.[6]

**Xanthopterin.**—Dihydroxanthopterin monohydrate (2.5 g., 0.0125 mole) was dissolved at room temperature in 200 ml. of water containing 1.4 g. of potassium hydroxide. Potassium permanganate solution (84 ml. of 0.01 $M$) was added dropwise over the course of ten minutes. After coagulation of the manganese dioxide, the solution was separated by centrifugation. The manganese dioxide was extracted with 100 ml. of water; the combined supernatant fluids were filtered and acidified with acetic acid. The yellow-orange xanthopterin precipitate was collected by centrifugation, washed seven times with water, then with alcohol, finally with ether and dried *in vacuo*. The yield was 1.95 g. of xanthopterin monohydrate (79%). At *p*H 11.0 the monohydrate has an $E^{1\%}_{1\text{ cm.}}$ of 0.92 at 255 mμ and 0.355 at 390 mμ.

### Microbiological

Each compound was tested for its ability to serve as a substitute for adenine in the growth of *Lactobacillus casei* with thymine as nutrilite at a concentration of 10 γ per ml.[7] It will be seen (Table I) that whereas pure xanthopterin (Expt. 1) and dihydroxanthopterin (Expt. 5) have only inhibitory effects, the product of the complete Totter procedure (Expt. 2) the product of further purification[8] of this material (Expt. 3) and that obtained by the oxidation of pure dihydroxanthopterin by silver oxide (Expt. 4) all possess purine-like activity. This activity is not due to the starting material (Expt. 6), the intermediate oxalyl derivative (Expt. 7) or leucopterin (Expt. 8). The activities appear to be properties of by-products which are formed in the various steps and in some instances deposit slowly on standing of the solutions (Expt. 9, Expt. 10). This finding demonstrates the necessity for the isolation and purification of the intermediates as a requisite for the preparation of pure xanthopterin.

TABLE I

PURINE-LIKE ACTIVITY OF XANTHOPTERIN AND INTERMEDIATES

| Expt. | Compound | Titer: With compound 1 mg. per 10 ml. | Titer: Control |
|---|---|---|---|
| 1 | Xanthopterin I[a] | 0.4 | 1.1 |
| 2 | Xanthopterin II[b] | 2.5 | 1.1 |
| 3 | Xanthopterin III[c] | 2.25 | 1.0 |
| 4 | Xanthopterin IV[d] | 1.9 | 1.3 |
| 5 | Dihydroxanthopterin | 0.3 | 0.6 |
| 6 | 2,4,5-Triamino-6-hydroxypyrimidine | 0.5 | 0.5 |
| 7 | 2,4-Diamino-6-hydroxy-5-oxalamidopyrimidine | 0.8 | 1.1 |
| 8 | Leucopterin | 0.4 | 0.6 |
| 9 | Precipitate A | 3.7 | 1.2 |
| 10 | Precipitate B | 5.0 | 1.2 |
| 11 | Adenine sulfate (0.1 mg.) | 7.1 | 1.2 |

[a] Permanganate oxidation of purified dihydroxanthopterin. [b] Silver oxide oxidation of crude dihydroxanthopterin. [c] Purified sample of II.[8] [d] Silver oxide oxidation of purified dihydroxanthopterin.

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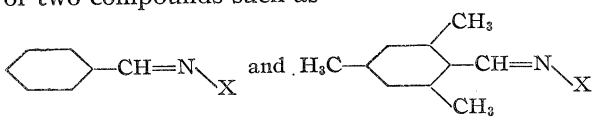
RECEIVED JUNE 1, 1948

(1) Totter, *J. Biol. Chem.*, **154**, 105 (1944).
(2) Purrmann, *Ann.*, **546**, 98 (1940).
(3) Purrmann, *ibid.*, **548**, 284 (1941).
(4) Koschara, *Z. physiol. Chem.*, **277**, 159 (1943).
(5) Purrmann, *Ann.*, **544**, 182 (1940).
(6) Hitchings and Elion, THIS JOURNAL, **71**, 467 (1949).
(7) Hitchings, Falco and Sherwood, *Science*, **102**, 251 (1945).
(8) Crude xanthopterin prepared by Totter's method was dissolved in $N$ sulfuric acid, treated with norite and filtered. The product was precipitated with ammonium hydroxide, washed, dried, rewashed and redried. This treatment increased the $E^{1\%}_{1\text{ cm.}}$ at 390 mμ in glycine buffer of *p*H 11.0 from a value of 0.31 to 0.35, the latter indicating approximate purity. The greater part of the microbiological activity remained, however.

## Absorption Spectra of Some Benzal and Mesitylal Schiff Bases

By Lloyd N. Ferguson and John K. Robinson

When considering the relative light absorptions of two compounds such as



where X is any simple group, it is difficult to predict whether the steric effect of the *ortho* methyl groups in the mesityl compound will decrease absorption from that of the simple phenyl compound or whether there will be an increase in absorption due to hyperconjugation of the methyl groups. For this reason, the spectra of several Schiff bases of benzaldehyde and mesitylaldehyde were measured. The spectral characteristics are listed in Table I.

Table I

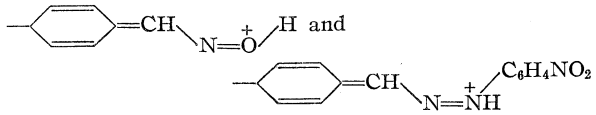
Spectral Characteristics of Some Benzal and Mesitylal Schiff Bases

| Compound | Oxime $\lambda_m$ (mμ) | Oxime $\epsilon_m$ | *p*-Nitrophenylhydrazone $\lambda_m$ (mμ) | *p*-Nitrophenylhydrazone $\epsilon_m$ | Ethylenediamine $\lambda_m$ (mμ) | Ethylenediamine $\epsilon_m$ |
|---|---|---|---|---|---|---|
| Benzal | 252 | 14,300 | 407 | 34,200 | 247[1] | 29,000[1] |
| Mesitylal | 252 | 9,400 | 411 | 31,700 | 264 | 8,100 |
| Difference | 0 | 4,900 | 4 | 2,500 | 17 | 20,900 |

From these results, it is observed that there are no significant differences between the wave lengths of maximum absorption of the two oximes or of the two *p*-nitrophenylhydrazones. In going from dibenzalethylenediamine to dimesitylalethylenediamine there is a bathochromic effect. This, perhaps, is due to the hyperconjugation of the methyl groups becoming more prominent since the chromophoric system is double. Actually upon constructing the Fisher–Hirschfelder models of these three classes of compounds there appears to be only a small steric hindrance between the mesityl methyl groups and the group X.[2]

It has been observed before[3] that small steric hindrances have little effect upon $\lambda_{max.}$ but do decrease $\epsilon_{max.}$. This is illustrated in the present case by the oximes and the ethylenediamines. It is noted that this effect is very small in the case of the nitrophenylhydrazones; however, this is understandable. The nitrophenylhydrazones have absorption bands near 400 mu[4] without the aid of the phenyl or mesityl groups at the other end of the molecule, and consequently steric hindrance does not affect appreciably the molecular extinction.

The only explanation offered at this time for the trend in the differences of $\lambda_{max.}$ is to say that forms such as



contribute to the resonances of benzaldoxime and benzal-*p*-nitrophenylhydrazone. Such forms would be opposed by the hyperconjugation of the methyl groups in the mesityl nucleus. It may be that the two effects just cancel one another in the mesitylaldoxime, that the hyperconjugation is slightly more effective than the opposing resonance in the mesitylal-*p*-nitrophenylhydrazone and that in the ethylenediamine compounds, where the corresponding resonant forms cannot exist and the chromophoric system is double, the hyperconjugation causes a much larger bathochromic effect.

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Received October 9, 1948

(1) Taken from Ferguson and Branch, This Journal, **66**, 1467 (1944).

(2) O'Shaughnessy and Rodebush found the steric interference between the *ortho* methyl groups and the carbonyl oxygen of 2,4,6-trimethylacetophenone to be hardly strong enough to prevent a coplanar configuration, *ibid.*, **62**, 2910 (1940).

(3) O'Shaughnessy and Rodebush, *ibid.*, **62**, 2910 (1940).

(4) Ferguson and Battle, Report presented before the Organic Division of the Washington Chemical Society, Oct., 1948, at Washington, D. C.

## Comparison of Age with the Relative Abundance of Argon and Potassium in Rocks

By R. L. Farrar, Jr., and George H. Cady

The study reported in this communication was done as a test of the proposal of Thompson and Rowlands[1] that the accumulation of argon resulting from decay by K electron capture of $K^{40}$ should serve as a measure of the age of rocks containing potassium. For this study solid rocks of known geologic age were kindly furnished by G. E. Goodspeed of our Department of Geology.

The analytical procedure involved the following steps: (1) A 60-g. sample of sodium carbonate was freed of argon by pumping away gas for three hours from the molten salt held in a stainless steel vessel at about 950°. (2) Argon and other gases were removed from the surface of a 10-g. sample of rock composed of pea-sized pieces by allowing the material to stand for about an hour at room temperature in a vacuum. (3) The rock was then dissolved in the sodium carbonate at 950 to 1000°. This process was allowed to continue for a twenty-four-hour period to secure complete liberation of rare gases. (4) He + Ne and A + Kr + Xe were determined in the gas, using methods previously described by Cady and Cady.[2] Since spectroscopic tests showed that not more than traces of Ne, Kr or Xe could have been present in each case, the results of the analyses are reported in the table as helium and argon, respectively. (5) Potassium was determined in the mass resulting from the sodium carbonate fusion.

Conclusions: (1) These analyses indicate no regular increase of the A/K ratio with age. (2) The range in argon content is much less than that of helium. (3) Most of the argon in at least the first two samples probably originated from a source, perhaps the atmosphere, other than the

(1) F. C. Thompson and S. Rowlands, *Nature*, **152**, 103 (1943).

(2) G. H. Cady and H. P. Cady, *Ind. Eng. Chem., Anal. Ed.*, **17**, 760 (1945).

TABLE I

COMPARISON OF AGE WITH THE RATIO A/K IN ROCKS

| Description of sample | Location from which obtained | He, cc./g. at S. T. P. | A, cc./g. at S. T. P. | K, % | G. ats. A / G. ats. K | Approximate age in millions of years |
|---|---|---|---|---|---|---|
| Quartz, Cornucopia formation | Cornucopia, N. E. Oregon | $0.022 \times 10^{-4}$ | $1.3 \times 10^{-4}$ | 0.027 | $8.4 \times 10^{-4}$ | 100 (Late Mesozoic) |
| Soda feldspar | Ohanepecosh Hot Springs, Washington | $0.062 \times 10^{-4}$ | $1.9 \times 10^{-4}$ | 0.43 | $7.7 \times 10^{-5}$ | 30 (Tertiary) |
| Potash feldspar, Cornucopia formation | Cornucopia, N. E. Oregon | $0.19 \times 10^{-4}$ | $3.25 \times 10^{-4}$ | 12.8 | $4.4 \times 10^{-6}$ | 100 (Late Mesozoic) |
| Bostonite | Marblehead, Massachusetts | $<0.005 \times 10^{-4}$ | $0.81 \times 10^{-4}$ | 2.08 | $6.8 \times 10^{-6}$ | 300 (Carboniferous) |
| Granite, Silver Plume Formation | Silver Plume, Colorado | $2.4 \times 10^{-4}$ | $1.4 \times 10^{-4}$ | 1.91 | $1.3 \times 10^{-5}$ | 940[3] |
| Granite | Sudbury, Ont. | $0.65 \times 10^{-4}$ | $4.5 \times 10^{-4}$ | 3.33 | $2.4 \times 10^{-5}$ | 700 (Keweenawan) |
| Granite gneiss | Sudbury, Ont. | $0.51 \times 10^{-4}$ | $5.2 \times 10^{-4}$ | 1.05 | $8.6 \times 10^{-5}$ | 1050 (Laurentian) |

decay of potassium-40 in the existing minerals. (4) A careful isotopic analysis would be required to establish the relative proportions of "atmospheric" argon and that formed by the decay of $K^{40}$ in the rock. (5) Without such an analysis, the ratio, A/K, appears not to be a good measure of the age of a rock.[4]

(3) Age by U, Th, Pb method: E. N. Goddard and J. J. Glass, *Am. Mineralogist*, **21**, 199 (1936).

(4) Aldrich and Nier (*Phys. Rev.*, **74**, 876 (1948)) have reported since the date of submission of this note, that the ratio $A^{40}/A^{36}$ is higher in potassium minerals than in air. Their analyses of four samples indicate an increase in the ratio Radio A/K with age.

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RECEIVED SEPTEMBER 22, 1948

[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

## Some New Polyhalogenated Phenyl Isocyanates

BY LOUIS W. GEORGES[2] AND CARL HAMALAINEN

Previously reported work on the reaction of organic isocyanates with cellulose has been concerned with (1) the preparation of new cellulose derivatives of possible utility in the plastics field, and (2) the production of a more or less superficial esterification of cotton textiles to impart new properties. Thus, cellulose carbamate and cellulose acetate carbamate,[3] soluble in common organic solvents, and chlorophenyl carbamate of methyl cellulose with as much as 12% chlorine have been obtained.[4] By the preparation of carbamates, cotton textiles have been rendered water repellent,[5] their dyeing characteristics have been modified,[6] and the softening point and solubility properties of cellulose acetate rayon have been altered.[7]

The object of the present study was to investigate the possibility of providing a fire-resistant cotton textile by chemical combination of a fire-retarding agent with the cellulose molecule yet preserving the fibrous character of the cotton. Halogen-containing organic compounds are either not combustible or, in general, burn with difficulty. It seemed likely that partial carbamylation of cellulose with a polyhalogenated phenyl isocyanate would introduce sufficient halogen (27–31%) in cellulose to achieve fire-proofness and still retain the fiber structure. Such partial carbamylations could be successfully effected in a manner similar to that described by Hearon, Hiatt and Fordyce[3c] in which phenyl isocyanate was used. A patent covering the fireproofing of lint cotton has been issued.[8]

It is believed that the polyhalogenated phenyl isocyanates used in the reaction with cotton in the manner described in the patent are new compounds. The preparation of these compounds is given in the experimental section below.

### Experimental

**2,5-Dichlorophenyl Isocyanate.**—Forty-five grams of 2,5-dichloroaniline hydrochloride was suspended in 500 ml. of chlorobenzene and phosgene[9] was passed through the suspension in a steady stream with stirring until complete solution of the hydrochloride was effected. During the

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Present address: Firestone Tire and Rubber Company, Akron, Ohio.

(3) (a) P. E. C. Goissedet, U. S. Patent 1,357,450 (November 2, 1920); (b) C. J. Malm and G. F. Nadeau, U. S. Patent 1,991,107 (February 12, 1935); (c) W. M. Hearon, G. D. Hiatt and C. R. Fordyce, THIS JOURNAL, **65**, 829 (1943); (d) W. M. Hearon and J. L. Lobsitz, *ibid.*, **70**, 296 (1948).

(4) E. Dyer and K. L. McCormick, *ibid.*, **68**, 986 (1946).

(5) (a) E. Schirm, U. S. Patent 2,303,364 (December 1, 1942); (b) W. Kaase, U. S. Patent 2,370,405 (February 27, 1945); (c) R. W. Maxwell, U. S. Patent 2,343,920 (March 14, 1944); (d) I. G. Farbenindustrie, A.-G., British Patent 461,179 (February 8, 1937); (e) British Patent 474,403 (November 1, 1937).

(6) P. S. Pinkney, U. S. Patent 2,350,188 (May 30, 1944).

(7) D. D. Coffman and J. S. Reese, British Patent 548,807 (December 25, 1942).

(8) L. W. Georges and C. Hamalainen, U. S. Patent 2,428,843 (October 14, 1947).

(9) (a) D. V. N. Hardy, *J. Chem. Soc.*, 2011 (1934); (b) J. Hilger, U. S. Patent 1,916,314 (July 4, 1933); (c) W. Hentrich and H. J. Engelbrecht, U. S. Patent 2,261,156 (November 4, 1941).

course of the reaction the temperature was raised gradually until there was a gentle refluxing of the solvent. After concentrating the clear chlorobenzene solution under reduced pressure the product was distilled and 26.3 g. (62%) of colorless 2,5-dichlorophenyl isocyanate was obtained; b. p. 83–84° at 3–4 mm. The isocyanate was identified by means of the crystalline di-(2,5-dichlorophenyl)-urea; m. p. 289° (cor.).

*Anal.* Calcd. for $(C_6H_3Cl_2)_2(NH)_2CO$: N, 8.0; Cl, 40.1. Found: N, 7.9; Cl, 40.0.

**2,4,6-Trichlorophenyl Isocyanate.**—Phosgene was passed through a suspension of 50 g. of 2,4,6-trichloraniline hydrochloride in 500 ml. of chlorobenzene. The temperature was raised gradually to the reflux point. The bulk of the suspended material dissolved. The small amount of crystalline compound that was separated by filtration proved to be the disubstituted urea derivative. The clear filtrate was concentrated under reduced pressure until free of chlorobenzene. The hot residue was transferred to a crystallizing dish and stored in a vacuum desiccator in which upon cooling the product crystallized. The yield of crude 2,4,6-trichlorophenyl isocyanate was 29.2 g. (61%). Pure material was obtained on recrystallization from petroleum ether; m. p. 64–65°.

*Anal.* Calcd. for $C_6H_2Cl_3NCO$: N, 6.3; Cl, 47.9. Found: N, 5.9; Cl, 47.3.

The crystalline di-(2,4,6-trichlorophenyl)-urea was prepared; m. p. 295° (cor.).

**2,4,6-Tribromophenyl Isocyanate.**—Dry hydrogen chloride was passed into a solution of 107 g. of 2,4,6-tribromoaniline in 500 ml. of chlorobenzene until a voluminous precipitate of the hydrochloride was formed. Phosgene was then passed into the reaction mixture in a steady stream with continuous stirring until solution of the 2,4,6-tribromoaniline hydrochloride was effected. The reaction mixture was heated gradually during the course of the reaction to the reflux temperature of the solvent. An appreciable amount of the crystalline disubstituted urea was formed and this product was separated by filtration. The clear filtrate was concentrated under reduced pressure until free of solvent and the hot liquid residue transferred to a crystallizing dish. After cooling in a vacuum desiccator a crystalline mass was obtained. The yield of crude 2,4,6-tribromophenyl isocyanate was 44.6 g. (39%). Pure material was obtained on recrystallization from petroleum ether; m. p. 92–94°.

*Anal.* Calcd. for $C_6H_2Br_3NCO$: N, 3.9; Br, 67.5. Found: N, 3.9; Br, 66.8.

The addition of water to a pyridine solution of the isocyanate yielded the di-(2,4,6-tribromophenyl)-urea; m. p. 323° (cor.).

**Acknowledgment.**—We are indebted to Miss Alva Faust and Mr. Richard H. Robinson for the chemical analyses, and to Mr. Frank C. Magne for the melting point determinations.

SOUTHERN REGIONAL RESEARCH LABORATORY
NEW ORLEANS, LOUISIANA RECEIVED AUGUST 30, 1948

## The Chloromethylation of Veratrole[1]

BY OSCAR GAWRON

In connection with a synthesis of a compound of pharmaceutical interest, a large supply of 4-chloromethyl-veratrole was needed. Recourse to the literature showed several unsuccessful attempts[2,3] at chloromethylation of veratrole by the usual procedures and a successful attempt[4] by a two phase chloromethylation. The unsuccessful attempts yielded 2,3,6,7-tetramethoxy-9,10-dihydroanthracene as a condensation product.[3,4]

The successful Bide and Wilkinson[4] procedure was tried and found to give somewhat erratic results, probably due to the critical conditions involved, −2 to +2°, rate of stirring, and rate of passage of the hydrogen chloride. In addition, temperature control of large scale laboratory preparations was difficult, although this was partially solved by the direct addition of dry ice to the reaction mixture from time to time.

Since the above procedure did not prove entirely satisfactory, several chloromethylation experiments were run with chloromethyl ether in glacial acetic acid. These were found to be satisfactory. The conditions used were essentially those employed by Vavon, Bolle and Calin[5] in their study of the influence of substituents on rates of chloromethylation of aromatic compounds.

The procedure finally adopted was as follows: In a one-liter, three-necked, round-bottom flask, equipped with a thermometer, a mercury seal stirrer, and a calcium chloride tube, were placed 282 g. of glacial acetic acid, 247 g. of veratrole (1.8 moles) and 288 g. of chloromethyl ether (3.6 moles). The stirrer was started and the initial temperature was noted. If below 20°, the reaction mixture was gently warmed to 20 to 21°. The reaction was then allowed to proceed for seven hours. In four to six hours the temperature rose to 30° and subsequently the reaction mixture was kept below 30° by means of a cold water-bath. The reaction, which had proceeded to almost 50% completion (analytical method of Vavon, Bolle and Calin[5]) at the end of seven hours was then stopped by pouring with stirring, onto 800 g. of cracked ice and 400 ml. of chloroform. Stirring was continued until most of the ice had melted. The chloroform layer was then separated and the water layer extracted twice with 100-ml. portions of chloroform. The combined chloroform extracts were washed once with 50 ml. of water and then dried over anhydrous sodium sulfate. The chloroform was removed *in vacuo* and the residue distilled at less than 1 mm. The fore run was unchanged veratrole and then the 4-chloromethylveratrole distilled at 100–103°. It crystallized on cooling the receiver; m. p. 48–50°; yield, 62 g. (54%), based on recovered veratrole.

Further preparatory studies and kinetic studies on the mechanism of the general chloromethylation reaction are in progress.

(1) Work done at the New York Quinine and Chemical Works, Inc., Brooklyn, N. Y.

(2) Carré and Liberman, *Compt. rend.*, **199**, 791 (1934).

(3) Fitscher and Bogert, *J. Org. Chem.*, **4**, 71 (1939).

(4) Bide and Wilkinson, *J. Chem. Soc.*, 84 (1945).

(5) Vavon, Bolle and Calin, *Bull. soc. chim.*, [5] **6**, 1025 (1939).

DUQUESNE UNIVERSITY
PITTSBURGH 19, PA. RECEIVED OCTOBER 11, 1948

## Substituted Quinolyl Dodecyl Sulfides

BY HENRY GILMAN AND SAMUEL P. MASSIE

The therapeutic activities of some quinoline ethers and the germicidal activities of some aryl sulfides[1] suggested the preparation of some quinoline sulfides for pharmacological testing. It was also considered desirable to incorporate a fat-soluble group into the molecule, so as to increase the possibility of absorption of the drug by the animal body. These considerations initiated the preparation of some high-molecular weight alkyl quinolyl sulfides for therapeutic investigation.

(1) Foss, Dunning and Jenkins, THIS JOURNAL, **56**, 1978 (1934).

TABLE I

QUINOLYL DODECYL SULFIDES

| Haloquinoline | Dodecyl sulfide | Yield, % | M. p., °C. | Color | Formula | S Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 5-Nitro-6-chloro- | 5-Nitro-6-quinolyl | 80 | 44–5° | Yellow | $C_{21}H_{30}O_2N_2S$ | 8.56 | 8.50 |
| 5-Nitro-6-chloro-8-acetamido- | 8-Amino-5-nitro-6-quinolyl | 93 | 89.5–90.5 | Orange | $C_{21}H_{31}O_2N_3S$ | 8.23 | 8.30 |
| 6-Methoxy-2-chloro-4-methyl- | 6-Methoxy-4-methyl-2-quinolyl | 70 | 71–72 | Cream | $C_{23}H_{35}ONS$ | 8.58 | 8.70 |
| 4,7-Dichloro- | 7-Chloro-4-quinolyl | 87 | 59–60 | White | $C_{22}H_{30}NSCl$ | 8.80 | 8.90 |

TABLE II

AMINOQUINOLYL DODECYL SULFIDES

| Nitro derivative | Amino derivative | Yield, % | M. p., °C. | Formula | S Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 5-Nitro-6-quinolyl | 5-Amino-6-quinolyl[a,b] | 76 | 59–60 | $C_{21}H_{32}N_2S$ | 9.30 | 9.02 |
| 8-Acetamido-5-nitro-6-quinolyl | 8-Acetamido-5-amino-6-quinolyl | 80 | 77–78 | $C_{23}H_{35}ON_3S$ | 7.98 | 6.97[c] |

TABLE III

ACETAMIDOQUINOLYL DODECYL SULFIDES

| Amine | Acetamide | M. p., °C. | Color | Formula | S Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|
| 5-Amino-6-quinolyl | 5-Acetamido-6-quinolyl | 121–122 | White | $C_{23}H_{34}ON_2S$ | 8.29 | 8.21 |
| 8-Amino-5-nitro-6-quinolyl | 8-Acetamido-5-nitro-6-quinolyl | 67–68 | Yellow | $C_{23}H_{33}O_3N_3S$ | 7.42 | 7.29 |
| 8-Acetamido-5-amino-6-quinolyl | 5,8-Diacetamido-6-quinolyl | 126–127 | Cream | $C_{25}H_{37}O_2N_3S$ | ..[d] | .. |

[a] This amine would not form a derivative with salicylaldehyde or acetonylacetone. [b] The dihydrochloride melted at 156–157°. Calcd. for $C_{21}H_{34}N_2Cl_2S$: S, 7.67. Found: S, 7.67. [c] This amine could not be purified, but the acetamido derivative gave the correct analysis. [d] Calcd. for $C_{25}H_{37}O_2N_3S$: N, 9.48. Found: N, 9.48.

A series of substituted quinolyl dodecyl sulfides was prepared from activated chloroquinolines and sodium dodecyl mercaptide in methyl cellosolve. The quinoline compounds used were 5-nitro-6-chloroquinoline,[2] 5-nitro-6-chloro-8-acetamidoquinoline,[3] 4,7-dichloroquinoline[4] and 6-methoxy-2-chlorolepidine.[5] The nitroquinolyl sulfides were then reduced to the amino derivatives and these, in turn, were acetylated to the acetamido derivatives.

These compounds were tested against tuberculosis; reports on their activities will be published elsewhere. The authors are grateful to Parke, Davis and Co. for arranging for the tests, and to William Meikle for assistance.

### Experimental

**Quinolyl Dodecyl Sulfides.**—The general method of preparation was to add a solution of sodium dodecyl mercaptide in methyl cellosolve to the chloroquinoline in hot methyl cellosolve.[6] The mixture was refluxed for an hour, cooled, poured into 200 ml. of water, acidified with acetic acid, filtered, and the precipitate recrystallized from methanol.

**Aminoquinolyl Dodecyl Sulfides.**—The nitroquinolyl dodecyl sulfides were reduced with hydrogen and Raney nickel in absolute ethanol. Recrystallization was not necessary. The amines were yellow solids.

**Acetamidoquinolyl Dodecyl Sulfides.**—The acetamido derivatives were prepared by heating the amine and acetic anhydride in glacial acetic acid. The mixture was poured into water, filtered and recrystallized from absolute ethanol.

The results are given in Tables I, II and III.

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IOWA STATE COLLEGE
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RECEIVED OCTOBER 11, 1948

(2) Kindly furnished by Mrs. Martha Mackin.

(3) Gilman and co-workers, THIS JOURNAL, **68**, 1577 (1946).

(4) Surrey and Hammer, *ibid.*, **68**, 115 (1946).

(5) Prepared by directions of Dr. K. N. Campbell, The University of Notre Dame, South Bend, Indiana.

(6) 5-Nitro-6-chloroquinoline yielded only a small amount of the sulfide by this procedure. It was found desirable to stir the solution of the reactants at room temperature for two hours or more before heating.

## A New Synthesis of 2,4-Dihydroxyquinoline

BY E. H. HUNTRESS AND J. BORNSTEIN

A recent review[1] of 4-hydroxyquinolines prompts us to report a synthesis of 2,4-dihydroxyquinoline from isatin, giving better results by simpler procedure than prior methods.

The most widely used method for the preparation of 2,4-dihydroxyquinoline has been the treatment of the esters of N-acetylanthranilic acid with sodium metal in toluene or xylene.[2,3,4] Although Camps[2] reported 60% crude yield, subsequent investigators[2,3,4] (including ourselves) have been unable to obtain more than 28–40%.

Reaction of isatin with chloroacetyl chloride gave N-(chloroacetyl)-isatin which on refluxing with aqueous potassium hydroxide, followed by acidification of the reaction mixture with hydrochloric acid, precipitated 2,4-dihydroxyquinoline with the simultaneous evolution of carbon dioxide.

### Experimental

**N-(Chloroacetyl)-isatin.**—Isatin (10 g., 0.068 mole) was vigorously refluxed with chloroacetyl chloride (70 ml., 100 g., 0.89 mole) for five hours. The dark brown reaction mixture was cooled for two hours in an ice-bath

(1) Reitsema, *Chem. Revs.*, **43**, 43 (1948).

(2) Camps, *Arch. Pharm.*, **237**, 689–691 (1899).

(3) Ashley, Perkin and Robinson, *J. Chem. Soc.*, 388 (1930).

(4) Brooker and Smith, THIS JOURNAL, **59**, 72 (1937).

and the precipitate filtered. The filtrate was saved and the solid washed twice with 20 ml. portions of ether and air-dried. The N-(chloroacetyl)-isatin (10.0 g., 66%) consisted of fine-golden-yellow needles, m. p. 210–211° cor., suitable for use without additional purification. The reaction filtrate was replenished with fresh chloroacetyl chloride (10 ml.) and the run repeated with additional isatin (10 g.) giving more equally pure product (12.0 g., 78%). For analysis the N-(chloroacetyl)-isatin was recrystallized from ethyl acetate.

*Anal.* Calcd. for $C_{10}H_6O_3NCl$: C, 53.71; H, 2.71; N, 6.26; Cl, 15.85. Found: C, 53.32; H, 2.91; N, 6.41; Cl, 15.79.

On recrystallization from methanol the yellow N-(chloroacetyl)-isatin separated with one mole of solvent as fine, *colorless* needles, m. p. 83.0–83.5° cor.

*Anal.* Calcd. for $C_{11}H_{10}O_4NCl$: C, 51.68; H, 3.95; N, 5.48; Cl, 13.88. Found: C, 51.52; H, 4.09; N, 5.46; Cl, 14.02.

**2,4-Dihydroxyquinoline.**—Into 150 ml. of an aqueous boiling solution of potassium hydroxide (5.0 g., 0.09 mole) was added all at once 5.0 g. (0.022 mole) of yellow N-(chloroacetyl)-isatin. The straw-colored solution was refluxed for two hours and then cooled to room temperature. On acidification of the reaction mixture with concentrated hydrochloric acid a cream-colored solid separated which was filtered and washed three times with 10-ml. portions of cold water. The crude yield was 2.0–2.5 g., 56–70%. From the filtrate small amounts of isatin were isolated. The 2,4-dihydroxyquinoline was purified by dissolving in the minimum amount of 10% sodium carbonate solution, filtering, boiling the filtrate with Darco for five minutes, filtering, and then reacidifying. On recrystallizing from methanol the compound separated as fine, colorless needles; m. p. 352–354° cor., recorded m. p. 355°.[5]

*Anal.* Calcd. for $C_9H_7O_2N$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.21; H, 4.63; N, 8.65.

The identity of the 2,4-dihydroxyquinoline was confirmed by means of its nitroso derivative, m. p. 208° dec., uncor. (recorded 208°[6]), which melted at the same temperature when mixed with an authentic sample. In addition, the (mono) acetyl derivative was prepared; m. p. 215.0–215.5° uncor. (recorded 214–215°[3]), mixed melting point with authentic sample was 215.0–215.5° uncor.

(5) Niementowski, *Ber.*, **40**, 4289 (1907).

(6) Baeyer and Homolka, *ibid.*, **16**, 2216 (1883); *cf.* Meyer, Heimann, *Compt. rend.*, **203**, 335–337 (1936).

DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACHUSETTS

RECEIVED NOVEMBER 3, 1948

## The Synthesis of Boron Trichloride

BY DALLAS T. HURD

A well known and convenient method for preparing small amounts of boron trichloride or boron tribromide comprises passing boron trifluoride gas over aluminum chloride or aluminum bromide.[1] I recently have found that a reaction may occur at elevated temperatures between aluminum chloride and boric oxide to produce boron trichloride.

**Experimental.**—120 grams of anhydrous boric acid and 440 g. of aluminum chloride were ground together and placed in a steel pressure vessel. The reaction mixture was heated at 350° for sixteen hours. The bomb then was cooled and the gaseous reaction product was bled off and caught in a trap held at −80°. The collected product was a clear colorless liquid boiling at 12° (reported boiling point of boron trichloride +12.5°). This material fumed in moist air, reacting with the moisture to produce white solid boric acid. A small amount of the liquid was dissolved in water to give a solution which, when tested with silver nitrate, gave a strong test for chloride.

The total amount of product collected was 30 g. or about 7.5% yield based on a complete conversion of boric oxide to boron trichloride.

It also was observed that a molten mixture of boric oxide and calcium chloride at 800–900° evolved boron trichloride very slowly and became more viscous, precipitating an infusible residue in the magma. This solid residue was treated with water after it was cool and a strongly alkaline solution resulted, indicating a conversion of some of the calcium chloride to calcium oxide.

**Discussion.**—The low yields of boron trichloride are ascribed to: (1) the reaction between aluminum chloride and boric oxide to form aluminum oxide and boron trichloride may be an equilibrium reaction which did not go to completion in the sealed bomb; and/or (2) part of the boric oxide may become bound chemically as aluminum borate by reaction with the aluminum oxide as this material is formed. It is noteworthy that attempts to prepare boron trichloride by a reaction of sodium borate or tetraborate with aluminum chloride were unsuccessful at reaction temperatures up to 350°.

(1) Gamble, Gilmont and Stiff, THIS JOURNAL, **62**, 1257 (1940).

GENERAL ELECTRIC RESEARCH LABORATORY
SCHENECTADY, N. Y. RECEIVED OCTOBER 25, 1948

## Reactions of Polyhaloparaffins with Grignard Reagents. 1,1,1-Trichloropentane

BY CORLISS R. KINNEY AND WILLIAM L. SPLIETHOFF

Binaghi[1] has shown that chloroform and carbon tetrachloride react readily with ethylmagnesium bromide, but that gaseous reduction products are formed for the most part. We have reëxamined the reaction from the point of view of controlling its course for the production of tri- and tetrasubstituted paraffins. However, even at −78°, using the less reactive *n*-butylmagnesium chloride, and carrying the halide into the reaction flask vaporized in a stream of dry nitrogen, a vigorous reaction occurs and the products are largely gaseous.

On the other hand, the reaction may be controlled to a certain extent by using the inverse Grignard technique. Thus, adding *n*-butylmagnesium chloride to a solution of carbon tetrachloride in ether gives a small yield of the first step in the reaction, 1,1,1-trichloropentane. The new compound loses hydrogen chloride at about 140° but could be vacuum distilled without decomposition. This thermal instability further indicates activity of the vicinal chlorine atoms. No attempt was made to treat this compound with additional Grignard reagent, but instead the more available 1,1,1-trichloroethane was investigated. This compound, like chloroform, gave largely

(1) Binaghi, *Gazz. chim. ital.*, **52**, II, 132–138 (1922); **53**, 879 (1923).

gaseous products and the reaction appeared to be unsuited as a synthetic method. To complete the series, methylene chloride also was tried but did not react at the boiling point of ether. These results indicate a marked difference in the reactivity of vicinal chlorides at the trichloro level. This is of interest in connection with the behavior of chloral for which only reduction at the carbonyl group with aliphatic Grignard reagents containing β-hydrogen atoms has been reported[2] and the behavior of monochloroacetone which was found to react with isoamylmagnesium bromide at the chlorine atom as well as adding on the reagent at the carbonyl group.[3]

Considering the violence of the reaction of carbon tetrachloride, even at −78°, carbon tetrafluoride was also treated with *n*-butylmagnesium chloride at the boiling point of ether. However, no reaction was observed.

### Experimental

**1,1,1-Trichloropentane.**—*n*-Butylmagnesium chloride was prepared from one mole of *n*-butyl chloride, one gram atom of magnesium and 300 ml. of dry ether. The solution was forced by means of dry nitrogen under pressure, into a stirred mixture of 2 moles of carbon tetrachloride and 300 ml. of dry ether cooled in a bath of Dry Ice and acetone. A vigorous reaction occurred with the formation of a white precipitate and a gas which decolorized bromine in carbon tetrachloride. White fumes were also formed which settled on the walls of the flask as a white solid. Since this was very soluble in water it was concluded that it was magnesium chloride. After the reagent had been added the cooling bath was removed and the mixture allowed to come to room temperature and stand for two hours. It was then refluxed gently for forty-five minutes and after cooling was decomposed with ice-water. Some basic magnesium precipitate was filtered out with suction and the organic layer separated, dried with calcium chloride and distilled to 100° to remove ether and excess carbon tetrachloride. The residue weighed about 30 g. and constituted a crude yield of 16.5%. On continuing the distillation, hydrogen chloride was evolved copiously at about 140°; consequently, the residue was vacuum distilled. Refractionation at 20 mm. through a 10-plate column packed with glass helices gave a heart-cut boiling at 56–57°. The index of refraction was $n^{20}D$ 1.4540.

*Anal.* Calcd. for $C_5H_9Cl_3$: Cl, 60.5. Found: Cl, 60.2, 60.1.

**Acknowledgments**—The authors are indebted to Mr. H. L. Lovell for the analysis reported above and to the Fluorine Laboratories of The Pennsylvania State College for the sample of carbon tetrafluoride used.

(2) Gilman and Abbott, *J. Org. Chem.*, **8**, 224 (1945); Floutz, THIS JOURNAL, **67**, 1615 (1945).

(3) Kinney and Spliethoff, to be published in the *Journal of Organic Chemistry*.

DIVISION OF FUEL TECHNOLOGY
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RECEIVED OCTOBER 4, 1948

## Decomposition of Aliphatic Azo Compounds

BY FREDERICK M. LEWIS AND MAX S. MATHESON

Certain aliphatic azo compounds have several properties which make them especially suitable as sources of free radicals for kinetic investigations. These properties include stability, clean first order decompositions nearly independent of reaction media, and the ability to act as efficient photosensitizers in the near ultraviolet.

The decomposition rates (Table I) as measured by nitrogen evolution, were in all cases first order after a short induction period, probably due to a thermal adjustment after sample addition and to the disappearance of oxygen traces introduced with the sample. Thiele and Heuser[1] and Dox[2] have described the method of preparation of these compounds. Further, it has been shown that 2-azo-bis-isobutyronitrile heated at 110° in high boiling petroleum ether quantitatively splits out nitrogen, tetramethyl succinonitrile being formed in 50% yield.[1] Of course such fragments of the azo compound as initiate polymerization in the presence of monomer will not appear as tetramethyl succinonitrile.

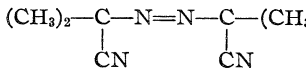
TABLE I

DECOMPOSITION OF AZO COMPOUNDS IN XYLENE AT 80°

| Material, 0.1–0.3 mole/l. | *k*, min.$^{-1}$ | *Ea*, kcal. |
|---|---|---|
| 2-Azo-bis-isobutyronitrile | 0.0092 | 31.3 |
| 2-Azo-bis-2-methylbutyronitrile | .00598 | 29.4 |
| 2-Azo-bis-2-methylheptonitrile | .0107 | 30.2 |
| 1-Azo-bis-1-cyclohexanecarbonitrile | .000282 | 39.9 |
| Dimethyl-2-azo-bis-isobutyrate | .00653 | 35.8 |
| 4-Azo-bis-4-cyanopentanoic acid | .00538[a] | 34.0 |

[a] In water, insoluble in xylene.

Table II shows that there is little change in rate for 2-azo-bis-isobutyronitrile (sold as Porofor N by Naugatuck Chemical Division of U. S. Rubber Co.) with widely different reaction solvents, and



even a powerful inhibitor (tetrachloroquinone) has little effect. Accordingly these materials offer several advantages over peroxides as free radical sources when a constant rate of production of radicals is desired. (As an example of free radical activity 0.096 g./l. of Porofor N in purified vinyl acetate induces 4.7% polymerization per hour at 50°.) Several authors[3] have shown that

TABLE II

SOLVENT EFFECT IN THE DECOMPOSITION OF 2-AZO-BIS-ISOBUTYRONITRILE (~0.3 mole/l.) AT 80°

| Solvent | *k*, min.$^{-1}$ |
|---|---|
| Xylene | 0.0092 |
| Xylene contg. 0.012 mole/l. tetrachloroquinone | .00898 |
| Glacial acetic acid | .00914 |
| N-Dimethylaniline | .011 |
| Dodecyl mercaptan | .00875 |
| Carbon tetrachloride | .00725 (77°) |

(1) Thiele and Heuser, *Ann.*, **290**, 1 (1896).

(2) Dox, THIS JOURNAL, **47**, 1473 (1925).

(3) Nozaki and Bartlett, *ibid.*, **68**, 1686 (1946); Cass, *ibid.*, **68**, 1976 (1946).

the rate of decomposition of benzoyl peroxide varies widely with solvent and concentration.

These compounds are highly efficient photosensitizers as well as thermal initiators for free radical reactions. An absorption band has its peak at 3500 Å. (measurements on 2-azo-bis-isobutyronitrile) so that the compounds are especially suited for work using the 3660 Å. line of the mercury arc. Table III illustrates some results obtained in irradiations with Type A Hanovia mercury arc light filtered through Pyrex. Because of the characteristics of the absorption, the absorbed light is >80% 3660 Å. Slightly smaller values than those given in the Table have been found for 2-azo-bis-isobutyronitrile using monochromatic 3660 Å. radiation. The quantum yields show the aliphatic azo nitriles to be superior in efficiency to such a photosensitizer as biacetyl.[4] The first six compounds in the table vary little in efficiency in styrene, and the variations in vinyl acetate are probably less than shown, as it is believed the reactions with vinyl acetate overheated several degrees. These polymerizations were carried out *in vacuo* to eliminate the effects of oxygen. Light intensities were measured with the uranyl oxalate actinometer.

TABLE III

PHOTOPOLYMERIZATION WITH AZO SENSITIZERS AT 3660 Å.[a] AND 30°

| Sensitizer (~0.038 m./l.) | Quantum yield polymerization[b] Vinyl acetate | Styrene |
|---|---|---|
| 2-Azo-bis-isobutyronitrile | 360 | 55 |
| 2-Azo-bis-propionitrile (unstable) | ... | 50 |
| Dimethyl-2-azo-bis-isobutyrate | >600 | 50 |
| 1-Azo-bis-1-cyclohexanecarbonitrile | 600 | 50 |
| 2-Azo-bis-2-methylheptonitrile | 230 | 55 |
| 2-Azo-bis-2-methylbutyronitrile | 255 | 60 |
| 4-Azo-bis-4-cyanopentanoic acid | 284 | ... |
| 2-Azo-bis-propane[c] | 80 | 2.80 |
| Biacetyl | 10.3 | 1.4[d] |

[a] λ>3000 Å. but largely 3660 Å. absorbed so quantum yield calculated on basis of 3660 radiation absorbed. [b] Molecules monomer polymerized per quantum of 3660 Å. radiation absorbed by sensitizer. Quantum yield cor. to $3.94 \times 10^{-5}$ einstein/hr./cc. ~50% of 3660 Å. light absorbed in 1 cm. with sensitizer concentrations used. [c] This azo compound does not initiate polymerizations at room temperature in the absence of light. [d] With monochromatic 3660 Å.

(4) C. L. Agre (U. S. Patent 2,367,660, Jan. 23, 1945, to du Pont.)

CONTRIBUTION 80 FROM THE
UNITED STATES RUBBER CO.
PASSAIC, NEW JERSEY

RECEIVED OCTOBER 11, 1948

## Reaction of Hydrogen Bromide with Di-*t*-butyl Peroxide

BY NICHOLAS A. MILAS AND CHARLES N. WINNICK[1]

Vaughan and Rust[2] claimed the preparation of di-*t*-butyl peroxide by the vapor oxidation of isobutane in the presence of hydrogen bromide. More recently Raley, Rust and Vaughan[3] reported that hydrogen chloride sensitizes the vapor phase decomposition of di-*t*-butyl peroxide, but that under comparable conditions hydrogen bromide has little effect on this decomposition. However, the behavior of hydrogen bromide with liquid di-*t*-butyl peroxide is different. We have found recently that at 0° it reacts rapidly and exothermically with di-*t*-butyl peroxide in accordance with the equations

$$(CH_3)_3COOC(CH_3)_3 + 4HBr \longrightarrow 2(CH_3)_3CBr + Br_2 + 2H_2O \quad (1)$$

$$(CH_3)_3CBr + Br_2 \text{ (peroxide)} \longrightarrow (CH_3)_2CBrCH_2Br + HBr \quad (2)$$

The validity of the second reaction was determined experimentally by allowing *t*-butyl bromide to react with bromine in the presence of di-*t*-butyl peroxide as a catalyst. A yield of 64% of isobutylene dibromide was obtained.

### Experimental

**Reaction of Di-*t*-butyl Peroxide with Hydrogen Bromide.**—A sample (16.4 g., 0.181 mole) of di-*t*-butyl peroxide prepared and purified according to directions given elsewhere[4] was cooled to 0° and a slow stream of hydrogen bromide (Dow Chemical Co.) from a tank was allowed to come in contact with the peroxide. The reaction, which was immediate and exothermic, was continued for three hours, the temperature being kept as close to 0° as possible. At the end of this period the mixture separated into two distinct layers which were separated and weighed. The bromine was estimated in each layer iodimetrically and the hydrogen bromide plus bromine by titration against standard alkali. The water in the aqueous layer was estimated by difference. The remainder of the non-aqueous layer was washed with concentrated sodium bisulfite solution, dried over anhydrous magnesium sulfate, then fractionated. A fraction (24 g.) boiling at 72–73° was collected; $n^{25}D$ 1.426. This was identified as *t*-butyl bromide. Another fraction (21.4 g.) was collected at 143–145° which was refractionated through a six-plate Podbielniak column; b. p. 145–148°; $n^{25}D$ 1.5050; $d^{25}_{25}$ 1.7426. From the analysis and physical constants, this fraction was identified as isobutylene dibromide. *Anal.* Calcd. for $C_4H_8Br_2$: C, 22.22; H, 3.70; Br, 74.07. Found: C, 22.44; H, 3.87; Br, 74.62. In addition to the two bromides, a black residue remained in the distillation flask.

From 26.4 g. (0.181 mole) of di-*t*-butyl peroxide and excess hydrogen bromide, we obtained 0.1685 mole (92.2%) of bromine (free 0.0695 mole; reacted, 0.099 mole), 0.35 mole of water (96.6%), and 0.274 mole of *t*-butyl bromide (0.175 mole) plus isobutylene dibromide (0.099 mole).

**Catalyzed Bromination of *t*-Butyl Bromide.**—A mixture of 50 g. of *t*-butyl bromide and 5 g. of di-*t*-butyl peroxide was cooled to 0° and to it was added slowly with frequent shaking 58 g. of liquid bromine. No apparent reaction was noticed during the first few minutes of bromine addition, then a vigorous reaction set in with copious evolution of hydrogen bromide. The reaction mixture was allowed to stand overnight at 0°, then shaken with anhydrous potassium carbonate and distilled. Only 7 g. distilled below 90°, 76 g. between 90–160° and a small tarry residue remained in the distilling flask. The main product was fractionated and the fraction (51 g., 64%) boiling at 148–151° collected and identified as isobutylene dibromide; $n^{26}D$ 1.5075.

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RECEIVED SEPTEMBER 14, 1948

(1) Research Assistant under a special grant from the Union Bay State Chemical Company; present address, Department of Chemistry, University of Illinois.

(2) Vaughan and Rust, U. S. Patent 2,403,771, July 9 (1946).

(3) Raley, Rust and Vaughan, THIS JOURNAL, **70**, 2767 (1948).

(4) Milas and Surgenor, *ibid.*, **68**, 205 (1946).

## Base Strength of Urea and Thiourea in Methanol

BY RALPH G. PEARSON AND JAMES TUCKER

In some work with solutions containing thiourea and strong acids dissolved in methanol it became apparent that salt formation was appreciable even though thiourea is generally considered too weak a base to form salts stable in solution. The explanation lies in the inherent weak basicity of methanol which causes other bases to appear abnormally strong in this solvent.[1]

The hydrolysis constants for thiourea and urea in dry methanol were determined by a conductimetric method essentially the same as that used by Goldschmidt and Dahlls[1a] to find the base strength of water in methanol. β-Naphthalenesulfonic acid was recrystallized from water and dried to the composition of the monohydrate in a vacuum oven at 60°. Methanol was dried by the use of magnesium turnings.[2] C. P. thiourea and urea were used.

Resistances were measured at 25.0 ± 0.03° on a Jones bridge of solutions containing a fixed amount of acid and varying amounts of base. If $R_0$ is the resistance of the solution containing only acid and $R$ the resistance of a solution with added base, then $R/(R - R_0)$ plotted against the reciprocal of the base concentration[3] gave straight lines which could be extrapolated to infinite base concentration. From this a value of $R_\infty$ could be found corresponding to the resistance of a solution completely converted to the salt of the base. From $R_0$, $R_\infty$ and $R$ the fraction of acid converted to salt could be found for each solution and the concentration equilibrium constant, $K_h$, for the reaction could be determined.

$$BH^+ + CH_3OH \rightleftharpoons B + CH_3OH_2^+ \qquad (1)$$

Table I shows the experimental results, the calculated values of $R_\infty$ and the average value of $K_h$ for each base. The effect of urea and thiourea on the resistances of methanolic solutions of lithium acetate and potassium chloride was checked and found to be negligible except for the more concentrated urea solutions. Assuming the effect here to be due to viscosity, an equivalent correction was made on the measured conductances of the acid solutions before any calculations were made.

TABLE I

THIOUREA

| Thiourea, molar | Resistance, ohms |
|---|---|
| 0.00556 *M* β-Naphthalene Sulfonic Acid | |
| 0.0000 | 3111[a] |
| .0314 | 3709 |
| .0628 | 4164 |
| .1257 | 4643 |
| .2514 | 5103 |
| ∞ | 5942 |

$K_h = 5.46 \pm 0.1 \times 10^{-2}$

Urea, 0.00525 *M* Acid

| Urea, molar | Resistance, ohms |
|---|---|
| 0.00000 | 2764[a] |
| .00271 | 3552 |
| .00525 | 4370 |
| .01080 | 5108 |
| .0314 | 5331[b] |
| .0627 | 5447[b] |
| ∞ | 5447 |

$K_h = 4.37 \pm 0.2 \times 10^{-4}$

0.00592 *M* Potassium Chloride

| | |
|---|---|
| 0.0000 | 3974 |
| .0314 | 3986 |
| .0627 | 4002 |

[a] Different conductivity cells were used. [b] Not corrected for viscosity.

The basic ionization constant can be obtained by dividing the hydrolysis constant into the ion product for methanol, $2.0 \times 10^{-17}$ at 25°.[1b] The corresponding hydrolysis constants in water are 9.0 for thiourea and 0.67 for urea.[4] The stability of the salts is thus increased several hundred-fold in methanol.

(1) (a) Goldschmidt and Dahlls, *Z. physik. Chem.*, **108**, 121 (1924); (b) Unmack, *ibid.*, **133**, 45 (1928).

(2) Lund and Bjerrum, *Ber.*, **64B**, 210 (1931).

(3) The concentration of free base must be used, correcting for that used up in salt formation. Successive approximations as to the magnitude of $K_h$ are needed to bring the solutions of low base concentration into line.

(4) Walker, *J. Chem. Soc.*, **67**, 576 (1895).

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RECEIVED SEPTEMBER 9, 1948

## Isomerization of Saturated Hydrocarbons. VI.[1] Effect of Benzene upon the Isomerization of Methylcyclopentane

BY HERMAN PINES, EUGENE ARISTOFF[2] AND V. N. IPATIEFF

The study of the isomerization of *n*-butane[3] and cyclohexane and methylcyclopentane[1] in the presence of aluminum bromide–hydrogen bromide catalyst using a high vacuum technique and highly purified materials has been reported recently. This work has shown that under certain carefully controlled conditions the isomerization of saturated hydrocarbons does not proceed unless a small amount of an olefin or an alkyl or cycloalkyl halide is present.

In the study of isomerization of methylcyclopentane it was found that small amounts of impurities which are present commonly in this hydrocarbon, such as benzene, have a profound effect upon the rate of isomerization. By fractional distillation it is difficult to eliminate the last traces of benzene; this can, however, be accom-

(1) For paper V of this series see H. Pines, B. M. Abraham and V. N. Ipatieff, THIS JOURNAL, **70**, 1742 (1948).

(2) Universal Oil Products Company Research Fellow 1947–1948.

(3) H. Pines and R. C. Wackher, THIS JOURNAL, **68**, 585 (1946), **68**, 2518 (1946).

plished by passing methylcyclopentane over silica gel.[4]

The following table shows the inhibiting effect of benzene upon the isomerization of methylcyclopentane promoted by *s*-butyl bromide. The experiments were carried out by a general procedure described previously[3]; the reaction temperature was 25° and the duration of each experiment was two hours. On the average about 0.04 mole of methylcyclopentane was used in each experiment.

TABLE I

EFFECT OF BENZENE UPON THE ISOMERIZATION OF METHYLCYCLOPENTANE

| Expt. | Reagents used: moles per 100 moles of methylcyclopentane $AlBr_3$ | HBr | *s*-$C_4H_9Br$ | Benzene | Cyclohexane formed, mole % |
|---|---|---|---|---|---|
| 1 | 2 | 1.0 | 0.0 | 0.000 | 0 |
| 2 | 2 | 0.9 | .1 | .000 | 51 |
| 3 | 2 | .9 | .1 | .022 | 22 |
| 4 | 2 | .9 | .1 | .072 | 5 |
| 5 | 2 | .9 | .1 | .140 | 3 |
| 6 | 2 | 1.0 | .0 | .140 | 0 |

The concentration of benzene in methylcyclopentane was determined by ultraviolet analysis. Experiment 4 was made by the addition of benzene to a purified sample of methylcyclopentane.

The inhibiting effect of benzene upon the isomerization, which was also observed to occur in the case of *n*-pentane,[5] is probably due to the ease with which the benzene reacts with the chain initiator. The ultraviolet absorption spectra taken of the hydrocarbons obtained from experiment 5 after removal of the catalyst by washing show that probably a mono-alkylbenzene was formed during the reaction. The absorption spectrum of the methylcyclopentane containing 0.14% of benzene and that of the reaction product was taken. The spectrum of the product showed a slight peak at 258.5 mμ where *s*-butylbenzene has a strong absorption band.

In expt. 3 the benzene caused only a partial inhibition of isomerization. This is not surprising since the molal ratio of *s*-butyl bromide to benzene used was over four, and the alkylation usually does not proceed beyond the formation of a tributylbenzene. There was therefore still some *s*-butyl bromide left to act as a chain initiator.

It was also noticed that in the experiments 3, 4, and 5 where benzene and *s*-butyl bromide were used an oily-yellow layer deposited on the walls of the reaction tube; in all the other experiments the product was homogeneous and free of color.[6] It is probable that the alkylbenzenes or cycloalkylbenzenes produced in the reaction formed a complex with the aluminum bromide and hydrogen bromide, similar to the type reported by Norris and Rubinstein.[7]

The inhibition of the isomerization of methylcyclopentane by benzene is in accordance with the proposed chain mechanism of isomerization.[1,8]

In the presence of benzene the chain may break by the reaction

$$[R^+AlBr_4^-] + \bigcirc \longrightarrow \bigcirc\!\!-R + AlBr_3 + HBr$$

$R^+$ may correspond to the carbonium ion obtained from the original olefin or from the product resulting from an exchange reaction between methylcyclopentane or cyclohexane formed and the *s*-butylcarbonium ion.

(4) B. J. Mair and A. F. Forziati, *J. Research Natl. Bur. Standards*, **32**, 151, 165 (1944).

(5) J. M. Mavity, H. Pines, R. C. Wackher, and J. A. Brooks, *Ind. Eng. Chem.*, **40**, 2374 (1948).

(6) In the last paper of this series[1] it was reported that the isomerization of methylcyclopentane to cyclohexane was usually accompanied by the formation of an oily layer even though the methylcyclopentane used did not contain any traces of benzene. It was observed now that when methylcyclopentane is further purified by passing it over silica gel certain impurities not detectable by spectrographic analysis and responsible for the formation of an oily layer are removed.

(7) J. F. Norris and D. Rubinstein, THIS JOURNAL, **61**, 1163 (1939).

(8) H. S. Bloch, H. Pines and L. Schmerling, *ibid.*, **68**, 153 (1946).

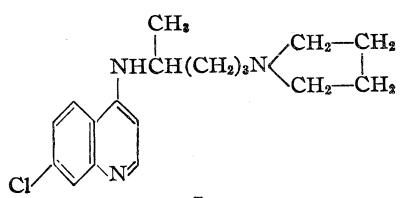
THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS

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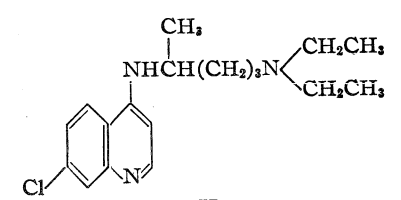
## Synthesis of 7-Chloro-4-[1-methyl-(1-pyrrolidyl)-butylamino]-quinoline

BY ROBERT H. REITSEMA AND JAMES H. HUNTER

Studies on the effects resulting from an exchange of a pyrrolidyl group for a dialkylamino substituent in various chemotherapeutic agents[1] has now been extended briefly into the field of antimalarials. The synthesis of 7-chloro-4-[1-methyl-4-(1-pyrrolidyl)-butylamino]-quinoline (I), the pyrrolidyl analog of Chloroquine (II) was undertaken in consequence of the utility reported[2] for the latter in the control of malaria.



I



II

(1) (a) Wright, Kolloff and Hunter, THIS JOURNAL, **70**, 3098 (1948); (b) Reid, Wright, Kolloff and Hunter, *ibid.*, **70**, 3100 (1948); (c) Reitsema and Hunter, *ibid.*, in press.

(2) Wiselogle, "A Survey of Antimalarial Drugs," Vol. I, J. W. Edwards, Ann Arbor, 1946, pp. 388-392.

Preparation of 5-(1-pyrrolidyl)-2-aminopentane (III) from ethyl acetoacetate and β-1-pyrrolidylethyl chloride[1a] was patterned after the synthesis used for noval diamine.[3] Alkylation of III with 4,7-dichloroquinoline occurred smoothly to give the desired aminoquinoline (I).

In suppressive tests on *p. gallinaceum* in the chick, the order of activity and toxicity of I was analogous to that of Chloroquine.[4]

### Experimental

**5-(1-Pyrrolidyl)-3-carbethoxypentanone-2.**—A solution of 400 g. (2.35 moles) of pyrrolidylethyl chloride hydrochloride in 200 ml. of water was treated with Nuchar C twice. The resulting light yellow solution was covered with 200 ml. of benzene, cooled to 5° and cold 50% potassium hydroxide was added with stirring and cooling below 12°. The upper organic layer was separated and the aqueous layer extracted twice with 100-ml. portions of benzene. Titration of a sample of the combined layers indicated 2.25 moles of base in solution or 96% of theory.

The sodium salt of 172 g. of acetoacetic ester in 1 l. of dry benzene was prepared with 26.0 g. of sodium sand. After addition of the ester was complete the mixture was boiled under reflux for one hour. One half of the above benzene solution of pyrrolidylethyl chloride was added dropwise. No reaction was apparent and the mixture was boiled under reflux for ten hours. After two hours nearly all the material was in solution.

**5-Pyrrolidylpentanone-2.**—To the above solution was added dilute sulfuric acid (from 160 ml. of water, 140 g. of ice, and 75 ml. of sulfuric acid). When about two-thirds of the acid had been added the solution was filtered and the layers separated. The remainder of the acid was used to dissolve the solid on the filter and to wash the benzene layer. The combined aqueous layers were washed with 100 ml. of benzene. The benzene was removed by distillation and the residual solution was boiled under reflux for seventeen hours. To the cooled solution was added 430 ml. of 30% sodium hydroxide with cooling and an organic layer of 184 g. was removed. The aqueous layer was extracted three times with 100-ml. portions of benzene. The dried organic layer was distilled to give 129 g. (74%) of material boiling at 92–98° (11–13 mm.). Redistillation of this gave a fraction which weighed 98.2 g.; b. p. 93–95° (11 mm.), $n^{20}D$ 1.4589.

*Anal.* Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 70.10; H, 11.07; N, 8.35.

**5-Pyrrolidyl-2-aminopentane.**—A solution of 88.1 g. (0.568 mole) of 5-pyrrolidylpentanone-2, in a mixed solvent consisting of 100 ml. of dry ammonia and 100 ml. of dry methanol was reduced in two portions in the presence of Raney nickel catalyst. Reduction was complete after one and one-third to two hours at 100°. After filtration and removal of solvent the residue was distilled to give 86.8 g. of 5-pyrrolidyl-2-aminopentane, b. p. 92–97° (11–12 mm.), $n^{20}D$ 1.4665. This was purified through the dithiocarbamate[5] to give a product which boiled at 93–94° (11 mm.), $n^{20}D$ 1.4674.

*Anal.* Calcd. for $C_9H_{20}N_2$: C, 69.17; H, 12.89. Found: C, 69.45; H, 12.44.

The picrate after recrystallization from ethanol melted at 148–149°.

*Anal.* Calcd. for $C_{21}H_{26}N_8O_{14}$: C, 41.04; H, 4.27. Found: C, 41.06; H, 4.27.

**7-Chloro-4-[1-methyl-4-(1-pyrrolidyl)-butylamino]-quinoline.**—A mixture of 29.0 g. (0.147 mole) of 4,7-dichloroquinoline and 50.0 g. (0.322 mole) of 5-pyrrolidyl-2-aminopentane was heated with stirring for six hours at 160–170°. The cold mixture was taken up in 120 ml. of 50% acetic acid with cooling. After addition of 100 ml. of ether, 140 ml. of 30% sodium hydroxide was added to give a strongly basic solution. The mixture was shaken, the ether layer separated, and the aqueous layer was extracted with three 100-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate. After removal of the solvent, 20.1 g. of an oil boiling at 93° (11 mm.) was obtained leaving a residue of 45.7 g. (98%). A portion (31 g.) of this dark green fluorescent residue was taken up in 100 ml. of hot methylcyclohexane. Upon cooling 28 g. of yellow solid, m. p. 98–107°, was obtained. Three recrystallizations from methylcyclohexane gave some oily solid as a first precipitate and 13 g. of white 7-chloro-4-[1-methyl-4-(1-pyrrolidyl)-butylamino]-quinoline, m. p. 110–111°.

*Anal.* Calcd. for $C_{18}H_{24}N_3Cl$: C, 68.01; H, 7.61; N, 13.22. Found: C, 68.11; H, 7.52; N, 12.68.

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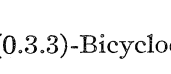
(3) Research and Manufacturing at I. G. Farbenindustrie; British Intelligence Objectives Subcommittee, Appendix 9, Processes 3-7.

(4) We wish to express our appreciation to the National Institute of Health and to William Longenecker for these pharmacological data.

(5) Jones, *Ind. Eng. Chem., Anal. Ed.*, **7**, 431 (1944).

## The Preparation and Properties of *cis*-(0.3.3)-Bicycloöctane

BY A. W. RYTINA,[1] ROBERT W. SCHIESSLER AND FRANK C. WHITMORE[2]

*cis*-(0.3.3)-Bicycloöctane  was prepared previously in very small quantity by Linstead and Cook[3] by heating the semicarbazone of *cis*-α-(0.3.3)bicycloöctanone with potassium hydroxide at 200–210°. A small-scale trial of this method by the present workers resulted in a poor (less than 40%) yield of hydrocarbon, therefore the conversion of the ketone to hydrocarbon was accomplished by the modified Wolff–Kishner reaction.[4] A 68% yield of bicycloöctane was realized, based on carefully purified material.

The hydrocarbon was purified by fractional distillation through a 25-plate helix-packed column, and the following properties determined.

| °C. | Density,[a] g./ml. | Viscosity,[b] cp. |
|---|---|---|
| 0.0 | 0.8863 | 2.839 |
| 20.0 | .8695 | 1.859 |
| 37.8 | .8543 | 1.350 |
| 60.0 | .8353 | 0.9598 |

B. p.: 136.5° (±0.2°) at 738.3 mm.

M. p.: *ca.* −49° (much difficulty was encountered with glass formation)

$n^{20}D$: 1.4622

Mol. refraction (20°C.): found 34.85; calcd. 34.76

[a] ±0.0001; corrected for air buoyancy. [b] ±0.2%.

### Experimental

Following the method of Linstead,[3] a total of 300 g. of pure *cis*-α-(0.3.3)bicycloöctanone was prepared from indene by hydrogenation to hydrindene, sulfonation, fusion with potassium hydroxide of the resultant 5-hydrin-

(1) Present address: Rohm and Haas, Philadelphia, Pa.

(2) Deceased.

(3) Linstead and Cook, *J. Chem. Soc.*, 946 (1934).

(4) Whitmore, Herr, Clarke, Rowland and Schiessler, THIS JOURNAL, **67**, 2059 (1945).

denesulfonic acid, hydrogenation to 5-hydrindanol, nitric acid oxidation to 1-carboxy-2-cyclopentane-beta-propionic acid,[3] and cyclo-decarboxylation to the desired ketone over barium oxide.

To a 300-ml. Aminco hydrogenation bomb was charged 53 g. (0.43 mole) of purified *cis*-α-[0.3.3]bicycloöctanone, 43 g. (0.86 mole) of 100% hydrazine hydrate, 225 g. (4.0 moles) of potassium hydroxide and one liter of triethylene glycol.[4] The mixture was shaken at 195° for twenty-three hours in the sealed bomb. After cooling to room temperature, the reaction mixture was removed from the bomb (foaming), diluted with water, and the mixture steam-distilled. The two liters of steam distillate was acidified with 10% hydrochloric acid and extracted with 400 ml. of ethyl ether. The ether was removed from the separated, dried organic layer by distillation through a 20-plate fractionating column. To the residue was added 35 ml. of 2-octanone, and the mixture carefully fractionated through a 20-plate column to yield 32 g. of material boiling at 136–137° at 735 mm.

This product was combined with 19 g. of material prepared by the semicarbazone method[3] and distilled through a 25-plate column, yielding 49.5 g. of constant boiling, constant index *cis*-(0.3.3)bicycloöctane, b. p. 137° (735 mm.), $n^{20}D$ 1.4622. The hydrocarbon was filtered through a 2 × 20 cm. tube filled with activated silica gel (28–200 mesh), and the physical properties determined.

**Acknowledgment.**—The authors express their appreciation to the American Petroleum Institute for the grant which made this research possible.

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STATE COLLEGE, PA. RECEIVED OCTOBER 19, 1948

## The Preparation of α-Trifluoro-*p*-phenylacetophenone

BY J. H. SAUNDERS, R. J. SLOCOMBE AND EDGAR E. HARDY

Trifluoroacetic acid was converted to the acid chloride and this in turn to α-trifluoro-*p*-phenylacetophenone with an over-all yield of 53%. Recrystallization of this compound from methanol apparently gave the solvated ketone containing one molar equivalent of methanol.

**Trifluoroacetyl Chloride.**—A 1-liter 3-necked flask was equipped with a dropping funnel, stopper, and an 8-in. helix-packed column. A partial take-off still-head and a Hopkins type, Dry Ice-cooled condenser were attached to the column. The head and condenser gas outlet were then connected to a Dry Ice trap. Two hundred sixty grams (1.25 moles) of phosphorus pentachloride was placed in the flask and 96 g. (0.84 mole) of trifluoroacetic acid was added in 5-cc. portions. To ensure complete reaction the system was maintained under total reflux while the first 5 cc. of acid was added and for an additional ten minutes. Then all of the acid chloride produced from this portion of acid was distilled into the cold receiver before adding the next 5 cc. of acid. Proceeding in this manner about six hours were required for the entire reaction. When all of the acid had been added and had reacted the flask and its contents were warmed to 50° to drive out the last traces of acid chloride. The yield of the clear, straw-colored liquid, which contained some hydrogen chloride, was 119 g.

**α-Trifluoro-*p*-phenylacetophenone.**—The method of Simons and Ramler[1] was followed. From 205 g. (1.33 moles) of biphenyl, 178.5 g. (1.33 moles) of aluminum chloride, and the acid chloride from 96 g. (0.84 mole) of trifluoroacetic acid there was obtained 114 g. (55.6%) of recovered biphenyl and 112 g. (53.4% based on trifluoroacetic acid, 75.6% based on biphenyl consumed) of α-trifluoro-*p*-phenylacetophenone, b. p. 130–133° (3 mm.). After recrystallization from 60–70° petroleum solvent the compound melted at 51.2–51.4°.

*Anal.*[2] Calcd. for $C_{14}H_9OF_3$: C, 67.20; H, 3.62. Found: C, 67.48; H, 3.84.

When this product was recrystallized from methanol or methanol and water a new compound, m. p. 102.5–103.5°, was obtained. When this compound was heated above its melting point a condensable gas, presumably methanol, was evolved, and the residue again melted at 51.0–51.4°. Analysis indicated the presence of one mole of methanol per mole of ketone. The difficulty with which a solid of constant melting point was obtained indicated that this compound may have been unstable in methanol solution or that other states of solvation may have existed.

*Anal.* Calcd. for $C_{15}H_{13}O_2F_3$: C, 63.83; H, 4.64. Found: C, 64.03; H, 4.37.

The α-trifluoro-*p*-phenylacetophenone was insoluble in 10% sodium hydroxide solution but was rapidly hydrolyzed by warm alkali. The observed products were a gas, doubtless fluoroform,[1] and biphenyl-4-carboxylic acid, m. p. 226–228°. Gull and Turner reported m. p. 228° for this acid.[3]

(1) Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

(2) Microanalyses were made by the Clark Microanalytical Laboratory, Urbana, Illinois.

(3) Gull and Turner, *J. Chem. Soc.*, 491 (1929).

RESEARCH LABORATORY
PHOSPHATE DIVISION
MONSANTO CHEMICAL COMPANY
ANNISTON, ALABAMA RECEIVED SEPTEMBER 24, 1948

## Chlorination of *t*-Butylbenzene to 1-Chloro-2-methyl-2-phenylpropane

BY WILLIAM E. TRUCE, E. T. MCBEE AND C. C. ALFIERI

The side chain of *t*-butylbenzene has been considered too inert to undergo reaction directly with the halogens. It was claimed that chlorination of *t*-butylbenzene in the presence of sunlight caused ring substitution only.[1] However, we chlorinated *t*-butylbenzene to 1-chloro-2-methyl-2-phenylpropane in 48% conversion. (This compound had been obtained previously by the peroxide-induced chlorination of *t*-butylbenzene with sulfuryl chloride.[2])

Proof of structure consisted of oxidizing the product to benzoic acid in small yield with alkaline potassium permanganate,[3] and carbonation of the corresponding Grignard reagent to the known 3-methyl-3-phenylbutyric acid[4] in 49% over-all conversion. The poor yield of benzoic acid in the above oxidation is to be anticipated for *t*-alkylbenzenes.[5] The preparation of the Grignard reagent was difficult to initiate. When the reaction started, it proceeded slowly but smoothly and an

(1) Salibil, *Chem. Ztg.*, **35**, 97 (1911); *Chem. Zentr.*, **83**, 1581 (1912).

(2) Kharasch and Brown, THIS JOURNAL, **61**, 2142 (1939).

(3) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 163.

(4) Saboor, *J. Chem. Soc.*, 922 (1945); Hoffman, THIS JOURNAL, **51**, 2545 (1929).

(5) Legge, *ibid.*, **69**, 2079 (1947).

82% conversion of halide to Grignard reagent was achieved as determined by titration.[6]

### Experimental

Three moles (402 g.) of *t*-butylbenzene was placed in a long reaction tube which was strongly illuminated. Chlorine, which was first bubbled through a sulfuric acid absorption tube, was slowly bubbled through the hydrocarbon over a period of three hours until a total of three moles had passed. Subsequent rectification yielded 90 g. (0.67 mole) of *t*-butylbenzene, 240 g. (1.42 moles) of 1-chloro-2-methyl-2-phenylpropane, 45 g. of polychlorinated material and 70 g. of still residue. The physical constants of 1-chloro-2-methyl-2-phenylpropane are b. p. 111–112° (18 mm.), $n^{20}D$ 1.5245, and $d^{20}_4$ 1.047.

*Anal.* Calcd. for $C_{10}H_{13}Cl$: Cl, 21.02. Found: Cl, 21.0, 21.0.

We gratefully acknowledge the financial support of this work by the Procter and Gamble Company.

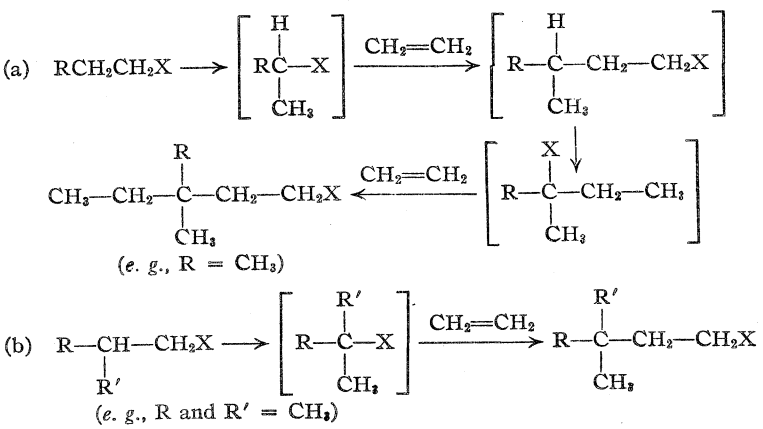
(6) Gilman, *et al.*, THIS JOURNAL, **45**, 150 (1923).

DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY
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LAFAYETTE, INDIANA RECEIVED AUGUST 5, 1948

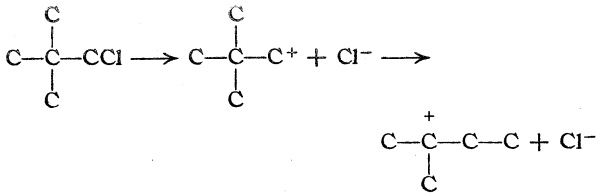
## Condensation of Saturated Halides with Unsaturated Compounds. VII. Condensation of Neopentyl Chloride with Ethylene[1]

BY LOUIS SCHMERLING AND E. E. MEISINGER

The metal halide catalyzed condensation of ethylene with alkyl halides (particularly chlorides and bromides) containing at least three carbon atoms offers a means of preparing 1-halo-3,3-dialkylalkanes.[2] The reaction of typical primary alkyl halides may be illustrated as:




An example of the reaction of ethylene with a third type of primary alkyl halide, namely, a 1-halo-2,2-dialkylalkane, will now be described. The condensation of neopentyl chloride with ethylene proceeded smoothly at −14 to −20° in the presence of aluminum chloride. There was obtained a 38% yield of chloroheptane which was identified as 1-chloro-3,3-dimethylpentane which is also the product of the condensation of ethylene with *t*-pentyl chloride. Isomerization of the neopentyl group to *t*-pentyl apparently occurred



The dissociation of the neopentyl chloride into the unstable positive neopentyl ion and the negative chloride ion is probably brought about by formation of a complex with the catalyst, $(CH_3)_3CCH_2^+AlCl_4^-$.

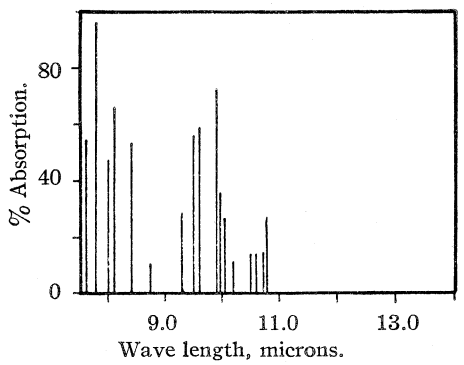



Fig. 1.—Infrared absorption spectrum of 1-chloro-3,3-dimethylpentane.

### Experimental

**Condensation of Neopentyl Chloride with Ethylene.**—A mixture of 40 g. (0.37 mole) of neopentyl chloride,[3] 50 g. of *n*-pentane diluent and 5 g. of aluminum chloride was placed in a three-necked flask immersed in a Dry Ice–acetone-bath. Ethylene was bubbled into the stirred mixture while the temperature was permitted to rise from −70 to −15° at which point absorption began (determined by difference of gas rates in inlet and outlet bubblers). The temperature was maintained at −14 to −20° for the duration of the addition of ethylene (three quarters of an hour) during which time the catalyst gradually coagulated. The liquid product was decanted from the 12 g. of yellow sludge and powder, washed with water, dried and distilled. There was obtained 19 g. (0.14 mole) of product b. p. 50–51° at 20 mm. pressure (150–151° at 760 mm.); $n^{20}D$ 1.4300. There was also obtained 22 g. of unidentified higher-boiling material which apparently consisted largely of chlorononane and chlorohendecane.

The product boiling at 50–51° at 20 mm. was shown to be 1-chloro-3,3-dimethylpentane by converting it to *β*-*t*-pentylpropionanilide by the method of Schwartz and Johnson[4]: m. p. 95–96°. This anilide did not depress the melting point of the analogous derivative of 1-chloro-3,3-dimethylpentane prepared by the condensation of *t*-pentyl chloride with ethylene.[2]

(1) Preceding paper in this series, THIS JOURNAL, **71**, 107 (1949).

(2) L. Schmerling, *ibid.*, **67**, 1152 (1945).

(3) Obtained by the chlorination of neopentane according to the method of F. C. Whitmore and G. H. Fleming, *ibid.*, **55**, 4161 (1933). We wish to thank Dr. Vladimir Haensel for the sample of neopentane which was prepared by the demethylation of neohexane: V. Haensel and V. N. Ipatieff, *Ind. Eng. Chem.*, **39**, 853 (1947).

(4) A. M. Schwartz and J. R. Johnson, THIS JOURNAL, **53**, 1063 (1931); see also H. W. Underwood, Jr., and J. C. Gale, *ibid.*, **56**, 2117 (1934).

Comparison of the infrared spectrum[5] (Fig. 1) of the product boiling at 50–51° at 20 mm. with that of the 1-chloro-3,3-dimethylpentane prepared from *t*-pentyl chloride and ethylene showed that samples contained at least 95% material in common.

(5) We are indebted to Dr. W. S. Gallaway, Physics Division, Universal Oil Products Company, for the infrared absorption analysis. For a description of the procedure used, see THIS JOURNAL, **69**, 1124 (1947).

RESEARCH AND DEVELOPMENT LABORATORIES
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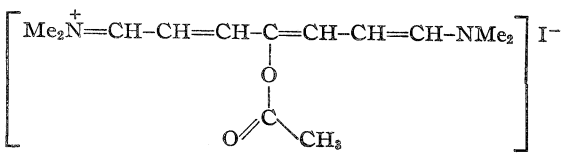
## Two Simple Amidinium Vinylogs[1]

BY WILLIAM T. SIMPSON[2]

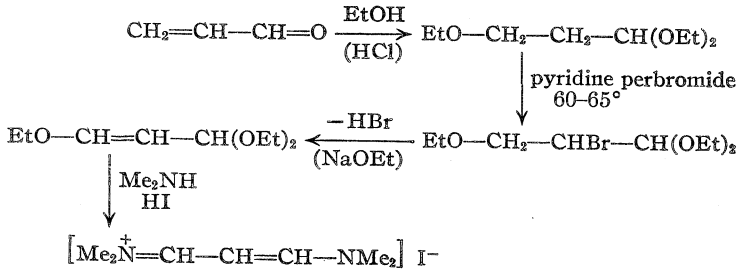
The vinylene homologous series

$$[Me_2\overset{+}{N}=CH-(CH=CH)_n-NMe_2]\ X^-$$

is interesting because of its simplicity[3] and yet its close relationship to several large families of dyestuffs. The second member ($n = 2$) was obtained by König and Regner.[4] Now the first member, ($n = 1$), N-methyl-(2-dimethylaminovinyl)-formimine methiodide, and a substance which is very closely related to the third member ($n = 3$) have been synthesized. The latter compound is N-methyl-(6-dimethylamino-3-acetoxy-1,3,5-hexatrienyl)-formimine methiodide



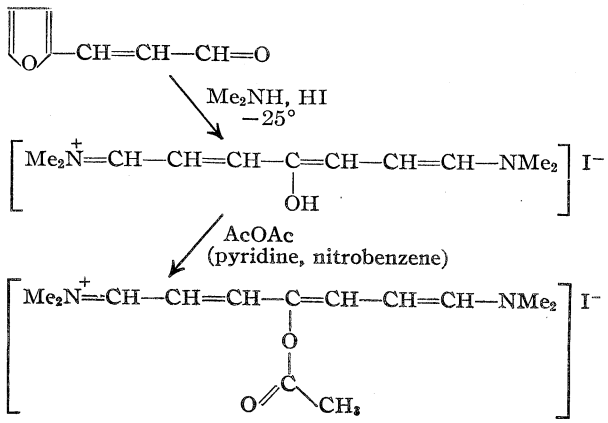
The former substance was prepared according to the scheme




The latter was synthesized by a splitting of the furan ring,[5] followed immediately by acetylation.

### Experimental

**β-Ethoxypropionaldehyde Diethylacetal.**—This material was prepared substantially as described by Pingert.[6] Since the yield of acrolein acetal is not important, the following changes in the procedure were made. The starting material, 80 g. (95 cc., 1.36 mole) of acrolein




(95% with stabilizer) was combined with 325 cc. (5.56 mole) of absolute ethanol (commercial). Approximately 0.7 g. of hydrochloric acid was used as a catalyst. The alcohol was removed under reduced pressure at 40–50°. The yield was 125.1 g. (52%); b. p. 95–97° (39 mm.). The material was used without further purification in the next step.

**Bromination of β-Ethoxypropionaldehyde Diethylacetal.**[7]—The acetal (67 g., 76 cc., 0.38 mole) and 30 g. (30.5 cc., 0.38 mole) of dry pyridine were combined. Then 61 g. (19.5 cc., 0.38 mole) of bromine was added at a rate of several drops a second. A mechanical stirrer operated continuously until the reaction was complete. After the bromine had been added the temperature was adjusted to 60–65°. The reaction was complete in two to four hours, as indicated by the disappearance of the red color of the pyridine perbromide. The reaction vessel was then washed with dry ether and the precipitate triturated with dry ether. Combined ether extracts were dried over anhydrous potassium carbonate and stored in an ice chest. Removal of the ether left 81 g. (83%) of the crude product. It was found that distillation of the crude material produced decomposition to the extent that a better yield in the next step was obtained if purification at this stage had been eliminated.

Dehydrobromination was carried out as described by Reitzenstein and Bonitsch.[8]

**N-Methyl-(2-dimethylamino-vinyl)-formimine Methiodide.**—Dimethylammonium iodide (6.0 g., 0.034 mole), 6.0 g. (0.034 mole) β-ethoxyacrolein diethylacetal, 4.8 g. (0.036 mole) 33% dimethylamine in methanol, and 10 cc. absolute methanol were sealed in a bomb tube. The tube was heated at 100° for five hours in the dark. The reaction mixture was washed with 200 cc. of ether; the precipitate which formed filtered and purified by several recrystallizations from acetic anhydride followed by ether throwdown. The material was dissolved in acetic anhydride at 100° and maintained at this temperature for five or ten minutes during each recrystallization. (This heating during recrystallization converted unchanged dimethylammonium iodide into ether soluble materials.) The yield after three recrystallizations was 3.8 g. (44%). An analytical sample was obtained after several additional recrystallizations from *n*-butyl alcohol. The pure material is crystalline, white with a faint suggestion of a metallic luster: m. p.[9] 188–188.5°.

*Anal.*[10] Calcd. for $C_7H_{15}N_2I$: C, 33.08; H, 5.95. Found: C, 33.18; H, 5.95.

(1) Taken from the writer's Ph.D. thesis.

(2) Present address: Department of Chemistry and Chemical Engineering, University of Washington, Seattle, Washington.

(3) Simpson, *J. Chem. Phys.*, **16**, 1124 (1948).

(4) König and Regner, *Ber.*, **63**, 2823 (1930).

(5) König, *ibid.*, **67**, 1274 (1934).

(6) Pingert, *Org. Syn.*, **25**, 1 (1945).

(7) This procedure was taken from the work of McElvain and Walters, THIS JOURNAL, **64**, 1963 (1942).

(8) Reitzenstein and Bonitsch, *J. prakt. Chem.*, **86**, 1 (1912).

(9) All melting points are corrected.

(10) The analyses were performed under the direction of Mr. Charles Koch.

**N-Methyl-(6-dimethylamino-3-acetoxy-1,3,5-hexatrienyl)-formimine Methiodide.**—Furylacrolein (1.0 g., 0.0082 mole) (Eastman Kodak Co., once recrystallized from ligroin), dissolved in 10 cc. of commercial isopropyl alcohol, was cooled to approximately −25°. A solution containing 1.4 g. (0.0079 mole) dimethylammonium iodide, 1.0 g. (0.0075 mole) of a 33% methanol solution of dimethylamine, and 5 cc. of isopropyl alcohol at room temperature was added to the furylacrolein suspension immediately upon its removal from the cooling bath. The addition, with shaking, required thirty seconds. The mixture was cooled immediately to −25° and kept at this temperature except for brief removal periods for stirring (at five-minute intervals). After thirty minutes the reaction mixture was removed from the cooling bath, 10 cc. of dry ether at 0° added, the solution stirred and filtered. The reaction flask and residue were washed with another cold 10-cc. ether portion. The residue was dried three minutes at the pump, and then transferred to a solution containing nitrobenzene (commercial) 100 cc., dry pyridine 10 cc., and acetic anhydride 10 cc. The solution was swirled until all of the crude material dissolved. The reaction required an hour at room temperature. The product was then thrown out with ether to give 1.2 g. (44%) of crude dye. Several recrystallizations from n-butyl alcohol gave an analytical sample with m. p. 191° (dec.). The crystals are a deep purple and possess a metallic luster.

*Anal.* Calcd. for $C_{13}H_{21}N_2O_2I$: C, 42.86; H, 5.81. Found: C, 42.89; H, 5.79.

of halogen compound and benzenesulfonhydrazide in the presence of one mole of hydrogen chloride (added as concentrated hydrochloric acid) increased the yields to 80–90%; the rate of condensation was also appreciably increased by this modification. The hydrochlorides were purified by crystallization from dilute or glacial acetic acid; excepting the pyrimidine derivative, the products were almost insoluble in water or dilute acids. Dilute bases produced the expected decomposition.[2]

1-Benzenesulfonyl-2-(7-chloroquinolyl-4)-hydrazine hydrochloride was also prepared, in 35% yield, by the action of benzenesulfonyl chloride on 7-chloro-4-hydrazinoquinoline in dry pyridine in the usual manner, followed by treatment of the product with dry hydrogen chloride in alcohol. The latter compound was prepared in 88.6% yield from 4,7-dichloroquinoline essentially by the general procedure of Koenigs and Loesch.[3] The compound formed white needles from alcohol, m. p. 231–232° (cor.) (dec.).

*Anal.* Calcd. for $C_9H_8ClN_3$: N, 21.70. Found: N, 21.68.

Surrey and Cutler[4] reported m. p. 220–221°.

1-Benzenesulfonyl-2-(5-nitropyridyl-2)-hydrazine was prepared from 2-hydrazino-5-nitropyridine[5] and benzenesulfonyl chloride in dry pyridine. This compound could not be prepared by the direct condensation of 2-chloro-5-nitropyridine with benzenesulfonhydrazide in either the presence or absence of hydrochloric acid.

The substituted hydrazines are listed in the accompanying table.

TABLE I

$N^1$-BENZENESULFONYL-$N^2$-SUBSTITUTED HYDRAZINE HYDROCHLORIDES

| $N^2$-Substituent | M. p., °C. | Formula | Analyses, % Sulfur Calcd. | Sulfur Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|
| Quinolyl-2- | 207–209[a] | $C_{15}H_{14}ClN_3O_2S$ | 9.55 | 9.60 | 10.56 | 10.58 |
| 4-Methylquinolyl-2-[b] | 171–172 | $C_{16}H_{18}ClN_3O_3S$ | 8.72 | 8.69 | 9.64 | 9.65 |
| 5-Chloroquinolyl-4- | 219.5–220.0[a] | $C_{15}H_{13}Cl_2N_3O_2S$ | 8.66 | 8.35 | 9.58[e] | 9.56 |
| 7-Chloroquinolyl-4- | 203–204[a] | $C_{15}H_{13}Cl_2N_3O_2S$ | 8.66 | 8.36 | 9.58[e] | 9.66 |
| 7-Chloro-3-methylquinolyl-4-[c] | 196–197[a] | $C_{18}H_{19}Cl_2N_3O_4S$ | 7.22 | 7.27 | 15.96 | 15.98 |
| 7-Phenoxyquinolyl-4- | 209–210[a] | $C_{21}H_{18}ClN_3O_3S$ | 7.49 | 7.51 | 8.29 | 8.20 |
| 2-Aminopyrimidyl-4- | 237–239[a] | $C_{10}H_{12}ClN_5O_2S$ | 10.63 | 10.52 | 11.75 | 11.61 |
| 5-Nitropyridyl-2-[d] | 196–197[a] | $C_{11}H_{10}N_4O_4S$ | 10.89 | 11.00 | ... | ... |

[a] With decomposition. [b] As the monohydrate. [c] With one mole of acetic acid of crystallization. [d] Free base. [e] Ionic halogen only.

I should like to thank Dr. L. G. S. Brooker for showing me an unpublished modification of reference 8, and Professors W. G. Dauben and G. E. K. Branch for much helpful advice.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

RECEIVED AUGUST 9, 1948

# NEW COMPOUNDS

## Some Heterocyclic-Substituted Hydrazines

The condensation of a 2- or 4-chloroquinoline or of 2-amino-4-chloropyrimidine with benzenesulfonhydrazide was carried out in two ways. Refluxing a mixture of one mole of the halogen compound and two moles of benzenesulfonhydrazide in alcohol for two to six hours gave 40–50% yields of condensation product as the hydrochloride. In confirmation of the observations of Banks[1] it was found that the condensation of molal proportions

(1) Banks, THIS JOURNAL, **66**, 1127 (1944).

(2) 1-Benzenesulfonyl-2-(7-chloroquinolyl-4)-hydrazine hydrochloride gave a 43.2% yield of 7-chloroquinoline, m. p. 31–32°, when steam distilled from excess sodium carbonate solution. 1-Benzenesulfonyl-2-(5-nitropyridyl-2)-hydrazine similarly gave a 32% yield of 3-nitropyridine, m. p. 39.5–40.5°. *Cf.* McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

(3) Koenigs and Loesch, *J. prakt. Chem.*, **143**, 59 (1935); *cf.* Perkin and Robinson, *J. Chem. Soc.*, **103**, 1978 (1913).

(4) Surrey and Cutler, THIS JOURNAL, **68**, 2570 (1946).

(5) Rath, U. S. Patent 1,733,695.

STERLING–WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK R. O. CLINTON

RECEIVED NOVEMBER 16, 1948

## Preparation of Organic Silicon Chlorides[1]

The general method of synthesis was to add the appropriate Grignard reagent dropwise into an excess of silicon

(1) This work was performed in 1945 as part of the research program of the Research and Development Branch, Military Planning Division, of the Office of the Quartermaster General. The opinions and conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or endorsement of the Department of the Army. Article not copyrighted. This work was performed with the assistance of Charles A. Miller, Joseph Rynasiewicz, Nelda Gulbransen, Esther Nielson and Eleanor Swenson.

tetrachloride essentially as has recently been described by Whitmore.[2] In many runs we found it practical to dissolve the silicon tetrachloride in either pure benzene or a mixture of dry ether and benzene (recovered from previous runs) rather than in pure ether. Yields were ordinarily 20–45%. Isopropylmagnesium bromide, however, gave 5–6% yield of the trichloride,[3] together with an equal weight of the dichloride (11% yield, based on the Grignard reagent).

For the preparation of diisobutylsilicon dichloride equimolar quantities of the Grignard reagent and isobutylsilicon trichloride (in benzene) were placed in reaction. The yield was about 20%.

(2) Whitmore, *et al.*, THIS JOURNAL, **68**, 475 (1946).

(3) Booth and Spessard, *ibid.*, **68**, 2660 (1946).

Silicon tetrachloride was inert toward ethynylsodium, HC≡CNa, or ethynebis-(magnesium chloride), ClMgC≡CMgCl.

NEW COMPOUNDS, $RSiCl_3$ AND $R_2SiCl_2$

| Substance | B. p. °C. | B. p. Mm. | $d^{20}_4$ | Anal., Cl Calcd. | Anal., Cl Found | |
|---|---|---|---|---|---|---|
| *p*-$CH_3OC_6H_4SiCl_3$ | 128–130 | 13 | 1.46 | 44.04 | 43.62 | 44.32 |
| *p*-$C_2H_5OC_6H_4SiCl_3$ | 137–138 | 13 | 1.36 | 41.62 | 41.42 | 41.18 |
| (*i*-$C_3H_7)_2SiCl_2$ | 67–69 | 11 | 1.06 | 38.31 | 39.20 | 38.90 |
| (*i*-$C_4H_9)_2SiCl_2$ | 93 | 16 | 1.00 | 33.26 | 33.26 | 33.17 |

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CHARLES D. HURD
W. A. YARNALL

RECEIVED SEPTEMBER 13, 1948

# COMMUNICATIONS TO THE EDITOR

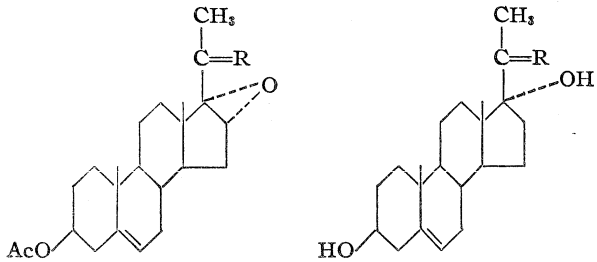
## 17α-HYDROXYSTEROIDS

*Sir:*

The recent communication by Plattner, Heusser and Feurer[1] impels us to record certain work on the reduction of steroid oxides which has been under way in these Laboratories for some time.

We have likewise prepared Reichstein's substances J and O by the reduction of 16,17-oxido-allopregnane-3β-ol-20-one acetate with lithium aluminum hydride. Furthermore, we have investigated the lithium aluminum hydride reduction of 16,17-oxido-5-pregnene-3β-ol-20-one acetate. The nature of the resulting 3,17,20-triol mixture was confirmed by oxidation with periodic acid to dehydroisoandrosterone (m. p. 148–149°; acetate, m. p. 166–168°).

We wish, particularly at this time, to report a novel procedure for the preparation of 17α-hydroxy steroids bearing a ketone group at position 20. The focal point in the facile preparation of these derivatives has been the protection of the 20-keto group through the formation of cyclic ketals. The 16,17-oxido-20-ketals undergo smooth reduction with lithium aluminum hydride and the resulting products are readily cleaved to the desired 17α-ol-20-ones.




**16,17-Oxido-5-pregnene-3β-ol-20-one Acetate (I).**—Plates from methanol, m. p. 154–155°; $[\alpha]^{26}D$ −9.0° (chloroform). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.43; H, 8.72. It was prepared by the action of perbenzoic acid on derivatives of 5,16-pregnadiene-3β-ol-20-one.

**Ketal of 16,17-Oxido-5-pregnene-3β-ol-20-one Acetate (II).**—From the oxido-pregnene (I) and ethylene glycol by refluxing a benzene solution with *p*-toluenesulfonic acid monohydrate as catalyst as thick, needle-like prisms from benzene-methanol, m. p. 195–197°; $[\alpha]^{27}D$ −37.8° (chloroform). *Anal.* Calcd. for $C_{25}H_{36}O_5$: C, 72.07; H, 8.71. Found: C, 71.92; H, 8.67.

**Ketal of 17α-Hydroxypregnenolone (III).**—From the reduction of the ketal (II) with lithium aluminum hydride in benzene–ether solution as plate-like prisms from acetone, m. p. 185–187°; $[\alpha]^{26}D$ −44.8° (chloroform). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.63; H, 9.70.

**17α-Hydroxypregnenolone (5-Pregnene-3β,17α-diol-20-one) (IV).**—From the ketal (III) by cleavage with sulfuric acid in aqueous methanol as fine prisms from methanol, m. p. 265°[2]; $[\alpha]^{23}D$ −34.4° (2 parts ethanol–1 part dioxane). *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.42; H, 9.84. Acetylation of the 17α-hydroxypregnenolone with acetic anhydride-pyridine gave the acetate, needles from benzene–petroleum ether (b. p. 35–60°), m. p. 232–234°.[2]

By the Oppenauer oxidation of 16,17-oxidopregnenolone (16,17-oxido-5-prenene-3β-ol-20-one) we have incidentally prepared 16,17-oxidoprogesterone (16,17-oxido-4-pregnene-3,20-dione) as fine prisms from aqueous methanol, m. p. 205–207°; $[\alpha]^{27}D$ +160.8° (chloroform). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.50; H, 8.68.

The investigations are being continued.

THE GLIDDEN COMPANY
RESEARCH LABORATORIES
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EDWIN W. MEYER
ISABELLE RYDEN

RECEIVED JANUARY 31, 1949

(1) Plattner, Heusser and Feurer, *Helv. Chim. Acta*, **31**, 2210 (1948).

(2) *Cf.* Fuchs and Reichstein, *Helv. Chim. Acta*, **24**, 804 (1941) Hegner and Reichstein, *ibid.*, **24**, 828 (1941).

## THE RESOLUTION OF SPARTEINE

*Sir:*

In consideration of the recently reported syntheses of sparteine[1,2] we wish to record herein the resolution of *dl*-sparteine, the total synthesis of which was first announced from this Laboratory.[3] Synthetic *dl*-sparteine was resolved by means of β-camphorsulfonic acid, and both *d*- and *l*-sparteine were isolated and identified.

Equimolar portions of racemic sparteine and *d*-β-camphorsulfonic acid in ethanol gave ***l*-sparteine *d*-β-camphorsulfonate.** After two recrystallizations from acetone the specific rotation remained constant, $[\alpha]^{29}D$ 24.8 ± 0.5° (*C*, 1.932 in chloroform), and consistent with that of an authentic sample of the *d*-β-camphorsulfonate of natural *l*-sparteine, $[\alpha]^{29}D$ 24.4 ± 0.5° (*C*, 2.298 in chloroform). Both natural and synthetic salts melted at 240–241°, as did a mixture of the two. ***l*-Sparteine dipicrate,** yellow needles, m. p. 207–208°, was prepared directly from the *d*-β-camphorsulfonate salt in ethanol by the addition of ethanolic picric acid (*Anal.* Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 47.13; H, 4.54; N, 15.94). The melting point was depressed when the compound was mixed with *dl*-sparteine dipicrate, m. p. 208°, undepressed when mixed with natural *l*-sparteine dipicrate, m. p. 208°.[4]

Following the separation of the *l*-sparteine *d*-β-camphorsulfonate, *d*-sparteine-enriched base was freed from the mother liquor and was converted, by treatment with *l*-β-camphorsulfonic acid,[5] to ***d*-sparteine *l*-β-camphorsulfonate.** After three recrystallizations from acetone, this salt melted at 239–241° and exhibited a specific rotation, $[\alpha]^{22}D$ −24.0 ± 0.5° (*C*, 2.040 in chloroform), approximately equal and opposite to that of its antipode. ***d*-Sparteine dipicrate,** yellow needles, m. p. 208–209°, was prepared directly from the *l*-β-camphorsulfonate salt and showed no depression in melting point when mixed with the dipicrate of natural *d*-sparteine,[6] m. p. 208°.[7] ***d*-Sparteine monoperchlorate,** colorless needles, m. p. 174°, was prepared by dissolving *d*-sparteine *l*-β-camphorsulfonate in a small amount of water, acidifying to *p*H 1–2 with 65% perchloric acid, and then basifying with ammonium hydroxide. The perchlorate separated on cooling and was recrystallized from ethanol–ether. A mixture with the monoperchlorate of natural *d*-sparteine,[6] m. p. 173°,[7] was also 173°.

The infrared absorption spectra of natural *l*-, resolved *l*-, natural *d*-, and resolved *d*-sparteine dipicrates were determined[8] and were found to be identical for these samples in the crystalline state and very slightly different from that of crystalline *dl*-sparteine dipicrate.[3]

(1) Clemo, Raper and Short, *Nature*, **162**, 296 (1948).

(2) Sorm and Keil, *Coll. Czechoslov. Chem. Commun.*, **13**, 544 (1948).

(3) Leonard and Beyler, THIS JOURNAL, **70**, 2298 (1948).

(4) Moureu and Valeur, *Bull. soc. chim.*, [3] **29**, 1135 (1903).

(5) Obtained by resolution of *dl*-β-camphorsulfonic acid according to the method of Burgess and Gibson, *J. Soc. Chem. Ind.*, **44**, 496T (1925).

(6) We wish to acknowledge the kindness of Dr. Léo Marion, National Research Council, Ottawa, Canada, in supplying us with authentic samples of *d*-sparteine dipicrate and *d*-sparteine perchlorate.

(7) Marion and Ouellet, THIS JOURNAL, **70**, 691 (1948); Marion and Turcotte, *ibid.*, **70**, 3253 (1948); Marion and Cockburn, *ibid.*, **70**, 3472 (1948).

(8) The authors are indebted to Mrs. James L. Johnson for determination of the infrared absorption spectra.

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RECEIVED JANUARY 14, 1949

## CRYSTALLINE XYLAN AND MANNAN

*Sir:*

I wish to report the isolation of a crystalline xylan from barley straw and birchwood. The weaker linkages of the xylan-rich fraction of the hemicelluloses of these materials, purified by the method of Salkowski, were hydrolyzed under mild conditions (0.2% oxalic acid at 100°); the reducing value of the hydrolysate was virtually constant after five hours. The insoluble portion from the hydrolysis, on autoclaving at 120°, was soluble in water to the extent of about 0.2%; on cooling to 60–70°, hexagonal platelets with rounded corners separated. The xylan was purified by heating a water paste for five hours at 120°, readily filterable spherocrystals being obtained. Barley xylan is purified more readily than birch xylan. Aging of the amorphous xylan or contact with dilute alkali renders it insoluble in 3 *N* sodium hydroxide. Wet heat at 120° and *p*H 5 restores its solubility. Attempts to prepare a slash pine xylan failed. The crystals are doubly refractive and give typical crystalline X-ray diffraction patterns. Crystalline D-xylose was prepared in good yield and its identity confirmed. A diphenylhydrazine test for arabinose in the mother liquor was negative. This, coupled with the high pentosan analysis, indicates relatively pure xylan. Breddy–Jones and Wise–Appling xylose determinations on 3% nitric acid hydrolysates confirmed this finding. Osmotic pressure measurements on methylated barley xylan indicate a degree of polymerization of 39. A newly developed aldose end-group method gave the

| | Material from selective hydrolysis | | Repeatedly recrystallized xylan | |
|---|---|---|---|---|
| | Barley | Birch | Barley | Birch |
| Pentosans as xylan (cor. for uronic acids), % | 97.4 | 92.4 | 99.5 | 97.9 |
| Uronic anhydride (cor. for $CO_2$ from xylose), % | 2.4 | 6.4 | 0.38 | 2.39 |
| Ash, % | 0.85 | .. | 0.34 | 0.39 |

same value. Birch xylan, compared viscometrically with barley xylan, had a degree of polymerization of 35. Optical rotational measurements indicate a 1,4′,β-linkage. This is based on the rotational shift method of Reeves and comparisons with Haworth's esparto xylan.

Mannan "A" of ivory nut readily forms supersaturated solutions of 1% concentration. Such a solution crystallizes if heated to 60–70° for several days. The crystals initially are rods and gradually become dumb-bell shaped as growth continues. Slight double refraction is evident. A mannan-rich fraction from slash pine gave similar crystals. Repeated recrystallization did not alter the facility or habit of crystallization. The crystals assayed only 50% mannan and had a light tan color.

This work will be published in full at a later date.

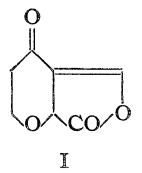
THE INSTITUTE OF PAPER CHEMISTRY
APPLETON, WISCONSIN ALBERT P. YUNDT

RECEIVED JANUARY 15, 1949

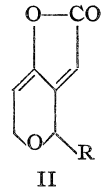
## THE STRUCTURE OF PATULIN

*Sir:*

We are reporting elsewhere in detail the considerations which led us to reject the accepted structure[1] (I, *and/or* tautomers) for the well-known mold metabolite and antibiotic, patulin, in favor of a new expression (I, R = OH). Here we re-record the synthesis of (II, R = H), which we designate as *desoxypatulin*, since its relevant physical properties resemble those of patulin so closely as to provide very strong support for our structural views.

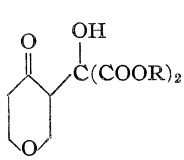


I

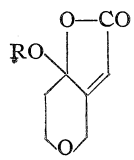


II

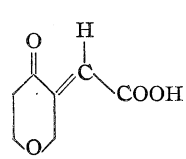
Condensation of tetrahydro-γ-pyrone with ethyl mesoxalate gave the ketol (III, R = Et), m. p. 58.5–60° (Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.57. Found: C, 52.73; H, 6.67). When the corresponding acid (III, R = H) was heated with acetic anhydride and acetic acid, among the products obtained were: (i) the *cis*-acid (IV, R = H), m. p. 122–123° (Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.13. Found: C, 53.77; H, 5.18), (ii) the lactol acetate (IV, R = Ac), m. p. 121.5–123° (Calcd. for $C_9H_{10}O_5$: C, 54.55; H, 5.05. Found: C, 54.64; H, 5.02), (iii) the *trans*-acid (V), m. p. 153° (Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.13. Found: C, 53.89;



III



IV



V

H, 5.25). Treatment of (IV, R = Ac) with warm acetic anhydride–acetic acid–sulfuric acid[2] gave desoxypatulin (II, R = H), m. p. 46–48° (Calcd. for $C_7H_6O_3$: C, 60.80; H, 4.35. Found: C, 60.62; H, 4.37), whose ultraviolet spectrum possessed a single maximum at 273 mμ (log ε, 4.17) (patulin: $\lambda_{max.}$, 276 mμ (log ε, 4.22)), and whose infrared spectrum in the double bond region reproduced in detail the very characteristic spectrum of patulin in the same region (Fig. 1).

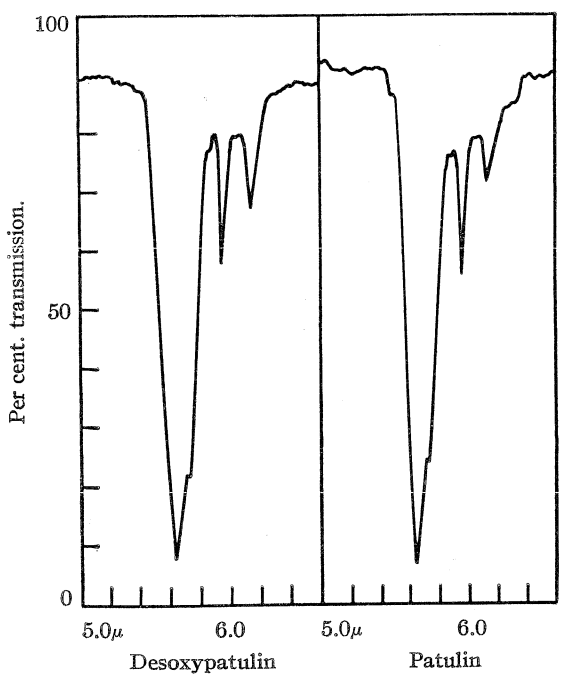
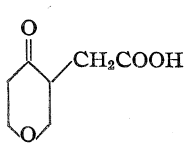
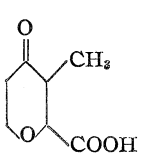



Fig. 1.—Spectra in $CH_2Cl_2$.

Further support for the structure (II, R = OH) was forthcoming when the oily acid (VI), obtained by the hydrogenation either of the *cis*-acid (IV, R = H) or the *trans*-acid (V), was shown to be identical, through comparison of the methyl ester 2,4-dinitrophenylhydrazones, m. p. 149–150°, with the acid $C_7H_{10}O_4$ originally obtained by Ber-



VI



VII

(1) For references *cf. Quart. Reviews Chem. Soc.*, **2**, 53 (1948).

(2) *Cf.* Shaw, THIS JOURNAL, **68**, 2510 (1946).

gel, *et al.*,[3] from patulin, and assigned by them the structure (VII).[4]

(3) Bergel, Morrison, Moss and Rinderknecht, *J. Chem. Soc.*, 415 (1944).

(4) A reduction of our *trans*-acid and the first comparison of (VI) with Bergel's acid was carried out by Professor Pl. A. Plattner and Dr. Engel (Zürich). We thank Professor Plattner warmly for his cooperation, and for samples of derivatives of Bergel's acid which enabled us to carry out the similar correlation with the *cis*-acid (IV, R = H).

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RECEIVED JANUARY 17, 1949

# NEW BOOK

**Carotinoide.** By PAUL KARRER AND ERNST JUCKER, Chemical Institute of the University of Zurich. (Lehrbücher und Monographien aus dem Gebiete der Exakten Wissenschaften, 17. Chemische Reihe, Band III.) Verlag Birkhäuser, Basel, Switzerland, 1948. 388 pp. 17 × 24.5 cm. Price, 39.-Swiss francs (paper binding); 43.-Swiss francs (linen binding).

With the rapid expansion of chemical research in the past twenty-five years, the organization and correlation of diverse observations in complex fields has become a great problem to all specialists, research workers, teachers and students. Although *Chemical Abstracts* and the numerous review journals provide leads to many isolated facts, there is as yet no satisfactory substitute for the comprehensive monograph written by an authority in the field. For this reason, there are widespread benefits when so productive research workers as Professor Karrer and his collaborator, Dr. Jucker, summarize the studies of the carotenoids, a highly specialized field in which they have made many significant contributions over a long period.

If a technical book is to be more than a handbook, the authors must select their material carefully, omitting the extraneous observations and including and emphasizing the pertinent facts that lead to progress in the field. The choice of material will of necessity reflect the aims, the interest and the experience of the writers. The readers, on the other hand, will examine the book from their particular points of view seeking new information often with a view toward further application in their own fields.

This new monograph on the carotenoids is divided into two parts; a general section of 100 pages and a special section of 231 pages. The general part contains rather brief descriptions of the state or condition of the carotenoids in plants and animals (4 pp.); the origin and physiological significance of the carotenoids in plants and animals (10 pp.); the isolation of the carotenoids (9 pp.); the chemical constitution of the carotenoids, represented by 31 formulas (8 pp.); *cis–trans* isomerization of the carotenoids (5 pp.); methods for determination of the chemical structure (10 pp.); relationship between constitution and color of the carotenoids (7 pp.); and partial syntheses of carotenoids (5 pp.). The last 35 pages of this general section are devoted to tables showing the occurrence of carotenoids in various species of plants and animals classified according to families. For these tables alone, 434 publications are cited. Here is a mass of information not readily available elsewhere.

The second part of this monograph describes the individual carotenoid pigments; particularly, their occurrence, with tables illustrating sources; methods for their preparation; their chemical constitution; their properties such as absorption maxima, solubility, optical activity, adsorbability, etc.; *cis–trans* isomers; and various derivatives of the pigments. Some 28 pigments of known structure and 37 pigments of unknown structure as well as numerous derivatives of these substances are described. Finally, there are 12 colored pictures of carotenoid crystals and 28 figures of spectral absorption curves determined in various solvents. Two indexes provide references to the plants and animals in which the pigments occur and to the usual subject matter.

All this diverse material has been brought together according to a carefully arranged outline, so that the included facts are readily found by readers with different points of view. As a result, this book provides a service to everyone interested in the carotenoid pigments, although at the price quoted ($13.50) it is rather expensive. Unfortunately, there are some omissions of important data; hence, this monograph cannot be relied upon as an impartial source of information.

All chemists, especially those in the food and fodder industries where determinations of the carotenoid pigments have contributed so much to the improvement of our food supply, will be amazed to find few if any references to the careful spectral absorption work carried out in the United States during the past fifteen years. Most of the American results, which have been obtained with different instruments calibrated in different ways and which are in remarkably good agreement, differ significantly from many of those presented in the monograph. As one example, Figure 28 showing lycopene with smaller absorption coefficients than carotenes is contrary to all this uncited experience and to the theories concerning the spectral absorption capacity of unsaturated compounds.

In view of Professor Karrer's contributions, chemists interested in the chromatographic adsorption method will not be surprised that so much emphasis has been placed upon the use of zinc carbonate as an adsorbent. They will be astonished, however, to find that so little attention has been devoted to other adsorbents which have been widely used and which occasionally have made possible separations and identifications not included in this monograph, specifically the separation of neoxanthin and violaxanthin and the confirmation of the identity of violaxanthin from leaves with violaxanthin from pansies. Variation of the adsorption sequence with variation of the solvent and adsorbent is not reported. For the one adsorption sequence of the carotenoids that is summarized in the form of a table, there is no record of the solvent and the adsorbent.

The universal occurrence of carotenoid pigments in the photosynthetic apparatus of green plants and the possible role of these pigments in the utilization of solar energy have stimulated a great deal of biological, physiological and chemical investigation in the past decade, but none of these publications are cited in the present monograph. This work on chloroplast pigments has led to the discovery of many new carotenoids that are not included in this book. Examples are: neoxanthin from leaves, dinoxanthin from dinoflagellates, diadinoxantin from diatoms and dinoflagellates, etc. The fact that fucoxanthin is the principal xanthophyll of diatoms is omitted as is also the universal occurrence of zeaxanthin in green leaves. No mention

is made of the fact that peridinin, the principal xanthophyll of dinoflagellates, is probably identical with the sulcatoxanthin from sea anemones or from the symbiotic algae of these anemones. Spirilloxanthin, the principal xanthophyll of many purple, chemo-autotrophic bacteria, does not appear in the index although it is admittedly identical with the subsequently discovered rhodoviolascin.

Apart from these omissions, the material in this monograph is extensive, and it is clearly presented. The book is certain to serve as a guide in this field for many years to come.

HAROLD H. STRAIN

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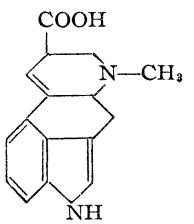
VOLUME 71 MARCH 19, 1949 NUMBER 3

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

# The Synthesis of 5-Keto-1,3,4,5-tetrahydrobenz[cd]indole. A Synthesis of 4-Substituted Indoles

BY FREDERICK C. UHLE

The alkaloids isolated from *Claviceps purpurea* have been shown to be substances of polypeptide nature derived from certain $\alpha$-amino acids of relatively low molecular weight combined through amide linkage with a characteristic,complex indole derivative, lysergic acid.[1] More recently, the tetracyclic structure originally postulated on the basis of degradation studies for this characteristic ampholyte has been confirmed by the total syn-




Lysergic acid

thesis of dihydro-*dl*-lysergic acid.[2] The unprecedented *ergoline* ring system[3] encountered as this expression in the ergot alkaloids represents the only example of an indole derivative condensed in the 3,4-position to other nuclei which has been observed in nature or obtained by synthesis. Hitherto, the sole synthetic route to this novel type of structure has involved the sodium–butanol reduction of appropriately substituted naphthostyril derivatives and benzo[f]quinoline lactams. This procedure, while feasible in certain cases with simple derivatives, fails, or at best affords the indole in yields of less than ten per cent. in the case of naphthostyrils substituted with highly reactive functional groups, and attempts to synthesize lysergic acid by procedures involving reduction to the indole stage as one of the final steps have appeared most unpromising. New methods of approach to the synthesis of the ergoline type of ring structure are accordingly required to facilitate study of the chemistry of these interesting and unique indole derivatives, as well as to provide intermediates for the eventual synthesis of the alkaloids themselves.

Simple indoles substituted in the 4-position have been rarely reported in the literature, inasmuch as the only methods available for their synthesis have been those (such as the Fischer synthesis from meta-substituted phenylhydrazones) which give a mixture of the 4- and 6-isomers which are difficult to separate and identify, or those which with few exceptions yield compounds with substituents in the hetero-ring not readily eliminated in subsequent reactions.[4] A procedure has now been developed by which it is possible to prepare directly and in pure form, free from isomers, indoles substituted only in the 4-position in the benz-nucleus. The synthesis leads directly to the 4-chloro- and 4-cyanoindoles, and further functions are obtained by operation upon these groups. This new method has been extended to the preparation of $\beta$-(4-carboxy-3-indole)-propionic acid (VII), and ring closure under specific conditions has led to the synthesis of the tricyclic 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).

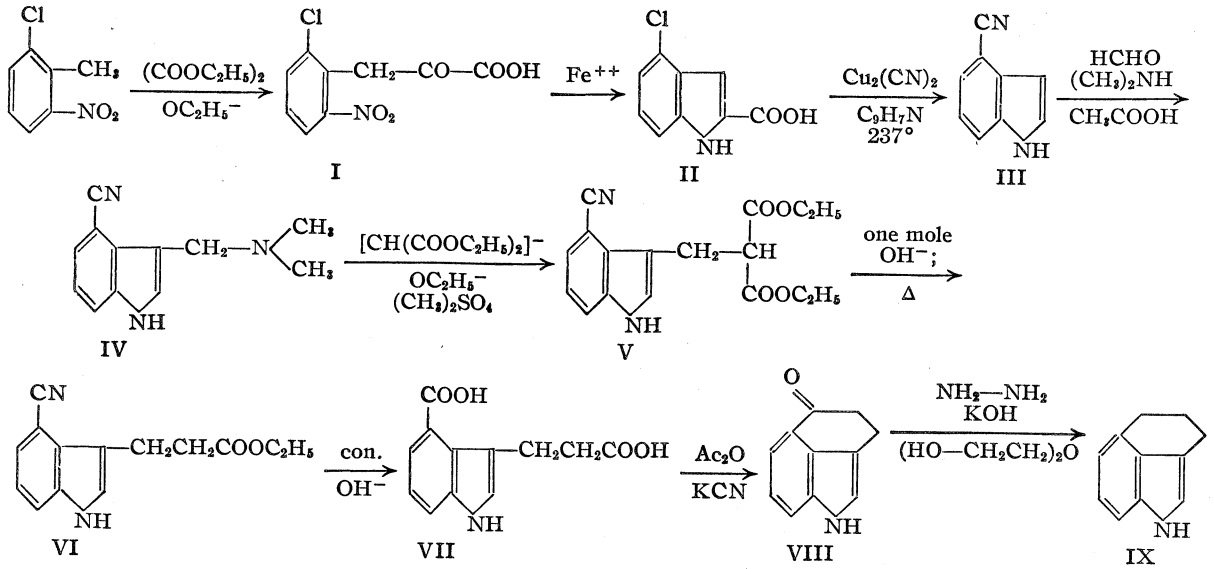
The starting material chosen for the synthetic sequence, the readily available dyestuff intermedi-

(1) For example, four of the principal alkaloids yield the following hydrolysis products, respectively: ergotamine—lysergic acid, *d*-proline, *l*-phenylalanine, pyruvic acid, and ammonia; ergosine—lysergic acid, *d*-proline, *l*-leucine, pyruvic acid, and ammonia; ergocornine—lysergic acid, *d*-proline, *l*-valine, isobutyrylformic acid, and ammonia; ergonovine—the least complex of the series—lysergic acid and *d*-2-aminopropanol.

(2) Uhle and Jacobs, *J. Org. Chem.*, **10**, 176 (1945).

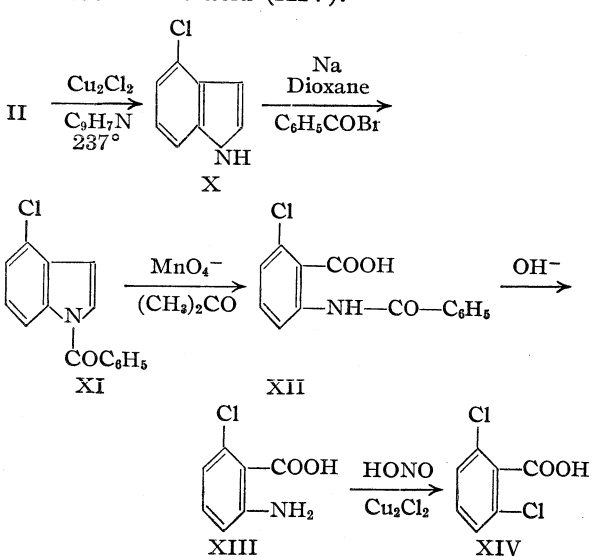
(3) Ring Index No. 2439.

(4) Marion and Oldfield, *Can. J. Res.*, **25B**, 1 (1947).

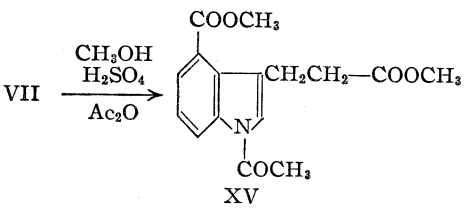



ate, 2-nitro-6-chlorotoluene, was condensed with ethyl oxalate, and the pyruvic acid derivative (I) reduced with ferrous hydroxide to 4-chloro-2-indolecarboxylic acid (II). Decarboxylation, as well as metathetical replacement of the halogen substituent occurred with cuprous cyanide in refluxing quinoline, and the 4-cyanoindole (III) isolated in good yield and characterized as 4-indolecarboxylic acid was converted through the Mannich base (IV) and the malonic ester derivative (V) to β-(4-carboxy-3-indole-)-propionic acid (VII).

The position of the substituent in the benz-nucleus was confirmed by the degradation of 4-chlorindole (X), obtained by decarboxylation of (II) with cuprous chloride in quinoline, to the known 6-chloroanthranilic acid (XIII) and 2,6-dichlorobenzoic acid (XIV).




Attempts to cyclize the dimethyl ester of the acid (VII) under the conditions of the Dieckmann condensation, using a wide variety of experimental variations and solvents, failed to give evidence of the formation of the desired tricyclic β-keto ester. Reaction with the metal occurred under some conditions leading to condensations involving presumably the indole nitrogen, but the products were difficult to isolate in a state of purity. N-Acetyl methyl-β-(4-carbomethoxy-3-indole)-propionate (XV) when allowed to react with sodium in re-

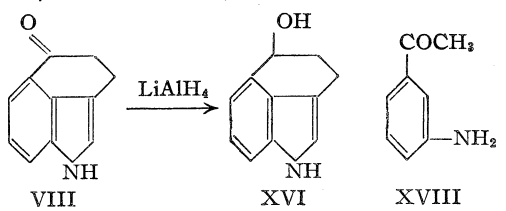



fluxing *p*-cymene gave no evidence of reaction. Ethyl β-(4-cyano-3-indole)-propionate (VI) likewise failed to exhibit tendency toward intramolecular condensation. Pyrolysis of the calcium or barium salt of β-(4-carboxy-3-indole)-propionic acid (VII) was not successful, and pyrolysis of the free dicarboxylic acid (VII) at 300° under diminished pressure led to decarboxylation of the nuclear carboxyl group, giving as the sublimate β-(3-indole)-propionic acid in low yield.

It was eventually found, however, that when a dilute solution of β-(4-carboxy-3-indole)-propionic acid (VII) in acetic anhydride containing a catalytic quantity of potassium cyanide was maintained at reflux temperature for an extended period and the reaction product hydrolyzed with alkali, a beautifully crystalline ketone was isolable in excellent yield. Uncyclized dicarboxylic acid was recovered from the alkaline filtrate, accounting for essentially the entire quantity of the compound used. The lemon-yellow keto-compound gave the usual carbonyl reactions and was characterized as the semicarbazone and as the *p*-nitrophenylhydrazone. A modified Wolff–Kishner

type reduction with hydrazine and potassium hydroxide in diethylene glycol, as well as a Clemmensen reduction, led to the formation of a compound which proved to be identical with 1,3,4,5-tetrahydrobenz[cd]indole (IX), prepared by sodium–butanol reduction of naphthostyril. The structure of the ketone is accordingly indicated to be 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).

Hydrogenation of (VIII) by means of lithium aluminum hydride in ether solution gave 5-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (XVI) in excellent yield. Reduction of the carbonyl function in anhydrous isopropyl alcohol in the presence of aluminum isopropoxide led to the formation of a derivative with properties and analytical data which indicated it to be the isopropyl ether (XVII) of the alcohol (XVI).[5]




VIII XVI XVIII

The ultraviolet absorption spectrum[6] of the ketone (VIII), Fig. 1, exhibits maxima at 245 and 325 mμ and a minimum at 267 mμ, values suggesting those given by lysergic acid, which shows peaks at 230 and 315 mμ and a minimum at 270 mμ.[7] *m*-Aminoacetophenone (XVIII) gives a curve of similar form with maxima at 235 and 340 mμ and a minimum at 285 mμ. The 5-hydroxy compound (XVI) prepared by lithium aluminum hydride hydrogenation of the ketone (VIII), the isopropyl ether (XVII) formed in the Meerwein reduction, and the 1,3,4,5-tetrahydrobenz[cd]-indole (IX) prepared by hydrazine reduction of the ketone (VIII) as well as by sodium–butanol reduction of naphthostyril, gave practically superimposable curves with maxima at 230 and 280 mμ and a minimum at 254 mμ in conformity with data previously observed for certain indoles and for heterocyclic compounds derived from the indole nucleus.[7,8]

Additional reactions and properties of (VIII) and its utilization in further synthetic work, as well as an extension of the general methods, will be reported in subsequent communications.

## Experimental[9]

**2-Nitro-6-chlorophenylpyruvic Acid (I).**—To a solution of 23 g. (1.0 mole) of sodium in 350 ml. of absolute ethanol was added 146 g. (1.0 mole) of ethyl oxalate and 171.6 g. (1.0 mole) of 2-nitro-6-chlorotoluene and the mixture maintained at reflux temperature for forty minutes. The dark red solution was diluted with water and distilled with steam until starting material no longer collected in the distillate. The aqueous residue from the distillation was clarified by filtration and acidified with hydrochloric acid. The heavy precipitate which separated was collected by filtration and recrystallized from benzene. The compound gave the characteristic deep red color with alkali and a dark green color with ferric chloride solution. The yield was 102 g. (42%), and 70 g. (41%) of 2-nitro-6-chlorotoluene was recovered unchanged; m. p. 114–115°.

*Anal.* Calcd. for $C_9H_6NO_5Cl$: C, 44.38; H, 2.48. Found: C, 44.39; H, 2.84.

The semicarbazone was prepared in dilute ethanol and recrystallized from ethanol; m. p. 204–205°.

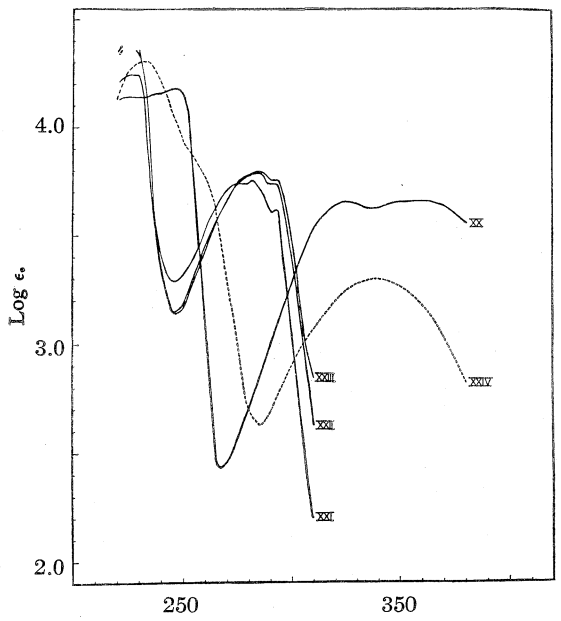
*Anal.* Calcd. for $C_{10}H_9N_4O_5Cl$: C, 39.95; H, 3.01. Found: C, 39.92; H, 3.05.

**4-Chloro-2-indolecarboxylic Acid (II).**—A solution of 81 g. (0.33 mole) of 2-nitro-6-chlorophenylpyruvic acid in dilute ammonium hydroxide solution was added to a suspension of ferrous hydroxide prepared from 560 g. (2.0 moles) of ferrous sulfate heptahydrate and 230 ml. of concentrated ammonium hydroxide solution in two liters of water and the mixture maintained at the boiling point for five minutes. The ferric hydroxide was separated by filtration, washed repeatedly with dilute ammonium hydroxide solution and water, and the filtrate acidified with dilute hydrochloric acid solution. The precipitate was recrystallized from a mixture of ethanol and water; yield 60 g. (92%); m. p. 259–260°.

*Anal.* Calcd. for $C_9H_6NO_2Cl$: C, 55.27; H, 3.09. Found: C, 55.38; H, 3.08.

The methyl ester was prepared by maintaining under reflux a solution of 3 g. of the acid in a mixture of 30 ml. of methanol and 3 ml. of concentrated sulfuric acid for fifteen hours. The solution was concentrated under diminished pressure, extracted with ether and aqueous sodium bicarbonate solution, and the residue from evaporation of the ether recrystallized from ethanol; yield 2.8 g. (87%); m. p. 146–147°.

*Anal.* Calcd. for $C_{10}H_8NO_2Cl$: C, 57.30; H, 3.84. Found: C, 57.42; H, 3.87.




Wave length in millimicrons.

Fig. 1.—Ultraviolet absorption spectra.

(5) Ether formation under the conditions of the Meerwein–Pondorff–Verley reduction has been observed in a few cases, Adams, *et al.*, "Org. Reactions," Vol. II, p. 190.

(6) The ultraviolet absorption spectra were determined on a Beckmann quartz spectrophotometer using a hydrogen discharge tube as a source of radiation, solvent, absolute ethanol; $\epsilon = 1/cd \log I/I_0$, $c = 0.0001$ molar, $d = 1$ cm.

(7) Jacobs, Craig and Rothen, *Science*, **83**, 166 (1936).

(8) Ward, *Biochem. J.*, **17**, 891 (1923).

(9) All melting points are micro melting points. Microanalyses by Stephen Nagy of the Massachusetts Institute of Technology.

**4-Chloroindole (X).**—A mixture of 49 g. (0.25 mole) of 4-chloro-2-indolecarboxylic acid, 75 g. (0.125 mole) of cuprous chloride and 150 g. of quinoline was maintained under reflux for eight hours. The hot mixture was poured into ice and hydrochloric acid and repeatedly extracted with ether. The ether solution was washed with hydrochloric acid, water and sodium bicarbonate solution, dried over magnesium sulfate, and the residue from the distillation of the ether submitted to fractionation *in vacuo*. The yield of colorless oil was 30 g. (77.5%); b. p. 143° (10 mm.); $d^{20}_{20}$ 1.2485; $n^{20}D$ 1.6254; $M_D$ calcd. 42.43; $M_D$ found 42.93.

*Anal.* Calcd. for $C_8H_6NCl$: C, 63.38; H, 4.00. Found: C, 63.95; H, 4.15.

The picrate was prepared in ethanol solution and recrystallized from the same solvent; m. p. 171–173°.

*Anal.* Calcd. for $C_{14}H_9N_4O_7Cl$: C, 44.16; H, 2.38. Found: C, 44.31; H, 2.52.

**N-Benzoyl-4-chloroindole (XI).**—To a suspension of 1.15 g. (0.05 mole) of sodium sand in 20 ml. of dioxane was added 7.6 g. (0.05 mole) of 4-chloroindole and the mixture maintained under reflux for two hours to complete formation of the sodium derivative. A solution of 9.25 g. (0.05 mole) of benzoyl bromide in 5 ml. of dioxane was then added and the mixture maintained at reflux temperature for fifteen hours. The dioxane was distilled under diminished pressure, the residue extracted with a mixture of ether and water and the residue from the dried ether solution recrystallized from absolute ethanol; yield 6.2 g. (49%); m. p. 130–131°.

*Anal.* Calcd. for $C_{15}H_{10}NOCl$: C, 70.46; H, 3.94. Found: C, 70.36; H, 4.13.

**N-Benzoyl-6-chloroanthranilic Acid (XII).**—To a solution of 2.56 g. (0.01 mole) of N-benzoyl-4-chloroindole in 100 ml. of acetone was added, in portions, 10 g. (0.063 mole) of finely powdered potassium permanganate and the mixture stirred for fifteen hours. Fifty milliliters of ethanol was added and when the purple color had been discharged the manganese dioxide was separated by filtration and washed repeatedly with ethanol. The combined filtrates were concentrated to dryness under diminished pressure, dilute sodium hydroxide solution was added, 0.30 g. (14%) of unchanged starting compound removed by filtration, the filtrate acidified with hydrochloric acid, and the precipitate recrystallized from a mixture of ethanol and water; yield 1.38 g. (50%); m. p. 188–190°.

*Anal.* Calcd. for $C_{14}H_{10}NO_3Cl$: C, 61.00; H, 3.66. Found: C, 61.10; H, 3.79.

**6-Chloroanthranilic Acid (XIII).**—A solution of 1.38 g. (0.005 mole) of N-benzoyl-6-chloroanthranilic acid in 25 ml. of 10% sodium hydroxide solution was maintained under reflux for five hours, cooled, and acidified with dilute hydrochloric acid. The benzoic acid which separated weighed 500 mg. (82%). The filtrate was neutralized to *p*H 4 with solid sodium acetate and a solution of cupric acetate added dropwise. The copper salt which separated was collected by filtration, suspended in water, decomposed with hydrogen sulfide, and the filtrate from the copper sulfide concentrated to dryness *in vacuo*. The residue was recrystallized from benzene; yield 350 mg. (41%); m. p. 153–154°.[10]

*Anal.* Calcd. for $C_7H_6NO_2Cl$: C, 49.00; H, 3.52. Found: C, 49.10; H, 3.66.

The N-acetyl derivative was prepared by stirring a solution of 50 mg. of the sodium salt in 2 ml. of water with 0.5 ml. of acetic anhydride. The precipitate which separated after the solution had been chilled was recrystallized from water; m. p. 215–216°.[10]

**2,6-Dichlorobenzoic Acid (XIV).**—To a suspension at 0° of 86 mg. of 6-chloroanthranilic acid obtained from the oxidation of N-benzoyl-4-chloroindole in 1 ml. of 20% hydrochloric acid was added 35 mg. of sodium nitrite and the solution of the diazonium salt poured into a solution of 50 mg. of cuprous chloride in 20% hydrochloric acid and the solution allowed to come to room temperature. The precipitate was recrystallized from a mixture of equal quantities of benzene and ligroin; yield 72 mg. (76%); m. p. 143–144°.[11]

**4-Cyanoindole (III).**—A mixture of 9.78 g. (0.05 mole) of 4-chloro-2-indolecarboxylic acid (II), 6.7 g. (0.0375 mole) of cuprous cyanide, and 35 g. of quinoline was maintained at the reflux temperature of 237° for twenty hours. The hot dark-brown solution was poured into a mixture of 25 ml. of concentrated hydrochloric acid and ice and the well stirred precipitate collected by filtration and washed with water. The filtrate and precipitate were repeatedly extracted with ether, the ether solutions combined and washed with hydrochloric acid solution and water, dried over magnesium sulfate and concentrated under diminished pressure. The crystalline compound which remained was recrystallized from a large volume of water from which it separated in long, white silken needles; yield 3.6 g. (51%); m. p. 120–121°.

*Anal.* Calcd. for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 75.94; H, 4.27; N, 19.53.

The picrate was prepared in methanol and recrystallized from the same solvent; m. p. 164–165°.

*Anal.* Calcd. for $C_{15}H_9N_5O_7$: C, 48.52; H, 2.44. Found: C, 48.32; H, 2.60.

**4-Indolecarboxylic Acid.**—A suspension of 1 g. of 4-cyanoindole in 10 ml. of 20% potassium hydroxide solution was maintained at reflux temperature for twenty hours. The alkaline solution was extracted with ether, the aqueous phase acidified with dilute hydrochloric acid solution and the precipitate recrystallized from water; yield 0.90 g. (80%); m. p. 213–214°.

*Anal.* Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 66.95; H, 4.57.

The methyl ester was prepared by maintaining at reflux temperature a solution of the acid in a mixture of 1 ml. of concentrated sulfuric acid in 10 ml. of methanol. The solution was concentrated under diminished pressure, extracted with ether and with dilute sodium bicarbonate solution and the residue from the ether recrystallized from methanol; m. p. 146–147°.

*Anal.* Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.20; H, 5.13.

**4-Cyanogramine (IV).**—To a solution of 71.0 g. (0.5 mole) of 4-cyanoindole in 250 ml. of acetic acid was added 41 g. (0.5 mole) of a 36.5% aqueous solution of formaldehyde and 90 g. (0.5 mole) of a 25% aqueous solution of dimethylamine and the mixture allowed to stand at room temperature for twelve hours. The acetic acid was distilled under diminished pressure, 500 ml. of water was added, the solution clarified by filtration, and the filtrate alkalinized with dilute sodium hydroxide solution. The crystalline base which separated was collected from the cold solution by filtration and recrystallized from acetone; yield 94.5 g. (95%). The compound appears to be somewhat unstable at elevated temperature but melts abruptly between 175 and 180° if the melting point is approached rapidly.

*Anal.* Calcd. for $C_{12}H_{13}N_3$: C, 72.32; H, 6.57. Found: C, 72.25; H, 6.83.

**Ethyl α-Carbethoxy-β-(4-cyano-3-indole)-propionate (V).**—To a solution of 2.30 g. (0.1 mole) of sodium in 150 ml. of absolute ethanol was added 16.0 g. (0.1 mole) of diethyl malonate, and 9.96 g. (0.05 mole) of 4-cyanogramine, and, while the mixture was cooled externally, 12.6 g. (0.1 mole) of dimethyl sulfate was added dropwise. The homogeneous solution was maintained at reflux temperature for five hours and the ethanol distilled *in vacuo*. Water and ether were added to the residue, and the product from the dried ether extract was stirred with petroleum ether. The crystalline solid which remained was recrystallized from ethanol; yield 10.2 g. (65%); m. p. 110–111°.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77. Found: C, 64.67; H, 5.61.

(10) Cohn, *Monatsh.*, **22**, 473 (1901).

(11) Norris and Bearse, THIS JOURNAL, **62**, 956 (1940).

**α-Carboxy-β-(4-cyano-3-indole)-propionic Acid.**—To a solution of 31.4 g. (0.1 mole) of ethyl α-carbethoxy-β-(4-cyano-3-indole)-propionate (V) in 250 ml. of ethanol was added a solution of 24 g. (0.4 mole) of potassium hydroxide in 25 ml. of water and the mixture maintained at reflux temperature for one-half hour. The solution was diluted with water, the ethanol removed under diminished pressure, the aqueous residue clarified by filtration, acidified with hydrochloric acid, and the precipitate collected by filtration and recrystallized from water; yield 24.6 g. (95%); m. p. 210–212°.

*Anal.* Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90. Found: C, 60.06; H, 4.01.

**β-(4-Cyano-3-indole)-propionic Acid.**—(a) The malonic acid derivative was maintained at the melting point until the evolution of carbon dioxide had ceased and the crystalline residue recrystallized from a mixture of ethanol and water. (b) To a solution of 2.42 g. (0.01 mole) of ethyl β-(4-cyano-3-indole)-propionate (VI) in 20 ml. of ethanol was added 7 ml. of 10% sodium hydroxide solution and the mixture maintained under reflux for one hour. The ethanol was removed under diminished pressure, the residue extracted with ether, and the aqueous solution acidified with dilute hydrochloric acid. The precipitate was recrystallized from a mixture of ethanol and water; yield 2.0 g. (93.5%); m. p. 205–207°.

*Anal.* Calcd. for $C_{12}H_{16}N_2O_2$: C, 67.27; H, 4.70. Found: C, 67.17; H, 4.75.

The methyl ester was prepared by maintaining under reflux a solution of the acid in a solution of 1 ml. of concentrated sulfuric acid in 10 ml. of methanol. The ester was recrystallized from methanol; m. p. 138–139°.

*Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30. Found: C, 68.36; H, 5.35.

**Ethyl β-(4-Cyano-3-indolepropionate (VI).**—A solution of 15.7 g. (0.05 mole) of ethyl α-carbethoxy-β-(4-cyano-3-indole)-propionate (V) in a mixture of 18 ml. (0.05 mole) of 10% sodium hydroxide solution, 50 ml. of ethanol and 50 ml. of water was maintained under reflux for five hours. The ethanol was removed under diminished pressure, the aqueous solution extracted with ether and the acid precipitated by the addition of dilute hydrochloric acid, filtered and dried. The yield was 12.2 g. (85%). The acid was decarboxylated by maintaining at 200° for five minutes. The ester which crystallized when the melt had been allowed to cool was recrystallized from a mixture of ethanol and water, yield 9.8 g. (95%); m. p. 153–154°.

*Anal.* Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.38; H, 5.96.

**β-(4-Carboxy-3-indole)-propionic Acid (VII).**—To 20 ml. of 30% potassium hydroxide solution was added 2.42 g. (0.01 mole) of ethyl β-(4-cyano-3-indole)-propionate (VI) and the mixture was maintained under reflux for fifty hours by which time the evolution of ammonia had nearly ceased. The solution was brought to the neutral point with hydrochloric acid, clarified with Norite, and the filtrate acidified with hydrochloric acid. The precipitate was collected by filtration and recrystallized from water; yield 2.1 g. (90%); m. p. 188–189°; molecular weight calcd. 233.22; found, by neut. equiv., 233.

*Anal.* Calcd. for $C_{12}H_{11}NO_4$: C, 61.80, H, 4.76. Found: C, 61.65; H, 4.94.

**Methyl β-(4-Carbomethoxy-3-indole)-propionate.**—A solution of 2.33 g. (0.10 mole) of β-(4-carboxy-3-indole)-propionic acid (VII) in a mixture of 3 ml. of concentrated sulfuric acid and 30 ml. of methanol was maintained under reflux for fifteen hours. The solution was concentrated under diminished pressure, extracted with ether and sodium bicarbonate solution, and the crystalline residue from the ether extract recrystallized from ethanol; yield 1.96 g. (75%); m. p. 84–85°.

*Anal.* Calcd. for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.79. Found: C, 64.30; H, 6.02.

The N-acetyl derivative (XV) was prepared by maintaining under reflux for ten hours an acetic anhydride solution of the ester, concentrating to dryness under diminished pressure, and recrystallizing from ethanol; m. p. 105–106°.

*Anal.* Calcd. for $C_{16}H_{17}NO_5$: C, 63.35; H, 5.65. Found: C, 63.12; H, 5.53.

**5-Keto-1,3,4,5-tetrahydrobenz[cd]indole (VIII).**—A solution of 2.33 g. (0.01 mole) of β-(4-carboxy-3-indole)-propionic acid (VII) and 0.20 g. of potassium cyanide in 100 ml. of acetic anhydride was maintained at reflux temperature for twenty hours. The acetic anhydride was distilled under diminished pressure, the residue dissolved in a mixture of 40 ml. of 10% potassium hydroxide solution and 40 ml. of ethanol and the solution maintained under reflux for one hour. The ethanol was distilled under diminished pressure and the crystalline product which separated was extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and 0.21 g. (9%) of unchanged dicarboxylic acid was collected by filtration. The washed and dried ether solution was concentrated and the crystalline residue recrystallized from ethanol; yield 1.37 g. (80%); m. p. 165–166°.

*Anal.* Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.96; H, 5.37; N, 8.21.

The semicarbazone was prepared in aqueous ethanol and recrystallized from ethanol; m. p. 215–216°.

*Anal.* Calcd. for $C_{12}H_{12}N_4O$: C, 63.14; H, 5.31. Found: C, 63.21; H, 5.30.

The *p*-nitrophenylhydrazone was prepared in ethanol and recrystallized from the same solvent; m. p. 235–236°.

*Anal.* Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61. Found: C, 66.68; H, 4.83.

**1,3,4,5-Tetrahydrobenz[cd]indole (IX).**—A mixture of 510 mg. (0.003 mole) of the ketone (VIII), 0.4 ml. of 85% hydrazine hydrate, 560 mg. of potassium hydroxide, and 4 ml. of diethylene glycol was maintained at 200° for four hours. The dark brown solution was poured into 10 ml. of water and extracted with ether. The residue from the washed ether extract was recrystallized from a mixture of ethanol and water. The glistening white plates melted at 55–56° and a mixed melting point with a sample of 1,3,4,5-tetrahydrobenz[cd]indole[12] prepared by sodium–butanol reduction of naphthostyril[13] was 55–56°; yield 300 mg. (64%).

*Anal.* Calcd. for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.21; H, 7.11; N, 9.04.

The picrate was prepared in ethanol and recrystallized from the same solvent. The melting point was 164–166° and a mixed melting point with a sample prepared from the indole obtained by sodium–butanol reduction of naphthostyril was 164–166°.

*Anal.* Calcd. for $C_{17}H_{14}N_4O_7$: C, 52.85; H, 3.65. Found: C, 52.80, H, 3.64.

**5-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole (XVI).**—To a solution of 227 mg. (0.006 mole, twice the theoretical quantity) of lithium aluminum hydride in 30 ml. of absolute ether was added dropwise a solution of 1.03 g. (0.006 mole) of the ketone (VIII) in 20 ml. of absolute ether. The yellow color was at once discharged and the metal complex separated as a flocculent white precipitate. After the mixture had been maintained under reflux for ten minutes, water was added dropwise and the ether solution washed with 20% sulfuric acid, water, and sodium bicarbonate solution, and dried over magnesium sulfate. The crystalline residue from the ether was recrystallized from water; yield 780 mg. (75%); m. p. 126–127°.

*Anal.* Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40. Found: C, 76.50; H, 6.63.

The *p*-nitrobenzoate was prepared with *p*-nitrobenzoyl chloride in pyridine and was recrystallized from methanol; m. p. 140–141°.

*Anal.* Calcd. for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38. Found: C, 66.80; H, 4.28.

(12) Ring Index No. 1681.

(13) Jacobs and Gould, *J. Biol. Chem.*, **120**, 141 (1937).

**5-Hydroxy-1,3,4,5-tetrahydrobenz[cd]indole Isopropyl-Ether (XVII).**—To a solution of 50 mg. of aluminum in 10 ml. of absolute isopropyl alcohol was added 171 mg. (0.001 mole) of the ketone (VIII) and the mixture maintained at reflux temperature for four hours. The isopropyl alcohol was distilled under diminished pressure and the residue extracted with ether and 10% sodium hydroxide solution. The residue from the washed and dried ether solution was recrystallized from a mixture of ethanol and water; yield 138 mg. (64%); m. p. 131–132°. The compound did not react with *p*-nitrobenzoyl chloride or with phenyl isocyanate.

*Anal.* Calcd. for $C_{14}H_{17}NO$: C, 78.11; H, 7.96. Found: C, 78.11; H, 7.91.

**Acknowledgments.**—This work was supported in part by a grant from the Eli Lilly and Company, Indianapolis, Indiana. The author is indebted to Louis S. Harris for assistance in certain of the experiments.

## Summary

A synthesis of 4-substituted indoles has been developed. 4-Cyanoindole has been converted through the Mannich base to β-(4-carboxy-3-indole)-propionic acid, and cyclization of the dicarboxylic acid has afforded a new synthesis of the tricyclic 1,3,4,5-tetrahydrobenz[cd]indole ring system.

BOSTON 15, MASS. RECEIVED JULY 26, 1948

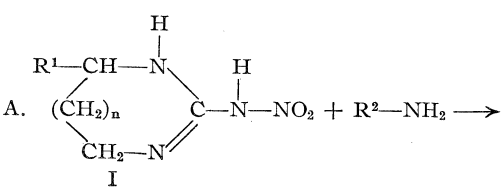
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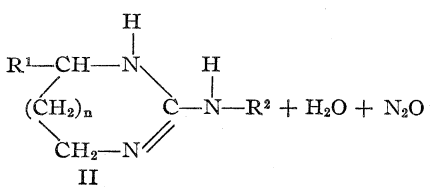
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY, AND THE RESEARCH AND BIOLOGICAL LABORATORIES, AYERST, MCKENNA AND HARRISON, LTD., MONTREAL]

# The Reaction of Primary Amines with 2-Nitramino-$\Delta^2$-1,3-diazacycloalkenes

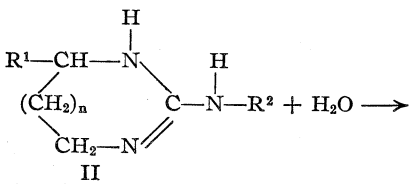
BY A. F. MCKAY, M. N. BUCHANAN AND GORDON A. GRANT

When 2-nitramino-$\Delta^2$-1,3-diazacycloalkenes[1] I are heated in the presence of primary amines a rapid evolution of gas occurs and the nitramino group is replaced by a substituted amino group. This reaction is analogous to the one described by Davis and Elderfield[2] in the preparation of *sym*-dibutylguanidine from N-butyl-N$^1$-nitroguanidine and butylamine in the presence of water. On the other hand, N-methyl-N$^1$-nitroguanidine and N-ethyl-N$^1$-nitroguanidine on heating with aqueous methylamine and aqueous ethylamine respectively gave the corresponding alkylureas. This would be expected because of the large volumes of water used by these authors. A. W. Hofmann[3] found that *sym*-triethylguanidine monohydrate on distillation decomposed into ethylamine and *sym*-diethylurea. Therefore, in order to eliminate the formation of cyclic ureas the 2-nitramino-$\Delta^2$-1,3-diazacycloalkenes I were heated with the anhydrous amines (reaction A). Water, however, is produced during this reaction in sufficient quantities to effect hydrolysis of part of the product II by reaction B.

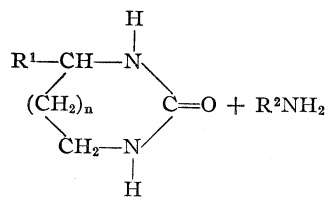




(1) A. F. McKay and G. F. Wright, THIS JOURNAL, **70**, 430 (1948).
(2) T. L. Davis and R. C. Elderfield, *ibid.*, **55**, 731 (1933).
(3) A. W. Hofmann, *Jahresber. Fortschr. Chem.*, 516 (1861).



(B)



III

$R^1$ = $CH_3$ or H; $R^2$ = alkyl or aralkyl; $n$ = 0 or 1

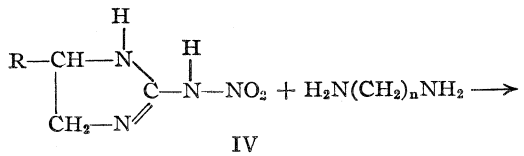
The 1,3-diazacyclopentene-2 I ($n$ = 0) compounds displayed less tendency to form urea derivatives than the 1,3-diazacyclohexene-2 I ($n$ = 1) compounds. On heating 2-nitramino-$\Delta^2$-1,3-diazacyclopentene or 2-nitramino-$\Delta^2$-1,3-diazacyclohexene with a primary amine until gas evolution ceased the former compound gave 4–8% 1,3-diazacyclopentanone-2 III ($n$ = 0, R′ = H) while the latter gave a 22% yield of 1,3-diazacyclohexanone-2 III ($n$ = 1; $R^1$ = H). These yields of cyclic ureas were decreased considerably by using a large excess (2–10 mole equivalents) of the amine which was slowly distilled during the course of the reaction. This excess amine on slow distillation carried with it the water produced during the reaction. The 2-alkylamino- and 2 aralkylamino-$\Delta^2$-1,3-diazacycloalkenes prepared in this manner are recorded along with their properties in Table I.

The formation of cyclic urea derivatives by the reaction of water with the 2-alkylamino- or 2-aralkylamino-$\Delta^2$-1,3-diazacycloalkenes II rather than with the corresponding 2-nitramino-$\Delta^2$-1,3-diazacycloalkenes I was verified by refluxing

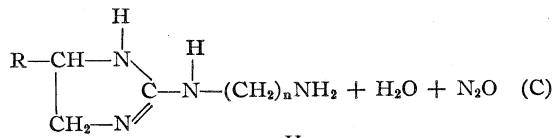
both types of compounds in water for a period of eight hours. 2-Nitramino-1,3-diazacyclohexene-2 was recovered unchanged while (4 or 6)-methyl-2-benzylamino-1,3-diazacyclohexene-2 gave a 58% yield of 4-methyl-1,3-diazacyclohexanone-2 III ($n = 1$, $R^1 = CH_3$).

During the course of these studies 1,3-diazacyclohexanone-2 and 4-methyl-1,3-diazacyclohexanone-2 were isolated and characterized. 1,3-Diazacyclohexanone-2[4] and 4-methyl-1,3-diazacyclohexanone-2[5] have been described previously.

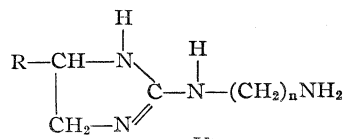
When diamines, *e. g.*, ethylenediamine, are used in place of primary amines, then two products may be obtained



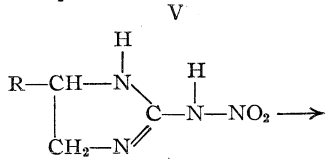
IV



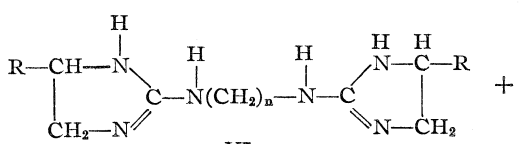
V (C)



V



IV



VI $H_2O + N_2O$ (D)

R = $CH_3$ or H

The expected compounds N-2-[4(or 5)-methyl-1,3-diazacyclopentene-2]-ethylenediamine V (R = $CH_3$) and N,N$^1$-2-[4(or 5)-methyl-1,3-diazacyclopentene-2]-ethylenediamine VI (R = $CH_3$) were obtained when ethylenediamine and 4 (or 5)-methyl-2-nitramino-1,3-diazacyclopentene-2 IV (R = $CH_3$) were heated together. On heating 2-nitramino-1,3-diazacyclopentene-2 IV (R = H) in a large excess of ethylenediamine N-2-(1,3-diazacyclopentene-2)-ethylenediamine V (R = H) was obtained. These compounds are described in Table I.

In the compounds prepared by reactions A, C and D, the double bond has been placed in the ring in agreement with the parent 2-nitramino-$\Delta^2$-1,3-diazacycloalkenes[1] and the results of the hydrolysis studies.

**Acknowledgment.**—The authors wish to thank Dr. A. S. Cook of Ayerst, McKenna and Harrison, Ltd., for a Grant-in-aid of this work and Miss C. Jockel of Ayerst, McKenna and Harrison Laboratories for the microanalyses.

## Experimental

**Preparation of 2-Alkylamino-$\Delta^2$-1,3-diazacyclopentenes.**—A mixture of the 2-nitramino-1,3-diazacyclopentene-2 with 1.1 to 4 mole equivalents of primary amine and xylene was heated under reflux for ten to thirty minutes. This was the time required for cessation of gas evolution which indicated that the reaction had gone to completion. The larger molar excesses of amines were used with the lower boiling amines. At the end of the reaction period the reaction mixture was distilled at atmospheric pressure until the vapor temperature reached 140°. The residue was then distilled at reduced pressure (0.1–5 mm.) to give the desired products as colorless crystalline solids or oils. The yields of 2-alkylamino-$\Delta^2$-1,3-diazacyclopentenes varied from 94.7–99% by theory. The picrates were formed by dissolving 0.5–1.0 g. of the 2-alkylamino-$\Delta^2$-1,3-diazacyclopentenes in a minimum of hot water and adding saturated picric acid solution until precipitation was complete. The crystalline picrates were recrystallized from water to a constant melting point and analyzed.

**2-Benzylamino-1,3-diazacyclopentene-2.**—A mixture of 74.6 g. (0.697 mole) of benzylamine and 46.5 g. (0.357 mole) of 2-nitramino-1,3-diazacyclopentene-2 was gently heated until the evolution of gas had ceased. The solution was then distilled *in vacuo* (1.0 mm.) to give a colorless oil which solidified on cooling, yield 60.7 g. (97%). The picrate of this compound was formed by dissolving 0.5 g. in a minimum amount of hot water and adding a saturated solution of picric acid. After two recrystallizations from water it melted at 150.5–151.5°.

**2-($\beta$-Phenylethylamino)-1,3-diazacyclopentene-2.**—Twenty-six grams (0.20 mole) of 2-nitramino-1,3-diazacyclopentene-2 and 48.5 g. (0.40 mole) of $\beta$-phenylethylamine were heated together cautiously to effect slow distillation of the excess amine. After the completion of gas evolution, the remaining liquid was distilled at reduced pressure. The distillate was a water-white oil which solidified on cooling, yield 35.6 g. (94.2%). The picrate was formed in the usual manner, and after two recrystallizations from water melted at 186.4–186.9°.

**N-$\alpha$-Naphthyl-N$^1$-1,3-diazacyclopentene-2-ethylenediamine.**—A suspension of 5.9 g. (0.045 mole) of 2-nitramino-1,3-diazacyclopentene-2 and 8.4 g. (0.045 mole) of N-$\alpha$-naphthylethylenediamine in 15 cc. of xylene was heated for twenty-five minutes. On cooling the reaction mixture solidified. This solid was triturated with ether (30 cc.) then filtered, washed with fresh ether (30 cc.) and dried. The crude yield was 9.2 g. (80.6%) which melted at 151–157°. A wasteful crystallization of 2.04 g. from 15 cc. of 95% ethanol raised the melting point to 175°. A sample of this material was converted to the picrate in the usual way and after two recrystallizations from water deep-red needles which melted at 144.8–145.6° were obtained.

**2-Benzylamino-1,3-diazacyclohexene-2.**—Seventy-two grams (0.50 mole) of 2-nitramino-1,3-diazacyclohexene-2 was added to 172 g. (1.60 mole) of benzylamine and heated to a temperature sufficient to maintain a slow rate of distillation of the excess benzylamine. This distillation at atmospheric pressure was continued until gas evolution ceased after which the residue was distilled *in vacuo*. A crystalline distillate of the desired product mixed with propylene urea (1,3-diazacyclohexanone-2) was obtained, yield 80.3 g. The cyclic urea by-product was separated by treating the distillate with sufficient chloroform to dis-

(4) E. Fischer and H. Koch, *Ann.*, **232**, 224 (1886); A. P. N. Franchimont and H. Friedmann, *Rec. trav. chim.*, **26**, 218 (1907).

(5) J. Tafel and A. Weinschenk, *Ber.*, **33**, 3378 (1900).

Table I

| Compound | Yield, % | B. p. °C.[b] | Mm. |
|---|---|---|---|
| 2-Butylamino-1,3-diazacyclopentene-2 | 97.5 | 140 | 0.5 |
| 2-Isobutylamino-1,3-diazacyclopentene-2 | 96.0 | 144 | 0.5 |
| 2-Amylamino-1,3-diazacyclopentene-2 | 96.0 | 158 | 0.1 |
| N-α-Naphthyl-N¹-1,3-diazacyclopentene-2-ethylenediamine | 80.6 | N. D.[f] | .. |
| 2-β-Phenylethylamino-1,3-diazacyclopentene-2 | 94.2 | 215 | 1.0 |
| 2-Benzylamino-1,3-diazacyclopentene-2 | 97.0 | 195 | 1.0 |
| 4(or 5)-Methyl-2-butylamino-1,3-diazacyclopentene-2 | 94.7 | 175 | 1.0 |
| 4(or 5)-Methyl-2-isobutylamino-1,3-diazacyclopentene-2 | 99.0 | 133 | 0.09 |
| 4(or 5)-Methyl-2-amylamino-1,3-diazacyclopentene-2 | 98.0 | ..... | .. |
| 2-Benzylamino-1,3-diazacyclohexene-2 | 77.5 | 165–172 | 0.1 |
| 2-β-Phenylethylamino-1,3-diazacyclohexene-2 | 76.6 | ..... | ... |
| 4(or 6)-Methyl-2-(3-diethylaminopropylamino)-1,3-diazacyclohexene-2 | 78.2 | 180 | 1.0 |
| 4(or 6)-Methyl-2-benzylamino-1,3-diazacyclohexene-2 | 92.0 | 172–175 | 0.1 |
| 4( or 6)-Methyl-2-β-phenylethylamino-1,3-diazacyclohexene-2 | 76.0 | 180 | .1 |
| 4(or 6)-Methyl-2-β-hydroxyethylamino-1,3-diazacyclohexene-2 | 98.0 | 180 | .1 |
| N-2-(1,3-Diazacyclopentene-2)-ethylenediamine | 78.1 | 188–191 | .7 |
| N-2-(4(or 5)-Methyl-1,3-diazacyclopentene-2)-ethylenediamine | 72.0[a] | 184–187 | .05 |
| N,N¹-2-(4(or 5)-Methyl-1,3-diazacyclopentene-2)-ethylenediamine | 17.0[a] | 250–260 | .2 |

[a] Both compounds obtained in the same reaction, total yield 89.0%. [b] These boiling points are high because the pressure in the distillation apparatus was found to be higher than that recorded by the manometer. [c] All melting points uncorrected. [d] Dipicrates. [e] This picrate crystallized in two forms melting at 148–149° and 159–159.5°. [f] N. D. Not distilled.

solve the 2-benzylamino-1,3-diazacyclohexene-2. The chloroform-insoluble cyclic urea was then removed by filtration, washed with fresh chloroform (20 cc.), and dried, yield 7.0 g. (14%). This crude 1,3-diazacyclohexanone-2 melted at 260°. Two recrystallizations from 95% ethanol raised the melting point to 265–266°.

*Anal.* Calcd. for $C_4H_8N_2O$: C, 48.0; H, 8.00; N, 28.0. Found: C, 47.9; H, 8.02; N, 27.9.

The picrate was prepared by dissolving 0.6 g. of the cyclic urea in 15 cc. of water and adding 200 cc. of a saturated aqueous picric acid solution. The crystalline picrate (m. p. 188–189°) after two recrystallizations from water melted at 190–191°.

*Anal.* Calcd. for $C_{10}H_{11}N_5O_8$: C, 36.4; H, 3.34; N, 21.26. Found: C, 36.4; H, 3.30; N, 21.32.

Another aliquot of the cyclic urea on nitration by the method described by McKay and Wright[6] gave an 86.0% yield of 1,3-dinitro-1,3-diazacyclohexanone-2 (m. p. 120–121°). This latter product did not depress the melting point of an authentic sample of 1,3-dinitro-1,3-diazacyclohexanone-2 (m. p. 121–122°).

The chloroform filtrate from the cyclic urea on evaporation gave 73.3 g. (77.5%) of 2-benzylamino-1,3-diazacyclohexane-2. Its picrate, made in the usual manner, was found to exist in two forms. Both are needles and can be crystallized from water, although this procedure sometimes converts one form into the other. The more common form melts at 147–148°, while the other melts at 159–159.5°. Both forms gave analytical values in agreement with the theoretical for the monopicrate of 2-benzylamino-1,3-diazacyclohexene-2.

**4(or 6)-Methyl-2-benzylamino-1,3-diazacyclohexene-2.**—A large excess (36.9 g., 0.34 mole) of benzylamine was added to 6.5 g. (0.041 mole) of 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 in a Claisen flask having a six-cm. Vigreux column side-arm. The excess amine was then distilled at a rate sufficient to maintain the vapor temperature at 160° until the reaction was complete. This required thirty minutes. The residue was then distilled at reduced pressure. The distillate was a clear, viscous, light-yellow oil, yield 7.7 g. (92.5%). The monopicrate prepared in the usual way melted at 128.7–129° after two recrystallizations from water.

(6) A. F. McKay and G. F. Wright, This Journal, **70**, 3990 (1948).

**2-(β-Phenylethylamino)-1,3-diazacyclohexene-2.**—To 35 g. (0.289 mole) of boiling β-phenylethylamine, in the reaction flask of a distillation apparatus, was added 34.6 g. (0.240 mole) of 2-nitramino-1,3-diazacyclohexene-2 suspended in 73.1 g. (0.604 mole) of β-phenylethylamine. The sludge was added slowly, enough time being allowed between portions for the frothing from the previous addition to subside. After the addition was complete, the reaction mixture was slowly distilled until no further gassing could be observed. The residue was then distilled under reduced pressure. The main fraction contained some sublimed cyclic urea derivative. Separation of the 1,3-diazacyclohexanone-2 from the 2-(β-phenylethylamino)-1,3-diazacyclohexene-2 was effected by solution of the latter compound in xylene (3.25 cc./g.) and filtering off the insoluble cyclic urea. It melted at 263° alone and on admixture with an authentic sample of 1,3-diazacyclohexanone-2 (m. p. 265°), yield 2.7 g. (11.2%). After removal of the xylene from the filtrate 37.4 g. (76.8%) of 2-(β-phenylethylamino)-1,3-diazacyclohexene-2 was obtained. The picrate of this compound after six recrystallizations from water melted at 197–198°.

**4(or 6)-Methyl-2-(β-phenylethylamino)-1,3-diazacyclohexene-2.**—The distillation procedure was used in treating 30.9 g. (0.195 mole) of 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 with 48.5 g. (0.40 mole) of β-phenylethylamine. The slow distillation was continued for twenty-five minutes until gassing stopped. To the cooled (20°) reaction mixture ether (50 cc.) was added, and the insoluble 4-methyl-1,3-diazacyclohexanone-2 was filtered off and washed with ether (10 cc.). The white crystals which melted at 200.5–205°, were obtained in 18.46% yield (4.1 g.). The cyclic urea after two sublimations *in vacuo* (11 mm.) melted at 203.5–205°. A sample of the final sublimate was taken for analysis.

*Anal.* Calcd. for $C_5H_{10}N_2O$: C, 52.6; H, 8.77; N, 24.5. Found: C, 52.4; H, 8.92; N, 25.0.

After evaporation of the ether from the filtrate, it was distilled under reduced pressure. A viscous yellow oil was obtained, yield 32.2 g. (76%). The picrate was recrystallized four times from water and finally melted at 175.5–176.5°.

**4(or 6)-Methyl-2-(3-diethylaminopropylamino)-1,3-diazacyclohexene-2.**—A mixture of 23.7 g. (0.15 mole) of 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 and 52.1 g. (0.40 mole) of 3-diethylaminopropylamine was

TABLE I (*Continued*)

| Picrate (m. p., °C.)[c] | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|
| 173–174 | $C_{13}H_{18}N_6O_7$ | 42.1 | 4.90 | 22.7 | 41.9 | 4.71 | 22.5 |
| 181–182 | $C_{13}H_{18}N_6O_7$ | 42.1 | 4.90 | 22.7 | 42.3 | 4.87 | 22.8 |
| 154–155.5 | $C_{14}H_{20}N_6O_7$ | 43.7 | 5.24 | 21.8 | 43.8 | 4.96 | 21.8 |
| 145.5 | $C_{21}H_{21}N_7O_7$ | 52.1 | 4.38 | 20.3 | 52.2 | 4.35 | 20.3 |
| 186.4–186.9 | $C_{17}H_{18}N_6O_7$ | 48.8 | 4.34 | 20.1 | 48.9 | 4.40 | 20.1 |
| 150.5–151.5 | $C_{16}H_{16}N_6O_7$ | 47.5 | 3.99 | 20.8 | 47.3 | 4.07 | 21.0 |
| 136–137 | $C_{14}H_{20}N_6O_7$ | 43.7 | 5.24 | 21.8 | 43.6 | 5.14 | 21.8 |
| 137–138 | $C_{14}H_{20}N_6O_7$ | 43.7 | 5.24 | 21.8 | 44.1 | 5.46 | 21.7 |
| 142–143 | $C_{15}H_{22}N_6O_7$ | 45.2 | 5.56 | 21.1 | 45.0 | 5.53 | 21.0 |
| 159–159.5[e] | $C_{17}H_{18}N_6O_7$ | 48.8 | 4.34 | 20.1 | 48.9 | 4.45 | 20.4 |
| 198.5–199.5 | $C_{18}H_{20}N_6O_7$ | 50.0 | 4.66 | 19.4 | 50.1 | 4.84 | 19.8 |
| 141–142 | $C_{24}H_{32}N_{10}O_{14}$[d] | 42.1 | 4.70 | 20.5 | 42.0 | 4.80 | 20.9 |
| 128.7–129 | $C_{18}H_{20}N_6O_7$ | 50.0 | 4.67 | 19.4 | 50.0 | 4.66 | 19.6 |
| 175.5–176.5 | $C_{19}H_{22}N_6O_7$ | 51.1 | 4.97 | 18.8 | 51.0 | 4.97 | 19.0 |
| 135.4–136 | $C_{13}H_{18}N_6O_8$ | 40.4 | 4.20 | 21.7 | 40.9 | 4.40 | 21.8 |
| 199–200 | $C_{17}H_{18}N_{10}O_{14}$[d] | 23.9 | 2.91 | 34.8 | 24.0 | 3.01 | 35.0 |
| 200–201 | $C_{18}H_{20}N_{10}O_{14}$[d] | 36.0 | 3.33 | 23.3 | 36.0 | 3.20 | 23.6 |
| 228–229 | $C_{22}H_{26}N_{12}O_{14}$[d] | 38.7 | 3.84 | 24.6 | 38.7 | 3.76 | 24.7 |

heated to distillation temperature and a slow rate of distillation was maintained until the reaction had gone to completion. The remaining excess of 3-diethylaminopropylamine was distilled over and the cooled (20°) residue was triturated with ether (30 cc.). The insoluble cyclic urea by-product was removed by filtration and washed with ether (10 cc.), yield 3.2 g. (18.7%). It melted at 202–205° alone and on admixture with an authentic sample of 4-methyl-1,3-diazacyclohexanone-2 (m. p. 203.5–205°).

The ether was evaporated from the ethereal filtrate and the residue distilled under reduced pressure. A viscous oil was obtained yield 27.2 g. (78%). A portion of this oil (0.5 g.) was dissolved in 95% ethanol and treated with a saturated aqueous solution of picric acid. The crystalline dipicrate thus obtained melted at 141–142° after three recrystallizations from water.

**4(or 6)-Methyl-2-(β-hydroxyethylamino)-1,3-diazacyclohexene-2.**—The distillation technique was applied in the reaction of 7.9 g. (0.050 mole) of 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 with 18.3 g. (0.30 mole) of ethanolamine. The temperature of the distilling vapors was not allowed to drop below 150°. The reaction proceeded very rapidly, about four minutes being required for completion. The residual oil was distilled *in vacuo*. The distillate had a slight haziness due to the presence of a small amount (0.1 g.) of the cyclic urea by-product. The yield was 7.7 g. or 98.2%. The monopicrate prepared in the usual way melted at 135.4–136° after one recrystallization from water.

**N-2-(1,3-Diazacyclopentene-2)-ethylenediamine.**—Thirty grams (0.50 mole) of ethylenediamine (98–100%) was placed in a beaker and heated to 80–90°. This temperature was maintained during the portionwise addition of 6.5 g. (0.05 mole) of 2-nitramino-1,3-diazacyclopentene-2 which required twenty minutes. The reaction mixture was heated for a further five minutes and then transferred to a Claisen distilling flask and distilled *in vacuo*. After the excess ethylenediamine had distilled, a white crystalline distillate was obtained, yield 5 g. (78.1%). A portion (0.7 g.) of this product was dissolved in 15 cc. of warm water and 200 cc. of a saturated aqueous picric acid solution was added. The crystalline picrate (3.1 g.) melted at 179–181°. This melting point was raised to 199–200° by three recrystallizations from water (100 cc./g.).

**N-2-(4(or 5)-Methyl-1,3-diazacyclopentene-2)-ethylenediamine and N,N¹-2-(4(or 5)-Methyl-1,3-diazacyclopentene-2)-ethylenediamine.**—Forty grams (0.278 mole) of 4(or 5)-methyl-2-nitramino-1,3-diazacyclopentene-2 was added portionwise to 200 g. (3.33 mole) of ethylenediamine (98–100%) over a period of forty-five minutes. During the reaction period the temperature was held at 80–90°. After the addition of the 2-nitramino compound, the reaction mixture was heated for a further fifteen minutes until all signs of gas evolution disappeared. The unreacted ethylenediamine was removed by distilling the reaction mixture at atmospheric pressure until the vapor temperature reached 116°. The residue was then distilled *in vacuo* to give a main fraction consisting of a light-yellow oil (b. p. (0.05 mm.) 184–187°). This proved to be the mono-substituted ethylenediamine, yield 28.4 g. (71.9%). A second fraction (b. p. (0.2 mm.) 250–260°) was distilled over as an orange liquid which crystallized on cooling, yield 5.3 g. (17.0%). A sample (1 g.) of this latter fraction was dissolved in 15 cc. of water and treated with 200 cc. of a saturated aqueous picric acid solution. The crystalline picrate melted at 213–215°, yield 1.7 g. A constant melting point of 228–229° was obtained after four recrystallizations from water (700 cc./g.). The analytical values of this compound were in good agreement with the calculated for the dipicrate of N,N¹-2-(4(or 5) methyl-1,3-diazacyclopentene-2)-ethylenediamine.

An aliquot of the yellow oil (b. p. (0.05 mm.) 184–187°) gave a crystalline dipicrate which first melted at 190–192°. Six recrystallizations from water (60 cc./g.) raised the melting point to 200–201°.

**Hydrolysis of 4(or 6)-Methyl-2-benzylamino-1,3-diazacyclohexene-2.**—A solution of 9.2 g. (0.045 mole) of 4(or 6)-methyl-2-benzylamino-1,3-diazacyclohexene-2 in 30 cc. of 37% aqueous ethanol was refluxed for eight hours. After removal of the water and ethanol *in vacuo*, the residue was distilled. The main fraction consisted of unchanged starting material and 4-methyl-1,3-diazacyclohexanone-2. These compounds were separated by dissolving in 100 cc. of hot absolute ethanol, adding 20 cc. of absolute ether and cooling to −20°. The white precipitate of the cyclic urea was recovered by filtration, washed with ether and dried. This product was obtained in 58% yield and melted at 178–200°. One recrystallization from ethanol–ether followed by a sublimation *in vacuo* gave crystals melting at 200–204° alone and on admixture with an authentic sample of 4-methyl-1,3-diazacyclohexanone-2.

**Effect of Refluxing 4(or 6)-Methyl-2-nitramino-1,3-diazacyclohexene-2 with Water.**—Seven grams (0.044 mole) of 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 in 25 cc. of water was refluxed continuously for ten hours. It was then concentrated to 15 cc. and cooled to room temperature. The white crystals melted at 146–147.5°

alone and on admixture with the original 4(or 6)-methyl-2-nitramino-1,3-diazacyclohexene-2 (m. p. 147–148°). The recovery of original material was 6.2 g. (88% by weight).


## Summary

A new method of preparation of 2-alkylamino- and 2-aralkylaminoimidazolines and -tetrahydropyrimidines is described. The formation of cyclic ureas, *e. g.*, 1,3-diazacyclohexanone-2, as by-products in this reaction is discussed.


KINGSTON, ONTARIO RECEIVED OCTOBER 4, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Acylations of Certain α-Alkoxy and α-Aryloxy Ketones and Esters[1]

BY JON MUNCH-PETERSEN[2] AND CHARLES R. HAUSER

Although many acylations of ketones[3] and esters[4] have been described in the literature, relatively few successful acylations of α-alkoxy and α-aryloxy ketones and esters have been reported previously. The present paper describes some new contributions to this field. Various condensing agents have been employed.

**Acylations of α-Alkoxy and α-Aryloxy Ketones.**—Apparently the only acylations of this type effected previously are those reported by Malkin and Robinson[5] who acylated α-methoxy and α-4-dimethoxyacetophenone with ethyl formate using sodium ethoxide. The copper salts of the resulting β-ketoaldehydes (named as enols) were obtained in yields of 16 and 81%, respectively.[6]

We have found that, in contrast to acetophenone, α-methoxyacetophenone fails to be acylated with ethyl acetate, ethyl propionate, or ethyl benzoate, and α-phenoxyacetophenone fails to be acylated with ethyl acetate, employing sodium amide under the usual conditions.[3a] Similarly α-methoxyacetophenone fails to be acylated with ethyl acetate employing potassium triphenylmethide[7] in refluxing ether. In each of these cases, the methoxy or phenoxy ketone was largely recovered. However, both of these ketones may be acylated with phenyl benzoate or phenyl propionate by means of sodium amide. The benzoylations of α-methoxyacetophenone and α-phenoxyacetophenone have been effected in yields of 26 and 59%, respectively.

$$C_6H_5COOC_6H_5 + C_6H_5OCH_2COC_6H_5 \xrightarrow{NaNH_2} C_6H_5COCHCOC_6H_5 + C_6H_5OH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OC_6H_5$$

The benzoylation of α-methoxyacetophenone has also been effected with benzoyl chloride but the yield was only 11%. The propionylations of α-methoxyacetophenone and α-phenoxyacetophenone have been effected in yields of 25 and 50%, respectively; however, the latter yield is only for the copper salt.

$$C_2H_5COOC_6H_5 + CH_3OCH_2COC_6H_5 \xrightarrow{NaNH_2} C_2H_5COCHCOC_6H_5 + C_6H_5OH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OCH_3$$

Since some starting materials were recovered in these cases, the yields of acylation products could probably be improved.

The acylation of α-methoxyacetophenone with acetic anhydride has been effected in 10% yield by means of boron trifluoride.

**Acylations of α-Alkoxy and α-Aryloxy Esters.**—The self-condensation of ethyl ethoxyacetate was first reported by Conrad[8] who used sodium, but no yield was given. Similarly, Pratt and Robinson[9] effected the self-condensation of methyl and ethyl methoxyacetate in yields of 40–50% using sodium. Darzens and Meyer[10] reported a 75% yield in the self-condensation of ethyl ethoxyacetate using sodium ethoxide. We have self-condensed isopropyl ethoxyacetate in 69% yield using potassium triphenylmethide and in 35% yield using sodium amide

$$2\ C_2H_5OCH_2COOCH(CH_3)_2 \xrightarrow[\text{or } NaNH_2]{KC(C_6H_5)_3} C_2H_5OCH_2COCHCOOCH(CH_3)_2 + (CH_3)_2CHOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OC_2H_5$$

The lower yield with the sodium amide may be accounted for on the basis that this reagent reacts

(1) Paper XLI on "Condensations"; paper XL, THIS JOURNAL, **69**, 2649 (1947).

(2) On leave of absence from the Department of Organic Chemistry, The Technical University of Denmark, Sølvgade 83, Copenhagen, Denmark.

(3) See especially (a) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945); (c) Hauser and Adams, *ibid.*, **66**, 345 (1944); (d) Adams and Hauser, *ibid.*, **67**, 284 (1945).

(4) See especially Hauser and Hudson, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., Vol. I, pp. 266–302.

(5) Malkin and Robinson, *J. Chem. Soc.*, **127**, 1190 (1925).

(6) We have verified this result with α-methoxyacetophenone, but the yield of the free β-ketoaldehyde was only 8%; most of the methoxy ketone was recovered. It should be pointed out that this reaction was carried out at 0° and that, when attempts were made to effect the formylation of the sodium derivative of α-methoxyacetophenone (prepared with sodium amide or potassium triphenylmethide) in refluxing ether, only the methoxy ketone was recovered.

(7) Levine, Baumgarten and Hauser, THIS JOURNAL, **66**, 1230 (1944).

(8) Conrad, *Ber.*, **11**, 58 (1878).

(9) Pratt and Robinson, *J. Chem. Soc.*, 168 (1925).

(10) Darzens and Meyer, *Compt. rend.*, **198**, 478 (1934).

not only with the α-hydrogen of the ester leading to condensation but also with the carbonyl carbon resulting in the formation of ethoxyacetamide which was isolated from the reaction mixture in 35% yield. Since sodium amide self-condenses isopropyl acetate in better yield (57%)[11] and apparently produces little if any acetamide,[12] the substitution of an α-hydrogen of this ester by the ethoxy group evidently activates the carbonyl carbon[13] relative to the α-hydrogen toward sodium amide.[14]

The self-condensation of ethyl α-ethoxypropionate could not be effected satisfactorily. With potassium triphenylmethide or sodium hydride only a small amount of product was obtained even though the ester anion appeared to be formed readily.[15] With di-isopropylaminomagnesium bromide a product was obtained but it was apparently contaminated with some of the di-isopropyl amide, giving a positive test for nitrogen. Since di-isopropylaminomagnesium bromide self-condenses ethyl *n*-butyrate and ethyl isobutyrate to form a nitrogen free β-ketoester,[16] the formation of some amide with the ethyl α-ethoxypropionate lends further support to the view expressed above, that the α-ethoxy group activates the carbonyl carbon relatively more than the α-hydrogen.

Ethyl phenoxyacetate was first self-condensed by Johnson and Hill[17] using sodium; the yield of the sodium derivative of the β-ketoester was good, but the free β-ketoester was not isolated. We have similarly obtained a good yield (76%) of the sodium derivative of the β-ketoester using di-isopropylaminomagnesium bromide. We also self-condensed methyl 2,4-dichlorophenoxyacetate; the free β-ketoester was obtained in a 65% yield

$$2Cl_2C_6H_3OCH_2COOCH_3 \xrightarrow{[(CH_3)_2CH]_2NMgBr} Cl_2C_6H_3OCH_2COCHCOOCH_3 + [(CH_3)_2CH]_2N + Mg(OCH_3)Br$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad OC_6H_3Cl_2$$

Ethyl α-phenoxypropionate and ethyl α-(2,4-dichlorophenoxy)-propionate apparently self-condensed in the presence of di-isopropylmagnesium bromide, but the pure products were not isolated.

Apparently an alkoxy ester has not previously been acylated with a different ester. In an attempt to acylate isopropyl ethoxyacetate with phenyl benzoate using sodium amide[11] or potassium triphenylmethide[7] we have obtained the self-condensation product of the ethoxyacetate (35%) even though the addition of the ethoxyacetate to the reagent was followed immediately by the addition of the phenyl benzoate.[18] Since isopropyl acetate has been benzoylated with phenyl benzoate by means of sodium amide under similar conditions,[11] either the anion of isopropyl ethoxyacetate is acylated more slowly by phenyl benzoate than the anion of isopropyl acetate or, more likely, isopropyl ethoxyacetate undergoes self-condensation more rapidly than isopropyl acetate. This again is an indication of the above-mentioned effect of the ethoxy group.

However, we have succeeded in acylating ethyl α-ethoxypropionate with isobutyryl chloride using potassium triphenylmethide. The yield was only 15% but it could probably be improved

$$(CH_3)_2CHCOCl + C_2H_5O\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOC_2H_5 \xrightarrow{KC(C_6H_5)_3} (CH_3)_2CHCO\underset{\displaystyle CH_3}{\underset{|}{C}}COOC_2H_5 + HCl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad OC_2H_5$$

Koelsch and Whitney[19] have acylated ethyl phenoxyacetate with ethyl oxalate and ethyl formate using sodium ethoxide. We have benzoylated ethyl α-phenoxypropionate with phenyl benzoate using sodium amide but, rather surprisingly, the β-ketoacid (13%) instead of the β-ketoester was obtained. Most of the ethyl α-phenoxypropionate was recovered.

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## Experimental[20]

α-Methoxyacetophenone[21] and α-phenoxyacetophenone[22] were prepared as described in the literature.

(11) Shivers, Dillon and Hauser, THIS JOURNAL, **69**, 120 (1947).

(12) Hauser, Levine and Kibler, *ibid.*, **68**, 26 (1946).

(13) That the carbonyl carbon is activated by the ethoxy group toward a basic anion is indicated by the six times larger rate of alkaline hydrolysis of methyl ethoxyacetate than methyl acetate. See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 212.

(14) In agreement with this, an attempt to carbonate isopropyl methoxyacetate after treatment with sodium amide failed; methoxyacetamide (m. p. 92–93°) was isolated in 70% yield. Under similar conditions isopropyl acetate gives the carbonation product (56%) and apparently none of the amide.[12]

(15) With potassium triphenylmethide, the color of the reagent was discharged immediately, see ref. 7. With sodium hydride the calculated amount of hydrogen was evolved when equivalent amounts of this reagent and the ester were refluxed in *n*-butyl ether (b. p. 140°). See Swamer and Hauser, THIS JOURNAL, **68**, 2647 (1946).

(16) Hauser and Frostick, unpublished work from this Laboratory.

(17) Johnson and Hill, *Am. Chem. J.*, **48**, 296 (1912); THIS JOURNAL, **35**, 1026 (1913).

(18) In these experiments isopropyl benzoate was obtained in yields of 67 and 50%, respectively. This ester was identified by its boiling point and by hydrolysis to benzoic acid and isopropyl alcohol. In the experiment with sodium amide a 35% yield of ethoxyacetamide (m. p. 80°) was obtained. The isopropyl benzoate was formed, presumably, by reaction of the phenyl benzoate with the isopropoxide ion which was produced as a by-product in the self-condensation of isopropyl ethoxyacetate and, in the experiment with sodium amide, also in the formation of ethoxyacetamide.

(19) Koelsch and Whitney, THIS JOURNAL, **63**, 1762 (1941).

(20) Boiling points and melting points are uncorrected; analyses are by Microchemical Laboratory, University of Pittsburgh, Pittsburgh, Pa.

(21) Moffett and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. 21, 1941, p. 79.

(22) Mohlau, *Ber.*, **15**, 2498 (1882).

Isopropyl ethoxyacetate, b. p. 161°, was prepared according to the procedure for ethyl ethoxyacetate,[23] using isopropyl alcohol in the esterification of the ethoxyacetic acid.

Ethyl α-ethoxypropionate was prepared according to the same procedure,[23] using α-chloropropionic acid instead of chloroacetic acid; the ester boiled at 153–155° (reported b. p. 155°).[24] The over-all yield was 58%, the yield of α-ethoxypropionic acid, b. p. 89–93° at 10 mm., being 77%.

Ethyl phenoxyacetate, b. p. 247–249° (reported b. p. 250°)[25] and ethyl α-phenoxypropionate, b. p. 242–244°[26] and b. p. 96° at 4 mm., were obtained in 80% yields from the corresponding acids by the general method involving the saturation of an ethanolic solution of the acid with hydrogen chloride.

Ethyl α-(2,4-dichlorophenoxy)-propionate, b. p. 129–130° at 4 mm. (reported b. p. 173–176° at 12 mm.)[27] was prepared by esterification of α-(2,4-dichlorophenoxy)-propionic acid, m. p. 115–116° (reported m. p. 117–118°),[27] which was obtained in 31% yield following the procedure given by Pakorny[28] for 2,4-dichlorophenoxyacetic acid.

**Acylations of α-Methoxy- and α-Phenoxyacetophenone by the Sodium Amide Method. Table I.**—The general procedure described previously[3a,29] has been modified. To a stirred suspension of 0.2 mole of sodium amide was added an ether solution of 0.1 mole of the ketone. After ten minutes, an ether solution of the ester was added. The mixture was refluxed for two hours and then poured onto ice. The water layer, after washing with ether, was acidified and extracted with ether. The ether layer, after washing with saturated sodium bicarbonate solution and water, was dried and the solvent distilled. Treatment of the residue varied.

TABLE I

ACYLATIONS OF $ROCH_2COC_6H_5$ USING SODIUM AMIDE

| R | Acylating compound | β-Diketone | M. p., °C. | Yield, % |
|---|---|---|---|---|
| $CH_3$ | PhBz | α-Methoxydibenzoylmethane[a] | 77–78 | 26 |
| $C_6H_5$ | PhBz | α-Phenoxydibenzoylmethane[b] | 97–100 | 59 |
| $CH_3$ | BzCl | α-Methoxydibenzoylmethane | 77–78 | 11 |
| $CH_3$ | PhPr | α-Methoxy-α-propionyl acetophenone[c] | B. p. 129–130 at 6 mm. | 25 |
| $C_6H_5$ | PhPr | α-Phenoxy-α-propionyl acetophenone | | 50[d] |

[a] *Anal.* Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.78; H, 5.20. [b] *Anal.* Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.91; H, 4.90. [c] *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.65. [d] Obtained as the copper salt.

In the benzoylation of α-methoxyacetophenone with phenyl benzoate the β-diketone was isolated by the copper salt method[3a] and recrystallized from methanol.

In the benzoylation of α-phenoxyacetophenone most of the phenol was distilled off *in vacuo*. The residue, which crystallized, was brought into solution in 2 *N* sodium hydroxide. By acidifying, the β-diketone was precipitated, filtered, washed with water and a little ice-cold ethanol and finally recrystallized from ethanol.

In the benzoylation of α-methoxyacetophenone with benzoyl chloride equivalent amounts of sodium amide, the ketone and benzoyl chloride were used; before adding the ketone, the ether suspension of sodium amide was refluxed for several hours.

In the propionylation of α-methoxyacetophenone with phenyl propionate the β-diketone was separated from the phenol by fractional distillation *in vacuo*.

In the propionylation of the α-phenoxyacetophenone with phenyl propionate most of the phenol was removed by heating *in vacuo* (4 mm.) in an oil-bath kept at 200° for thirty minutes. The residue, which gave a strong red enol test with ferric chloride, was treated with a saturated copper acetate solution and the copper salt[3a] of the β-diketone crystallized by standing overnight. After washing, the yield of the copper salt was 50%. From the copper salt, the β-diketone was recovered as a brown oil, the over-all yield being 37%, but it did not crystallize.

**Acetylation of α-Methoxyacetophenone by the Boron Trifluoride Method.**—The general procedure described previously[3c] has been modified. The reaction mixture of 0.2 mole of the ketone and 0.4 mole of acetic anhydride, after saturation with boron trifluoride at temperatures between −10 and 0°, was kept at 0° for one hour and at room temperature (28–30°) for another hour. The mixture was refluxed with sodium acetate for thirty minutes and cooled. After neutralization of most of the acetic acid with sodium hydroxide, the mixture was extracted with ether and the ether solution washed with sodium bicarbonate solution and water. α-Methoxybenzoyl acetone, isolated by the copper salt method, was obtained as a yellow liquid, boiling at 110–111° at 4 mm.

*Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.78; H, 6.12.

None of the ketone was recovered and a considerable amount of tar was obtained.

When the reaction mixture was worked up within twenty minutes after saturation below 0° as described for other ketones,[3c] no β-diketone was obtained and the ketone was largely recovered.

**Self-condensation of α-Alkoxy and α-Aryloxy Esters. Table II.**—The self-condensation of isopropyl ethoxyacetate with potassium triphenylmethide was carried out according to the general procedure,[7] except that the reaction mixture was refluxed for three hours. The condensation was also effected by sodium amide[11]; in this experiment ethoxyacetamide (m. p. 80°) was isolated.

Ethyl phenoxyacetate and methyl 2,4-dichlorophenoxyacetate (m. p. 39–40°)[30] were self-condensed by diisopropylaminomagnesium bromide by adaptation of the procedure for the condensation of certain esters using diethylaminomagnesium bromide.[31] The reactions were generally carried out on a 0.1 or 0.2 mole scale.

To the stirred solution of ethylmagnesium bromide was added an ether solution of an equivalent of diisopropylamine, b. p. 83–84°,[32] and after twenty minutes an ether solution of an equivalent of the ester was added. After spontaneous refluxing ceased, the mixture was refluxed on the steam-bath for one and one-half hours. After cooling in an ice–salt-bath, crushed ice and concentrated hydrochloric acid were added and the mixture stirred until no solid was left. The ether phase, after combining with an ether extract of the aqueous phase, was stirred with 2 *N* sodium hydroxide. The white precipitate of the sodium derivative of the β-ketoester was filtered off, washed with water and dried in the air.

In the experiment with ethyl phenoxyacetate the sodium derivative of the β-ketoester was a white powder, which melted under slight decomposition at 199°. It was converted into the free β-ketoester by shaking in a separatory funnel with ether and hydrochloric acid. The water layer was extracted with ether, the combined ether ex-

(23) Fuson and Wojcik, "Organic Syntheses," John Wiley and Sons, Inc., N. Y., Coll. Vol. II, 1943, p. 260.

(24) Schreiner, *Ann.*, **197**, 13 (1879); Purdie, *J. Chem. Soc.*, **73**, 863 (1898).

(25) Morel, *Bull. soc. chim.*, [3] **21**, 968 (1899).

(26) Saarbach, *J. prakt. Chem.*, [2] **21**, 152 (1880).

(27) Bischoff, *Ber.*, **33**, 1604 (1900).

(28) Pakorny, THIS JOURNAL, **63**, 1768 (1941).

(29) Hauser, Ringler, Swamer and Thompson, *ibid.*, **69**, 2649 (1947).

(30) We are indebted to J. T. Baker Chemical Company for a sample of this ester.

(31) Hauser and Walker, THIS JOURNAL, **69**, 295 (1947).

(32) We are indebted to the Shell Chemical Corporation for a sample of this amine.

TABLE II

SELF-CONDENSATION OF ALKOXY- AND ARYLOXYESTERS

| Ester | Condensing agent | β-Ketoester | B. p. °C. | Mm. | Yield % |
|---|---|---|---|---|---|
| Isopropyl ethoxyacetate | $NaNH_2$ | Isopropyl α,γ-diethoxyacetoacetate | 107–108 | 5 | 35 |
| Isopropyl ethoxyacetate | $KC(C_6H_5)_3$ | Isopropyl α,γ-diethoxyacetoacetate[a] | 103–104 | 4 | 69 |
| Ethyl phenoxyacetate | $(i\text{-Pr})_2NMgBr$ | Ethyl α,γ-diphenoxyacetoacetate[b] | | | 63[c] |
| Methyl 2,4-dichlorophenoxyacetate | $(i\text{-Pr})_2MgBr$ | Methyl α,γ-di-(2,4-dichlorophenoxy)-acetoacetate[b,d] | 102–104 (m. p.) | | 65 |

[a] *Anal.* Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.59; H, 8.82. [b] No nitrogen was found by the sodium fusion test. [c] The sodium derivative was obtained in 76% yield. [d] *Anal.* Calcd. for $C_{17}H_{12}O_5Cl_4$: C, 46.60; H, 2.76; Cl, 32.37. Found: C, 46.92; H, 2.78; Cl, 32.10.

tracts washed with a saturated sodium bicarbonate solution and water, and dried. After evaporation of the solvent, the β-ketoester was obtained as a yellow oil, which, however, did not crystallize. Attempts to distil the β-ketoester *in vacuo* (3 mm.) resulted in decomposition. Attempts to effect ketonic cleavage in acid[33] and slightly alkaline[9] solution gave phenol and tar.

In the experiment with methyl 2,4-dichlorophenoxyacetate, the sodium derivative of the β-ketoester was similarly converted into the free keto ester, and this, after evaporation of the ether, crystallized, and was recrystallized from ethanol.

**Acylation of Ethyl α-Ethoxypropionate with Isobutyryl Chloride.**—To an ether suspension of 0.2 mole of potassium triphenylmethide (freed from ammonia by refluxing the mixture for four hours followed by purging the apparatus with nitrogen) was added 29.2 g. (0.2 mole) of ethyl α-ethoxypropionate. The red color disappeared immediately. After ten minutes, 21.2 g. (0.2 mole) of isobutyryl chloride was added. After refluxing on the steam-bath for three hours, the mixture was poured onto ice and 5 ml. of glacial acetic acid. The ether layer, after combining with an ethereal extract of the aqueous phase, was washed with saturated sodium bicarbonate solution, then with water, and dried. The solvent was distilled and the residue fractionated *in vacuo*, yielding 53% of the original ester and 10 g. of crude β-ketoester. Redistillation gave 6.5 g. (15%) of ethyl α-isobutyryl-α-ethoxypropionate, b. p. 75–76° at 4 mm.

*Anal.* Calcd. for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 61.31; H, 9.41.

**Benzoylation of Ethyl α-Phenoxypropionate with Phenyl Benzoate.**—To the stirred suspension of 0.1 mole of sodium amide was added an ether solution of 19.4 g. (0.1 mole) of ethyl α-phenoxypropionate. After fifteen minutes, an ether solution of 19.8 g. (0.1 mole) of phenyl benzoate was added. The mixture was refluxed on the steam-bath for one hour and then poured onto ice and hydrochloric acid. The water layer was extracted with ether. The combined ether phase was extracted with sodium hydroxide solution. From the ether phase there was recovered 70% of ethyl α-phenoxypropionate, b. p. 241–248° and 20% of the phenyl benzoate, m. p. 68°. Acidification of the alkaline extract yielded a precipitate from which, after fractional crystallization, there was obtained 0.3 g. of α-phenoxypropionic acid, m. p. 114–115° (reported m. p. 115–116°)[34] and 3.5 g. (13%) of α-benzoyl-α-phenoxypropionic acid, m. p. 136–137°, neutr. equiv.: Calcd. 270.3; found 270.3 and 270.8.

*Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.47; H, 5.35.

## Summary

1. Although α-methoxy- and α-phenoxyacetophenone failed to be acylated with ethyl acetate, ethyl propionate, and ethyl benzoate by the sodium amide method, these ketones have been acylated with phenyl propionate and phenyl benzoate. α-Methoxyacetophenone has been acetylated by the boron trifluoride method.

2. Isopropyl ethoxyacetate has been self-condensed by potassium triphenylmethide and by sodium amide; ethyl phenoxyacetate and methyl 2,4-dichlorophenoxyacetate have been self-condensed by diisopropylaminomagnesium bromide.

3. Ethyl α-ethoxypropionate has been acylated with isobutyryl chloride by potassium triphenylmethide.

4. Certain related condensations have been studied. The effect of the α-ethoxy group on the relative reactivities of the carbonyl carbon and the α-hydrogen of esters has been considered.

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(33) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).

(34) Bischoff, *Ber.*, **33**, 926 (1900).

[CONTRIBUTION FROM THE INSTITUTE OF CHEMISTRY, NATIONAL ACADEMY OF PEIPING, PEIPING, CHINA]

# The Action of Grignard Reagents on Ethyl Ethylenetetracarboxylate. A General Method for Preparation of Monoalkylated and Monoarylated Succinic Acids

BY CHI-YI HSING[1] AND LIEN-TANG LI

The addition of Grignard reagents to $\alpha,\beta$-unsaturated carboxylic esters was studied intensively by Kohler and his co-workers.[2] The addition takes place either 1:2 or 1:4 depending on the character of the Grignard reagent and on the substituents in the unsaturated ester.[3] Kohler noted that by substituting a cyano or another carboxylic ester group on the $\alpha$-carbon atom, the addition of the Grignard reagent takes place exclusively 1:4. For instance, the reaction of benzal malonic ester with methylmagnesium iodide gives $\alpha$-phenethyl malonic ester. When an excess of Grignard reagent is used the ester groups are not further attacked. It is the object of the present investigation to test whether the generalization made by Kohler can be equally well applied to the action of Grignard reagents on ethyl ethylenetetracarboxylate. If one mole of Grignard reagent adds 1:4 to ethyl ethylenetetracarboxylate, a general method for the preparation of monosubstituted succinic acids will be available. The reactions are given as follows

$$(C_2H_5O_2C)_2C{=}C(CO_2C_2H_5)_2 \xrightarrow{RMgX}$$

$$(C_2H_5O_2C)_2C(R)-C(OMgX)=C(CO_2C_2H_5)-OC_2H_5 \xrightarrow{H_2O}$$

$$(C_2H_5O_2C)CR-CH(CO_2C_2H_5)_2 \longrightarrow$$

$$(HO_2C)_2CR-CH(CO_2H)_2 \xrightarrow{-CO_2} HO_2C-CHR-CH_2CO_2H$$

Bischoff[4] has also made monoalkylated succinic acids from monoalkylated $\alpha,\alpha,\beta,\beta$-ethanetetracarboxylic acid esters. The tetra-esters were obtained in poor yield by the alkylation of ethyl ethane-$\alpha,\alpha,\beta,\beta$-tetracarboxylate with an alkyl halide in the presence of sodium ethylate. The monoalkylated succinic acids were isolated as the final products by saponifying the crude esters. Arylated succinic acids could not be prepared by the method of Bischoff.

It was found that both aryl and alkylmagnesium bromide add to ethyl ethylenetetracarboxylate. When phenylmagnesium bromide was used, some coupling of the Grignard reagent with the formation of biphenyl was observed, while in the case of ethylmagnesium bromide, some reduction of ethyl ethylenetetracarboxylate took place. The reduced compound was isolated as ethyl ethane-$\alpha,\alpha,\beta,\beta$-tetracarboxylate. In general the yields were good, varying from 56–79%. The saponification of the tetra-ester and the decarboxylation of the poly-acid were carried out by the usual methods. The yield was satisfactory in the case of ethyl phenylethane-$\alpha,\alpha,\beta,\beta$-tetracarboxylate but poor in the case of ethyl methylethane-$\alpha$ $\alpha,\beta,\beta$-tetracarboxylate. It is our hope to extend the present investigation and to improve the experimental conditions in order to make the method useful for general synthetic purposes when more material is available for the investigation. No attempt was made to isolate the tetracarboxylic acids in the pure state; they were decarboxylated directly. When ethyl phenylethane-$\alpha,\alpha,\beta,\beta$-tetracarboxylate was saponified, an acid melting unsharply around 160° with decomposition was obtained. If the compound was heated at a temperature of 170° for some time until the decomposition ceased, the product melted sharply at 168°. This is the reported melting point of phenylsuccinic acid.[5,6] The identity between the methylsuccinic acid synthesized by our method and an authentic specimen was established.

Although a number of methods[7] for the preparation of monosubstituted succinic acids are available, the present method has the advantage of starting with readily prepared[8] material. Certain monosubstituted succinic acids may be prepared by the present method that can be prepared only with great difficulty by any other method.

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## Experimental

**Ethyl Ethylenetetracarboxylate.**—Ethyl ethylenetetracarboxylate was prepared as described by Corson and Benson.[8]

**Ethyl $\alpha$-Phenylethane-$\alpha,\alpha,\beta,\beta$-tetracarboxylate.**—In a 200-cc. 3-necked flask equipped with a dropping funnel, a mechanical stirrer through a mercury seal and a reflux condenser to the upper end of which was attached a calcium chloride tube, was placed 1.8 g. of magnesium shavings and 10 cc. of absolute ether. A mixture of 11.8 g. of bromobenzene in 15 cc. of absolute ether was added drop by drop through the funnel. When all the bromobenzene solution had been added, the mixture was refluxed for thirty minutes. A mixture of 4.7 g. of ethyl ethylene-

(1) Present address, Department of Agricultural Chemistry, National Peking University, Peiping, China.

(2) Kohler and Heritage, *Am. Chem. J.*, **33**, 21, 153 (1905).

(3) Kohler and Johnstin, *ibid.*, **33**, 35 (1905); Kohler, *ibid.*, **36**, 529 (1906); Kohler and Reimer, *ibid.*, **33**, 333 (1905); Kohler, *ibid.*, **34**, 132 (1905).

(4) Bischoff and Rach, *Ann.*, **234**, 65 (1886).

(5) Higson and Thorpe, *J. Chem. Soc.*, **89**, 1472 (1906).

(6) Lapworth and McRae, *ibid.*, **121**, 1704 (1922).

(7) Markownikov and Lebedev, *Ann.*, **182**, 327 (1876); Higson and Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906); Fittig, *Ann.*, **304**, 117, 127 (1899); Michael, *Ber.*, **29**, 1791 (1896).

(8) "Organic Syntheses," Coll. Vol. II, p. 273 (1947).

tetracarboxylate dissolved in 40–50 cc. of absolute ether was dropped in through the funnel in thirty to forty minutes. The mixture was refluxed and stirred for an hour. The reaction flask was then cooled with ice water and 25 cc. of 25% ammonium chloride solution was added gradually. Stirring was continued for thirty minutes after all the ammonium chloride solution had been added. The ethereal layer was separated and the aqueous layer containing much solid matter was dissolved in a proper amount of 10% acetic acid and extracted several times with ether. The combined ethereal extracts were evaporated and the residue was then steam-distilled in order to remove most of the biphenyl formed during the reaction. The amount of biphenyl formed (m. p. 67–69°) varied from 0.6–1.2 g. The oil remaining in the distilling flask was extracted with ether and dried over sodium sulfate. The ether was removed and the residual oil was fractionated under reduced pressure. The fraction boiling at 208–210° (5 mm.) was collected. The yield was 4.2 g. (71%).

*Anal.* Calcd. for $C_{20}H_{26}O_8$: C, 60.9; H, 6.5. Found: C, 61.1; H, 6.2.

**Saponification of Ethyl α-Phenylethane-α,α,β,β-tetracarboxylate.**—Forty cc. of 25% potassium hydroxide was refluxed with 1.7 g. of ethyl phenylethane-α,α,β,β-tetracarboxylate in an oil-bath until the oil had disappeared completely (twelve hours). The aqueous solution was once extracted with ether in order to remove all traces of biphenyl remaining in the ester, then cooled in ice water and acidified with 20% sulfuric acid. An amorphous solid separated. It was filtered and dried on a steam-bath and then pulverized. The white powder was heated in dilute sulfuric acid until complete solution occurred. The solution was combined with the former filtrate and extracted several times with ether. After drying and removing the ether a crystalline substance (0.96 g.) was obtained. The crude acid was crystallized from hot water using a little charcoal. A yield of 0.82 g. of crystals was obtained. It decomposed at about 160°.

**Phenylsuccinic Acid.**—The acid obtained above was placed in a small glass tube and heated in a sulfuric acid bath keeping the temperature at 170–175° while the carbon dioxide evolved briskly. When the evolution of gas had ceased, 0.77 g. (86% based on the tetra-ester) of crude phenylsuccinic acid was obtained. After one crystallization from water, the pure acid was obtained as fine needles weighing 0.73 g., m. p. 168° (Thorpe reported 168°; Lapworth reported 167°).[6]

*Anal.* Calcd. for $C_{10}H_{10}O_4$: neut. equiv., 97. Found: neut. equiv., 96.

**Ethyl α-Methylethane-α,α,β,β-tetracarboxylate.**—The procedure was similar to that used for the preparation of ethyl phenyl-ethanetetracarboxylate. From 4.7 g. of ethyl ethylenetetracarboxylate 3.8 g. (79%) of ethyl methyl ethanetetracarboxylate was obtained as a slightly yellowish oil boiling at 165–166° (5 mm.).

*Anal.* Calcd. for $C_{15}H_{24}O_8$: C, 54.2; H, 7.2. Found: C, 54.4; H, 7.8.

**Methylsuccinic Acid.**—In a 150-cc. 2-necked round-bottomed flask, which was fitted with a reflux condenser and a mechanical stirrer, 2.4 g. of ethyl methylethanetetracarboxylate and 40 cc. of 20% potassium hydroxide were heated under reflux with stirring for seven hours. The solution was acidified and then extracted with ether. The aqueous layer was further extracted with ether in a continuous extraction apparatus. The ethereal extracts were combined and dried. After the solvent had been removed, an oil was obtained which was then heated at a temperature 150–160° until no more carbon dioxide was evolved. The residue was dissolved in water, decolorized, and evaporated to dryness. The residual oil solidified slowly in the desiccator. It was crystallized from a mixture of petroleum ether and chloroform. The pure acid was obtained as beautiful crystals, m. p. 110–111° (Boettinger reported 112.5°; Bone and Sprankling reported 110°).[9] The melting point was not depressed by mixing with an authentic specimen.

**Ethyl α-Ethylethane-α,α,β,β-tetracarboxylate.**—The procedure was similar to that used in the previous experiment. The Grignard reagent was prepared from 6.5 g. of ethyl bromide and 1.4 g. of magnesium shavings and allowed to react with 4.2 g. of ethyl ethylenetetracarboxylate. The crude product was obtained as a yellowish oil. The oil was allowed to stand for a few days. The crystals which separated were filtered and washed with a small amount of cold alcohol. On further standing a second crop of crystals was obtained. The process was repeated until no more crystals separated. The total amount of crystals weighed about 1.8 g., m. p. 76°. The melting point was not depressed by mixing with ethyl ethane-α,α,β,β-tetracarboxylate. The oil, freed from the reduced compound, was fractionated under reduced pressure. The fraction boiling at 180–183° (6 mm.) was collected. The product was of pale yellow color and weighed 2.6 g. (56%).

*Anal.* Calcd. for $C_{16}H_{26}O_8$: C, 55.5; H, 7.5. Found: C, 54.8; H, 7.9.

**Ethylsuccinic Acid.**—The saponification of the ester was similar to that of the ethyl methylethanetetracarboxylate. The decarboxylation was carried out at a temperature of 150–160° for thirty minutes. The product was decolorized in hot water. On evaporation, 0.37 g. (36% of the theoretical amount based on the tetra-ester) of oil remained. The oil solidified completely on standing. It was crystallized from chloroform–petroleum ether mixture, and the pure ethyl succinic acid melting at 96–98° (Huggenberg reported 98°; Polk reported 97°)[10] was obtained as fine crystals.

*Anal.* Calcd. for $C_6H_{10}O_4$: neut. equiv., 73. Found: neut. equiv., 73.

## Summary

1. The mode of addition of both aryl and alkylmagnesium bromide to ethyl ethylenetetracarboxylate has been shown to take place exclusively 1:4.

2. A general method for the preparation of monosubstituted succinic acids has been described and phenyl-, methyl- and ethyl-succinic acids were synthesized in this way.

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(9) Boettinger, *Ber.*, **11**, 1352 (1878); Bone and Sprankling, *J. Chem. Soc.*, **75**, 860 (1899).

(10) Huggenberg, *Ann.*, **192**, 149 (1879); Polk, *ibid.*, **242**, 122 (1887).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

# The Catalytic Reduction of Bromobenzene to Biphenyl[1,2]

BY FRANK R. MAYO[3] AND MELVIN D. HURWITZ[4]

Busch and co-workers[5] have shown that bromobenzene and some other aromatic halides could be reduced in the presence of a palladium catalyst to yield both benzene and biphenyl. The latter reaction was unique in that only partial reduction of the carbon–halogen bond occurred, and a new carbon–carbon bond was formed. The object of the present work was to determine the effect of experimental conditions on the yield of biphenyl in the hope that it would extend knowledge of the mechanism of catalytic reduction, and might also make possible new applications of semi-reduction methods in organic synthesis.

**Standard Experiment.**—A set of experimental conditions was chosen as a standard of comparison for reagents and for the effect of varied conditions. Methanol served as both solvent and reducing agent.

In a 200-cc., 3-necked, round-bottomed flask, equipped with an oil-sealed stirrer and reflux condenser, 7.85 g., 0.05 m., of bromobenzene, 3 g. of 1% palladium-on-calcium carbonate (Pd–$CaCO_3$) catalyst, 10 cc. of 10 *N* aqueous potassium hydroxide, and 90 cc. of methanol were mixed and refluxed until the catalyst was completely black or reduced. The catalyst was then separated by filtration, and the filtrate evaporated on a steam-bath to a volume of 25 cc. Water was then added to precipitate the biphenyl which was collected on a filter, dried in a vacuum desiccator, and weighed. The filtrate was made up to 500 cc., and an aliquot was titrated for bromide by the Volhard method to determine the extent to which bromobenzene had been reduced.

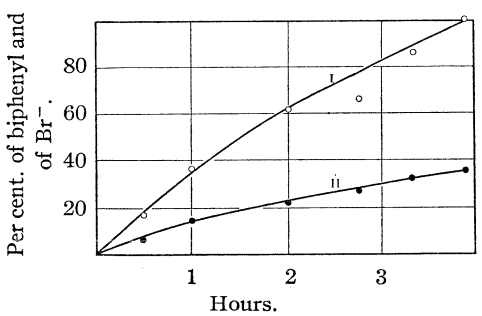



Fig. 1.—Reduction of bromobenzene to biphenyl and to $Br^-$ as a function of time: I, biphenyl; II, $Br^-$.

The two reactions occurring may be represented by the equations

$$C_6H_5Br + KOH + CH_3OH \longrightarrow C_6H_6 + KBr + H_2O + CH_2O \quad (1)$$

$$2C_6H_5Br + 2KOH + CH_3OH \longrightarrow (C_6H_5)_2 + 2KBr + 2H_2O + CH_2O \quad (2)$$

**End-Point of Reduction.**—The light brown palladium oxide catalyst was reduced to black palladium during the course of the reaction.

Six batches of 1% Pd–$CaCO_3$ catalyst, designated A to F, were prepared according to a modification of Busch's[5a] procedure by adding an aqueous solution of palladium chloride to the calculated amount of C. P. calcium carbonate in a water suspension and heating to complete the precipitation of palladium oxide. The product was then washed with water until free of chloride, and dried *in vacuo* over concentrated sulfuric acid.

Since the bromobenzene protected the metal oxide from reduction, the color change indicating complete reduction of the catalyst was sharp and indicated complete reduction of the bromobenzene. Catalyst B, which required 2.75 hours for complete reduction in a standard reaction mixture, was reduced in four minutes when the bromobenzene was omitted. Results of standard experiments with fresh portions of catalyst C are summarized in Fig. 1, which shows the correlation of yield of biphenyl and reduction of the bromobenzene with time.

As already indicated, the time for completion of a standard experiment, recorded in Table I, varied with the batch of catalyst. Although the reduction times varied over a wide range, the yields of biphenyl were constant within experimental error.

TABLE I

TIME FOR COMPLETE REDUCTION OF VARIOUS CATALYST BATCHES

| Catalyst | Reduction time, hr. | Found, % $Br^-$ | Found, % $(C_6H_5)_2$ |
|---|---|---|---|
| A | 0.50 | 96.4 | 34.0 |
| B | 2.75 | 98.8 | 35.6 |
| C | 3.91 | 100.6 | 35.3 |
| D | 1.00 | 99.0 | 35.3 |
| E | 2.00 | 100.5 | 35.0 |
| F | 6.50 | 99.8 | 34.0 |

**Properties of the Reduced Catalyst.**—The reduced catalyst was more active for reducing the halide, but less active for biphenyl production than the unreduced catalyst. This enhanced activity decreased with re-use, with the activity for biphenyl formation dropping off more sharply. A catalyst reduced originally in the absence of bromobenzene exhibited the same characteristics.

In a series of standard experiments Catalyst C was reused in seven successive runs. The time was held constant at 1.33 hours, since after the first run there was no indicator to give the end-point of the reduction. The fresh Catalyst C required 3.91 hours for complete reduction (see Fig. 1). In the second run 88.6% of the halide was

(1) Presented at the meeting of the American Chemical Society in New York City, September, 1947.

(2) From the Master's Thesis of M.D. Hurwitz, 1942.

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(5) (a) Busch and Stove, *Ber.*, **49**, 1063 (1916); (b) Busch, *Z. angew. Chem.*, 232 (1918); (c) Busch, *ibid.*, **38**, 519 (1926); **47**, 536 (1934); (d) Busch and Schultz, *Ber.*, **62**, 1458 (1929); (e) Busch and Schmidt, *ibid.*, **62**, 2612 (1929); (f) Busch and Weber, *J. prakt. Chem.*, **146**, 1 (1936).

reduced in 1.33 hours. This state of reduction would have taken about 3.5 hours with fresh catalyst, and indicated that the reduced catalyst was about 2.6 times more active. The activity of the reduced catalyst fell off, so that in the eighth run only 67.4% of the halide was reduced in 1.33 hours—or only 2.1 times as fast as with the unreduced catalyst. The yield of biphenyl decreased more rapidly, from 20.2% in the second to 11.4% in the eighth.

**Effect of Water.**—Water up to a concentration of 50% by volume increased the yield of biphenyl. Above 50%, where the reaction liquids separated into two phases, the biphenyl yield fell off rapidly.

TABLE II

EFFECT OF WATER ON BIPHENYL YIELD[a]

| % $H_2O$ by vol.[b] | Reduction time, hr. | Found, % $Br^-$ | Found, % $(C_6H_5)_2$ |
|---|---|---|---|
| 0.0 | 5.0 | 101.0 | 27.0 |
| 9.0[c] | 2.75 | 98.8 | 35.6 |
| 16.0 | 2.0 | 87.8 | 40.3 |
| 25.0 | 2.0 | 100.9 | 42.7 |
| 50.0 | 2.0 | 98.8 | 50.4 |
| 68.0 | 2.0 | 98.0 | 20.8 |

[a] Catalyst B. [b] In alcohol–water–KOH reaction mixture. [c] Standard experiment.

**Effect of Bases.**—To obtain the maximum yield of biphenyl, at least one equivalent of potassium hydroxide was required per mole of bromobenzene. The effect of additional alkali on the yield was small, but the rate of reduction was accelerated. Potassium carbonate, pyridine, aniline, and sodium methoxide were substituted for potassium hydroxide in the standard experiment. The reduction with potassium carbonate required about six times as long as with potassium hydroxide and only about half the usual yield was obtained. There was no reduction of the halide in the presence of pyridine or aniline unless potassium hydroxide was present, in which case they greatly retarded the rate of reduction and decreased the yield of biphenyl. With sodium methoxide there was no reduction in twenty hours of refluxing. Biphenyl and benzene were the only reduction products formed. These results are summarized in Table III.

TABLE III

EFFECT OF BASES ON REDUCTION[a]

| Ratio moles base/$C_6H_5Br$ | Reduction time, hr. | Found, % $Br^-$ | Found, % $(C_6H_5)_2$ |
|---|---|---|---|
| 0.0 KOH | 5.0[b] | Trace | 0.0 |
| 0.8 KOH | 5.0 | 76.0 | 26.5 |
| 1.0 KOH | 4.5 | 94.4 | 36.4 |
| 2.0 KOH[c] | 2.5 | 100.5 | 35.0 |
| 4.0 KOH | 2.0 | 99.6 | 34.8 |
| 1.7 $K_2CO_3$ | 25.0 | 100.8 | 18.2 |
| 1.0 $C_6H_5N$ | 24.0[b] | 0.0 | 0.0 |
| 2.0 KOH 1.0 $C_6H_5N$ | 24.0 | 98.4 | 26.5 |
| 2.1 $C_6H_5NH_2$ | 6.0[b] | 0.0 | 0.0 |
| 2.0 KOH 2.1 $C_6H_5NH_2$ | 6.0 | 58.4 | 21.8 |
| 1.0 MeONa | 20.0[b] | 0.0 | 0.0 |

[a] Catalyst B. [b] Catalyst not fully reduced. [c] Standard Experiment.

**Effect of Hydrogen Gas.**—In runs where hydrogen gas was bubbled through a standard reaction mixture, at reflux, the reduction of the halide was accelerated but the yield of biphenyl was decreased.

Catalyst F, requiring 6.5 hours for complete reduction in the absence of hydrogen, required only an hour in its presence; the biphenyl yield dropped to less than 2%. Re-use of the reduced catalyst gave the same results as the fresh catalyst.

**Effect of Solvent.**—Three other solvents, ethanol, isopropyl alcohol, and dioxane, were substituted for methanol in the standard experiment. Reduction was negligible; no biphenyl was isolated, and tars were formed.

**Other Catalysts.**—Metals other than palladium were tried as catalysts to check Busch's[5f] conclusion that palladium was truly specific for biphenyl formation. Nickel and copper catalyst, prepared like the standard Pd–$CaCO_3$ catalyst were found to be totally inert with or without hydrogen. Platinum oxide catalyst was inert in the absence of hydrogen and very sluggish with hydrogen in the standard aqueous-alcohol reaction mixture or in alcohol alone. No trace of biphenyl was found in any of the experiments described above. Raney nickel catalyst was active in reducing the halide in the presence of hydrogen only, but again there was no trace of biphenyl formed.

A colloidal palladium-on-polyvinyl alcohol catalyst (Pd-PVA), prepared according to the directions of Rampino and Nord,[6] was completely inert in the Standard Experiment, but very active in reducing the halide in the presence of hydrogen, yielding no biphenyl.

The reductions with the Pd-PVA catalyst with hydrogen were carried out in a conventional low pressure hydrogenator, at a hydrogen pressure of about 2 atmospheres. While this catalyst was not reduced readily if the bromobenzene was added before its reduction in the presence of hydrogen, the rate of the reduction of the bromobenzene was not affected.

**Vapor Phase Experiments.**—No biphenyl was produced in any of the vapor phase experiments using palladium catalysts, with or without hydrogen. The essentially quantitative recovery of the bromobenzene in all runs indicated little reaction.

Catalysts were prepared in the following manner: (a) Potassium hydroxide, 3.0 g., was powdered by grinding under ether and mixed there with 1.5 g. of the Pd–$CaCO_3$ catalyst. The powder left after evaporation of the ether was dispersed in glass wool which filled the 1.4 × 20 cm. U-tube reaction vessel. Each filling of the reaction vessel contained 0.05 g. of palladium metal. (b) Solutions of palladium chloride, with and without potassium hydroxide, were dried on clay chips and on asbestos fibers, used as catalyst carriers.

The reaction vessel was immersed in an oil-bath held at 195–200°, 50 cc. of methanol solution containing 0.05 m. of bromobenzene was dropped in from a separatory funnel at such a rate that complete addition took two

(6) Rampino and Nord, THIS JOURNAL, **63**, 2745, 3268 (1941).

hours. The solution volatilized on reaching the hot portion of the tube, and the gases that passed through the tube were condensed and collected at the other end.

**Effect of Catalyst Poisons.**—Catalytic amounts of nickel and copper salts had no significant effect on the rate of reduction of the bromobenzene in the standard experiment, but the biphenyl yield dropped to less than 5%. The stronger hydrogenation catalyst poisons, arsenic trioxide, and sulfides, completely inhibited all reaction.

**Miscellaneous Experiments.**—Analyses of the reduction products of each group of experiments showed only biphenyl, less than 1% of higher polyphenyls, and benzene. The biphenyl fractions of all runs were combined, and subjected to a sodium fusion. Only a trace of halide was found.

Benzene and biphenyl were added to standard runs without affecting either the expected yield of biphenyl, the rate of reaction, or the products. In runs using a standard reaction mixture with added biphenyl, but without bromobenzene, the recovery of biphenyl was the same as in a control run without catalyst after four hours of refluxing. Only biphenyl was recovered.

In a standard run using *p*-bromobiphenyl in place of bromobenzene, the reaction rate approximated that of the reaction with bromobenzene. The yield of quaterphenyl was 30.8%, biphenyl 61.0%.

## Discussion

In view of the fact that detailed mechanisms have not yet been formulated for common catalytic reductions, it would be surprising if the present work could present a detailed mechanism for a very unusual type of catalytic reduction, the formation of biphenyl from bromobenzene. This work, however, has produced evidence that this unusual reaction required a palladium catalyst in a fairly specific state, a reducing agent with specific properties, and experimental conditions favorable to the adsorption of bromobenzene on the catalyst.

Repeated recovery and re-use of a catalyst sample led to a gradual diminishing rate of reduction, but the rate of formation of the biphenyl decreased faster than the rate of formation of benzene. These effects suggest that the two reductions are at least partially independent, the biphenyl formation being more sensitive to poisons or the state of the catalyst. This conclusion is further indicated in that copper and nickel salts suppress the formation of biphenyl but do not affect the reduction to benzene. The fact that no biphenyl could be obtained with nickel, platinum, or even colloidal palladium indicated that biphenyl formation is a reaction probably highly specific for certain palladium surfaces.

A highly specific reducing agent also seems to be required for biphenyl formation. The only successful reducing agent employed in the present work was methanol in the presence of strong base, at least equivalent to the amount of bromobenzene used. If insufficient alkali was used in the standard experiment, the solution approached neutrality and the reduction stopped. These proportions suggest but do not prove, that methylate ion was the reducing agent. Ethanol and isopropyl alcohol were found to be ineffective reducing agents. Busch suggested that the differences between these alcohols were related to their dielectric constants, but the latter differ little. A more probable explanation depends on the relative ease of dehydrogenation of the alcohols and the effect of aldehyde or ketone condensation products on the catalyst. Hydrogen gas, by accelerating the formation of benzene, inhibited the formation of biphenyl. These observations suggested that the bromobenzene was reduced by the alcohol or alcoholate ion to phenyl radicals on the active centers on the surface of the catalyst. If further reduction did not occur too easily, the phenyl radicals combined to give biphenyl. In the presence of hydrogen, even at atmospheric pressure, practically all were reduced to benzene.

The effect of water and amines in the standard experiment can be explained on the basis of the probable effect of these factors on the ease of adsorption of the halobenzene on the catalyst. Increasing the proportion of water in the alcohol solution increased the yield of biphenyl, presumably by decreasing the solubility of the bromobenzene and increasing its adsorption on the catalyst. Addition of pyridine or aniline decreased the rate of reduction without greatly affecting the proportions of products formed by being preferentially adsorbed on the catalyst.

Failure of added benzene to increase the yield of biphenyl from bromobenzene or of biphenyl to yield terphenyl, showed that biphenyl and benzene were not intermediates in terphenyl and biphenyl formation, respectively. The fact that *p*-bromobiphenyl gave considerable quaterphenyl on reduction, and that only traces of quaterphenyl were formed from bromobenzene, showed that bromobiphenyls are probably not intermediates in the formation of biphenyl. All the evidence seems consistent with the view that the reduction of bromobenzene to biphenyl is a surface reaction probably proceeding through adsorbed phenyl radicals.

## Summary

The reduction of bromobenzene was studied using methanol as solvent and reducing agent, and palladium on calcium carbonate as catalyst. In the presence of strong base, up to 50% yield of biphenyl was obtained, benzene being the other reduction product. The effects of solvents, quantity and kind of base, other catalysts, hydrogen, metal salts, and end-products on the rate of reduction and on the benzene–biphenyl ratio were determined. Most changes in procedure reduced or eliminated the formation of biphenyl, often

without appreciably affecting the rate of formation of benzene. Biphenyl seems to be formed by coupling of adsorbed phenyl radicals on a specific surface in the absence of a more adequate source of hydrogen.

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[CONTRIBUTION FROM THE LABORATORY OF EXPERIMENTAL THERAPEUTICS, U. S. PUBLIC HEALTH SERVICE, AND JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH]

# Arsenoso Derivatives of Phenyl-substituted Fatty Acids[1]

BY LEON D. FREEDMAN[2] AND G. O. DOAK[3]

The substitution of an acidic group in arsenosobenzene or its derivatives generally inhibits the activity and decreases the potential therapeutic utility of this class of compound.[4] An exception has been found in γ-(*p*-arsenosophenyl)-butyric acid which possesses marked trypanocidal activity and has undergone extensive therapeutic trial.[5] This unusual activity is not shown by the homologous *p*-arsenosophenylacetic and β-(*p*-arsenosophenyl)-propionic acids.

The present paper describes the preparation and properties of two higher homologs, one isomer and one derivative of γ-(*p*-arsenosophenyl)-butyric acid, as well as two other acid-substituted derivatives of arsenosobenzene.

For the preparation of several of these compounds, the *p*-nitro- and *p*-aminophenyl derivatives of the corresponding fatty acids were required as intermediates. The method of Van der Scheer[6] was previously used in this Laboratory for the preparation of γ-(*p*-nitrophenyl)- and γ-*p*-aminophenyl)-butyric acids, necessary for the synthesis of γ-(*p*-arsenosophenyl)-butyric acid.[7] The nitration procedure gave poor yields, probably due to oxidation of the side chain at the temperature employed. In an attempt to improve the yield, γ-phenylbutyric acid was nitrated under a variety of conditions. The most satisfactory yield was obtained by a procedure described in the Experimental Part. This procedure was also used for the nitration of δ-phenylvaleric acid. An improved method for the reduction of these nitro compounds to the desired amino compounds is also described.

For the preparation of *m*-arsonocinnamic acid the Scheller reaction was used.[8] The remaining arsonic acids were synthesized by the method of Palmer and Adams.[9] Since *p*-arsonomandelic acid was obtained as a sirup, which could not be crystallized, it was converted to the disodium salt which was readily crystallized from alcohol.

The arsenoso compounds were prepared by reduction of the corresponding arsonic acids with sulfur dioxide and hydriodic acid in the presence of hydrochloric acid, followed by hydrolysis of the resulting dichloroarsines with sodium bicarbonate. We were unable to isolate *p*-arsenosomandelic and γ-(2-amino-4-arsenosophenyl)-butyric acids because of their solubility in water. Therefore these two compounds were isolated as the dichloroarsines and neutralized in solution just prior to therapeutic testing.

The chemotherapeutic activity of these compounds has been reported previously.[5,10] δ-(*p*-Arsenosophenyl)-valeric acid was one-half as active against *T. equiperdum* as γ-(*p*-arsenosophenyl)-butyric acid, while none of the remaining compounds possessed any appreciable activity.

## Experimental Part

**δ-Phenylvaleric Acid.**—This compound has previously been described by Ali, *et al.*,[11] but no yield was reported. Using a somewhat similar procedure[12] we reduced γ-benzoylbutyric acid to the desired compound, which was purified by distillation under reduced pressure. The yield was 63%; b. p. 164–168° (5 mm.); m. p. 51–53° (cor.).

**ε-Phenylcaproic Acid.**—The method used for the preparation of this compound differed from that previously described by Grateau[13] in that δ-benzoylvaleric acid, rather than the corresponding ethyl ester, was reduced by the Clemmensen method.[12] The yield was 86%; b. p. 165° (1 mm.); f. p. 10–11°.

**Nitration of γ-Phenylbutyric Acid.**—γ-Phenylbutyric acid (140 g.) was added in small portions to 250 ml. of fuming nitric acid (d. 1.50) which was maintained at a temperature between −20 and −30° by means of an alcohol–Dry Ice-bath. The time of addition was two to three hours and the mixture was stirred mechanically throughout this period. A further 10 ml. of acid was then used to wash down the sides of the reaction vessel and the temperature was kept at −10° for a further one-half hour. The clear solution was poured into a four-liter beaker filled with cracked ice. The oil which precipitated solidified on standing for fifteen minutes. The mixture was allowed to stand in the ice-box overnight after which the solid was removed by filtration and washed with cold water.

(1) Paper X in the series entitled "The Preparation of Phenylarsenoxides"; previous paper, THIS JOURNAL, **67**, 719 (1945).

(2) Present address: Department of Chemistry, Johns Hopkins University, Baltimore, Maryland.

(3) Present address: School of Public Health, Chapel Hill, North Carolina.

(4) Gough and King, *J. Chem. Soc.*, 669 (1930); Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **70**, 221 (1940).

(5) Eagle, Hogan, Doak and Steinman, *Pub. Health Rep.*, **59**, 765 (1944); Eagle, *ibid.*, **61**, 1019 (1946).

(6) Van der Scheer, THIS JOURNAL, **56**, 744 (1939).

(7) Doak, Steinman and Eagle, *ibid.*, **62**, 3012 (1940).

(8) Doak, *ibid.*, **62**, 167 (1940).

(9) Palmer and Adams, *ibid.*, **44**, 1356 (1922).

(10) Eagle, *J. Pharmacol.*, **85**, 265 (1945).

(11) Ali, Desai, Hunter and Muhammad, *J. Chem. Soc.*, 1013 (1937).

(12) Martin, Clemmensen method III in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., p. 166.

(13) Grateau, *Compt. rend.*, **191**, 947 (1930).

TABLE I

ARSONO-, ARSENOSO- AND DICHLOROARSINO- PHENYL SUBSTITUTED FATTY ACIDS

| Acid | M. p.,[b] °C. | Yield, % | Formula | As analyses,[c] % Calcd. | Found |
|---|---|---|---|---|---|
| **R = Arsono[a]** | | | | | |
| *p*-R-mandelic- (di-sodium salt) | | 43 | $C_8H_9AsNa_2O$ | 23.4 | 23.5 |
| α-(*p*-R-phenyl)-butyric | 148–149 | 25 | $C_{10}H_{13}AsO_5$ | 24.5 | 24.8 |
| *m*-R-cinnamic | >360 | 44 | $C_9H_9AsO_5$ | 27.5 | 27.3 |
| γ-(2-Nitro-4-R-phenyl)-butyric[d] | 262 | 68 | $C_{10}H_{12}AsNO_7$ | 22.5 | 22.4 |
| γ-(2-Amino-4-R-phenyl)-butyric[e] | 309.5 (decomp.) | 81 | $C_{10}H_{14}AsNO_5.H_2O$ | 23.3 | 23.5 |
| δ-(*p*-R-phenyl)-valeric | 204 | 62 | $C_{11}H_{15}AsO_5$ | 24.8 | 25.2 |
| ε-(*p*-R-phenyl)-caproic | 146–150 | 38 | $C_{12}H_{17}AsO_5$ | 23.7 | 23.4 |
| **R = Arsenoso[f]** | | | | | |
| *m*-R-cinnamic | >360 | 97 | $C_9H_7AsO_3$ | 31.5 | 31.0 |
| α-(*p*-R-phenyl)-butyric | Softens at 258 | 13 | $C_{10}H_{11}AsO_3.H_2O$ | 27.5 | 27.5 |
| δ-(*p*-R-phenyl)-valeric | >360 | 53 | $C_{11}H_{13}AsO_3$ | 26.2 | 26.2 |
| ε-(*p*-R-phenyl)-caproic | >360 | 66 | $C_{12}H_{15}AsO_3.H_2O$ | 25.0 | 25.2 |
| **R = Dichloroarsino[g]** | | | | | |
| *p*-R-mandelic | 167 | 60 | $C_8H_7AsCl_2O_3$ | 25.2 | 25.4 |
| γ-(2-Amino-4-R-phenyl)-butyric, hydrochloride[h] | 163–164 | 27 | $C_{10}H_{12}AsCl_2NO_2.HCl$ | 20.8 | 20.7 |

[a] Water was used as the solvent in the recrystallization of all arsonic acids. [b] The melting points were determined by the method described in paper VI of this series, Steinman, Doak and Eagle, THIS JOURNAL, **66**, 192 (1944), or by the method of Morgan and Hamilton, *ibid.*, **66**, 874 (1944). [c] All analyses are the average of two or more determinations. [d] Calcd: N, 4.21. Found: N, 4.21. [e] Calcd.: N, 4.36. Found: N, 4.44. [f] The arsenoso compounds were obtained in an amorphous form and could not be crystallized from common solvents. [g] The dichloroarsines were obtained in crystalline form by solution in water, followed by the addition of concentrated hydrochloric acid. [h] Calcd.: N, 3.89. Found: N, 3.86.

It was then recrystallized twice from benzene. The yield of pure γ-(*p*-nitrophenyl)-butyric acid was 74 g. (42%); m. p. 93°. From the benzene mother liquors, a solid was obtained which melted at 55–56° after repeated recrystallization from benzene. Oxidation of this fraction with alkaline permanganate gave a mixture of *o*- and *p*-nitrobenzoic acids (52% of the para isomer) which were easily separated by their differential solubility, and were identified by mixed melting points with authentic samples of the two substances. No attempt was made to further separate the two isomeric nitrophenylbutyric acids.

**δ-(*p*-Nitrophenyl)-valeric Acid.**—δ-Phenylvaleric acid (58.9 g.), nitrated by the above procedure, gave 29.0 g. (40%) of pure δ-(*p*-nitrophenyl)-valeric acid after three recrystallizations from benzene. It was obtained as light-yellow hexagonal needles; m. p. 83.8–84.4° (cor.). The structure was proved by oxidation to *p*-nitrobenzoic acid with alkaline permanganate.

*Anal.* Calcd. for $C_{11}H_{13}NO_4$: N, 6.28; neut. equiv., 223. Found: N, 6.04; neut. equiv., 224.

**ε-(*p*-Nitrophenyl)-caproic Acid.**—The above nitration procedure yielded an oil which could not be crystallized; accordingly the procedure of Van der Scheer[6] was used for the preparation of this compound.

**γ-(*p*-Aminophenyl)-butyric Acid.**—The corresponding nitro acid (20.9 g.) was dissolved in 25 ml. of alcohol and reduced catalytically at 40 lb. gage pressure, using Raney nickel as catalyst. The reduction was rapid and complete. After recrystallization from water, the amino compound (16.1 g., 90%) melted at 130–131° (cor.).

**δ-(*p*-Aminophenyl)-valeric Acid.**—This compound was prepared in 93% yield by a similar procedure. It crystallized from water in white needles; m. p. 111–112.3° (cor.).

*Anal.* Calcd. for $C_{11}H_{15}NO_2$: N, 7.25; neut. equiv., 193.2. Found: N, 7.18, 7.04; neut. equiv., 193.4.

**ε-(*p*-Aminophenyl)-caproic Acid.**[6]—Catalytic reduction of the corresponding nitro acid gave this compound in 67% yield; m. p. 105–107° (cor.).

**α-(*p*-Aminophenyl)-butyric Acid.**—Catalytic reduction gave the amino compound in 75% yield; m. p. 142° (cor.). It has previously been prepared by Fourneau and Sandulesco who used a different procedure.[14]

***p*-Aminomandelic Acid.**—Catalytic reduction of *p*-nitromandelic acid with Raney nickel as catalyst gave a red product, insoluble in acids, which was not further characterized. The desired amino compound was obtained by the method of Heller.[15]

**γ-(2-Nitro-4-arsonophenyl)-butyric Acid.**—γ-(*p*-Arsonophenyl)-butyric acid (14.4 g., 0.05 mole) was added in small portions to 16 ml. of concentrated sulfuric acid maintained at −10°. When no undissolved material remained, 3.8 g. of fuming nitric acid (sp. gr. 1.5) were added dropwise. The solution was stirred for one-half hour and then placed in a bath at 36°. The temperature of the mixture rose to 42°, then fell to bath temperature. After being stirred a further fifteen minutes it was poured onto ice. An oil separated which quickly solidified. The crude material as recrystallized from hot water.

**γ-(2-Amino-4-arsonophenyl)-butyric Acid.**—Catalytic reduction of the above nitro compound, using Raney nickel as catalyst, was not successful. The nitro compound was reduced by the method of Jacobs, Heidelberger and Rolf.[16] The resulting amino compound was recrystallized from alcohol and then from water. It crystallized with one molecular equivalent of water of crystallization.

## Summary

Several new arsenoso derivatives of phenyl-substituted fatty acids have been prepared. None of these compounds possess the unusual trypanocidal activity of γ-(*p*-arsenosophenyl)-butyric acid. Improvements in the preparation of the latter compound are also described.

BALTIMORE, MD. RECEIVED SEPTEMBER 1, 1948

(14) Fourneau and Sandulesco, *Bull. soc. chim.*, [4] **41**, 450 (1927).

(15) Heller, *Ber.*, **46**, 280 (1913).

(16) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1580 (1918).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

# The Spectra of Some Diaminotriphenylmethane Dyes in Concentrated Sulfuric Acid

BY GERALD E. K. BRANCH AND BERT M. TOLBERT

A diaminotriphenylcarbinol has three basic structures, namely, the two amino groups and the triphenylcarbinol structure. Under sufficiently acidic conditions it should neutralize three equivalents of acid. The final product would be a disubstituted triphenylmethyl ion. The substituent radicals are aminium not amino groups. The aminium group is not an auxochrome, and hence the third ion of the dye should not absorb light of long wave lengths. Triphenylmethyl ion absorbs very little light at wave lengths longer than 450 mμ.

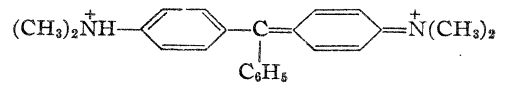
However Hill, Branch and Patapoff[1] observed a band at 678 mμ in the spectrum of viridine green (II) in concentrated sulfuric acid. This band could belong to neither the first nor the second ion, for under less acidic conditions the first ion is entirely converted to the second ion, whose longest band has its maximum at 495 mμ. Nor can one believe that a simple derivative of triphenylmethyl ion could have a strong absorption band with a maximum at 678 mμ. The authors of the above mentioned paper suggested that the band at 678 mμ was due to an intermediate product in the sulfonation of the dye, for on standing the band at 678 mμ was replaced by another at 580 mμ.

For further study of this phenomenon, the spectra of several diaminotriphenylmethane dyes were measured in a mixture of two volumes of acetic acid and ninety-eight volumes of concentrated sulfuric acid (d. 1.84 g./ml.). The spectra were measured immediately after making up the solutions, and after the solutions had stood twenty-six days at room temperature. In general the spectra changed on standing. No attempts were made to measure the rates and extents of these changes.

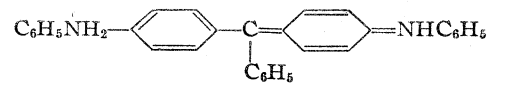
The formation of an ion of the dye, or an addition of sulfuric acid to the dye would be reversed when a solution in sulfuric acid is diluted with acetic acid. Sulfonation and decompositions would not be reversed. To study the nature of the irreversible changes, solutions in concentrated sulfuric acid were allowed to stand for a week, diluted with acetic acid, and their spectra compared with those of freshly prepared solutions in the same mixture of sulfuric acid and acetic acid. Generally sulfonation does not produce a large change in the spectra of the first and second ions of these dyes, but it must greatly reduce the basicity of the dye. When the spectra of a dye and its sulfonation derivative are measured at an acidity at which either the dye or the derivative exists as a mixture of first and second ions, the ratio of absorption by the first ion to that by the second ion is greater for the derivative than for the parent dye, and the two spectra differ markedly, and in an expected way.

(1) Hill, Branch and Patapoff, THIS JOURNAL, **67**, 545 (1945).

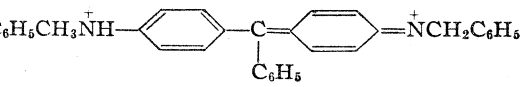
We think that the most illuminating results we obtained were those with malachite green (I), viridine green (II) and the N,N-dimethyl derivative of viridine green (III). The formulas of these dyes as their second ions are shown below



I



II



III

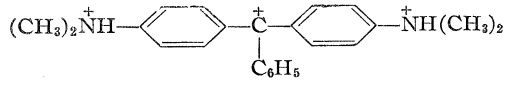
The results obtained with I were in sharp contrast with those obtained with II and III. We shall first describe and discuss the results with these three dyes, treating II and III as a unit. We shall then present and briefly discuss the spectra of five other dyes.

**Malachite Green** (I).—The spectrum of malachite green in concentrated sulfuric acid is shown in Fig. 1. This spectrum changed in no detectable way after standing for twenty-six days at room temperature. When a solution in concentrated sulfuric acid was allowed to stand for a week, and then diluted with acetic acid, the molecular extinction coefficients were, within experimental error, the same as those of a freshly prepared solution of (I) in the same solvent over the entire range of wave lengths measured (700 mμ to 300 mμ). Apparently no sulfonation or other irreversible reaction occurred.

The spectrum of malachite green in concentrated sulfuric acid is very similar to that of triphenylmethyl ion, and quite unlike that of the second ion of malachite green. This can be seen from the following comparison of the spectral data: For malachite green in concentrated sulfuric acid, $\lambda_1 = 434$ mμ, $\epsilon_1 = 3.2 \times 10^4$, $\lambda_2 = 388$ mμ, $\epsilon_2 = 2.7 \times 10^4$, $\lambda_3 = 288$ mμ, $\epsilon_3 = 2.3 \times 10^3$; for triphenylmethyl ion,[2] $\lambda_1 = 431$ mμ, $\epsilon_1 = 4 \times 10^4$, $\lambda_2 = 404$ mμ, $\epsilon_2 = 4 \times 10^4$, $\lambda_3 = 289$ mμ, $\epsilon_3 = 2 \times 10^3$; for the second ion of malachite green,[3] $\lambda_1 = 450$ mμ, $\epsilon_1 = 3.0 \times 10^4$, $\lambda_2 = 322$ mμ, $\epsilon_2 = 5.5 \times 10^3$, $\lambda_3 = 262$ mμ, $\epsilon_3 = 9.5 \times 10^3$. There seems little doubt that in concentrated sulfuric acid malachite green changes to an ion very similar to triphenylmethyl ion. The formula of this ion is IV.

(2) Orndorf, Gibbs, McNulty and Shapiro, *ibid.*, **49**, 1545 (1927).

(3) Tolbert and Branch, *ibid.*, **69**, 1083 (1947).



IV

In Fig. 1 the spectrum is not shown further toward the red than 560 mμ. The measurements were made beyond 700 mμ, but there was no absorption in this region. Malachite green does not show the phenomenon observed by Hill, Branch and Patapoff with viridine green.

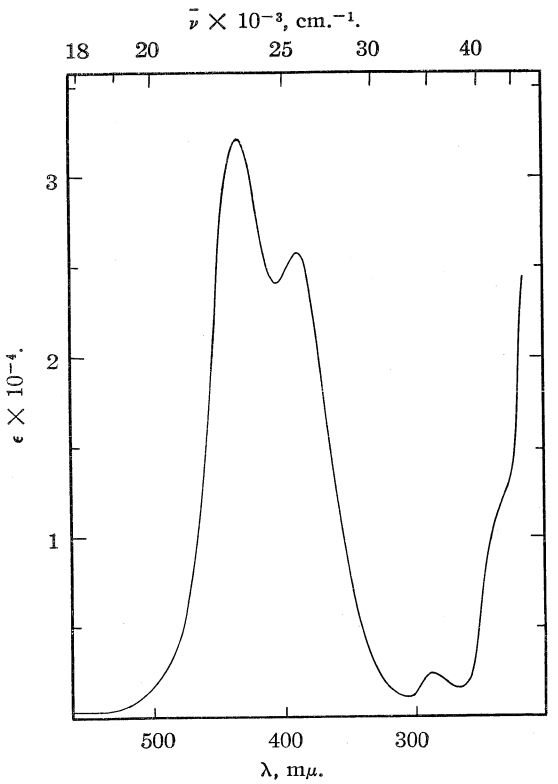



Fig. 1.—Spectrum of malachite green (I) in concentrated sulfuric acid.

**Viridine Green and its Dimethyl Derivative.**—The spectra of freshly prepared concentrated sulfuric acid solutions of II and III are shown in Fig. 2. The data for these spectra are $\lambda_1 = 677$ mμ, $\epsilon_1 = 1.9 \times 10^4$, $\lambda_2 = 512$ mμ, $\epsilon_2 = 2.1 \times 10^4$, $\lambda_3 = 349$ mμ, $\epsilon_3 = 1.1 \times 10^4$, $\lambda_4 = 269$ mμ, $\epsilon_4 = 1.3 \times 10^4$ for II, and $\lambda_1 = 710$ mμ, $\epsilon_1 = 2.25 \times 10^4$, $\lambda_2 = 485$ mμ, $\epsilon_2 = 2.3 \times 10^4$, $\lambda_3 = 270$ mμ, $\epsilon_3 = 1.3 \times 10^4$ with shoulders in the neighborhoods of 580 mμ, 450 mμ, and 350 mμ for III. The data for the second ions of these dyes are $\lambda_1 = 495$ mμ, $\epsilon_1 = 2.5 \times 10^4$, $\lambda_2 = 350$ mμ, $\epsilon_2 = 1.3 \times 10^4$, $\lambda_3 = 266$ mμ, $\epsilon_3 = 1.95 \times 10^4$ for II, and $\lambda_1 = 485$ mμ, $\epsilon_1 = 3.2 \times 10^4$, $\lambda_2 = 330$ mμ, $\epsilon_2 = 8.6 \times 10^3$, $\lambda_3 = 270$ mμ, $\epsilon_3 = 1.3 \times 10^4$ for III. The spectra in concentrated sulfuric acid are evidently those of the second ions with the spectra of other molecular species of the dyes superimposed on them. In both cases the new species have strong absorption bands in the neighborhood of 700 mμ.

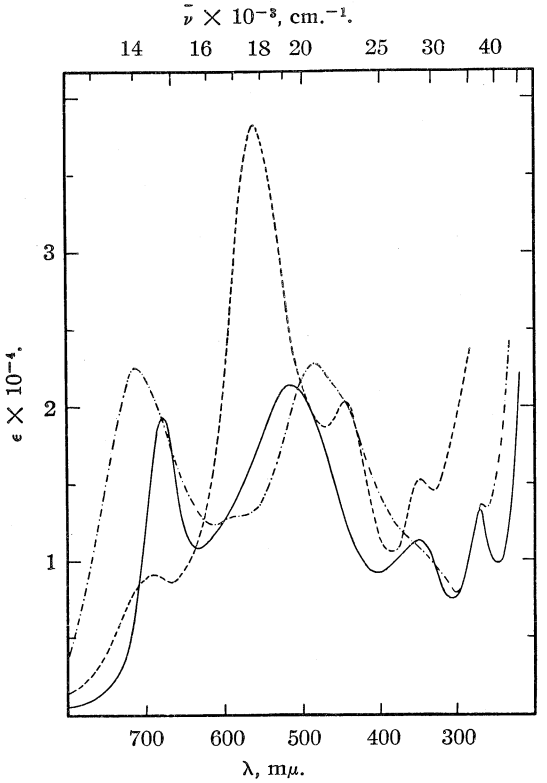



Fig. 2.—Spectra of dyes II, III and VIII in concentrated sulfuric acid: — dye II, -·-·- dye III, - - - dye VIII.

When solutions of II and III in concentrated sulfuric acid were allowed to stand and then diluted with acetic acid, the spectra of the resulting solutions were typical of first ions of diaminotriphenylmethane dyes, though at the same concentration of sulfuric acid the spectra of the parent dyes were those of mixtures of the first and second ions. This is illustrated in Fig. 3 for the case of II, at two volume per cent. of sulfuric acid. This is shown by the following data. For the first ion of II, $\lambda_x = 637$ mμ, $\epsilon_x = 4.7 \times 10^4$, $\lambda_y = 447$ mμ, $\epsilon_y = 1.3 \times 10^4$. With two per cent. of sulfuric acid $\lambda_x = 638$ mμ, $\epsilon_x = 2.9 \times 10^4$, and there was absorption covering the regions of the *x*-band of the second ion ($\lambda = 495$ mμ) and the *y*-band of the first ion ($\lambda = 447$ mμ). At this acidity an appreciable amount of the parent dye was converted to its second ion. But when II was allowed to stand for a week in concentrated sulfuric, the spectral data for the solution after it had been diluted to two per cent. sulfuric acid was $\lambda_x = 630$ mμ, $\epsilon_x = 4.4 \times 10^4$, $\lambda_y = 454$ mμ, $\epsilon_y = 1.6 \times 10^4$. This spectrum is very similar to that of the first ion of II. The irreversible change produced on standing in sulfuric acid was one that produces only small changes in the spectrum, but markedly decreases the basicity of the first ion. Evidently the irreversible reaction was sulfonation of benzene rings.

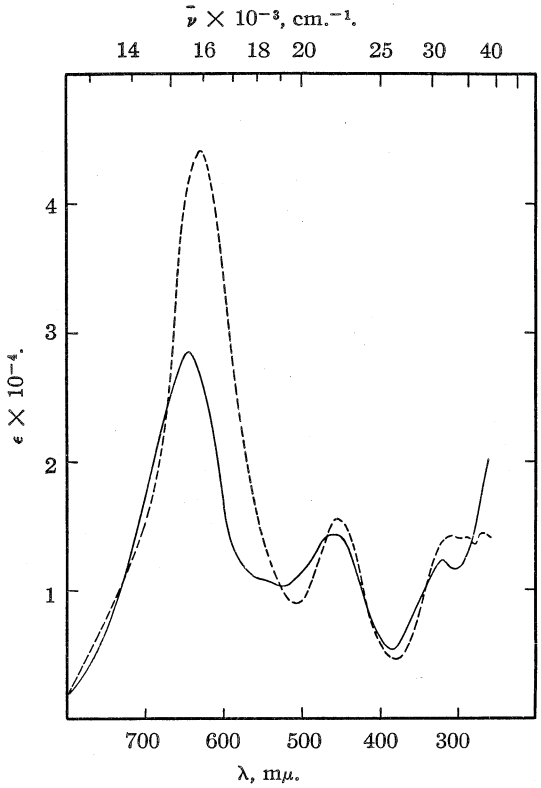



Fig. 3.—Spectra of dye II in acetic acid with 2% of sulfuric acid, before and after standing in concentrated sulfuric acid for a week: — after, - - - before.

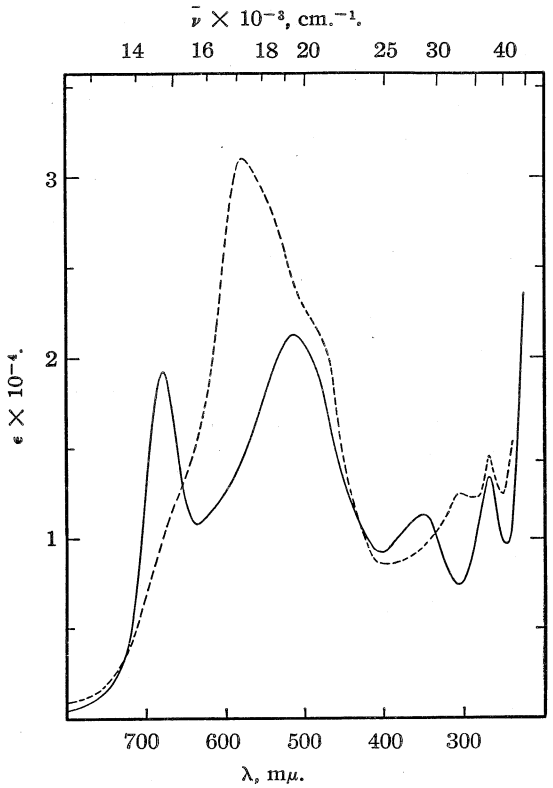



Fig. 4.—Spectra of dye II in concentrated sulfuric acid before and after standing for twenty-six days: — before, - - - after.

The spectrum of a freshly prepared solution of III in concentrated sulfuric had two regions of strong absorption. One of these was in the neighborhood of 700 mμ, and the other in the neighborhood of 500 mμ. The latter was due chiefly to the second ion, the former to a new species. The absorptions in the two regions were approximately equal. When the solution was allowed to stand the absorption in the neighborhood of 500 mμ grew at the expense of that at 700 mμ. During this period sulfonation of benzene rings occurred. Evidently sulfonation reduces the conversion of second ions to forms that absorb in the neighborhood of 700 mμ. This suggests that the forms absorbing at 700 mμ are higher ions, and that their disappearance is due to the reduction of basicity normally resulting from sulfonation.

The spectrum of II in concentrated sulfuric acid changed in a quite different way on standing. This change is shown in Fig. 4. The spectrum was measured after twenty-six days, but visual observation showed that the change was nearly complete in a day. The chief feature of the spectrum after standing is a strong band with $\lambda = 580$ mμ, and $\epsilon = 3.1 \times 10^4$. The same phenomenon was observed by Hill, Branch and Patapoff.[1]

To whatever compound the absorption at 580 mμ was due, it was evidently formed in good yield, but was entirely destroyed when the solution was diluted with acetic acid.

The chief difference between II and III is that II is a secondary amine while III is a tertiary amine. The difference observed in the spectra of the two dyes on standing is best explained as due to N-sulfonation. This reaction could occur with the secondary amine II, but not with the tertiary amine III. However there is no reason to believe that the second ion of any sulfonated product of II can have a band with $\lambda_{max}$ as great as 580 mμ. Sulfonation at the nitrogen atoms would greatly reduce the basicity of the dye, and hence could cause the reversion of the second ion to a first ion even in concentrated sulfuric acid. That $\lambda_x$ for the first ion of the N-sulfonated dye should be markedly smaller than that for the parent dye is to be expected. The value of $\lambda_x$ for the first ion of the N,N-diacetyl derivative of II is 539 mμ.

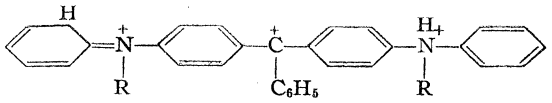
The acetyl groups are easily removed from the N-acetyl derivatives of II by hydrolysis in acid solution. By analogy one would expect that sulfonic acid groups are easily removed from N-sulfonic acid derivatives of II, by the lytic action of acetic acid. It is therefore not surprising that the band at 580 mμ disappeared when the solution was diluted. That C- as well as N-sulfonation occurred was shown by the spectrum of the diluted solution.

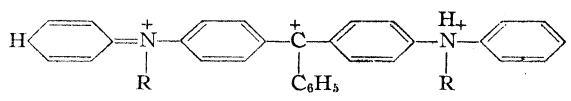
The value of the $\lambda_{max}$ of a diaminotriphenylmethane dye alternately increases and decreases by 100–200 m$\mu$ as protons are removed from or added to the nitrogen atoms, the greater $\lambda_{max}$ values occurring when the two nitrogen atoms have similar basicities. This alternation does not normally continue after the second ion has been reached, for on the next step both nitrogen atoms become neutralized by protons, thus insulating them from the chromophore and reducing $\lambda_{max}$. When as in II and III the alternation continues beyond the second ion, one might suppose that the amino groups have lost basicity, and the second ion has reverted to a first ion in spite of the increase in the acidity. But so great a reduction of the basicity of the amino groups would have a strong hypsochromic effect, and consequently such an explanation is not a valid explanation of the bands observed in the neighborhood of 700 m$\mu$, for the first ions of the parent dyes have $\lambda_{max}$ values a little smaller than 640 m$\mu$. It would appear therefore that the acid reacts to form a third ion in which the terminal rings extend the chromophoric conjugated system beyond the triphenylmethyl structure.

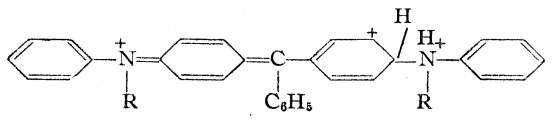
To assume that the band near 700 m$\mu$ is due to an addition of the acid to the $\pi$ electrons of a ring as a whole is begging the question. There is no known reason why such an addition should be strongly bathochromic. We shall assume an addition of the acid to a particular atom. For such an assumption to be acceptable it is necessary that the carbonium ion charge of the product should have a greater linear range of location than is found in triphenylmethyl ion in which the linear range for the charge is from the para position of one ring to the para position of another ring (9 atoms). Otherwise $\lambda_{max}$ would not be much greater than it is in triphenylmethyl ion (430 m$\mu$). Further it is also necessary that the carbonium ion charge of the addition product shall be locatable at more atoms than it is in triphenylmethyl ion (10 atoms). Otherwise, since the product has fewer benzenoidal rings than its type IV tautomer, and is for that reason very unstable with respect to its tautomer, it could not exist in appreciable quantities without the compensating factor of greater resonance of the charge.

We shall consider only the three product whose formulas are shown below. Other possibilities either could not absorb in the 700 m$\mu$ region, or are not acceptable for the same reasons that lead us to reject VII. In the formulas the added acid is represented by an H, and R is a methyl group when the parent dye is III, and a hydrogen atom when the parent dye is II.

In VII, the charge may vibrate over thirteen atoms, and consequently such a product might account for the high value of $\lambda_{max}$. But there are only ten locations for the charge in VII, and these do not include the favored central carbon atom, but do include an already positively charged nitrogen atom. Consequently VII must be rejected as being too unstable with respect to its type-IV tautomer. One cannot assume that the equilibrium between VII and IV is not achieved, for the formation of the addition product is a rapid reversible reaction, and a type-IV compound is formed rapidly and reversibly from malachite green.

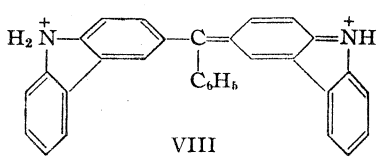

V

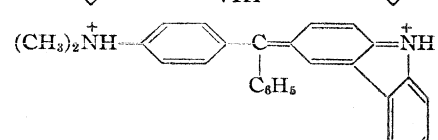

VI

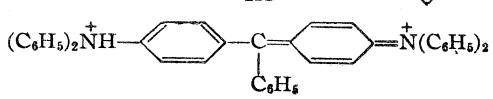

VII

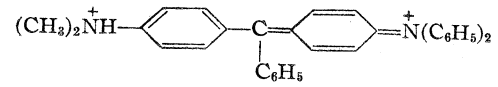
The charge of V or VI vibrates linearly over 13 atoms. In V the number is 15 if the atoms are counted round the terminal ring. In VI there is the additional bathochromic factor of a branched system of double bonds in the terminal ring. If these carbonium ions are treated by the same rules as the cyanines, $\lambda_{max}$ of V or VI should be between 200 and 300 m$\mu$, greater than $\lambda_{max}$ of triphenylmethyl ion. That is, $\lambda_{max}$ should be between 650 and 750 m$\mu$. Both V and VI have thirteen locations for the charge, including the favored location on the central carbon atom. It is therefore possible that V and VI are stable with respect to their type IV tautomers. Since we have no preference between structures V and VI, we shall use V to mean V and/or VI.

**Other Phenylated Dyes.**—Experiments similar to those already described were done with some other phenylated diaminotriphenylmethane dyes. We shall use formula numbers instead of the complicated names to indicate these dyes. The formulas of the second ions are given below

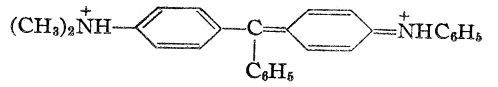

VIII


IX


X



XI



XII

The change of the spectrum on ageing the solutions in concentrated sulfuric acid was not investigated for VIII and IX. The results obtained with X (Fig. 5) were inconclusive. The first ion of this dye is so weakly basic that in a 50–50 mixture of acetic and sulfuric acids there was no sign of the second ion. Hence there is a probability that the first ion was present in the sulfuric acid solution, which contained a considerable amount of the second ion. The *x*-bands of the first ions of II and III are greatly affected by the presence of the second ion. Although the absorption by X at long wave lengths was greatly changed in going from fifty per cent. to ninety-eight per cent. sulfuric acid, one cannot say whether the change was due to the effect of the second ion on the *x*-band of the first ion, or the production of higher than second ions. On standing, the sulfuric acid solution of X lost its optical clarity, and no conclusion could be drawn from the spectrum.

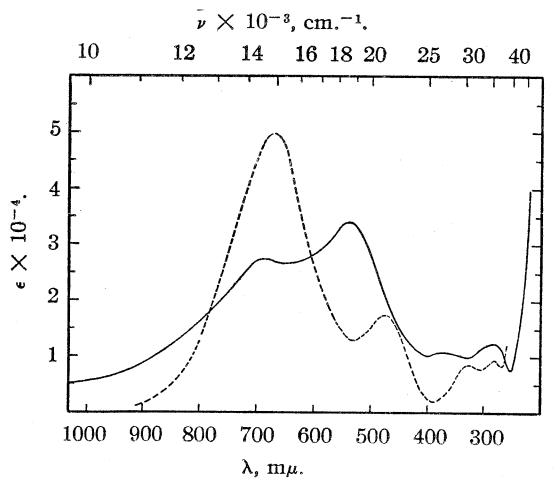



Fig. 5.—Spectra of dye X in a fifty–fifty mixture of acetic and sulfuric acids, and in concentrated sulfuric acid: — in concentrated sulfuric acid, – – – in fifty–fifty mixture.

The spectra observed for IX and XI indicated the presence of nothing but the second ions. The spectrum of IX in concentrated sulfuric acid was an exact replica of that shown for the second ion in reference 3. A shift of the bands toward the red was observed in XI. This is presumably a solvent effect. The spectral data for XI in sulfuric acid (Fig. 6) are $\lambda_1 = 538$ mμ, $\epsilon_1 = 3.7 \times 10^4$; $\lambda_2 = 355$ mμ, $\epsilon_2 = 1.1 \times 10^4$; $\lambda_3 = 270$ mμ, $\epsilon_3 = 1.3 \times 10^4$. The data in ten per cent. sulfuric acid are $\lambda_1 = 515$ mμ, $\epsilon_1 = 3.3 \times 10^4$; $\lambda_2 = 343$ mμ, $\epsilon_2 = 1.0 \times 10^4$, $\lambda_3 = 270$, $\epsilon_3 = 1.2 \times 10^4$.

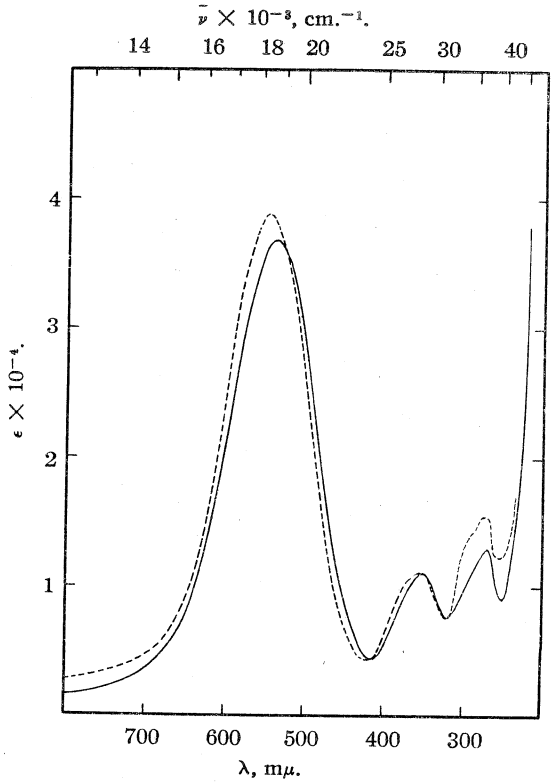



Fig. 6.—Spectra of dye XI in concentrated sulfuric acid before and after standing for twenty-six days: — before, – – – after.

The other two dyes VIII and XII (Figs. 2 and 7) showed the presence of type V ions. A definite band, $\lambda_{max} = 680$ mμ and $\epsilon = 9 + 10^3$, was obtained with VIII. A shoulder 680–700 mμ was obtained with XII.

The spectra of III, VIII and XII cannot be accounted for by bands in the neighborhood of 700 mμ and absorption by the second ions. In all three dyes some of this extra absorption was in the neighborhood of 450 mμ. This extra absorption appeared as a shoulder on the *x*-band of the second ion in III, as a small band, with $\lambda = 446$ mμ in VIII and as the most intense band ($\lambda = 440$ mμ) in the spectrum of XII. Since the strengths of these absorptions are related inversely to the intensity of the absorption by type V ions, presumably they are not due to type V ions; but to some other species, which we think is the type IV ion.

Terminal aryl groups on both nitrogen atoms are insulated in a type IV ion, but those on only one of the nitrogen atoms of a second ion are insulated. Hence the basicity of the second ion depends chiefly on the terminal groups on one nitrogen atom. Hence the relative basicities of the second ions should be correlated to the relative basicities of the less basic of the pair of amines out

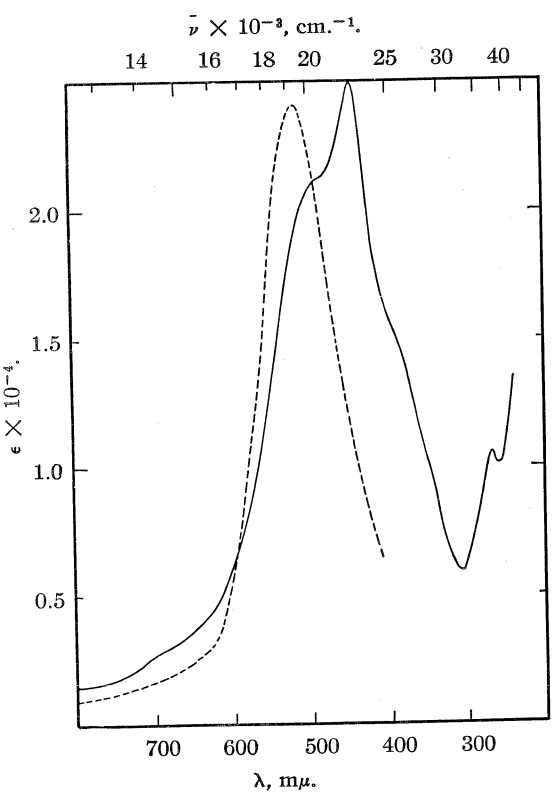



Fig. 7.—Spectra of dye XII in concentrated sulfuric acid before and after standing for twenty-six days: — before, – – – after.

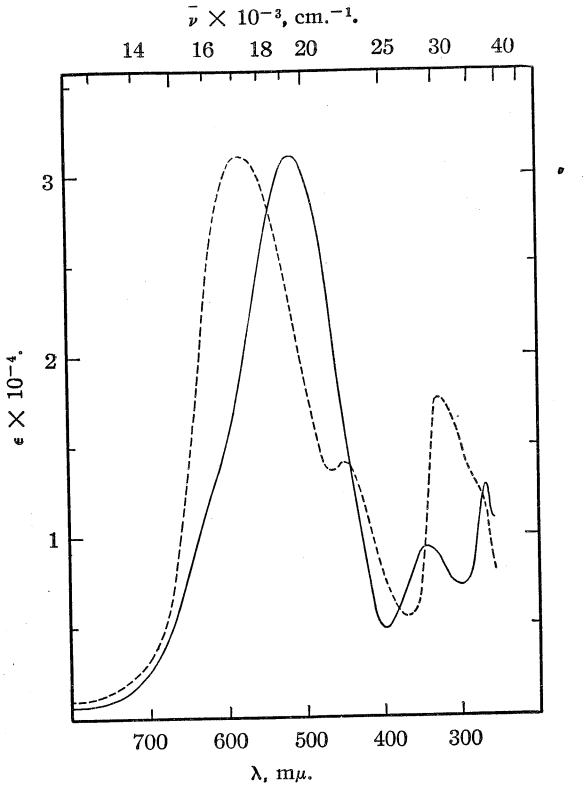



Fig. 8.—Spectra of dye XI in acetic acid with 2% sulfuric acid, before and after standing in concentrated sulfuric acid for a week: — before, – – – after.

of which the dye is made, the terminal groups from the more basic amine being insulated by the addition of the proton to form the second ion from the first. To obtain a type V ion one terminal aryl group is necessary. Other terminal aryl groups are either insulated or have only a small interaction with the rest of the molecule. Hence extra aryl groups or resonance either should have only a small effect on the amount of type V ion, or if located on the already phenylated nitrogen atom should reduce the conversion of the second ion to the type V ion.

Assuming that the relative intensities of the bands roughly mirror the relative concentrations of the three species the above deductions were to some extent confirmed by the experiments. Thus the second ion of I, which is derived from dimethylaniline, was completely neutralized, the second ions of VIII, IX and XI, which are derived in part or *in toto* from the very weakly basic amines, triphenylamine and carbazole, were the least affected by sulfuric acid, and II, III and XIII were of intermediate basicity. However, the agreement between deduction and experiment was far from perfect. The insulated aryl group has the effect of stabilizing the type V ion. Thus the type V ion was abundant in II and III, but only a trace was present in XII. The type V ion of VII was found, but at the same acidity no type V ion was observed in IX. Apparently the insulation is not complete. Tolbert and Branch[3] found bathochromic effects on the *x*-bands of the second ions leaking through the insulation.

The main thesis of this article is that the bands observed in the neighborhood of 700 mμ could have been due to a third ion that is tautomeric with the type IV ion, and derivable from it by a tautomeric shift of a proton from a nitrogen atom to an ortho or para position of a terminal aryl group. The arguments for this conclusion apply equally to a shift of this type from both nitrogen atoms. Against this double shift it can be argued that the band in the red was also found in the sulfuric acid solution of XII, which has only one terminal aryl group, and that calculation of $\lambda_{max}$ of the product of a double shift, by methods used to predict $\lambda_{max}$ values in cyanines, gives too large a value. Neither of these arguments is conclusive. The absorption in the red observed in XII was so small that it could have been due to an impurity with terminal groups on both nitrogen atoms. The amount needed would be too small to detect by analysis, or in the spectra of the first and second ions. Such an impurity could have been formed by disproportionation. Indeed Tolbert and Branch actually separated from the crude preparation of some of these dyes small amounts of dyes with spectra characteristic of triaminotriphenyl-

methane dyes. Although there is little doubt that structures like V represent oscillators very similar to the cyanines, it is not known that the constant for the increase of $\lambda_{max}$ with the number of interpolated double bonds would be the same as that found in cyanines. Were this constant half of what it is in the cyanines, the observed $\lambda_{max}$ would indicate the double shift.

With the exception of I, in all solutions in sulfuric acid that had stood, absorption due to third ions diminished. On dilution, such solutions, again with the exception of I, gave spectra that were characteristic of a diaminotriphenylmethane dye, but of one whose first ion was less basic than the first ion of the corresponding parent dye. It is natural that sulfonation should decrease the basicities of both first and second ions.

On standing, the spectra of XI changed very little (Fig. 6). That it had sulfonated was shown by the spectrum after dilution (Fig. 8). This spectrum was chiefly that of a first ion as can be seen from the bands in the far ultraviolet. However the main band comes at a wave length that is short for a phenylated dye. In dye XI the two amino groups are sufficiently different in basicities for the Brooker effect to be appreciable, on sulfonation of the terminal phenyl groups the difference of basicities of the two amino groups is increased, and the hypsochromic Brooker effect becomes accentuated. The appearance of the spectrum showed that there was a mixture in the solution as would be expected, since sulfonation would have reached different degrees in different molecules. Some second ions were probably present, but their bands were obscured by those of the first ions.

## Experimental

The spectra were measured with a Beckman spectrophotometer. The experimental details and the materials were all the same as those described or given by reference in the author's paper on the spectra of the second ions.[3] One detail should be repeated because of its special importance in this work. The mixtures of acetic and sulfuric acids in the comparison cell of the spectrophotometer were compounded and aged in the same way as the liquid in which the dye was dissolved. This was necessary to compensate for absorption, especially in the ultraviolet, that developed when mixtures of the two acids were aged. The absorption developed especially fast in mixtures of approximately equal proportions. In general the method of compensating for the charring appears to have been successful. The greatest error would have arisen when solutions that were treated with concentrated sulfuric acid were diluted. Heating was not always avoided during dilution. In solutions made in this way, the spectra at wave lengths less than 300 m$\mu$ should be considered dubious.

## Summary

The spectra in concentrated sulfuric acid of malachite green and some more phenylated diaminotriphenylmethane dyes were measured.

The spectrum of malachite green was so similar to that of triphenylmethyl ion, that it was assumed that, in concentrated sulfuric acid, malachite green exists as a triply charged ion with a structure similar to that of triphenylmethyl ion except for two dimethylaminium ion groups at the $p$ and $p'$ positions.

With some of the phenylated dyes bands were observed in the neighborhood of 700 m$\mu$. These bands have been attributed to the addition of a proton to one of the terminal benzene rings, resulting in a carbonium ion compounded of a large number of mesomers, differing from each other in the location of the charge, and the distribution of the double bonds. This mesomeric ion can be considered as a triphenylmethyl ion in which the conjugate system has been extended by three more double bonds. Bands attributed to this type of ion were found mixed with bands due to the second ion and to ions of the simple triphenylmethyl type. They were prominent only when both amino groups were phenylated, though a small band in the neighborhood of 700 m$\mu$ were found in one case in which only one of the amino groups was phenylated.

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# Maintenance of Near Equilibrium during Isentropic Expansions through a Nozzle*

BY S. S. PENNER

## Introduction

The rates of homogeneous gas reactions in flow systems have been discussed by Benton,[1] Hulburt,[2] and Harris.[3] Brinkley and Weller[4] have recently reported a generalized form of the reaction-rate law in flow systems.

The rates of reactions in flow systems are of considerable importance in the determination of rocket performance.[5,6] During the flow through a rocket nozzle, many chemical reactions occur so slowly, relative to the rate of cooling of the gases, that the chemical composition (mole fraction of each constituent) remains nearly unchanged, thus leading to near-constant-composition flow. On the other hand, some reactions involving atoms or free radicals take place very rapidly, and nearly complete chemical equilibrium may be reached with respect to these rapid reactions at each temperature; *i.e.*, near-equilibrium flow obtains. In general, the rates of all of the chemical reactions which may occur are not sufficient to maintain nearly complete chemical equilibrium during flow, and the flow process as a whole is therefore intermediate between the two extremes mentioned above.

If thermodynamic equilibrium is reached for the chemical reactions in the combustion chamber, then the thrust on the rocket motor will reach a maximum value if complete equilibrium is also maintained during flow through the nozzle. The nature of the flow process can always be determined by a laborious numerical analysis, provided the necessary kinetics data are available.[5,6] Because of the importance of the nature of the flow process through the rocket nozzle on the performance of rockets, it is desirable to derive a simple criterion for determining the existence of near-equilibrium flow and thus obviate the necessity of laborious calculation for many reactions. Accordingly, the present paper is devoted to a discussion of a criterion for near equilibrium during isentropic expansion similar to the criterion developed by Schaefer.[7]

* Presented before the Division of Physical and Inorganic Chemistry at the 114th Meeting of the American Chemical Society in Portland, Oregon, September, 1948.

(1) A. F. Benton, THIS JOURNAL, **53**, 2984 (1931).

(2) H. M. Hulburt, *Ind. Eng. Chem.*, **36**, 1012 (1944); *ibid.*, **37**, 1063 (1945).

(3) G. M. Harris, *J. Phys. and Colloid Chem.*, **51**, 505 (1947).

(4) S. R. Brinkley and S. Weller, THIS JOURNAL, **69**, 1319 (1947).

(5) D. Altman and S. S. Penner, Paper 26 presented before the 112th meeting of the American Chemical Society in New York City, September 1947 (to appear shortly in *J. Chem. Phys.*).

(6) S. S. Penner and D. Altman, *J. Franklin Institute*, **245**, 421 (1948).

(7) K. Schaefer, "On the Thermodynamics of Rocket Propulsion, I," available through Headquarters, Air Materiel Command, Wright Field, Dayton, Ohio, February, 1947.

## Requirements for Thermodynamic Equilibrium

The present analysis is restricted to a discussion of triple-body collisions[8] which lead to the combination of atoms A and B to form the molecule AB

$$M + A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} AB + M \qquad (1)$$

where $k_f$ and $k_b$ denote, respectively, the rates of the recombination and dissociation reactions. Assuming the validity of the perfect gas law, the equilibrium constant $K_c$ for reaction 1 is

$$K_c = (AB)/(A)(B) = K_p RT = k_f/k_b \qquad (2)$$

where (A), (B), and (AB) represent the respective concentrations, $K_p$ is the equilibrium constant defined by the relation

$$K_p = P_{AB}/P_A P_B \qquad (3)$$

$P_A$, $P_B$ and $P_{AB}$ denote the partial pressures of components A, B, and AB, respectively, $T$ is the absolute temperature, and $R$ is the molar gas constant. From equation 2 it can now be seen that flow under conditions of thermodynamic equilibrium is characterized by the relation

$$d \ln K_c/dt = d \ln (AB)/dt - d \ln (A)/dt - d \ln(B)/dt \qquad (4)$$

where $t$ represents the time.

Flow through a rocket nozzle is accompanied by changes in pressure and temperature. The concentrations of the reacting components A, B, and AB therefore change for two reasons during flow through the rocket nozzle: (1) a concentration change associated with the change in pressure and temperature (this concentration change occurs without time lag since it depends only on the physical state of the system); (2) a concentration change associated with chemical reaction according to equation 1 [this concentration change depends on the reaction rate constants $k_f$ and $k_b$ and cannot exceed in magnitude the concentration change which has to be added to (1) in order to make the sum of the concentration changes of (1) and (2) equal to the concentration changes required to maintain thermodynamic equilibrium as specified by equation (4)].

It is now necessary to derive analytic relations for the concentration changes defined by (1) and (2).

(8) The recombination of free atoms as the result of collision between two atoms, without the presence of a third body, does not make an appreciable contribution to the number of molecules actually formed, at least not for small atoms such as hydrogen. Chemical reactions other than atomic recombinations generally occur too slowly to allow near-equilibrium flow during expansions through a rocket nozzle. For this reason, only reaction 1 will be considered in this discussion.

## Concentration Change Caused by a Change in Temperature and Pressure

The concentration of an idealized gas is a function of pressure and temperature. Only the concentration changes associated with a change of state are considered in this section.

The concentration of the $j$'th constituent of a system whose physical state is changing is

$$c_j = c_j[p(t),T(t)]$$

where $p$ is the total pressure.

Differentiation with respect to time leads to the result

$$dc_j/dt = (\partial c_j/\partial p)(dp/dt) + (\partial c_j/\partial T)(dT/dt) \quad (5)$$

Adiabatic flow of ideal gases is characterized by the relation[9]

$$dp/dT = \gamma p/T(\gamma - 1) \quad (6)$$

where $\gamma$ is the instantaneous ratio of the specific heat at constant pressure to the specific heat at constant volume. Introducing equation 6 into equation 5 leads to the result

$$dc_j/dt = \{[p\gamma/T(\gamma - 1)](\partial c_j/\partial p) + (\partial c_j/\partial T)\}(dT/dt) \quad (7)$$

Equation 7 will be used only for ideal systems[10] in the present discussion.

The partial pressure $p_j$ of the $j$'th constituent is

$$p_j = c_j RT = n_j p/n$$

where $n_j/n$ represents the mole fraction of the $j$'th component. Hence

$$\partial c_j/\partial T = -p_j/RT^2$$

and

$$p(\partial c_j/\partial p) = p[\partial c_j/\partial(np_j/n_j)] = p_j(\partial c_j/\partial p_j) = p_j/RT$$

Replacing $p(\partial c_j/\partial p)$ and $(\partial c_j/\partial T)$ in equation 7, the desired result is obtained

$$dc_j/dt = (\gamma - 1)^{-1}(p_j/RT^2)(dT/dt) \quad (8)$$

Equation 8 shows the instantaneous concentration change of ideal gases which accompanies a change in pressure and temperature during adiabatic flow.

## Concentration Change Caused by Chemical Reaction

For the recombination of atoms according to equation 1, the rate of change of concentration with time for components A, B, and AB is given by the relation

$$\begin{aligned} -d(A)/dt &= -d(B)/dt = +d(AB)/dt \\ &= k_f(A)(B)(M) - k_b(AB)(M) \\ &= k_f(A)(B)(M)[1 - (AB)/(A)(B)K_c] \end{aligned} \quad (9)$$

From equation 9 it is evident that the rates of concentration change of ideal gases caused by chemical reaction according to equation 1 depend on the rate constants $k_f$ and $k_b$.

(9) Equation 6 is valid even if the composition changes as the result of chemical reaction, provided the heat capacity ratio $\gamma$ is changed appropriately. The effective heat capacity of the system is redefined to include a term involving the heat release associated with chemical reaction.[6]

(10) An ideal system is defined as a system for which the activity coefficient of each constituent is unity at all times.

## A Criterion for Near-Equilibrium Flow

Flow through a rocket nozzle occurs under conditions where concentration changes are caused by changes in the physical state of the system as well as by chemical reaction. It is therefore necessary to equate the total concentration changes $d \ln (AB)/dt$, $-d \ln (A)/dt$, and $-d \ln (B)/dt$ in equation 4 to the sum of the concentration changes given by equations 8 and 9. Thus

$$d \ln (AB)/dt = [(\gamma - 1)T]^{-1}(dT/dt) + k_f[(A)(B)(M)/(AB)][1 - (AB)/(A)(B)K_c] \quad (10)$$

$$-d \ln (A)\, dt = -[(\gamma - 1)T]^{-1}(dT/dt) + k_f(B)(M)[1 - (AB)/(A)(B)K_c] \quad (10a)$$

$$-d \ln (B)/dt = -[(\gamma - 1)T]^{-1}(dT/dt) + k_f(A)(M)[1 - (AB)/(A)(B)K_c] \quad (10b)$$

where use has been made of the ideal gas relations

$$P_{AB}/(AB)RT^2 = P_A/(A)RT^2 = P_B/(B)RT^2 = 1/T$$

Introducing equations 10, 10a and 10b into equation 4 leads to an equation as requirement for thermodynamic equilibrium

$$(d \ln K_c/dT)(dT/dt) = -[(\gamma - 1)T]^{-1}(dT/dt) + k_f(M)[(A) + (B) + (A)(B)/(AB)] \times [1 - (AB)/(A)(B)K_c] \quad (11)$$

It is evident from equation 11 that complete thermodynamic equilibrium during expansion, which exists only if

$$(AB)/(A)(B) = K_c$$

leads to the requirement that $k_f$ is infinite unless

$$-d \ln K_c/dT = [(\gamma - 1)T]^{-1}$$

*i.e.*, unless the concentration change associated with a change of state is just sufficient to fulfill the requirements of thermodynamic equilibrium.

The ratio $(AB)/(A)(B)$ at any temperature $T$ may be replaced by the equilibrium constant $K_c'$ at the temperature $T'$. For equilibrium flow $T' = T$, whereas for near-equilibrium flow $|T' - T|$ is a small number which will be chosen arbitrarily later on. Replacing $(AB)/(A)(B)$ by $K_c'$ in equation 11 leads to the result

$$k_f(M)[(A) + (B) + 1/K_c'][1 - K_c'/K_c] = \{d \ln K_c/dT + [(\gamma - 1)T]^{-1}\}(dT/dt) \quad (12)$$

Equation 12 can be simplified by making use of the same artifice employed previously by Schaefer.[7] Thus for sufficiently small values of $x$, $\ln (1 - x) \simeq -x$. Hence

$$\ln (K_c'/K_c) = \ln [1 - (1 - K_c'/K_c)] \simeq -(1 - K_c'/K_c)$$

or

$$1 - K_c'/K_c \simeq -\ln (K_c'/K_c) \simeq (-d \ln K_c/dT)(T' - T) \quad (13)$$

where the approximate equation 13 is the more nearly valid the more closely $T'$ approaches $T$. From equations 12 and 13 it follows that

$$k_f(M)[(A) + (B) + 1/K_c'] = \{1 + [(d \ln K_c/dT) \times (\gamma - 1)T]^{-1}\}(-dT/dt)/(T' - T) \quad (14)$$

Following Schaefer,[7] near-equilibrium flow

through the rocket nozzle is arbitrarily defined by the relation

$$(T' - T) \leqslant 50°\text{K.} \quad (15)$$

*i.e.*, flow through the rocket nozzle is considered to be near-equilibrium flow if the ratio (AB)/(A)·(B) at the actual temperature $T$ corresponds to the equilibrium ratio at the temperature $T'$ where $T'$ does not differ from $T$ by more than 50°K. Equation 14 thus leads to the following criterion for near-equilibrium flow

$$k_f(\text{M})[(\text{A}) + (\text{B}) + 1/K_c'] \geqslant 2 \times 10^{-2}\{1 + [(\text{d} \ln K_c/\text{d}T)(\gamma - 1)T]^{-1}\}(-\text{d}T/\text{d}t) \quad (16)$$

Equation 16 differs from the result obtained by Schaefer, who does not consider explicitly the concentration change associated with changes of pressure and temperature. However, criterion 16 can be replaced by Schaefer's criterion in most of the cases which are of interest in connection with adiabatic expansion through a rocket nozzle. Thus the term

$$[(\text{d} \ln K_c/\text{d}T)(\gamma - 1)T]^{-1}$$

is usually negative and smaller than unity. Therefore if

$$k_f(\text{M})[(\text{A}) + (\text{B}) + 1/K_c'] \geqslant 2 \times 10^{-2}(-\text{d}T/\text{d}t) \quad (17)$$

then inequality 16 is certainly satisfied. Inequality 17 is identical with Schaefer's criterion for near-equilibrium flow. For a more complete discussion of equation 16 it is convenient to note that

$$\text{d} \ln K_c/\text{d}T = \text{d} \ln K_p/\text{d}T + 1/T = \Delta H/RT^2 + 1/T$$

where $\Delta H$ is negative for the formation of molecules, since heat is evolved during the combination of atoms. Thus equation 16 becomes

$$k_f(\text{M})[(\text{A}) + (\text{B}) + 1/K_c'] \geqslant 2 \times 10^{-2}\{1 - [(Q/RT - 1)(\gamma - 1)]^{-1}\}(-\text{d}T/\text{d}t) \quad (18)$$

where $Q = -\Delta H$.

The following special cases arise:

Case 1. If $Q/RT > 1$ but $[(Q/RT - 1)(\gamma - 1)]^{-1} < 1$, then Schaefer's criterion 17 is applicable. This is the case for most practical applications to adiabatic expansion through a rocket nozzle since $Q \simeq 10^5$ cal./mole, $T \simeq 3000°$K., and $\gamma \simeq 1.2$.

Case 2. If $Q/RT = 1$, then $\text{d} \ln K_c/\text{d}T = 0$.[11] In this case equation 11 leads to the expression

$$k_f(\text{M})[(\text{A}) + (\text{B}) + (\text{A})(\text{B})/(\text{AB})] \times [1 - (\text{AB})/(\text{A})(\text{B})K_c] = [(\gamma - 1)T]^{-1}(\text{d}T/\text{d}t)$$

which requires a definition of near-equilibrium flow different from equation 15. A useful near-equilibrium criterion is obtained by imposing the condition $|(\text{AB})/(\text{A})(\text{B})K_c| \geqslant 0.99$.

Case 3. If $Q/RT < 1$, then equation 18 must be used directly. In particular, if $Q/RT$ is only very slightly less than unity, then the term $[(1 - Q/RT)(\gamma - 1)]^{-1}$ may become very large, and the requirements of inequality 18 are far more stringent than those of inequality 17. This case may be encountered in the future with rocket motors operating at exceedingly high temperatures.

Case 4. If $Q/RT > 1$ and also $[(Q/RT - 1)(\gamma - 1)]^{-1} > 1$, then the right-hand side of equation 18 becomes negative and criterion 18 is no longer applicable. The physical reason for this situation is the fact that the concentration change caused by the change of state is larger than the concentration change required to maintain chemical equilibrium, and therefore reaction according to equation 1 proceeds now from right to left; *i.e.*, molecules must dissociate in order to maintain chemical equilibrium. This case is of no practical importance at present.

As was noted previously, the conditions $Q/RT > 1$ and $[(Q/RT - 1)(\gamma - 1)]^{-1} < 1$ are usually fulfilled during expansion through a rocket nozzle. Therefore Schaefer's criterion 17 is usually applicable and can be used to test for the existence of near-equilibrium flow. Near equilibrium during the entire expansion can be shown to exist if the requirements of equation 17 are fulfilled at each point during flow. In practice, it is sufficient to show that equation 17 holds at a few representative points in the rocket nozzle.

Schaefer's discussion[7] of equation 17 is not applicable for expansions through the nozzles of small rockets[5,6] since $-\text{d}T/\text{d}t \simeq 3 \times 10^7$ (°K./sec.), rather than $-\text{d}T/\text{d}t \simeq 5 \times 10^6$ (°K./sec.), as used by Schaefer.[12] For atomic recombinations as the result of triple collisions, $k_f$ is of the order[7,13] of $10^{11}$ liter$^2$ × sec.$^{-1}$ × mole$^{-2}$ at temperatures close to 3000°K.[14] Equation 17 permits determination of the minimum atomic concentrations required for near-equilibrium flow with respect to atomic reactions. Thus if $[(\text{A}) + (\text{B})] \geqslant 3 \times 10^7/50 \times 10^{11}(\text{M})$, then near-equilibrium flow will occur. For the adiabatic expansion of gases from a rocket chamber at a pressure of about 20 atm., the total concentration of atoms and molecules = $\text{M} \simeq 3 \times 10^{-2}$ (mole/liter) and therefore, $[(\text{A}) + (\text{B})] \geqslant 2 \times 10^{-4}$ (mole/liter); *i.e.*, a mole fraction of about $1.5 \times 10^{-2}$ or greater is required to assure near-equilibrium flow with respect to atomic recombinations. This value for the required mole fraction of atoms is, of course, appreciably greater than the value of $1 \times 10^{-3}$ arrived at by Schaefer[7] by using too small a value for $(-\text{d}T/\text{d}t)$. Thus the conclusion is reached that near equilibrium during flow with respect to atomic reactions is strongly dependent on atomic concentrations. Application of the near-equilibrium criterion given in equation 17 to the flow of hydrogen gas through the rocket nozzle for the conditions

(11) This condition can be satisfied at only one point if the temperature changes continuously with time.

(12) $-\text{d}T/\text{d}t$ is decreased as the rocket motor size is increased. Schaefer's value probably refers to the V-2 rocket.

(13) I. Amdur, THIS JOURNAL, **60**, 2347 (1935).

(14) The values of $k_f$ have been measured only at low pressures and for a limited number of reactants A, B, and M. The assumptions that similar rate constants can be used at high pressures for all atomic recombinations in gaseous mixtures, and that the activation energy for the recombination of atoms is zero, are highly questionable and justified only by the lack of better data.

considered previously[6] shows that near equilibrium during flow is maintained in this special case.

## Summary

A criterion for near-equilibrium flow during isentropic expansion through a rocket nozzle has been derived. Schaefer's result[7] is shown to be valid for atomic recombinations in a system in which temperature and pressure changes produce concentration changes which are superimposed on the concentration changes associated with chemical reaction provided $-\Delta H/RT > 1$ and $\{[(-\Delta H/RT) - 1](\gamma - 1)\}^{-1} < 1$. These conditions are satisfied in the rocket motors usually encountered. Criteria for near-equilibrium flow under conditions which may be encountered in future work with rockets operating at exceedingly high temperatures are also discussed.

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# Extrapolation of Adsorption Isotherms to High Relative Pressures and the Determination of the Surface Pressure of Adsorbed Films on Solids

BY MELVIN A. COOK AND DOUGLAS H. PACK[1]

A recent publication[2] outlined the development of the equation for the unrestricted multimolecular

$$v/v_m = \sum_1^\infty ix^i d_i \Big/ \left(1 + \sum_1^\infty x^i d_i\right) \qquad (1)$$

adsorption of gases on solids. Here the $d_i$'s are a series of interrelated constants different for each adsorbed layer and made up of $\alpha_i$ and $\beta_i$ components such that $d_i = \alpha_i\beta_i$. The $\alpha_i$'s are factors determined by the energies of interaction of the adsorbate with the surface of the adsorbent, and the $\beta_i$'s account for the interactions between the adsorbate molecules in the film. Equation (1) differs from the BET[3] equation only in the fact that the $d_i$'s are all the same constant $c$ in the BET theory; the theoretical basis for (1) differs from that of the BET equation only in the description of the adsorption forces.

In reference (2) only the important van der Waals attraction term for the adsorbate–adsorbent interactions, varying as $r_i^{-3}$ ($r_i$ = distance of the $i^{th}$ layer from the surface of the solid), was taken into account, the repulsive and second and higher order attractive terms being neglected. In this approximation the $\alpha_i$'s were defined by the equation

$$\alpha_i = \text{exp. } E_1(1 + 1/8 + 1/27 + \ldots + 1/i^3)/RT \qquad (2)$$

where $E_1$ is the (final) adsorbate–adsorbent interaction energy in the (nearly filled) first layer evaluated as an empirical constant. The $\beta_i$'s were defined as

$$\beta_i = \text{exp. } E_L(c_1 + c_2 + c_3 + \ldots c_i - i)/RT \equiv \text{exp. } E_L(c_1 - 1)(1 + 1/2 + 1/3 + \ldots + 1/i)/RT \qquad (3)$$

where $E_L$ is the heat of condensation in the corresponding bulk liquid state of the adsorbate and the $c_i$'s are constants related to the empirical constant $c_1$ as shown. Equation (3) was developed semi-empirically from the consideration that entropy variations in the various layers of the adsorbed film may be related to the average coördination number ratios between an *i-layer* film and the bulk liquid.

On the above basis equation (1) was found to reproduce quite accurately four experimental isotherms over the range from 0.05 to about 0.7–0.8 in relative pressure $x = p/p_0$, the experimental data in these cases being taken only in this range. More recently equation (1) has been examined by comparing it with some experimental isotherms in which the experimental data covered the entire range of relative pressures ($0 < x < 1.0$). Employing the definitions of $d_i$ (equations (2) and (3)), equation (1) was found to reproduce the isotherm over the range from $x = 0.05$ to $x \cong 0.8$, but it predicted too much adsorption for $x > 0.9$ and too little adsorption for $x < 0.05$. It is considered that the discrepancies in the very low pressure region involve a fundamental weakness of the theory incurred by its failure to take account of (1) surface heterogeneities, and (2) the non-constancy of $\beta_1$ for various stages of filling of the first adsorbed layer. The discrepancies in the very high relative pressure region on the other hand apparently involve only the deliberate approximations in $\alpha_i$ and evidently may be largely eliminated by simply taking into account the repulsive term.

The present article introduces a simple modification of equation (2) including a theoretical repulsive term, and illustrates the utility of equation (1) in extrapolating isotherms to the relative pressure $x = 1.0$. Also, it seemed worth while to discuss in this article some of the convergence–divergence characteristics of equation (1) and to outline some methods designed to render the equation tractable in practical applications.

**Repulsive Term in $\alpha_i$.**—According to approximate quantum mechanical treatments, the repulsive term in the van der Waals interaction should have the form $B_r e^{-r/\rho}$ ($B_r$ and $\rho$ being

(1) This work was supported by a grant from the University of Utah Research Fund.

(2) M. A. Cook, THIS JOURNAL, **70**, 2925 (1948).

(3) S. Brunauer, P. H. Emmett and E. Teller, *ibid.*, **60**, 309 (1938).

empirical constants). The form $B_r r^{-n}$ is, however, more frequently used and, because of its simplicity for the present purpose, it will be adopted here. Irrespective of the particular form adopted for the repulsive term, however, it is clear that it must show a much more rapid variation with distance than the $r^{-6}$ (bulk matter) and $r^{-3}$ (surface) attractive term. Consequently, this term will need to be included only in accounting for the binding energy in the first layer of the film. One may thus show that the inclusion of the repulsive term in $\alpha_i$ simply introduces a constant $a$ as follows

$$\alpha_i = \text{exp. } E_1(1 + a/8 + a/27 + \ldots + a/i^3)/RT \quad (4)$$

in which $a$ is related to $n$ in the term $B_r r^{-n}$ by the equation

$$3a/(a - 1) = n \quad (4a)$$

While $n$ will probably not be the same constant for all adsorbate–adsorbent systems, Hill[4] has suggested applying Lennard–Jones' formula for the van der Waals interaction in the bulk state from which he obtained an adsorbate–adsorbent interaction of the form (using the present notations)

$$E_i = A/r_i^3 - B/r_i^9 \quad (5)$$

Here $A$ and $B_r$ are constants which may be related by taking the derivative of (5) with respect to $r_i$ and equating $(dE_i/dr_i)\ r_i = r_1$ to zero. This gives

$$E_i = A/r_i^3 - Ar_1^6/3r_i^9 \quad (6a)$$

the more general case being

$$E_i = A/r_i^3 - \frac{3Ar_1^{n-3}}{nr_i^n} \quad (6b)$$

from which equations (4) and (4a) are derived. Using Hill's equation (6a) with $n = 9$, we obtain $a = 1.5$. Hill suggests applying (6a) to each separate adsorbate atom, taking account of the fact that the distance $r_i$ will not be the same for each atom in the molecule. Here, however, we shall assume that (6a or 6b) may be applied with sufficient accuracy to the whole molecule assuming that $r_i$ represents the distance from the effective center of the molecule to the active center on the solid surface, any greater refinement in $E_i$ being unjustified at this stage in the present theory.

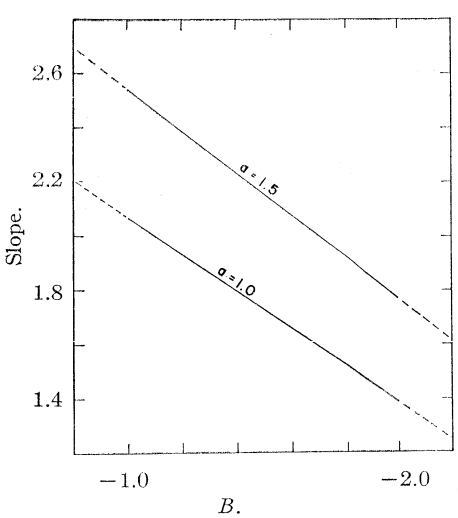



Fig. 1.—Slope $(v/v_m \div x)$ of linear part of $S$-curve *vs.* $B$.

(4) T. L. Hill, *J. Chem. Phys.*, **16**, 181 (1948).

**Manipulation of Equations at Large x.**—The application of the equation (1) requires the evaluation of the two (major) infinite series $\sum_1^\infty ix^i d_i$ and $\sum_1^\infty x^i d_i$ which are further complicated by the two (minor) series in the $d_i$'s. In view of the rapid convergence of the major series for small $x$, the solution of (1) offers no serious difficulties in the low relative pressure regions, and even up to relative pressures around $x = 0.8$. However, for $x > 0.8$ the series converge so slowly that their evaluation becomes very tedious. Fortunately, it is possible to shorten the labor considerably by replacing the summations beyond a certain number of terms by suitable integrals without incurring appreciable error.

The two empirical constants, $E_1$ and $c_1$ may be evaluated at small values of $x$ (preferably for $x < 0.5$) by the methods outlined in reference (2) no problems of convergence being encountered in this region. In spite of this the evaluation of these constants would be quite tedious unless one were to make use of various labor saving devices such as tables of $ix^i$, $x^i$, etc. It is of interest to note in this connection that one seldom needs to carry through the process of iteration for $c_1$ and $E_1$ more than three times if the fact is taken into consideration that $t_2 (= v_2/v_m$ ref. 2) varies approximately linearly with $c_1$. Thus, after calculations have been made for two assumed values of $c_1$, one may nearly always pick out the true value by means of a linear $c_1$ *vs.* $v_2/v_m$ plot, unless either, or both, of the first two assumed values of $c_1$ should happen to be selected too far from the true value. This can be easily avoided, and, as a matter of fact, the correct value of $c_1$ may sometimes be selected in the first trial by making use of Fig. 1 in which $B$, defined by the equation

$$B \equiv E_L\ (c_1 - 1)/RT \quad (7)$$

is plotted against the slope (in reduced $-\ v/v_m\ -$ units) of the essentially straight line portion of the sigmoid isotherms (usually extending from about 0.1 to perhaps 0.5 in $x$). Figure 1 was obtained by drawing the best straight lines through all of the points for $a = 1.0$ and $a = 1.5$, respectively, obtained in this and the previous study. It will be shown below that for $|B| > 2.0$ equation (1) is not properly divergent at $x = 1.0$. To avoid this difficulty when it occurs one might simply calculate $c_1$ directly from equation (7) for $B = -2.0$ (assuming that $|B|$ will never be appreciably greater than 2.0) leaving only a two empirical con-

stant ($v_m$ and $E_1$) equation to fit the curve. If it should turn out in some cases that $|B| >> 2$, $B$ could be fixed at $-2.0$, and the $a$ adjusted to be consistent with Figure 1 (by extrapolating or interpolating linearly between the two straight lines of Fig. 1) again leaving only the two constants ($v_m$ and $E_1$) to be evaluated. That this procedure evidently leads to results generally in good agreement with observed isotherms even as $x$ approaches closely to unity, and the further fact that values of $B$ evidently hover around $-2.0$ for $a = 1.5$, are of possible interest in regard to the general validity of the theory.

The previous paper (ref. 2) outlined the evaluation of $c_1$ and $B$. As a further remark in connection with the evaluation of the constants of equation (1), it is convenient in computing $E_1$, after selecting an appropriate value for $c_1$ or $B$, to make use of tables of $\alpha_1/\alpha_2$ for various values of $\alpha_2$ and of the equation

$$\alpha_2 = 1 \Big/ \left\{ \sum_2^\infty (i-1) x_m^i \beta_i \, (\alpha_i/\alpha_2) \right\} \qquad (8)$$

where $x_m$ is the relative pressure at which $v = v_m$, ($v_m$ being evaluated[2] by the method of BET.).

For solving equation (1) all but the first $q - 1$ terms may be evaluated by replacing $\sum_q^\infty i x^i d_i$ and $\sum_q^\infty x^i d_i$ by suitable integrals. The accuracy of this approximation will, of course, depend on the magnitude of $q$. With suitable tables of functions at hand it is convenient to select $q$, e. g., equal to 20, in which case the integral approximation will be well within tolerable limits of accuracy. For $q = 20$, $\alpha_i$ will have become substantially constant, hence

$$\sum_q^\infty i x^i d_i \cong \alpha_q \int_q^\infty i x^i \, e^{B \sum_1^i 1/i} \, di \cong \alpha_q \, \beta_{q-1} \, q^{-B} \int_q^\infty x^i \, i^{(B+1)} \, di \qquad (9)$$

$x$ being a particular relative pressure and $i$ the variable.

Making the substitution $i \ln x = -y$, (9) becomes

$$\sum_q^\infty i x^i d_i \cong \alpha_q \, \beta_{q-1} \, q^{-B} \frac{1}{(-\ln x)^{(B+2)}} \int_{y=-q \ln x}^\infty e^{-y} y^{(B+1)} \, dy$$

For $B = -2$, this becomes

$$\sum_q^\infty i x^i d_i \cong d_{q-1} \, q^2 \int_{-q \ln x}^\infty \frac{e^{-y}}{y} \, dy \qquad (9a)$$

which may be evaluated from tables by Jahnke and Emde,[5a] or W.P.A. tables.[5b] For values of $B$ from $-1$ to $-2$ (the allowable range as shown below) (9) may be evaluated from tables of gamma functions $\Gamma(n)$ as follows:

$$\sum_1^\infty i x^i d_i \cong d_{q-1} \, q^2 (-q \ln x)^{-(B+2)} \left[ \int_0^\infty e^{-y} \, y^{B+1} \, dy - \int_0^{-q \ln x} e^{-y} \, y^{B+1} \, dy \right] = d_{q-1} \, q^2 \, (-q \ln x)^{(-B+2)} \left\{ \Gamma(B+2) - \int_0^{-q \ln x} \left[ 1 - y + \frac{y^2}{2!} - \frac{y^3}{3!} + \frac{y^4}{4!} - \ldots \right] y^{B+1} \, dy \right\} =$$

$$d_{q-1} q^2 (-q \ln x)^{-(B+2)} \Gamma(B+2) - d_{q-1} q^2 \left\{ \frac{1}{B+2} + \frac{q \ln x}{B+3} + \frac{(q \ln x)^2}{(B+4)\,2!} + \frac{(q \ln x)^3}{(B+5)\,3!} + \frac{(q \ln x)^4}{(B+6)\,4!} + \ldots \right\} \qquad (9b)$$

Values of $\Gamma(B+2)$ may be obtained, for example, from Dwight[6] and the relation $\Gamma(n+1) = n\,\Gamma(n)$.

Similarly we obtain

$$\sum_q^\infty x^i d_i \cong d_{q-1} \, q^{-B} \int_q^\infty x^i i^B di \qquad (10)$$

which, for $B = -2.0$, becomes

$$\sum_q^\infty x^i d_i \cong d_{q-1} \, q^2 \left\{ \frac{e^{q \ln x}}{q} + \ln x \int_{-q \ln x}^\infty \frac{e^{-y}}{y} \, dy \right. \qquad (10a)$$

and for $-1 > B > -2.0$

$$\sum_q^\infty x^i d_i \cong d_{q-1} \, q (-q \ln x)^{-(B+1)} \left\{ \Gamma(B+1) - \int_0^{-q \ln x} \left( 1 - y + \frac{y^2}{2!} - \frac{y^3}{3!} + \frac{y^4}{4!} + \ldots \right) y^B dy \right\} =$$

$$d_{q-1} q (-q \ln x)^{-(B+1)} \Gamma(B+1) - d_{q-1} q \left\{ \frac{1}{B+1} + \frac{q \ln x}{B+2} + \frac{(q \ln x)^2}{(B+3)\,2!} + \frac{(q \ln x)^3}{(B+4)\,3!} + \ldots \right\} \qquad (10b)$$

Equation (1) for $B = -2$ thus becomes

$$v/v_m = \frac{\left( \sum_1^{q-1} i x^i d_i \right) + d_{q-1} q^2 \int_{-q \ln x}^\infty \frac{e^{-y}}{y} \, dy}{1 + \left( \sum_1^{q-1} x^i d_i \right) + d_{q-1} q^2 \left\{ \frac{e^{q \ln x}}{q} + \ln x \int_{-q \ln x}^\infty \frac{e^{-y}}{y} \, dy \right.} \qquad (1b)$$

and for $-1 > B > -2$, (1) may be written

(5) (a) Jahnke and Emde, "Tables of Functions," Dover Publications, New York, N. Y., 4th ed., 1945, pp. 1, 6–9. (b) Federal Works Agency, W. P. A., New York City, "Tables of Sine, Cosine and Exponential Integrals" (1940).

(6) H. B. Dwight, "Tables of Integrals and other Mathematical Data," The Macmillan Co., New York, N. Y., 1947.

$$v/v_m = \frac{\left(\sum_1^{q-1} ix^i d_i\right) + d_{q-1}q^2(-q\ln x)^{-(B+2)}\Gamma(B+2) - d_{q-1}q^2\left\{\frac{1}{B+2} + \frac{(q\ln x)}{B+3} + \frac{(q\ln x)^2}{(B+4)\,2!} + \frac{(q\ln x)^3}{(B+5)\,3!} + \cdots\right\}}{1 + \left(\sum_1^{q-1} x^i d_i\right) + d_{q-1}q(-q\ln x)^{-(B+1)}\Gamma(B+1) - d_{q-1}q\left\{\frac{1}{B+1} + \frac{q\ln x}{B+2} + \frac{(q\ln x)^2}{(B+3)\,2!} + \frac{(q\ln x)^3}{(B+4)\,3!} + \cdots\right\}} \quad (1c)$$

**Limits on $B$.**—For $x = 1.0$ we have

$$v/v_m = \frac{\left(\sum_1^{q-1} id_i\right) + d_{q-1}q^{-B}\int_q^\infty i^{B+1}\,di}{1 + \left(\sum_1^{q-1} d_i\right) + d_{q-1}q^{-B}\int_q^\infty i^B\,di} = \infty \quad (11)$$

From (7) we see that $B < 0$, since $c_1 < 1.0$. Moreover, from (11) $B \gtrsim -2$ in order that $v/v_m \to \infty$ as $x \to 1.0$. Also, (11) becomes indeterminate for $B \gtrsim -1$. In fact, it will be shown that values of $B \gtrsim -1$ are unacceptable because they lead to infinite values of the surface pressure $\pi$ of the adsorbed film. We thus conclude that $B$ will be restricted by the physical conditions of the problem to the region $-1.0 > B \gtrsim -2.0$. In view of uncertainties in the theory of $a$ and the fact that errors in $E_1$ will in general be largely compensated in $c_1$ (and $B$) one has little reason, however, to be disturbed if $B$ should sometimes turn out to be a little less than $-2.0$ (for we are still assured of the fact that $v$ will be infinite for $x >$ 1.0). One could, of course, avoid this technical difficulty by adjusting $a$ to make $B = -2.0$ and this should perhaps be done if the discrepancy should turn out to be quite large, (*e.g.*, $-B = 2.5$).

**High Relative Pressure Extrapolations.**—Jura and Harkins[7] have published several type II isotherms admirably suited for a careful evaluation of equations (1), (4) and (4a) in that their data extend over the entire region $0 < x < 1.0$. Figure 2 presents their experimental data for nitrogen (at 77.3°K.) on anatase, together with theoretical curves for $a$ values of 1.0, 1.3 and 1.5. It is quite significant that, while the agreement between the observed and calculated curves is independent of $a$ for $x < 0.8$, excellent agreement is obtained only for $a = 1.5$ as $x \to 1.0$ in agreement with Hill's form (6a) of $E_i$. Calculations were also made for water, *n*-butane and *n*-heptane on anatase only for $a = 1.5$, and, except for *n*-heptane, the agreement is excellent over the entire range $0.05 < x < 1.0$ as shown in Fig. 3. In *n*-heptane a large discrepancy between the experimental and calculated data are encountered for $x > 0.9$. There seems to be no way of resolving this difficulty except that perhaps the saturation pressure used in

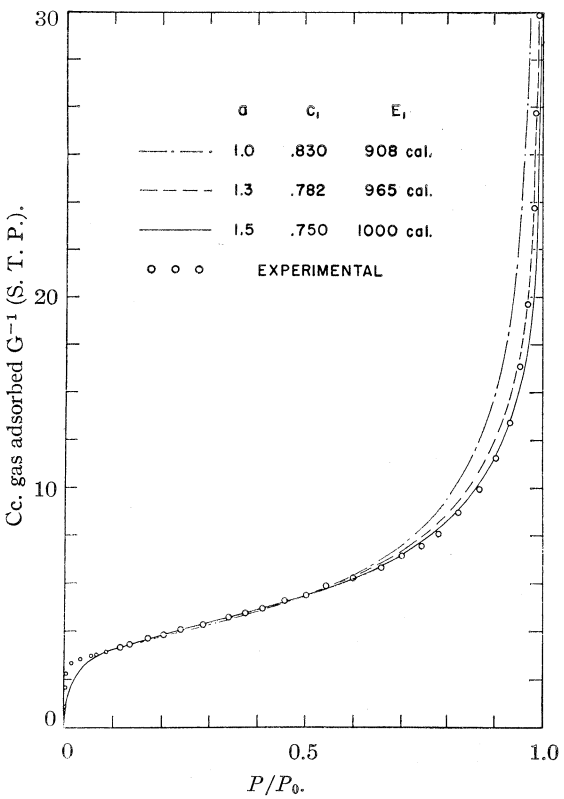



Fig. 2.—Influence of the repulsive term on the calculated adsorption isotherm of nitrogen on anatase—comparison with experimental.

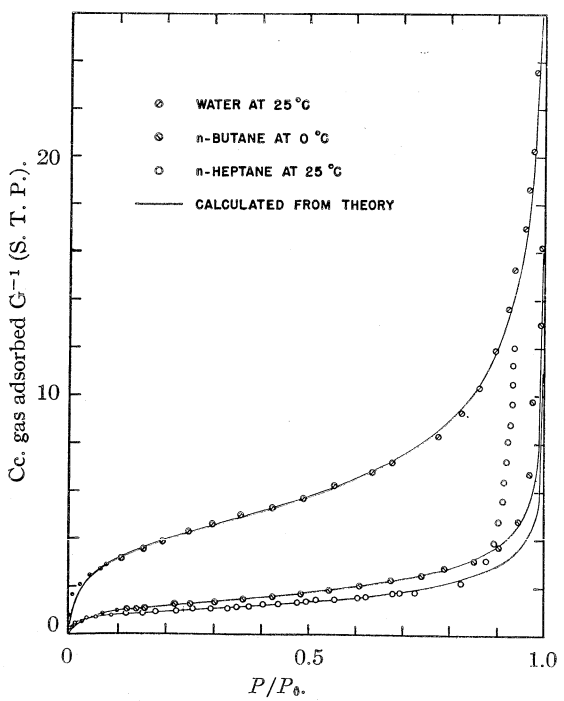



Fig. 3.—Comparison of theoretical and experimental adsorption isotherms.

(7) G. Jura and W. D. Harkins, THIS JOURNAL, **66**, 1356 (1944).

TABLE I

CONSTANTS OF EQUATION (1) FROM SEVERAL ADSORPTION ISOTHERMS

| Adsorbate | Adsorbent | $T$, °K. | $v_m$, cc./g. | $a$ | $c_1$ | $-B$ | $E_1$, cal./mole | Constants from data of |
|---|---|---|---|---|---|---|---|---|
| Nitrogen | Anatase | 77.3 | 3.23 | 1.0 | 0.830 | 1.473 | 908 | Jura and Harkins |
| Nitrogen | Anatase | 77.3 | 3.23 | 1.3 | .782 | 1.888 | 965 | Jura and Harkins |
| Nitrogen | Anatase | 77.3 | 3.23 | 1.5 | .750 | 2.166 | 1000 | Jura and Harkins |
| Water | Anatase | 298.1 | 3.50 | 1.5 | .884 | 2.056 | 3420 | Jura and Harkins |
| *n*-Butane | Anatase | 273.1 | 1.07 | 1.5 | .796 | 2.00 | 3030 | Jura and Harkins |
| *n*-Heptane | Anatase | 298.1 | .776 | 1.5 | .863 | 2.00 | 3800 | Jura and Harkins |
| Methyl acetate | Vitrous | 298.1 | 1.12 | 1.0 | .952 | .675 | 2410 | Palmer and |
| Methyl acetate | silica | 298.1 | 1.12 | 1.5 | .912 | 1.250 | 2730 | Clark[8] |
| Nitrogen | Fe-$Al_2O_3$ | 77.3 | 135 | 1.0 | .862 | 1.200 | 898 | Emmett and |
| Nitrogen | catalyst | 77.3 | 135 | 1.5 | .775 | 1.950 | 998 | Brunauer[9] |
| Argon | Fe-$Al_2O_3$ | 90.1 | 126 | 1.0 | .884 | 0.970 | 852 | Emmett and |
| Argon | catalyst | 90.1 | 126 | 1.5 | .823 | 1.49 | 918 | Brunauer[9] |

computing the experimental data may have been in error. This is indicated from the fact that the experimental curve seems to be approaching about $x = 0.94$ asymptotically rather than $x = 1.0$ as one would expect. In fact, assuming this to be the case there is no difficulty in fitting the experimental curve with equation (1) with $a = 1.5$. It is interesting that no indication of this strange occurrence is to be found in any part of the curve below a relative pressure of 0.9. Table I lists values of the various constants of equation (1) for the cases illustrated in Figs. 2 and 3 together with others studied in reference (2) which are here recalculated for $a = 1.5$, previous calculations being carried out only for $a = 1.0$. While, as shown in Table I, $B < -2.0$ in nitrogen and water on anatase for $a = 1.5$, this discrepancy is not considered significant. The divergence difficulty at $x = 1.0$ would be cleared up by taking $B = -2.0$ and $a = 1.38$, but the agreement in the range $0.85 - 0.95$ in $x$ would not be as good as when the values $B = -2.166$ and $a = 1.5$ are used. It is of interest that the use of $a = 1.5$ tends to change the values of $E_1$ and $c_1$ in the right direction to agree with experimental differential net heats and expected theoretical coördination ratios, respectively, although several extraneous factors must still be operating to give values of $c_1$ which from theory seem peculiarly high.

**Surface Pressure of the Adsorbed Film.**—Bangham's[10,11] equation for the surface pressure $\pi$ of an adsorbed film of gas on a solid obtained by the integration of Gibbs' adsorption equation in terms of data from the adsorption isotherm may be written

$$\pi = \gamma_s - \gamma_{sf} = \frac{RT}{V\Sigma}\int_0^{x_v} \frac{dx}{x} \qquad (12)$$

where $\gamma_s$ is the surface tension of the solid, $\gamma_{sf}$ that of the film covered solid, $V$ is the molar volume of the gas, $\Sigma$ the specific area of the solid, $v$ the volume of gas adsorbed per gram of adsorbent, and $x$ the relative pressure $p/p_0$ of the gas. Evaluating the integral (12) between zero and the saturation pressure $p_0$, we obtain in cases of perfect wettability

$$\pi_{0-1} = \gamma_s - \gamma_{Ls} - \gamma_L \qquad (13)$$

where $\gamma_{Ls}$ is the interfacial tension between the solid and the film, and $\gamma_L$ is the surface tension of the adsorbate in the liquid state, the subscripts on $\pi$ indicating the limits of integration. Equation (13) is useful, as shown by Jura and Harkins,[12] in determining the work of adhesion $W_A$, the spreading coefficient $S_{L/s}$, and the free energy of emersion $f_E$. It may also be used to establish a lower limit to the surface tension of the solid which, when a sufficiently polar adsorbate is used, may, in some cases, approach quite closely the true surface tension $\gamma_s$. By correlating this with theoretical data, from which one may establish an upper limit to $\gamma_s$, one may be able to bracket $\gamma_s$ in some cases within quite close limits. Equations (12) and (13) are of further considerable interest in that they may be used to provide a critical test of the validity of the various theoretical adsorption equations. In this connection Jura and Harkins[12] have carried out graphical integrations of (12) for several of their own experimental isotherms. Their method is complicated by two troublesome extrapolations, one in the region where $x$ approaches zero and the other in the region where $x$ approaches unity. They minimized the difficulties inherent in these extrapolations, however, by obtaining experimental adsorption data covering as completely as possible the entire adsorption isotherm. Their work thus provides valuable data for an evaluation of our theoretical adsorption equation.

**Integration of Surface Pressure Equation.**—The validity of the theoretical adsorption equation (1) with

$$d_i = \alpha_i\beta_i = \exp\left\{E_1\left(1 + \frac{1.5}{8} + \ldots + \frac{1.5}{i^3}\right) + E_L(c_1 - 1)\left(1 + 1/2 + \ldots + \frac{1}{i}\right)\right\}\Big/RT \qquad (14)$$

(8) W. G. Palmer and R. E. D. Clark, *Proc. Roy. Soc.* (*London*), **A149**, 360 (1935).

(9) P. H. Emmett and S. Brunauer, THIS JOURNAL, **59**, 1552 (1937).

(10) D. H. Bangham, *J. Faraday Soc.*, **33**, 805 (1937).

(11) Alexander, "Colloid Chemistry," Vol. VI, Chapter 1, Reinhold Publishing Corp., New York, N. Y., 1946.

(12) G. Jura and W. D. Harkins, THIS JOURNAL, **66**, 1356 (1944)

may be evaluated by means of equation (12) and the results of Jura and Harkins. Substituting (1) and (14) in (12) and integrating we obtain

$$\pi_{x_1-x_2} = \frac{RTv_m}{V\Sigma}\int_{x_1}^{x_2}\frac{\sum_1^\infty (ix^{i-1}d_i)dx}{1+\sum_1^\infty x^i d_i} \equiv \frac{2.303RTv_m}{V\Sigma}\left|\log\left(1+\sum_1^\infty x^i d_i\right)\right|_{x_1}^{x_2} \quad (15)$$

This integration is performed by making use of the identity

$$\sum_1^\infty ix^i d_i \equiv x\frac{d}{dx}\left(1+\sum_1^\infty x^i d_i\right) \quad (16)$$

(Whenever it is necessary to evaluate $\sum_1^\infty x^i d_i$ where $x$ is less than unity but still large enough that the series converges very slowly, one may make use of the integral approximations of equation (10)). Equation (15) integrated over the entire isotherm becomes

$$\pi_{0-1.0} = 2.303\frac{RTv_m}{V\Sigma}\log\left(1+\sum_1^\infty d_i\right) \quad (17)$$

The term $\sum_1^\infty d_i$ may be evaluated as accurately as desired by means of the approximation

$$\sum_1^\infty d_i \cong \sum_1^{q-1} d_i + \alpha_q\int_q^\infty \beta_i\,di \cong \alpha_q\,\beta_{q-1}q^{-B}\int_q^\infty i^B\,d_i = d_{q-1}q^{-B}\left|\frac{i^{(B+1)}}{B+1}\right|_q^\infty \quad (18)$$

where $B = E_L\,(c_1 - 1)/RT$ and the integer $q$ is chosen large enough that $\alpha_q$ is, within close limits, the limiting value of the series $\alpha_i$. Hence, (17) becomes

$$\pi_{0-1} = \frac{2.303RTv_m}{V\Sigma}\log\left\{1+\sum_1^{q-1} d_i + d_{q-1}q^{-B}\left|\frac{i^{(B+1)}}{B+1}\right|_q^\infty\right\} \quad (19)$$

It is evident that $B$ must be less than minus one in order that $\pi_{0-1}$ will remain finite. This and the fact that $v \to \infty$ as $x \to 1.0$, show that the acceptable limits on $B$ are $-1 > B \geqslant -2$. For $B < -1.0$, (19) gives

$$\pi_{0-1} = 2.303\frac{RTv_m}{V\Sigma}\log\left(1+\left(\sum_1^{q-1} d_i\right)\frac{-d_{q-1}\,q}{B+1}\right) \quad (19a)$$

In the BET equation (ref. 3)

$$v/v_m = c\sum_1^\infty ix^i \Big/ \left(1+c\sum_1^\infty x^i\right) \quad (20)$$

$B$ is zero. The BET equation is, therefore, unsatisfactory from the viewpoint of the Gibbs adsorption equation. This situation was pointed out by Cassel.[13] The same argument of course, applies to the various modifications of the BET equation (*e.g.*, Anderson's[14] and Pickett's[15] equations in which attempts are made to apply the BET equation at high relative pressures). In the low relative pressure region ($x < 0.35$) one can, of course, justify the BET equation and various modifications of it[16,17] from the viewpoint of the Gibbs theorem. Moreover, in this region the present theory is consistent with the BET equation because of the very rapid convergence of the series of equation (14) at low $x$.

## Results

Since (14) is not in agreement in most cases with experimental isotherms for $x < 0.05$, the integration of (12) by application of (1) and (14) can logically be carried out only over the range $0.05 < x < 1.0$. Thus, it is still necessary to employ a graphical integration such as that of Jura and Harkins[12,18,19] to evaluate $\pi_{0-0.05}$. Our evaluations of $\pi_{0-1.0}$, therefore make use of the equations

$$\pi_{0-1.0} = \pi_{0-.05} + \frac{2.303RTv_m}{V\Sigma}\log\left\{\frac{1+\left(\sum_1^{q-1} d_i\right) - d_{q-1}q/(B+1)}{\left(1+\sum_1^\infty (0.05)^i\,d_i\right)}\right\} \quad (21)$$

in which $\pi_{0-.05}$ is taken from the work of Jura and Harkins. Table II gives values of $\pi_{0.05-1.0}$ calculated from (15) for $x_1 = 0.05$ and $x_2 = 1.0$. Values of $\pi_{0-.05}$ shown in Table II were taken from Jura and Harkins[12] (Fig. 8). The values $\pi_{0-1.0}$ obtained from (21) are compared with $\pi_{0-1.0}$ data obtained by Jura and Harkins using the graphical method.

TABLE II

SURFACE PRESSURE OF VARIOUS FILMS ON ANATASE (DYNES/CM.) ($\Sigma$ = 13.8 SQ. M./G.)

| Adsorbate | $\pi_{0-.05}$[a] Graphical | $\pi_{0-1.0}$[a] Graphical | $\pi_{0-1.0}$ Equation (11) |
|---|---|---|---|
| Nitrogen (77.5°K.) | 23.2 | 55.5 | 53.2 |
| Water (298.1°K.) | 63.6 | 187.0 | 183.8 |
| *n*-Butane (273.1°K.) | 8.0 | 42.3 | 41.6 |
| *n*-Heptane (298.1°K.) | 10.7 | | 39.7 |
| | | 37.1 ($\pi_{0-0.9}$) | 38.9 ($\pi_{0-0.9}$) |

[a] Taken from Fig. 8 of ref. 7.

(13) H. M. Cassel, *J. Phys. Chem.*, **48**, 195 (1944).
(14) R. B. Anderson, THIS JOURNAL, **68**, 686 (1946).
(15) G. Pickett, *ibid.*, **67**, 1958 (1945).
(16) S. McMillan, *J. Chem. Phys.*, **15**, 390 (1947).
(17) W. C. Walker and A. C. Zettlemoyer, *J. Phys. Colloid Chem.*, **52**, 47, 58 (1948).
(18) M. H. A. Armbruster and J. B. Austin, THIS JOURNAL, **66** 159 (1944).
(19) W. B. Innes and H. H. Rowley, *J. Phys. Chem.*, **45**, 158 (1944).

The results in Table I show that the theoretical adsorption isotherm (1) not only has the correct form required by the Gibbs adsorption theorem but also that it yields quite accurate data on surface tension lowering for relative pressures above about 0.05. It should perhaps be noted, however, that this is true in all cases studied only when the repulsive term in the adsorbate–adsorbent interaction is taken into account, two examples being found (Table I, in which equation (1), with $a = 1.0$ instead of 1.5, leads to an improper ($B > -1$) solution of the Gibbs equation.

The method developed in this paper for calculating $\pi_{0.5-1.0}$ is not necessarily restricted to type II (and III) isotherms; it may be applied equally well to isotherms (types IV and V) in which capillary condensation occurs, since the surface pressure $\pi$ will not be affected by the pore structure of the solid. It is necessary only that the isotherm have a large enough free or unrestricted adsorption region for $x > 0.05$, *e.g.*, $0.05 < x < 0.2$ or $0.05 < x < 0.5$, etc.), to allow one to evaluate the constants $E_1, c_1$, and $v_m$.

One will observe that the surface pressure of the film which forms at $x = 0.05$, *i.e.*, $\pi_{0-0.05}$, is generally a large part of the surface pressure of the film at saturation pressures, *i.e.*, $\pi_{0-1.0}$. For example, Table II shows that $\pi_{0-0.05}/\pi_{0-1.0}$ is 0.43 for nitrogen on anatase. Moreover, one cannot be sure of the accuracy of $\pi_{0-0.05}$ determined graphically in view of the uncertainties in the graphical method of extrapolation to $x = 0$ and necessary experimental errors in the adsorption data in the low $x$ region. These considerations thus emphasize the need for further theoretical developments for handling problems in the $0 < x < 0.05$ region.

## Summary

The theory of adsorption developed in an earlier publication including, however, the repulsive term previously neglected is shown to agree with several type II isotherms over the entire range of relative pressures from 0.05 to 1.0. Methods are outlined for handling the complex infinite series of the theoretical equation, and the convergence and divergence properties of the equation are discussed.

The Bangham equation derived from the Gibbs adsorption equation for the surface pressure $\pi$ of an adsorbed film is integrated by means of the theoretical adsorption isotherm. The calculated surface pressures are shown to be in excellent agreement with data determined by Jura and Harkins from graphical integration of the Bangham equation employing the experimental adsorption isotherms. The theory offers a method for evaluation of surface pressure from all types of physical adsorption isotherms including those exhibiting capillary condensation.

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[CONTRIBUTION NO. 13 FROM THE THERMODYNAMICS LABORATORY, PETROLEUM EXPERIMENT STATION, BUREAU OF MINES]

# Thermodynamic Properties of Thiophene[1]

BY GUY WADDINGTON, J. W. KNOWLTON,[2] D. W. SCOTT, G. D. OLIVER,[3] S. S. TODD,[4] W. N. HUBBARD, J. C. SMITH AND HUGH M. HUFFMAN

The thermodynamic properties of sulfur compounds are of interest for several reasons. From a practical point of view, the increasing interest in the sulfur compounds occurring in or derivable from petroleum makes it important to have an extensive knowledge of the properties of these substances. Such information would be useful in the refining of petroleum and in the preparation of sulfur derivatives of hydrocarbons. Also, the thermodynamic properties of the simpler sulfur compounds are of interest because of the information such data would yield with respect to their molecular structures. Finally, as in the case of hydrocarbons, a study of representative members of a homologous series of sulfur compounds would yield relationships permitting the estimation of properties of compounds which had not been studied.

The study of some sulfur compounds of interest to the petroleum industry has recently been added to the Bureau of Mines program of thermodynamic research. Thiophene, because of its importance and intrinsic interest, was chosen as the first compound to be studied in this field. Listed below, in their order of presentation in this paper, are the several types of investigation carried out: Section (1), low-temperature heat capacity; Section (2), vapor pressure; Section (3), heat of vaporization, vapor heat capacity, gas imperfection, and entropy of the ideal gas; Section (4), heat of combustion and heat of formation; Section (5), thermodynamic functions from spectroscopic and molecular structure data. From these investigations, relatively complete thermodynamic information about thiophene in the low pressure region has been obtained.

**The Material.**—Two samples of thiophene differing somewhat in their histories were used

(1) Portions of this paper were presented at the Atlantic City Meeting of the American Chemical Society, April, 1947.

(2) Deceased.

(3) Present address: Carbide and Carbon Chemical Corp., Oak Ridge, Tenn.

(4) Present address: Pacific Experiment Station, Bureau of Mines, Berkeley, California.

in the several investigations. Sample I was a selected cut from the Socony Vacuum Oil Company's pilot plant at Paulsboro, N. J., and was used without further purification for measurements of vapor heat capacities, heats of vaporization, and vapor pressures by the ebulliometric method. The apparent purity of this sample deduced from melting point studies by the time–temperature method was approximately 99.96 mole per cent. Sample II, used for the low-temperature studies, for the measurements of vapor pressures by the static method, and for the measurement of the heat of combustion, was prepared from material similar to Sample I by distillation in an efficient fractionating column at the Laramie Station of the Bureau of Mines.

TABLE I

MELTING POINT OF THIOPHENE

$N_x = 0.0111\Delta T$

| % Melted | $T_{(obs.)}$ | $T_{(calcd.)}$ |
|---|---|---|
| 16.08 | 234.7532 | 234.698 |
| 38.13 | .8494 | .8434 |
| 66.95[a] | .8891 | .8891 |
| 91.40[a] | .9053 | .9053 |
| 100.00 | | .9091 |
| Pure | | 234.950 |
| Triple point | | 234.95 ± 0.05°K. |
| Impurity = 0.045 mole % | | |

[a] Computation based on these 2 points.

A mass spectrometer analysis, which was carried out at the Socony Vacuum laboratories, showed Sample II to have the composition: thiophene 99.954 mole %, benzene 0.030 mole %, carbon bisulfide 0.008 mole % and methylthiophene 0.008 mole %.[5] Melting point studies were made in this laboratory by the calorimetric method. The results of these investigations are summarized in Table I. Since thiophene and benzene are known to form solid solutions, too much reliance should not be placed on the value of the purity obtained from the melting point data. Direct determinations of sulfur made during the combustion measurements indicated that the sulfur content was in substantial agreement with theory.

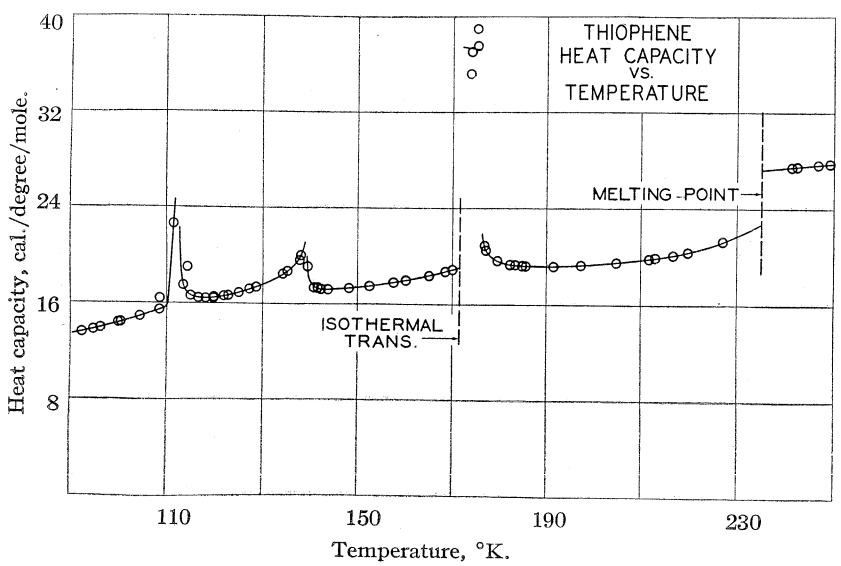



Fig. 1.—Plot of the heat capacity against temperature in the region of anomalous behavior.

## Section 1: Low-Temperature Heat Capacity

**The Apparatus.**—The measurements were made in the apparatus described by Ruehrwein and Huffman.[6] Very briefly, the method was as follows: About 0.5 mole of the material under investigation was contained in a sealed copper calorimeter, which was mounted in the adiabatic calorimetric system. A measured amount of electrical energy was supplied to the calorimeter, and at all times the temperature of the environment was maintained at that of the calorimeter to prevent heat interchange. The initial and final temperatures of the calorimeter were measured by means of a platinum resistance thermometer. The electrical measurements required for the determination of the resistance of the thermometer and the electrical energy were made on a "White" double potentiometer in conjunction with a high-sensitivity galvanometer and accurately calibrated resistances. The potential was in terms of a bank of six thermostated saturated cadmium cells, which had been certified by the National Bureau of Standards. Time measurements were made with an electric stop clock, which was operated by an a. c. power supply, the frequency of which was accurate to 0.001%. The precision of the measurements was, in general, better than 0.1%, and above 30° K. it is believed that the accuracy uncertainty should not be greater than 0.2%. The energy measurements were made in terms of the international joule and were converted to calories by dividing by 4.1833.

**The Results.**—The results of the heat capacity measurements are given in Table II and shown graphically in Fig. 1 over the region 90 to 250° K. Inspection of this figure shows that the thermal properties of thiophene vary with temperature in an unusual manner. The material appears to undergo two second-order transitions of the lambda type

(5) Private communication from D. E. Badertscher.

(6) Ruehrwein and Huffman, THIS JOURNAL, 65, 1620 (1943).

TABLE II

MOLAL HEAT CAPACITY OF THIOPHENE IN CAL./DEG.

| $T$, °K. | $\Delta T$ | $C_{sat.}$ | $T$, °K. | $\Delta T$ | $C_{sat.}$ |
|---|---|---|---|---|---|
| 11.70 | 1.027 | 0.842 | 129.20 | 5.252 | 17.459 |
| 12.97 | 1.526 | 1.131 | 132.23 | 12.698 | 18.153 |
| 13.07 | 1.120 | 1.155 | 134.24 | 5.458 | 18.448 |
| 14.58 | 1.727 | 1.494 | 135.18 | 8.090 | 18.717 |
| 14.72 | 2.233 | 1.539 | 137.84 | 1.742 | 19.852 |
| 16.71 | 2.534 | 2.006 | 138.02 | 1.292 | 20.034 |
| 17.43 | 3.204 | 2.195 | 139.22 | 1.280 | 18.214 |
| 19.51 | 3.078 | 2.719 | 139.36 | 1.397 | 18.129 |
| 20.18 | 2.301 | 2.895 | 140.52 | 1.323 | 17.373 |
| 22.68 | 3.268 | 3.523 | 140.78 | 1.442 | 17.384 |
| 23.32 | 3.984 | 3.691 | 141.55 | 5.664 | 17.413 |
| 26.72 | 4.812 | 4.501 | 142.22 | 1.449 | 17.230 |
| 27.60 | 4.575 | 4.703 | 143.67 | 1.447 | 17.228 |
| 31.35 | 4.445 | 5.518 | 143.97 | 9.487 | 17.288 |
| 32.32 | 4.869 | 5.716 | 148.15 | 7.545 | 17.303 |
| 37.44 | 5.371 | 6.691 | 150.16 | 17.947 | 17.420 |
| 43.17 | 6.083 | 7.618 | 152.44 | 7.457 | 17.508 |
| 49.15 | 5.879 | 8.604 | 157.33 | 10.033 | 17.836 |
| 54.75 | 6.411 | 9.347 | 159.80 | 7.251 | 18.016 |
| 54.84 | 5.492 | 9.357 | 159.94 | 5.369 | 17.965 |
| 54.92 | 5.018 | 9.377 | 162.36 | 6.453 | 18.196 |
| 55.91 | 6.219 | 9.509 | 165.01 | 5.323 | 18.391 |
| 60.29 | 5.738 | 10.039 | 168.50 | 1.421 | 18.708 |
| 61.64 | 7.362 | 10.184 | 170.06 | 1.691 | 18.866 |
| 62.53 | 7.024 | 10.311 | 172.07 | 1.897 | 27.45 |
| 69.02 | 7.398 | 11.002 | 173.79 | 1.534 | 35.23 |
| 69.65 | 7.220 | 11.087 | 173.98 | 1.282 | 37.15 |
| 76.62 | 7.804 | 11.811 | 175.24 | 1.228 | 38.98 |
| 76.96 | 7.389 | 11.856 | 175.28 | 1.450 | 37.58 |
| 84.56 | 8.071 | 12.699 | 175.87 | 2.296 | 28.61 |
| 84.58 | 7.858 | 12.701 | 176.89 | 2.079 | 20.89 |
| 92.32 | 7.626 | 13.542 | 177.21 | 2.405 | 20.528 |
| 92.74 | 8.300 | 13.584 | 178.15 | 2.259 | 20.075 |
| 92.97 | 5.642 | 13.604 | 179.65 | 2.482 | 19.689 |
| 94.67 | 5.329 | 13.775 | 182.30 | 2.511 | 19.325 |
| 95.06 | 6.194 | 13.828 | 183.33 | 6.793 | 19.313 |
| 99.01 | 6.439 | 14.258 | 184.35 | 10.137 | 19.287 |
| 99.88 | 5.096 | 14.368 | 184.82 | 2.525 | 19.245 |
| 100.27 | 4.239 | 14.401 | 185.57 | 6.745 | 19.229 |
| 100.41 | 8.550 | 14.430 | 191.47 | 5.058 | 19.199 |
| 104.12 | 3.777 | 14.854 | 197.34 | 6.688 | 19.307 |
| 104.45 | 4.102 | 14.894 | 204.81 | 8.242 | 19.530 |
| 104.52 | 15.260 | 15.079 | 211.76 | 8.220 | 19.848 |
| 107.84 | 3.658 | 15.349 | 212.98 | 8.100 | 19.912 |
| 108.42 | 3.856 | 15.417 | 216.82 | 6.275 | 20.133 |
| 108.49 | 7.603 | 16.423 | 219.88 | 8.021 | 20.390 |
| 110.41 | 1.482 | 15.756 | 226.98 | 6.185 | 21.294 |
| 111.55 | 2.405 | 22.604 | | Liquid | |
| 111.72 | 1.148 | 21.975 | 240.33 | 4.847 | 27.456 |
| 112.55 | 0.807 | 33.89 | 242.30 | 5.720 | 27.503 |
| 113.50 | 1.481 | 17.526 | 246.76 | 8.012 | 27.675 |
| 113.88 | 1.844 | 17.202 | 249.21 | 8.103 | 27.731 |
| 114.29 | 4.001 | 19.093 | 258.06 | 9.609 | 28.057 |
| 115.01 | 1.545 | 16.572 | 267.61 | 9.487 | 28.403 |
| 115.75 | 1.899 | 16.444 | 277.03 | 9.366 | 28.775 |
| 116.56 | 1.553 | 16.422 | 286.34 | 9.254 | 29.128 |
| 118.11 | 1.551 | 16.395 | 295.54 | 9.141 | 29.500 |
| 119.66 | 1.543 | 16.465 | 297.45 | 6.002 | 29.599 |
| 119.83 | 7.088 | 16.493 | 304.18 | 7.459 | 29.857 |
| 121.29 | 19.184 | 16.608 | 304.62 | 9.028 | 29.881 |
| 121.96 | 3.052 | 16.623 | 311.60 | 7.383 | 30.187 |
| 122.77 | 5.986 | 16.669 | 319.67 | 8.762 | 30.527 |
| 124.98 | 2.999 | 16.920 | 327.92 | 7.741 | 30.863 |
| 127.26 | 7.762 | 17.199 | 336.08 | 8.565 | 31.255 |
| 128.64 | 5.755 | 17.375 | | | |

having maxima at approximately 112 and 138° K., both transitions involving only small amounts of energy. At approximately 171.6° K. the crystals undergo an isothermal transition involving about 150 calories per mole. Immediately following this isothermal absorption of energy, the heat capacity is abnormally high, but drops rapidly to the normal level in a manner similar to the high temperature side of a lambda-type transition. Similar behavior was observed in an unpublished investigation in the organic laboratory at Stanford University.[7]

Because of this unusual behavior, the transition zones were investigated with considerable care in order to define the shape of the heat-capacity curve as definitely as possible. From the experimental data there can be no doubt of the negative slope of the heat-capacity curve on the high-temperature side of the transitions. Since it was thought that the shape of the curve might be characteristic of the crystals formed at low temperatures, measurements were made on the high-temperature side of each transition without allowing the material to cool below the temperature of maximum heat capacity. The usual practice is to cool the material to a suitably low temperature and then to make measurements at progressively higher temperatures. In the present case a reversal of this procedure was attempted, *i. e.*, measurements of heat capacity were made at progressively lower temperatures. In laboratory parlance this is described as "backing into a transition." These experiments demonstrated that the heat capacity was independent of the history of the sample.

Because of the peculiar behavior between 171 and 184° K., a time–temperature study was made over this region. In this study, electrical energy was supplied to the calorimeter at an approximately steady rate and the temperature of the resistance thermometer recorded at integral minutes. These data have been plotted in Fig. 2 and are in agreement qualitatively and semi-quantitatively with the deductions made from the heat-capacity measurements. [These measurements are inherently less reliable than the usual heat capacity measurements for two reasons: (1) Because of the location of the thermometer coil next to the heater coil, in the combination thermometer and heater, the temperature of the thermometer coil would always be higher than the contents of the calorimeter during energy input. However, if the rate of energy input to the heater is constant and the conduction and radiation paths are also constant, this temperature

(7) Private communication from G. S. Parks.

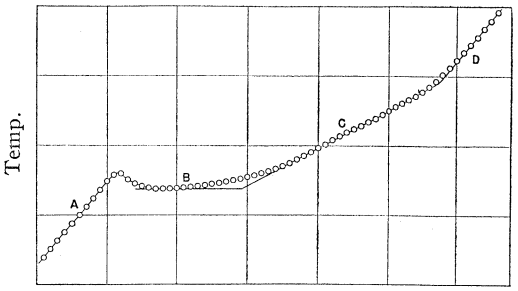



Fig. 2.—Time–temperature study of thiophene between 171 and 184°K. This study includes isothermal transition and the region of abnormally high heat capacity. Units are arbitrary.

head should be constant and the above investigation should give a good picture of the relative temperature change. (2) There will be another uncertainty due to the fact that the system is not in thermodynamic equilibrium during the heating process.] The initial portion of the curve shows a nearly uniform slope which is inversely proportional to $\Delta E/\Delta T$, the heat capacity. The low temperature material tends to superheat, and when the transition begins, the excess energy is absorbed by the transition process and the temperature drops rapidly. For some time thereafter the temperature remains nearly constant, then begins to increase slowly, forming another portion of the curve having a slope which is nearly uniform but considerably smaller than the slope of the initial part of the curve. The curve finally breaks again into another portion of uniform but higher slope. By drawing straight lines through the uniform portions of the curve it may be divided into four parts. In portion (A) the energy absorbed raises the temperature of the low-temperature crystals. In this region the heat capacity calculated from the time–temperature curve is in good agreement with the observed heat capacity values. Portion (B), which is almost flat, corresponds to an isothermal absorption of energy. This is followed by portion (C), which has a small slope and corresponds to the short temperature interval of high heat capacity. Portion (D) corresponds to the temperature range in which the heat capacity of the crystals has an apparently normal value. All of the data are in agreement, so there can be little question in regard to the thermal behavior of the material upon which the measurements were made. Because this behavior is so unusual, the question of the purity of the material has been carefully considered. All of the evidence at this time indicates that the amount of impurity was so small that it would probably have no significant effect on the thermal properties. For this reason it must be concluded that the observed behavior is characteristic of thiophene.

The value for the heat of the isothermal transition at 171.6° K. is rather arbitrary because of the uncertainties in the heat capacity of the high-temperature form and also of the temperature of transition. Check measurements were made of the energy requirements over a selected temperature interval, including the isothermal transition and the high heat capacities, and good agreement was obtained. This indicates that the transition was reproducible. The arbitrary distribution of the energy absorbed as heat of transition and heat capacity should have no significant effect on the entropy. The value assigned for the heat of transition is 152.4 cal./mole.

Two measurements were made of the heat of fusion. The experimental values were 1214.4 and 1216.6 giving a mean value $\Delta H^\circ = 1215.5 \pm 1.1$ cal./mole.

**Section 2: Vapor Pressure.**—The vapor pressure of thiophene was measured from 0 to 40° by a static method and from 40 to 120° by an ebulliometric method.

The apparatus used for the static vapor pressure measurements is shown schematically in Fig. 3. A sample container, A, and a mercury manometer, B (shown in isometric projection in the insert of Fig. 3), are contained in a constant-temperature water-bath, C, having a plate glass window, D, through which the manometer may be observed. When a sample is to be introduced into or removed from the sample container, the mercury in the manometer may be lowered into the mercury reservoir, E, by applying suction through the stopcock, F. The glass tube connecting the mercury reservoir with the manometer enters the bottom of the constant-temperature bath

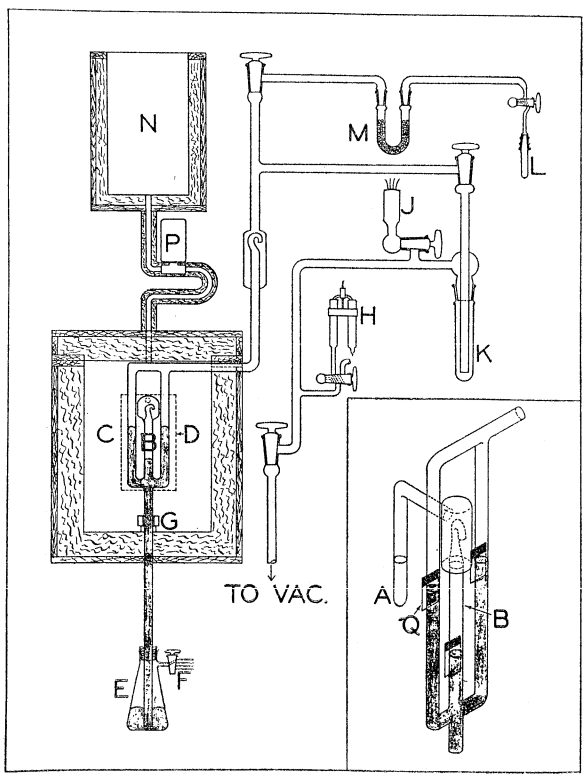



Fig. 3.—Apparatus for vapor pressure measurements by the static method.

through the packing gland, G. The two outer arms of the manometer are connected to a high-vacuum system. The Pirani gage, H, and ionization gage, J, included in this high-vacuum system, may be isolated by stopcocks when not in use and are protected from mercury vapor and other condensible materials by the refrigerated trap, K.

The procedure used for introducing and outgassing the sample is as follows: Approximately 5 ml. of the substance to be investigated is placed in the bulb, L, where it is frozen. The space over the solid is evacuated to a pressure of $10^{-5}$ mm. or less. The material is then distilled under its own vapor pressure into the sample container, A, during which operation the vapor passes through the U-tube, M, containing a suitable drying agent. The sample is again frozen and the space over it evacuated. The material is subjected to several additional bulb-to-bulb distillations between the sample container, A, and the bulb, L, and back again, and after each of these distillations it is frozen and any residual gas is pumped out. After the final distillation into the sample container, the material is melted, and about 20% of it is pumped off and caught in the trap, K (from where it is subsequently transferred to bulb L for storage). A series of vapor-pressure measurements is now made with the 80% of the sample remaining. Following these measurements, an additional 60% of the original sample is pumped off and a second series of vapor-pressure measurements is made with the 20% of the sample remaining. If the vapor pressures measured on 80% of the sample and on 20% are found to be in good agreement, this is taken as evidence that the sample was adequately outgassed and contained only negligible amounts of impurities of different volatility.

The constant-temperature bath is controlled by electrical heating when operating above room temperature and by intermittent addition of cold water from the container, N, by means of the solenoid valve, P, when operating below room temperature. In this type of apparatus, with both the sample container and manometer in the same constant-temperature bath, it is essential that there be no temperature gradients which will cause sample to distill from the sample container to the mercury surface of the manometer. For this reason, the various elements in the constant-temperature bath are so arranged that any small gradients, not eliminated by vigorous stirring, are in such a direction that the manometer is never colder than the sample container. The tube for addition of cold water is in the rear of the bath. Two immersion heaters, one a steady heater for compensating most of the heat loss of the bath, and the other an auxiliary heater used in heating the bath rapidly from one operating temperature to another, are located in the front of the bath, between the window and the manometer (but not obscuring the view of the mercury columns). The intermittent heater used for controlling the bath temperature and the stirrer are located in a 3-inch-diameter tower in one corner of the bath (not shown). A sensitive mercury-in-glass thermoregulator and a calorimetric-type platinum resistance thermometer, calibrated and certified by the National Bureau of Standards, are both in close proximity to the sample container. The resistance of the thermometer is measured by means of a G-2 Mueller bridge and a sensitive galvanometer. The bath is controlled to $\pm$ 0.01° at 15°, $\pm$ 0.005° at 40°, and $\pm$ 0.01° at 75°. When making measurements at 0°, the water is drained from the bath, and the sample container is surrounded by a Dewar flask containing crushed ice.

The manometer is read by means of a Gaertner M904 cathetometer certified by the National Bureau of Standards. The vernier of the cathetometer scale is graduated in 0.05-mm. divisions, and it is possible to estimate visually between vernier divisions to 0.01 mm. Each meniscus is observed against a background, Q, made from a rectangle of white plastic with a black strip across the top. The black reflects in the mercury surface and makes the outline of the meniscus clearly visible against the white background. The backgrounds are so mounted that they may be adjusted for vertical height by means of rods extending through the lid of the constant-temperature bath. The manometer is illuminated by "Lumiline" incandescent lamps on each side of the window.

To test the window of the constant-temperature bath for any optical imperfections that would introduce errors into the pressure readings, a standard meter bar was mounted behind the window in the place ordinarily occupied by the manometer. Cathetometer readings of the distance between graduations on the standard meter bar showed that there were no optical imperfections in the window that would affect the pressure readings significantly. The walls of the manometer arms were also tested for optical imperfections by taking "blank" pressure readings with the sample container evacuated. The pressure readings obtained did not differ significantly from zero.

When taking pressure readings, the meniscus heights are always read in order from one side to the other at approximately equal time intervals and the readings for the two outer arms are averaged. This procedure automatically corrects for any regular variation of meniscus height with time or with position, such as might be caused by a temperature drift of the mercury reservoir or by failure of the axis of the cathetometer telescope to rotate in an exactly horizontal plane. Capillary depression corrections, taken from the tables of Cawood and Patterson,[8] are applied and the readings are reduced to 0° and standard acceleration of gravity. The acceleration of gravity at this location is calculated from the latitude and altitude to be 979.82 cm./sec.$^2$, and the standard acceleration of gravity is taken as 980.665 cm./sec.$^2$. Corrections for the vapor pressure of mercury are applied to the values obtained at the higher temperatures where this correction becomes significant.

To test the performance of the apparatus, the vapor pressure of benzene was measured at six temperatures between 0° and 35°. The results obtained, when compared with values calculated from the equation given in the A.P.I. Tables,[9] showed an average deviation of 0.03 mm. of Hg and a maximum deviation of 0.06 mm.

The results obtained for thiophene are listed in the first part of Table III. Each value listed is the average of five or more pressure readings taken within a period of about an hour. Three readings of the bath temperature were taken within the same period, and if these were significantly different from the integral temperature, the appropriate corrections were applied to the pressure readings.

In the ebulliometric vapor-pressure measurements, the boiling temperature of thiophene was compared directly with the boiling temperature of water in a closed system filled with nitrogen gas, the pressure of which could be adjusted to any predetermined value between 100 and 2500 mm. The boiling temperature of each liquid was measured in a differential ebulliometer, Fig. 4, which is a modification of one described by Swietoslawski.[10] The strain-free platinum resistance thermometer used to measure the boiling points had been calibrated and certified by the National Bureau of Standards. Its resistance was measured with the same bridge and galvanometer used with the static vapor pressure apparatus.

At atmospheric pressure, the boiling and condensation temperatures of the thiophene sample

(8) Cawood and Patterson, *Trans. Faraday Soc.*, **29**, 514 (1933).

(9) American Petroleum Institute Research Project 44 at the National Bureau of Standards, Selected Values of Properties of Hydrocarbons. Table No. 5k (Part 1), alkyl benzenes, $C_6$ to $C_8$, vapor pressures and boiling points, at 10 to 1500 mm., dated June 30, 1944.

(10) W. Swietoslawski, "Ebulliometric Measurements," Reinhold Publishing Corp., New York, New York, 1945, p. 11.

TABLE III

VAPOR PRESSURE OF THIOPHENE

STATIC METHOD

| $t$, °C. | Vapor pressure, mm. 80% of sample | 20% of sample | Calcd. (eq. 1) |
|---|---|---|---|
| 0 | 21.44 | 21.41 | 21.39 |
| 15 | 48.73 | 48.64 | 48.68 |
| 20 | 62.67 | 62.59 | 62.60 |
| 25 | 79.71 | 79.67 | 79.68 |
| 30 | 100.49 | 100.47 | 100.45 |
| 35 | 125.51 | 125.45 | 125.50 |
| 40 | 155.53 | 155.47 | 155.47 |

EBULLIOMETRIC METHOD

| Boiling point, °C. Water | Thiophene | Vapor pressure, mm. Obs. | Calcd. (eq. 1) |
|---|---|---|---|
| 60 | 39.061 | 149.41 | 149.43 |
| 65 | 44.560 | 187.57 | 187.67 |
| 70 | 50.094 | 233.72 | 233.84 |
| 75 | 55.663 | 289.13 | 289.22 |
| 80 | 61.276 | 355.22 | 355.26 |
| 85 | 66.931 | 433.56 | 433.53 |
| 90 | 72.629 | 525.86 | 525.76 |
| 95 | 78.370 | 633.99 | 633.84 |
| 100 | 84.155 | 760.00 | 759.80 |
| 105 | 89.985 | 906.06 | 905.88 |
| 110 | 95.860 | 1074.6 | 1074.5 |
| 115 | 101.776 | 1268.0 | 1268.0 |
| 120 | 107.738 | 1489.1 | 1489.3 |
| 125 | 113.741 | 1740.8 | 1741.0 |
| 130 | 119.787 | 2026.0 | 2026.3 |

differed by only 0.003°. This result indicates that the sample did not contain sufficient impurities of different volatility to have any significant effect on the boiling point measurements.

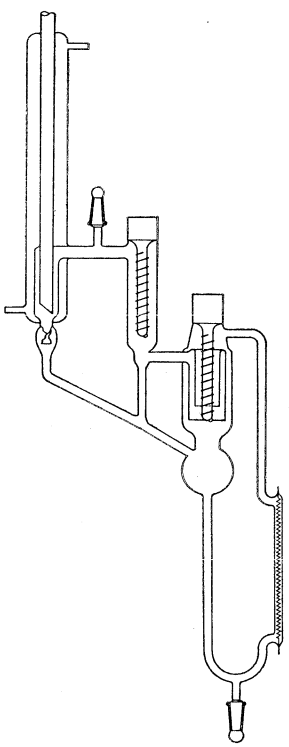


Fig. 4.—Differential ebulliometer.

The vapor pressure data obtained by the ebulliometric method are listed in the second part of Table IV. The pressures corresponding to the observed boiling points of water were obtained from the tables of Osborne, Stimson and Ginnings.[11]

The vapor pressure data obtained by both methods were fitted to an Antoine equation by the least squares treatment of Willingham, Taylor, Pignocco, and Rossini.[12] In weighting the individual points, the expected standard deviation of each temperature measurement was arbitrarily taken as 0.01° and the expected standard deviation of each pressure measurement by the static method was arbitrarily taken as 0.10 mm. The equation obtained is

$$\log_{10} P = 6.95926 - 1246.038/(221.354 + t) \quad (1)$$

Values of the vapor pressure calculated by means of this equation are included in Table III for comparison with the observed values. In the deviation plot, Fig. 5, the results of prior investigations of the vapor pressure of thiophene[13] are compared with those reported here.

## Section 3: Heat of Vaporization, Vapor Heat Capacity, Gas Imperfection, and Entropy of the Ideal Gas

**Heat of Vaporization and Vapor Heat Capacity.**—The heat of vaporization of thiophene was determined at three temperatures, and the heat capacity of the vapor was measured at two or more pressures at each of five temperatures between 70 and 200°. The cycling vaporizer and flow calorimeter, described in previous publications from this laboratory,[14] were used for these measurements. The heat of vaporization data are given in Table IV; the accuracy of these values is estimated to be about 0.1%. The following empirical equation may be used for interpolation over the temperature range of the experiments

$$\Delta H_{vap.} = 9543 + 2.740T - 0.02349T^2 \quad (2)$$

Table V lists the vapor heat-capacity data. The values of $C_p°$ (obs.) were obtained at each temperature by linear extrapolation to zero pressure, of plots of heat capacity *vs.* pressure. Al-

TABLE IV

HEAT OF VAPORIZATION OF THIOPHENE

1 cal. = 4.1833 int. joules; mol. wt. = 84.132

| $t$, °C. | No. expts. | $\Delta H_{vap.}$, cal./mole |
|---|---|---|
| 45.36 | 4 | 8032 ± 7[a] |
| 63.08 | 3 | 7808 ± 3[a] |
| 84.16 | 3 | 7522 ± 3[a] |

[a] Maximum deviation

TABLE V

VAPOR HEAT CAPACITY OF THIOPHENE, CAL./DEG/MOLE

1 cal. = 4.1833 int. joules; mol. wt. = 84.132; 0° C. = 273.16° K.

| $T$, °K. | 343.95 | 371.20 | 402.30 | 436.20 | 471.15 |
|---|---|---|---|---|---|
| $C_p$ (759 mm.) | | 22.03 | 23.47 | 24.96 | 26.41 |
| $C_p$ (378 mm.) | 20.43 | 21.80 | | | |
| $C_p$ (192 mm.) | 20.25 | 21.67 | 23.24 | 24.81 | 26.31 |
| $C_p°$ (obs.) | 20.05 | 21.55 | 23.17 | 24.76 | 26.27 |
| $C_p°$ (calcd.)[a] | 19.91 | 21.36 | 22.92 | 24.48 | 25.96 |
| $C_p°$ (obs.) − $Cp°$ (calcd.) | 0.14 | 0.19 | 0.25 | 0.28 | 0.31 |

[a] Harmonic oscillator-rigid rotator approximation.

(11) Osborne, Stimson and Ginnings, *J. Research Natl. Bur. Standards*, **23**, 261 (1939).

(12) Willingham, Taylor, Pignocco and Rossini, *J. Research Natl. Bur. Standards*, **35**, 219 (1945).

(13) (a) Milazzo, *Gazz. chim. ital.*, **74**, 58 (1944); (b) Nasini, *Proc. Royal Soc. (London)*, **A123**, 704 (1929); (c) Fawcett and Rasmussen, THIS JOURNAL, **67**, 1705 (1945).

(14) (a) Waddington, Todd and Huffman, THIS JOURNAL, **69**, 22 (1947); (b) Waddington and Douslin, *ibid.*, **69**, 2275 (1947).

though the accuracy of vapor heat capacity measurements of polyatomic molecules is difficult to assess, the accuracy uncertainty of the $C_p^\circ$ values given here is believed to be about $\pm 0.2\%$. Over the range of temperatures studied, $C_p^\circ$ is given without significant loss of accuracy by the empirical relationship

$$C_p^\circ = -7.017 + 0.10045T - 6.325 \times 10^{-5}T^2 \quad (3)$$

**Gas Imperfection and the Second Virial Coefficient.**—Values of the second virial coefficient, $B$, in the equation of state $PV = RT + BP$ were calculated from the heat of vaporization and vapor pressure data by means of the relation

$$B = \frac{\Delta H_{vap.}}{T(dP/dT)} - \frac{RT}{P} + V_l \quad (4)$$

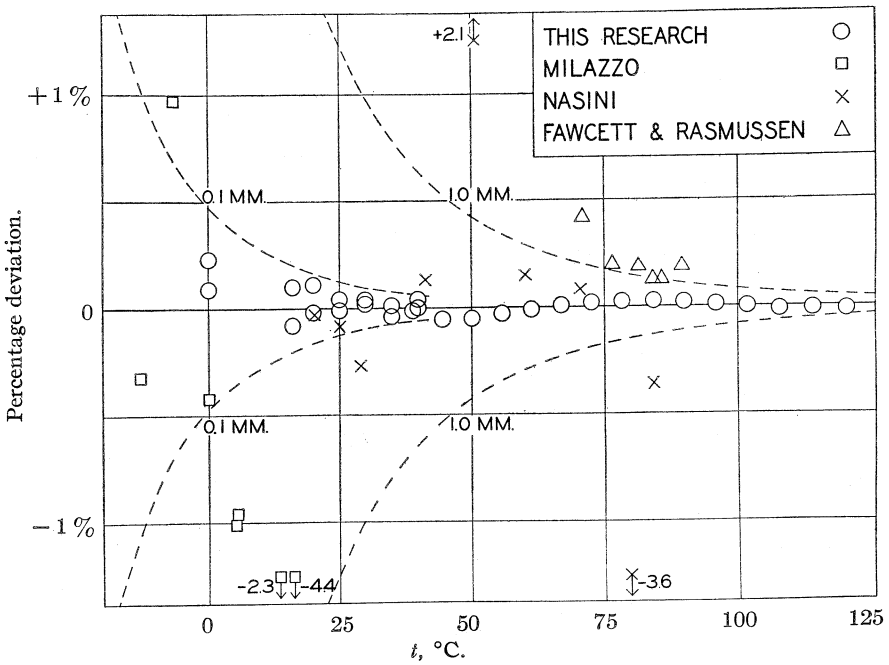



Fig. 5.—Deviation plot of vapor pressure data for thiophene, comparing the results of this research with those of previous investigators (ref. 13). Equation 1 was used for the base line. The dashed lines represent the percentage deviations arising from absolute deviations of 0.1 mm. and 1.0 mm., respectively.

where $V_l$ is the molal volume of the liquid. Use of the experimental data for the pressure dependence of the vapor heat capacity in the equation $(\partial Cp/\partial P)_T = -T(\partial^2 B/\partial T^2)_P$ yielded values of the second derivative of $B$ with respect to temperature. These results were used to obtain the following empirical equation for the second virial coefficient of thiophene vapor

$$B(\text{liters}) = -0.435 - 0.0172 \exp.\ (1200/T) \quad (5)$$

The method of evaluating the constants has been discussed previously.[15]

In Table VI the observed values of the second virial coefficient and of $(\partial Cp/\partial P)_T$ are compared with those calculated from Eq. 5.

TABLE VI

SECOND VIRIAL COEFFICIENT AND $(\partial Cp/\partial P)_T$ FOR THIOPHENE

| | $B$, liters | | | $(\partial Cp/\partial P)_T$, cal./deg./mole/atm. | |
|---|---|---|---|---|---|
| $t$, °C. | Obs. | Calcd. | $t$, °C. | Obs. | Calcd. |
| 45.36 | −1.173 | −1.179 | 70.79 | 0.77 | 0.78 |
| 63.08 | −1.025 | −1.045 | 98.04 | .48 | .48 |
| 84.16 | −0.957 | −0.930 | 129.14 | .31 | .30 |
| | | | 163.04 | .20 | .20 |
| | | | 197.99 | .13 | .13 |

**Entropy from Calorimetric Data.**—The calorimetric data have been used to calculate the entropy in the usual way. In the transition regions the heat capacity curves are not necessarily accurate because of rapid curvature. However, the curves have been made in such a way that $\int_{T_x}^{T_y} C_p dT$ gives the observed enthalpy change; hence there will be no significant error in the entropy.

Since the heat-capacity measurements were carried out up to 340° K., it was possible, with a small extrapolation, to obtain the entropy of the liquid at the temperatures corresponding to those at which the heat of vaporization had been measured. The entropy calculations are summarized in Table VII.

TABLE VII

THE MOLAL ENTROPY OF THIOPHENE, CAL./DEG.

| | |
|---|---|
| $S_{0-12°K.}$ (Debye, 4° freedom, $\Theta$ = 102.7) | = 0.322 |
| $\Delta S_{12-171.6}$ (graphical) | = 23.265 |
| $\Delta S_{171.6}$ (152.4/171.6) | = 0.888 |
| $\Delta S_{171.6-234.94}$ (graphical) | = 6.896 |
| $\Delta S_{234.94}$ (1215.5/234.94) | = 5.174 |
| $\Delta S_{234.94-298.16}$ (graphical) | = 6.755 |
| $S_{298.16}$ Liq. | = 43.30 ± 0.10 |

| $T$, °K. | 318.52 | 336.24 | 357.32 |
|---|---|---|---|
| Entropy of liquid at 298.16°K. | 43.30 | 43.30 | 43.30 |
| $\Delta S_{298.16-T}$ (graphical) | 1.98 | 3.66 | 5.58 |
| Vaporization, $\Delta H_{vap.}/T$ | 25.22 | 23.22 | 21.05 |
| Compression, $R$ ln $(P/760)$ | −2.72 | −1.38 | 0.00 |
| Gas imperfection[a] | +0.05 | +0.08 | +0.11 |
| Entropy of ideal gas at 1 atm. | 67.83 ±0.20 | 68.88 ±0.20 | 70.40 ±0.20 |

[a] For calculating the correction for gas imperfection, which is given by $P(\partial B/\partial T)_P$, in terms of the second virial coefficient, eq. 5 was used.

(15) Scott, Waddington, Smith and Huffman, *J. Chem. Phys.*, **15**, 565 (1947).

The uncertainties in the experimental heat capacity measurements in certain temperature regions are probably higher than usual because of the rapid curvature and slow approach to equilibrium. Nevertheless it is believed that the experimentally determined entropy of the liquid is reliable to ±0.1 cal./deg./mole, and that of the gas is reliable to ± 0.20 cal./deg./mole.

## Section 4: Heat of Combustion and Heat of Formation

**Calorimetric Method.**—The calorimetric method has been described previously.[16]

Certain modifications in the apparatus as described by Hubbard, Knowlton and Huffman[17] had been made, but the operating principles were unchanged. All of the combustions were carried out in a platinum-lined bomb having a volume of 0.330 liter. The general method of Huffman and Ellis[16] for the combustion of sulfur compounds was followed; that is, an atmosphere of air was left in the bomb to supply nitrogen required for the complete oxidation of sulfur to sulfur trioxide and no (liquid) water was introduced into the bomb before the combustion. The combustion samples were contained in thin-walled glass ampules drawn down to a capillary neck which was not sealed.

The ampules were filled by the following procedure. The weighed empty ampules were placed neck down in the receiver of an all-glass distilling apparatus. The system was then evacuated and the thiophene allowed to distill into the receiver under its own vapor pressure. When a sufficient quantity had been distilled, air was admitted to the system and the pressure forced liquid into the ampules. Shortly before a combustion experiment an ampule was taken from the receiver, external material was removed, and a small amount of thiophene was forced out of the ampule so as to bring the liquid level, at room temperature, below the fine part of the capillary, to avoid losses due to expansion caused by temperature fluctuations subsequent to weighing. Because of the fineness of the opening and the small surface exposed, there appeared to be no significant evaporation of sample or solution of air during the experimental period. The method was tested by burning benzene in both sealed and unsealed ampules. In both cases very satisfactory agreement was obtained with the accepted value for its heat of combustion.

**Calibration.**—The energy equivalent of the system was determined by the combustion of benzoic acid NBS standard sample #39f having the certified value of 26,428.4 NBS international joules per gram for the isothermal heat of combustion under standard conditions.[18] Since the conditions of this investigation were not quite standard, this value was corrected to 26,426.6 NBS int. joules/g. Joules were converted to conventional calories by dividing by 4.1833. The average value of the energy equivalent of the system, from eight calibration experiments, was found to be 3225.7 cal./degree, with an average deviation of 0.004% and a maximum deviation of 0.017%.

**Corrections and Analytical Procedures.**—The reactions involved in the combustion of sulfur compounds are rather complex and require corrections not usually applied in C, H, O combustions. Under the conditions of the experiment, part of the nitrogen in the bomb is fixed. Hence it is necessary to determine both the type of nitrogen compound and the quantity so that proper calorific corrections may be applied for these secondary reactions. Because of the large heat of dilution of sulfuric acid, it is necessary to know its concentration with considerable certainty. Finally, because there is a difference in the amount of water vapor initially present in the bomb and the amount existing over the sulfuric acid solution in the final state, a correction must be applied for its condensation.

Qualitative tests indicated that nitrogen was fixed in the form of nitric acid and nitrous acid. The $NO_2^-$ ion was determined by the colorimetric method of Treadwell and Hall[19] and the total nitrogen was determined as ammonia after reduction by Devarda's method.[20] It was assumed that all of the nitrogen was in the form of nitrous and nitric acid; hence nitric acid was taken as the difference between total nitrogen and nitrous acid nitrogen. The heat effects ($\Delta E$) associated with the formation of nitrous and nitric acid were taken as 6.4 and −14.96 kcal. per mole, respectively.

The concentration of the sulfuric acid was calculated from the stoichiometric relations of the materials entering into the reaction. In a number of cases the sulfate ion was determined gravimetrically and the amount found was on the average 99.8% of the calculated amount. The data of Huffman and Ellis[16] were used to correct the observed heats to one corresponding to a standard sulfuric acid concentration. The correction for the condensation of water vapor was determined from measurements of the humidity, the volume of the bomb, the known heat of vaporization of water, and the vapor pressure of aqueous sulfuric acid.[21]

The results of the six combustions are summarized in Table VIII. In addition to the final results this table shows the magnitude of the various correction terms used.

(16) (a) Huffman and Ellis, THIS JOURNAL, **57**, 41 (1935); (b) Stiehler and Huffman, *ibid.*, **57**, 1734 (1935); (c) Huffman, *ibid.*, **60**, 1171 (1938).

(17) Hubbard, Knowlton and Huffman, *ibid.*, **70**, 3259 (1948).

(18) Jessup, *J. Research Natl. Bur. Standards*, **29**, 247 (1942).

(19) Treadwell and Hall, "Analytical Chemistry," 9th ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 306.

(20) Hillebrand and Lundell, "Applied Inorganic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1929, p. 639.

(21) "International Critical Tables," Vol. III, McGraw-Hill Book Co., New York, N. Y., 1926, p. 303.

TABLE VIII

SUMMARY OF THIOPHENE COMBUSTIONS

For the Isothermal Reaction at 25°: $C_4H_4S(l) + 13/2\ O_2(g) + 0.7\ H_2O(l) = 4\ CO_2(g) + [H_2SO_4 \cdot 1.7H_2O](l)$

| Mass of thiophene g. (in vac.) | Mass of oil, g.(in air) | $C_p \times \Delta t$ total cal. | $\frac{n_{H_2O}}{n_{H_2SO_4}}$ | Calories correction[a] $Q_{diln.}$ | $Q_{cond.}$ | $Q_{HNO_2}$ | $Q_{HNO_3}$ | $Q_{fuse+oil+ign.}$ | Ash found, mg. | $-\Delta U_B/M$, cal./g. | Dev., cal./g. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.74153 | 0.05190 | 6454.62 | 1.45 | + 6.71 | −3.63 | +2.84 | −3.08 | − 597.23 | 5.2 | 7910.6 | −2.1 |
| .75114 | .04007 | 6396.36 | 1.34 | +10.11 | −3.03 | +2.26 | −4.17 | − 465.11 | 6.0 | 7910.7 | −2.0 |
| .71659 | .06929 | 6459.56 | 1.60 | + 2.32 | −2.58 | +2.10 | −4.48 | − 791.19 | 6.2 | 7914.1 | +1.4 |
| .71031 | .07539 | 6478.65 | 1.66 | + 1.05 | −2.54 | +2.45 | −5.29 | − 861.06 | 6.7 | 7909.9 | −2.8 |
| .71005 | .7431 | 6469.56 | 1.65 | + 1.18 | −2.68 | +2.52 | −4.96 | − 848.64 | 6.8 | 7918.1 | +5.4 |
| .68715 | .09056 | 6466.65 | 1.82 | − 2.71 | −2.47 | +2.30 | −2.17 | −1029.80 | 5.4 | 7912.6 | −0.1 |
| | | | | | | | | Average | | 7912.7 ± 2.3 = 0.03% | |
| | | | | | | | | Max. spread | | 8.2 cal./g. = 0.1% | |

[a] $Q_{diln.}$ = correction for dilution of $H_2SO_4$, $Q_{cond.}$ = correction for condensation of water, $Q_{HNO_2}$ = correction for nitrous acid, $Q_{HNO_3}$ = correction for nitric acid.

In Table IX are given the derived data for thiophene. It should be borne in mind that $-\Delta U_R$ and $-\Delta H_R$ apply to the combustions only when the composition of the aqueous sulfuric acid corresponds to $H_2SO_4 \cdot 1.7H_2O$ and that the Washburn correction has not been applied.

TABLE IX

THIOPHENE, MOL. WT. = 84.132; DERIVED DATA AT 298.16°

| in kcal./mole | | | |
|---|---|---|---|
| $\Delta U_R$ | $\Delta H_R$ | $\Delta H°_f$(liq.) | $\Delta H°_f$(gas) |
| −665.71 | −667.19 | 19.52 | 27.82 |

$\Delta U_R$ and $\Delta H_R$ refer to the reaction in which $H_2O/H_2SO_4 = 1.7$. $\Delta H_f°$ refers to the formation from the elements.

**Discussion.**—The above value for the heat of formation of thiophene is to be looked upon as a preliminary value only, for several reasons that will be discussed below. The corrections for the fixed nitrogen were based on the assumption of the formation of aqueous nitrous acid and nitric acid. Actually this assumption may not be warranted as is borne out by the following evidence. According to the above assumption the products of the combustion of the sulfur and the nitrogen are all acidic. Hence from the total nitrogen and sulfur known to be present it is possible to calculate the moles of acid to be expected. This calculated value was always greater than the value found from titration by approximately 0.4–0.5 millimole or 2 to 3%. Because the gravimetric sulfur analyses accounted for practically 100% of the theoretical $SO_4^{--}$ ion and no known cations were present, it is believed that the discrepancy is due to nitrogen being fixed in some form other than nitrous acid or nitric acid. This problem is being investigated.

Furthermore, a small amount of solid material is found after each combustion when the solutions formed in the combustion are evaporated to dryness. Presumably this solid residue comes from the reaction of the products of combustion with either platinum or glass or both. The amount of residue is far too small to account for the discrepancy between calculated and found hydrogen ion. A series of combustions made in an illium bomb showed about twice as much residue and the combustion values were definitely higher.

The heat of combustion of thiophene has also been studied by Moore, Renquist and Parks[22] in an illium bomb. Their value for $-\Delta U_B/M$ corrected for the change in the heat of combustion of benzoic acid[18] and a change in calibration[23] is 7918.3 ± 2.5 calories per gram and in good agreement with the value 7916.8 obtained in this laboratory using an illium bomb.

In the opinion of the authors, the data obtained in this Laboratory using the platinum bomb are probably the most reliable. In spite of the uncertainty attached to their experimental quantities, it seems desirable to publish these results as being the best available and because of the need of a value of the heat of formation for thermodynamic calculations.

## Section 5: Thermodynamic Functions from Spectroscopic and Molecular Structure Data

**Vibrational Assignment.**—With the aid of the vapor-heat-capacity data, a complete, although not entirely certain, vibrational assignment for thiophene was made. No complete vibrational assignment has been proposed heretofore, but Thompson and Temple[24] have assigned 14 of the 21 fundamental frequencies. The assignment given here is based primarily on the Raman data of Reitz[25] and the infrared data of Thompson and Temple, as given in Table X, although all of the other available spectroscopic data[26] were consid-

(22) Moore, Renquist and Parks, THIS JOURNAL, **62**, 1505 (1940).

(23) Private communications from G. S. Parks.

(24) Thompson and Temple, *Trans. Faraday Soc.*, **41**, 27 (1945).

(25) Reitz, *Z. physik. Chem.*, **B33**, 179 (1936); *B38*, 275 (1937).

(26) (a) Venkateswaren, *Indian J. Physics*, **5**, 145 (1930); *Phil. Mag.*, **15**, 263 (1933). (b) Bhagavantam, *Indian J. Physics*, **7**, 79 (1932). (c) Venkateswaren and Bhagavantam, *Indian J. Physics*, **7**, 585 (1933). (d) Bonino and Monzani-Ansidei, *Z. physik. Chem.*, **B25**, 327 (1934); *Atti. accad. Lincei, Classe sci. fis. mat. nat.*, **24**, 207 (1936); *Ricerca sci.*, **7**, I, 315 (1936). (e) Coblentz, "Investigation of Infrared Spectra," Publ. Carnegie Inst. of Wash., D. C. No. 35 Part I (1905). (f) Manzoni-Ansidei and Rolla, *Atti. accad. Lincei, Classe sci. fis. mat. nat.*, **27**, 410 (1938). (g) Barnes and Brattain, *J. Chem. Phys.*, **3**, 446 (1935). (h) American Petroleum Institute Research Project 44 at the National Bureau of Standards. Catalog of Infared Spectrograms. Serial No. 364, Thiophene (liquid), contributed by the Socony-Vacuum Oil Company, Paulsboro, New Jersey. (i) Barnes, Liddel and Williams, *Ind. Eng. Chem., Anal. Ed.*, **15**, 659 (1943).

ered. The assignment is given in Table XI; the numbering of the modes of vibration follows that used by Lord and Miller[27] for the analogous molecule pyrrole.

TABLE X

SPECTRA OF THIOPHENE[a]

| Raman (Reitz[25]) | | | Infrared (Thompson and Temple[24]) | | |
|---|---|---|---|---|---|
| $\Delta\nu$ | $I$ | $\rho$ | Vapor | Liquid | Assignment |
| 375 | 0 | (d$\rho$) | | | 832–453 = 379 |
| 453 | 3 | d$\rho$ | | | 23 |
| 565 | 1 | d$\rho$ | | | 18 |
| 604 | 6 | 0.34 | 605 | 605 | 1 |
| 686 | 2 | 1.01 | | | 19 |
| | | | 710 | 710 | 22 |
| 748 | 4 | 1.00 | | | 20 |
| 832 | 7 | 0.08 | 836 | 836 | 3 and 24 |
| 866 | 1 | 1.00 | 872 | 870 | 10 |
| 898 | ½ | d$\rho$ | 909 | 904 | 11 |
| 1032 | 10 | 0.11 | 1035 | 1035 | 2 |
| 1079 | 9 | 0.43 | 1077 | 1080 | 4 |
| | | | 1252 | 1255 | 14 |
| | | | | 1290 | 12 |
| 1358 | 9 | 0.13 | | | 5 |
| 1404 | 12 | 0.35 | 1405 | 1405 | 6 |
| | | | | 1479 | Combination |
| | | | | 1565 | Combination |
| | | | | 1590 | 15 |
| 2996 | 1 | $\rho$ | | | 7 and 16 |
| 3078 | 8b | $\rho$(Hg) | 3110 | | Resonance 8 and 17 |
| 3108 | 10 | 0.33 (Hg) | | | 3 (1032) = 3096 |

[a] Omitting the region 1700–2800 cm.$^{-1}$

TABLE XI

VIBRATIONAL ASSIGNMENT FOR THIOPHENE

| Class $A_1$ | | Class $A_2$ | | Class $B_2$ | | Class $B_1$ | |
|---|---|---|---|---|---|---|---|
| No. | $\nu$, cm.$^{-1}$ | No. | $\nu$, cm.$^{-1}$ | No. | $\nu$, cm.$^{-1}$ | No. | $\nu$, cm.$^{-1}$ |
| 1 | 604 | 18 | 565 | 22 | 710 | 10 | 872 |
| 2 | 1032 | 19 | 686 | 23 | 453 | 11 | 909 |
| 3 | 832 | 20 | 748 | 24 | (832)[a] | 12 | 1290 |
| 4 | 1079 | | | | | 14 | 1252 |
| 5 | 1358 | | | | | 15 | 1590 |
| 6 | 1404 | | | | | 16 | (2996) |
| 7 | 2996 | | | | | 17 | (3093) |
| 8 | 3093 | | | | | | |

[a] Parentheses denote frequencies used for the second time.

In class $A_1$, the assignment of the frequencies below 1600 cm.$^{-1}$ follows that of Thompson and Temple. These frequencies appear as strong polarized lines in the Raman effect, and their assignment is unambiguous. There are two C–H stretching frequencies in this symmetry class, but three polarized Raman lines are observed in the 3000 cm.$^{-1}$ region of the spectrum. The frequency 2996 cm.$^{-1}$ was assigned to $\nu_7$ and the doublet 3078–3108 cm.$^{-1}$ was interpreted as Fermi resonance between $\nu_8$ and $3(\nu_2)$. The average value, 3093 cm.$^{-1}$, was used for $\nu_8$.

In assigning the frequencies in class $A_2$, use was made of the fact that the vibrations in this symmetry class do not involve motion of the sulfur atom, and consequently the frequencies should not differ greatly from those of the corresponding vibrations in pyrrole. The $A_2$ frequencies in pyrrole occur at 510, 711, and 868 cm.$^{-1}$;[27] the evident choices for thiophene are the frequencies 565, 686 and 748 cm.$^{-1}$ observed in the Raman effect. In conformity with the selection rules for $A_2$ frequencies, these do not appear in the infrared.

In class $B_2$, Thompson and Temple assigned the strong infrared band at 710 cm.$^{-1}$ to $\nu_{22}$. The out-of-plane ring bending frequency, $\nu_{23}$, would be expected in the region of the spectrum below 500 cm.$^{-1}$; the choice is between the Raman lines at 375 and 453 cm.$^{-1}$. Thompson and Temple suggest that the former is the difference tone 832 − 453 = 379 cm.$^{-1}$. Additional evidence for this interpretation is the fact that if 375 cm.$^{-1}$ is assumed to be a fundamental frequency, no reasonable assignment of the other frequencies can be made to agree with the gas heat capacity data. This leaves the 453 cm.$^{-1}$ Raman line for $\nu_{23}$. The remaining $B_2$ frequency, $\nu_{24}$, arises from an out-of-plane hydrogen bending mode which would be expected to involve little motion of the heteroatom or group in the series pyrrole, pyrrole-N-d, furan and thiophene. Hence it would be expected to have roughly the same value in all of these molecules. In pyrrole and pyrrole-N-d, $\nu_{24}$ is found at 838 and 833 cm.$^{-1}$, respectively,[28] and the $B_2$ frequency of furan at 837 cm.$^{-1}$ is very likely also $\nu_{24}$. In thiophene a $B_2$ frequency in this region of the spectrum would be obscured in both the Raman and infrared spectra by the $A_1$ frequency, $\nu_3$, at 832 cm.$^{-1}$, and the value 832 cm.$^{-1}$ was used for $\nu_{24}$, as well as for $\nu_3$.

Thompson and Temple have assigned the observed frequencies 872, 1252, and 1590 cm.$^{-1}$ to class $B_1$; these probably are the ring frequencies $\nu_{10}$, $\nu_{14}$, and $\nu_{15}$. As all the C–H stretching frequencies of thiophene have not been resolved, the same values were used for $\nu_{16}$ and $\nu_{17}$ in class $B_1$ as for $\nu_7$ and $\nu_8$ in class $A_1$, namely, 2996 and 3093 cm.$^{-1}$. This leaves only the two C–H bending frequencies, $\nu_{11}$ and $\nu_{12}$, to be assigned. The weak Raman line at 898 cm.$^{-1}$ (corresponding to the infrared band for thiophene vapor at 909 cm.$^{-1}$) was used for $\nu_{11}$; it is depolarized and hence cannot be the overtone of $\nu_{23}$. To fix the remaining frequency, $\nu_{12}$, use was made of the gas heat capacity data. Assuming all the other frequencies assigned correctly, the gas heat capacity data require $\nu_{12}$ to be approximately 1300 cm.$^{-1}$. Liquid thiophene has a weak infrared band at 1290 cm.$^{-1}$. Although this can be interpreted as a combination band (453 + 832 = 1285) it seems more probable that it is the fundamental frequency, $\nu_{12}$, and it was so assigned.

In Table V the observed values of $C_p°$ are compared with those calculated by means of the harmonic oscillator-rigid rotator approximation, using the vibrational assignment of Table XI. If the

(27) Lord and Miller, *J. Chem. Phys.*, **10**, 328 (1942).

(28) Actually, Lord and Miller assign these frequencies to $\nu_{23}$, but it seems more probable that they correspond to $\nu_{24}$, and that the lowest $B_2$ frequencies, 565 and 450 cm.$^{-1}$, correspond to $\nu_{23}$.

vibrational assignment is correct, the values of $C_p°$(obs.) − $C_p°$ (calcd.) in the last line of Table V represent the contribution to the heat capacity of anharmonicity and other factors neglected in the harmonic oscillator–rigid rotator treatment. In the case of benzene,[15] for which there can be little doubt as to the correctness of the vibrational assignment, values of $C_p°$(obs.) − $C_p°$ (calcd.) were found which were similar both in magnitude and in temperature dependence to those found here for thiophene.

**Entropy from Molecular Structure Data.**—The calorimetric values of the entropy are compared in Table XII with those calculated from molecular structure data. In these calculations the values of the fundamental constants given by Wagman, *et al.*[29] were used. The moments of inertia, calculated from the geometrical data of Schomaker and Pauling[30] and 1941 atomic weights, are $I_x = 156.5 \times 10^{-40}$, $I_y = 262.1 \times 10^{-40}$, and $I_z = 105.6 \times 10^{-40}$ g. sq. cm. The symmetry number is 2. The vibrational assignment of Table XI was used.

TABLE XII

| $T$, °K. | Entropy, cal./deg./mole: Calorimetric | Molecular structure |
|---|---|---|
| 318.52 | 67.83 | 67.81 |
| 336.24 | 68.88 | 68.84 |
| 357.32 | 70.04 | 70.05 |

The close agreement of the two sets of entropy values shows that crystalline thiophene approaches zero entropy at the absolute zero. It is also a confirmation of the planar structure ($C_{2v}$ symmetry) for the thiophene molecule.

**Statistically Calculated Thermodynamic Functions.**—The free-energy function, heat-content function, entropy, and heat capacity of gaseous thiophene have been calculated for various temperatures up to 1500° K. The values obtained are listed in Table XIII.

TABLE XIII

THERMODYNAMIC FUNCTIONS OF THIOPHENE

| $T$, °K. | $(H_0^0 - FT^0)/T$, cal./deg./mole | $HT^0 - H_0^0$, kcal./mole | $ST^0$, cal./deg./mole | $C_p{}^0T$, cal./deg./mole |
|---|---|---|---|---|
| 298.16 | 55.98 | 3.172 | 66.62 | 17.32 |
| 300 | 56.05 | 3.204 | 66.72 | 17.43 |
| 400 | 59.45 | 5.224 | 72.51 | 22.81 |
| 500 | 62.62 | 7.728 | 78.08 | 27.10 |
| 600 | 65.64 | 10.59 | 83.32 | 30.46 |
| 800 | 71.27 | 17.22 | 92.80 | 35.27 |
| 1000 | 76.42 | 24.61 | 101.03 | 38.56 |
| 1500 | 87.52 | 45.24 | 117.68 | 43.33 |

These thermodynamic functions were calculated on the basis of the harmonic oscillator–rigid rotator approximation and may be somewhat in error, especially at the higher temperatures, because of neglect of the contributions of anharmonicity and other factors. Some values in the table are given to more significant figures than are warranted by their absolute accuracy, in order to retain the internal consistency of the several thermodynamic functions.

**Acknowledgments.**—The authors are indebted to J. S. Ball of the Petroleum and Oil-Shale Experiment Station, Bureau of Mines, Laramie, Wyo., and to the Socony Vacuum Oil Co., Paulsboro, N. J., for the samples of purified thiophene used in this work, and for analytical data on the samples. Helpful discussion of certain features of the vibrational assignment with Dr. Kenneth S. Pitzer of the University of California is gratefully acknowledged.

## Summary

The heat capacity of thiophene was measured over the temperature range 11–340° K. The solid has two lambda-type transitions at approximately 112 and 138° K., an isothermal transition at approximately 171.6° K., and a short region of anomalously high heat capacity on the high-temperature side of the latter transition. The heat of transition (152.4 cal./mole), heat of fusion (1215.5 ± 1.1 cal./mole), and the triple point (234.95 ± 0.05° K.) were measured.

The vapor pressure of thiophene was measured over the temperature range 0 to 120°, and the following equation was found to fit the vapor-pressure data: $\log_{10} P(\text{mm.}) = 6.95926 - 1246.038/(221.354 + t)$. The normal boiling point is 84.16°.

The heat of vaporization was measured at three different temperatures, and the values found were 8032, 7808 and 7522 cal./mole at 45.36, 63.08 and 84.16°, respectively.

The heat capacity of thiophene vapor was measured at five different temperatures in the range 343 to 472° K. The experimental values for $Cp°$, the heat capacity in the ideal gas state, may be represented by the equation $Cp° = -7.017 + 0.10045T - 6.325 \times 10^{-5}T^2$. An equation for the second virial coefficient, $B$, in the equation of state $PV = RT + BP$, was obtained from thermal data. The equation is $B$ (liters) $= -0.435 - 0.0172 \exp.(1200/T)$.

The entropy of liquid thiophene at 298.16° K. is 43.30 ± 0.10 cal./deg./mole. The entropy of the ideal gas at the normal boiling point (357.32° K.) and 1 atmosphere pressure is 70.04 ± 0.20 cal./deg./mole.

The heat of combustion of thiophene was determined. For the reaction at 298.16° K., $C_4H_4S(l) + 13/2\ O_2(g) + 0.7H_2O = 4\ CO_2(g) + H_2SO_4 \cdot 1.7H_2O$, $\Delta H_R = -667.19$ kcal./mole. The heat of formation of liquid thiophene is 19.52 kcal./mole and the heat of formation of the gas is 27.82 kcal./mole, both at 298.16° K.

A complete vibrational assignment was proposed for thiophene. Using this vibrational as-

(29) Wagman, Kilpatrick, Taylor, Pitzer and Rossini, *J. Research Natl. Bur. Standards*, **34**, 143 (1945).

(30) Schomaker and Pauling, THIS JOURNAL, **61**, 1769 (1939).

signment and other molecular structure data, values of the free energy function, heat-content function, entropy and heat capacity were calculated by the methods of statistical mechanics for various temperatures up to 1500° K.

BARTLESVILLE, OKLA. RECEIVED OCTOBER 1, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CHICAGO]

# Solubilization of Polar–Non-polar Substances in Solutions of Long Chain Electrolytes[1a]

BY WILLIAM D. HARKINS AND HANS OPPENHEIMER

## I. Introduction

Earlier work in this Laboratory[1b,2] on the effects of long chain alcohols and amines on both the X-ray bands and the critical micelle concentration of soap solutions indicates that their effects are very different from those of the hydrocarbons. This suggests that the locus in which the alcohols dissolve is also different, and thus that the relations exhibited in the solubilization of the alcohols should be different from those of the hydrocarbons.

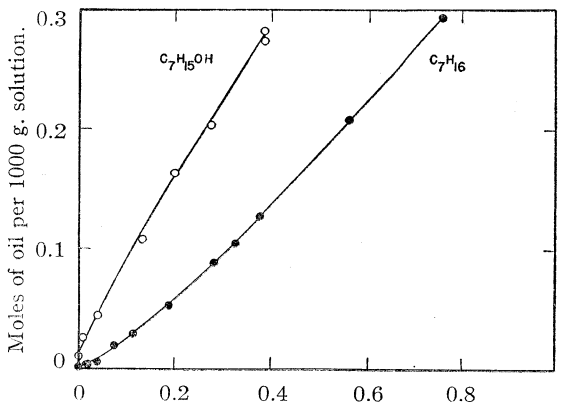



Fig. 1a.—Solubility of normal primary heptyl alcohol and of normal heptane in solutions of potassium dodecanate.

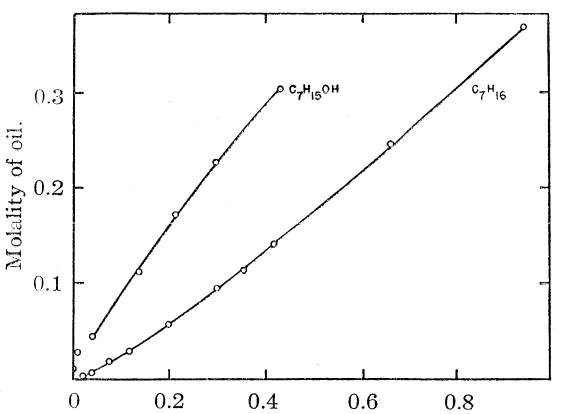



Fig. 1b.—Solubility of normal primary heptyl alcohol and of normal heptane in solutions of potassium tetradecanoate.

In Fig. 1a it is shown that the solubility in aqueous solutions of heptanol in aqueous solutions of potassium dodecanoate is twice as great as that of heptane at the higher soap concentrations. At low concentrations the ratio is much larger. In this figure the concentrations are given in moles per 1000 g. of the solution, but since the density of the soap solutions is, at all concentrations, very close to unity, these are very close to the molar concentrations. In Fig. 1b the concentrations are expressed in terms of molality, but the general relations remain as before.

The curve which represents the *non-polar* solubilization is, in both figures, convex toward the concentration axis. This is the usual relationship: the rate of increase of the non-polar solubilization with soap concentration, increases with soap concentration.

That which represents heptanol is concave toward the axis. Both curves are most highly curved just above the critical micelle concentration.

These curves indicate that, according to expectation, these two types of compounds exhibit two types of solubilization. These are considered further in a later section.

## II. Experimental Methods

The solubility of the mercaptans was determined by an amperometric method, according to Kolthoff.[3]

That of the amines, alcohols and acids was found by use of a turbidimetric method, in which a photometer was used to determine the turbidity. It was assumed as a criterion of solubility that as the saturation point is exceeded, the excess oil is emulsified and the solutions therefore become increasingly turbid.

To determine the solubility of an alcohol in a soap solution at one given concentration the following procedure was adopted. The soap solution was weighed into a glass ampule, a weighed amount of oil was added, and the ampule was sealed. At a constant soap concentration a series of ampules was prepared, each successive ampule

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(1a) This investigation was carried out under the sponsorship of the Reconstruction Finance Corporation, Office of Rubber Reserve, in connection with the Government's synthetic rubber program.

(1b) M. L. Corrin and W. D. Harkins, *J. Chem. Phys.*, **14**, 640 (1946).

(2) W. D. Harkins, R. W. Mattoon and R. Mittelmann, *ibid.*, **14**, 763 (1947).

(3) I. M. Kolthoff and V. A. Stanger, "Volumetric Analysis," Interscience Pub., New York, N. Y., 1942, p. 264.

containing an increasing amount of the alcohol. The samples were shaken vigorously for forty-eight hours or more in order to attain equilibrium. That equilibrium was actually obtained was shown by approaching saturation from both undersaturation and supersaturation in enough instances to make certain that the times allotted were more than sufficient.

At the end of the time the turbidity of the solutions was measured by the use of a photometer. For those samples in which the amount of alcohol added was below the saturation value the turbidity was equal to that of the original soap solution. When an excess of alcohol was present, the solutions exhibited a rapid increase of turbidity, caused by the appearance of emulsion droplets, with increase in the amount of alcohol. A plot was made of the turbidity against the amount of alcohol added, and the sharp break in the curve was considered as the saturation point. Fig. 2 shows the type of curve obtained upon addition of benzene to a 6.89% solution of potassium laurate. The method works well if there is a large difference between the refractive index of the alcohol and that of the soap solution.

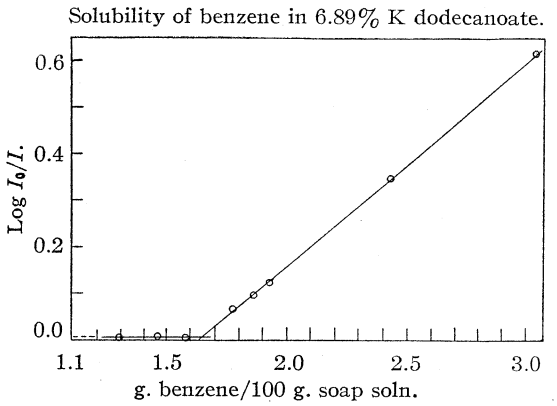



Fig. 2.—Turbidity of solutions of benzene in 6.89% potassium dodecanoate. The solubility is given by the intersection of the two straight lines.

The **soaps** were prepared as follows: No commercial soaps were used. The fatty acid (Eastman Kodak Co.) was dissolved in ethyl alcohol. This solution was slowly added to a hot solution of the base (usually KOH) in ethanol. The amount of base was about 10% more than the theoretical amount necessary for neutralization. On cooling, the soap crystallized. It was allowed to stand overnight and then was filtered off. It was purified by two or three recrystallizations from a mixture of ethyl alcohol and acetone. The final drying was done *in vacuo* over potassium hydroxide.

**Sodium dodecyl sulfate** (Procter and Gamble) was extracted with ether once or twice until it had lost its yellow appearance. Then it was recrystallized from 95% ethyl alcohol for two or three times. The crystals were very well formed. The drying was done *in vacuo* over potash.

The **alcohols** were obtained from Eastman Kodak Co. and Connecticut Hard Rubber Company, and were purified by fractional distillation, with the higher alcohols at a low pressure.

**III. Effect of Length of the Hydrocarbon Chain.**—The solubility of the *n*-long chain alcohols in solutions of potassium tetradecanoate is found to fall rapidly in the series, 7, 10, and 12 carbon atoms (Fig. 3). This is the general relation found for the hydrocarbons, but the solubilities exhibited here are in all cases much greater at the same chain length as pointed out earlier for heptane and heptanol.

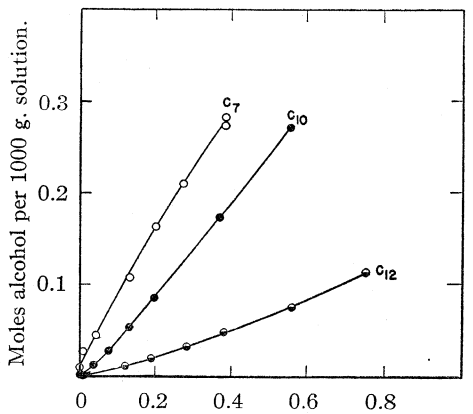
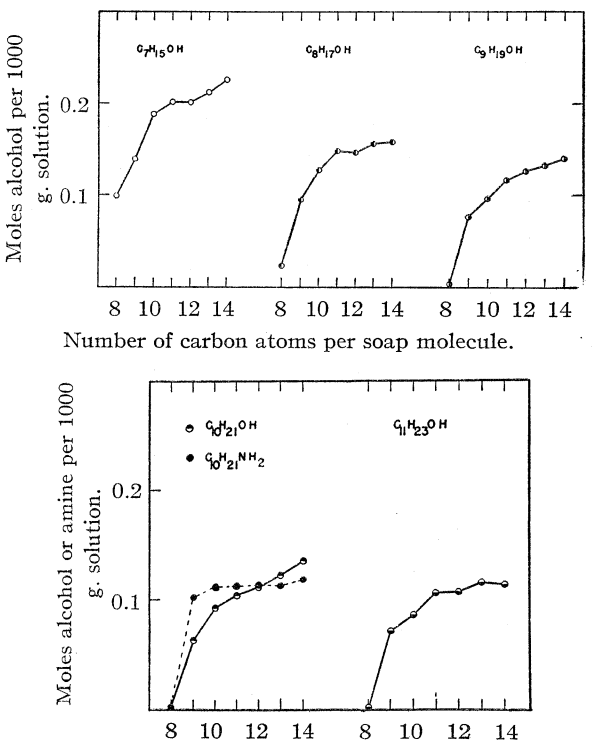



Fig. 3.—Solubility of heptanol, decanol and dodecanol (normal primary alcohols) in solutions of potassium tetradecanoate.

A general increase in the solubility of alcohols with chain length of the soap is exhibited in Figs. 4a and b, with soaps of from 8 to 14 carbon atoms. All alcohols, except heptanol, show by far the greatest increase between the 8 and the 9 carbon atom soap.




Figs. 4a and b.—Solubility of normal primary alcohols of 7 to 11 carbon atoms in solutions of soaps from 8 to 14 carbon atoms at 0.3 molar concentration.

A decrease in solubility with length of the hydrocarbon chain of the alcohol is brought out in

TABLE I

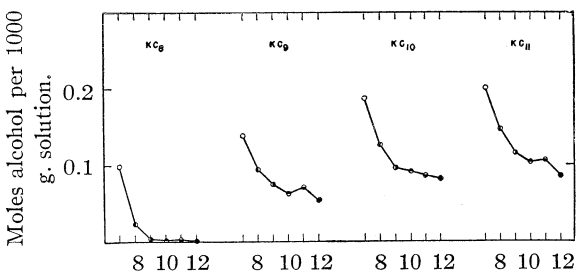
NON-POLAR SOLUBILIZATION OF *n*-HEPTANE IN POTASSIUM TETRADECANOATE

| $\left(\frac{\text{Grams soap}}{100\text{ g. soln.}} \times 100\right)$ % K-tetradecanoate | Moles K-tetradecanoate / 1000 g. solution | Soap molality | Grams oil / 1000 g. soap soln. | *n*-Heptane molality |
|---|---|---|---|---|
| $H_2O$ | ... | ... | 0.07 | 0.0007 |
| 0.50 | 0.019 | 0.019 | .39 | .0039 |
| 1.04 | .039 | .040 | .58 | .0059 |
| 2.03 | .076 | .078 | 1.92 | .0196 |
| 3.02 | .114 | .118 | 2.9 | .0298 |
| 5.04 | .189 | .199 | 5.3 | .0557 |
| 7.47 | .280 | .303 | 8.8 | .0956 |
| 8.69 | .326 | .357 | 10.5 | .115 |
| 10.0 | .376 | .418 | 12.7 | .141 |
| 14.9 | .560 | .658 | 21.0 | .246 |
| 20.1 | .757 | .948 | 29.5 | .369 |

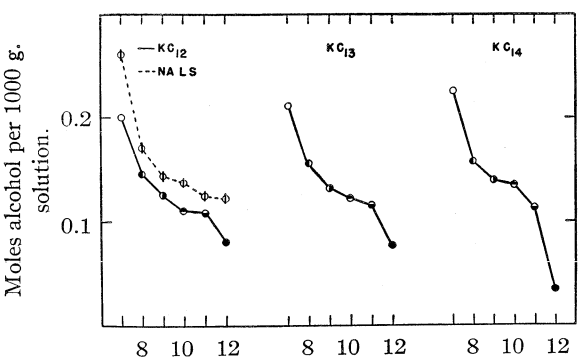
POLAR SOLUBILIZATION OF *n*-HEPTANOL IN POTASSIUM DODECANOATE

| $\left(\frac{\text{Grams soap}}{100\text{ g. soln.}} \times 100\right)$ % K-dodecanoate | Moles K-dodecanoate / 1000 g. solution | Molality | Moles alcohol / 1000 g. soap sol. | Molality alcohol |
|---|---|---|---|---|
| .... | 0.0 | .... | 0.0103 | 0.0103 |
| 0.206 | .0077 | 0.0077 | .026 | .026 |
| 1.056 | .0397 | .0401 | .044 | .044 |
| 3.511 | .132 | .137 | .108 | .112 |
| 5.32 | .200 | .211 | .163 | .172 |
| 7.315 | .275 | .297 | .210 | .227 |
| 10.268 | .386 | .430 | .273 | .304 |

Figs. 5a and b. In general the increase from 7 to 8 carbon atoms has by far the largest effect.




Concentration of soap: 0.3 molar.




Figs. 5a and b.—Effects of soaps from 8 to 14 carbon atoms in length upon the solubility of alcohols from 7 to 12 carbon atoms in length. Concentration of soap: 0.3 molar.

The data upon which the figures are based are assembled in Tables I to III.

TABLE II

SOLUBILITY OF ALCOHOLS IN SOLUTIONS OF POTASSIUM DODECANOATE AND TETRADECANOATE

| Moles $KC_{14}$ per 1000 g. soap solution | Moles alcohol per 1000 g. soap solution |
|---|---|
| *n*-Heptanol in potassium tetradecanoate | |
| ..(water) | 0.0103 |
| 0.00774 | .026 |
| .0397 | .044 |
| .132 | .108 |
| .200 | .163 |
| .275 | .210 |
| .386 | |
| *n*-Decanol in potassium tetradecanoate | |
| ..(water) | 0.0003 |
| 0.037 | .012 |
| .075 | .028 |
| .131 | .054 |
| .197 | .085 |
| .370 | .174 |
| .556 | .272 |

Figure 6 gives a few curves which illustrate the relationship between soap concentration and the solubility of non-polar oils,[4] in solutions of potassium tetradecanoate, with a curve for decanol added for comparison. From other experiments it is known that decanol is about twice as soluble as heptanol. With the 10 C atom chain the curva-

(4) R. S. Stearns, H. Oppenheimer, E. Simon and W. D. Harkins, *J. Chem. Phys.*, **15**, 496–507 (1947)

TABLE III

SOLUBILITY OF *n*-PRIMARY ALCOHOLS, AMINES AND MERCAPTANS IN SOLUTIONS OF DETERGENTS OF 0.3 MOLE PER 1000 G. SOLUTION (SOLUBILITY IN MOLES PER 1000 G. SOAP SOLUTION)

| Soap | $KC_8$ | $KC_9$ | $KC_{10}$ | $KC_{11}$ | $KC_{12}$ | $KC_{13}$ | $KC_{14}$ | Na dodecyl sulfate |
|---|---|---|---|---|---|---|---|---|
| | | | | Alcohol | | | | |
| $C_7H_{15}OH$ | 0.099 | 0.139 | 0.188 | 0.201 | 0.201 | 0.212 | 0.226 | 0.260 |
| $C_8H_{17}OH$ | .023 | .095 | .127 | .148 | .146 | .156 | .158 | .171 |
| $C_9H_{19}OH$ | .004 | .076 | .0965 | .1165 | .126 | .132 | .140 | .144 |
| $C_{10}H_{21}OH$ | .003 | .063 | .0923 | .104 | .111 | .122 | .136 | .138 |
| $C_{11}H_{23}OH$ | .003 | .072 | .0865 | .107 | .1075 | .116 | .114 | .125 |
| | | | | Amine | | | | |
| $C_{10}H_{21}NH_2$ | 0.004 | 0.102 | 0.11 | 0.113 | 0.113 | 0.113 | 0.119 | 0.110 |
| | | | | Mercaptan | | | | |
| $C_7H_{15}SH$ | 0.0007 | 0.0014 | 0.0102 | 0.0171 | 0.0393 | 0.0591 | 0.090 | 0.0925 |

ture is not so different from that in non-polar solubilization as with 7 C atoms.

**IV. Discussion. Solubilization of Polar-Nonpolar Long Chain Molecules.**—Papers on solubilization alone, such as that presented here and those of others,[5,6] give no evidence whatever to show where in the micelle polar–non-polar molecules are solubilized.

However, earlier work in this Laboratory[1b,2] and extensive X-ray investigations[7] give evidence, on the basis of the effects of long chain alcohols and amines on the X-ray bands and on the critical micelle concentration, which shows that the position and orientation of a polar–non-polar molecule is similar to that of a soap molecule. Thus the long polar–non-polar molecules are found to lie with their chains between those of the soap molecules, and their polar-hydrogen-bonding groups toward the water.

## Summary

The solubility relations exhibited by polar–non-polar long chain substances in solutions of long chain electrolytes are found to be different from those with non-polar compounds. The former are in general more soluble than the latter. The curve for *n*-heptanol is concave, that for *n*-heptane convex, toward the concentration axis. Curves which relate polar–non-polar solubility are given for all of the ordinary soaps of from 7 to 14 C atoms for all of the *n*-primary alcohols of from 7 to 11 C atoms.

The effects of long chain polar–non-polar molecules on the X-ray bands and on the critical micelle concentration as presented in other communications from this Laboratory indicate the locus of such molecules in the micelle. Their position is like that of the soap molecules in that their polar groups are oriented toward the water and their hydrocarbon chains lie between those of the soap.

No work on solubilization gives evidence for this point of view. It shows merely that whereas two types of solubility behavior are expected on the above basis, they are also found.

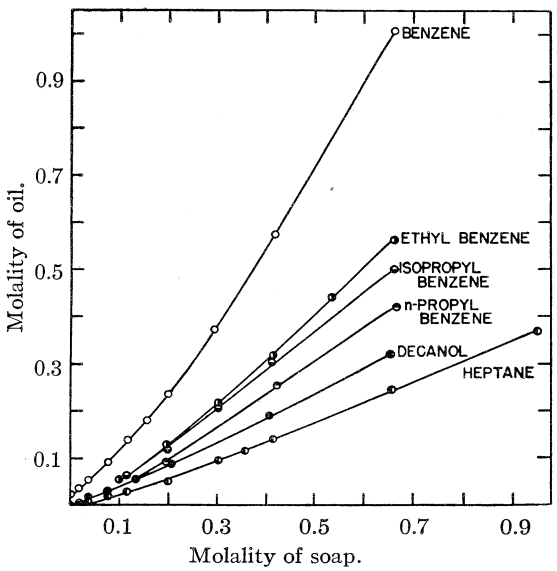



Fig. 6.—Solubility of decanol and of five hydrocarbons in solutions of potassium tetradecanoate.

(5) A. W. Ralston and D. N. Eggenberger, THIS JOURNAL, **70**, 983 (1948).

(6) P. H. Richards and J. W. McBain, *ibid.*, **78**, 1338 (1948). J. W. McBain and M. McHan, unpublished work, Chicago meeting, A. C. S., Sept. 1947.

(7) W. D. Harkins and R. Mittelmann, presented for publication.

ORIGINAL MANUSCRIPT RECEIVED MAY 28, 1948
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[CONTRIBUTION FROM MELLON INSTITUTE AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PITTSBURGH]

# Infrared Absorption of Hydroxy Compounds in Autoxidizing Linseed Oil[1]

BY F. J. HONN, I. I. BEZMAN AND B. F. DAUBERT

Infrared absorption measurements have been rather widely employed for routine analysis, industrial process control, and the elucidation of molecular structure and reaction mechanisms. Although the deterioration of rubber and other high polymers has been studied with the aid of infrared techniques,[2] there has been little information published demonstrating the application of these techniques to the problem of drying oil oxidation.[3]

Preliminary examination of the infrared spectrum of raw linseed oil before and after vigorous oxidation reveals a marked increase in the intensity of two absorption bands (Fig. 1). The first, a rather broad band at 10.2 $\mu$, is known to be characteristic of the general configuration R—CH=CH—R.[4] Its appearance during the oxidation process may result from the production of geometric isomers of the naturally occurring unsaturated fatty acids.[5] The second, a far more distinct band at 2.9 $\mu$, is said to be characteristic of the bonded hydroxyl group. In this instance, as in the many others, the wave length of the infrared absorption band is indicative of the nature of the absorbing group or configuration, while the intensity of absorption is dependent upon the concentration of that group.[6]

Because of its role in the autoxidation process, the hydroxyl band at 2.9 $\mu$ has been selected for further study. The degree of absorption at 2.9 $\mu$ and therefore the hydroxyl content of a drying oil do not vary uniformly with oxidation time. In Fig. 2, the 2.0–3.0 $\mu$ region has been scanned at several stages throughout the oxidation process.

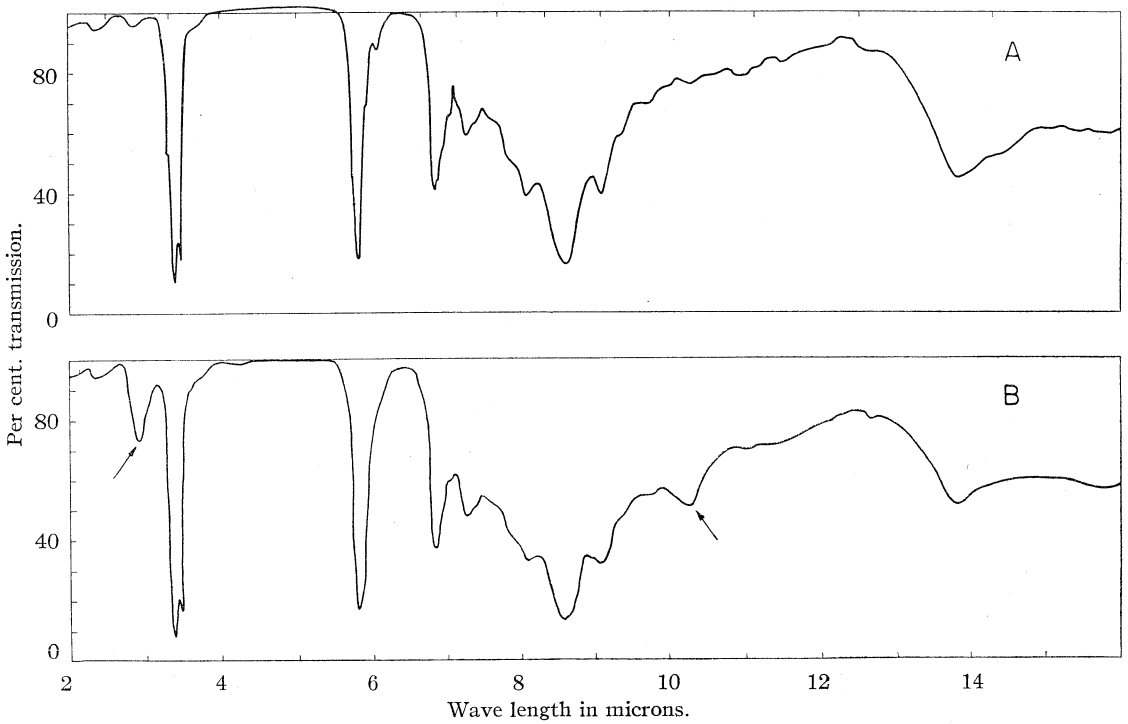



Fig. 1.—Infrared spectra of raw linseed oil: A, before oxidation; B, after oxidation.

During the induction period (zero to four hours), when oxygen uptake and peroxide formation are sluggish, the increase in intensity of absorption at 2.9 $\mu$ is correspondingly slow. At the end of the induction period, however, the 2.9 $\mu$ band quickly increases in intensity as the various oxidation reactions proceed at a rapidly accelerating pace.

In the autoxidation process there are formed several functionally distinct groups containing the (O–H) linkage, which can contribute to 2.9 $\mu$ absorption. They are (1) the hydroperoxide group (O–O–H), (2) the carboxy group (–CO–

(1) Contribution from the Multiple Fellowship on Cork sustained at Mellon Institute by the Armstrong Cork Co., Lancaster, Pa.

(2) J. O. Cole and J. E. Field, *Ind. Eng. Chem.*, **39**, 174 (1947).

(3) F. J. Kolb and E. A. Hauser, *Paint, Oil, Chem. Rev.*, **110**, No. 23, 104 (1947).

(4) R. B. Barnes, R. C. Gore, R. W. Stafford and V. Z. Williams, *Anal. Chem.*, **20**, 403 (1948).

(5) P. C. Rao and B. F. Daubert, THIS JOURNAL, **70**, 1102 (1948).

(6) R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120–140 (1947).

OH), (3) the simple alcoholic group (–C–OH), and (4) possibly other groups, such as that found in free liquid water (H–O–H). Classes (3) and (4) may be grouped conveniently as the "R–OH fraction."

Each of these hydroxy compounds can be accounted for by mechanisms usually advanced to explain drying oil autoxidation.[7–11] Farmer and co-workers[7–8] have demonstrated the formation of hydroperoxides by the attack of molecular oxygen upon the carbon alpha to a double bond. They have indicated, moreover, that such hydroperoxides may undergo further reaction with a carbon–carbon double bond to form epoxy and hydroxy derivatives.[9] More vigorous oxidation of the C=C linkage, of course, may result in its complete rupture, with the formation of carboxylic acids. Later in the oxidation process, particularly at elevated temperatures, water is released by the condensation of hydroxy derivatives to form polymers.[10] Other hydroxy substances, such as phospholipids and mucilages, are to be found in unrefined drying oils.[11]

Where associated in a mixture as complex as a raw drying oil, the various hydroxy components appear only as the single, broad 2.9 $\mu$ absorption band. Their individual peaks, occurring at closely neighboring wave lengths, are not resolved even by a high dispersion calcium fluoride prism.

Because the spectroscopic approach alone has failed to delineate the relative concentrations of the various hydroxy compounds, we have devised a combined chemical–spectroscopic method. Of the three types of hydroxy compounds mentioned, two can be estimated with considerable accuracy by chemical means. Hydroperoxides can be determined iodometrically and carboxylic acids by acid–base titration. In contrast, alcoholic hydroxyl analyses, such as the acetyl or Zerewitinoff procedures, do not yield reliable, unequivocal data in the presence of hydroperoxides. Furthermore, drying oils in the process of oxidation contain unstable substances, so that milder analytical techniques are desirable.

By means of the chemical–spectroscopic method, the so-called ROH fraction can be calculated by subtracting the sum of the hydroperoxide and carboxylic acid contributions, measured chemically, from the total hydroxyl content, measured optically. To perform this subtraction, the specific absorption coefficients of the (–OOH) and (–COOH) groups must be known, to permit conversion of their chemical concentrations to "optical concentrations."

From measurements of the optical densities of representative hydroxy compounds at several concentrations, it has been demonstrated that these compounds, in the range of concentrations encountered in an autoxidizing drying oil, obey Beer's law: $-\log T$ = optical density = $kcl$, where $k$ is specific absorption coefficient, a proportionality constant; $c$ is concentration of absorbing group, in g./l.; and $l$ is thickness of absorbing medium, in cm. From the data plotted in Fig. 3, these absorption coefficients have been calculated and expressed in appropriate units.

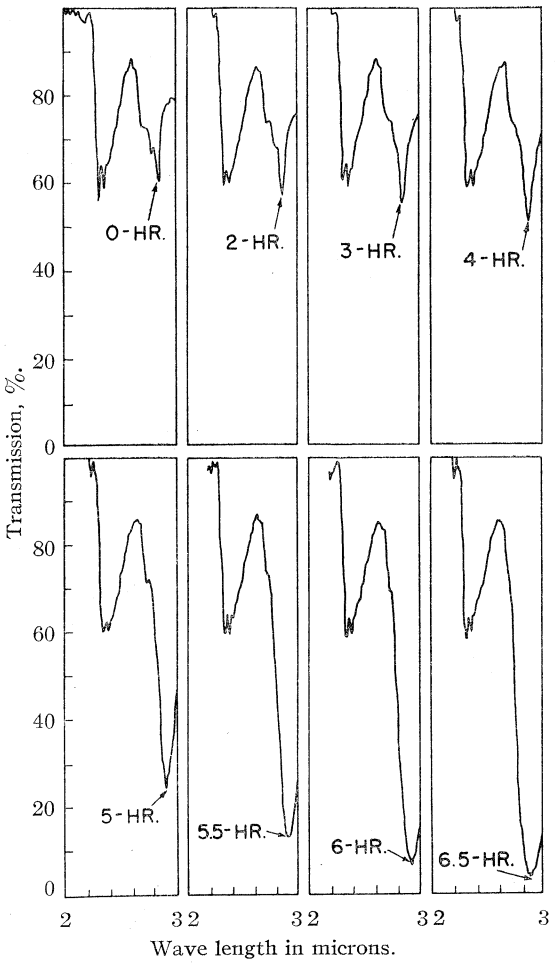



Fig. 2.—Changes in 2.9$\mu$ hydroxyl band during linseed oil autoxidation.

## Experimental

**Apparatus.**—All spectroscopic measurements for which data are presented were made on a Baird infrared recording spectrophotometer, equipped with a rock salt prism. Experiments involving the use of a calcium fluoride prism, however, were conducted with a Perkin–Elmer spectrometer. A quartz cell, of fixed 0.187 mm. thickness, proved convenient for autoxidized oils as well as solutions of representative hydroxy compounds. Because only the hydroxyl band at 2.9 $\mu$ was of immediate concern, the quartz cut-off near 4.0 $\mu$ did not interfere.

**Hydroxy Compounds.**—Ethyl myristate (Eastman Kodak Co., m.p. 10–12°) was employed as a stable, inert ester solvent for the various hydroxy compounds. Methyl

(7) E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, 119–122 (1943).

(8) D. A. Sutton, *ibid.*, 242–243 (1944).

(9) E. H. Farmer, G. F. Bloomfield, A. Sundralingam and D. A. Sutton, *Trans. Faraday Soc.*, **38**, 348–356 (1942).

(10) K. S. Markley, "Fatty Acids," Interscience Publishers, Inc., New York, N. Y., 1947, p. 324.

(11) A. E. Bailey, "Industrial Oil and Fat Products," Interscience Publishers, Inc., New York, N. Y., 1945, p. 22 ff.

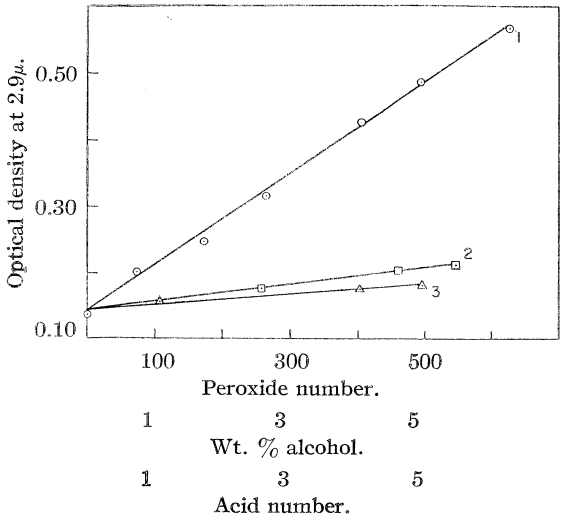



Fig. 3.—Optical densities of solutions of hydroxy compounds in ethyl myristate as a function of their concentrations: 1, methyl hydroperoxide oleate; 2, *n*-octadecanol; 3, palmitic acid.

hydroperoxide oleate was prepared[12] by ultraviolet irradiation and autoxidation of pure methyl oleate, and isolated by low-temperature crystallization. Its Wheeler peroxide number of 4200 indicated a purity of about 69%. The balance of the material was substantially unreacted methyl oleate. Palmitic acid (m.p., 61–62°) was highly purified by recrystallization from acetone. The alcohol employed was *n*-octadecanol, an Eastman Kodak Co. product of m.p. 56.5–58°.

**Procedure of Absorption Coefficient Measurement.**—Solutions of each of the hydroxy compounds were made to several known concentrations. The optical density of each solution was then determined at 2.9 μ (Table I); for each compound, optical density was plotted as a function of a concentration. The resulting linear relationships are shown in Fig. 3. Absorption coefficients were calculated from the slopes of these straight lines. By preparing several mixtures, calculating their total hydroxyl contents from the appropriate coefficients and comparing the values so obtained with observed optical densities (Table II), infrared absorption of the three compounds at 2.9 μ was shown to be an additive function of their concentrations. In every case, the deviation lay close to or within the ± 1% transmission error normally expected of the Baird instrument.

TABLE I

OPTICAL DENSITIES OF METHYL HYDROPEROXIDO OLEATE, PALMITIC ACID AND *n*-OCTADECANOL IN ETHYL MYRISTATE SOLUTION

| Wt. % COOH | Wt. % OOH | Wt. % OH | Acid no.[a] | Peroxide no.[b] | Optical density at 2.9μ |
|---|---|---|---|---|---|
| ....Ethyl myristate solvent only.... | | | | | 0.138 |
| 0.495 | ... | .. | 1.08 | ... | .155 |
| 1.84 | ... | .. | 4.03 | ... | .172 |
| 2.26 | ... | .. | 4.96 | ... | .180 |
| ... | 6.30 | .. | .. | 265 | .316 |
| ... | 9.63 | .. | .. | 404 | .426 |
| ... | 1.78 | .. | .. | 75 | .201 |
| ... | 11.7 | .. | .. | 492 | .484 |
| ... | 4.10 | .. | .. | 172 | .247 |
| ... | 14.9 | .. | .. | 627 | .567 |
| ... | ... | 5.44 | .. | ... | .210 |
| ... | ... | 2.57 | .. | ... | .174 |
| ... | ... | 4.60 | .. | ... | .202 |

[a] Defined as the mg. of potassium hydroxide required to neutralize free acids in a 1-g. sample. [b] Wheeler method; *cf.* K. S. Markley, *op. cit.*, p. 463.

(12) C. E. Swift, F. G. Dollear and R. T. O'Connor, *Oil and Soap*, **23**, 355–359 (1946).

TABLE II

ADDITIVITY OF INFRARED ABSORPTION OF HYDROXY COMPOUNDS

| Acid no. | Peroxide no. | Wt. % OH | Calcd. optical density equiv. to total OH content | Observed optical density at 2.9μ |
|---|---|---|---|---|
| ... | 166 | .. | 0.247 | 0.244 |
| ... | 389 | .. | .389 | .385 |
| 10.3 | 168 | .. | .312 | .305 |
| 5.57 | ... | 3.72 | .214 | .210 |
| 3.33 | 100 | 1.59 | .241 | .220 |
| 3.17 | 188 | 4.91 | .332 | .332 |

**Linseed Oil Oxidation.**—Raw linseed oil, in 1500-ml. quantities, was oxidized in a glass and stainless steel apparatus at 85° by passing dry air through the oil at the rate of 4000 ml./min. and vigorously agitating the oil with a beater rotating at 1725 r.p.m.

## Results and Discussion

The absorption coefficients determined for three representative hydroxy compounds are: (1) Palmitic acid, $k$ = 0.375/acid no.-cm.; (2) methyl hydroperoxido oleate, $k$ = 0.0364/peroxide no.-cm.; (3) *n*-octadecanol, $k$ = 0.675/wt. per cent.-cm.

In Fig. 4, a typical linseed oil autoxidation has been analyzed by means of the chemical–spectroscopic method. The total hydroxyl content has been divided into its three major components: R–OOH, R–COOH, R–OH. The concentration of each component, expressed in optical density, has been plotted as a function of oxidation time. The data from which the curves are drawn are assembled in Table III.

Curve 1 represents the change in total hydroxyl content, measured by infrared absorption at 2.9 μ. Curve 4 depicts the change in hydroperoxide concentration, determined chemically by the Wheeler method and converted to optical units by means of the absorption coefficient. Carboxylic acid optical concentrations, obtained similarly and then added to the hydroperoxide concentrations, yield curve 3. If curve 3 is subtracted point by point from curve 1, the resultant curve 2 indicates the change in the R–OH component.

Initially the R–OH fraction in a raw drying oil is a complex mixture of alcoholic hydroxy compounds, phospholipids, mucilages and water. As autoxidation proceeds, however, the increase in the R–OH component depicted in Fig. 4 can be ascribed only to an increase in the concentration of alcoholic hydroxy compounds. Although water is liberated in the process, its contribution to the 2.9 μ absorption band seems to be negligible. During the first stages of oxidation, linseed oil is

TABLE III

CONCENTRATIONS OF HYDROXY COMPOUNDS IN AN AUTOXIDIZING DRYING OIL

| Oxidation time, hr. | Total OH content | Peroxide no. | Peroxide O. D.[a] | Acid no. | Acid O. D. | Net ROH[b] |
|---|---|---|---|---|---|---|
| 0 | 0.26 | 5 | 0.02 | 3.0 | 0.02 | 0.22 |
| 1 | .26 | 13 | .03 | 2.9 | .02 | .21 |
| 2 | .27 | 20 | .03 | 2.9 | .02 | .22 |
| 3 | .27 | 27 | .04 | 3.0 | .02 | .21 |
| 4 | .29 | 38 | .045 | 2.9 | .02 | .225 |
| 4.5 | .. | 44 | .05 | 3.0 | .02 | ... |
| 5 | .31 | 50 | .055 | 3.0 | .02 | .235 |
| 5.5 | .31 | 59 | .06 | 3.2 | .02 | .23 |
| 6 | .32 | 72 | .07 | 3.0 | .02 | .23 |
| 6.5 | .36 | 98 | .09 | 3.1 | .02 | .25 |
| 7 | .43 | 161 | .13 | 3.2 | .02 | .28 |
| 7.5 | .55 | 260 | .20 | 3.6 | .025 | .325 |
| 8 | .72 | 368 | .27 | 4.2 | .03 | .42 |
| 8.5 | .79 | 402 | .295 | 4.8 | .035 | .46 |
| 9.5 | .92 | 382 | .28 | 5.8 | .04 | .60 |

[a] Values for peroxide optical density include the constant cell absorption of 0.02. [b] Net ROH = (total OH) − (peroxide O.D. + acid O.D.)

not sufficiently hydrophilic to dissolve an appreciable quantity of water. In one instance saturation of an unoxidized linseed oil with water raised the water content from 0.14 to 0.33% and the optical density at 2.9 $\mu$ from 0.276 to 0.284—a difference within the limits of error of the spectrophotometer. Saturation of an oxidized linseed oil, on the other hand, lifted the water content form 0.37 to 0.95%. But in this case the optical density at 2.9 $\mu$ was already so great that no increment could be detected.

During the induction period in a typical linseed oil autoxidation (zero to six hours in Fig. 4), no carboxylic acids are formed. Curves 3 and 4, therefore, are parallel. Since these curves rise at the same rate as the total hydroxyl content, the R–OH component remains substantially constant. It appears, on the basis of this evidence, that those peroxides formed during the induction period are essentially all hydroperoxides.

Later in the oxidation process, however, there is not as much assurance that all peroxides formed are of R–OOH type, because the Wheeler iodometric procedure, from which the R–OOH is derived, measures the sum total of all oxidizing compounds in the oil. The hydroperoxide values should then be regarded as maximum values.

During the "transition" period (six to eight hours in Fig. 4), the R–COOH contribution begins to increase, while the R–OOH component rises rapidly to a maximum. At the same time the total hydroxyl content rises even more rapidly, causing a sharp increase in the R–OH fraction. The transition period, then, is a time of rapid peroxide formation and decomposition.

As the drying oil begins to polymerize (over eight hours in Fig. 4), the rate of peroxide decomposition exceeds that of formation, while carboxylic acids continue to form. Curves 3 and 4, therefore, diverge, while the R–OH component rises even more sharply.

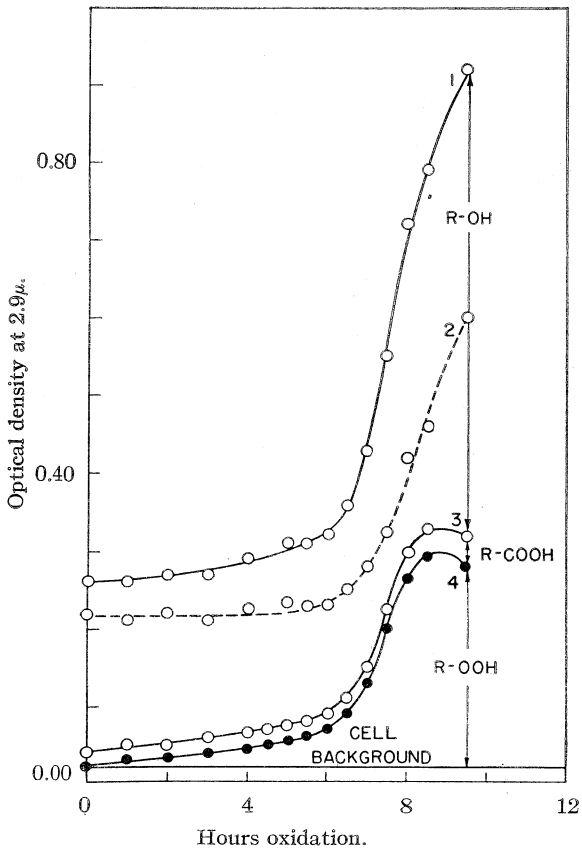



Fig. 4.—Analysis of a typical linseed autoxidation process: 1, total hydroxyl content; 2, net R–OH component; 3, sum of hydroperoxide and acid contributions; and 4, hydroperoxide contribution.

Infrared absorption measurements of autoxidizing drying oils at 2.9 $\mu$ serve as a rapid means of determining the end of the induction period, since the total hydroxyl content rises sharply at that point. In conjunction with chemical analyses, infrared techniques offer further confirmation of the role of hydroperoxides in autoxidation. It should now be possible to make use of the absorption coefficient reported for the alcoholic hydroxyl group and so determine the reaction products of peroxide decomposition.

**Acknowledgment.**—We wish to thank Messrs. J. H. Lieblich and R. B. Hannan of the Department of Research in Chemical Physics of Mellon Institute for their aid in making spectroscopic measurements.

## Summary

1. A combined chemical–spectroscopic analytical method has been devised to permit a detailed breakdown of the autoxidation reaction.

2. Infrared absorption coefficients have been

determined for three representative hydroxy compounds.

3. The role of hydroperoxides and their decomposition products in autoxidation has been further investigated.

PITTSBURGH, PENNSYLVANIA RECEIVED AUGUST 9, 1948

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[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

# Pyrolysis and Chlorinolysis of Some Perchlorinated Unsaturated Hydrocarbons[1]

BY J. A. KRYNITSKY AND H. W. CARHART

In earlier work,[2] it was shown that the pyrolysis of octachlorocyclopentene yields hexachlorocyclopentadiene, chlorine and small amounts of hexachlorobenzene. It has been reported[3] that both hexachloroethane and octachloropropane give carbon tetrachloride and tetrachloroethylene on thermal decomposition. Carbon tetrachloride and tetrachloroethylene have been reported[4] as being highly stable.

Prins[6,7] has shown that one mole of chlorine adds rapidly and quantitatively in sunlight to tetrachloroethylene, hexachloropropene and hexachlorocyclopentadiene without causing rupture of the carbon chain. On the other hand, hexachloroethane,[3] hexachloro-1,3-butadiene,[5] octachloro-1,3-pentadiene,[7,8] and octachlorocyclopentene,[2,8,9,10] have been reported either to resist the action of chlorine or, under drastic conditions, to be cleaved by it.

In the present work, tetrachloroethylene, hexachloropropene, hexachloro-1,3-butadiene and octachloro-1,3-pentadiene were subjected both to vapor phase pyrolysis and to the action of chlorine at temperatures up to 500°. In addition, hexachloropropene and octachloro-1,3-pentadiene were exposed to prolonged heating in the liquid state at their reflux temperatures and to chlorination under similar conditions. Small samples of two isomeric $C_6Cl_8$ compounds having melting points of 43–44° and 182–183° were also decomposed at 500°, and a sample of hexachloro-1,3-butadiene was treated with chlorine in bright sunlight for an extended period of time.

## Results and Discussion

**Pyrolyses.**—Both tetrachloroethylene and hexachloro-1,3-butadiene were found to be quite thermostable as no pyrolysis products were found on heating at 500°.

Hexachloropropene was recovered unchanged after a six-hour reflux (210–213° pot temperature). Vapor phase pyrolysis became appreciable at temperatures over 400° and yielded carbon tetrachloride, tetrachloroethylene and hexachloroethane as the major products. The amounts of these products obtained are summarized in Table I. In addition to these, a minor quantity of hexachlorobenzene was isolated from the 490–500° pyrolysis but not at the lower temperatures. A compound, $C_6Cl_8$ (m. p. 43–44°), was also obtained from the products of pyrolysis at 450–460° and 490–500°. It is believed that this compound is the same as the $C_6Cl_8$ (m. p. 45°) prepared by Prins[11] to which he assigns the structure 1-(trichloromethyl)-pentachloro-2,4-cyclopentadiene. In the pyrolysis of hexachloropropene, carbonization was insignificant and very little, if any, chlorine was evolved. In contrast to hexachloropropene, prolonged refluxing decomposed octachloro-1,3-pentadiene completely. The principal products of the reflux and vapor phase pyrolyses were carbon tetrachloride, hexachloro-1,3-butadiene and hexachlorocyclopentadiene. The amounts of these compounds and hexachlorobenzene found are given in Table II. Small amounts of hexachloroethane were obtained from the vapor phase but not from the reflux pyrolyses. Traces of tetrachloroethylene were found in all but the 400–410° pyrolyses. Two other compounds, octachlorocyclopentene and $C_6Cl_8$ (m. p. 182–183°) were isolated from the products of the reflux pyrolysis. The latter compound was shown to be identical with a $C_6Cl_8$ compound prepared by Prins[6] to which he assigns the probable structure 1-(dichloromethylene)-hexachloro-2-cyclo-

TABLE I

PRINCIPAL PYROLYSIS PRODUCTS OF HEXACHLOROPROPENE

| Temp., °C. | Moles product/mole starting material | | | |
|---|---|---|---|---|
| | $CCl_4$ | $C_2Cl_4$ | $C_2Cl_6$ | $C_3Cl_6$ (recovered) |
| Reflux[a] | 0 | 0 | 0 | *ca.* 1 |
| 400–410 | Trace | 0.03 | 0.01 | 0.94 |
| 450–460 | 0.04 | .28 | .12 | .57 |
| 490–500 | .11 | .67 | .21 | Trace |
| 490–500 | .14 | .70 | .24 | Trace |

[a] Refluxed six hours. Pot temperature, 210–213°.

(1) The opinions contained in this paper are the authors' and are not to be construed as official or reflecting the views of the Department of the Navy.

(2) Krynitsky and Bost, THIS JOURNAL, **69**, 1918 (1947).

(3) McBee, Hass, *et al.*, *Ind. Eng. Chem.*, **33**, 176 (1941).

(4) Hurd, "The Pyrolysis of Carbon Compounds," Reinhold Publishing Corp., New York, N. Y., 1929, p. 132. It is also stated that hexachloro-1,3-butadiene is quite thermostable; however, Fruhwirth[5] has shown that the compound previously thought to have been hexachloro-1,3-butadiene was in all probability octachlorocyclopentene.

(5) O. Fruhwirth, *Ber.*, **74B**, 1700 (1941).

(6) H. J. Prins, *J. prakt. Chem.*, **89**, 414 (1914).

(7) H. J. Prins, *Rec. trav. chim.*, **65**, 455 (1946).

(8) Bost and Krynitsky, THIS JOURNAL, **70**, 1027 (1948).

(9) McBee, Hass and Pierson, *Ind. Eng. Chem.*, **33**, 181 (1941).

(10) McBee, Hass and Bordenca, *ibid.*, **35**, 317 (1943).

(11) H. J. Prins, *Rec. trav. chim.*, **65**, 184 (1946).

TABLE II

PRINCIPAL PYROLYSIS PRODUCTS OF OCTACHLORO-1,3-PENTADIENE

| Temp., °C. | Moles product/mole starting material $CCl_4$ | $C_4Cl_6$ | $C_5Cl_6$ | $C_6Cl_6$ | $C_5Cl_8$ (recov.) |
|---|---|---|---|---|---|
| Reflux[a] | 0.32 | 0.55 | 0.08 | 0.22[b] | 0 |
| 400–410 | .01 | .03 | .04 | 0 | 0.86 |
| 450–460 | .22 | .36 | .30 | .02 | .25 |
| 490–500 | .37 | .42 | .39 | .08 | 0 |

[a] Refluxed five hours. Pot temperature, 261–279°. [b] Combined $C_6Cl_8$ and $C_6Cl_6$. Calcd. as $C_6Cl_7$.

pentene.[11] In the pyrolyses of octachloro-1,3-pentadiene, small amounts of chlorine were evolved; however, carbonization was insignificant.

When small samples of the two $C_6Cl_8$ isomers (m. p. 43–44° and 182–183°) were heated at 500°, hexachlorobenzene and chlorine were found to be the major products. However, the pyrolysis of the 43–44° compound was not as complete as that of the 182–183° isomer.

TABLE III

CHLORINOLYSIS PRODUCTS OF TETRACHLOROETHYLENE

| Temp., °C. | Moles product/mole starting material $C_2Cl_6$ | $C_2Cl_4$ (recovered) |
|---|---|---|
| 350–360 | Trace | 0.99 |
| 400–410 | 0.01 | .96 |
| 490–500 | .06 | .91 |

TABLE IV

CHLORINOLYSIS PRODUCTS OF HEXACHLOROPROPENE

| Temp., °C. | Moles product/mole starting material $CCl_4$ | $C_2Cl_4$ | $C_2Cl_6$ | $C_3Cl_6$ (recovered) |
|---|---|---|---|---|
| Reflux[a] | 0.32 | 0.44 | 0 | 0.50 |
| 300–310 | .08 | .09 | 0 | .88 |
| 350–360 | .62 | .69 | 0.02 | .26 |
| 400–410 | .92 | .96 | .04 | 0 |
| 490–500 | .90 | .90 | .12 | 0 |

[a] Refluxed seven hours. Pot temperature, 207–211°.

TABLE V

PRINCIPAL CHLORINOLYSIS PRODUCTS OF OCTACHLORO-1,3-PENTADIENE

| Temp., °C. | Moles product/mole starting material $CCl_4$ | $C_4Cl_6$ | *Cycl.* $C_5Cl_6$ | *Cycl.* $C_5Cl_8$ | $C_5Cl_8$ (recov.) |
|---|---|---|---|---|---|
| Reflux[a] | [b] | 0.61 | Trace | 0.18 | 0 |
| 350–360 | 0.13 | .14 | 0.05 | [c] | .79[d] |
| 400–410 | .56 | .59 | .20 | [c] | .16[d] |
| 490–500 | .60 | .62 | .27 | 0.04 | 0 |

[a] Refluxed seven hours [b] 0.48 found. An additional undetermined amount lost during recovery. [c] Undetermined. [d] Contains unknown amount of octachlorocyclopentene

**Chlorinolyses.**—Tetrachloroethylene was found to be stable toward chlorinolysis at temperatures up to 500° as no carbon tetrachloride was found. However, as shown in Table III, addition of chlorine did occur to a limited extent.

Hexachloro-1,3-butadiene was found to be inert to chlorination in the dark since no reaction products were found even at 500°. On the other hand, prolonged exposure to chlorine in bright sunlight at 10–20° cleaved this compound to hexachloroethane.

As may be seen in Table IV, the principal products of both the reflux and vapor phase chlorinolyses of hexachloropropene were found to be carbon tetrachloride and tetrachloroethylene. The vapor phase reaction became appreciable at temperatures above 300° and was complete at 400–410°. Small amounts of hexachloroethane were also found at the higher temperatures. In addition to the compounds mentioned, the reflux chlorinolysis produced a small amount of higher boiling material which was not identified.

Both reflux and vapor phase chlorinolyses of octachloro-1,3-pentadiene yielded carbon tetrachloride and hexachloro-1,3-butadiene as the major products. Lesser amounts of hexachlorocyclopentadiene and octachlorocyclopentene were also isolated from these reactions. The amounts of products obtained are summarized in Table V. In addition to these compounds, small quantities of tetrachloroethylene were found in all but the 350–360° reaction. Small amounts of hexachlorobenzene were also isolated from the reflux and 490–500° chlorinolyses.

In all reactions involving chlorine, carbonization was insignificant. The vapor phase chlorinolyses of both hexachloropropene and octachloro-1,3-pentadiene were observed to be exothermic. It is noteworthy that the chlorinolysis of these compounds is essentially complete at 400–410°. This is in contrast to their simple pyrolysis where decomposition is only slight at this temperature. There is insufficient evidence to substantiate complete mechanisms for these reactions; however, the results indicate that they probably proceed through free radical chain reactions involving several steps.

It was observed that hexachlorocyclopentadiene has a strong tendency to supercool. By using a Dry Ice-bath, however, two different crystalline forms may be obtained. One of these melts at 10–10.8° and the other at −0.8 to −0.2°. The lower melting form is converted to the higher melting form by sudden strong cooling (liquid air) or by seeding with a small crystal of the latter. In view of this and the fact that the higher melting form is the one more frequently obtained on freezing, it is indicated that it is the more stable form. Samples of both crystalline forms have remained unchanged when kept for several months at a temperature a few degrees below their melting points.

## Experimental

**Materials.**—Hexachloropropene (b.p. 140–142° at 100 mm.) and octachloro-1,3-pentadiene (b.p. 139–140° at 10 mm.) were prepared through condensation and dehydrohalogenation reactions from chloroform, tetrachloroethylene and trichloroethylene as described by Prins.[6,7,12] Hexachloro-1,3-butadiene (b.p. 142–144° at 100 mm.) was obtained from the pyrolysis and chlorinolysis products

(12) H. J. Prins, *ibid.*, **51**, 1065 (1932).

of octachloro-1,3-pentadiene. The two $C_6Cl_8$ compounds (m. p. 43–44° and 182–183°) were obtained from the pyrolysis products of hexachloropropene and octachloro-1,3-pentadiene.

**Vapor Phase Pyrolyses.**—In general, the vapor phase pyrolyses of tetrachloroethylene, hexachloropropene, hexachloro-1,3-butadiene and octachloro-1,3-pentadiene were carried out at 400, 450 and 500° by passing approximately 200 g. of compound through a 20-mm. Pyrex tube heated over a 30-cm. zone. The rate was adjusted so that the passage was between 70 and 120 g. per hour. This resulted in contact times which varied from twelve to fifteen seconds for the first three compounds and sixteen to twenty-four seconds for the last. All pyrolyses involving hexachloropropene and octachloro-1,3-pentadiene were carried out in the dark to prevent photocatalytic action of chlorine should it be formed. When evolution of chlorine was detected, it was removed from the warmed products by air aspiration in the dark using suitable traps for retaining volatile components. The pyrolysis of hexachloropropene at 500° will serve to illustrate the method used.

Two hundred grams of hexachloropropene was passed dropwise, in the dark, over a period of two hours through the tube set at a slight incline and electrically heated to 490–500°. The product which was collected in an ice-cooled receiver weighed 199 g., was red in color and contained some solid material. During the pyrolysis, tests of the exit vapors with potassium iodide paper showed that very little, if any, chlorine was evolved. Fractionation of the product through a 17 mm. × 60 cm. helix-packed column gave the following principal fractions: (1) 14 g. b.p. 77–78°, (2) 6 g. b.p. 78–120°, (3) 90 g. b.p. 120–122°, (4) 44 g. (solid) b.p. 123–130° (100 mm.), (5) 5 g. b.p. 130–150° (100 mm.), and (6) 17 g. b.p. 164–165° (20 mm.).

Fraction 1 was carbon tetrachloride and fraction 3 was tetrachloroethylene. Refractive index measurements showed fraction 2 to be composed of approximately 3 g. each of carbon tetrachloride and tetrachloroethylene. Fraction 4 was hexachloroethane which was collected as a solid in the still head. An additional 2 g. of hexachloroethane was obtained by cooling the intermediate fraction 5. Fraction 6 solidified on standing to a reddish-orange solid melting at 36–40°. Two recrystallizations from ethanol yielded 10 g. of a white compound melting at 43–44°, which was not changed by further treatment. Analyses showed this compound to be $C_6Cl_8$. *Anal.* Calcd. for $C_6Cl_8$: Cl, 79.74; mol. wt., 355.8. Found: Cl 79.7, 79.4; mol. wt., 354.

Ten grams of hexachlorobenzene was isolated from the fractionation residue by crystallization using carbon tetrachloride and ethanol.

**Reflux Pyrolysis.**—Octachloro-1,3-pentadiene (152 g.) was placed in a still pot fitted to a 17 mm. × 60 cm. helix-packed column connected to an ice-cooled receiver. The column jacket was maintained at 200–215° by an external heater. The material was heated for five hours in the dark at the end of which time reaction seemed to be complete. During this period, the pot temperature varied between 261 and 279° and a slight amount of chlorine was detected in the exit vapors. The free chlorine was removed from the warmed distillate (in the dark) by aspirating dry air through it until the effluent air gave a negative test for chlorine. A reflux condenser and efficient ice-cooled trap was used to prevent loss of volatile materials. The product obtained was combined with the residue in the still pot. Fractionation yielded the following principal fractions: (1) 22 g. b.p. 77–78°, (2) 1 g. b.p. 58–65° (100 mm.), (3) 58 g. b.p. 141–145° (100 mm.), (4) 8 g. b.p. 145–160° (100 mm.), (5) 7 g. b.p. 117–121° (20 mm.), (6) 12 g. b.p. 157–163° (20 mm.), and (7) 28 g. residue.

Fraction 1 was carbon tetrachloride. Fraction 2 was shown to be chiefly tetrachloroethylene by chlorination to hexachloroethane. On refractionation of fraction 3, the main bulk distilled at 143.0–143.1° (100 mm.). This was identified as hexachloro-1,3-butadiene through its physical constants which are in good agreement with those previously reported[5] and by analyses: b.p. 213° (775 mm.), 123° (50 mm.), 101° (20 mm.); m.p. −20 to −19°; $n^{20}D$ 1.5558, $n^{25}D$ 1.5535; $d^{20}_4$ 1.6804. *Anal.* Calcd. for $C_4Cl_6$; Cl, 81.58; mol. wt., 260.8; *MR*, 48.94.[13] Found: Cl, 81.3, 81.6; mol. wt., 262; *MR*, 49.87.

Fraction 5 was identified as hexachlorocyclopentadiene by comparison with a known sample. Purified hexachlorocyclopentadiene has the following properties in addition to those given previously:[2,7,14] b.p. 163.6–163.8° (100 mm.), m.p. 10–10.8° and −0.8 to −0.2°, $n^{20}D$ 1.5647.

Refractive index measurements of fraction 4 showed it to be composed of approximately 5 g. hexachloro-1,3-butadiene and 3 g. hexachlorocyclopentadiene. On crystallizing fraction 6 from ethanol and carbon tetrachloride, there was obtained 3 g. of a compound m. p. 182–183° and 7 g. of octachlorocyclopentene. The 182–183° compound was shown to be identical to the $C_6Cl_8$ compound obtained by the action of copper on hexachloropropene, by a mixed melting point and by hydrolysis to a diketone[6] which melted at 226–228° (sealed tube).

Fractional crystallization of the 28 g. of residue from ethanol–carbon tetrachloride yielded several grams each of the $C_6Cl_8$ compound and hexachlorobenzene.

**Pyrolyses of $C_6Cl_8$ Compounds at 500°.**—Four grams of the 43–44° isomer was melted over four to five minutes into the heated zone (8 mm. × 30 cm.) of a Pyrex tube set at a slight incline. During this time, the exit vapors gave a strong test for chlorine. The pyrolysis product was a solid which when worked up with ethanol–carbon tetrachloride yielded approximately 1 g. of hexachlorobenzene. In addition, approximately 1.5 g. of $C_6Cl_8$ was recovered.

In a like fashion, 4 g. of the 182–183° isomer evolved chlorine and yielded approximately 2 g. of hexachlorobenzene and a very small amount of liquid which was not identified. None of the original $C_6Cl_8$ could be recovered.

**Photochlorinolysis of Hexachloro-1,3-butadiene.**—A 12.7-g. sample of hexachloro-1,3-butadiene was placed in a Pyrex test-tube fitted with a gas bubbler tube. The system was exposed to direct sunlight and chlorine was admitted in a slow stream. During this time, the ambient temperature varied from 10 to 20°. The reaction was stopped after a total of sixteen hours as the material had become semisolid. After removal of the unreacted chlorine by air aspiration through the warmed mixture, the sample showed a gain in weight of 6.3 g. The solid reaction product was identified as hexachloroethane.

**Vapor Phase Chlorinolyses.**—In general the vapor phase chlorinolyses of tetrachloroethylene, hexachloropropene, hexachloro-1,3-butadiene and octachloro-1,3-pentadiene were carried out in the dark at various temperatures up to 500° by passing approximately 200 g. of compound through a 20-mm. Pyrex tube heated over a 30 cm. zone. An ice-cooled receiver was used for collection of the products. Chlorine gas was admitted at a rate such that a bubbler at the end of the system indicated that an excess was always present. The rate of compound addition was between 70 and 120 g. per hour. Unreacted chlorine was removed from the warmed products (in the dark) by air aspiration using suitable traps to retain volatile components. The methods used for separation and identification of the products were the same as those given earlier.

**Reflux Chlorinolyses.**—The reflux chlorinolyses of hexachloropropene and octachloro-1,3-pentadiene were carried out in a manner similar to the reflux pyrolysis of the latter compound except that an excess of chlorine was maintained in the system by bubbling the gas into the liquid. The products were analyzed by methods already described.

## Summary

1. Tetrachloroethylene and hexachloro-1,3-

(13) Does not include value for exaltation due to conjugation.

(14) The melting point in ref. 2 was listed erroneously as −10 to −9° rather than 9–10°.

butadiene were found to be stable at a temperature of 500°.

2. The pyrolysis of hexachloropropene yielded principally carbon tetrachloride, tetrachloroethylene, and hexachloroethane. Smaller amounts of hexachlorobenzene and a compound $C_6Cl_8$ (m. p. 43–44°) were obtained under some conditions.

3. The pyrolysis of octachloro-1,3-pentadiene yielded principally carbon tetrachloride, hexachloro-1,3-butadiene and hexachlorocyclopentadiene. Smaller amounts of tetrachloroethylene, hexachloroethane, octachlorocyclopentene, hexachlorobenzene and a compound $C_6Cl_8$ (m. p. 182–183°) were obtained under some conditions.

4. The pyrolysis of two $C_6Cl_8$ compounds (m. p. 43–44° and 182–183°) yielded chiefly hexachlorobenzene and chlorine.

5. Hexachloro-1,3-butadiene yielded hexachloroethane slowly on chlorinolysis in sunlight at 10–20°. In the dark, it was found to resist the action of chlorine at a temperature of 500°.

6. Tetrachloroethylene was found to be stable to thermal chlorinolysis at temperatures up to 500°; however, small amounts of hexachloroethane were produced by addition of the halogen.

7. Thermal chlorinolysis of hexachloropropene yielded principally carbon tetrachloride and tetrachloroethylene and smaller amounts of hexachloroethane.

8. Thermal chlorinolysis of octachloro-1,3-pentadiene yielded carbon tetrachloride and hexachloro-1,3-butadiene as the principal products and lesser amounts of hexachlorocyclopentadiene and octachlorocyclopentene. Small amounts of tetrachloroethylene and hexachlorobenzene were also obtained under some conditions.

WASHINGTON, D. C. RECEIVED AUGUST 19, 1948

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[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

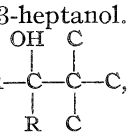
# Hydrocarbons. IX.[1] 2,2,4-Trimethylheptane, 2,2,4-Trimethyloctane, 2,2,4,6-Tetramethylheptane and 2,2,4,5,5-Pentamethylhexane

BY GEORGE W. MOERSCH[2] AND FRANK C. WHITMORE[3]

In a continuation of previous work the present paper reports the syntheses of a decane and three undecanes containing the neopentyl system, and the determination of several of their physical constants.

With some exceptions, the hydrocarbons were prepared by catalytic hydrogenation of the olefins resulting from dehydration of the tertiary alcohols, 2,2,4-trimethyl-4-heptanol, 2,2,4-trimethyl-4-octanol, 2,2,4,6-tetramethyl-4-heptanol, and 2,2,3,-5,5-pentamethyl-3-hexanol. In the case of 2,2,-3,5,5-pentamethylhexane, the alcohol was prepared by two different methods and the olefins were also obtained by a Kolbe electrolysis of Butlerow's beta acid, methyl-*t*-butylneopentylacetic acid.

The reactions involved in these syntheses are not of the type usually accompanied by rearrangement[4] except for the dehydration of 2,2,3,5,5-pentamethyl-3-heptanol.[5] Structures similar to the latter,



always rearrange to a small degree, about 5% under the conditions employed here,[4] and it is therefore reasonable to assume that the 2,2,3,5,5-pentamethylheptane contains some 2,3,3,5,5-pentamethylheptane. This contamination from a closely related isomer could not be expected to affect appreciably the physical properties of the compound. This was substantiated when the electrolysis of Butlerow's beta acid gave material that checked the product made by dehydration of the alcohol.

The decane, 2,2,4-trimethylheptane, is mentioned in the literature[6] in connection with the investigation of impurities in isoöctane. From still residues there was isolated a material of b. p. 151.97° at 760 mm., $d^{20}$ 0.7349, $n^{20}_D$ 1.41278. It was suggested that this compound was either 2,2,4- or 2,2,5-trimethylheptane. The physical properties of the 2,2,4-trimethylheptane reported in this paper are not in agreement with the values found for the above material.

## Experimental

Distillations were made through columns of the adiabatic, total reflux, variable take-off type, packed with (A) one-eighth inch glass helices, packed section 1.7 × 67 cm., 11 theoretical plates, (B) three thirty-second inch stainless steel helices, 1.0 × 100 cm., 25 theoretical plates, and (C) one-sixteenth inch stainless steel helices, 1.0 × 100 cm., 65 theoretical plates.

**2,2,4-Trimethylheptane.**—A typical preparation of methyl neopentyl ketone is given.[7] Sodium dichromate

(1) For previous papers of this series see: Whitmore, Marker and Plambeck, THIS JOURNAL, **63**, 1626 (1941); Whitmore and Southgate, *ibid.*, **60**, 2571 (1938); Whitmore and Orem, *ibid.*, 2573; Whitmore, Fleming, Rank and Larson, *ibid.*, **56**, 749 (1934); Whitmore and Laughlin, *ibid.*, **55**, 5056 (1933); Whitmore and Fleming, *ibid.*, 3803; Whitmore, Stehman and Herndon, *ibid.*, 3807; Laughlin and Whitmore, *ibid.*, 2607.

(2) Present address: Research Department, Parke, Davis and Co., Detroit, Michigan.

(3) Deceased.

(4) Unpublished work, this Laboratory.

(5) Whitmore and Laughlin, THIS JOURNAL, **54**, 4011 (1932).

(6) Brooks, Cleaton and Carter, *J. Research Natl. Bur. Standards*, **19**, 319 (1937).

(7) The authors are indebted to Dr. Sutherland for preparation of the methyl neopentyl ketone: L. H. Sutherland, Ph.D. Thesis, Penn State, 1942.

TABLE I

SUMMARY OF PHYSICAL PROPERTIES

| Hydrocarbon | B. p., °C., 760 mm. | $dt/dp$, 760 mm. | $n^{20}D$ | $dn/dt$ | $d^{20}_4$ | $dd/dt$ | Viscosity, centipoises at 20° | 30° | 40° |
|---|---|---|---|---|---|---|---|---|---|
| 2,2,4-Trimethylheptane | 149.4 | 0.05° | 1.4092 | 0.00042 | 0.7275 | 0.00076 | 0.554 | 0.482 | 0.421 |
| 2,2,4-Trimethyloctane | 171.5 | .05° | 1.4149 | .00041 | .7381 | .00074 | .730 | .624 | .539 |
| 2,2,4,6-Tetramethylheptane | 162.2 | .05° | 1.4121 | .00041 | .7335 | .00075 | .681 | .590 | .510 |
| 2,2,4,5,5-Pentamethylhexane | 166.0 | .05° | 1.4214 | .00041 | .7519 | .00074 | 1.045 | .876 | .741 |

dihydrate, 59 kg., diisobutylene (Rohm & Haas), 207 kg. and 80 liters of water were charged to a 50-gallon glass-lined Pfaudler kettle. Sulfuric acid, 45 liters, was added over a period of thirty-six hours while cold water was passed through the jacket of the reactor, keeping the temperature at 30–40°. Stirring was continued for an additional two hours and then the oxidation product steam-distilled from the kettle, giving 13.4 kg. of organic material. The oil layer was treated with 1.82 kg. of sodium hydroxide, the neutral products siphoned off, 10.22 kg., and the organic acids regenerated with sulfuric acid, yield 2.85 kg. The neutral products were fractionated to give 8.03 kg. (38%) of methyl neopentyl ketone, b. p. 126°, $n^{20}D$ 1.4030–1.4036.

Five moles, 120 g., of magnesium turnings was weighed into a three-liter flask and four moles, 492 g., of *n*-propyl bromide added in four portions of 500 ml. of anhydrous ether each. Addition was completed in five and a half hours, yield 98%. Two moles, 228 g., of methyl neopentyl ketone was added with stirring during one and a half hours, the mixture refluxed for three hours and then decomposed by pouring into 2 l. of cracked ice. A fine suspension resulted which was coagulated by distilling of about 1.5 l. of ether. The entire mass of precipitated salts was washed by decantation with four portions of ether totalling 2.5 l. The ether solution was concentrated by distillation through a modified Vigreux column. The residue was dried over potassium carbonate and distilled from 10 g. of potassium carbonate through Column A, giving a 58% yield of 2,2,4-trimethyl-4-heptanol, b. p. 119.8° at 100 mm., 59.6° at 7 mm., $d^{20}$ 0.833, $n^{20}D$ 1.4373.

The carbinol, 585 g., was dropped onto a mixture of 25 g. of anhydrous copper sulfate and 10 g. of powdered pumice heated to 200° at 200 mm. After separating the water layer, 35 ml., the olefin product was dried over potassium carbonate and distilled. About half was found to be unchanged carbinol and was dehydrated in Column A by distilling with 25 g. of copper sulfate and 10 g. of pumice at atmospheric pressure. The water layer was 18 ml. The olefin mixture was dried over potassium carbonate and distilled to give 454 g., 88% yield, b. p. 149–150° at 741 mm., $n^{20}D$ 1.4255–1.4277.

The olefin mixture, 202 g., was hydrogenated over 20 g. of UOP nickel on kieselguhr at 110–130° at 1200 p. s. i. The product was filtered and fractionated through Column C and constant index material rehydrogenated and then fractionated again through Column C, giving only constant boiling, constant index material.

**2,2,4-Trimethyloctane.**—Methyl neopentyl ketone was added to *n*-butylmagnesium bromide in the usual way and the product distilled under reduced pressure to give 57% yield of 2,2,4-trimethyl-4-octanol,[8] b. p. 137.1° at 100 mm., 79.8° at 8 mm., $n^{20}D$ 1.4405, $d^{20}$ 0.835.

The alcohol was dehydrated with copper sulfate and pumice as previously described to give an 84% yield of olefin mixture. Ozonolysis of the product showed no rearrangement of the carbon skeleton.[9]

The olefins were hydrogenated in glacial acetic acid using platinum oxide at 3 atm. and room temperature.

The saturated hydrocarbon was also obtained by hydrogenation of the alcohol over Raney nickel at 200° and 150 atm.

**2,2,4,6-Tetramethylheptane.**—Methyl neopentyl ketone was added to isobutylmagnesium bromide in the usual way. The product was distilled at reduced pressure to give a 29% yield of 2,2,4,6-tetramethyl-4-heptanol, b. p. 126.8° at 100 mm., 64.0° at 7 mm., $d^{20}$ 0.828, $n^{20}D$ 1.4368.

The alcohol was dehydrated by dropping onto copper sulfate and pumice at 200° giving a 77% yield of olefins, b. p. 159–161°, $n^{20}D$ 1.4260–61. The mixture was ozonized in olefin-free, low-boiling (0–30°) hydrocarbon solvent and the ozonide decomposed with zinc dust and water in the presence of traces of hydroquinone and silver nitrate. The products obtained were: formaldehyde (dimetol deriv. m. p. 189–190°), isobutyraldehyde (dimetol deriv. m. p. 147–148°, 2,4-dinitrophenylhydrazone m. p. 182–183°), methyl neopentyl ketone (semicarbazide m. p. 173–173.5°), and isobutyl neopenyl ketone. Isobutyl neopentyl ketone failed to yield a carbonyl derivative but when reduced with sodium in moist benzene gave isobutylneopentylcarbinol (α-naphthylurethan m. p. 99–100°). Mixed melting points were made in all cases. These products show no rearrangement of the carbon skeleton, the olefins being 2,2-dimethyl-4-isobutyl-4-pentene and 2,2,4,6-tetramethyl-4-heptene.

The olefin mixture was hydrogenated over a nickel–kieselguhr catalyst at 120–135° and 1700 p. s. i.

**2,2,4,5,5-Pentamethylhexane.**—(A) *t*-Butylacetic acid was prepared in 77% yield by the bromoform reaction with methyl neopentyl ketone.[10] The acid was converted to the chloride in 91% yield with thionyl chloride. The *t*-butylacetyl chloride was treated with *t*-butylmagnesium chloride in equi-molar quantity and the complex then treated with an equal amount of methylmagnesium chloride. The reaction mixture was decomposed and the 2,2,4,5,5-pentamethyl-4-hexanol distilled under reduced pressure, 13% yield, b. p. 124.1° at 100 mm., 60.2° at 7 mm., $d^{20}$ 0.841, $n^{20}D$ 1.4412, m. p. 11.4°. (B) The same alcohol was also prepared by adding methyl neopentyl ketone to *t*-butylmagnesium chloride in the usual way, yield 7.5%.

The alcohol was dehydrated with copper sulfate and pumice at 180° in 98% yield, and the products fractionated through Column C, b. p. 152–162°, $n^{20}D$ 1.4309–1.4333. The olefins were ozonized and the products identified as: formaldehyde (dimetol deriv. m. p. 189–90°), trimethylacetaldehyde (2,4-dinitrophenylhydrazone, m. p. 206–207°), pinacolone (2,4-dinitrophenylhydrazone m. p. 122–124°, semicarbazone m. p. 156–156.5°), and *t*-butyl neopentyl ketone which was identified by reduction with sodium in moist benzene to the corresponding alcohol (phenylurethan m. p. 124–126°). These products indicate the olefins as 4,4-dimethyl-2-*t*-butyl-1-pentene and 2,2,4,5,5-pentamethyl-3-hexene. Hydrogenation of the olefins gave material of b. p. 165°, $n^{20}D$ 1.4216.

Although no rearranged product was identified, it is quite certain that a small amount, about 5%, of 2,3,3,5,5-pentamethyl-1-hexene was formed during the dehydration.

A mixture of these same olefins was obtained by dissolving one mole of Butlerow's beta acid, methyl-*t*-butylneopentylacetic acid,[11] m. p. 125.5–127.5°, in 1.2 moles of potassium hydroxide in 500 ml. of water and electrolyzing between smooth platinum electrodes at 8.2 to 8.5 amp. for eight hours. The oil layer (50% yield) was separated

(8) Whitmore, Popkin, Whitaker, Mattil and Zech, THIS JOURNAL, **60**, 2461 (1938).

(9) Whitmore and Rohrman, *ibid.*, **63**, 2033 (1941).

(10) Homeyer, Whitmore and Wallingford, *ibid.*, **55**, 4209 (1933).

(11) Whitmore and Laughlin, *ibid.*, **56**, 1128 (1934).

and distilled into two portions, (I) b. p. 156–161, $n^{20}D$ 1.4247–1.4320; (II) b. p. 162–165, $n^{20}D$ 1.4325–1.4380.

Refractionation of the lower boiling fractions (I) through Column A gave material boiling at 152–162°, $n^{20}D$ 1.4297–1.4336. Ozonolysis of this material gave formaldehyde, trimethylacetaldehyde and pinacolone, identified as their 2,4-dinitrophenylhydrazones.[12] Hydrogenation of these lower boiling fractions gave material boiling mainly at 165°, $n^{20}D$ 1.4216.

Refractionation of the higher boiling portion (II) through Column B gave material of b. p. 162–166°, $n^{20}D$ 1.4314–1.4396. This when hydrogenated gave material boiling mainly at 171°, $n^{20}D$ 1.4278–90, having a mol. wt. of 166 (dodecane = 168) and which was insoluble in cold concd. sulfuric acid.

**Physical Properties.**—The constants determined for the hydrocarbons are given the accompanying table. The boiling points were measured in a Cottrell-type apparatus using a thermometer with 0.2° divisions checked against a Bureau of Standards calibrated Anschutz thermometer. Refractive indices were read on a Valentine No. 454 refractometer. Densities were measured in pycnometers; and viscosities, with the Ostwald-type viscometer recommended by Cannon and Fenske[13] for use with non-viscous liquids.

The physical properties were determined by N. C. Cook and Andrew Carson; some of the hydrogenations were performed by R. E. Meyer and N. C. Cook.

(12) Identification by H. H. Johnson, Ph.D. Thesis, Penn State, 1940.

## Summary

Four highly branched hydrocarbons, 2,2,4-trimethylheptane, 2,2,4-trimethyloctane, 2,2,4,6-tetramethylheptane, and 2,2,4,5,5-pentamethylhexane have been synthesized and a number of their physical properties determined.

(13) Cannon and Fenske, *Ind. Eng. Chem., Anal. Ed.*, **10**, 299 (1938).

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

# Substituted 1,10-Phenanthrolines. II. Di- and Tri-methyl Phenanthrolines Related to 5-Methyl-1,10-phenanthroline[1]

BY FRANCIS H. CASE

Continuing the work described in the first article of this series[2] with the object of preparing a series of substituted phenanthrolines which in the form of their ferrous complexes would be suitable for use as oxidation–reduction indicators, all possible di- and tri-methyl-1,10-phenanthrolines were synthesized in which one methyl group is in the 5- or 6- position and each of the others in a different ring, but none adjacent to nitrogen. The quinolines and phenanthrolines described here were synthesized from a substituted aniline or aminoquinoline by a Skraup reaction using arsenic acid as oxidizing agent and either glycerol, α-methylacrolein diacetate (2-methyl-2-propene-1,1-diol diacetate) or methyl vinyl ketone as the second component. In the case of 3,5-dimethyl-8-nitroquinoline this method proved much more satisfactory than that previously described,[3] while with 4,5-dimethyl-8-nitroquinoline no improvement in yield was noted.

Under these conditions 3,5-dimethyl-1,10-phenanthroline (III) was obtained from 6-methyl-8-aminoquinoline[4] (II) and α-methylacrolein diacetate.

The action of α-methylacrolein diacetate and 3-nitro-4-aminotoluene (I) yielded, in a two-step reaction, 3,6-dimethyl-8-aminoquinoline (IV) which with glycerol was converted to 3,6-dimethyl-1,10-phenanthroline (V).

I, with methyl vinyl ketone under Skraup conditions yielded in a two-step reaction 4,6-dimethyl-8-aminoquinoline (VI) from which the following compounds were made: 3,5,7-trimethyl-1,10-phenanthroline (VII) (with α-methylacrolein diacetate); 4,6-dimethyl-1,10-phenanthroline (VIII) (with glycerol); 4,5,7-trimethyl-1,10-phenanthroline (IX) (with methyl vinyl ketone). From 3,5-dimethyl-8-aminoquinoline (XI) and α-methylacrolein diacetate, 3,5,8-trimethyl-1,10-phenanthroline (XII) was obtained. This also resulted in very small yield if 3,6-dimethyl-8-aminoquinoline (IV) were used as the base. From 4,5-dimethyl-8-aminoquinoline (XIII) and glycerol, 4,5-dimethyl-1,10-phenanthroline (XIV) resulted, while if α-methylacrolein diacetate were used as the second component, 3,6,7-trimethyl-1,10-phenanthroline (XV) was formed.

It should be noted that in the synthesis of each substituted phenanthroline two possible methods were available. For example, 4,5-dimethyl-1,10-phenanthroline might theoretically be prepared by the action of 4,5-dimethyl-8-aminoquinoline with glycerol or of 6-methyl-8-aminoquinoline with methyl vinyl ketone. Both methods were tried, but in the latter case, no yield was obtained. The choice of methods was conditioned by the availability of the starting aminoquinoline as well as by the fact that the yield is highest when glycerol is used as the second component, less with α-methylacrolein diacetate and least with methyl vinyl ketone. When both possible methods were attempted this fact is indicated by a footnote in Table I.

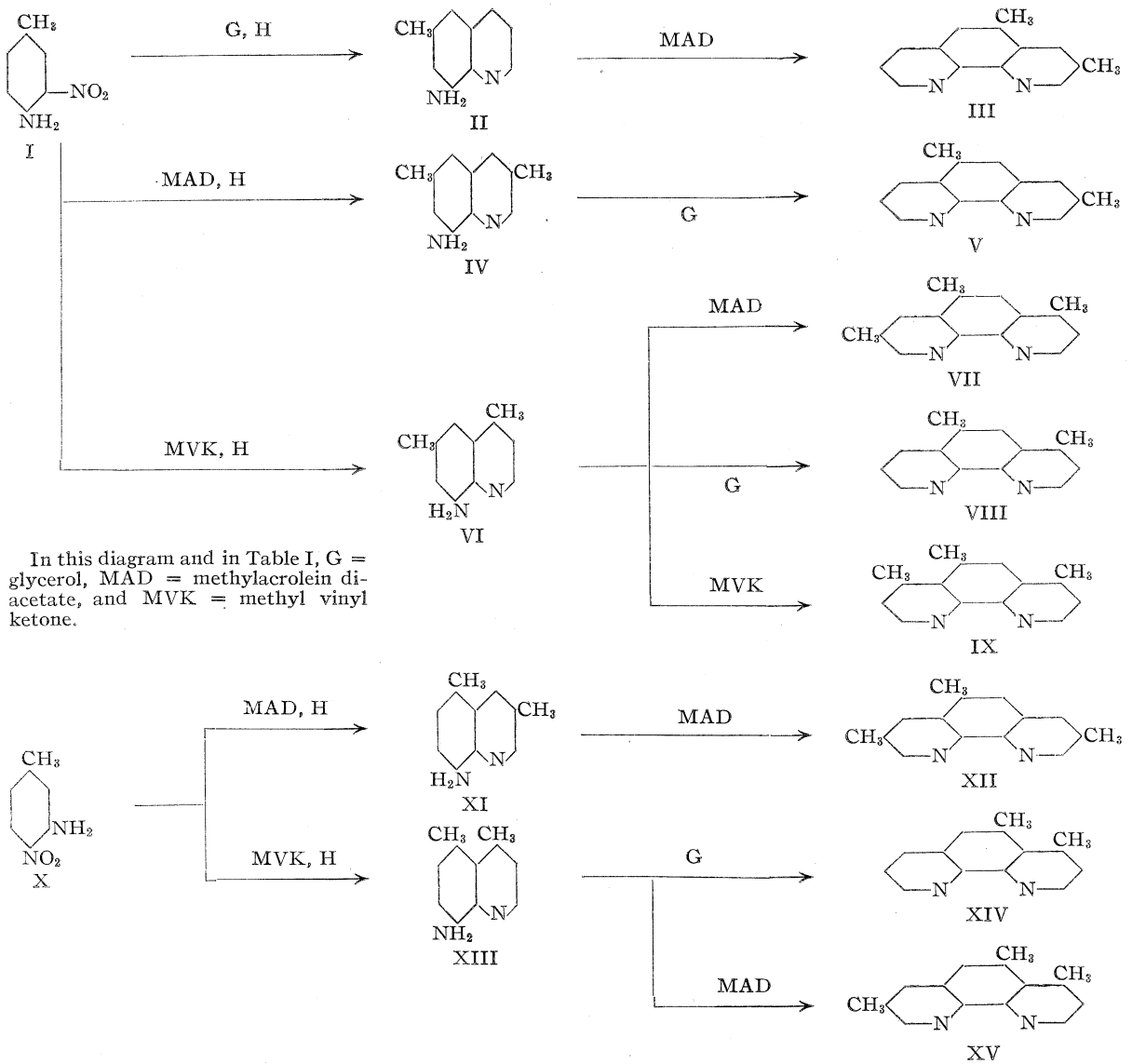
All the phenanthrolines described in this paper give a positive ferroin reaction.

(1) This work was supported by a Grant from the Committee on Research and Publications of Temple University.

(2) Case, THIS JOURNAL, **70**, 3994 (1948).

(3) Manske, *Can. J. Res.*, **20B**, 133 (1942).

(4) Baldwin, *J. Chem. Soc.*, 2959 (1929).




I II III IV V VI VII VIII IX X XI XII XIII XIV XV

In this diagram and in Table I, G = glycerol, MAD = methylacrolein diacetate, and MVK = methyl vinyl ketone.

## Experimental

**Methyl Vinyl Ketone.**—The cooled azeotrope obtained from du Pont containing 15% water, was shaken with anhydrous potassium carbonate, dried over calcium chloride and distilled *in vacuo*. The resulting liquid nearly all boiled at 34–40° (150 mm.).

**4,6-Dimethyl-8-nitroquinoline.**—A mixture of 25.3 g. of 2-nitro-4-methylaniline, 36 ml. of concentrated sulfuric acid, 12 ml. of water and 25.0 g. of arsenic oxide was warmed to 100°. Methyl vinyl ketone (17 g.) was then added at such a rate that the temperature did not exceed 140°. The mixture was maintained at this temperature for two hours with stirring, then poured on ice, and made alkaline with sodium hydroxide. The resulting precipitate was removed by filtration, dried, and extracted with hot benzene. Removal of the benzene and crystallization from the same solvent yielded 12 g. of pure product, m.p. 147–148°; yield, 35.6%.

*Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98. Found: C, 65.24; H, 4.76.

**4,6-Dimethyl-8-aminoquinoline.**—This compound was obtained by reduction of the nitro compound (67 g.) with 229 g. of $SnCl_2 \cdot 2H_2O$ in 1200 ml. of boiling ethanol; yield, 51 g., b.p. 195–205° (9 mm.). The pure substance, on crystallization from petroleum ether, melts at 85–86°.

*Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 77.18; H, 6.99.

**3,6-Dimethyl-8-nitroquinoline.**—The preparation of this compound was identical with that of 4,6-dimethyl-8-nitroquinoline, the same amounts of materials being used except that 50 g. of $\alpha$-methylacrolein diacetate was substituted for methyl vinyl ketone. The yield of product, melting at 163–164° after crystallization from benzene was 11.5 g. or 34.2%.

*Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98. Found: C, 65.75; H, 4.97.

**3,6-Dimethyl-8-aminoquinoline.**—Reduction of 57 g. of the corresponding nitro compound by 193 g. of $SnCl_2 \cdot 2H_2O$ in 1100 ml. of boiling ethanol yielded 32 g. of 3,6-dimethyl-8-aminoquinoline, b.p. 202–220° (5 mm.). The pure product melts at 107–108° after crystallization from benzene–petroleum ether.

*Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 76.95; H, 7.47.

TABLE I

| 1,10-Phenanthroline | 1st component, quinoline | 2nd component | M. p., °C. | Yield, % | Analyses,[d] % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| 3,5-Dimethyl | 6-Methyl-8-amino- | MAD | 169–170 | 4.2 | 80.74 | 5.81 | 80.90 | 5.44 |
| 4,5-Dimethyl[a,c] | 4,5-Dimethyl-8-amino- | G | 151–152 | 24.0 | 80.74 | 5.81 | 80.42 | 5.73 |
| 3,6-Dimethyl[b,c] | 3,6-Dimethyl-8-amino- | G | 117–118 | 2.6 | 80.74 | 5.81 | 80.49 | 5.93 |
| 4,6-Dimethyl | 4,6-Dimethyl-8-amino- | G | 161–162 | 11.4 | 80.74 | 5.81 | 80.67 | 5.73 |
| 3,5,7-Trimethyl | 4,6-Dimethyl-8-amino- | MAD | 201–202 | 14.5 | 81.05 | 6.35 | 81.21 | 6.10 |
| 3,5,8-Trimethyl[c] | 3,5-Dimethyl-8-amino- | MAD | 185–186 | 8.7 | 81.05 | 6.35 | 80.78 | 6.12 |
| 3,6,7-Trimethyl[a,c] | 4,5-Dimethyl-8-amino- | MAD | 177–178 | 2.1 | 81.05 | 6.35 | 81.07 | 6.24 |
| 4,5,7-Trimethyl | 4,6-Dimethyl-8-amino- | MVK | 184–185 | 1.3 | 81.05 | 6.35 | 80.84 | 6.37 |

[a] These samples are hygroscopic. [b] Crystallized from benzene–petroleum ether. [c] Alternate method tried, but yield of phenanthroline negligible. [d] Analyses were done by the Clark Microanalytical Laboratory, Urbana, Illinois.

**3,5-Dimethyl-8-nitroquinoline.**[3]—The preparation of this compound was similar to that of 3,6-dimethyl-8-nitroquinoline except that 2-nitro-5-methylaniline was used as the first component; yield, 9.5 g. or 28.0%, m.p. 189–190° (from 25.5 g. of 2-nitro-5-methylaniline).

**4,5-Dimethyl-8-nitroquinoline.**[3]—This compound was prepared exactly as in the case of 4,6-dimethyl-8-nitroquinoline except that 2-nitro-5-methylaniline was used as the first component; yield, 3 g. or 8.9%, m.p. 139–140° (from 25.3 g. of 2-nitro-5-methylaniline).

**General Procedure for the Synthesis of Di- and Trimethyl-1,10-Phenanthrolines.**—A mixture of one molar proportion of the appropriate methyl- or dimethyl-8-aminoquinoline, 0.65 mole of arsenic oxide, 4 moles of sulfuric acid in 96.8% solution and a volume of water equal to one third of the volume of sulfuric acid used was heated to 100° and treated with glycerol (3.6 moles), α-methylacrolein diacetate (1.8 moles), or methyl vinyl ketone (1.8 moles) at such a rate that the temperature did not exceed 140°. It was then heated with stirring for two more hours at this temperature. The mixture was then poured into water, made alkaline, and the tarry precipitate removed by filtration. The filtrate was extracted three times with hot benzene, which was then used to extract the phenanthroline from the solid material. After removal of the benzene the phenanthroline was crystallized from benzene. The results are shown in Table I.

## Summary

The following phenanthrolines have been synthesized: 3,5-, 4,5-, 3,6-, 4,6-dimethyl- and 3,5,7-, 3,5,8-, 3,6,7- and 4,5,7-trimethyl-1,10-phenanthrolines.

3,6- and 4,6-dimethyl-8-nitroquinolines and the corresponding amino derivatives have been prepared.

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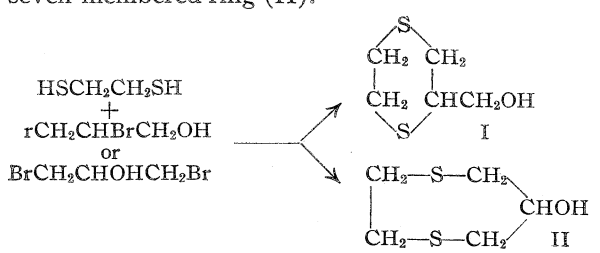
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

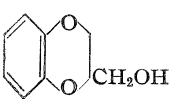
# Formation of a Seven-membered Cyclic Disulfide from 1,2-Dibromohydrin and a 1,2-Dithiol

BY REYNOLD C. FUSON AND A. JOHN SPEZIALE[1]

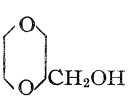
In connection with other studies, an attempt was made to prepare 2-hydroxymethyl-1,4-dithiane (I) and 6-hydroxy-1,4-dithiacycloheptane (II) by condensing ethanedithiol with 2,3-dibromo-1-propanol and 1,3-dibromo-2-propanol, respectively. It was found that the two reactions yielded the same product—the carbinol with the seven-membered ring (II).




It had been observed that, in the preparation of acyclic diethers from 1,2- or 1,3-dihalohydrins or from epihalohydrins, the 1,3-diethers are produced in preference to the 1,2-diethers.[2] In the formation of cyclic ethers, however, it was to be expected that a six-membered ring would be produced to the exclusion of a seven-membered ring as observed in the synthesis of 2-hydroxymethyl-1,4-benzodioxane (III) from pyrocatechol and the dihalohydrins,[3] and of 2-hydroxymethyl-1,4-dioxane (IV) from ethylene glycol and epichlorohy-



III



IV

(1) American Chemical Society Predoctoral Fellow, 1946–1947; present address: Monsanto Chemical Company, St. Louis, Mo.

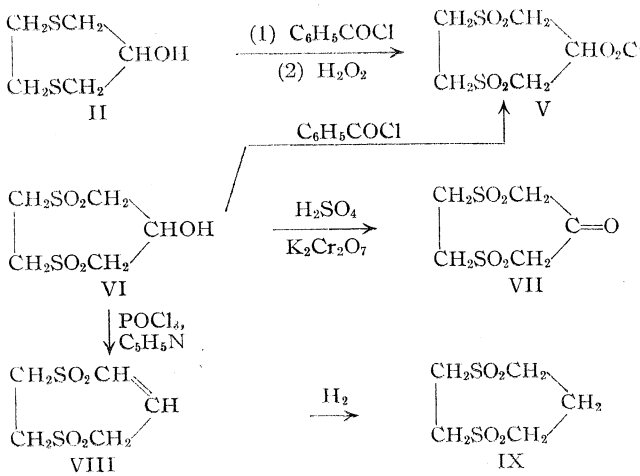
(2) (a) Gilchrist and Purvis, *J. Chem. Soc.*, **127**, 2735 (1925); (b) Zunino, *Atti. accad. Lincei*, **6**, 348 (1897); *J. Chem. Soc.*, **76**, 410 (1899); (c) Rossing, *Ber.*, **19**, 63 (1886); (d) Lindemann, *ibid.*, **24**, 2145 (1891); (e) Fairbourne, *J. Chem. Soc.*, 1151 (1929); (f) Fairbourne, Gibson and Stephens, *ibid.*, 1965 (1932); (g) Fairbourne, Gibson and Stephens, *ibid.*, 445 (1931); (h) Boyd, *ibid.*, **79**, 1221 (1901); (i) Boyd and Marle, *ibid.*, **93**, 838 (1908); (j) Delaby and Dubois, *Bull. soc. chim.*, **47**, 565 (1930).

(3) (a) Moureu, *Ann. chim. phys.*, **18**, 76 (1899); (b) Fourneau, *J. pharm. chim.*, **1**, 55 (1910); (c) French Patent 770,485, September 14, 1934; (d) U. S. Patent 2,366,661, January 2, 1945.

drin.[4] Our observation that a seven-membered ring (II) is produced with either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol appears, accordingly, to be anomalous.

The low yield (average 30%) of the 6-hydroxy-1,4-dithiacycloheptane (II) may be attributed to the predominance of intermolecular condensation; large amounts of polymer were formed.

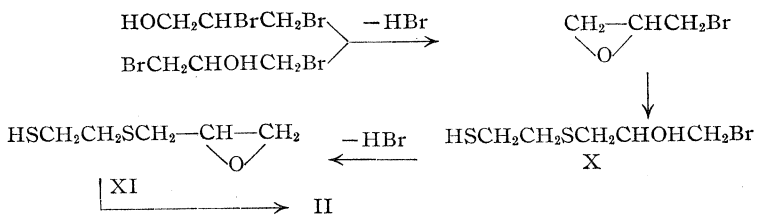
Proof of the structure of this carbinol is afforded by the following transformations.




Careful oxidation of 6-hydroxy-1,4-dithiacycloheptane tetroxide (VI) with potassium dichromate and sulfuric acid led to the keto sulfone (VII) from which a phenylhydrazone was prepared. Dehydration of the tetroxide (VI) with phosphorus oxychloride in pyridine produced the cycloheptene tetroxide (VIII) which gave the known[5,6,7] 1,4-dithiacycloheptane tetroxide (IX, m. p. 279–280° (dec.)) when hydrogenated catalytically with 10% palladium chloride on carbon.

If the initial condensation product had been 2-hydroxymethyl-1,4-dithiane (I), oxidation of its sulfone would have given the corresponding acid, and dehydration and hydrogenation of the sulfone would have produced 2-methyl-1,4-dithiane tetroxide. 2-Methyl-1,4-dithiane, prepared from ethanedithiol and propylene bromide, had a melting point which was in agreement with that reported.[5] The disulfone, not previously described, was obtained by treating 2-methyl-1,4-dithiane with 30% hydrogen peroxide in glacial acetic acid. It had a melting point of 304–306°.

The cyclization can be accounted for by assuming the following changes, involving two epoxide intermediates.




Kharasch and Nudenberg[4] reported the formation of the oxygen analogs of X and XI by the reaction between ethylene glycol and epichlorohydrin.

## Experimental

**6-Hydroxy-1,4-dithiacycloheptane (II).**—A modification of the method of Tucker and Reid[5] was adopted. To 500 ml. of absolute ethanol, 24 g. of clean sodium was added. After the reaction was completed, 48.9 g. of freshly distilled ethanedithiol[8] was added dropwise over a period of one-half hour at 20°. The sodium mercaptide solution and a solution of 113.3 g. of freshly distilled 2,3-dibromo-1-propanol in 500 ml. of absolute ethanol were added dropwise and at approximately the same rate to 500 ml. of absolute ethanol in a 2-l. flask equipped with a stirrer. The temperature was maintained at 20–25° during the addition, which required seven hours. The mixture was stirred overnight at room temperature. The white solid consisting of sodium bromide and polymeric material was discarded. The volume of the alcohol solution was reduced to about 150 ml. by evaporation under slightly diminished pressure. One liter of benzene was added, the insoluble material separated by filtration and the benzene filtrate dried over anhydrous magnesium sulfate. Evaporation of the solvent left an oil which crystallized when allowed to stand in the cold. After recrystallization from a cyclohexane–ethanol mixture (9:1), the hydroxy sulfide melted at 64.5–65.5°; yield 25 g. (32%).

*Anal.* Calcd. for $C_5H_{10}OS_2$: C, 39.96; H, 6.71; S, 42.67. Found: C, 40.13; H, 6.64; S, 42.33.

The same compound was formed when 1,3-dibromo-2-propanol was used in place of the 1,2-dibromohydrin.[9]

**The benzoate,** made in the usual manner and recrystallized from ethanol, melted at 75–76°; yield 76%.

*Anal.* Calcd. for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.63; H, 5.54.

**The disulfone** (V) was produced by dissolving 0.4 g. of the benzoate in 10 ml. of glacial acetic acid and adding to the mixture slowly and with stirring, 0.11 g. of hydrogen peroxide (30%). After the exothermic reaction had subsided, 0.22 g. of hydrogen peroxide was added rapidly. The reaction mixture was stirred at 60° for 24 hours and the white, matted crystals of the sulfone benzoate were collected on a filter; m. p. 229–230°; yield 0.43 g. (86.5%). Repeated recrystallization of the sulfone from acetone did not change its melting point.

*Anal.* Calcd. for $C_{12}H_{14}O_6S_2$: C, 45.27; H, 4.43. Found: C, 45.32; H, 4.46.

**6-Hydroxy-1,4-dithiacycloheptane Tetroxide (VI).**—This compound was prepared in the usual manner from 1.35 g. of 6-hydroxy-1,4-dithiacycloheptane in 25 ml. of glacial acetic acid and 1.8 g. of hydrogen peroxide (30%). After the mixture had been stirred at 70° for twenty-four hours, the white, needle-like crystals (VI) were collected

(4) Kharasch and Nudenberg, *J. Org. Chem.*, **8**, 189 (1943).
(5) Tucker and Reid, THIS JOURNAL, **55**, 775 (1933).
(6) Meadow and Reid, *ibid.*, **56**, 2177 (1934).
(7) Autenrieth and Wolff, *Ber.*, **32**, 1375 (1899).

(8) Mathias, *Bol. faculdade filosofia, cienc. letras, Univer. Sao Paulo*, 14, Quimica No. 1, 75 (1942).

(9) The melting points of the *p*-nitrobenzoates of these dibromohydrins, prepared according to the procedures of Fairbourne and Foster (*J. Chem. Soc.*, 3146, 3148 (1926)) and Conant and Quayle, (THIS JOURNAL, **45**, 2771 (1923)) were in agreement with the reported values.

on a filter, washed with cold water and dried over potassium hydroxide in a vacuum desiccator; m. p. 230–231°; yield 1.40 g. (72.5%). Removal of the solvent left a solid which weighed 0.3 g. and melted at 209–210°. Recrystallization of these solids from water raised their melting points to 233–234° and 210–211°, respectively.

**The benzoate** of the higher melting material, prepared in the usual manner, melted at 228–230° after recrystallization from acetone. A mixture melting point with the benzoate of 6-hydroxy-1,4-dithiacycloheptane tetroxide (V) showed no depression. Attempts to prepare the benzoate of the lower melting material failed.

**1,4-Dithia-6-cycloheptanone Tetroxide (VII).**—One gram of the hydroxy sulfone (VI) was suspended in 10 ml. of water to which had been added 0.92 g. of potassium dichromate. Concentrated sulfuric acid (10 ml.) was added dropwise over a period of one-half hour at 20–25°. Stirring was continued for one hour after which 50 ml. of water was added to the green reaction mixture. The ketone was collected on a filter and recrystallized from dioxane or water; yield 0.72 g. (72.7%); m. p. 252–253° (dec.).

*Anal.* Calcd. for $C_5H_6O_5S_2$: C, 28.29; H, 3.79; S, 30.21. Found: C, 28.68, 28.71; H, 3.66, 3.42; S, 30.07.

**The phenylhydrazone** was prepared by dissolving 0.2 g. of the ketone in 10 ml. of hot dioxane, cooling the solution and adding 1 ml. of phenylhydrazine and two drops of glacial acetic acid. The mixture was then heated on the steam-bath for ten minutes and cooled in ice. The addition of 20 ml. of water caused the immediate precipitation of the phenylhydrazone; m. p. 235–236° (dec.); yield 0.2 g. (70%). Recrystallization of the derivative from a dioxane–water mixture did not change its melting point.

*Anal.* Calcd. for $C_{11}H_{14}N_2O_4S_2$: C, 43.69; H, 4.66; N, 9.26; S, 21.21. Found: C, 43.95; H, 4.93; N, 9.24; S, 21.09.

**1,4-Dithia-5-cycloheptene Tetroxide (VIII).**—Five grams of 6-hydroxy-1,4-dithiacycloheptane tetroxide was dissolved in 75 ml. of hot anhydrous pyridine. The mixture was cooled in an ice-bath, and 4.6 ml. of phosphorus oxychloride was added dropwise with stirring. The reaction mixture was allowed to come to room temperature and then stirred at 60–70° for three hours. The slightly colored cycloheptene tetroxide was collected on a filter and washed well with ice-water; m. p. 279–280° (dec.); yield 3.4 g. (74%). Repeated recrystallization of the unsaturated sulfone from water raised its melting point to 280–280.5° (dec.). An aqueous solution of potassium permanganate was instantly decolorized when added to a dioxane solution of this compound.

*Anal.* Calcd. for $C_5H_8O_4S_2$: C, 30.60; H, 4.11. Found: C, 30.80, 30.75; H, 3.78, 3.71.

**1,4-Dithiacycloheptane Tetroxide (IX).**—Five grams of 10% palladium chloride on carbon[10] was reduced in 25 ml. of anhydrous dioxane at three atmospheres pressure. To the reduced catalyst a solution of 0.6 g. of the cycloheptene tetroxide (VIII) in 75 ml. of dioxane was added. The hydrogenation was completed after seven hours at three atmospheres pressure. The contents were transferred to a flask, boiled and filtered. Two additional extractions of the catalyst were carried out with 100-ml. portions of dioxane. The 1,4-dithiacycloheptane tetroxide, which separated when the combined extracts were allowed to stand in the cold, was recrystallized from water; m. p. 279–280° (dec.); yield 0.4 g. (66%).

*Anal.* Calcd. for $C_5H_{10}O_4S_2$: C, 30.29; H, 5.08. Found: C, 30.41; H, 5.38.

1,4-Dithiacycloheptane was synthesized in 7.9% yield (m. p. 47°) according to the procedure of Reid,[5,6] who reported the same melting point and a yield of 8.2%. The sulfone was prepared with 30% hydrogen peroxide in glacial acetic acid in a yield of 59%; m. p. 277.5–278.5° (dec.). A mixture of this sulfone with that prepared in the preceding experiment decomposed at 278–279°. The melting point of the sulfone has been given as 282°[7] and 287–288°[5,8].

*Anal.* Calcd. for $C_5H_{10}O_4S_2$: C, 30.29; H, 5.08. Found: C, 30.41; H, 5.00.

**2-Methyl-1,4-dithiane Tetroxide.**—2-Methyl-1,4-dithiane, prepared according to the method of Tucker and Reid,[5] melted at 20–22°. The reported melting point is 20°. After two sublimations at low pressure, the clear, colorless sulfide was converted to the sulfone by the usual method. It was recrystallized from water; m. p. 304–306° (dec.).

*Anal.* Calcd. for $C_5H_{10}O_4S_2$: C, 30.29; H, 5.08. Found: C, 30.09; H, 5.11.

## Summary

Ethanedithiol has been found to react with 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol to give 6-hydroxy-1,4-dithiacycloheptane. The structure of the product has been established by unequivocal methods.

(10) Mozingo, "Org. Syntheses," **26**, 77 (1946).

URBANA, ILLINOIS RECEIVED OCTOBER 14, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

# A Polymer-homologous Series of Sugar Acetates from the Acetolysis of Cellulose[1]

BY E. E. DICKEY[2] AND M. L. WOLFROM

The chain scission of cellulose by hydrolysis in mineral acids and by acetolysis has yielded, in addition to D-glucose and cellobiose, specific sugars composed of three, four and six D-glucopyranose units as fragments of the original cellulose chains.[3] We wish to report herein the isolation of such a polymer-homologous series of sugars (as the α-D form of the acetates) complete from α-D-glucopyranose pentaacetate through a α-cellohexaose eicosaacetate (Table I). This has been accomplished through the application of the general method for the chromatography of sugar acetates as developed in this Laboratory.[4,5]

α-D-Glucopyranose pentaacetate, *aldehydo*-D-glucose heptaacetate[6] and α-cellobiose octaacetate

(1) Presented before the combined meeting of the Division of Cellulose Chemistry and the Division of Sugar Chemistry and Technology at the 114th Meeting of the American Chemical Society, Portland, Oregon, September 13–17, 1948.

(2) Research Foundation Associate, The Ohio State University, Project 212.

(3) A survey of the products obtained from the acid degradation of cellulose may be found in E. Heuser, "The Chemistry of Cellulose," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 512–515.

(4) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(5) L. W. Georges, R. S. Bower and M. L. Wolfrom, *ibid.*, **68**, 2169 (1946).

(6) K. Freudenberg and K. Soff, *Ber.*, **70**, 264 (1937).

TABLE I

CONSTANTS OF SUGAR ACETATES ISOLATED FROM CELLULOSE ACETOLYZATE BY CHROMATOGRAPHIC PROCEDURES

| | D. P. (degree of polymerization) | $[\alpha]^{20-25}D$ chloroform ($c > 5$) | Melting point,[a] °C. | Molecular weight Calcd. | Found (Rast)[b] | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| α-D-Glucopyranose pentaacetate | 1 | + 97.3° | 105–109 | | 383 | | | | |
| | | | | 390 | 382 | ... | ... | ... | .. |
| | | +101.6[e] | 113 (cor.)[e] | | 355 | | | | |
| α-Cellobiose octaacetate | 2 | + 39.6 | 225–226 | | 750 | | | | |
| | | | | 678 | 668 | ... | ... | ... | .. |
| | | + 41.0[c] | 229 (cor.)[c] | | 640 | | | | |
| α-Cellotriose hendecaacetate | 3 | + 22.6 | 223–224 | | 1000 | | | | |
| | | | | 967 | 990 | 49.69 | 5.630 | 49.78 | 5.65 |
| | | + 22.4[d] | 219–220 (cor.)[d] | | 930 | | | 49.73 | 5.68 |
| α-Cellotetraose tetradecaacetate | 4 | | | | 1340 | | | | |
| | | + 13.4 | 230–234 | 1255 | 1180 | 49.76 | 5.622 | 49.82 | 5.65 |
| | | | | | 1150 | | | 49.73 | 5.60 |
| α-Cellopentaose heptadecaacetate | 5 | | | | 1480 | | | | |
| | | + 4.17 | 240–241 | 1543 | 1470 | 49.80 | 5.617 | 49.67 | 5.54 |
| | | | | | 1360 | | | 49.73 | 5.51 |
| | | | | | 1340 | | | | |
| | | | | | 1300 | | | | |
| α-Cellohexaose eicosaacetate | 6 | | | | 2030 | | | | |
| | | − 0.23 | 252–255 | 1831 | 1840 | 49.83 | 5.613 | 49.62 | 5.54 |
| | | | | | 1700 | | | 49.63 | 5.57 |
| | | | | | 1670 | | | | |
| | | | | | 1600 | | | | |

[a] All melting points were taken on a Fisher–Johns melting point block, Fisher Scientific Co., Pittsburgh, Pa., and are uncorrected. [b] The precautions cited by J. H. C. Smith and W. G. Young, *J. Biol. Chem.*, **75**, 289 (1927), and W. B. Meldrum, L. P. Saxer and T. O. Jones, THIS JOURNAL, **65**, 2023 (1943), were followed in the determination of molecular weights by the method of Rast. [c] Accepted values as reported by Hudson and Johnson, ref. 15. [d] Specific rotation and melting point reported by Hess and Dziengel, ref. 10. [e] Accepted values.

are known products of the acetolysis of cellulose.[7] The trisaccharide, "procellulose," was first obtained by Bertrand and Mlle. Benoist,[8] as an amorphous solid after saponification and fractionation of a cellulose acetolyzate. By a similar procedure, Ost[9] succeeded in isolating the crystalline trisaccharide and named it cellotriose. By the acetolysis of cotton linters followed by saponification and fractionation, Hess and Dziengel[10] prepared a carefully purified sample of cellotriose which evidently crystallized as the α-form, $[\alpha]_D$ +32.0°, initial → +23.2°, final (in water). α-Cellotriose hendecaacetate was then prepared by acetylating the free sugar in pyridine and acetic anhydride, and repeatedly crystallizing the acetate to maximum purity (Table I). Crystalline cellotetraose was obtained by Willstätter and Zechmeister[11] from wood cellulose by hydrolysis in fuming hydrochloric acid ($d^{15}_4$ 1.21), and later, crystalline cellohexaose was isolated from the hydrolyzate by Zechmeister and Tóth.[12] Crystalline cellotriose hendecaacetate and cellotetraose tetradecaacetate were prepared by Zechmeister and Tóth[12] by acetylating the free sugars in acetic anhydride and pyridine, but cellohexaose failed to yield a crystalline acetate. As indicated by the specific rotation, the acetates prepared by Zechmesiter and Tóth were undoubtedly mixtures of both the α- and β-forms. The viscosity and molecular weight (Rast) of the cellohexaose acetate,[13] along with the lower members of the series, were determined by Staudinger and Leupold[14] who believed that the hexaose was actually a cellopentaose heptadecaacetate. Until all the free sugars of this series have been prepared and characterized, the identity of Zechmeister and Tóth's hexaose will remain somewhat in question. The triose and the tetraose have been obtained, also, in the form of their crystalline methyl ethers and phenylosazones.[3]

As shown by Hudson and Johnson,[15] mainly the α-form of a sugar acetate exists in an acetylating mixture of acetic anhydride and sulfuric acid. Since, in the present investigations, a cellulose acetolyzate was resolved directly into the polymer-homologous series, the preponderance of the α-form of each sugar acetate is to be expected (Table I).

(7) A. P. N. Franchimont, *Ber.*, **12**, 1938 (1879); Z. H. Skraup and J. König, *ibid.*, **34**, 1115 (1901); *Monatsh.*, **22**, 1011 (1901).

(8) G. Bertrand and Mlle. S. Benoist, *Bull. soc. chim.*, [4] **33**, 1451 (1923).

(9) H. Ost, *Z. angew. Chem.*, **39**, 1117 (1926).

(10) K. Hess and K. Dziengel, *Ber.*, **68**, 1594 (1935).

(11) R. Willstätter and L. Zechmeister, *ibid.*, **62**, 722 (1929).

(12) L. Zechmeister and G. Tóth, *ibid.*, **64**, 854 (1931).

(13) The sample was prepared by Zechmeister and Tóth, ref. 12.

(14) H. Staudinger and E. O. Leupold, *Ber.*, **67**, 479 (1934).

(15) C. S. Hudson and J. M. Johnson, THIS JOURNAL, **37**, 1276 (1915).

TABLE II

YIELDS OF SUGAR ACETATES ISOLATED FROM CELLULOSE ACETOLYZATE (10 G.) BY CHROMATOGRAPHIC PROCEDURES

| | 1st chromatographic separation on "Silene EF" (*cf.* Fig. 1), g. | Effluent fraction on "Magnesol" (*cf.* Fig. 2), g. | After rechromatographing to maximum purity, mg. | Recrystallized material | |
|---|---|---|---|---|---|
| | | | | Mg. | Crystallization medium |
| α-D-Glucopyranose pentaacetate | 3.07 | 0.305 | ... | 50 | Ether–petroleum ether (b. p. 65–69°) |
| α-Cellobiose octaacetate | | 1.16 | ... | 915 | Ethanol (95%) |
| α-Cellotriose hendecaacetate | | 0.99 | 470 | 384 | Chloroform–ether |
| α-Cellotetraose tetradecaacetate | 1.68 | .. | 323 | 220 | Dioxane–ether |
| α-Cellopentaose heptadecaacetate | 1.33 | .. | 305 | 218 | Dioxane–ether |
| α-Cellohexaose eicosaacetate | 1.09 | .. | 246 | 178 | Dioxane–ether |
| Remainder (highly adsorbed material) | 2.50 | .. | ... | .. | ..... |
| Total recovered | 9.47 | .. | ... | 1965 | ..... |

In the work herein described, cellulose in the form of filter paper was subjected to the procedure of Hess and Dziengel[10] for mild acetolysis. The cellulose acetolyzate was chromatographed on "Silene EF"[5] to effect a preliminary fractionation of the mixture. Three zones, as shown in Table II and Fig. 1, subsequently yielded the tetraose, pentaose and hexaose acetates, respectively. The

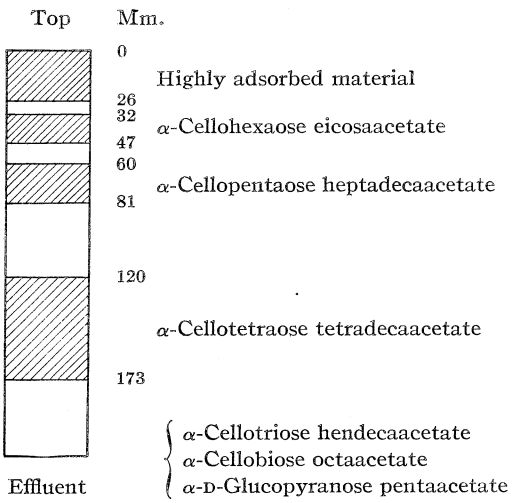



Fig. 1.—Cross section of a typical chromatogram of 1.5 g. of cellulose acetolyzate in 30 ml. of chloroform adsorbed on a column of adsorbent (44 mm. in diameter and 215 mm. long) composed of 5 parts by wt. of "Silene EF"[19] and 1 part of "Celite"[20] as developed with 1.4 liters of benzene–ethanol (100:1 by vol.).

highly adsorbed material at the top of the column is under further investigation. The solids recovered from the effluent were then chromatographed on "Magnesol"[4] to yield the three lower sugar acetates (Table II and Fig. 2) as well as two unidentified, crystalline substances under further investigation. It is probable that these substances represent impurities originating in the wood which was the source of the cellulose used. Corresponding zones from several chromatograms were combined, rechromatographed on "Magnesol" or "Silene EF" and crystallized from a suitable solvent (Table II). The data for the purified samples of specific sugars obtained from the cellulose acetolyzate are summarized in Table I and Fig. 3.

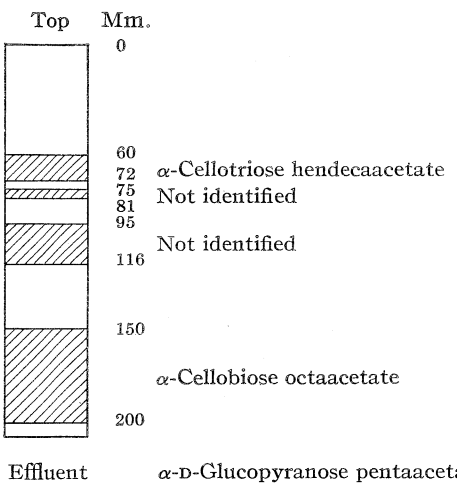



Fig. 2.—Cross section of a typical chromatogram of 1.8 g. of solids from the "Silene EF" effluent (*cf.* Fig. 1) in 30 ml. of chloroform adsorbed on a column of absorbent (44 mm. in diameter and 220 mm. long) composed of 5 parts by wt. of "Magnesol"[22] and 1 part of "Celite"[20] as developed with 1.5 liters of benzene–ethanol (100:1 by vol.).

The trend of melting points and specific rotations (Table I) is toward the constants for cellulose triacetate, $[\alpha]_D$ *ca.* −20°[16] and m. p. (softening point) *ca.* 295°.[17] Such a trend was found by Zechmeister and Tóth[12] for the corresponding series of free sugars, excluding the cellopentaose.

Freudenberg and co-workers[18] have shown that if the type of linkage in a polymer-homologous series is uniform, the expression $[M]_n/n$ plotted against $(n-1)/n$ (where $[M]$ is the molecular rotation and $n$ is the degree of polymerization)

(16) K. Hess, G. Schultze and E. Messmer, *Ann.*, **444**, 266 (1925).

(17) K. Hes "Die Chemie der Zellulose und ihrer Begleiter," Akademische Verlagagesellschaft m. b. H., Leipzig, 1928, p. 512.

(18) K. Freudenberg, "Tannin, Cellulose, Lignin," J. Springer, Berlin, 1933, p. 104.

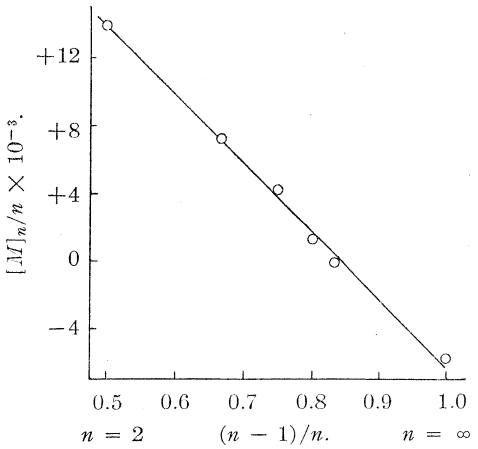



Fig. 3.—Relation between D. P. and molecular rotation.

should yield a straight line for $n \geqq 2$. Figure 3 shows that this linear relation holds for the α-D acetates of this series.

The determination of molecular weight by the method of Rast, Table I, tends to decrease in reliability as the molecular weight is increased. However, when the experimental molecular weights were correlated with specific rotations, melting points and relative positions on the chromatographic columns (Figs. 1–3) agreement with the proposed series was evident. As more material of better quality becomes available, the physical properties herein reported may be somewhat revised.

## Experimental

**Cellulose Acetolyzate.**—Using the general procedure of Hess and Dziengel,[10] 90 g. of filter paper (no. 1, prepared by W. &. R. Balston, Ltd., England) was dissolved with mechanical stirring in a mixture of 340 ml. of glacial acetic acid, 340 ml. of acetic anhydride and 36 ml. of concentrated sulfuric acid. The temperature of the reaction mixture was held at *ca.* 40° by external cooling with ice-water during the addition of the filter paper. After standing at room temperature for sixty hours, the clear, yellow solution was filtered through a sintered glass funnel and the filtrate poured slowly and with efficient mechanical stirring into 3 liters of cold water. The mixture was neutralized with sodium bicarbonate until just acid to congo red paper and allowed to stand overnight. The white precipitate was removed by filtration, washed on the filter with water until the filtrate was neutral to litmus and dried to constant weight in a vacuum desiccator over anhydrous calcium chloride; yield *ca.* 140 g. The product was powdered in a mortar and stored in a desiccator over solid sodium hydroxide and anhydrous calcium chloride.

**First Chromatographic Fractionation of Cellulose Acetolyzate.**—Using the general procedure of Georges, Bower and Wolfrom[5] for the chromatographic separation of sugar acetates on "Silene EF"[19] and "Celite,"[20] the cellulose acetolyzate was fractionated as shown in Fig. 1 and Table II. The extruded column was brushed with the streak reagent[21] and showed three zones in addition to the strongly adsorbed material at the top of the column (Fig. 1). The zones were separated, eluted with acetone and the eluates evaporated to dryness. The effluent from the chromatogram was also evaporated to dryness; the yields obtained are shown in Table II.

**Chromatographic Resolution of the Effluent Fraction on "Magnesol."**—Following the general procedure of McNeely, Binkley and Wolfrom,[4] the effluent fraction of solids was chromatographed on "Magnesol"[22] as shown in Fig. 2 and Table II. The column was extruded and brushed with the streak reagent. The α-D-glucopyranose pentaacetate was washed from the column and was recovered from the effluent by evaporating the solvent. α-Cellobiose octaacetate and α-cellotriose hendecaacetate along with the two unidentified substances were obtained by sectioning the column and eluting with acetone (Fig. 2 and Table II).

**Final Purification of Fractions.**—The α-D-glucopyranose pentaacetate and α-cellobiose octaacetate were not rechromatographed but were crystallized twice as shown in Table II. α-Cellotriose hendecaacetate was rechromatographed twice in the above-described manner on "Magnesol" and was then chromatographically pure. The product was finally crystallized twice. α-Cellotetraose tetradecaacetate was rechromatographed twice in the above-described manner on "Silene EF" and was finally crystallized as shown. α-Cellopentaose heptadecaacetate and α-cellohexaose eicosaacetate were each rechromatographed once on "Silene EF" and were crystallized as shown (Table II). The constants and elementary analyses obtained on these finally purified fractions are shown in Table I and are plotted in Fig. 3.

**Acknowledgment.**—This work was supported by the Ordnance Department under contract (W-33-019ord-3978, supervising agency Ballistic Research Laboratories, Aberdeen Proving Ground, Maryland) with The Ohio State University Research Foundation (Project 212). We wish to express our appreciation to Dr. W. W. Binkley and Mr. R. S. Bower of this Laboratory for their interest and coöperation in developing the chromatographic procedures used in this investigation.

## Summary

1. A product obtained by the acetolysis of cellulose has been resolved by a chromatographic technique into a polymer-homologous series of crystalline α-D acetates ranging in D. P. (degree of polymerization) from 1 to 6, inclusive.

2. A correlation of melting points and specific rotations with degrees of polymerization has been made.

COLUMBUS, OHIO RECEIVED AUGUST 19, 1948

(19) A synthetic calcium acid silicate manufactured by the Pittsburgh Plate Glass Co., Columbia Chemical Division, Barberton, Ohio.

(20) No. 535, a siliceous filter-aid manufactured by Johns-Manville Co., New York, N. Y.

(21) 100 mg. of potassium permanganate dissolved in 10 ml. of 2.5 *N* sodium hydroxide.

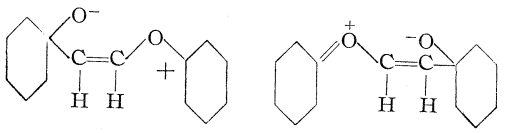
(22) A synthetic, hydrated magnesium acid silicate manufactured by the Westvaco Chlorine Products Co., South Charleston, West Virginia.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

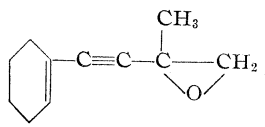
# Synthesis and Properties of Spiranes Containing Oxygen Heterocycles

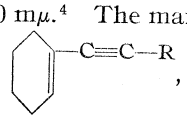
BY J. D. CHANLEY

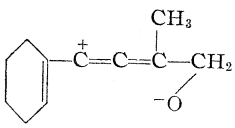
This investigation[1e] concerns itself with the preparation and properties of the *dl*-bis-epoxide of symmetric dicyclohexylethane (IV). This compound contains a new and interesting dispirane system. Numerous investigations of the ultraviolet absorption spectra of compounds containing a cyclopropyl group[1d] or epoxy group,[1c,2] adjacent to an unsaturated grouping, such as an ethylenic linkage, a carbonyl, phenyl, or pyridyl group, have shown that such compounds exhibit a shift of absorption to the longer wave lengths. This phenomenon as well as chemical evidence[3] indicates that three-membered rings resemble in many respects the ethylenic linkage. In these systems, the observed shift in the spectrum is commonly attributed to the participation of the three-membered ring in some of the excited (ionic) states of the molecule.[1a-d] It was of interest to investigate whether an epoxy-group, adjacent to a second one or to an acetylenic linkage, would display similar spectral properties. The *dl*-bis-epoxide of *sym*-dicyclohexylethane (IV) was prepared and proved to be completely transparent down to $\lambda = 214$ m$\mu$. A possible explanation is that such excited states as



which presumably would favor a shift in the spectrum toward the longer wave lengths, are extremely improbable. In this connection, it is of interest to know that the maximum of the 3,4-epoxide of 1-cyclohexenyl-3-methyl-1-butyne is



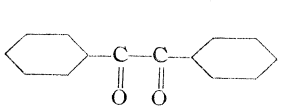
as low as 230 m$\mu$.[4] The max. values[4] for systems of the type , with R denoting a saturated group, lie in the range 227–229 m$\mu$. The epoxy group in this instance does not appear to possess double bond character. It is extremely unlikely that hypothetical excited states as



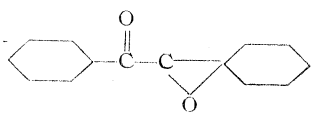
which would produce a shift of absorption to longer wave lengths, occur.

The synthesis and proof of structure of the bis-epoxide (IV) are outlined in the Scheme. The assigned *cis* configuration for 1,1′-vinylene-bis-cyclohexanol (II) is based on the general experience that mild catalytic hydrogenation of an acetylenic linkage produces the *cis* ethylenic derivative.[5] The $\alpha,\beta$-(1,1′-dihydroxycyclohexyl)-$\alpha,\beta$-dibromoethane (III), obtained by bromination of the ethylenic compound (II), is a racemate since bromine adds *trans* to ethylenic linkages.[6] The assigned structure for compound III was further confirmed by catalytic reduction of the dibromide to the *sym*-1,1′-ethylene bis-cyclohexanol (XII), identical with the product resulting from the complete catalytic reduction of 1,1′-ethynylene-bis-cyclohexanol (I), or of 1,1′-vinylene-bis-cyclohexanol (II).

Dehydrohalogenation of the double bromohydrin III yielded the *dl*-bis-epoxide of *sym*-dicyclohexylethane (IV). Since it is generally accepted that, both in the opening and in the formation of epoxy rings, an inversion at one of the carbon atoms ensues,[7a-h] it is therefore postulated that the racemic form only of the bis-epoxide IV may be expected from the racemic double bromohydrin III, since inversion would occur at each of the carbon atoms,[7d,g,h] bearing bromine atoms in III. Other conceivable structures for the new compound with the correct empirical elementary composition such as



(A)



(B) and VII

were considered at the time, but eliminated for the following reasons: (a) Compound IV gave no ketonic derivatives; (b) Compound A has been

(1) (a) Carr and Burt, THIS JOURNAL, **40**, 1590 (1918); (b) Klotz, *ibid.*, **66**, 88 (1944); (c) Rogers, *ibid.*, **69**, 2544 (1947); (d) Mariella, Peterson and Ferris, *ibid.*, **70**, 1494 (1948); (e) the results of this investigation were presented before the Section of Organic Chemistry at the Semi-Annual Meeting of the American Chemical Society, August 30, 1948, in Washington, D. C.

(2) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942).

(3) Kohler and Conant, THIS JOURNAL, **39**, 1404 (1917).

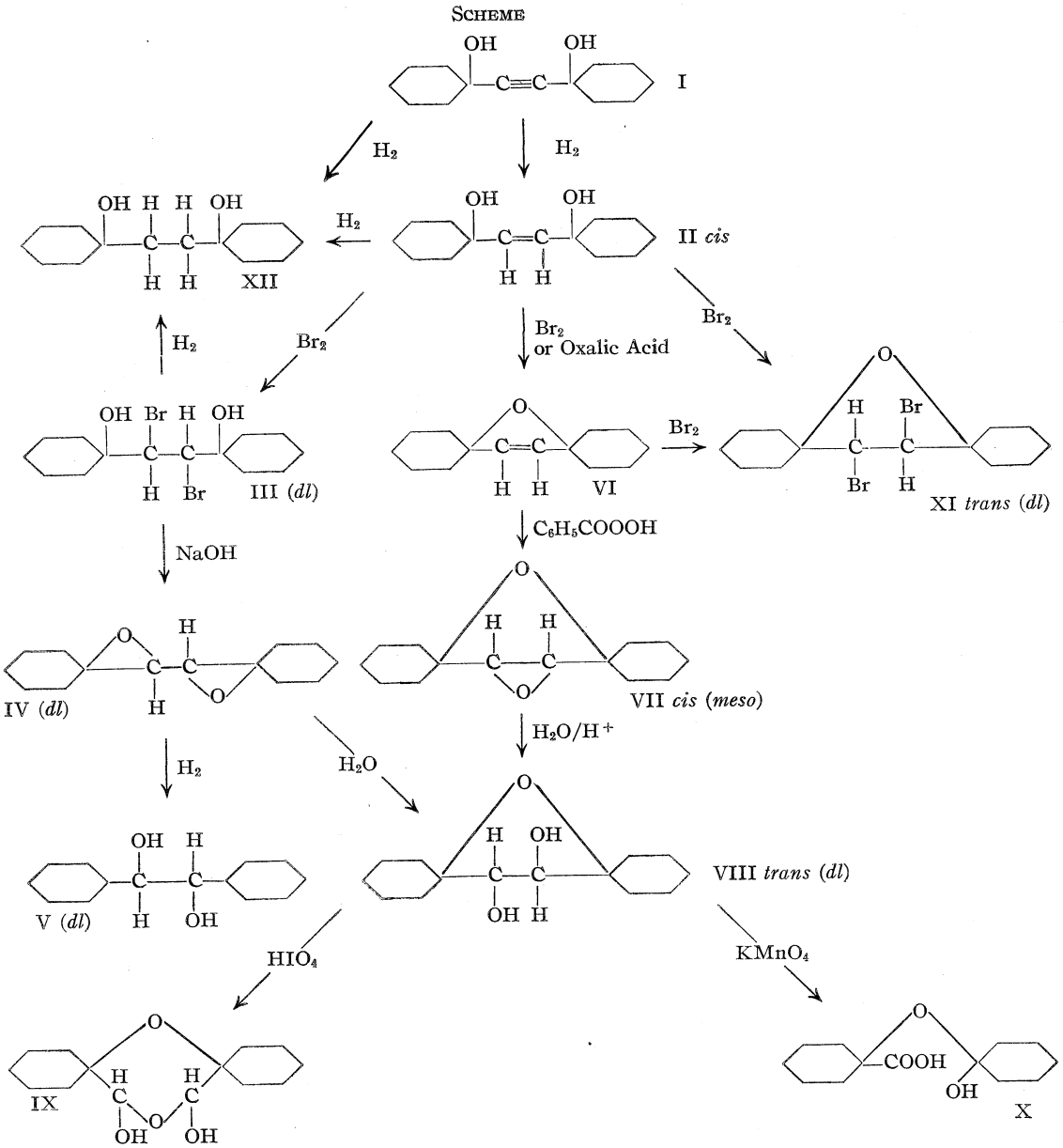
(4) Sobotka and Chanley, *ibid.*, **70**, 3914 (1948); *cf.* Milas, *et al.*, *ibid.*, **70**, 1584 (1948).

(5) Bourguel, *Bull. soc. chim.*, [4] **45**, 1067 (1929); Campbell and O'Connor, THIS JOURNAL, **61**, 2897 (1939).

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 147.

(7) (a) Kuhn and Ebel, *Ber.*, **58**, 919 (1925); (b) Böeseken, *Rec. trav. chim.*, **47**, 683 (1928); (c) Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936); (d) Winstein and Lucas, *ibid.*, **61**, 1576, 1581 (1939); (e) Lucas, Schlatter and Jones, *ibid.*, **63**, 22 (1941); (f) Lucas and Gould, *ibid.*, **63**, 2541 (1941); (g) Winstein and Grunwald, *ibid.*, **70**, 828 (1948); (h) Swern, *ibid.*, **70**, 1235 (1948).

SCHEME




synthesized[8] and its properties bear no resemblance to those of compound IV; (c) compound VII was prepared in the course of the present investigation and proved to be different from compound IV. Confirmatory evidence for the assigned structure was obtained when the bis-epoxide yielded, on catalytic hydrogenation, the *dl*-$\alpha,\beta$-dicyclohexylethylene glycol (V). Since the oxygen atoms remain attached to the same carbon atom after hydrogenolysis of the racemic bis-epoxide, the glycol of m. p. 154° must necessarily be a racemate. This compound is identical with the so-called "iso-$\alpha,\beta$-dicyclohexylethylene-glycol" of m. p. 153°, prepared by Buck and Ide[9] by condensation of glyoxal and cyclohexylmagnesium bromide. Thus, the *meso* configuration should be assigned to the isomeric $\alpha,\beta$-dicyclohexylethylene glycol, m. p. 194°, obtained by the catalytic reduction of benzoin.[10]

Treatment of the bis-epoxide IV with water in a sealed tube did not give the tetrahydroxy compound, but rather the 3,4-dihydroxy-dispiro[dicyclohexane-tetrahydrofuran] (VIII).[11,12] This was confirmed by the following synthesis; di-

(8) Pinkney, Nesty, Wiley and Marvel, *ibid.*, **58**, 972 (1936); Fisher and Stoffers, *Ann.*, **500**, 253 (1933).

(9) Buck and Ide, THIS JOURNAL, **54**, 820 (1932).

(10) Buck and Ide, *ibid.*, **53**, 3510 (1931).

(11) *Cf.* Przybytek, *Ber.*, **18**, 1352 (1885).

(12) This designation follows rule 23 for nomenclature of spiro systems, Patterson and Capell, "Ring Index," Reinhold Publ. Corp., New York, N. Y., 1940, p. 27. Under rule 22 this compound would be named 7,8-dihydroxy-15-oxa-trispiro[5,2,5,1]-pentadecane.

spiro[dicyclohexane-2,5-dihydrofuran] (VI), was prepared from compound II according to Burkhardt and Hindley.[13] This compound, when treated with perbenzoic acid, yielded the 3,4-epoxide (VII). This epoxide, on hydrolysis with a trace of acid, gave the expected *trans*-glycol, 3,4-dihydroxy-dispiro[dicyclohexane-2,5-tetrahydrofuran] (VIII). The *trans* position of the hydroxy groups with reference to the plane of the furan ring is anticipated since oxide rings open with inversion.[7]

This compound (VIII), on treatment with an equivalent amount of periodic acid, gave a quantitative yield of a new compound of elementary composition and molecular weight $C_{14}H_{24}O_4$. It gave no fuchsin test for aldehyde nor is it soluble in strong base, thus excluding a lactone formulation; therefore it is tentatively formulated as an internal acetal of a dialdehyde with a *p*-dioxane structure (IX). On oxidation of compound VIII with potassium permanganate in water or pyridine, a new acid $C_{13}H_{22}O_4$ was formed which has been tentatively assigned the structure X.

The bromination of 1,1′-vinylene-dicyclohexanol (II) yielded, in addition to the main product (III), relatively minor quantities of two by-products. One of them was free of bromine and proved to be identical with the dihydrofuran derivative VI. Evidently, the hydrobromic acid, whose evolution was observed during the bromination and must be ascribed to some minor side-reaction, is responsible for the furan formation from the 1,4-glycol (II). This is in analogy to the cyclizing effect of oxalic acid, leading to the same product.[13]

As the second by-product in the bromination, we have found *dl*-3,4-*trans*-dibromo-dispiro[cyclohexane-2,5-tetrahydrofuran] (XI). This substance was also obtained by bromination of the dihydrofuran (VI), which as stated in the preceding paragraph, was obtained in two ways: by the procedure of Burkhardt and Hindley and as the first by product in the above reaction. The transformation of compound III into compound XI by boiling with oxalic acid could not be effected.

## Experimental

**1,1′-Ethynylene-bis-cyclohexanol (I).**—This was prepared from acetylenedimagnesium bromide[14] and cyclohexanone according to the procedure of Du Pont[15] and Marvel[8] m. p. 108–109°; reported[8] m. p. 108–110°.

**1,1′-Vinylene-bis-cyclohexanol (II).**—Forty grams of compound I was dissolved in 100 cc. of absolute ethanol and hydrogenated at 2–3 atm. pressure in the presence of 0.5 g. of platinum oxide as catalyst. Hydrogenation was interrupted after 1 mole of hydrogen had been absorbed after twenty to thirty minutes, hydrogen uptake then slackened perceptibly and the product precipitated in the hydrogenation flask. The mixture was boiled down to 35 cc., filtered, cooled and the product recrystallized from ethanol; yield, 60–70%, m. p. 150–151°; reported 153–154[16]; 152°.[17] The same product was obtained when hydrogenation was carried out in the presence of a 5% palladium on barium sulfate catalyst at atmospheric pressure.

*Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.79. Found: C, 75.00; H, 10.88.[18]

***dl*-α,β-(1,1′-Dihydroxycyclohexyl)-α,β-dibromoethane (III).—Dispiro[dicyclohexane-2,5-dihydrofuran] (VI). 3,4-*trans*-Dibromo-dispiro[dicyclohexane-2,5-tetrahydrofuran] (XI).**—A solution of 64.8 g. (0.4 mole) of bromine in 600 cc. of dry carbon tetrachloride was added over a period of three hours to a vigorously stirred, ice cooled, illuminated (light bulb or sunlight) suspension of 90 g. (0.4 mole) compound II in 600 cc. of dry carbon tetrachloride. The reaction was allowed to continue for an additional forty-five minutes at the end of which time the evolution of hydrogen bromide became particularly evident. The precipitated product, after filtration and washing with small portions of cold carbon tetrachloride (the filtrates and washings were combined and will henceforth be referred to as filtrate A), was immediately refluxed for sixteen hours with 1000 cc. of carbontetrachloride, at the end of this refluxing period the evolution of hydrogen bromide ceased and formation of water droplets in the condenser was noted. The refluxing is necessary because attempts to purify the product by recrystallization alone gave material contaminated with an impurity which turned purple on standing. The carbon tetrachloride solution was decanted from precipitated tar, evaporated to 450 cc., cooled and the dibromohydrin collected. (The filtrate will henceforth be referred to as B.) Recrystallization from carbon tetrachloride gave product III m. p. 128–130° (decomposition) in 50% yield.

*Anal.* Calcd. for $C_{14}H_{24}O_2Br_2$: C, 43.74; H, 6.30; Br, 41.61. Found: C, 43.54; H, 6.19; Br, 40.78.

Filtrate A after refluxing for sixteen hours, during which time a copious evolution of hydrogen bromide and formation of water was noted, was then combined with filtrate B and the burgundy-colored solution was evaporated to dryness. The residue was treated with 500 cc. of petroleum ether (40–60° b. p.), cooled in ice and filtered from a dark violet solid (unidentified) (5–7 g.). The petroleum ether solution after two successive passages through a column (16 cm. length and 1.5 cm. internal diam.) of activated aluminum oxide (−80 mesh ALCOA) was evaporated to dryness. The partially crystalline residue (30 g.) was triturated with 100 cc. of cold 95% ethanol and filtered. Four grams of compound VI was obtained on recrystallization from ethanol m. p. 95–96°; it showed no depression of m. p. on admixture with an authentic sample of m. p. 95–96°.[13]

Distillation of the alcohol soluble portion gave 3 g. of the pure dihydrofuran VI b. p. 117–118° (9.5 mm.); $n^{25}D$ 1.4915. Reported 116–118° (10 mm.).[13] The identity of this fraction was confirmed by the preparation of its dibromo derivative which melted at 95–96° and showed no depression of melting point on admixture with the authentic sample. Four grams of unidentified high boiling material was present in the alcohol soluble portion.

**Hydrogenation of *dl*-α,β-(1,1′-Dihydroxycyclohexyl)-α,β-dibromoethane (III) to 1,1′-Ethylene-bis-cyclohexanol (XII).**—One hundred and ninety-eight mg. of compound XII in 25 cc. of ethanol was hydrogenated at atmospheric pressure employing 200 mg. of 5% palladium on calcium carbonate as catalyst. Hydrogenation ceased after the theoretical quantity (2 mole) of hydrogen was absorbed. The saturated glycol, obtained in quantitative yield, was recrystallized from petroleum ether (40–60°). It melted at 128–129° and showed no depression in m. p. on admixture with an authentic sample m. p. 128–129°

(13) Burkhardt and Hindley, *J. Chem. Soc.*, 987 (1938).

(14) Jozitch, *Bull. soc. chim.*, [3] **32**, 552 (1904); *cf.* Werner and Reynolds, THIS JOURNAL, **69**, 633 (1947).

(15) Du Pont, *Ann. chim.*, [8] **30**, 485 (1913).

(16) Pinkney, Nesty, Pearson and Marvel, THIS JOURNAL, **59**, 2662 (1937).

(17) Zal'kind, *J. Gen. Chem. (USSR)*, **5**, 1723 (1935); *C. A.*, **30**, 3407 (1936).

(18) We are indebted for the microanalyses to the late Dr. Gertrude Oppenheimer, Microchemical Laboratory, California Institute of Technology, Pasadena, Calif.

prepared by the hydrogenation of 1,1′-vinylenebiscyclohexanol (II) in glacial acetic acid at atmospheric pressure in the presence of $PtO_2$ as catalyst. Reported 128–129°.[16]

*dl*-**Bis-epoxide of *sym*-Dicyclohexylethane (IV).**—A solution of 17.2 g. (0.45 mole) of sodium hydroxide in 600 cc. of ethanol was added over a period of five minutes to a solution of 68 g. (0.177 mole) of the double bromohydrin (III) and set aside to stand for one to two days. After removal of the precipitated sodium bromide, the alcohol solution was evaporated almost to dryness *in vacuo* and the residue was treated with 400 cc. of ice water. The solid product was collected by filtration and recrystallized from petroleum ether (40–60°); colorless crystals, m. p. 58–58.7°; yield, 35–36 g. (90%).

*Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.91; H, 10.02.

*dl*-$\alpha,\beta$-**Dicyclohexylethylene Glycol (V).**—Two and three-tenths grams of the bis-epoxide IV dissolved in 30 cc. of purified glacial acetic acid was hydrogenated at atmospheric pressure in the presence of 200 mg. of platinum oxide as catalyst. It was necessary to add an additional 200 mg. of catalyst to bring the hydrogenation to completion (2 mole of hydrogen were absorbed). Evaporation of the solvent and recrystallization of the residue from Skellysolve L (b. p. 93–129°) gave crystals of m. p. 153–154°; reported 153°.[9]

*Anal.* Calcd. for $C_{14}H_{26}O_2$: C, 74.30; H, 11.58. Found: C, 74.18; H, 11.49.

**3,4-Expoxide of Dispiro[dicyclohexane-2,5-tetrahydrofuran] (VII).**—Compound VI (b. p. 116–118° (10 mm.) $n^{25}D$ 1.4900) was prepared according to the method of Burkhardt and Hindley[13] by boiling compound II with oxalic acid. It gave the authentic dibromide, m. p. 95–96°, on bromination according to the procedure of the same authors.

A solution of 16 g. (0.077 mole) compound (VI) was allowed to stand for one week at room temperature with 275 cc. of perbenzoic acid solution in carbon tetrachloride which contained 1.58 g. (0.1 mole) of active oxygen. At the end of this time the theoretical amount of oxygen had been absorbed. The carbon tetrachloride solution was washed thoroughly with 10% sodium hydroxide, water and dried over anhydrous sodium sulfate. Distillation gave a slight forerun of starting material and 10 g. of pure compound (VII) b. p. 143° (10 mm.) $n^{25}D$ 1.4930.

*Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.58; H, 10.06.

*dl*-**3,4-Dihydroxy-dispiro[dicyclohexane-2,5-tetrahydrofuran] (VIII).** (a) **From Compound (IV).**—A sealed tube containing 25 g. of the bis-epoxide (IV) and 75 cc. of water was heated at 120° for two to three days. After separating the water by decantation the residual viscous oil was mixed with 300 cc. of petroleum ether (40–60°) and cooled in ice; the product crystallized in felt-like needles. Recrystallization from Skellysolve L, b. p. 93–129° gave 7 g. of pure material m. p. 145–146°.

*Anal.* Calcd. for $C_{14}H_{24}O_3$: C, 70.07; H, 10.00. Found: C, 70.18; H, 9.67.

The residue after evaporation of the original petroleum ether was evaporatively distilled at 0.1 mm. and the fraction collected at 50–60° was redistilled to yield 4 g. of starting material boiling at 118–119° (0.5 mm.) $n^{25}D$ 1.4940 which solidified on standing. After recrystallization from petroleum ether (40–60°) it melted at 57–58° and showed no depression in melting point on admixture with the bis-epoxide (IV). The remainder of the petroleum ether solution were intractable polymers; yield, 30–35% based on recovered starting material.

(b) **From Compound (VII).**—One gram of compound (VII) was mixed with 10 cc. of water, containing three drops of dilute hydrochloric acid (hydrolysis did not occur with water alone) and heated in a sealed tube for two days at 120°. The reaction mixture was worked up as described above. Three-tenths of a gram of product, m. p. 145–146°, was obtained which showed no depression in m. p. when mixed with the glycol (VIII) as obtained above.

**Compound $C_{14}H_{24}O_4$ (IX).**—A suspension of 1.23 g. (0.005 mole) of the glycol (VIII) in 35 cc. of the solution of periodic acid containing 0.0054 equivalent of oxidizing agent was shaken mechanically for sixteen hours. The product was collected by filtration and recrystallized from 35% aqueous ethanol; yield 90% m. p. 133° (dec.). Molecular weight determination by Rast: 243 (camphor); average of four determinations (pinene dibromide): 260, calcd. 256.

*Anal.* Calcd. for $C_{14}H_{24}O_4$: C, 65.59; H, 9.45. Found: 65.76; H, 9.46.

**Compound $C_{13}H_{22}O_4$ (X).**—A mixture of 700 mg. (0.0029 mole) of compound (VIII), 1.05 g. (0.006 equivalent) of potassium permanganate in 30 cc. of 3.3% sodium hydroxide solution was heated on steam-bath with occasional shaking for fifteen to twenty minutes. The mixture was cooled and filtered. Acidification with dilute hydrochloric acid of the filtrate yielded the acid which after recrystallization from Skellysolve C (86–100°) melted with decomposition at 132–134°. The same product was obtained by oxidation of compound (VIII) by potassium permanganate in dried pyridine.

*Anal.* Calcd. for $C_{13}H_{22}O_4$: C, 64.42; H, 9.15. Found: C, 63.96; H, 9.02.

**Acknowledgment.**—The author wishes to express his gratitude to Dr. Harry Sobotka, Chief Chemist of the Mount Sinai Hospital, for his many valuable suggestions and interest in this work; and to acknowledge the able technical assistance of Miss Bernice Hamerman.

## Summary

The preparation and properties of the *dl*-bis-epoxide of symmetric dicyclohexylethane and of the isomeric 3,4-epoxide of dispiro[dicyclohexane-2,5-tetrahydrofuran] are described and discussed.

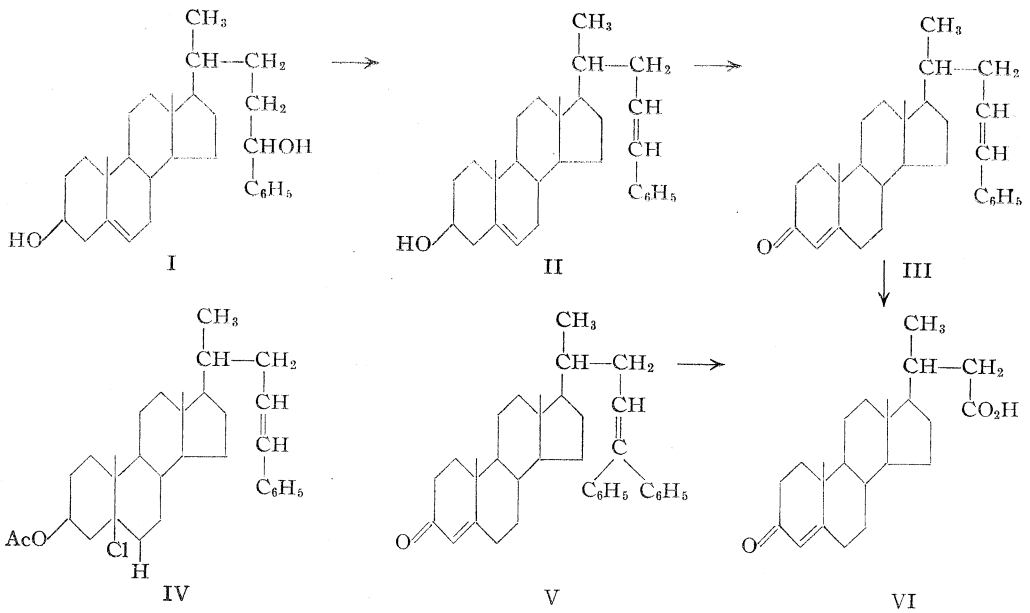
NEW YORK 29, N. Y. RECEIVED SEPTEMBER 27, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

# Steroid Acids and Their Transformation Products. V. 24-Phenyl-5,23-choladien-3β-ol and Derivatives

BY GEORGE B. SPERO, A. VERN MCINTOSH, JR., AND ROBERT H. LEVIN

The preparation of two 24-phenyl-5-cholen-3β,24-diols (I), epimeric at C-24, has been reported recently.[1] When the mixture of epimeric diols, or either pure isomer, was treated with anhydrous oxalic acid in refluxing Dowtherm A[2] selective dehydration occurred, giving a choladiene in 60–75% yield. The dehydration product (II) was precipitable with digitonin and readily formed a monoacetate which, on treatment with excess bromine in carbon tetrachloride, gave a tetrabromide. The acetate of II exhibited an ultraviolet absorption curve having a principal peak at 251 mμ and two smaller maxima at 285 mμ and 293 mμ, respectively. This is in good agreement with published data for substituted phenylethylene,[3] indicating that the dehydration product is 24-phenyl-5,23-choladien-3β-ol (II). If dehydration had occurred at C-3 the product would have been a derivative of 2,4-cholestadiene, or 3,5-cholestadiene, having absorption maxima in the region 267–275 mμ and 234–240 mμ, respectively.[4]



I II III IV V VI

An Oppenauer oxidation of 24-phenyl-5,23-choladien-3β-ol (II) with aluminum isopropoxide and cyclohexanone gave 24-phenyl-4,23-choladien-3-one (III), whose absorption curve exhibited maxima at 247, 285 and 293 mμ. The same ketone (III) was obtained by oxidizing the tetrabromide of II with chromic acid in acetic acid, debrominating with zinc, and isomerizing the 5,6 double bond with alkali. To complete the structure proof of these compounds, the ketone (III) was oxidized with chromic acid to give 3-keto-nor-4-cholenic acid (VI) in 50% yield. This keto acid, which has not been recorded previously in the literature, was also obtained, in 25% yield, by a similar oxidation of the corresponding diphenylethylene (V).

The acetate of the dehydration product (II) was treated at 0° with a saturated solution of hydrogen chloride in chloroform and acetic acid (1:1). The product of this reaction was characterized as 5-chloro-24-phenyl-23-cholene-3β-ol acetate (IV) on the basis of analysis and the fact that its ultraviolet absorption spectrum is identical with that of compound (II). When the acetate of 24-phenyl-5,23-choladien-3β-ol (II) was treated with hydrogen chloride in acetic acid–ether (1:16) at 0°, a mixture of mono- and dihydrohalogenated products was formed, as indicated by analysis and ultraviolet absorption data. Attempts to separate the components by fractional crystallization were not successful.

When cholesterol was treated with anhydrous oxalic acid in refluxing Dowtherm A for a period four times as long as the optimum time for the dehydration of the diol (I), better than 70% of the cholesterol was recovered unchanged. The selectivity of the dehydrating action of the oxalic

(1) Paper IV of this series, Levin, Spero, McIntosh and Rayman, THIS JOURNAL, **70**, 2958 (1948).

(2) Dowtherm A is a mixture consisting of 90% diphenyl ether and 10% biphenyl.

(3) Campbell, Linden, Godshalk and Young, THIS JOURNAL, **69**, 880 (1947); see also Campbell and Young, *ibid.*, **71**, 296 (1949).

(4) Dimroth, *Angew. Chem.*, **52**, 545 (1939).

acid on these secondary alcohols may be due to the influence of activating groups adjacent to the hydroxyl. Experiments designed to study and extend this reaction are now under way.

**Acknowledgment.**—We wish to express our appreciation to Dr. George Pish for the ultraviolet absorption data reported in this paper.

## Experimental[5]

**24-Phenyl-5,23-choladien-3β-ol Acetate (II).**—Eight grams (0.018 mole) of a mixture of the two epimers of 24-phenyl-5-cholen-3β,24-diol (I)[1] was allowed to reflux for ninety minutes with 16 g. of anhydrous oxalic acid[6] and 160 ml. of Dowtherm A. Most of the Dowtherm A was then removed by distillation *in vacuo*. During the distillation the oxalic acid sublimed out of the reaction mixture. The residue was cooled, dissolved in 200 ml. of ether and washed with 2% sodium bicarbonate solution and water. The ether solution was dried over anhydrous sodium sulfate and the solvent removed. The residue was dissolved in 200 ml. of hexane and passed over 230 g. of alumina[7] in a column 5 cm. in diameter. Elution with 700 ml. of hexane–benzene (1:1) removed the Dowtherm A, and the product (II) was obtained by the use of 800 ml. of benzene–methanol (92:8). The benzene–methanol eluate was taken to dryness and the residue crystallized from ether, giving 5.28 g. (69%) of 24-phenyl-5,23-choladien-3β-ol, m.p. 105–118°. This material could not be crystallized to a sharper melting point because of its tendency to solvate. It was heated for three hours on the steam-bath with acetic anhydride and pyridine, giving 4.88 g. (87%) of the acetate, m.p. 172–176°. Recrystallization from methanol–ether gave pure material, m.p. 176.5–177.5°; $[\alpha]^{24}D$ −31.4° (62.1 mg. in 10 ml. of chloroform; 2-dm. tube: $\alpha_D$ −0.39°). Absorption spectrum: maxima at 251 mμ (log *E*, 4.29), 285 mμ (log *E*, 3.25), 293 mμ (log *E*, 2.97), taken in 95% alcohol (*c*, 2.210 mg. in 100 ml.).

*Anal.* Calcd. for $C_{32}H_{44}O_2$: C, 83.43; H, 9.63; $CH_3CO$, 9.3. Found: C, 83.10; H, 9.60; $CH_3CO$, 9.5.

**The tetrabromide** was formed by treating 60 mg. of the acetate in 2 ml. of carbon tetrachloride with an excess of bromine in the same solvent. After standing at room temperature the solution was evaporated to dryness and the residue crystallized from methanol–ether, m.p. 168–175°. Recrystallization gave the tetrabromide of 24-phenyl-5,23-choladien-3β-ol acetate, m.p. 171–175°.

*Anal.* Calcd. for $C_{32}H_{44}O_2Br_4$: Br, 40.96. Found: Br, 40.56, 40.88.

Saponification of 3.94 g. of the acetate in 225 ml. of methanol with 3.9 g. of potassium hydroxide in 9 ml. of water gave 3.12 g. (84%) of recrystallized hydroxy compound (II), m.p. 107–113°. Numerous recrystallizations from ether, benzene, alcohol, acetone and other solvents failed to give sharper melting material. Analysis indicated varying degrees of solvation.

**24-Phenyl-4,23-choladien-3-one (III). A. By Oppenauer Oxidation.**—Three grams (0.007 mole) of 24-phenyl-5,23-choladien-3β-ol was dissolved in 90 ml. of toluene and 60 ml. of cyclohexanone. Ten ml. of the solution was distilled to remove traces of moisture and 3 g. of aluminum isoproxide was added. The mixture was heated under reflux for two and one-half hours, cooled, and diluted with a mixture of 200 ml. of 5% hydrochloric acid and 100 ml. of ether. The aqueous phase was separated and extracted with 100 ml. of fresh ether. The combined ether solution was washed with 5% hydrochloric acid and water, then dried and concentrated *in vacuo*. The residue was crystallized from methanol giving 2.6 g. (86%) of the keto diene (III), m.p. 130–154°. Recrystallization from ether–methanol gave 76% of pure material, m.p. 159–160.5°; $[\alpha]^{25}D$ +99.8° (52.6 mg. in 5 ml. of chloroform; 2-dm. tube; $\alpha_D$ +2.10°. Absorption spectrum: maxima at 244 mμ (log *E*, 4.50), 285 mμ (log *E*, 3.24), 293 mμ (log *E*, 2.98) taken in 95% alcohol (*c*, 2.192 mg. in 100 ml.).

*Anal.* Calcd. for $C_{30}H_{40}O$: C, 86.47; H, 9.68. Found: C, 86.51; H, 9.43.

**B. By Chromic Acid Oxidation of the Tetrabromide of II.**—The tetrabromide prepared from 270 mg. of 24-phenyl-5,23-choladien-3β-ol was oxidized with chromic anhydride in acetic acid, debrominated with zinc dust and acetic acid in ether, and isomerized with alkali to give 55 mg. (32%) of crystals melting at 159–163°. The 3-keto compounds (III) prepared by the two methods gave the same melting point on admixture.

**5-Chloro-24-phenyl-23-cholen-3β-ol Acetate (IV).**—A solution of 2.25 g. (0.005 mole) of 24-phenyl-5,23-choladien-3β-ol acetate in 9 ml. of chloroform and 4.5 ml. of glacial acetic acid was cooled to 0° and saturated with dry hydrogen chloride. After standing at 0° for twelve days, the solution was evaporated to dryness *in vacuo*. The residue was crystallized from ether, giving 0.8 g. (33%) of the 5-chloro compound (IV), m.p. 160–188°. Several recrystallizations from acetone gave a small recovery of pure material, m.p. 194–198° (dec.). Absorption spectrum: maxima at 251 mμ (log *E*, 4.30), 285 mμ (log *E*, 3.27), 295 mμ (log *E*, 2.99), taken in 95% alcohol (*C*, 2.171 mg. in 100 ml.); $[\alpha]^{25}D$ +21.4° (163.8 mg. in 10 ml. of chloroform; $\alpha_D$ +0.35°).

*Anal.* Calcd. for $C_{32}H_{45}O_2Cl$: C, 77.31; H, 9.12; Cl, 7.13. Found: C, 77.30; H, 9.05; Cl, 6.99.

When 4.7 g. of 24-phenyl-5,23-choladien-3β-ol acetate was dissolved in 800 ml. of ether and 50 ml. of acetic acid and similarly treated with dry hydrogen chloride, 4.3 g. of material, m.p. 178–186°, was obtained. Repeated crystallizations gave material with a constant m.p. of 185–187°. Analyses indicated it was essentially the dichloro compound, contaminated with some of the monochloro derivative. On refluxing this mixture with quinoline pure 24-phenyl-5,23-choladien-3β-ol acetate, m.p. and mixed m.p. 175–176.5°, was recovered in poor yield. Similar treatment with pyridine and dimethylaniline gave intractable mixtures.

**3-Keto-nor-4-cholenic Acid (VI).**—A solution of 700 mg. of chromic anhydride in 0.7 ml. of water and 7 ml. of acetic acid was added over a period of an hour to 400 mg. (0.0009 mole) of 24-phenyl-4,23-choladien-3-one (III) dissolved in 15 ml. of acetic acid at room temperature. The mixture was allowed to stand one hour, then the excess chromic acid was decomposed with 3 ml. of methanol. The solution was poured into 4 volumes of water, extracted with ether, and the ether solution washed with dilute hydrochloric acid and with water. On extraction of the ether solution with 5% aqueous sodium carbonate an insoluble sodium salt was formed. The aqueous suspension was separated and acidified with 3 *N* hydrochloric acid, giving 187.5 mg. (54%) of the keto acid (VI), m.p. 190–200°. Several crystallizations from acetone–water (1:1) brought the melting point to 208–211°.

*Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.29; H, 9.64.

**The methyl ester** of 3-keto-nor-4-cholenic acid was prepared with diazomethane and was crystallized from alcohol–water, m.p. 140–142°; $[\alpha]^{25}D$ +96.2° (15.6 mg. in 2 ml. chloroform; $\alpha_D$ +0.75°). Absorption spectrum: maximum at 241 mμ (log *E*, 4.20 in absolute alcohol).

*Anal.* Calcd. for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.58; H, 9.58.

Oxidation of 350 mg. of 24,24-diphenyl-4,23-choladien-3-one (V)[8] with 500 mg. of chromic anhydride under similar conditions over a period of three hours gave a

(5) All m. p.'s are corrected. Analyses and rotations by the Upjohn microanalytical and physics group. Ultraviolet absorption spectra taken on a Beckman Quartz Spectrophotometer, Model DU.

(6) "Org. Syntheses," Coll. Vol. I, 421, 2nd ed., 1941.

(7) Fisher Adsorption Alumina; obtained from the Fisher Scientific Co. and used without further treatment.

(8) Meystre, Wettstein and Miescher, *Helv. Chim. Acta*, **30**, 1022 (1947).

gummy acid fraction, which on crystallization from acetone–water yielded 66.6 mg. of 3-keto-nor-4-cholenic acid, m.p. 200–207°; methyl ester, m.p. 139–142°. A mixture of the methyl esters obtained from the monophenylethylene (III), and the diphenylethylene (V) gave no depression of the melting point.

**Treatment of Cholesterol with Oxalic Acid.**—A mixture of 1.0 g. of cholesterol, 4.0 g. of anhydrous oxalic acid, and 30 ml. of Dowtherm A was heated under reflux for five hours in an atmosphere of nitrogen. The Dowtherm was removed by steam distillation, and the water insoluble residue was adsorbed on 116 g. of chromatographic alumina from petroleum ether solution. Elution with petroleum ether–benzene (3:2) gave 90 mg. of material which was not further investigated. Elution with benzene–methanol (96:4) gave 727 mg. of cholesterol which after one recrystallization from 95% alcohol melted at 148–149°.

## Summary

24-Phenyl-5-cholen-3β,24 diols, epimeric at C-24, have been dehydrated by anhydrous oxalic acid to give 24-phenyl-5,23-choladien-3β-ol.

24-Phenyl-4,23-choladien-3-one has been prepared and oxidized to 3-keto-nor-4-cholenic acid.

The addition of hydrogen chloride to 24-phenyl-5,23-choladien-3β-ol acetate has been studied.

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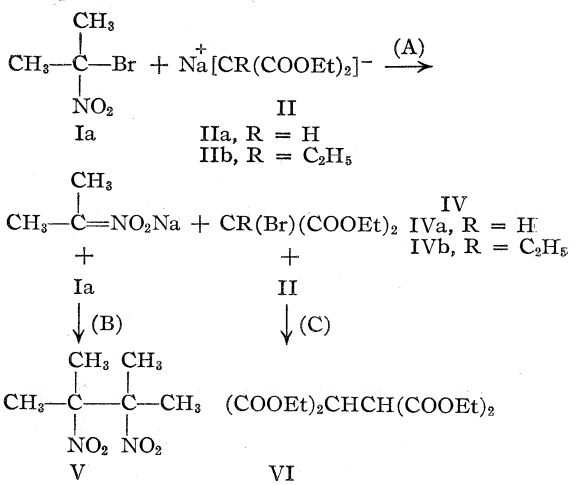
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOPE COLLEGE]

# The Malonic Ester Reaction with 1-Halo-nitroparaffins

BY EUGENE E. VAN TAMELEN[1] AND GERRIT VAN ZYL

In view of the present availability of the nitroparaffins, the reaction of the readily prepared 1-halo-nitroparaffins with malonic ester was undertaken with the purpose of determining the effect, if any, of the highly electronegative nitro group upon the course of the reaction. In only one instance was a normal alkylation accomplished which resulted in a 1-nitroalkyl malonic ester.

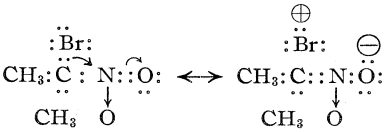
2-Bromo-2-nitropropane, Ia, was selected as a model for the bromo series, since there is no acidic hydrogen present to complicate the reaction. Upon carrying out the reaction of Ia with sodium malonic ester, IIa, under the usual conditions, two organic products were isolated: 2,3-dinitro-2,3-dimethylbutane, V, and ethane tetracarboxylic ester, VI. Since bromomalonic ester, IVa, is known to react rapidly with IIa to yield VI, IVa was postulated as an intermediate.




According to this series, one-half mole of Ia should be sufficient to convert IIa completely to VI, provided the known reaction (B) is slow.[2] It was found that the rapid addition of one-half mole of Ia to IIa gave 73% VI, with no detectable amount of V.

Since the reaction of alkyl bromomalonic esters with sodium alkyl malonic esters is not nearly as rapid as that of IVa and IIa,[3] it seemed likely that an intermediate, IVb, could be isolated if sodium ethyl malonic ester, IIb, were employed instead of IIa. Indeed, a 69% yield of IVb was obtained in this way. No matter how rapidly Ia was added to IIb, however, the formation of V could not be completely avoided—a reflection of the less rapid reaction rate of alkyl malonic esters. Increased time of addition of Ia and prolonged stirring may result in as high a yield as 30% of V.

Reaction (A) may probably be best interpreted in terms of a positively charged bromine ion. Similar reactions have been recorded in which one of the reactants possesses a halogen atom attached to the same carbon atom as one or more highly negative groups.[3] The displacement of halogen as a positive ion may be attributed to two causes: (1) the higher attraction of electrons by the nitro group as illustrated in the resonance forms




and (2) the stabilization of the resulting nitro carbanion through resonance.

The mixture of sodium salts which precipitated from the alcoholic medium during the course of the reaction was shown to consist of sodium 2-nitropropane, III, sodium bromide and sodium nitrite VII. The presence of VII along with III was unexpected, but is paralleled by the observations of Meyer[4] and Nygaard, *et al.*[5]

(1) Present address: Harvard University, Cambridge, Massachusetts.

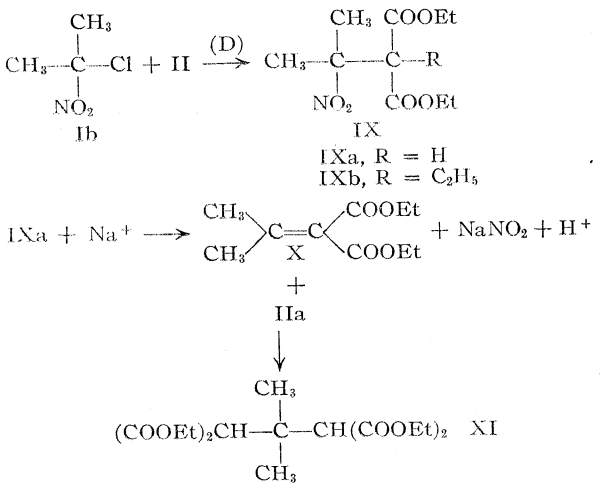
(2) L. W. Seigle and H. B. Hass, *J. Org. Chem.*, **5**, 100 (1940).

(3) C. L. Jackson and F. C. Whitmore, THIS JOURNAL, **37**, 1919 (1915).

(4) V. Meyer, *Ann.*, **175**, 88–93 (1875).

(5) E. M. Nygaard, J. H. McCracken and T. T. Noland, U. S. Patent 2,370,185.

Whereas the reaction of Ia and II proceeds *via* the positive bromine route, 2-chloro-2-nitropropane, Ib, and II result in a normal nucleophilic displacement on carbon. This is somewhat surprising in view of the foregoing, since the chlorine substituent, like the bromine, is less electronegative than the nitro group. The treatment of IIa with Ib resulted in the production of two esters: isopropylidene malonic ester, X, and isopropylidene dimalonic ester, XI



The nitro group in IXa is labilized by the acidic hydrogen in the 2-position; in the presence of strong base, sodium nitrite is easily lost with the formation of X. The addition of IIa to X yields XI.

*A priori*, it was not possible to determine at this point whether the series of reactions actually proceeded as outlined above; displacement of the nitro group in (D), yielding 1-chloro-1-methylethylmalonic ester, followed by loss of sodium chloride would also account for the formation of X. The question was simply solved by employing sodium ethyl malonic ester, which would yield a stable, substituted ester with no reactive hydrogen. 1-Nitro-1-methylethyl ethylmalonic ester, IXb, was obtained in a 68% yield along with 13% ethyl isopropyl malonic ester. The mechanism by which the latter compound is formed is not obvious, but a similar malonic ester alkylation is known in which one of the chlorine atoms in carbon tetrachloride is replaced by hydrogen during reaction.[6]

An attempt to synthesize IXb by refluxing a suspension of dry sodium 2-nitropropane in a xylene solution of IVb was unsuccessful; only starting materials were recovered.

As a model of a 1-halo-nitroparaffin with an acidic hydrogen, 1-chloronitroethane, XII, was selected for reaction with sodium malonic ester. Under conditions similar to those described above for the reaction with Ia, the preponderant part of the ester was recovered, in spite of the fact that a great deal of solid material was precipitated during an exothermic reaction. Apparently the initial reaction is merely the regeneration of malonic ester from its sodium salt by the stronger acid XII. XII could not be regained, however, upon acidification of the salt material, which proved to be mainly sodium chloride rather than the expected sodium 1-chloronitroethane.

(6) O. Dimroth, *Ber.*, **35**, 2883 (1902).

## Experimental[7]

**2-Bromo-2-nitropropane.**[8]—The following procedure was used for the preparation of a pure starting material. 2-Nitropropane[9] (178 g., 2 moles) was dissolved, with external cooling, in a solution of 132 g. 85% potassium hydroxide pellets in 500 cc. of water. The resulting solution of sodium 2-nitropropane was cooled in an ice-bath while bromine (320 g., 2 moles) was dropped in with stirring at such a rate as to maintain the temperature at 35–40°. After the addition was complete, the reaction mixture was usually colored red; solid sodium sulfite was added with vigorous stirring until the mixture became colorless. The heavy, oily layer of the bromonitroparaffin was separated from the water layer and washed twice with 100-cc. portions of water. The product, after drying over sodium sulfate, was essentially pure, since 99% distilled at 151.7–151.8° (745 mm.) forerun: 150.5–151.7°); yield 89%. Many of the 1-halonitroparaffins are lachrymators, and care should be exercised in their use.

**The Reaction of 2-Bromo-2-nitropropane with Sodium Malonic Ester.**—Sodium malonic ester (0.4 mole) was prepared in 200 cc. of absolute alcohol contained in a 500-cc. three-neck flask equipped with a stirrer, thermometer, dropping funnel and reflux condenser with calcium chloride tube attached (a similar set-up was used in the subsequently described experiments). 2-Bromo-2-nitropropane (33.6 g., 0.2 mole) was dropped in with stirring over a period of twenty-five minutes; the temperature of the contents was maintained at 35° by external cooling. Stirring was continued at room temperature for four hours. Petroleum ether (50 cc.) was added and the flask cooled in an ice-bath and the contents filtered. The colorless material collected was washed with petroleum ether and was then added to 200 cc. of water. The salts dissolved, and the white needles of ethane tetracarboxylic ester which floated on top were filtered off and dried at 60°; yield, 41.6 g., m.p. 72–73°. After two recrystallizations from alcohol–petroleum ether, the melting point was 75.0–75.3°, which was not depressed upon admixture with an authentic sample (m.p. 75.0–75.3°).[10] Approximately five additional g. of the ester may be obtained from the initial alcoholic mother liquor by removing the excess alcohol and adding an excess of water; the thick oil which comes down is redistilled under reduced pressure.

The identity of the sodium 2-nitropropane which was obtained mixed with the ester was indicated in the following way. The aqueous solution obtained when the mixture was added to water was acidified with sodium bisulfite, the resulting 2-nitropropane extracted with ether and identified by its boiling point and conversion to the blue monomeric isopropylpseudonitrole, $(CH_3)_2C(NO)NO_2$, by means of nitrous acid (red, white and blue test).

**Reaction of 2-Bromo-2-nitropropane with Sodium Ethyl Malonic Ester.**—2-Bromo-2-nitropropane (50.4 g., 0.3 mole) was added dropwise over a period of four minutes to a solution of 0.32 mole sodium ethyl malonic ester in 175 cc. absolute alcohol maintained at 40° by external cooling. Stirring was continued for ten minutes. The thick mush of sodium 2-nitropropane and sodium bromide which had formed was filtered off with suction and washed

(7) All melting points corrected. All yields based upon the amount of starting material consumed.

(8) V. Meyer and J. Tscherniak, *Ann.*, **180**, 118 (1876).

(9) Eastman Kodak Co. practical grade was redistilled with a Todd column: b. p. range, 119.7–120.0° (745 mm.)

(10) H. F. Finkelstein, *Ber.*, **43**, 1532 (1910).

with 50 cc. of ether. The salt mixture was then triturated with 200 cc. of ether and again filtered. The ether washings were added to the main filtrate. The excess ether and alcohol was removed by distillation under reduced pressure using a heating mantle; the internal temperature was not allowed to rise above 95°. After cooling to room temperature, 100 cc. of water was added and the two phases were allowed to stand overnight. After this time, a small amount of snow-white crystals had separated from the ethyl bromomalonic ester layer. It was filtered off, washed with a few cc. of ether and dried at room temperature (1.5 g.). The melting point 215.0–215.5° was not lowered upon mixing with 2,3-dinitro-2,3-dimethylbutane[2] (m.p. 215.5–216.0°, purified by sublimation). The halomalonic ester was separated from the water layer and the latter extracted with 50 cc. of ether. The combined ester and extract were dried over sodium sulfate. Fractionation was begun in a Todd column but had to be discontinued after a forerun of 14.5 g. ethyl malonic ester had been collected, since the dinitrohexane which sublimed at the same time clogged the narrow takeoff passage. Distillation was continued from a Claisen flask. Two rectifications gave 44.0 g. of ethyl bromomalonic ester, b.p. 121–124° (12 mm.). The product was contaminated with small amounts of the dinitrohexane, which could not be completely removed by further fractionation. The infrared spectrum of a middle cut was identical with that of an authentic sample[11] (b.p. 124.0° (11.5 mm.) cor.) which had been saturated with dinitrohexane for comparison purposes.

**Reaction of 2-Chloro-2-nitropropane with Sodium Malonic Ester.**—2-Chloro-2-nitropropane (24.7 g., 0.2 mole), b.p. 88.5–88.7° (174 mm.), was added in one lot to 0.4 mole of sodium malonic ester dissolved in 200 cc. absolute alcohol. Stirring was continued for sixty-five hours while the internal temperature was maintained at 40–45° by a heating mantle. Stirring was discontinued, and the mixture of salts which had precipitated was filtered out. The excess alcohol was then removed under reduced pressure and 100 cc. of water added. The ester layer was separated and one ether extract of the water layer added to it. After drying over sodium sulfate, fractionation was begun in a Todd column. After a forerun of malonic ester, 17.6 g. (44%) of isopropylidene malonic ester was collected. The remainder was distilled from a Claisen flask, yielding 19.6 (27%) of isopropylidene dimalonic ester (b.p. 195–200° (12 mm.)). The unsaturated ester was identified by a characteristic, known reaction:[12] the concomitant ammonation and hydrolytic cleavage to acetone (isolated as the semicarbazone, m.p. 190.0–191.5°) and malonamide (m.p. 173.2–173.6°; mixed m.p. 173.2–173.6°). The reported melting points of these compounds are, respectively, 190–191° and 170°.[13] The tetra-ester was hydrolyzed to 2,2-dimethyl-1,5-pentanedioic acid (m.p. 99.8–100.0°); the anhydride (m.p. 125.0–125.5°) and the monoanilide (m.p. 135.0–135.5°) were prepared. The melting points given in the literature are, respectively, 100–101°[14] (103–104°[15]), 124°[14] and 131°.[16]

**1-Nitro-1-methylethyl Ethyl Malonic Ester.**—2-Chloro-2-nitropropane (123.5 g., one mole) was added dropwise over a period of four to five hours to a refluxing, stirred solution of one mole of sodium ethyl malonic ester in 550 cc. of dry ether. Refluxing and stirring were continued for thirty-six hours. The excess ether was removed by distillation under diminished pressure and the crude ester isolated in the manner previously described. Fractionation with a Todd column gave 47 g. unreacted 2-chloro-2-nitropropane and 18.5 g. ethyl isopropyl malonic ester (b.p 129.5–132.0° (20 mm.); 231–234° (742 mm.)). Crossley and Le Sueur[17] give 232–233° as the boiling point of the latter compound. The remaining, undistilled ester was transferred to a Claisen flask and 116 g. of 1-nitro-1-methylethyl ethyl malonic ester collected at 161–165° (14.0 mm.). A middle cut boiling at 164.0° (14.0 mm.) was used for analysis.

*Anal.* Calcd. for $C_{12}H_{21}O_6N$: C, 52.42; H, 7.69; N, 5.09; mol. wt., 275; sapn. equiv., 91.8.[18] Found: C, 52.68, 52.56; H, 7.17, 7.06; N, 5.17; mol. wt. (Rast), 276; sapn. equiv., 89.8; $n^{22}D$ 1.4335. The Bose[19] method for the detection of a nitrite or nitro group was positive. The infrared spectrum of the ester showed distinct absorption maxima at 1550 and 1350 $cm.^{-1}$; the characteristic maxima of the nitro group are at 1550 and 1380 $cm.^{-1}$ whereas those of the nitrite group fall at 1660–1730 and 1160 $cm.^{-1}$.[20]

The infrared spectrum of the ethyl isopropylmalonic ester was not identical with that of an authentic sample; however, they were so nearly so that the slight discrepancy may be assumed to be due to an impurity in the experimental product.

**Acknowledgment.**—The authors wish to express their gratitude to the Commercial Solvents Corporation, who supplied the chloronitroparaffins used in this investigation.

## Summary

2-Bromo-2-nitropropane reacts with sodium malonic esters to give, as the initial products, sodium 2-nitropropane and bromomalonic esters. Additional products encountered are described. A "positive bromine ion" mechanism is proposed.

2-Chloro-2-nitropropane reacts normally with sodium malonic esters to give 1-nitro-1-methylethyl malonic esters as the initial products. In the case of the reaction with unsubstituted malonic ester, the nitroalkyl malonic ester is unstable and loses the elements of nitrous acid to yield isopropylidene malonic ester.

HOLLAND, MICHIGAN RECEIVED SEPTEMBER 27, 1948

(11) C. S. Palmer and P. W. McWherter, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 245.

(12) A. Koetz, *J. prakt. Chem.*, [2] **75**, 498 (1907).

(13) J. V. Backes, R. W. West and M. A. Whitely, *J. Chem. Soc.*, **119**, 359 (1921).

(14) K. Auwers, *Ber.*, **28**, 1132 (1895).

(15) I. Guareschi, *Chem. Centr.*, **72**, I, 821 (1901).

(16) W. H. Perkin, Jr., *J. Chem. Soc.*, **69**, 1476 (1896).

(17) A. W. Crossley and H. R. Le Sueur, *J. Chem. Soc.*, **77**, 90 (1900).

(18) Assuming the complete displacement of the nitro group, which apparently takes place under the drastic conditions necessary for complete saponification, *viz.*, refluxing for two hours in an ethylene glycol solution of potassium hydroxide.

(19) Bose, *Analyst*, **56**, 504 (1931).

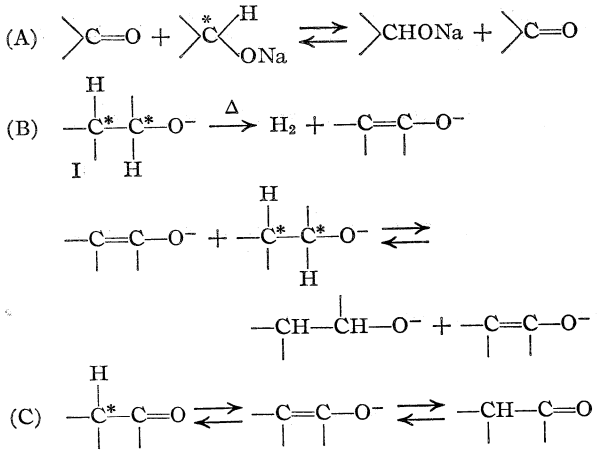
(20) H. Lenormant and P. L. Clement, *Bull. soc. chim. France*, 559 (1946)

[CONTRIBUTION FROM THE CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

# Stereochemical Equilibration of Alcohols[1]

BY W. VON E. DOERING AND T. C. ASCHNER

From many examples in the literature,[2,3,4] it is apparent that alcohols of the general structure I may be brought to stereochemical equilibrium[5] by treatment with alkoxide ion. Both Wagner-Jauregg[2] and Hückel[3] have suggested that the equilibration is initiated by the dehydrogenation of sodium alcoholate to aldehyde or ketone which then takes part in a Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation. Wagner-Jauregg has formulated



the reaction in general terms (A) and has left an explanation of the stereochemical equilibration of alcohols of type I to the more specific suggestions of Hückel (B) although, as has been pointed out,[4] recognition of the inevitable enolization of the carbonyl compounds related to alcohols of type I suffices to accommodate the stereochemical equilibration of the latter (C).

Doering, Cortes and Knox[4] have presented considerable evidence in support of the modified mechanism (A and C) but have been unable to demonstrate (in the case of quinine) the striking consequence of the mechanism, that optically active alcohols should not be racemized in the complete absence of oxidants. In the present work, it is shown that the racemization of (−)-phenylmethylcarbinol by potassium *t*-butoxide at 100° can be completely inhibited by excluding oxygen, potassium peroxides and carbonyl compounds, and that, under otherwise non-racemizing conditions, the addition of the rapid oxidation–reduction system,[6] fluorenone (3 mole %)–fluorenol (6 mole %), causes 56% racemization. In another example, (−)-2-methylbutanol-1, stable to boiling for twenty hours with 5 mole % of sodium, is racemized in a few hours by adding 5 mole % of benzophenone.[7] Similarly with aluminum isopropoxide as catalyst, no racemization occurs until an oxidant, benzophenone, is added.

These experiments establish with considerable certainty that the presence of carbonyl compound is a necessary condition for effecting the stereochemical equilibration of alcohols of type I and can be interpreted to mean that a reversible oxidation–reduction process is the essential mechanism of the equilibration. The further conclusion can be drawn that no initiating carbonyl compound is formed by the elimination of hydrogen gas as proposed by both Wagner-Jauregg and Hückel, at least not at the comparatively low temperature of these equilibrations, although at higher temperatures where alkoxide ion is known to decompose to hydrogen,[8] dehydrogenation may serve as a way of introducing initiating carbonyl compound.

The unique structural consequence of mechanism B, that it should be impossible stereochemically to equilibrate those secondary alcohols in which lack of α-hydrogen prohibits dehydrogenation to a related enolate ion, has been given temporary confirmation in the negative observation that α- and β-fenchol cannot be epimerized, even under conditions drastic enough to form the corresponding ketone, fenchone.[9] Contrarywise it has now been established that both α- and β-fenchol can be epimerized when the rapid oxidation–reduction system, fluorenol–fluorenone, is added. Coupled with the ability of non-enolizable ketones such as benzophenone and fluorenone to initiate stereochemical equilibration, the successful epimerization of the fenchols invalidates direct dehydrogenation to an enolate ion as the mechanism of the effectual oxidation–reduction process. Hückel's mechanism (B) is presumably generally incorrect in that it limits the reaction to alcohol–carbonyl systems having alpha hydrogen.

(1) This work, taken from a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University, was presented at the 112th meeting of the American Chemical Society, September 7, 1947, New York, N. Y., by T. C. Aschner, present address, Smith, Kline and French Laboratories, Philadelphia, Pa.

(2) Wagner-Jauregg in Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, pp. 866–867.

(3) Hückel, "Theoretische Grundlagen der organischen Chemie," Akademische Verlagsgesellschaft, Leipzig, 2nd ed., 1934, Vol. I, pp. 286–288.

(4) Doering, Cortes and Knox, THIS JOURNAL, **69**, 1700 (1947).

(5) The term "stereochemical equilibration" is defined to embrace racemization, partial racemization, epimerization, and *cis-trans* interconversion, the specific process depending on the detailed structure of the alcohol under consideration.

(6) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

(7) In the absence of consciously added oxidant, Stevens [*ibid.*, **54**, 3732 (1932)] has observed a much slower rate of racemization.

(8) Hückel cites the Guerbet reaction and the inversion of *cis-cis*-α-decalol [Hückel and Naab, *Ber.*, **64**, 2137 (1931)]. Compare footnote 18 of ref. 4.

(9) Hückel, Kindler and Wolowski, *ibid.*, **77**, 220 (1944).

The failure to epimerize the fenchols in the presence of fenchone and the vain attempt to effect the partial racemization of quinine in the presence of quininone[4] clearly indicate that excessively slow rates of oxidation–reduction may conspire to make the necessary presence of carbonyl compound an insufficient condition for stereochemical equilibration. In these, as well as in less extreme cases, the stereochemical equilibration can be catalyzed by adding a much more rapid oxidation–reduction system.[6] For example, in the very slowly reacting fenchol–fenchone system (1), the addition of fluorenol and fluorenone, which interact very rapidly (2), introduces a cross reaction (3) of intermediate rate that results in the more rapid establishment of equilibrium (1).[10]

Fenchone* + Fenchol $\underset{\leftarrow}{\overset{\rightarrow}{(1)}}$ Fenchol* + Fenchone

Fluorenol* + Fluorenone $\underset{\leftarrow}{\overset{\rightarrow}{(2)}}$ Fluorenone* + Fluorenol

Fluorenol + Fenchone $\underset{\leftarrow}{\overset{\rightarrow}{(3)}}$ Fluorenone + Fenchol

## Experimental[11]

**Racemization of Phenylmethylcarbinol.**—(−)-Phenylmethylcarbinol, $[\alpha]^{27}D$ −50.6° ($c$ = 3, toluene), b.p. 86.5–87.5° (8 mm.), was obtained by resolution of the acid phthalate according to Downer and Kenyon.[12] Decomposition of the active acid phthalate and distillation of the active alcohol were carried out under nitrogen. The racemizations were effected in thiophene-free toluene which had been distilled repeatedly from sodium under nitrogen. Potassium $t$-butylate was prepared by dissolving freshly cut and carefully washed potassium in $t$-butyl alcohol in a nitrogen atmosphere. $t$-Butyl alcohol was purified by refluxing over potassium permanganate and twice distilling from sodium under nitrogen. Preliminary experiments, carried out in the simple apparatus customarily used to avoid contact with air, led to considerable and unpreventable racemization even in the absence of added oxidant. The more complicated apparatus shown in Fig. 1 prevented contamination by oxidants when employed according to the following procedure: After the system had been flushed with nitrogen, 10 cc. of toluene from flask A, containing purified toluene and 1 g. of sodium, was distilled under nitrogen into D. The remaining system was closed at G and E, D was detached and potassium, freshly cut and weighed under toluene, was quickly dropped into D which was then reattached to G and flushed with nitrogen through L, F and E. L and I were closed, G was opened and toluene was forced through E into F by nitrogen pressure. Five drops of $t$-butyl alcohol was added through B to A and was distilled with 10 cc. of toluene into D. All liquid was forced out of D into F as before and the surface of the potassium was further cleaned by rinsing with two additional 10-cc. portions of toluene distilled from A; $t$-butyl alcohol (3.0 g.) was added through B to A and was distilled into D with 10 cc. of toluene. Still under positive nitrogen pressure, D was heated in an oil-bath until all the potassium had reacted. A weighed amount of (−)-phenylmethylcarbinol was added through H to D and the volume in D was adjusted to 30 cc. by distilling additional toluene from A. All reagents added through H or B were forced into the system by applying excess nitrogen pressure. Finally D was heated in an oil-bath at 99–100°. In experiments 1 and 4, fluorenol and fluorenone in toluene were added to D through H prior to the final heating. After being cooled, the reaction mixture was forced into the cleaned flask F, and neutralized under nitrogen with dilute hydrochloric acid added through J. Phenylmethylcarbinol was isolated from reactions 1 to 3 by fractionation of the washed reaction mixtures through a 10-cm. Vigreux column, the specific rotation of the main fraction b.p. 203–204° (760 mm.), being determined at 27° ($c$ = 3, toluene). Partly racemized phenylmethylcarbinol from reaction 4 was separated from non-alcoholic impurities by conversion to the acid phthalate. Treatment of alkali-insoluble compounds extracted from the alkaline solution of the acid phthalate with 2,4-dinitrophenylhydrazine, yielded only 0.04 g. of acetophenone-2,4-dinitrophenylhydrazone. The results of these experiments are compiled in Table I.

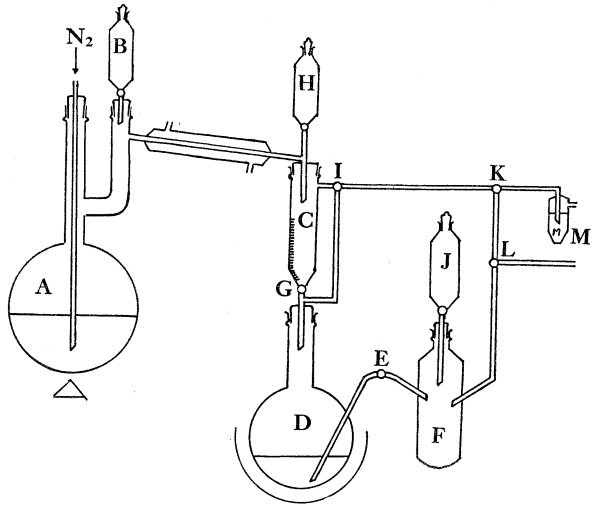



Fig. 1.

TABLE I

| Expt. | Potassium in mole % | $t$-Butyl alcohol in mole % | Phenylmethylcarbinol, g. | Reaction time, hours | $[\alpha]^{27}D$ of phenylmethylcarbinol | % Racemization |
|---|---|---|---|---|---|---|
| 1 | 20 | 100 | 2.0 | 19 | −49.3° | 2 |
| 2[a] | 20 | 100 | 2.0 | 17 | −27.5° | 46.5 |
| 3[b] | 20 | 100 | 4.0 | 17 | −49.4° | 2 |
| 4[b] | | | | 17 | −22.4° | 56 |

[a] Prior to the start of heating, 1 mole % of fluorenone and 2 mole % of fluorenol were added to the reaction mixture; [b] One-half of reaction 3 was forced into flask F after seventeen hours of heating and phenylmethylcarbinol was isolated; to the remaining reaction mixture, 3 mole % of fluorenone and 6 mole % of fluorenol were added and heating was continued seventeen hours longer (reaction 4).

**Racemization of (−)-2-Methylbutanol-1.**—From a commercially available fraction of fusel oil containing about 17% of (−)-2-methylbutanol-1, and about 80% of 3-methylbutanol-1, various fractions of (−)-2-methylbutanol-1 (75–100% optically active) were obtained by two fractionations (at a reflux ratio of 1:100) through a four-foot adiabatic column packed with metal helices.

From 2.2 to 8.8 g. of optically active alcohol was treated with sodium under an atmosphere of nitrogen or, in other experiments, was added to aluminum isopropoxide. The resulting alkoxide solution was then heated at 120° with or without previous addition of oxidants, for various periods of time under positive nitrogen pressure. After being cooled, the reaction mixture, made weakly acidic by adding hydrochloric acid, was extracted with 100 cc. of ether. The ether extract was washed with water, dried over

(10) It may be mentioned that the acceleration depends in no way on oxidation-reduction potentials; in fact, equilibrium concentrations could be chosen so that no concentration changes would accompany the acceleration of (1).

(11) All melting points are corrected.

(12) Downer and Kenyon, *J. Chem. Soc.*, 1156 (1939).

magnesium sulfate and fractionated through a 10 cm. Vigreux column. The fraction boiling at 127–128° was collected, the specific rotation being measured in methanol at 27°. From blank runs it was established that further purification of the recovered alcohol was not necessary. The results of various experiments are compiled in Table II.

TABLE II

| Catalyst in mole % | Added reagents in mole % | Reaction time, hours[a] | $[\alpha]^{27}D$ starting alcohol[b] | $[\alpha]^{27}D$ recovered alcohol | Racemization in % |
|---|---|---|---|---|---|
| 5[c] | 5 Fluorenone; 10 fluorenol | 16 | −5.3 | 0.0 | 100 |
| 5[c] | | 17 | −5.3 | −5.3 | 0 |
| 5[c] | 5 Heptaldehyde | 17 | −4.3 | 0.0 | 100 |
| 5[c] | | 17 | −4.3 | −3.9 | 11 |
| 5[c] | 5 Benzophenone | 5 | −3.8 | −0.3 | 89 |
| 5[c] | | 20 | −3.8 | −3.8 | 0 |
| 5[d] | 5 Benzophenone | 4.5 | −4.3 | −3.4 | 21 |
| 5[d] | | 4.5 | −4.3 | −4.3 | 0 |
| 5[d] | 5 Benzophenone | 14 | −4.3 | −2.6 | 42 |
| 5[e] | | 5 | −6.6 | −6.6 | 0 |

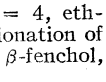
[a] Reaction temperature was 120°. [b] The specific rotations were measured in methanol ($c$ = 3). Starting materials with identical specific rotations were obtained from the same sample. [c] Sodium. [d] Aluminum isopropoxide.

**Epimerization of α- and β-Fenchol.**—α-Fenchol was prepared from purified $d$-fenchone by reduction with sodium and amyl alcohol[13]; m.p. 43.6–44.5°, $[\alpha]^{27}D$ −12.7° ($c$ = 3, 95% ethanol); acid phthalate, m.p. 145–146°, $[\alpha]^{27}D$ + 20.2° ($c$ = 5, methanol). β-Fenchol was prepared by catalytic reduction of $d$-fenchone with copper chromite catalyst in ethanol at 100 atmospheres and 110°.[14] The alcohol was isolated from the reduction mixture via the acid phthalate (twice crystallized from $n$-hexane), m.p. 151–151.6° $[\alpha]^{22}D$ + 11.7° ($c$ = 4, ethanol), which yielded upon hydrolysis and fractionation of the hydrolysate in a molecular still, 94.4% pure β-fenchol, $[\alpha]^{27}D$ −21.8° ($c$ = 4, ethanol).

A mixture of 7.7 g. of β-fenchol (0.05 mole), 9.1 g. of fluorenol (0.05 mole) and 0.91 g. of fluorenone (0.005 mole) in 38 cc. of $t$-butyl alcohol containing 0.12 g. of sodium (0.005 mole) was heated in a bomb-tube under nitrogen for seventy hours at 165°. The high-boiling fraction [7 g., b.p. 83–86° (20 mm.)] of the neutralized reaction mixture was heated twenty-five hours with 7.0 g. of phthalic anhydride in 8.5 g. of pyridine at 100° to give 9.6 g. of crude fenchyl acid phthalate, which was crystallized from glacial acetic acid. The first crop (4.8 g., m.p. 139–141°, $[\alpha]^{27}D$ +17.2°) yielded after two recrystallizations from the same solvent, 3.0 g. of α-fenchyl acid phthalate, m.p. 145–145.6°, $[\alpha]^{27}D$ +20.8° ($c$ = 3, ethanol); the second crop (3.0 g., m.p. 138–143.5°, $[\alpha]^{27}D$ + 14.1°) yielded after three recrystallizations from glacial acetic acid an additional 0.48 g., m.p. 143–145.2°, $[\alpha]^{27}D$ + 19.1°. Hydrolysis and sublimation of the combined samples of α-fenchyl acid phthalate yielded 1.1 g. of α-fenchol, $[\alpha]^{27}D$ −12.2° ($c$ = 4, ethanol), m.p. 43.5–44.6°, mixed m.p. 43.5–44.5°. The combined acid phthalate mother liquors yielded after three recrystallizations from $n$-hexane 3.0 g. of solid, m.p. 148–149.5°, $[\alpha]^{27}D$ + 13.8° ($c$ = 3, ethanol), from which 1.1 g. of β-fenchol was recovered upon hydrolysis, $[\alpha]^{27}D$ −19.0° ($c$ = 3, ethanol).

A mixture of 6.1 g. of α-fenchol (0.04 mole), 7.3 g. of fluorenol (0.04 mole) and 0.75 g. of fluorenone (0.004 mole) in 30 g. of butyl alcohol containing 0.09 g. of sodium (0.004 mole) was heated in a bomb-tube under nitrogen for thirty-five hours at 160–180°. After removal of solvent from the neutralized reaction mixture, fenchol was co-distilled with 12 cc. of decalin from the residue of fluorenol and fluorenone. From the distillate, b.p. 118–119° (100 mm.), fenchol (3.6 g., $[\alpha]^{22}D$ −14.9°) was separated by conversion to the acid phthalate, extraction of neutral impurities, hydrolysis, steam distillation and fractionation. Upon redistillation through a molecular still, some α-fenchol crystallized on the cold finger and the distillate was thus further enriched in β-fenchol[15], $[\alpha]^{27}D$ −15.7° ($c$ = 2, ethanol).

## Summary

From the fact that (−)-phenylmethylcarbinol and (−)-2-methylbutanol-1 are not racemized by alkoxide ion in the complete absence of oxidants but are racemized in the presence of ketones, it is concluded that the stereochemical equilibration of alcohols () is accomplished through an oxidation–reduction mechanism. α- and β-fenchols, thought previously to be unepimerizable because of lack of α-hydrogen, have now been epimerized.

NEW YORK 27, N. Y. RECEIVED SEPTEMBER 20, 1948

(13) Gardner, *J. Chem. Soc.*, **73**, 276 (1898).

(14) We are grateful to Dr. H. R. Snyder for suggesting and carrying out, in the laboratories of the University of Illinois, the reduction of $d$-fenchone with copper chromite catalyst, when Raney nickel failed.

(15) In agreement with Hückel's findings,[9] we were unable to isolate pure β-fenchol from the mixture which contained a substantial excess of α-fenchol. However, the change in specific rotation from −12.7° to −15.7° can only be assigned to the formation of β-fenchol, since the likely optically active contaminant, fenchone ($[\alpha]^{27}D$ +62°), would have changed the rotation in the opposite direction.

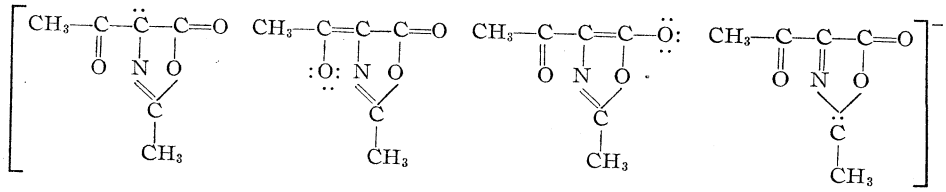
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1241]

# Some Observations on the Dakin–West Reaction

BY GEORGE H. CLELAND AND CARL NIEMANN

The reaction of α-amino acids with acetic anhydride in the presence of a base to give α-acetamidoalkyl methyl ketones[1,2] was recognized as an aldol reaction by Dakin and West[2] and it appears[1–3] that the over-all reaction proceeds through acetylation of the amino acid, cyclization to the azlactone, reaction of the latter compound with base to give a resonance stabilized carbanion, the reaction of this ion with acetic anhydride to give the azlactone of an α-acetamido-β-keto acid and acetate ion, and the subsequent conversion of this azlactone to the acetamido ketone and carbon dioxide. The mechanism of the last transformation is obscure though it is probable that it may be dependent upon an attack by acetate ion upon the azlactone of the α-acetamido-β-keto acid.

Although many α-acetamidoalkyl methyl ketones have been prepared *via* the Dakin–West reaction[1–5] the applicability of this reaction to the preparation of ketones other than methyl ketones has not been explored beyond Dakin and West's observation that "the homologues of acetic anhydride are much less reactive than the latter substance" and the recent report of Wiley and Borum[6] relative to the formation of 1-phenyl-1-propionamido-2-butanone from α-aminophenylacetic acid and propionic anhydride. The fact that a number of α-amino acids react smoothly in the presence of pyridine with such diverse acid anhydrides as propionic, butyric, methoxyacetic, and benzoic anhydrides to give the corresponding acylamidoalkylethyl, propyl, methoxymethyl, and phenyl ketones indicates that the reaction is generally applicable to acyclic alkyl and aryl acid anhydrides. The reaction of acetyl chloride with α-amino acids in the presence of pyridine[2] was found difficult to control and with both acetyl and benzoyl chloride the ketones were obtained in poor yield. However benzoyl fluoride was found to react smoothly in the presence of pyridine with the single α-amino acid investigated to give good yields of the corresponding acylamidoalkylphenyl ketone and it appears that the acyl fluoride may be used in lieu of the acid anhydride in the Dakin–West reaction.



The preparation of oxazoles by the dehydration of the crude reaction product obtained by treating an α-amino acid with acetic anhydride and sodium acetate[7,8] has been interpreted by Wiley[6,9] as proceeding through the intermediate α-acetamidoalkyl methyl ketone. In view of the above observations and those of Attenburrow, *et al.*,[3] it was not surprising to find that with an α-amino acid such as phenylalanine comparable yields of the α-acetamidobenzyl methyl ketone were obtained by using either pyridine or sodium acetate as a condensing agent. The difference in the behavior of pyridine and of acylate ion noted by Attenburrow, *et al.*,[3] in the case of glycine may be explained on the basis of the greater basic strength of the acylate ion favoring more complete formation of the ion, which would be expected to be more inert toward ring cleavage and subsequent decarboxylation than the corresponding acid. The difference noted by Dakin and West[2] and by Wiley and Borum[6] in the behavior of glycine and the other α-amino acids is also explainable in terms of the formation of the above resonance stabilized ion in the case of glycine and the impossibility of its formation in the case of the other α-amino acids.

From Dakin and West's observations[2] one would expect that a dipeptide would react with acetic anhydride in the presence of a base to give one equivalent of carbon dioxide and that the corresponding diketopiperazine would not react at all. These expectations have been realized and it may be concluded that all evidence is consistent with the previously stated proposition[2] that only those α-amino acids or their derivatives which are capable of forming azlactones containing an active α-hydrogen atom will undergo the Dakin-West reaction. Complicating competitive reactions are to be found in the case of the β-hydroxy-α-amino acids where the base catalyzed intermolecular dehydration reaction takes obvious precedence over the intramolecular carbonyl addition reaction and in the case of glutamic acid where pyrrolidone carboxylic acid formation limits azlactone formation.[2]

(1) Levene and Steiger, *J. Biol. Chem.*, **74**, 689 (1927); **79**, 95 (1928).
(2) Dakin and West, *ibid.*, **78**, 91, 745, 757 (1928).
(3) Attenburrow, Elliott and Penny, *J. Chem. Soc.*, 310 (1948).
(4) Wood and du Vigneaud, THIS JOURNAL, **67**, 210 (1945).
(5) Wiley, *J. Org. Chem.*, **12**, 43 (1947).
(6) Wiley and Borum, THIS JOURNAL, **70**, 2005 (1948).
(7) Wrede and Keil, *Z. physiol. Chem.*, **203**, 279 (1931).
(8) Wrede and Feurerriegel, *ibid.*, **218**, 129 (1933).
(9) Wiley, *Chem. Rev.*, **37**, 401 (1945).

## Experimental[10]

**1-Phenyl-2-acetamido-3-butanone.**[2]—(A) A mixture of 12.4 g. (0.075 mole) of DL-phenylalanine, 39.3 g. (0.5 mole) of pyridine and 65.2 g. (0.64 mole) of acetic anhydride was heated on a steam-bath for five hours, steam distilled until free of pyridine, the residue treated with an excess of aqueous sodium bicarbonate, and extracted with six 100-ml. portions of ether. The ethereal extract was dried, the solvent removed and the waxy orange-yellow solid recrystallized twice from xylene to give 12.1 g. (79%) of 1-phenyl-2-acetamido-3-butanone,[2] colorless needles, m. p. 98–99° (cor.).

(B) A mixture of 1.65 g. (0.01 mole) of DL-phenylalanine, 4 g. (0.05 mole) of anhydrous sodium acetate and 10.8 g. (0.11 mole) of acetic anhydride was heated with stirring for thirty minutes at 130–135°, and the reaction product worked up substantially as described in (A) to give 0.94 g. (46%) of acetamidoketone, colorless needles, m.p. 98–99° (cor.).

(C) A mixture of 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine and 8.8 g. (0.11 mole) of acetyl chloride was heated with stirring for one hour at 60° and the reaction mixture worked up as described previously to give 0.15 g. (8%) of 1-phenyl-2-acetamido-3-butanone, colorless needles, m. p. 97–99° (cor.) after one recrystallization from xylene.

**1-Phenyl-2-propionamido-3-pentanone.**—A mixture of 3.3 g. (0.02 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 26 g. (0.2 mole) of propionic anhydride was refluxed at 140–145° for thirty minutes, the solution concentrated *in vacuo*, treated with an excess of aqueous sodium bicarbonate, extracted successively with two 100-ml. portions of ether and of chloroform, the non-aqueous phases combined, dried, and the solvents evaporated to give approx. 5 g. of a light-orange oil. The oil was taken up in hot ligroin, b. p. 90–130°, filtered, the volume reduced to 25 ml., and the solution stored at 5° overnight. The colorless needles so obtained were recrystallized first from ligroin and then from aqueous-acetone to give 1.7 g. (36%) of 1-phenyl-2-propionamido-3-pentanone, colorless needles, m. p. 67–68° (cor.). In a second experiment the reaction mixture resulting from heating 5 g. (0.03 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 26 g. (0.2 mole) of propionic anhydride at 135° for one and one-half hours was fractionally distilled to give 2.9 g. (41%) of 1-phenyl-2-propionamido-3-pentanone, colorless needles, m. p. 67–68° (cor.).

*Anal.* Calcd. for $C_{14}H_{19}O_2N$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.9; H, 8.2; N, 5.9.

The oxime, colorless needles, m. p. 152–153° (cor.), was recrystallized from 95% ethanol.

*Anal.* Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.7; H, 8.1; N, 11.3. Found: C, 67.6; H, 8.4; N, 11.1.

The 2,4-dinitrophenylhydrazone, yellow needles, m. p. 153–154° (cor.), was recrystallized alternately from ethyl acetate and 95% ethanol.

*Anal.* Calcd. for $C_{20}H_{23}O_5N_5$: N, 16.9. Found: N, 16.8.

**1-Phenyl-2-butyramido-3-hexanone.**—A mixture of 3.3 g. (0.02 mole) of DL-phenylalanine, 16 g. (0.2 mole) of pyridine and 40 g. (0.25 mole) of butyric anhydride was heated for three hours at 145–150°, and the reaction product worked up as described for the preceding preparation to give a light-orange oil which crystallized upon standing at 5°. This product was recrystallized successively from xylene and ligroin, 30–60°, to give 1.4 g. (27%) of 1-phenyl-2-butyramido-3-hexanone, colorless needles, m. p. 59–60° (cor.).

*Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.6; H, 8.7; N, 5.4.

The oxime, colorless needles, m. p. 145–146° (cor.) was recrystallized twice from water.

*Anal.* Calcd. for $C_{16}H_{24}O_2N_3$: C, 69.5; H, 8.8; N, 10.1. Found: C, 69.3; H, 8.7; N, 10.1.

The 2,4-dinitrophenylhydrazone, bright yellow needles, m. p. 173–174° (cor.) was obtained after successive recrystallization from ethanol and ethyl acetate.

*Anal.* Calcd. for $C_{22}H_{27}O_5N_5$: C, 59.9; H, 6.2; N, 15.9. Found: C, 60.1; H, 6.4; N, 16.0.

**1-Methoxy-3-methoxyacetamido-4-phenyl-2-butanone.**—A mixture of 5 g. (0.03 mole) of DL-phenylalanine, 12 g. (0.15 mole) of pyridine and 24 g. (0.15 mole) of methoxyacetic anhydride[11] was heated with stirring at 115° for one hour, the solution evaporated *in vacuo*, the residue treated with an excess of aqueous sodium bicarbonate, extracted successively with two 100-ml. portions of ether and of chloroform, the non-aqueous phases combined, dried, the solvents removed, the residual oil taken up in 60% ethanol, the solution treated with Norite, filtered, and the solvents evaporated to give 6.2 g. (78%) of a neutral light-yellow oil which could not be induced to crystallize. A portion of the oil was treated with *p*-nitrophenylhydrazine to give a *p*-nitrophenylhydrazone, stout orange rhombs, m. p. 179–181° (cor.) after two recrystallizations from 95% ethanol.

*Anal.* Calcd. for $C_{20}H_{24}O_5N_4$: C, 60.0; H, 6.0; N, 14.0. Found: C, 60.2; H, 6.1; N, 14.1.

The 2,4-dinitrophenylhydrazone was obtained as light-yellow needles, m. p. 168–169° (cor.) after two recrystallizations from chloroform.

*Anal.* Calcd. for $C_{20}H_{23}O_7N_5$: C, 53.9; H, 5.2; N, 15.7. Found: C, 53.8; H, 5.2; N, 15.8.

The semicarbazone, rosettes of colorless needles, m. p. 116–117° (cor.), was recrystallized twice from water.

*Anal.* Calcd. for $C_{15}H_{22}O_4N_4$: C, 55.9; H, 6.9; N, 17.4. Found: C, 55.7; H, 7.0; N, 17.5.

**α-Benzamidopropiophenone.**—A mixture of 3 g. (0.034 mole) of DL-alanine, 12 g. (0.15 mole) of pyridine and 34 g. (0.15 mole) of benzoic anhydride[12] was heated with stirring at 130–135° for two and one-half hours, and the reaction product worked up as previously described. The solid obtained was recrystallized once from ligroin and twice from aqueous ethanol to give 3.6 g. (42%) of α-benzamidopropiophenone, colorless prisms, m. p. 104–105° (cor.). α-Benzamidopropiophenone has been reported to have a m. p. of 103°[13] and 104–105°.[14]

*Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.9; H, 6.0; N, 5.5. Found: C, 76.0; H, 6.0; N, 5.4.

The oxime, rosettes of colorless needles, m. p. 157–158° (cor.), was recrystallized twice from aqueous ethanol.

*Anal.* Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.9; H, 6.2; N, 10.3.

The ketone (3 g.) in 3 ml. of cold concd. sulfuric acid was diluted with ice water, the solid collected, washed with water and recrystallized twice from ligroin to give 2,5-diphenyl-4-methyl-oxazole, prisms, m. p. 81–82° (cor.). Lister and Robinson[14] give a m. p. of 82°.

*Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.6; N, 6.0. Found: C, 81.8; H, 5.7; N, 5.8.

**α-Benzamido-β-phenyl-propiophenone.**—(A) A stirred mixture of 2.5 g. (0.015 mole) of DL-phenylalanine, 8 g. (0.10 mole) of pyridine, and 22.5 g. of benzoic anhydride (0.10 mole) was heated at 140–145° for two hours. The reaction mixture was worked up as described for α-benzamidopropiophenone to give 2.2 g. (44%) of α-benzamido-β-phenyl-propiophenone, long colorless needles, m. p. 146–147° (cor.) after two recrystallizations from aqueous-ethanol.

*Anal.* Calcd. for $C_{22}H_{19}O_2N$: C, 80.2; H, 5.8; N, 4.3. Found: C, 80.3; H, 5.8; N, 4.3.

(10) In the following experiments no attempt has been made to determine the conditions leading to maximum yields.

(11) Prepared by a method similar to that described by Allen, *et al.*, "Organic Syntheses," **26**, 1 (1946).

(12) Clarke, *et al.*, "Organic Syntheses," Coll. Vol. **1**, 91 (1941).

(13) Behr-Bregowski, *Ber.*, **30**, 1515 (1897).

(14) Lister and Robinson, *J. Chem. Soc.*, **101**, 1297 (1912).

The oxime was obtained after two recrystallizations from 95% ethanol as colorless needles, m. p. 188–189° (cor.).

*Anal.* Calcd. for $C_{22}H_{20}O_2N_2$: C, 76.7; H, 5.8; N, 8.1. Found: C, 76.7; H, 6.0; N, 8.0.

A solution of 0.4 g. of α-benzamido-β-phenyl-propiophenone in 30 ml. of 6 *N* hydrochloric acid and 10 ml. of ethanol was refluxed for three hours, the solvents removed, the residue extracted with ether, and dissolved in 10 ml. of ethanol. The addition of 25 ml. of ether gave the hydrochloride of α-amino-β-phenylpropiophenone, lustrous needles, m. p. > 200° with decomposition.

*Anal.* Calcd. for $C_{15}H_{16}ONCl$: C, 68.8; H, 6.2; N, 5.4; Cl,13.6. Found: C, 68.6; H, 6.4; N, 5.2; Cl, 13.8.

(B) A mixture of 2.7 g. (0.01 mole) of N-benzoyl-DL-phenylalanine, 5.9 g. (0.075 mole) of pyridine and 11.3 g. (0.05 mole) of benzoic anhydride heated at 135–140° for two hours with stirring when treated as described above gave 1.2 g. (36%) of α-benzamido-β-phenylpropiophenone, colorless needles, m. p. 146–147° (cor.).

(C) When 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine, and 17 g. (0.12 mole) of benzoyl chloride was heated for one hour at 135–140°, 39–42% of the anticipated quantity of carbon dioxide was evolved but on working up the dark tarry reaction product only 0.36 g. (9%) of α-benzamido-β-phenyl-propiophenone, m. p. 146–147° (cor.), was obtained.

(D) A mixture of 2 g. (0.012 mole) of DL-phenylalanine, 7.9 g. (0.1 mole) of pyridine and 12.5 g. (0.1 mole) of benzoyl fluoride[15] was heated for two hours at 135–140° with stirring and from the reaction mixture there was obtained 1.55 g. (39%) of α-benzamido-β-phenylpropiophenone, m. p. 146–147° (cor.).

(15) Meslans and Girardet, *Bull. soc. chim.*, [3] **15**, 877 (1896).

**Studies Based upon Evolution of Carbon Dioxide.**—A mechanically stirred mixture of 0.7 g. (0.0044 mole) of DL-alanylalanine, 3.6 g. (0.045 mole) of pyridine, and 4.6 g. (0.045 mole) of acetic anhydride heated for two hours at 110–115° gave 0.004 mole of carbon dioxide. In a second experiment heating for one and one-half hours at 115° gave 92% of the anticipated amount of carbon dioxide (one equivalent) and when the reaction mixture was refluxed with 6 *N* hydrochloric acid no more carbon dioxide was obtained.

A mixture of 0.44 g. (0.004 mole) dimethyldiketopiperazine, 2 g. (0.025 mole) of pyridine and 3.6 g. (0.035 mole) of acetic anhydride was heated with stirring at 120° for two hours. No carbon dioxide was evolved during this period nor after refluxing with 6 *N* hydrochloric acid.

## Summary

The Dakin–West reaction has been shown to be applicable to the synthesis of α-acylamidoalkyl aryl ketones as well as to the synthesis of α-acylamidoalkyl alkyl ketones other than methyl ketones. It has been found that acetate ion may be used in lieu of pyridine as a condensing agent and that the acid anhydride may be replaced by the corresponding acyl fluoride. The nature of the base catalyzed reaction involving a dipeptide and an acid anhydride has been considered in a preliminary manner.

RECEIVED AUGUST 31, 1948

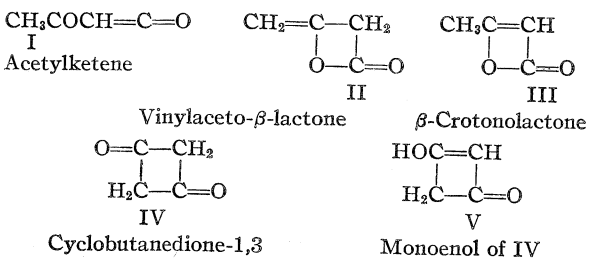
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# The Use of Carbon-14 in the Determination of the Structures of Aldoketene Dimers[1,2]

BY JOHN D. ROBERTS, ROSE ARMSTRONG, R. F. TRIMBLE, JR., AND MARION BURG

The structures of aldoketene dimers prepared by the dehydrohalogenation of acyl halides have not been conclusively established. Recent infrared spectroscopic studies by Miller and Koch[3] indicate that the parent compound, diketene, is probably an equilibrium mixture of compounds having structures II and III although IV could not be excluded as a component of the mixture by the infrared data.




It was considered that I and V were unlikely because of the absence of absorption at the characteristic hydroxyl and C=C=O frequencies.

(1) Assisted by the joint program of the Office of Naval Research and the Atomic Energy Commission.

(2) Presented at the St. Louis Meeting of the American Chemical Society, September 7, 1948.

(3) Miller and Koch, THIS JOURNAL, **70**, 1890 (1948).

The higher aldoketene dimers prepared from acyl halides by the Wedekind procedure[4,5,6,7] have chemical and physical properties which are generally similar to those of diketene and presumably present a similar structural problem.[8] It is apparently agreed that the dimers of dialkyl-substituted ketenes (ketoketene dimers) have tetraalkylcyclobutanedione-1,3 structures.[6]

In the present investigation the isotopic tracer

(4) Wedekind, *Ber.*, **34**, 2070 (1901); *Ann.*, **323**, 246 (1902); **378**, 261 (1910); Wedekind and Haeussermann, *Ber.*, **41**, 2297 (1908).

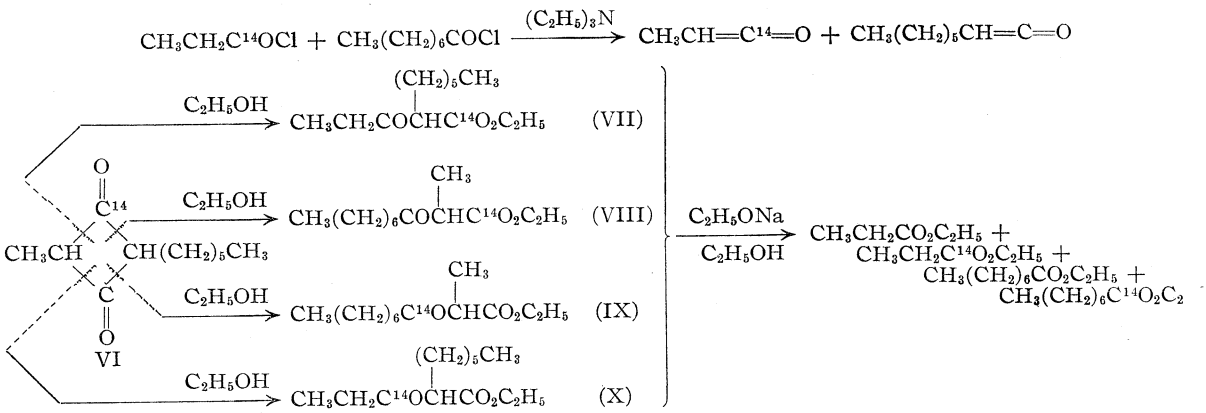
(5) Hill, Ph.D. Thesis, Cornell University, 1941.

(6) Hanford and Sauer, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1947, pp. 127 ff.

(7) Sauer, U. S. Patent 2,369,919; THIS JOURNAL, **69**, 2444 (1947).

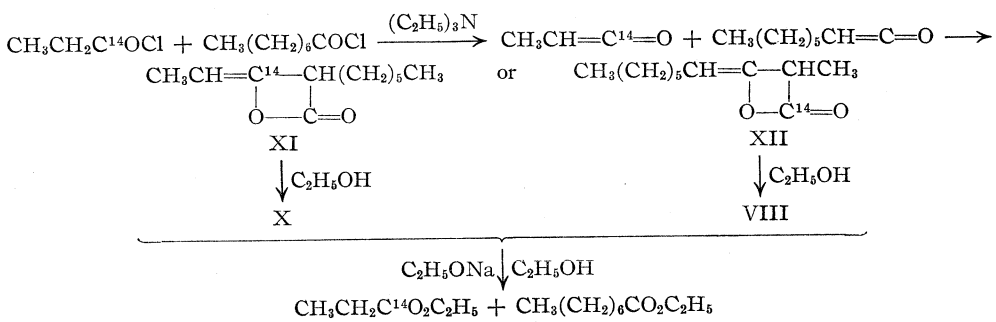
(8) Two seemingly isomeric forms have been reported for methylketene dimer. A liquid, b. p. 50–52° (9 mm.), has been prepared from the dehydrohalogenation of propionyl chloride[5,7] having properties similar to those of diketene and a solid form, m. p. 140°, has been obtained from the polymerization of methylketene prepared from the debromination of α-bromopropionyl bromide with zinc by Staudinger and Klever, *Ber.*, **41**, 906 (1908); Staudinger, *ibid.*, **44**, 533 (1911). The solid compound has also been synthesized by Schroeter, *ibid.*, **49**, 2697 (1916); **53**, 1917 (1920); **59**, 977 (1926), from diethyl α,α′-dimethylacetonedicarboxylate. The structure, 1,3-dimethylcyclobutene-2-ol-4-one was assigned to the solid compound by Staudinger on the basis of its pronounced enolic properties. However, this assignment can only be regarded as tentative in the absence of a molecular weight determination.

technique was used to show that a mixed dimer of methyl- and hexylketenes which was convertible to alkylacetoacetic esters with alcohol probably does not have a structure similar to IV or V. The method utilized the mixed dimer[7] prepared by the Wedekind reaction from $C^{14}$ carbonyl-labeled propionyl and unlabeled capryloyl chlorides and was based on the fact that IV is unique among the five structures proposed for ketene dimers in having two equivalent carbonyl groups. If any of the mixed dimer had the cyclobutanedione-1,3 structure (VI), treatment of this material with alcohol would be expected to give a mixture of four different substituted acetoacetic esters, VII, VIII, IX, and X.




The esters constitute two pairs (VII and X or VIII and IX) comprised of chemically but not isotopically equivalent components. Regardless of the ratio of formation, (VII + X)/(VIII + IX), the equivalence of the carbonyl groups in VI would be expected to make VII/X and VIII/IX equal to unity.[9] Cleavage of the $\beta$-ketoester mixture derived from the dimer with sodium ethoxide would result in the formation of *radioactive* ethyl caprylate. If all of the mixed dimer had the structure VI then the radioactive carbon atoms would be expected to be distributed equally between the ethyl propionate and ethyl caprylate fractions. Similar results should be obtained from a structure like V since this form should be formed from VI and possess for an instant, at least, the symmetry of VI.

If the mixed dimer had a structure related to I, II or III it could exist in two forms depending on which ketene furnished the C=C=O group of a structure like I, or the carbonyl groups of the lactonic structures similar to II or III. Regardless of the mixture of dimers, degradation through the substituted acetoacetic esters should give only *non-radioactive* caprylic acid derivatives. These reactions are illustrated below using structure II as an example.




In the present investigation, the carbonyl-labeled propionyl chloride was prepared from carboxyl-labeled propionic acid which was made from ethylmagnesium chloride and radioactive carbon dioxide.[10] The mixed dimer was made following the directions of Sauer[7] and was separated from the simultaneously formed methyl- and hexylketene dimers by fractional distillation. The mixed dimer was degraded through the substituted acetoacetic esters as outlined above. Since the separation of a small amount of ethyl propionate from ethyl alcohol is not possible by

(9) It is recognized that differences in the zero-point energies of $C^{12}$–$C^{14}$ and $C^{12}$–$C^{12}$ bonds may prevent the bonds of an isotopic cyclobutanedione-1,3 ring from cleaving so as to give exactly the expected product ratios. An effect of this type has been reported by Calvin (paper presented at the Chicago Meeting of the American Chemical Society, April 21, 1948) for the decarboxylation of carboxyl-labeled malonic acid. In the present case, the error so introduced should probably not amount to more than 5%.

(10) The carbon dioxide was prepared from $C^{14}$-barium carbonate supplied by the Clinton Laboratories, Oak Ridge, Tenn., and obtained on allocation from the U. S. Atomic Energy Commission.

distillation the mixture of esters was saponified and the resulting propionic and caprylic acids separated by fractional distillation. The radioactivity analyses were made by the previously reported procedure.[11] The results are summarized in Table I.

TABLE I

RADIOACTIVITY ANALYSES

| Compound | Measured activity, counts/min.[a] | No. of tagged positions per molecule | Counts/min./mg. of $BaCO_3$/tagged position[b] |
|---|---|---|---|
| Methylketene dimer | 372 | 2 | 390 |
| Hexylketene dimer | 10[c] | 2[d] | 28 |
| $CO_2$ from decarboxylation of ethyl α-capryloylcaprylate | 5 | 1[e] | 2 |
| Mixed dimer (methyl- and hexyl- ketenes) | 105 | 1 | 400 |
| Acetoacetic esters from mixed dimer | 94 | 1 | 420 |
| $CO_2$ from decarboxylation of acetoacetic ester mixture | 806 | 1 | 280 |
| Propionic acid | 374 | 1 | 390 |
| Caprylic acid (Frac. 1) | 8.6 (2)[f] | 1 | 6[g] |
| (Frac. 2) | 9.7 (3)[f] | 1 | 8[g] |
| (Frac. 3) | 8.8 (2)[f] | 1 | 6[g] |
| Propionic acid[h] | 294 | | |
| Caprylic acid[h] (Frac. 1) | 6.2 | | |
| (Frac. 2) | 4.1 | | |

[a] Activity (corrected for background) of "infinitely thick" barium carbonate samples having a cross-sectional area of 2.90 cm.² measured with a Lauritsen electroscope (see Ref. 11) or a methane-filled windowless counter ("Nucleometer") manufactured by the Radiation Counter Laboratories. [b] Corrected for self absorption, calculated from (specific activity) × (number of carbon atoms)/(number of labeled positions). [c] The activity of this material must be due to impurities since the activity of the carbon dioxide from the decarboxylation of a sample of ethyl α-capryloylcaprylate prepared from the dimer was much lower. [d] Two tagged positions were assumed since the carbonyl groups are equivalent in this compound. [e] The number of tagged positions is taken as unity since the specific activity of the carbonyl positions is the important consideration and the activity would not be increased even if both carbonyl positions were decarbonylated at once. [f] Values in parentheses are corrected for the efficiency of the separation of the propionic and caprylic acids. The correction factor was taken as (6.2 + 4.1) (374)/2 (294) = 6.6 counts/min. [g] Corrected for efficiency of the separation process. [h] Blank separation using radioactive and non-radioactive caprylic acids.

The activity of the caprylic acid (corrected for the efficiency of the separation of propionic and caprylic acids in the apparatus used) from the degradation of the mixed dimer was 1.5% of the activity per labeled carbon atom of the mixed dimer. From this value, the maximum amount of the material in the mixed dimer with structure VI which is convertible to acetoacetic esters with alcohol is 3%.

With the knowledge that practically none of the mixed dimer has the VI structure it is possible to determine the composition of the forms XI and XII (or the corresponding unsymmetrical compounds derived from I or III) of the dimer by radioactive analysis of the carbon dioxide formed by decarboxylation of the acetoacetic acids resulting from the hydrolysis of the mixture of esters, VIII and X. The carbon dioxide so formed had 67% of the activity of the acetoacetic ester mixture and hence the composition of the original mixed dimers must be 33% of XI and 67% of XII.

In order to effectively utilize the information obtained from the radiochemical work a comparison was made between the physical properties of diketene, methylketene dimer, hexylketene dimer and the mixed dimer. The dipole moments (Table II) which were determined in benzene solution are large and quite close together. If the hypothesis is accepted that all of the compounds have similar structures the increase in moment (0.25 *D*) in going up the series from diketene to hexylketene dimer may well be due to induced moments in the long alkyl side chains. The molar refractivities of the compounds (Table II) are in best agreement with the lactone structures although some exaltation is noticed as might be expected for small ring structures.

The ultraviolet absorption spectra (Fig. 1) were determined in cyclohexane and may be taken as indicating that diketene is different in structure from the other aldoketene dimers. The spectrum of diketene has previously been interpreted by Calvin, Magel and Hurd[12] as being in agreement with expectations for form II. The differences in

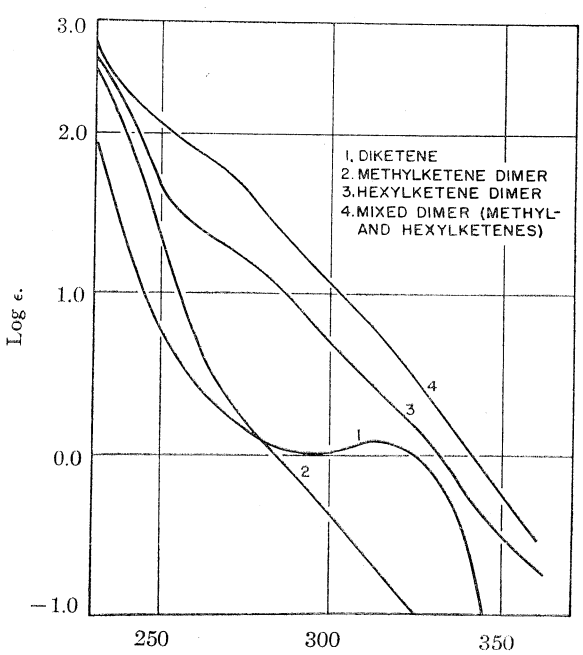



Fig. 1.—Ultraviolet spectra.

(11) Roberts, Bennett, Holroyd and Fugitt, *Anal. Chem.*, **20**, 904 (1948).

(12) Calvin, Magel and Hurd, THIS JOURNAL, **63**, 2174 (1941).

TABLE II

MOLAR REFRACTIVITIES, POLARIZATIONS AND DIPOLE MOMENTS OF ALDOKETENE DIMERS

| Compound | $n^{25}D$ | $d^{25}_4$ | $MR_D$ | Calculated $MR_D$ for structures corresponding to I | II or III | IV | V | $P_\infty$ [b] | $\mu$(Debye) |
|---|---|---|---|---|---|---|---|---|---|
| Diketene[a] | 1.4313 | 1.0626 | 20.49 | 20.18 | 20.30 | 19.00 | 20.08 | 234.6 | 3.23[c] |
| Methylketene dimer[a] | 1.4322 | 0.9864 | 29.49 | 29.44 | 29.56 | 28.26 | 29.34 | 252.7 | 3.30 |
| Mixed dimer[a] (methyl- and hexylketenes) | 1.4453 | 0.9130 | 53.16 | 52.59 | 52.71 | 51.41 | 52.49 | 292.8 | 3.42 |
| Hexylketene dimer[a] | 1.4517 | 0.8959 | 75.95 | 75.74 | 75.86 | 74.68 | 75.64 | 338.6 | 3.58 |

[a] Non-radioactive materials prepared by the methods of Sauer (ref. 7). [b] Data for calculation of $P_\infty$ given in Table III [c] Oesper and Smyth, THIS JOURNAL, **64**, 768 (1942), report 3.31 $D$ in benzene solution.

ultraviolet spectra between diketene and the higher aldoketene dimers might be due to considerably higher proportions of substances corresponding to III in the higher dimers although this conclusion may not be safe in view of the small extinction coefficient of the 312 mμ absorption maximum of diketene and the unknown influence which substitution of alkyl groups might have on the spectrum of II.

The infrared and Raman spectra of all four dimers have been obtained by Dr. R. C. Lord, Jr., Mr. R. S. McDonald, and Mr. E. J. Slowinski, to whom we are much indebted. The spectra, which will be published in detail later, are in satisfactory agreement with those previously reported[3,13,14] although the infrared spectrum of diketene shows a double peak at about 1060 cm.$^{-1}$ which has been reported earlier as a single shoulder on the 1020 cm.$^{-1}$ bond by Whiffen and Thompson.[13]

The infrared and Raman absorption of all of the dimers are similar and seem to be consistent with the lactone structures, II and III. The absence of absorption at 2153 cm.$^{-1}$ and above 3200 cm.$^{-1}$ typical of C=C=O and OH groups, respectively, appears to exclude structures I and V for all of the compounds. The presence of three widely separated C—H stretching frequencies at 2972, 3024 and 3120 cm.$^{-1}$ is in agreement with the conclusion that diketene is not a single pure compound since none of the structures I–V have more than two different varieties of C–H bonds.

The physical evidence is generally consistent with the hypothesis that the aldoketene dimers prepared in the present work have similar structures. The physical evidence in conjunction with the tracer study favors the assignment of structures of the type II or III which may be in equilibrium as suggested by Miller and Koch.[3]

**Acknowledgment.**—We wish to acknowledge the assistance of Miss Winifred Bennett with the radioactivity analyses and Mr. D. R. Smith with the preparation of the radioactive propionyl chloride.

## Experimental

**Preparation of Mixed Dimer of Methyl- and Hexylketenes.**—The preparation was carried out as described by Sauer.[7] The procedure is described in detail since consistent yields were not always obtained using other conditions. A solution containing 37 g. (0.4 mole) of carbonyl-labeled propionyl chloride (0.015 mc. of $C^{14}$) and 65 g. (0.4 mole) of capryloyl chloride in 500 ml. of dry ether was placed under nitrogen in a 2-l. three-necked flask equipped with Dry Ice condenser, efficient sealed stirrer and dropping funnel. To the stirred solution was added dropwise 80.9 g. (0.8 mole) of purified triethylamine[7] over a period of three hours. The reaction mixture was allowed to stand at room temperature for three days and the solution of the ketene dimers separated from the amine salt by inverted filtration. The ethereal solution was concentrated under reduced pressure and finally distilled at 0.1 mm. using a Dry Ice-cooled receiver. The distillate was fractionated under reduced pressure using a 1.5 × 35 cm. Vigreux column equipped with a total condensation partial take-off distilling head. The yields were: methylketene dimer, b. p. 41–49° (11.5 mm.), 5.5 g. (24.5%); hexylketene dimer, b. p. 148° (1.3 mm.), 12.0 g. (24%); and mixed dimer, b. p. 86–89.5° (1.3 mm.), 18.6 g. (25.5%). Intermediate fractions amounted to 7.1 g. and 5.2 g. of brown viscous residue remained.

**Degradation of Mixed Dimer.**—The mixed dimer (10.4 g., 0.057 mole) was refluxed with 23 g. of absolute alcohol containing dry hydrogen chloride for five hours. The alcohol was removed by distillation and the residual mixture of ethyl α-propionylcaprylate and ethyl α-capryloylpropionate distilled under reduced pressure. After collection of a forerun of 1.9 g., b. p. 60–105° (0.5 mm.), the ester mixture distilled at 105° (0.5 mm.). The yield was 9.1 g. (70%). The mixture of ethyl α-propionylcaprylate and ethyl α-capryloylpropionate was analyzed.

*Anal.* Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60; $OC_2H_5$, 19.74. Found: C, 68.53; H, 10.37; $OC_2H_5$, 19.55.

The mixture of ethyl α-propionylcaprylate and ethyl α-capryloylpropionate (4.5 g., 0.0197 mole) was refluxed with a solution of 0.3 g. of sodium in 50 ml. of dry alcohol for five hours. Sodium hydroxide solution was added and the mixture was refluxed for an additional two hours to hydrolyze the ethyl propionate and ethyl caprylate. The solution was evaporated under reduced pressure and the residue acidified with phosphoric acid and boiled for an hour. The solution was made basic and any non-acidic material steam-distilled. The residual solution was acidified and extracted continuously for three days with methylene chloride. The methylene chloride solution was dried over calcium sulfate and the solvent removed through a glass helices-packed column. The residue was transferred to a small flask and fractionated through a small center-tube column.[15] The yield of propionic acid, b. p. 135–136°, was 0.62 g. (43%). The yield of caprylic acid, b. p. 231–227°, was 1.34 g. (47%). Intermediate fractions amounted to 0.07 g.

As a test of the efficiency of the column, a mixture of 1.3 g. of radioactive propionic acid and 2.0 g. of caprylic acid was fractionated. The recoveries were: 1.03 g. (80%) of propionic acid and 0.91 g. (45%) of caprylic acid. Radioactivity analyses of the products are given in Table I.

To determine the composition of the possible unsymmetrical forms of the mixed dimer such as XI or XII, 0.116

(13) Whiffen and Thompson, *J. Chem. Soc.*, 1005 (1946).

(14) Taufen and Murray, THIS JOURNAL, **67**, 754 (1945).

(15) The fractionating section of this column was similar to that described by Naragon and Lewis, *Ind. Eng. Chem., Anal. Ed.*, **18**, 448 (1946).

TABLE III

DIELECTRIC CONSTANTS, DENSITIES AND POLARIZATIONS IN BENZENE AT 25°

| $f_2$ | $\epsilon$ | $d$ | $P_2$ |
|---|---|---|---|
| | Diketene | | |
| 0.00000 | (2.2725)[a] | 0.87222 | $P_1$ = 26.6720 |
| .006407 | 2.3642 | .87355 | 228.4 |
| .013211 | 2.4659 | .87485 | 228.4 |
| .022613 | 2.6109 | .87625 | 226.8 |
| .032564 | 2.7604 | .87793 | 220.5 |
| .040303 | 2.8783 | .87911 | 216.3 |
| .060383 | 3.1746 | .88246 | 203.8 |
| | Methylketene dimer | | |
| 0.00542 | 2.3497 | 0.87307 | 239.7 |
| .011488 | 2.4550 | .87396 | 258.6 |
| .022082 | 2.6462 | .87533 | 264.4 |
| .032160 | 2.8227 | .87677 | 258.9 |
| .041811 | 3.0214 | .87811 | 260.8 |
| .057532 | 3.3055 | .88022 | 250.1 |
| | Mixed dimer of methyl- and hexylketenes | | |
| 0.006361 | 2.3748 | 0.87293 | 292.7 |
| .009736 | 2.4376 | .87330 | 302.6 |
| .011827 | 2.4634 | .87317 | 291.0 |
| .014545 | 2.5165 | .87324 | 298.3 |
| | Hexylketene dimer | | |
| 0.004751 | 2.3555 | 0.87291 | 336.4 |
| .009643 | 2.4398 | .87272 | 335.4 |
| .021604 | 2.6502 | .87369 | 331.4 |
| .039671 | 2.9547 | .87438 | 321.3 |
| .047347 | 3.2051 | .87491 | 346.6 |
| .062258 | 3.3259 | .87472 | 311.7 |

[a] Hartshorn and Oliver, *Proc. Roy. Soc.* (*London*), **A123**, 664 (1929).

g. of the mixture of ethyl $\alpha$-propionylcaprylate and ethyl $\alpha$-caprylylpropionate was hydrolyzed by refluxing with a carbon dioxide-free solution of sodium hydroxide prepared by dissolving 0.05 g. of clean sodium in 10 ml. of boiled alcohol and diluting with 10 ml. of boiled water. The hydrolysis mixture was acidified with dilute perchloric acid and heated to boiling. The evolved carbon dioxide was swept out with nitrogen and precipitated as barium carbonate which was analyzed in the usual manner.[11]

**Ultraviolet Absorption Spectra.**—The ultraviolet spectra were determined in purified cyclohexane solution using a Beckman Quartz Spectrophotometer.[16]

**Dipole Moments.**—The dielectric constants were measured at a frequency of 954 kilocycles using a modification of the heterodyne heat apparatus described by Smyth.[17] The standard condenser was a General Radio Type 722-N. The dielectric cell was similar to the one described previously.[18] The replaceable capacity of the cell at 25° was 123.50 $\mu\mu$ fd. and the volume about 40 ml. The pycnometers were of the graduated type described by Robertson.[19]

The dipole moments were obtained from the dielectric constants and densities of dilute solutions using the customary equations.[17] Values of $P_\infty$ were obtained by least squares extrapolation of $P_2$ to infinite dilution and the sum of the electronic and atomic polarizations at infinite wave length was assumed to be equal to the experimental value of the molar refraction for the sodium D line, $MR_D$. The data are given in Tables II and III.

## Summary

The isotopic tracer technique has been used to demonstrate that the mixed aldoketene dimer of methyl- and hexylketenes prepared by the Wedekind reaction does not have a cyclobutanedione-1,3 structure.

The physical properties of several aldoketene dimers indicate that these substances probably have structures similar to diketene and are best formulated as vinylaceto-$\beta$-lactone or $\beta$-crotonolactone derivatives.

(16) Cary and Beckman, *J. Optical Soc. Am.*, **31**, 682 (1941).

(17) Smyth, in Weissberger, "Physical Methods of Organic Chemistry," Vol. 2, Interscience Publishers, Inc., New York, 1946, Chap. XX.

(18) Rogers and Roberts, THIS JOURNAL, **68**, 843 (1946).

(19) Robertson, *Ind. Eng. Chem., Anal. Ed.*, **11**, 464 (1939).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# The Binding of Organic Ions by Proteins. Effect of Temperature

BY IRVING M. KLOTZ AND JEAN M. URQUHART

The affinity of serum albumin for organic ions has been found to depend on the charge and structure of the anion, as well as on the *p*H and nature of the buffer and on the concentration of the protein.[1-6] From the magnitude of the effects of these different factors, it has been possible to obtain some insight into the molecular nature of the anion–protein complex. Since entropy and enthalpy changes accompanying a chemical transformation are frequently also very illuminating in this respect, it has seemed appropriate to examine also the temperature dependence of the binding process.

In his exploratory work on sulfonamide–plasma protein complexes, Davis[1] observed no marked change in degree of binding with rise in temperature. Similarly Putnam and Neurath[7] in their electrophoretic investigations of complexes between albumin and sodium dodecyl sulfate obtained no indication of a temperature dependence.

(1) B. D. Davis, *J. Clin. Invest.*, **22**, 753 (1943).

(2) P. D. Boyer, F. G. Lum, G. A. Ballou, J. M. Luck and R. G. Rice, *J. Biol. Chem.*, **162**, 181 (1946).

(3) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

(4) J. D. Teresi and J. M. Luck, *J. Biol. Chem.*, **174**, 653 (1948).

(5) I. M. Klotz, H. Triwush and F. M. Walker, THIS JOURNAL, **70**, 2935 (1948).

(6) I. M. Klotz and J. M. Urquhart, *J. Phys. and Colloid Chem.*, **3**, in press (1949).

(7) F. W. Putnam and H. Neurath, *J. Biol. Chem.*, **159**, 195 (1945).

Boyer, Ballou and Luck[8] also have reported a zero temperature coefficient in the binding of caprylate by serum albumin.

The results of the present investigation indicate that the temperature dependence is indeed quite small. At least for methyl orange and azosulfathiazole, however, significant differences in binding by albumin are observed at 0 and 25°, and these can be used to calculate values for the appropriate thermodynamic functions. These quantities, in turn, lead to some pertinent conclusions on the nature of the binding process.

## Experimental

The extent of binding of the reference anions by bovine serum albumin was measured by the differential dialysis technique described in detail previously.[3] Experiments were carried out, with mechanical shaking for an eighteen-hour period, in an ice-bath at 0.0 ± 0.1° for the low temperature measurements and at 25.00 ± 0.05° for the upper temperature results.

As in past work, the reference anions used were monovalent methyl orange and divalent azosulfathiazole of high purity.[3] Analyses were made by optical density, as measured by the Beckman spectrophotometer.

Buffers were prepared from reagent grade salts and acid. The acetate buffer of *p*H 5.00 had an ionic strength of 0.1000. The phosphate buffer of *p*H 6.83 had an ionic strength of 0.132.

The bovine serum albumin was a crystallized product of Armour and Company. Its water content was determined by drying a separate portion in an oven at 110°. Binding was measured with solutions containing near 0.2% of the protein.

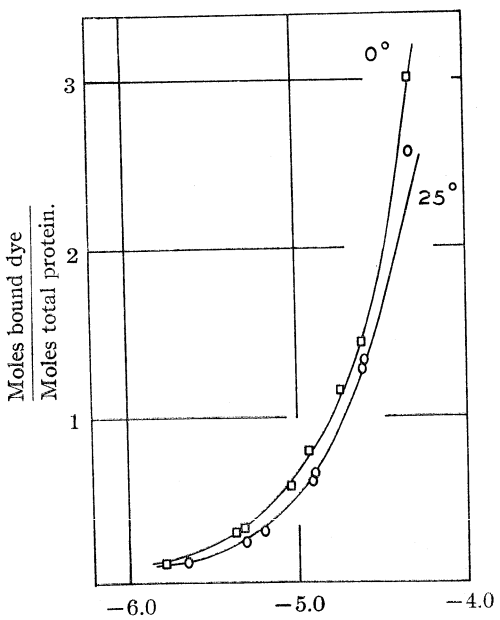



Fig. 1.—Effect of temperature on binding of methyl orange by bovine serum albumin at *p*H 6.8.

(8) P. D. Boyer, G. A. Ballou and J. M. Luck, *ibid.*, **167**, 407 (1947).

## Results

The data on the binding of the monovalent anion, methyl orange, by bovine serum albumin in phosphate buffer are presented in Fig. 1. As in the past, the moles of bound ion per mole of protein, $r$, have been plotted as a function of the concentration of the free ion (A), in equilibrium with the protein complex. Phosphate buffer has been used since previous work[6] has indicated that competition with buffer anions is small in this system.

Corresponding data on the binding of azosulfathiazole, the divalent anion, are assembled in Fig. 2. Acetate buffer at *p*H 5, rather than phosphate at *p*H 6.8, was used in this case, in order to prevent the dissociation of the dye into a trivalent species.

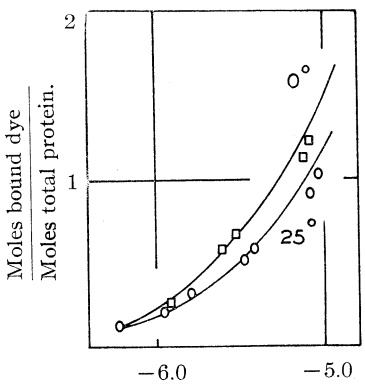



Fig. 2.—Effect of temperature on binding of azosulfathiazole by bovine serum albumin at *p*H 5.0.

## Discussion

A cursory glance at the data shows that the extent of binding is not a sensitive function of the temperature. One can conclude immediately, then, that the enthalpy change for the binding process must be small (since $\Delta H = RT^2 \, \mathrm{d} \ln K/\mathrm{d}T$) and that the major contribution to the favorable free energy change comes from the entropy term (since $\Delta F = \Delta H - T\Delta S$). To present these considerations in a more precise and quantitative form, however, requires further calculations.

**Calculation of Binding Constants for First Complex.**—A method of evaluation of free energies of formation of anion–protein complexes, $PA_i$, from the experimental data on binding has been presented previously.[3] Depending on the application of the law of mass action to the multiple equilibria

$$PA_{i-1} + A = PA \qquad (1)$$

this method enables one to calculate the successive equilibrium constants, $k_i$, and, in princi-

ple, $n$, the maximum number of sites on the protein available to the anion.

In practice, however, the determination of $n$ with assurance is a very difficult problem. In previous work, an approach has been made by a plot of $1/r$ *vs.* $1/(A)$. As (A) approaches infinite concentration, $r$ should approach $n$. Hence the intercept on the ordinate in a graph of $1/r$ *vs.* $1/(A)$ should be $1/n$, since the value (of zero) for $1/(A)$ at that point corresponds to infinite (A). Such extrapolations have been limited largely to situations where electrostatic factors are negligible, and hence where the binding data can be expressed by the linear function[3]

$$\frac{1}{r} = \frac{1}{kn}\frac{1}{(A)} + \frac{1}{n} \qquad (2)$$

In equation (2), $k$ is the intrinsic binding constant and is related to $k_i$ by the expression

$$k_i = \frac{n - (i - 1)}{i} k \qquad (3)$$

However, as has been pointed out recently by Scatchard,[9] this type of extrapolation tends to obscure non-statistical, interaction effects, particularly when data at high anion concentrations are lacking, and may lead to incorrect values of $n$. An alternative method of plotting has been proposed by Scatchard and is based on the use of the function

$$\frac{r}{(A)} = kn - kr \qquad (4)$$

when electrostatic factors are negligible, and of an appropriately modified expression when such factors must be taken into account. As is evident from equation (4), the intercept on the *abscissa* of a graph of $r/(A)$ *vs.* $r$, must be $n$, since $r/(A)$ at this point is zero. This type of graph shows one quite clearly the length of the extrapolation from the region of experimental data, and hence gives a good indication of the reliability of the value obtained for $n$.

An analysis of our present data by the Scatchard method indicates that no reliable value of $n$ can be obtained. Nevertheless, for our present purpose, an investigation of the effect of temperature on binding by albumin, it is unnecessary to know $n$, for the thermodynamic changes accompanying the formation of $PA_i$ can be evaluated readily *for small values of* $i$ by the following procedure.

From data on the extent of binding at low values of (A), it is possible to evaluate $k_1$ quite readily. It is evident from equation (3) that for $i = 1$

$$k_1 = nk \qquad (5)$$

Thus $k_1$ can be obtained from a knowledge of the product $nk$ even if the individual factors are unknown. This product can be obtained in turn from equation (4), for it corresponds to the intercept on the *ordinate* in a graph of $r/(A)$ *vs.* $r$. This intercept, in contrast to that on the abscissa, can be evaluated readily, for it can be obtained by an extrapolation in the region of low values of $r$, and hence low concentrations of (A), a region in which adequate experimental data are available.

This procedure has been used to obtain values of $k_1$ for albumin complexes with each of the two anions, methyl orange and azosulfathiazole, at each of the two temperatures, 0 and 25°. The results obtained are listed in Table I.

TABLE I

BINDING CONSTANTS FOR COMPLEXES WITH BOVINE ALBUMIN

| Anion | Constant | Temperature 0° | Temperature 25° |
|---|---|---|---|
| | $k_1$ | $6.9 \times 10^4$ | $5.0 \times 10^4$ |
| Methyl orange | $k_2$ | $3.4 \times 10^4$ | $2.5 \times 10^4$ |
| | $k_3$ | $2.2 \times 10^4$ | $1.6 \times 10^4$ |
| Azosulfathiazole | $k_1$ | $2.4 \times 10^5$ | $1.75 \times 10^5$ |
| | $k_2$ | $0.88 \times 10^5$ | $0.64 \times 10^5$ |
| | $k_3$ | $0.43 \times 10^5$ | $0.31 \times 10^5$ |

**Calculation of Binding Constants for Higher Complexes.**—Since the binding data in the present series cover complexes with an average value of $i$ as high as nearly 3, it has seemed pertinent to attempt to calculate binding constants up to $k_3$. Strictly speaking this cannot be done without a knowledge of $n$ since an evaluation of the statistical contribution from equation (3), or its equivalent, depends on the value of $n$. However, if we assume that $n$ is large, for example 20 or more, it can be shown readily that the magnitude of the statistical contribution is not sensitive to the specific value chosen for $n$ so long as only small values of $i$ are considered.

Starting from known values of $k_1$, one can obtain succeeding equilibrium constants by means of the equation[3]

$$RT \ln (k_{i-1}/k_i) = RT \ln \left[\frac{n - (i - 2)}{n - (i - 1)}\frac{i}{i - 1}\right] - \Delta F_{elect.} \qquad (6)$$

where $\Delta F_{elect.}$ is the change in electrostatic free energy in the reaction

$$PA_i + PA_{i-2} = 2PA_{i-1} \qquad (7)$$

The term in the brackets on the right-hand side of equation (6) is the statistical factor. That it is not sensitive to the value of $n$, so long as $n$ is large, is shown by the comparison of numerical values listed in Table II. In a more general fashion, this characteristic of the statistical contribution is evident also from the fact that the first factor,

TABLE II

COMPARISON OF STATISTICAL FACTOR FOR DIFFERENT VALUES OF $n$

| | $\frac{n - (i - 2)}{n - (i - 1)}\frac{i}{i - 1}$ | |
|---|---|---|
| | $n = 22$ | $n = 50$ |
| 2 | 2.10 | 2.04 |
| 3 | 1.58 | 1.53 |
| 4 | 1.40 | 1.36 |
| 5 | 1.32 | 1.28 |
| 6 | 1.27 | 1.23 |

(9) G. Scatchard, *Annals N. Y. Acad. Sci.*, in press.

$n(i-2)/n-(i-1)$, will be close to unity for different values of $i$, so long as $n$ is large, and $i$ is kept to the first few integers. Thus the numerical value of the bracket in equation (6) is determined essentially by the second factor $i/(i-1)$, which is obviously independent of $n$.

For the data on the binding of methyl orange, $\Delta F_{\text{elect.}}$ was assumed to be zero, as in previous work, because the results did fit a linear presentation in terms of equation (2). The constants $k_2$ and $k_3$ can then be evaluated readily at each temperature by application of equation (6). The results obtained have been included in Table I. The corresponding free energy changes can be expressed in the form of the following equations (in units of calories/mole)

$$\text{At } 0°: \quad \Delta F_i^0 = -6049 + \sum_{j=2}^{j=i} RT \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} \tag{8}$$

$$\text{At } 25°: \quad \Delta F_i^0 = -6411 + \sum_{j=2}^{j=i} RT \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} \tag{9}$$

In complexes between serum albumin and azosulfathiazole, on the other hand, electrostatic interactions between successively bound anions do not seem to be negligible. The term $\Delta F_{\text{elect.}}$ in equation (6) was calculated, as previously,[3] on the assumption of a spherical protein molecule of radius 30 Å., and a value of 4 Å. for the radius of the dye anion. At 0°, $\Delta F_{\text{elect.}}$ turns out to be 160 cal./mole, and at 25°, 177 cal./mole. With these values, $k_2$ and $k_3$ can be calculated readily from equation (6), and the results obtained have also been placed in Table I. The corresponding free energy changes may be expressed by the following equations (in units of calories/mole)

$$\text{At } 0°: \quad \Delta F_i^0 = -6725 + \sum_{j=2}^{j=i} RT \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} + 160(i-1) \tag{10}$$

$$\text{At } 25°: \quad \Delta F_i^0 = -7151 + \sum_{j=2}^{j=i} RT \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} + 177(i-1) \tag{11}$$

The additional term in each of the equations (10) and (11), in comparison with (8) and (9), represents the contribution of the electrostatic interaction factor.

**Calculation of Enthalpies and Entropies of Binding.**—From the equations for the free energy changes it is possible to deduce expressions for the enthalpy and entropy changes accompanying the formation of the respective protein–anion complexes by standard thermodynamic procedures. These functions can be summarized as follows (the units for $\Delta H$ being calories/mole, those for $\Delta S$ being calories/mole degree)

Methyl orange–albumin complexes

$$\Delta H^0 = -2100 \tag{12}$$

$$\Delta S_i^0 = 14.5 - \sum_{j=2}^{j=i} R \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} \tag{13}$$

Azosulfathiazole–albumin complexes

$$\Delta H^0 = -2000 \tag{14}$$

$$\Delta S_i^0 = 17.1 - \sum_{j=2}^{j=i} R \ln \frac{n-(j-2)}{n-(j-1)} \frac{j}{j-1} \tag{15}$$

Strictly speaking, the $\Delta H^0$ for azosulfathiazole complexes should have two additional terms, one containing the factor $\Delta F_{\text{elect.}}$ and the second its temperature coefficient. In practice, however, it turns out that these terms balance each other approximately, so that $\Delta H^0$ does not vary significantly for different values of $i$.

**Significance of the Thermodynamic Changes in Binding.**—In considering the magnitudes of the thermodynamic changes associated with the binding process, one is struck particularly by the positive entropy values. Despite the fact that the formation of the complex, as represented by the simple expression in equation (1), is an association reaction, the entropy of the system does not drop, but increases. Thus the formation of albumin–anion complexes stands in direct contrast with that of cellulose–anion complexes, where the association reactions are accompanied by negative entropy changes,[10] as one would expect from a simple molecular picture. The difference between these two systems may be, however, in the use of fibers, rather than soluble macromolecules, in the cellulose investigations; for the values of the equilibrium constants and temperature coefficients for anion–wool fiber combinations reported by Steinhardt[11] indicate a decrease in entropy for the uptake of organic ions.

The positive entropies associated with many reactions involving proteins are attributed frequently to disorientation and unfolding of the protein molecule, and a similar explanation might be offered here. Such a picture in connection with anion–protein complexes seems unlikely, however, since the enthalpy changes involved are negative and small, whereas a process of unfolding presumably requires the breaking of several bonds and hence should be an endothermic reaction of appreciable magnitude.

An alternative explanation, which is consistent with both the observed entropy and enthalpy changes, would focus attention on the electrostatic nature of the species involved in the formation of these anion–protein complexes. Though the anion may be indicated merely by the symbol $A^-$, it is recognized that this ion has several polarized water molecules "frozen" to it in the aqueous solution. Similarly the protein molecule is highly hydrated, particularly, perhaps, around the charged loci of the free carboxyl groups and the quaternary nitrogen atoms. Recent evidence from measurements of the decrease in binding with increasing $p$H,[12] as well as from observations of

(10) W. J. Marshall and R. H. Peters, *J. Soc. Dyers Colourists*, **63**, 446 (1947).

(11) J. Steinhardt, *Annals N. Y. Acad. Sci.*, **41**, 287 (1941).

(12) I. M. Klotz and F. M. Walker, THIS JOURNAL, **69**, 1609 (1947).

loss in binding ability on acetylation of the amino groups of albumin,[13] points to the participation of the charged nitrogen loci in the bond with the anion. The formation of such an electrostatic bond would release some of the "frozen" water molecules from the constituent ions. Thus there would be an *increase* in the number of molecular species upon formation of the anion–protein complex, rather than a decrease, as indicated by equation (1), and hence one would reasonably expect an increase in entropy for the process. It is of interest in connection with this interpretation that Lundgren[14] has observed an increase in the volume of the solution when an alkylsulfonate anion is bound by egg albumin.

This view of the mechanism of the binding process makes it analogous to the ionization process of organic carboxylic acids. Written as an association reaction, the ionic changes in these acids may be represented by the equation

$$H^+ + A^- \rightleftarrows HA \qquad (16)$$

For the aliphatic organic acids the entropy change accompanying the reaction shown is around 20 calories/mole degree and the enthalpy change of the order of several hundred calories/mole.[15] Here too, then, there is an increase in entropy in a reaction which superficially involves a reduction in the number of molecular species. When one recognizes, however, that the disappearance of the free ions is accompanied by the release of fixed water molecules, the positive entropy for reaction (16) becomes reasonable.

The volume changes accompanying the ionization processes of organic acids also parallel those for anion–protein complexes. Thus it has been observed[16] in several different ionic systems that reaction (16) is associated with an increase in volume of the order of 20 cc./mole. While corresponding quantitative data for the binding process by albumin are not available, the qualitative observations of Lundgren[14] are of the correct sign. In both cases, an increase in volume fits the assumption that water molecules are released in the association reaction.

The analogy between these two processes may be pursued even further by a comparison of the changes in the thermodynamic quantities for the association process with variation in the structure of the anion. It is of interest to note that the change of 1369 calories/mole[15] in $\Delta F^0$ for reaction (16) in going from formic to acetic acid is due almost entirely to the 4.5 calories/mole degree difference in $\Delta S^0$ for the reaction with hydrogen ion, a difference which may be attributed to the greater degree of hydration of the neutral molecule with the single carbon atom. Correspondingly, in the present investigation with a protein, a comparison of the thermodynamic changes in the formation of the first[17] complex, $PA_1$, with methyl orange and azosulfathiazole, respectively, reveals that the more favorable free energy of binding of the latter ion is due to the greater change in entropy in the formation of the protein complex. On the molecular level, then, these characteristics of the thermodynamic quantities associated with the binding process indicate that the higher affinity for some of the larger anions is not due so much to increased van der Waals interaction, but rather to a greater degree of dehydration of the complex.

**Conclusion.**—While the present investigations have been carried out with a single type of molecule, sulfonated azo compounds, the qualitative observations on other anions[1,7,8] of very different atomic structure indicate that here too the heat of binding is quite small and that the favorable free energy for association is due primarily to the positive entropy term. It is of interest to note also that substantially the same conclusions have been reached in a study of metallic cation–albumin complexes.[18] It becomes apparent, then, that in comparisons of changes in binding energy with variations in structure of the small ion, greater attention should be paid to the ability of the ion to force the release of frozen water molecules on the ion–protein complex.

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## Summary

The binding of methyl orange and of azosulfathiazole, respectively, by bovine serum albumin has been examined quantitatively at 0 and at 25°. For the formation of the first anion-protein complex, the following thermodynamic changes have been calculated: Methyl orange; $\Delta F_0^0 = -6049$ cal./mole, $\Delta F_{25}^0 = -6411$ cal./mole, $\Delta H^0 = -2100$ cal./mole, $\Delta S^0 = 14.5$ cal./mole deg.; azosulfathiazole: $\Delta F_0^0 = -6725$ cal./mole, $\Delta F_{25}^0 = -7151$ cal./mole, $\Delta H^0 = -2000$ cal./mole, $\Delta S^0 = 17.1$ cal./mole deg.

The large positive entropy of binding, coupled with the small enthalpy of binding, have been interpreted to mean that the major contribution to the free energy of binding comes from the release of solvent molecules from the anion–protein complex.

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(13) Unpublished work in this Laboratory.

(14) H. P. Lundgren, *Textile Research J.*, **15**, 335 (1945).

(15) D. H. Everett and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **35**, 1380 (1939); H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p. 514.

(16) H. H. Weber, *Biochem. Z.*, **218**, 1 (1930); I. M. Klotz and C. F. Eckert, THIS JOURNAL, **64**, 1878 (1942).

(17) The first complex only has been chosen for comparison since electrostatic interactions between successively bound ions would obscure the picture in considerations of higher complexes.

(18) I. M. Klotz and H. G. Curme, THIS JOURNAL, **70**, 939 (1948).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

# Dielectric Properties and Ultraviolet Absorption Spectra of Addition Compounds of Sulfur Dioxide and Sulfur Trioxide with Tertiary Amines[1]

BY J. A. MOEDE[2] AND COLUMBA CURRAN[3]

Studies on the addition compounds of tertiary amines with sulfur dioxide have been summarized by Bateman, Hughes and Ingold.[4] Later work includes the phase equilibrium studies of VanderWerf and co-workers.[5] An adequate discussion of the type of bonding in these compounds has been given by Burg.[6]

The addition compounds of amines with sulfur trioxide have been less extensively studied. They are higher melting, more stable, less reactive and much less soluble in inert solvents than their sulfur dioxide analogs.[6]

The present investigation was undertaken to evaluate the N–S bond moment, to study the effect of the formation of this bond on ultraviolet absorption spectra, and to determine the extent of dissociation of the addition compounds in solution. Dielectric constant and absorption measurements complement each other in that the latter may be made at solute mole fractions of about one-thousandth of the concentrations required for the former measurements.

## Experimental

**Preparation and Purification of Compounds.**—**Sulfur dioxide,** an Ohio Chemical Company product, was dried by passing through two phosphoric anhydride towers.

**Sulfur trioxide** was obtained by distillation from a mixture of fuming sulfuric acid and phosphoric anhydride.

**Trimethylamine,** an Eastman Kodak Co. product, was purified by passing through sodium hydroxide. Analysis by titration indicated a purity of 99.3%.

**Triethylamine** and **tri-*n*-butylamine,** Eastman Kodak Co. white label products, were refluxed over sodium and distilled. The following constants were obtained for tri-*n*-butylamine: b. p. 219° (750 mm.), $d^{25}_4$ 0.7743, $n^{25}D$ 1.4278.

**Pyridine** was refluxed over calcium oxide and distilled.

**Dimethylaniline,** a Merck product, was distilled and stored over activated alumina in an atmosphere of nitrogen.

**Trimethylamine–sulfur dioxide** was prepared under moisture-free conditions by the method of Burg[6]; m. p. 77°.

**Pyridine–sulfur dioxide,** m. p. −7.0°, was prepared by the addition of sulfur dioxide to pyridine at −20°.

**Pyridine–sulfur trioxide,** m. p. 137°, was prepared by a variation of the method of Baumgarten.[7]

**Dimethylaniline–sulfur trioxide** was prepared by the method of Willcox.[8] The dried product melted between 85 and 90° and solutions were prepared immediately after drying, as the compound is not stable over long periods.

**Trimethylamine–sulfur trioxide,** m. p. 240°, was prepared in the same manner as dimethylaniline–sulfur trioxide and purified by washing with water.

**Triethylamine–sulfur trioxide,** m. p. 91.5°, was prepared in the same manner as pyridine–sulfur trioxide, using carbon tetrachloride as a solvent. The product was crystallized from acetone and the crystals were dried in a vacuum desiccator over phosphoric anhydride.

**Tri-*n*-butylamine–sulfur trioxide** was prepared by adding 5 ml. of liquid sulfur trioxide with stirring to 30 ml. of tri-*n*-butylamine in 300 ml. of carbon tetrachloride at 0°. The lower layer was washed with cold concentrated hydrochloric acid and then with water, dried over calcium chloride and decolorized with activated charcoal. The solvent was evacuated off and the product crystallized from acetone, m. p. 94°. Its molecular weight was determined cryoscopically in benzene as 266, compared to the calculated value, 265.4.

**Dimethylaniline hydrochloride** was prepared as described by Scholl and Escales.[9]

*trans*-**Dichloroethylene,** obtained from the Columbia Organic Chemicals Company, was washed successively with silver nitrate, hydrochloric acid, sodium carbonate and water and partially dried with calcium chloride. It was then refluxed over phosphoric anhydride and twice fractionally distilled through a 1 meter Fenske column in an atmosphere of nitrogen.

**Triethylamine–sulfur dioxide** and **tri-*n*-butylamine–sulfur dioxide** were prepared in solution. For the absorption measurements, all sulfur dioxide addition compounds were prepared in solution.

**Chloroform,** a U. S. P. grade, was dried over activated alumina. Where alcohol-free chloroform was necessary a technical grade was washed with water, dried over activated alumina and activated silica and used as soon as possible after drying.

*n*-**Butyl chloride,** an Eastman product, was washed with water and dried with activated alumina and activated silica. Other solvents were purified as in earlier work.

**Preparation of Solutions.**—Solutions for dielectric constant measurements were prepared in a dry air box and were introduced into the dielectric cell without contacting moist air. The master solutions for absorption measurements were prepared in a similar manner, but dilutions were made outside the box and the Beckman absorption cells were not sealed. Small amounts of a white solid, probably the bisulfite, formed on the addition of sulfur dioxide to butyl chloride solutions of triethylamine, preventing a quantitative treatment of the absorption measurements on these solutions.

Solutions of sulfur dioxide in *trans*-dichloroethylene were prepared by direct addition of sulfur dioxide gas to the solvent. Concentrations were determined by the addition of excess sodium hydroxide, titration with hydrochloric acid to the phenolphthalein end-point, oxidation of the sulfite with hydrogen peroxide and continued titration to the methyl orange end-point.

**Physical Measurements.**—Dielectric constants were obtained at radio frequencies using a modified Armstrong oscillator in the tuning circuit, constructed with the aid of a circuit diagram kindly furnished by Professor W. D. Kumler. The dielectric cell was similar to that described by Svirbely and co-workers,[10] having a capacity of 110 $\mu\mu$f. As the dielectric constants of dioxane solutions of the sulfur trioxide addition compounds varied with time, capacity readings on these solutions were taken as soon as possible after preparation. The 20-ml. pycnometer used to obtain densities was a modification of that described by

(1) Presented in part at the New York meeting of the American Chemical Society, September, 1947.

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(3) Brother Columba Curran of the Congregation of Holy Cross.

(4) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 243 (1944).

(5) Hoffman and VanderWerf, THIS JOURNAL, **70,** 264 (1948).

(6) Burg, *ibid.*, **65,** 1629 (1943).

(7) Baumgarten, *Ber.*, **59,** 1166 (1926).

(8) Willcox, *Am. Chem. J.*, **32,** 450 (1904).

(9) Scholl and Escales, *Ber.*, **30,** 3134 (1897).

(10) Davis, Bridge and Svirbely, THIS JOURNAL, **65,** 857 (1943).

Lipkin.[11] Absorption measurements were made with a Beckman DU quartz spectrophotometer. All extinctions were corrected for the difference in transparency of the two 1-cm. fused silica cells. The precision limit of the molar extinction coefficients is estimated as 3%.

## Calculations

The dissociation constant of trimethylamine–sulfur dioxide in chloroform and *n*-butyl chloride was calculated from the variation of the extinction of the solution with solute concentration, assuming Beer's law. For the equilibrium mixture, using 1-cm. cells, the observed extinction $E = \epsilon_C c_C + \epsilon_A c_A + \epsilon_B c_B$, where $\epsilon$ is the molar extinction coefficient, $c$ is the molar concentration and the subscripts A, B and C refer to the amine, sulfur dioxide and the addition compound, respectively. The molar extinction coefficient of the undissociated addition compound could not be obtained experimentally. That value of $\epsilon_C$ was chosen, by trial and error, which gave the smallest variation with concentration of $K_c = c_A^2/c_2 - c_A$ where $c_2$ is solute molarity considering no dissociation. The value of the molar extinction coefficient of trimethylaminesulfur dioxide yielding the most consistent set of $K_c$ values was the same in both solvents, 6250. The dissociation constant of dimethylaniline hydrochloride was calculated in a similar manner; the molar extinction coefficient of this compound was taken as the experimental value obtained in a solution containing a large excess of hydrogen chloride, where the extent of dissociation is negligible.

The solute polarizations at infinite dilution reported in Table II were calculated by the method of Hedestrand. The distortion polarizations were taken as 1.05 $MR_D$, with the exception of tri-*n*-butylamine for which the atomic polarization was assumed to be zero.[12] The electric moment of trimethylamine–sulfur dioxide in benzene calculated from the data for the three most concentrated solutions listed in Table I is 4.90. The moment calculated assuming a dissociation constant equal to that obtained from spectral measurements in chloroform is 5.0. Dissociation in benzene is expected to be less than in chloroform, and the change in polarization with concentration likewise indicates a smaller degree of dissociation in benzene. Therefore, a mean value, 4.95, has been taken as the moment of this addition compound.

TABLE I

DIELECTRIC CONSTANTS AND DENSITIES OF SOLUTIONS AT 25°

| $N_2$ | $D$ | $d$ |
|---|---|---|
| Benzene--Tri-*n*-butylamine | | |
| 0.00000 | (2.2760) | 0.87299 |
| .04079 | 2.2813 | .86156 |
| .05950 | 2.2843 | .85687 |
| .08158 | 2.2868 | .85184 |
| *trans*-Dichloroethylene–Sulfur dioxide | | |
| 0.00000 | 2.1886 | 1.24658 |
| .00217 | 2.1968 | 1.24648 |
| .00341 | 2.2008 | 1.24642 |
| .00422 | 2.2030 | ..... |
| Benzene--Trimethylamine–sulfur dioxide | | |
| 0.00000 | 2.276 | 0.8738 |
| .00343 | 2.390 | ..... |
| .00376 | 2.402 | .8749 |
| .00538 | 2.456 | .8756 |
| Benzene--Triethylamine–sulfur dioxide | | |
| 0.00000 | 2.2760 | 0.87315 |
| .00153 | 2.3088 | .87360 |
| .00238 | 2.3348 | .87382 |
| .00557 | 2.4261 | .87469 |
| .00877 | 2.5259 | .87562 |
| Benzene--Tri-*n*-butylamine–sulfur dioxide | | |
| 0.00000 | 2.2760 | 0.87318 |
| .00169 | 2.3062 | .87355 |
| .00229 | 2.3220 | .87366 |
| .00464 | 2.3840 | .87404 |
| .00686 | 2.4491 | .87461 |
| .01022 | 2.5450 | .87549 |
| Benzene--Pyridine–sulfur dioxide | | |
| 0.00000 | 2.276 | 0.8735 |
| .00507 | 2.335 | .8756 |
| .00698 | 2.360 | .8769 |
| .00813 | 2.372 | .8769 |
| .00931 | 2.390 | .8774 |
| .01099 | 2.412 | .8779 |
| .01256 | 2.437 | .8784 |
| Benzene--Triethylamine–sulfur trioxide | | |
| 0.00000 | 2.275 | 0.8731 |
| .00567 | 2.644 | .8767 |
| .00895 | 2.856 | .8789 |
| .01043 | 2.951 | ..... |
| .01223 | 3.064 | .8810 |
| Dioxide--Triethylamine–sulfur trioxide | | |
| 0.00000 | 2.212 | 1.0291 |
| .00198 | 2.362 | 1.0295 |
| .00200 | 2.365 | 1.0296 |
| .00345 | 2.468 | 1.0304 |
| Benzene--Tri-*n*-butylamine–sulfur trioxide | | |
| 0.000000 | 2.2750 | 0.87313 |
| .000717 | 2.3282 | .87342 |
| .000797 | 2.3332 | ..... |
| .002035 | 2.4215 | .87414 |
| .005260 | 2.6582 | .87595 |
| $CCl_4$--Tri-*n*-butylamine–sulfur trioxide | | |
| 0.000000 | 2.2332 | 1.5851 |
| .000681 | 2.2777 | ..... |
| .001093 | 2.3055 | ..... |
| .002218 | 2.3831 | ..... |
| .004600 | 2.5875 | 1.5793 |
| .006039 | 2.7349 | 1.5776 |
| .008480 | 2.9970 | 1.5748 |

(11) Lipkin, Davison, Harvey and Kurtz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 55 (1944).

(12) Le Fevre and Russel, *Trans. Faraday Soc.*, **43**, 374 (1947).

Both the $\Delta D/N_2$ and $\Delta d/N_2$ ratios for benzene solutions of the addition compounds of triethylamine, tri-*n*-butylamine and pyridine with sulfur dioxide decreased sharply with decreasing solute concentration, indicating appreciable dissociation. Assuming that these compounds were in equilibrium in solution with the amines and sulfur dioxide, dissociation constants were calculated in the following manner: The electric moments of triethylamine–sulfur dioxide and tri-*n*-butylamine–sulfur dioxide were assumed to be 0.05 and 0.10 debyes greater than the moment of trimethylamine–sulfur dioxide. The calculation of the moment of pyridine–sulfur dioxide is indicated in the Discussion. The polarizations at infinite dilution of these compounds were calculated from the moments and molar refractions. The polarizations of tri-*n*-butylamine and sulfur dioxide are listed in Table II.

TABLE II

POLARIZATIONS AND ELECTRIC MOMENTS

| Compound | $P_{2\infty}$ | $MR_D$ | $\mu$ |
|---|---|---|---|
| Sulfur dioxide | 63.2 | 11.5 | 1.6 |
| Tri-*n*-butylamine | 73.6 | 61.6 | 0.77 |
| Trimethylamine–sulfur dioxide | 522 | 31.5 | 4.95 |
| Triethylamine–sulfur trioxide (benzene) | 985 | 44.7 | 6.84 |
| Triethylamine–sulfur trioxide (dioxane) | 1136 | 44.7 | 7.3 |
| Tri-*n*-butylamine–sulfur trioxide (benzene) | 1149 | 72.6 | 7.2 |
| Tri-*n*-butylamine–sulfur trioxide ($CCl_4$) | | | |
| $N_2$ = 0.008480 | 1533 | 72.6 | 8.4 |
| $N_2$ = 0.000681 | 1132 | 72.6 | 7.2 |

TABLE III

POLARIZATIONS AND DISSOCIATION CONSTANTS IN BENZENE AT 25°

| $N_2$ | $V$ | $P_T$ | $K_c$ |
|---|---|---|---|
| Triethylamine–Sulfur Dioxide | | | |
| 0.00877 | 90.07 | 30.07 | 0.0084 |
| .00557 | 89.86 | 28.95 | .0069 |
| .00238 | 89.63 | 27.60 | .0047 |
| .00153 | 89.56 | 27.20 | .0063 |
| | | Mean | .007 |
| Tri-*n*-butylamine–Sulfur Dioxide | | | |
| 0.01022 | 91.22 | 31.01 | 0.0173 |
| .00686 | 90.66 | 29.53 | .0134 |
| .00464 | 90.27 | 28.50 | .0130 |
| .00229 | 89.85 | 27.48 | .0122 |
| .00169 | 89.75 | 27.22 | .0136 |
| | | Mean | .013 |
| Pyridine–Sulfur Dioxide | | | |
| 0.01256 | 89.86 | 29.10 | 3 |
| .01099 | 89.79 | 28.74 | 4 |
| .00931 | 89.72 | 28.41 | 4 |
| .00813 | 89.68 | 28.14 | 5 |
| .00698 | 89.59 | 27.95 | 4 |
| .00507 | 89.58 | 27.58 | 5 |
| | | Mean | 4 |

Table II. The values for triethylamine and pyridine were taken from the literature. It was assumed that at the low solute concentrations listed in Table III the polarization of each component was independent of concentration. The concentration of each component and the value of $K_N$ were calculated from the total polarization of each solution by relations similar to those used by Earp and Glasstone.[13] Values of $K_c$ were obtained from the equation $K_c = K_N/V$ where $V$ is the molar volume of the solution in liters.

TABLE IV

EXTINCTIONS AND THE DISSOCIATION CONSTANT OF TRIMETHYLAMINE–SULFUR DIOXIDE AT 24 ± 3°

| $c$ | $E$ | $K_c \times 10^4$ |
|---|---|---|
| In *n*-Butyl Chloride at 267 mμ | | |
| 0.000561 | 2.020 | 1.9 |
| .000448 | 1.560 | 1.8 |
| .000420 | 1.395 | 2.0 |
| .000374 | 1.187 | 2.0 |
| .000187 | 0.467 | 1.9 |
| | Mean | 1.9 ± 0.4 |
| In Chloroform at 260 mμ | | |
| 0.000539 | 1.985 | 1.7 |
| .000359 | 1.126 | 2.0 |
| .000270 | 0.800 | 1.8 |
| .000180 | 0.462 | 1.7 |
| .000135 | 0.280 | 2.1 |
| | Mean | 1.9 ± 0.4 |

TABLE V

EXTINCTIONS OF DIMETHYLANILINE HYDROCHLORIDE IN CHLOROFORM AND THE VARIATION OF $K_c$ WITH CONCENTRATION AT 24 ± 3°

| $c$ | $E$ | $K_c \times 10^6$ |
|---|---|---|
| 0.008442 | 1.675 | 0.38 |
| .008120 | 1.630 | 0.71 |
| .005627 | 1.160 | 1.9 |
| .005413 | 1.105 | 1.4 |
| .004221 | 0.910 | 5.3 |
| .004060 | .845 | 3.2 |
| .003248 | .695 | 4.5 |
| .002814 | .602 | 4.6 |
| .002707 | .600 | 8.2 |
| .001407 | .325 | 14 |
| .001203 | .300 | 31 |
| (0.000000) | | 200 |

## Discussion of Results

The low moment obtained for tri-*n*-butylamine in benzene, 0.77, compared to the values reported[12] for triethylamine, 0.90, and trimethylamine, 0.86, suggest a slight increase in the nitrogen valence angle in tri-*n*-butylamine due to steric hindrance.

A consideration of the configurations of sulfur dioxide,[14] thionyl chloride[15] and sulfuryl chloride[15] has led the authors to choose 55° as the angle between the N → S and $SO_2$ moment vectors in the

(13) Earp and Glasstone, *J. Chem. Soc.*, 1709 (1935).
(14) Cross and Brockway, *J. Chem. Phys.*, **3**, 821 (1935).
(15) Palmer, THIS JOURNAL, **60**, 2360 (1938).

amine–sulfur dioxide addition compounds. Assuming the moments of the amine, 0.86, and sulfur dioxide, 1.6, each to be increased by 0.2 in the addition compound, the moment calculated for the N → S bond from the moment of trimethylamine–sulfur dioxide, 4.95, is 2.7 ± 0.4.

This N → S moment is appreciably lower than the N → O bond moment, 4.2, in amine oxides,[16] and the difference is greater than expected from a comparison of the C–S and C–O bond moments. It has been suggested by one of the authors[17] that a coördinate bond may result from resonance between a dipole–dipole bond, $R_3N\text{--}SO_2$, and a purely covalent bond in which the electrons are equally shared, $R_3\overset{+}{N}—\overset{-}{S}O_2$. The dipole–dipole structure should make an appreciable contribution to the amine–sulfur dioxide molecule and thus reduce the N → S moment appreciably below the N → O moment in amine oxides, as the latter bond can have practically no dipole–dipole character.

The moment of pyridine–sulfur dioxide, 6.2 ± 0.7, used in calculating the dissociation constant for this compound in benzene listed in Table III was approximated as the vector sum of the pyridine, N → S and $SO_2$ moments.

Compound formation between trimethylamine and sulfur dioxide is accompanied by a marked increase in ultraviolet absorption, as is evident from Fig. 1. The lower absorption maxima of the addition compounds of sulfur dioxide with triethylamine and tri-*n*-butylamine are attributed to the greater dissociation of these compounds at corresponding concentrations. The absorption maxima for these two compounds shifted with decreasing concentration and the absorption curves approached the envelopes of the amine and sulfur dioxide curves at very low concentrations. The variation of the molar extinction coefficients with concentration is illustrated in Fig. 2. The dissociation constant calculated for trimethylamine–sulfur dioxide from spectral data is $1.9 \times 10^{-4}$ in both chloroform and butyl chloride, compared to the values 0.007, 0.013 and 4 calculated for the sulfur dioxide addition compounds of triethylamine, tri-*n*-butylamine and pyridine from the changes in polarization with concentration in benzene. The variation with time of the extinction values observed for U.S.P. chloroform, alcohol-free chloroform and *n*-butyl chloride solutions of triethylamine–sulfur dioxide and tri-*n*-butylamine–sulfur dioxide prevented the calculation of dissociation constants for these compounds from spectral data. It is evident from Fig. 3 that pyridine–sulfur dioxide is practically completely dissociated at concentrations of the order of $10^{-4}$ molar.

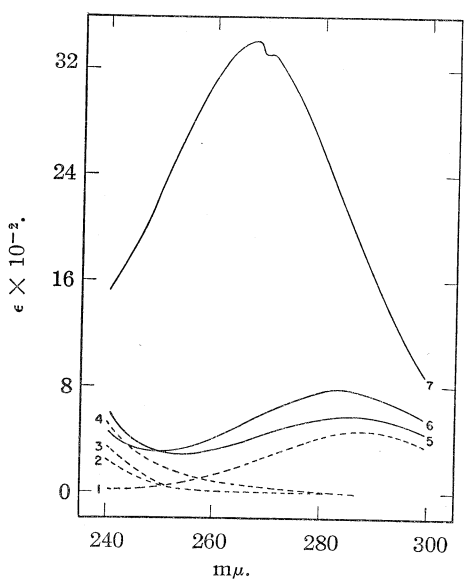



Fig. 1.—Absorption spectra in *n*-butyl chloride: (1) sulfur dioxide; (2) trimethylamine; (3) triethylamine; (4) tri-*n*-butylamine; (5) tri-*n*-butylamine–sulfur dioxide, $c = 5.1 \times 10^{-4}$; (6) triethylamine–sulfur dioxide, $c = 2.9 \times 10^{-4}$; (7) trimethylamine–sulfur dioxide, $c = 5.6 \times 10^{-4}$.

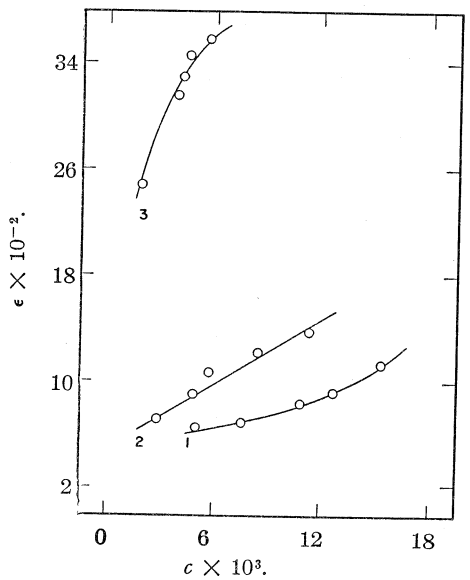



Fig. 2.—Change in molar extinction coefficient in *n*-butyl chloride with concentration: (1) tri-*n*-butylamine–sulfur dioxide at 284 mμ; (2) triethylamine–sulfur dioxide at 284 mμ; (3) trimethylamine–sulfur dioxide at 267 mμ.

Both the dielectric and absorption data reveal that the order of decreasing dissociation of the sulfur dioxide addition compounds is pyridine > tri-*n*-butylamine > triethylamine > trimethylamine. The chief factors determining this order appear to be the weak basicity of pyridine and the steric effects of alkyl groups. The steric factors affecting the stability of this type of compound have been characterized by Brown.[18]

The dielectric and density data reveal that the sulfur trioxide addition compounds of triethylam-

(16) Linton, *ibid.*, **62**, 1945 (1940).

(17) McCusker and Curran, *ibid.*, **64**, 614 (1942).

(18) Brown and Pearsall, *ibid.*, **67**, 1765 (1945).

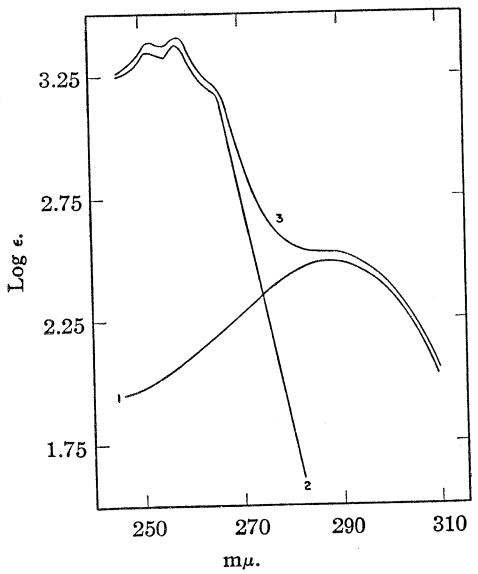



Fig. 3.—Absorption spectra in chloroform: (1) sulfur dioxide; (2) pyridine; (3) pyridine–sulfur dioxide, $c = 5.4 \times 10^{-4}$.

ine and tri-*n*-butylamine do not dissociate in benzene solution. This lack of dissociation is also evidenced by the molecular weight obtained for tri-*n*-butylamine–sulfur trioxide from a freezing point measurement on a benzene solution. Association of this compound in carbon tetrachloride at solute mole fractions in excess of 0.001 is indicated by the large $\Delta D/N_2$ ratios that increase with increasing concentration. To illustrate this effect the electric moment of tri-*n*-butylamine–sulfur trioxide has been calculated from $\Delta D/N_2$ ratios for two concentrations in carbon tetrachloride and listed in Table II. The solubilities of the addition compounds of sulfur trioxide with trimethyl amine, pyridine and dimethylaniline in non-polar solvents were too low for dielectric constant measurements.

Assuming tetrahedral valence angles in sulfur trioxide addition compounds and an increase of 0.3 in the triethylamine moment, the sum of the N → S and S–O bond moments in triethylamine–sulfur trioxide is 5.6. As a fair approximation a value of 3.6 is assigned to the N → S vector and 2.0 to the S–O bond moment. The increase in the N → S moment from the sulfur dioxide to the sulfur trioxide addition compounds is probably due to the greater residual positive charge on the trioxide sulfur and to the distorted character of the sulfur bond angles in the $R_3N{-}{-}SO_3$ dipole–dipole structure, resulting in an increased contribution of the $R_3\overset{+}{N}—\overset{-}{S}O_3$ structure to the molecule. The large moment of the S–O bond in this addition compound indicates a decrease in the S=O double bond character compared to that in sulfur dioxide.

The transparency of sulfur trioxide in the near ultraviolet limits the study of compound formation from absorption spectra to a comparison of the spectrum of the addition compound with that of the amine. Trimethylamine–sulfur trioxide and triethylamine–sulfur trioxide were observed to be transparent in the region available with chloroform, above 240 mμ, indicating, in support of the interpretation of dielectric data, that these compounds are not dissociated in solution. The absorption of tri-*n*-butylamine-sulfur trioxide, Fig. 4, is about 0.2% of that of the amine at 243 mμ, suggesting the possibility of a small amount of dissociation. The molar extinction coefficient of this compound increased slightly with decreasing concentration, but the change was less than the precision error of the measurements at these low extinction values.

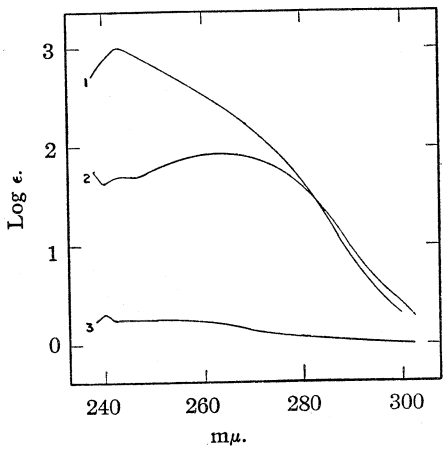



Fig. 4.—Absorption spectra in chloroform: (1) tri-*n*-butylamine; (2) tri-*n*-butylamine + 0.04 molar hydrogen chloride; (3) tri-*n*-butylamine–sulfur trioxide, $c = 0.1$.

The transparency of sulfur trioxide and its addition compounds compared to the absorption by sulfur dioxide and the amines and the strong absorption by the sulfur dioxide addition compounds suggests that absorption by these compounds is associated with excitation of the unshared nitrogen and sulfur electrons. This view is consistent with the decrease in the absorption by butylamine in acid solution illustrated in Fig. 4. The very strong absorption by trimethylamine–sulfur dioxide suggests that compound formation results in a loosening of the unshared sulfur electrons, perhaps by increasing the $sp^3$ hybrid character of the orbitals of these electrons.

The addition of a proton to pyridine increases the electron demand of the nitrogen atom and thus facilitates electron migration from the ortho and para carbon atoms, resulting in stronger absorption. The addition of sulfur trioxide alters the pyridine spectrum in a similar manner, as illustrated in Fig. 5. Lewis and Bigeleisen have shown a similar relation between the proton and stannic chloride in altering the spectrum of methylene blue.[19] The slightly lower maximum of pyridine–

(19) Lewis and Bigeleisen, *ibid.*, **65**, 1144 (1943).

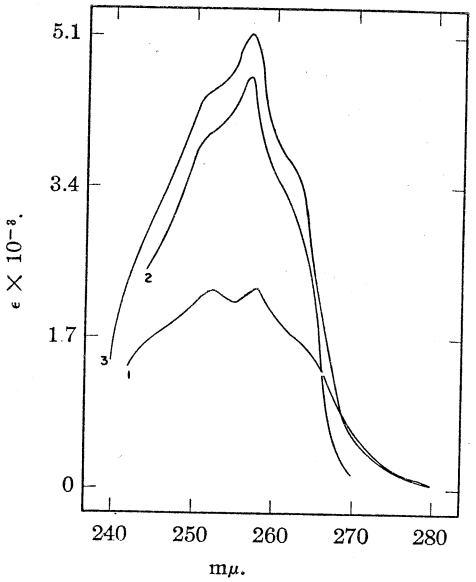



Fig. 5.—Absorption spectra in chloroform: (1) pyridine; (2) pyridine–sulfur trioxide +1% ethyl alcohol; (3) pyridine + 0.1 molar hydrogen chloride.

sulfur trioxide compared to the pyridinium ion may result from the action of the alcohol required to dissolve the addition compound. The very low solubility of this compound prevented a study of the effect of concentration on the molar extinction coefficient.

The addition of a proton to dimethylaniline prevents the migration of the nitrogen electrons to the ring and decreases sharply the absorption maximum at 255 mμ.[20] Figure 6 reveals that sulfur trioxide addition has a similar effect on the spectrum of dimethylaniline. The change in the molar extinction coefficient with concentration in U.S.P. chloroform indicates appreciable dissociation of the addition compound in this solvent. In alcohol-free chloroform, as illustrated in Fig. 7, this dissociation is decreased considerably; the extent of dissociation of the sulfur trioxide complex is very little different from that of the dimethylanilinium ion in this solvent. The absorption maxima for dimethylaniline–sulfur trioxide at varying concentrations in alcohol-free chloroform could not be determined with sufficient precision (the extinction values changed slightly with time) to obtain a reliable dissociation constant for this compound.

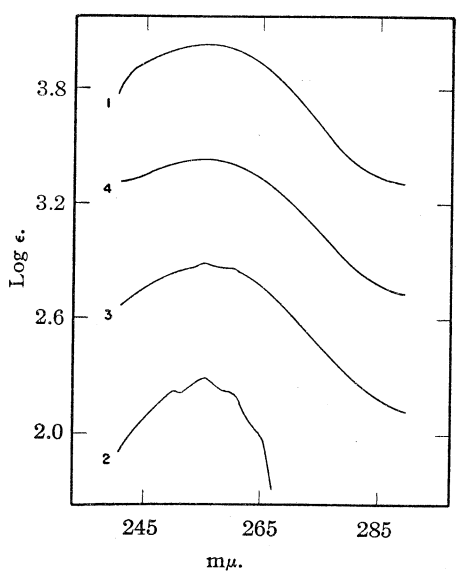



Fig. 6.—Absorption spectra of (1) dimethylaniline in chloroform and (2) dimethylaniline hydrochloride in chloroform + 0.1 molar hydrogen chloride compared with (3) $1.2 \times 10^{-3}$ molar and (4) $2.0 \times 10^{-4}$ molar dimethylaniline–sulfur trioxide in U. S. P. chloroform.

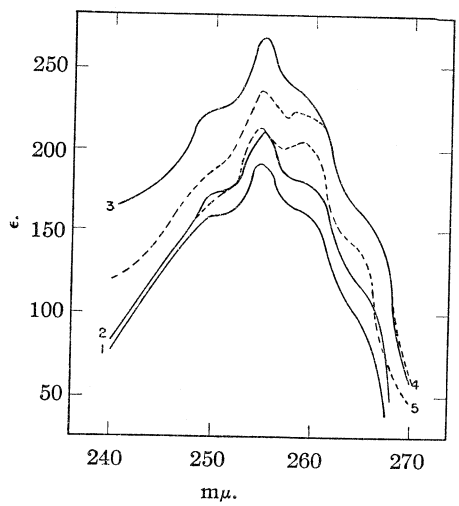



Fig. 7.—Absorption spectra in alcohol-free chloroform: (1) dimethylaniline hydrochloride + 0.1 molar hydrogen chloride; (2) 0.0081 *M* and (3) 0.0012 *M* dimethylaniline hydrochloride; (4) 0.0017 *M* and (5) 0.0069 *M* dimethylaniline–sulfur trioxide.

The values of the dissociation constant calculated for dimethylaniline hydrochloride in chloroform from observed extinctions at different concentrations increased with decreasing concentration. Dr. W. H. Hamill suggested to the authors that this increase might be due to the salt effect of the hydrochloride. The conductance of a 0.1 molar solution of dimethylaniline hydrochloride in chloroform was observed to be about a thousand times that of hydrogen chloride in chloroform. The dissociation constant was therefore calculated considering the equilibrium to be $C_8H_{11}NH^+ + Cl^- \rightleftarrows C_8H_{11}N + HCl$. The values of $K_c$ are given in Table V. From the Debye–Hückel limiting law it follows that $-\log K_c = -\log K_a + 2k\sqrt{\mu}$, where $k$ for chloroform at 25° is 32.8. The plot of

(20) This is actually a comparison of the primary band of dimethylaniline with the secondary band of the ion. For simplicity of illustration the shift of the dimethylaniline secondary band to higher frequencies on ionization is ignored. See Doub and Vandenbelt, *ibid.*, **69**, 2714 (1947).

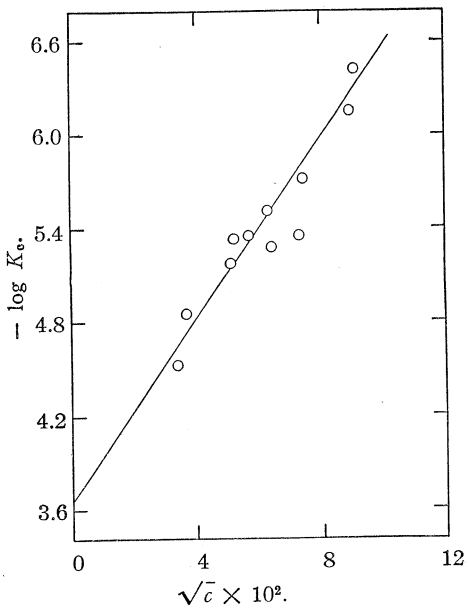



Fig. 8.—Variation of $-\log K_c$ for the reaction $C_8H_{11}NH^+ + Cl^- \rightleftharpoons C_8H_{11}N + HCl$ with concentration of dimethylanilinium ions.

$-\log K_c$ *versus* $\sqrt{c}$ given in Fig. 8, where $c$ is the concentration of dimethylanilinium ions calculated from the spectral data, yielded a value of $K_a = 2 \times 10^{-4}$ and a value of $k = 14$. Other authors have reported low values of $k$ for solvents of low dielectric constant from conductance measurements. In this instance the low value appears to be due in part to the presence of a large number of $C_8H_{11}NH^+ \cdots Cl^-$ ion pairs, which reduces the ionic strength below the calculated value.

## Summary

Electric moments have been determined for sulfur dioxide, tri-*n*-butylamine, trimethylamine–sulfur dioxide, triethylamine–sulfur trioxide and tri-*n*-butylamine–sulfur trioxide. The N → S bond moments in these addition compounds have been evaluated.

Dissociation constants have been calculated for trimethylamine–sulfur dioxide and dimethylaniline hydrochloride in chloroform from ultraviolet absorption measurements, and for the sulfur dioxide addition compounds of pyridine, triethylamine, and tri-*n*-butylamine in benzene from dielectric constant and density measurements. Both absorption and dielectric constant measurements reveal that the order of decreasing stability of the sulfur dioxide addition compounds is trimethylamine > triethylamine > tri-*n*-butylamine > pyridine. The sulfur trioxide addition compounds of trimethylamine and triethylamine appear to be undissociated in benzene and chloroform solutions.

Interaction of trialkylamines with sulfur dioxide results in a very large increase in absorption in the 270 mμ region. The addition compounds of sulfur trioxide with trialkylamines are transparent in this region. Sulfur trioxide shows an effect similar to that of the proton in altering the spectra of pyridine and dimethylaniline.

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[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY, COLUMBUS, OHIO]

# Rate of Adsorption of Barium Ions in Extreme Dilution, by Hydrous Ferric Oxide

BY M. H. KURBATOV

## Introduction

In earlier work it was realized that the extent of adsorption of divalent ions from very dilute solutions on hydrous ferric oxide depended not only on the usually recognized factors of temperature, *p*H, amount of adsorbent, volume and salt concentration but also on the duration of adsorption. It was observed that adsorption was not discontinued with the separation of the solid adsorbent, but that when the co-precipitation procedure was used in the case of very dilute solutions, there was an observable adsorption rate. Particularly was this true when the amount of adsorbate was less than $10^{-6}$ gram atom, the volume of solution of the order of 10–30 ml. and the quantity of adsorbent 1 or $2 \times 10^{-5}$ gram atom of iron, the effect being more pronounced with decreased amounts of adsorbate. From this observation there arose the possibility of determining a rate of ion adsorption from solution.

## Procedure

The adsorption procedure and the preparation of barium 133 as carrier-free tracer are described in a previously published paper.[1] For the rate studies, $2 \times 10^{-5}$ gram mole ferric chloride was mixed with the chosen quantity of stable barium chloride and tracer, all in acid solution, and the mixture titrated rapidly with ammonium hydroxide to the selected *p*H. Thus, the so-called co-precipitation procedure, in which hydrous ferric oxide was precipitated in the presence of barium ions, was used. Some barium was adsorbed during titration in the *p*H interval from the formation of the solid phase to the selected *p*H of a particular series of experiments, the amount adsorbed during titration increasing with *p*H (see Table II).

The co-precipitation procedure has some advantage over the "real" adsorption procedure (in

(1) M. H. Kurbatov, Fu-Chun Yu and J. D. Kurbatov, *J. Chem. Phys.*, **16**, 87 (1948).

which latter case barium ions in solution are added to a solution containing the previously precipitated hydrous ferric oxide) in that the selected conditions such as salt concentration, volume of liquid phase, etc., are more reproducible and these conditions are of significance in the rate of adsorption in this liquid–solid system.

The time intervals at which adsorption was measured were from one to several hours; the zero time being taken as that at which the final *p*H was reached. Each determination was made on a separate sample, the rate of adsorption being found from a series of samples, initially prepared, under experimentally identical conditions.

## Experimental

**Rate of Adsorption of Barium Ions in Concentrations of $3 \times 10^{-6}$ and $3 \times 10^{-10}$ Gram Atom per Liter.**—In studies of adsorption isotherms it has been established that the fraction of barium adsorbed (under specified conditions) in a given time interval of, for instance, one, two or four hours, increases with dilution down to a concentration of $10^{-8}$ gram atom per liter. Below this concentration the fraction adsorbed becomes experimentally constant for the given time interval.[2]

Therefore, it is possible to study the rate of adsorption after titration is completed in concentration ranges in which the fraction adsorbed is either independent or not independent of the changing concentration. To exemplify these two conditions and to observe the variation in rate due to concentration, the barium quantities selected were $1 \times 10^{-11}$ gram atom and $1 \times 10^{-7}$ gram atom per 32 ml. of liquid phase. The results are given in Table I.

It can be seen that in equal time intervals the fraction of barium adsorbed is higher for the lower concentration in agreement with the previous isotherm studies. Also the rate of change with time of the fraction of barium adsorbed is greater for the lower concentration.

After sixty hours the quantity of adsorbed barium, within the limits of experimental observation, remains constant for both concentrations.

**The Dependence of Rate of Adsorption on Hydrogen Ion and Ammonium Chloride Concentrations.**—The procedure used in securing the data in Tables II, III, and IV differed from that used in obtaining the data in Table I in that the volume of liquid phase (~32 ml. initially) decreased at each successive measurement. That is, the five determinations of barium adsorbed at a given *p*H and salt concentration in the time interval from 0.5 to 30, 50 and 45 hours, respectively, were obtained by successive removals

TABLE I

RATE OF ADSORPTION OF BARIUM ION ON HYDROUS FERRIC OXIDE

Constant factors: *p*H, 8.00 ± 0.01; temp., 25° ± 1°; Fe, $2 \times 10^{-5}$ g. at., vol. of sol. 31.98 ± 0.02 ml., $NH_4Cl$ concn., $3.5 \times 10^{-2}$ *N*; Ba = $1 \times 10^{-7}$ g. at.

| Adsorp. period, hr. | Activity in sol., counts/min. | Tracer, counts/min. | Ba adsorbed, g. at. $\times 10^{8}$ |
|---|---|---|---|
| 1.0 | 916 | 1110 | 1.80 |
| 2.1 | 868 | 1095 | 2.05 |
| 4.0 | 784 | 1020 | 2.32 |
| 7.0 | 828 | 1120 | 2.62 |
| 20.1 | 724 | 1065 | 3.21 |
| 41.2 | 381 | 610 | 3.75 |
| 65.8 | 746 | 1213 | 3.85 |
| 99.9 | 422 | 702 | 4.00 |
| 122.2 | 227 | 374 | 3.93 |

Vol. of soln., 32.00 ± 0.05 ml. Ba = $1 \times 10^{-11}$ g. at.

| | | | g. at. $\times 10^{12}$ |
|---|---|---|---|
| 1.0 | 833 | 1075 | 2.26 |
| 2.2 | 800 | 1085 | 2.63 |
| 4.0 | 759 | 1090 | 3.04 |
| 10.1 | 670 | 1070 | 3.75 |
| 20.2 | 559 | 1070 | 4.78 |
| 42.8 | 316 | 688 | 5.40 |
| 67.7 | 547 | 1190 | 5.47 |
| 100.3 | 323 | 707 | 5.43 |
| 126.5 | 218 | 470 | 5.54 |

(2) M. H. Kurbatov and J. D. Kurbatov, THIS JOURNAL, **69**, 438 (1947).

TABLE II

CHANGE IN ADSORPTION WITH TIME AND REMOVAL OF PORTIONS OF SOLUTION

$NH_4Cl$ concentration $3.8 \times 10^{-3}N$; constant factors: temp., 25° ± 1; total Ba, $1 \times 10^{-11}$ g. at.; Fe, $2 \times 10^{-5}$ g. at.; vol. of sol., 32.6 ± 0.5 ml.

| Adsorp. period (from time titrated), hours | Activity in 5 ml. sol. removed, counts/min. | Tracer, counts/min. | Ba adsorbed, g. at. $\times 10^{12}$ | Total Ba present at each time, g. at. $\times 10^{12}$ |
|---|---|---|---|---|
| | | *p*H 9.02 | | |
| 0.5 | 84 | 2100 | 7.38 | 10.00 |
| 5.0 | 62 | 2035 | 7.97 | 9.60 |
| 10.0 | 33 | 1595 | 8.44 | 9.31 |
| 20.0 | 20 | 1395 | 8.66 | 9.12 |
| 30.0 | 14 | 1258 | 8.73 | 8.99 |
| | | *p*H 8.66 | | |
| 0.5 | 130 | 2120 | 5.95 | 10.00 |
| 5.0 | 95 | 2000 | 6.80 | 9.39 |
| 10.0 | 54 | 1540 | 7.47 | 8.94 |
| 20.0 | 32 | 1325 | 7.90 | 8.61 |
| 30.0 | 26 | 1175 | 7.92 | 8.40 |
| | | *p*H 8.00 | | |
| 0.5 | 231 | 2160 | 3.15 | 10.00 |
| 5.0 | 199 | 1921 | 3.90 | 8.97 |
| 10.0 | 135 | 1383 | 4.55 | 8.00 |
| 20.0 | 115 | 1118 | 4.68 | 7.22 |
| 30.0 | 91 | 732 | 4.53 | 6.48 |
| | | *p*H 7.60 | | |
| 0.5 | 283 | 2165 | 1.50 | 10.00 |
| 5.0 | 266 | 1884 | 1.95 | 8.69 |
| 10.0 | 204 | 1294 | 2.15 | 7.46 |
| 20.0 | 175 | 983 | 2.35 | 6.28 |
| 30.0 | 121 | 581 | 2.46 | 5.16 |

TABLE III

CHANGE IN ADSORPTION WITH TIME AND REMOVAL OF PORTIONS OF SOLUTION

$NH_4Cl$ concentration $3.3 \times 10^{-2} N$; constant factors: temp., 25 ± 1°; total Ba, $1 \times 10^{-11}$ g. at.; Fe, $2 \times 10^{-5}$ g. at; vol. of sol., 33.1 ± 0.4 ml.

| Adsorp. period (from time titrated), hours | Activity in 5 ml. sol. removed, counts/min. | Tracer counts/min. | Ba adsorbed, g. at. × $10^{12}$ | Total Ba present at each time, g. at. × $10^{12}$ |
|---|---|---|---|---|
| | | *p*H 8.99 | | |
| 0.5 | 101 | 2050 | 6.74 | 10.00 |
| 5.0 | 78 | 1950 | 7.36 | 9.51 |
| 20.0 | 40.6 | 1418 | 7.92 | 9.13 |
| 30.0 | 20.4 | 962 | 8.19 | 8.87 |
| 50.0 | 12.0 | 842 | 8.36 | 8.68 |
| | | *p*H 8.51 | | |
| 0.5 | 179 | 2055 | 4.30 | 10.00 |
| 5.0 | 147 | 1880 | 5.18 | 9.13 |
| 20.0 | 90 | 1273 | 5.58 | 8.22 |
| 30.0 | 46 | 852 | 6.20 | 7.67 |
| 50.0 | 31.5 | 699 | 6.42 | 7.26 |
| | | *p*H 8.13 | | |
| 0.5 | 244 | 2070 | 2.25 | 10.00 |
| 5.0 | 198 | 1835 | 3.39 | 8.82 |
| 20.0 | 123 | 1235 | 4.28 | 7.87 |
| 30.0 | 79 | 795 | 4.50 | 7.09 |
| 50.0 | 60.5 | 612 | 4.76 | 6.38 |
| | | *p*H 7.68 | | |
| 0.5 | 306 | 2110 | 0.47 | 10.00 |
| 5.0 | 276 | 1785 | 1.20 | 8.54 |
| 20.0 | 175 | 1128 | 2.11 | 7.22 |
| 30.0 | 112.5 | 672 | 2.46 | 6.10 |
| 50.0 | 106.5 | 485 | 2.71 | 5.08 |

TABLE IV

CHANGE IN ADSORPTION WITH TIME AND REMOVAL OF PORTIONS OF SOLUTION

$NH_4Cl$ concentration $3.0 \times 10^{-1} N$; constant factors: temp., 25 ± 1°; total Ba, $1 \times 10^{-11}$ g. at; Fe, $2 \times 10^{-5}$ g. at; vol. of sol., 34.1 ± 0.6 ml.

| Adsorp. period (from time titrated), hours | Activity in 5 ml. soln. removed, counts/min. | Tracer counts/min. | Ba adsorbed, g. at. × $10^{12}$ | Total Ba present at each time, g. at. × $10^{12}$ |
|---|---|---|---|---|
| | | *p*H 9.1 | | |
| 0.5 | 154 | 1475 | 2.73 | 10.0 |
| 5.0 | 121 | 1334 | 4.11 | 8.95 |
| 15.0 | 116 | 1332 | 4.61 | 8.13 |
| 25.0 | 61.3 | 827 | 5.24 | 7.42 |
| 45.0 | 53 | 682 | 5.28 | 6.86 |
| | | *p*H 8.5 | | |
| 0.5 | 182 | 1470 | 1.65 | 10.0 |
| 5.0 | 168 | 1284 | 2.19 | 8.76 |
| 15.0 | 159 | 1254 | 3.06 | 7.62 |
| 25.0 | 109 | 732 | 2.95 | 6.63 |
| 45.0 | 86 | 559 | 3.28 | 5.64 |
| | | *p*H 8.02 | | |
| 0.5 | 288 | 2025 | 0.30 | 10.0 |
| 5.0 | 200 | 1350 | 1.18 | 8.58 |
| 15.0 | 196 | 1184 | 1.46 | 7.31 |
| 25.0 | 132 | 674 | 1.53 | 6.10 |
| 45.0 | 121 | 477 | 1.38 | 4.91 |
| | | *p*H 7.50 | | |
| 0.5 | 297 | 2035 | 0 | 10.0 |
| 5.0 | 235 | 1350 | 0 | 8.51 |
| 15.0 | 219 | 1138 | 0.66 | 7.02 |
| 25.0 | 159.5 | 634 | 0.39 | 5.66 |
| 45.0 | 139 | 417 | 0.40 | 4.07 |

of portions of solution from one original sample. This procedure so reduced the number of individual samples as to allow simultaneous study of several different hydrogen ion concentrations and salt concentrations. The main distinction between Tables II, III and IV is the ammonium chloride concentration, $3.8 \times 10^{-3}$, $3.3 \times 10^{-2}$ and $3.0 \times 10^{-1}$ $N$, respectively.

These experiments even though they involved repeated removals of the liquid phase resulted in a continued increase in adsorption in consecutive periods.

From Table II ($3.8 \times 10^{-3}$ $N$ $NH_4Cl$) it may be seen that the rate of change of adsorbed barium increases as the *p*H increases from *p*H 7.6 to 8.7 but then the rate drops off at *p*H 9.0.

A similar though not so marked trend may be seen in Table III ($3.3 \times 10^{-2}$ $N$ $NH_4Cl$). The change in the amount adsorbed between 0.5 and 30.0 hours increases with *p*H from *p*H 7.7 to 8.1 but then appears to decrease as the *p*H is increased farther. In the experiments represented in Table IV the salt concentration was $3 \times 10^{-1}$ $N$ and the tracer measurements consequently less accurate. However, the data show similar trends to those in Tables II and III.

If Tables II, III and IV are compared (recognizing the more approximate nature of the data in Table IV) using the change in the amount adsorbed from 0.5 to 25 or 30 hours at similar *p*H values it can be seen that:

(a) At *p*H 9, changing the ammonium chloride concentration from $3.8 \times 10^{-3}$ to $3.0 \times 10^{-1}$ $N$ has no significant effect on the rate of adsorption after titration although the amount adsorbed initially (during titration) is decreased by increased salt.

(b) At *p*H 8.5 or 8.6 there is little difference in the effect of $3.8 \times 10^{-3}$ and $3.3 \times 10^{-2}$ $N$ salt on the rate.

(c) At *p*H 8 and 7.5 the change in adsorption with time is increased as the salt concentration is increased from $3.8 \times 10^{-3}$ to $3.3 \times 10^{-2}$ $N$.

(d) The difference in the rate referred to in (c) results largely from decreased initial adsorption with increased salt, the total adsorption after 30 hours being essentially the same for $3.8 \times 10^{-3}$ $N$ or $3.3 \times 10^{-2}$ $N$ salt at approximately *p*H 7.5 or 8.

The following data selected from Tables II and III show the direction and greatest observed extent of the effects of salt and hydrogen ion concentration on rate of adsorption (after titration)

| $(H^+)$ | $NH_4Cl$ concn., $N$ | Change in g. at. Ba adsorbed in interval from 0.5 to 30 hours after titration $\times 10^{12}$ |
|---|---|---|
| $2.5 \times 10^{-8}$ | $3.8 \times 10^{-3}$ | $2.46 - 1.50 = 0.96$ |
| $2.7 \times 10^{-9}$ | $3.8 \times 10^{-3}$ | $7.92 - 5.95 = 1.97$ |
| $2.1 \times 10^{-8}$ | $3.3 \times 10^{-2}$ | $2.46 - 0.47 = 1.99$ |

## Discussion of Results

It has been established that, in spite of extreme dilution ($1 \times 10^{-11}$ gram atom of Ba per 32 ml.) barium is not completely adsorbed by $2 \times 10^{-5}$ gram atom of hydrous ferric oxide under the conditions used though this quantity of adsorbent can remove $4 \times 10^{-8}$ gram atom barium from a solution originally containing $1 \times 10^{-7}$ gram atom barium, other conditions being comparable. The maximum adsorption observed for the two above quantities of barium was 54 and 39%, respectively, and was obtained within forty to sixty hours.

It has also been found that the *p*H of the solution and salt concentration not only affect the initial amount of adsorption (from a solution containing $1 \times 10^{-11}$ gram atom barium), but affect the rates as well. In the interval from *p*H 7.5 to 8.0 or 8.5 the rate (after the initial adsorption) increases with decrease in hydrogen ion concentration and the quantity adsorbed, at any given time interval, increases with decreased hydrogen ion concentration. In the range of ammonium chloride concentrations from $3.8 \times 10^{-3}$ to $3 \times 10^{-2}$ $N$ the rate (after the initial adsorption) increases with increase in salt concentration where the *p*H is 7.5 or 8.0 although the quantity adsorbed at any given time decreases with increased salt concentration.

In considering these rate studies several possible mechanisms suggest themselves as rate-determining processes.

Since the adsorption system used involves initial mixing followed by rapid settling of the solid phase and no further stirring, ionic diffusion through solution might be considered as the rate-determining process after settling. However, if the usual equation for diffusion of ions through solution to a solid electrode is applied the fraction left in solution is found to decrease from 83 to 1% in 100 hours while experimentally it decreases from 82% to only 60% in that time. The equation indicates as much adsorption in four hours as is observed in 100 hours.

Diffusion in and through solid particles[3] has similarly been ruled out as the major process since that equation contains a constant ratio[4] which when evaluated from the above data is not constant but varies from a value of 0.19 at $t = 1$ to 0.07 at $t = 10$.

The adsorption of divalent cations may be considered as competitive[1] with adsorption of monovalent cations, $H^+ + NH_4^+$. To treat this more specifically an ionic displacement reaction can be written as

$$Ba^{++} + S_2Ad \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2S^+ + BaAd$$

in which $Ba^{++}$ represents the moles of $Ba^{++}$ in solution, $S_2Ad$ represents the adsorbent with $H^+$ and/or $NH_4^+$ ions adsorbed, $S^+$ represents $H^+$ and/or $NH_4^+$ in the solution and BaAd the adsorbent with adsorbed barium. It is not intended to imply here that $H^+$ and $NH_4^+$ ion effects are directly additive, nor of magnitude proportional to their concentrations, but the effect of both, though they may be competitive with each other, is assumed to be in opposite direction to that of the divalent ion.

In the systems studied experimentally the initial $Ba^{++}$ concentrations were $3 \times 10^{-6}$ and $3 \times 10^{-10}$ gram atom per liter ($1 \times 10^{-7}$ and $1 \times 10^{-11}$ g. at. per 32 ml.) while the salt concentration was $10^{-2}$ $N$ and the $H^+$ concentration $10^{-8}$ $N$.

It may be postulated that in the initial rapid adsorption—the rate of which has not been measured because of changing conditions—both monovalent and divalent ions are adsorbed and that the slow measured rate represents the subsequent desorption of monovalent ions and preferential adsorption of divalent ions.

The rate of formation of BaAd would then be

$$d[BaAd]/dt = k_1[Ba^{++}][S_2Ad] - k_2[S^+]^2[BaAd]$$

which may be rewritten in the form

$$d[BaAd]/dt = -[BaAd](k_1[Ba^{++}] + k_2[S^+]^2) + k_1[Ba^{++}G]$$

in which G is a constant equal to the sum of $S_2Ad$ and BaAd.

It has been shown experimentally[2] that the fraction of barium adsorbed is independent of the original concentration if the latter is below $10^{-7}$ gram atom per liter so the *effect* of the $Ba^{++}$ concentration in solution can be considered constant for the lower concentration of barium used in the rate studies (*i. e.*, $3 \times 10^{-10}$ g. at./liter). With an initial salt concentration of the order of $10^{-2}$ $N$ any $H^+$ or $NH_4^+$ ion desorbed (being of the order of magnitude of $10^{-10}$) would represent a negligible change in $S^+$ concentration during its desorption.

Therefore $k_1[Ba^{++}] + k_2[S^+]^2$ can be considered as a constant D and the equation can be simplified to

$$d[BaAd]/dt = -[DBaAd] + k_1[Ba^{++}G]$$

which on integration gives

$$[BaAd] = \frac{k_1[Ba^{++}G]}{(k_1[Ba^{++}] + k_2[S^+]^2)}[1 - Ke^{-Dt}] \quad (1)$$

If the value of [BaAd] is $Q$ at $t$, is $Q_0$ at $t_0$ and is $Q_\infty$ at $t_\infty$ then Equation (1) can be shortened to

$$Q = Q_\infty - Ke^{-Dt}Q_\infty$$

and if the fraction of Ba adsorbed at $t = Q/Q_\infty = F$ and at $t_0 = Q_0/Q_\infty = F_0$ the expression becomes

(3) C. E. Boyd, A. W. Adamson and L. S. Myers, Jr., THIS JOURNAL, **69**, 2836 (1947).

(4) $D^i\pi^2/r_0^2$ in which $D^i$ is diffusion coefficient in the solid and $r_0$ the radius of solid particles.

$$\log (1 - F) = \frac{-D}{2.303} t + \log (1 - F_0) \qquad (1a)$$

$(1 - F_0)$ being constant for any given set of conditions.

This equation indicates that a straight line should result from a plot of log $(1 - F)$ against $t$ when the conditions assumed in the derivation are met. Accordingly it was found that the rate of adsorption of barium from the lower concentration studied gives the straight semi log plot while the higher concentration does not give a straight line (Fig. 1).

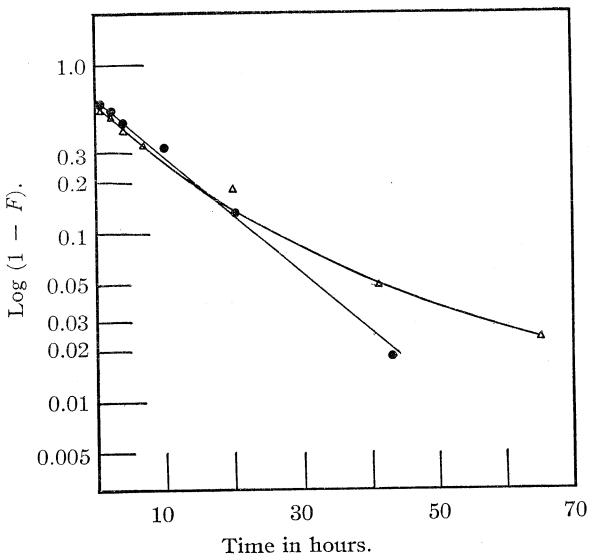



Fig. 1.—Adsorption of barium on hydrous ferric oxide represented as ion exchange rate: O, Ba = $1 \times 10^{-11}$ g. at.; △, Ba = $1 \times 10^{-7}$ g. at.; $p$H = 8.00 ± 0.01; Fe = $2 \times 10^{-5}$ g. at.; vol. = 32.00 ± 0.05 ml.; $NH_4Cl$ = $3.5 \times 10^{-2}$ $N$.

Although this equation is essentially the same as the equation for diffusion through a thin liquid film[3] the displacement mechanism is favored because the equation based on displacement shows several relations which are compatible with previous experimental observations. Some of these are:

(1) The fraction of barium adsorbed at any given time with a constant quantity of adsorbent is independent of total barium when the concentration of $Ba^{++}$ used is less than $10^{-7}$ g at./liter with a salt concentration of $6 \times 10^{-3}$ $N$. When this is true the ratio of adsorbed barium to barium left in solution is also constant. Equation (1) indicates that $[BaAd]/[Ba^{++}]$ is dependent upon the sum of $k_1[Ba^{++}]$ and $k_2[S^+]^2$. If $k_1[Ba^{++}]$ is insignificant as compared to $k_2[S^+]^2$ the fraction $[BaAd]/[Ba^{++}]$ is independent of $Ba^{++}$ concentration but when $k_1[Ba^{++}]$ becomes significant when added to $k_2[S^+]^2$ the fraction $[BaAd]/[Ba^{++}]$ not only changes but decreases as has been observed.

(2) The fraction $[BaAd]/[Ba^{++}]$ (at constant time) decreases as salt or hydrogen ion concentration ($S^+$) increases which is consistent with the $[S^+]^2$ factor being in the denominator of equation (1).

(3) The quantity adsorbed from a given concentration of barium (at constant time) increases with increased quantities of hydrous ferric oxide. This is consistent with the G factor being in the numerator of equation (1).

(4) The rate of change with time of the quantity of barium adsorbed under the conditions described above increases with increased salt concentration. Increase in $S^+$ should decrease the rate if $K$ were constant for all conditions but it is not. $K$ which is $(1 - F_0)$ increases with salt concentration in such a manner as to more than balance the effect of increased $S^{+2}$.

(5) An increase in hydrogen ion concentration from $p$H 8.5 or 8.0 to $p$H 7.6 (other factors being constant) decreases the rate after the initial coagulation. This is in accord with the equation if the change in $K$ is neglected. Actually, $K$ increases in value with increased hydrogen ion concentration but the change (in the case of $3.8 \times 10^{-3}$ salt) may be approximated as from 0.25 to 0.40 for a change from $p$H 8.6 to 7.6 while a change from $3.8 \times 10^{-3}$ $N$ to $3.3 \times 10^{-2}$ $N$ $NH_4Cl$ at $p$H 7.6 results in a change of $K$ from 0.40 to 0.83.

In conclusion it may be said that while the observed rate of attachment of barium ions to hydrous ferric oxide after the initial co-precipitation adsorption may involve more than one mechanism the rate for very dilute solutions is well expressed by a simple chemical equilibrium. The equation derived on this basis is consistent with both current and previous observations on the effect of salt, hydrogen ion concentration and quantity of adsorbent on quantities adsorbed at constant time and on rate of adsorption.

**Acknowledgment.**—It is a pleasure to express thanks to Prof. Edward Mack, Jr., whose stimulating support of nuculear chemistry research made this work possible.

A grant, for instruments, made by the Ohio State University Development Fund, is greatly appreciated by the author.

## Summary

The rate of adsorption of barium ions has been studied with the purpose of selecting optimum conditions for carrier-free target chemistry relative to the nuclear reactions $Cs(dn)Ba^{133}$ and $Cs(d2n)Ba.^{134}$

At a concentration of barium ions of $3 \times 10^{-10}$ gram atom per liter with $1 \times 10^{-5}$ gram mole of hydrous ferric oxide as adsorbent, other conditions being as described, the rate of adsorption was observed in an interval from one to 100 hours. It was found that in spite of the extreme dilution of barium its adsorption did not proceed to complete removal of the divalent ions from solution but reached its highest value within forty to sixty hours.

From studies of the dependence of rate of adsorption (after titration) on *p*H and salt concentration it was established that a decrease in hydrogen ion concentration from *p*H 7.5 to 8.0 or 8.5 increased the rate while an increase in ammonium chloride concentration from $3.8 \times 10^{-3}$ to $3.0 \times 10^{-1}$ *N* increased the rate.

A rate equation has been derived postulating a displacement of adsorbed monovalent cations by divalent cations. The experimental data on rate of adsorption of barium ions from dilute solution ($3 \times 10^{-10}$ gram atom per liter) were found to fit this equation.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GODFREY L. CABOT, INC.]

# The Adsorption of Helium on Carbon Black at Liquid Helium Temperatures[1]

BY W. D. SCHAEFFER, W. R. SMITH AND C. B. WENDELL

Previous investigators[2,3,4,5] have studied the adsorption of helium on various adsorbents of poorly defined total surface area. In one investigation[4] the heat of adsorption of helium on charcoal (Carbotax) was calculated from isotherms at liquid and solid hydrogen temperatures. Values ranging from 416 to 127 calories were reported. van Dingenen[3] reported heats of 93 to 52 cal./mole calculated from the isotherms of helium on glass at and below the temperature of liquid helium. Stout and Giauque[2b] report values of 131 to 148 calories for the heat of adsorption of helium on $NiSO_4 \cdot 7H_2O$ at 4.23°K. These values were computed from the Sackur–Tetrode equation, assuming zero entropy for the adsorbed helium. Keesom and Schweers[2a] measured the quantity of helium adsorbed in the temperature range, 4 to 1°K., on layers of hydrogen, neon, nitrogen and oxygen all solidified on glass. Isosteric heats of adsorption varied from 100 to 29 cal./mole, and led to the conclusion of multimolecular adsorption since the adsorption energy rapidly decreased at adsorbate concentrations representative of completed layers.

The Brunauer, Emmett and Teller procedure[6] for determining surface area from low temperature adsorption isotherms has been widely used in determining the area of commercial carbon blacks,[7,8,9] and has been particularly successful when the isotherms were determined at 78°K. with nitrogen as the adsorbate. The question as to the nature of the isotherm and the atomic area which might be revealed when helium was used as the adsorbate at 4.2°K. has interested us for some time. In addition to evaluating the B.E.T. expression at 4.2°K., adsorption studies with helium on carbon black of well defined area provide a simple system for observing the vigor of the van der Waals association between a simple atom and an essentially graphitic surface.[10]

Since a supply of liquid helium has recently become available in close proximity to our laboratory we have been able to determine the helium isotherms on two samples of commercial carbon black, Spheron 6 and Spheron C, at 4.2°K.

## Experimental

By arrangement with Arthur D. Little, Inc., of Cambridge, Massachusetts, a supply of 2 to 3 liters of liquid helium per day was assured. The helium was liquefied in the Little laboratories in the Collins cryostat.[11] A system of double Dewar flasks, the outer containing liquid nitrogen, served to transport the liquid helium, and also provided the bath for the adsorption system. The inner helium Dewar flask of 1100 cc. capacity was constructed of unsilvered Pyrex and was 71 mm. in diameter and 267 mm. deep. The neck was constricted to 33 mm.; 250 mm. of 15-mm. Pyrex tubing ending in a well-ground stopcock was sealed to the neck of the flask. There was, of course, no need to evacuate the interspace of this Dewar flask since when the stopcock was closed and the flask filled with liquid helium the air in the interspace rapidly solidified, providing an excellent vacuum. This arrangement also facilitates the precooling of the entire system with liquid nitrogen prior to filling with liquid helium. The "helium Dewar" was immersed to the neck in liquid nitrogen contained in a tall 9-liter stainless steel Dewar flask. The inner flask, after cooling to −195° C., was then filled to the neck with liquid helium by siphoning directly from the Collins cryostat, and the mouth of the flask closed with a plug of glass wool. It was possible to transport the helium in this system by car to the authors' laboratory, a matter of five miles, without appreciable loss of liquid helium.

The familiar type of constant pressure adsorption apparatus used in surface area determinations was employed.[9] The adsorption cell was only 1 cc. in volume in order to keep the "dead" space to a minimum. To insure rapid cooling with a minimum loss of liquid helium the walls of the adsorption cell were made as thin as possible. As shown in Fig. 1, the cell was joined to the adsorption line through a Pyrex capillary about 1 mm. in diameter. The cell was immersed some 35 cm. into the helium bath. During a run the level of the liquid helium dropped 2 to 3 cm. Since the liquid helium in the bath could not be replenished by any of the usual siphon arrangements, the variations in temperature of the exposed capillary dead

(1) Presented before the Division of Colloid Chemistry, Chicago Meeting, American Chemical Society, April 19, 1948.

(2) (a) W. H. Keesom and J. Schweers, *Physica*, **8**, 1032 (1941); (b) J. W. Stout and W. F. Giauque, THIS JOURNAL, **60**, 393 (1938).

(3) W. van Dingenen, *Physica*, **6**, 353 (1939).

(4) A. van Itterbeek and W. van Dingenen, *ibid.*, **5**, 529 (1938).

(5) A. van Itterbeek, W. van Dingenen and I. Borghs, *Nature*, **144**, 249 (1939).

(6) S. Brunauer and P. H. Emmett, THIS JOURNAL, **59**, 2682 (1937).

(7) R. A. Beebe, J. Biscoe, W. R. Smith and C. B. Wendell, *ibid.*, **69**, 95 (1947).

(8) R. A. Beebe, M. H. Polley, W. R. Smith and C. B. Wendell, *ibid.*, **69**, 2294 (1947).

(9) W. R. Smith, F. S. Thornhill and R. I. Bray, *Ind. Eng. Chem.*, **35**, 1303 (1941).

(10) J. Biscoe and B. E. Warren, *J. Appl. Phys.*, **13**, 364 (1942).

(11) Anonymous, *Chem. Eng. News*, **25**, 3370, 3450 (1947).

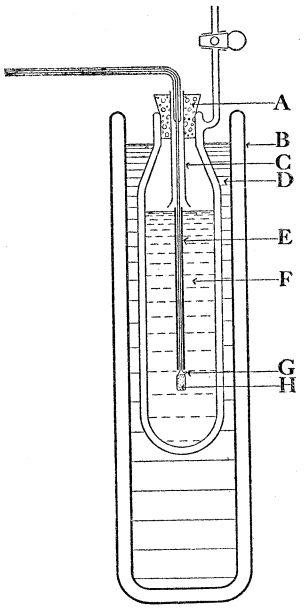



Fig. 1.—Helium bath and adsorption cell: A, cork stopper; B, stainless-steel Dewar flask; C, flared glass tube for exciting gases; D, liquid nitrogen; E, copper tube; F, liquid helium; G, stem for filling adsorbent cell; H, adsorbent.

space were reduced by encasing the capillary stem in a copper sheath which extended well below the level of the liquid helium. A section of Pyrex tubing with one end belled out as shown served to guide the helium vapors boiling off the bath around the upper portion of the stem.

Helium at liquid nitrogen temperatures was used to determine the dead space for the nitrogen isotherms. The volume of helium in the dead space at 4.2°K. was calculated from $PVT$ relations.

Spheron 6, a medium processing rubber grade of channel black, and Spheron C, a much smaller particle size rubber black, were used as adsorbents. Spheron 6 had a surface area as determined by nitrogen adsorption of 113 sq. m./g. Its mean diameter, as observed under the electron microscope, is 285 Å. Spheron C had an area of 227 sq.m./g. and a mean diameter of 190 Å., 0.2-g. samples of each black were employed. The blacks were introduced and removed from the Pyrex adsorption cell through the small stem G which could be sealed and unsealed without causing observable changes in the dead space of the system. Prepurified grades of nitrogen and helium obtained from the Matheson Company were used without further treatment, while the helium was passed through degassed, evacuated charcoal at 78°K. prior to use.

The carbon black samples were degassed at 200 ± 10°C. for two hours. Nitrogen surface areas were first obtained at 78°K. The nitrogen was then pumped off, and the sample degassed for another hour at 200°C. After precooling with liquid nitrogen, the liquid helium bath, as shown in Fig. 1 was slowly lifted over the cell until the latter was immersed some 35 cm. in the bath. The system was then allowed to equilibrate for approximately fifteen minutes before starting the adsorption. Over the entire pressure range the adsorption was characterized by rapid approach to equilibrium. Ten minutes was sufficient to attain this condition in all instances. Pressures lower than 10 mm. must be viewed with reservations due to the possibility of thermal transpiration[12] at the gas outlet inducing non-equilibrium pressures between adsorbent and manometer.

## Discussion

Figure 2 presents the helium isotherms at 4.2°K. on Spheron 6 and Spheron C. The isotherms are of the sigmoid type normally encountered with non-polar gases on carbon black.[13,9] The adsorption fits the simple B.E.T. expression

$$\frac{x}{V(1-x)} = \frac{1}{V_m C} + \frac{C-1}{V_m C}\,x \qquad (1)$$

(12) E. F. Burton, H. G. Smith and J. O. Wilhelm, "Phenomena at the Temperature of Liquid Helium," Am. Chem. Soc. Monograph No. 83, Reinhold Publishing Corp., New York, N. Y., 1940.

(13) J. Holmes and P. H. Emmett, *J. Phys. Colloid Chem.*, **51**, 1262 (1947).

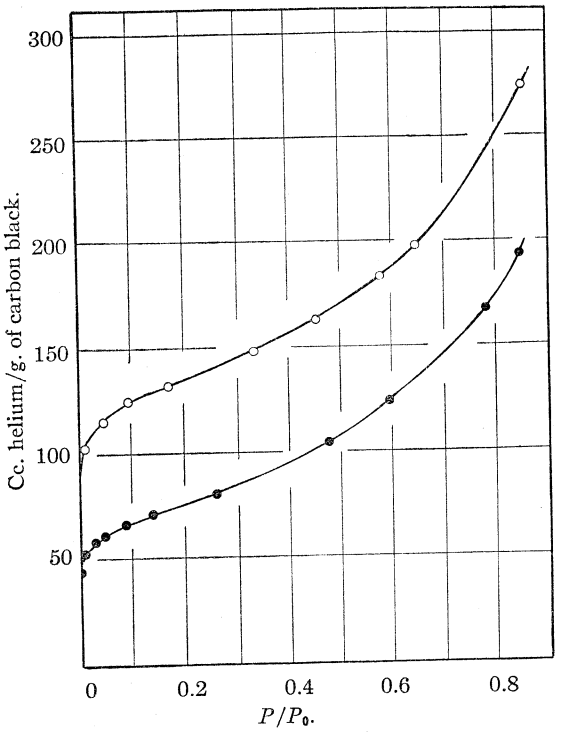



Fig. 2.—Adsorption isotherms of helium at 4.2°K. on O, Spheron 6 and ●, Spheron C.

in which $V_m$ is the volume of adsorbate (S.T.P.) required to form a monolayer, $V$ is the volume of gas (S.T.P.) adsorbed at the relative pressure, $x$, and $C$ is a constant peculiar to the adsorbent, adsorbate and temperature employed. The B.E.T. plots are illustrated in Fig. 3. At relative pressures larger than 0.25 there is some deviation from linearity as is generally encountered when the simple B.E.T. expression is employed. The $V_m$ and $c$ values obtained by least squares treatment of these data are summarized in Table I.

TABLE I

| Adsorbent | Adsorbate | $V_m$, cc. at NTP | $c$ | $E_1 - E_L$, cal. | $\frac{V_m(He)}{V_m(N_2)}$ | Area, sq. m./g. |
|---|---|---|---|---|---|---|
| Spheron 6 | Helium | 62.1 | 310 | 20.9 | 2.4 | 257.6[a] |
| | Nitrogen | 25.9 | 187 | 352 | | 113.0[b] |
| Spheron C | Helium | 113.9 | 820 | 24.4 | 2.2 | 472.7 |
| | Nitrogen | 52.1 | 853 | 454 | | 227.8 |

[a] Assuming cross section of 15.4 Å.² calculated from density of liquid. [b] Assuming cross section of 16.2 Å.² calculated from density of liquid.

The generally accepted cross sectional area of the nitrogen molecule is 16.2 Å.² as calculated from the equation[14]

$$A = 4(0.866)\left(\frac{M}{4\sqrt{2}\,N a D_L}\right)^{2/3}$$

in which $A$ is the average area occupied by each adsorbed molecule, $M$ is the molecular weight of

(14) P. H. Emmett and S. Brunauer, THIS JOURNAL, **59**, 1558 (1937).

the gas, $D_L$ is the density of the normal liquid or solid, $N_a$ is Avogadro's number, and the molecules are assumed to be hexagonally close-packed in a face-centered cubic lattice. The cross sectional area of the helium atom, as computed from its liquid density of 0.125 g./ml.[15] is 15.4 Å.$^2$; consequently, the volume of helium required to fill a monolayer on a non-porous carbon black should be only slightly larger than that for nitrogen. Experimentally, however, the expectation of similar $V_m$'s for the adsorption of nitrogen and helium is not realized.

Two obvious explanations of the anomalous $V_m$'s may be offered. Either the carbon blacks have a large percentage of pores which accommodate the helium atoms, but are too small to admit the nitrogen molecules, or the cross sectional area of the helium atom as calculated from the liquid density is much larger than the space actually occupied by an adsorbed helium atom. The first interpretation appears rather improbable in view of the substantial agreement of the ratios of helium to nitrogen $V_m$'s on Spheron 6 and Spheron C; the possibility of similar pore size as well as pore size distributions for two carbon blacks of markedly different average diameters being extremely remote. Moreover, electron micrographs and nitrogen adsorption at high relative pressures[13] indicate negligible porosity. It appears more logical to assume that the greater volume of helium adsorbed is due to a cross sectional area much smaller than that computed from the liquid helium density. If the cross sectional area of the hexagonally-packed helium atom is modified to yield surface areas of the two carbon blacks in agreement with those obtained with nitrogen, values of 6.77 and 7.43 Å.$^2$ are obtained. These areas correspond to interatomic distances of 2.80 Å. and 2.92 Å. X-Ray diffraction patterns of solid helium[16] at 1.45°K. and 37 atmospheres indicate a close-packed hexagonal structure with interatomic distances of 3.07 Å. in the (100) plane and 2.75 Å. in the (101) plane, and a density of 0.207 g./c. Thus, the interatomic distance of 2.80 Å. calculated above for the adsorbed helium is nearly identical to that for solid helium.

The possibility of penetration of helium atoms of 1.40 Å. radius between the planes of the quasi-graphitic crystallites constituting the carbon black particles was considered. A calculation similar to that of Barrer's[17] indicates an energy barrier of only 34 cal./mole to the migration of a helium atom across the graphite hexagon, and slightly less than 68 cal./mole for penetration between the graphite planes. Although the heats of adsorption of helium at low surface coverage are unquestionably greater than 68 cal./mole, the work of Rossman and Smith[18] demonstrates that even at 25° C. no significant penetration of helium into graphite lattices could be detected. If, on the other hand, adsorbed helium at 4.2°K. were to partake to a certain degree the energy and physical characteristics of helium II, the enhanced helium adsorption on carbon black could probably be attributed to diffusion into the graphite lattice. The phase diagram does not permit the presence of He II at 4.2°K., and until possible phase changes of helium in the adsorbed state have been investigated this consideration remains purely speculative.

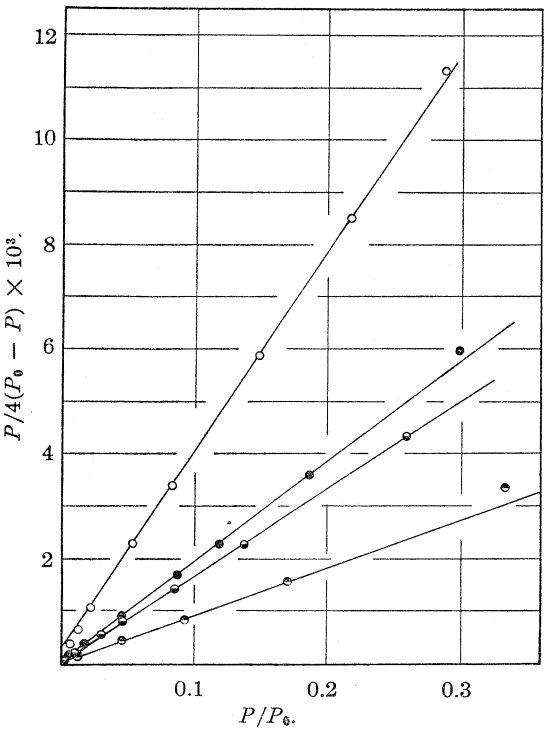



Fig. 3.—B. E. T. plots of helium and nitrogen: ○, nitrogen on Spheron 6 at 78°; ●, nitrogen on Spheron C at 78°; ◒, helium on Spheron 6 at 4.2°; ◓, helium on Spheron C at 4.2°.

The relatively large compressibility of liquid and solid helium suggests that the force field at the carbon black surface compresses or distorts the filled electron shell of the atom, resulting in a diminished cross sectional area for the adsorbed helium atoms. The electron shells of the other inert gases might be expected to behave similarly; however, Emmett, *et al.*,[19] have found it necessary to revise the area of the krypton atom upward when adsorbed as a solid at 78°K. on various surfaces. The differences in behavior of these inert gases can probably be ascribed to the influence of residual motion or zero point energy magnified in the case of helium by its low atomic weight.[20]

A calculation of the heat of adsorption for he-

(15) W. H. Keesom and Schweers, *Physica*, **8**, 1020 (1941).
(16) W. H. Keesom and K. W. Taconis, *ibid.*, **5**, 161 (1938).
(17) R. M. Barrer, *Proc. Roy. Soc. (London)*, **A161**, 476 (1937).
(18) R. P. Rossman and W. R. Smith, *Ind. Eng. Chem.*, **35**, 972 (1943).
(19) R. T. Davis, Jr., T. W. DeWitt and P. H. Emmett, *J. Phys. Colloid Chem.*, **51**, 1233 (1947).
(20) W. H. Keesom, "Helium," Elsevier, Amsterdam, Holland, 331 (1942).

lium on carbon black at 4.2°K. has been carried out according to the method described by Giauque and Stout.[2] They calculated the heats of adsorption of helium on $NiSO_4 \cdot 7H_2O$ at 4.2°K. from the Sackur–Tetrode equation assuming a negligible entropy for the adsorbed phase and the ideality of helium at the pressures employed. Thus, the entropy of adsorption becomes equal to the entropy of the gas at 4.2°K.

$$\Delta S_{ads} = S_{gas} = R \ln \frac{M^{3/2}T^{5/2}}{P} - 2.317 \qquad (2)$$

The expression for $\Delta H$ is then

$$\Delta H = T\Delta S \qquad (3)$$

since $\Delta F$ is zero for the isothermal process, gaseous helium at equilibrium pressure, $P$, to adsorbed helium at pressure, $P$. Since the pressures (1–650 mm.) employed in the present investigation are considerably higher than those used by Stout and Giauque ($10^{-2}$–$10^{-3}$ mm.), the assumption of ideality is somewhat suspect. However, heats have been calculated in the manner described above, and are compared in Fig. 4 with those computed from entropies obtained by interpolation of Keesom's data.[21] The latter $\Delta H$ values are significantly lower than those calculated on the assumption of ideality only for surface coverages in the second and successive multilayers. Near $V/V_m$ equal to 2.5 the heats approach a limiting value of 33.7 cal./mole, some 12.7 calories greater than the heat of vaporization of 21 cal. mole. If the limiting value of 33.7 cal./mole is used as the heat of vaporization, in conjunction with the B.E.T. $c$ value reported in Table I, a heat of adsorption ($E_1$) of 56 ± 2 cal./mole is obtained, surprisingly close to the heat of adsorption at the completion of the monolayer as calculated from the aforementioned entropy considerations.

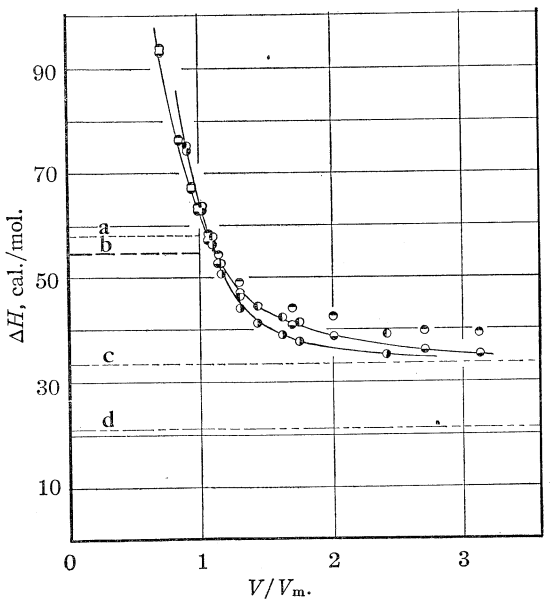



Fig. 4.—Heats of adsorption of helium on Spheron 6 and Spheron C: ◐, Spheron C, $\Delta H$ calculated from Sackur–Tetrode equation; ◑, Spheron C, $\Delta H$ calculated from Keesom[21]; ◓, Spheron 6, $\Delta H$ calculated from Sackur–Tetrode equation; ◒, Spheron 6, $\Delta H$ calculated from Keesom[21]; a, ———, B. E. T. "heat of adsorption" ($E_1$), for Spheron C; b, — — —, B. E. T. "heat of adsorption," ($E_1$), for Spheron 6; c, — — —, limiting value of heat of adsorption; d, — · — ·, helium heat of vaporization.

(21) W. H. Keesom, *ibid.*, p. 247.

The oxygen chemisorbed on the surface of Spheron 6 carbon black in the form of various complexes[22] is generally considered sufficient (23 cc. S.T.P.) to constitute a monolayer; thus, a comparison of these results with those of Keesom and Schweers[11] employing a glass surface covered with frozen oxygen proves instructive. The calculated differential heats of adsorption of helium at the completion of the first, second, and third layers ($V/V_m$) on Spheron 6 are 62, 39 and 35 cal./mole, respectively. Keesom and Schweers report heats, determined from the Clausius–Clapeyron equation, on oxygen covered glass to be 62 and 42 cal./mole at the completion of the second and third layers. The agreement is good. In fact, since they assumed a helium diameter of 4.04 Å. in computing surface coverage while 2.80 Å. was employed in the present work, one is perhaps justified in comparing Keesom and Schweers' second and third layer values of 62 and 42 cal./mole with our first and second layer values of 62 and 39 cal./mole. While agreement of this order is doubtless fortuitous, it does lend support to our assumption of negligible entropy for the adsorbed helium.

The fact that both Keesom's and our values for the heat of adsorption of helium remain considerably in excess of the heat of vaporization after a two or three layer coverage, while puzzling, is at least reproducible.

**Acknowledgments.**—It is a pleasure to acknowledge the coöperation of Arthur D. Little, Inc., and especially the helpful discussions with Dr. H. O. McMahon and Dr. G. King of that organization.

## Summary

1. A system of Dewar flasks successfully used for transporting liquid helium with negligible losses is described.

2. The helium isotherms at 4.2°K. on the carbon blacks, Spheron 6 and Spheron C, have been determined, and the application of the B.E.T. equation has been extended to liquid helium temperature.

3. The area of the helium atom adsorbed on carbon black at 4.2°K. is 7.0 ± 0.3 square ångström units.

4. The calculated heats of adsorption of he-

(22) W. R. Smith and W. D. Schaeffer, "Proceedings Rubber Technology Conference," London, England, 1948.

lium on Spheron 6 and Spheron C range from 93 to 34 cal./mole.

5. The heat of adsorption, as defined by the B.E.T. "*c*" value is in substantial agreement with the calculated heat curves.

RECEIVED MAY 4, 1948

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

# A Polarographic Study of Cobalt Cyanide Complexes[1]

BY DAVID N. HUME[2] AND I. M. KOLTHOFF

The characteristic properties of a solution of a cobaltous salt in excess alkali cyanide have frequently been attributed to the presence of hexacyanocobalt(II)ate ions.[3] There is much evidence, however, that in at least moderately concentrated solutions the complex which is formed is a pentacyanide rather than a hexacyanide.[4] The oxidation state of the cobalt in these solutions has never been definitely established. In the present investigation, a study of the reduction at the dropping mercury electrode of various cobalt complexes in cyanide medium has led to an understanding of the nature and identity of the complex cobalt ions formed in cyanide medium.

## Experimental

The usual polarographic technique was employed. Details of the apparatus and methods have been described in a previous communication.[5] The capillary had a drop time of 3.18 sec. and a value of 1.98 for $m^{2/3}t^{1/6}$ in 0.1 *M* potassium chloride at a potential of 0.0 v. against the saturated calomel electrode.

The reduction of cobalt(II) salts in potassium cyanide as a supporting electrolyte was first studied. In agreement with previous investigators[3d,3e] well-defined reduction waves were found for 0.002 *M* cobalt solutions in 0.1 *M* and 1.0 *M* potassium cyanide. The height of these waves was observed to be almost exactly one half that of the corresponding wave in potassium chloride, implying a one-electron reduction (Fig. 1). The shape of the waves obviously indicated irreversibility and no effort was made at analysis. It was also noted that the half wave potential was shifted to more positive values with increasing cyanide concentration, a confirmation of the irreversibility of the electrode reaction. The solutions obtained were yellow-green in color.

Previous investigators had interpreted the apparent one-electron reaction as a reduction of cobalt(III) hexacyanide ion produced spontaneously by water-oxidation of the cobalt(II) hexacyanide ion initially formed. In order to test this hypothesis, pure potassium hexacyanocobalt (III)ate (cobalticyanide) was prepared by the method of Benedetti-Pichler.[6] The product was obtained in large, clear, very pale yellow crystals which dissolved readily in water giving a clear solution. Polarograms were taken on millimolar solutions of the pure complex salt in 0.1 *M* and 1.0 *M* potassium cyanide as a supporting electrolyte.

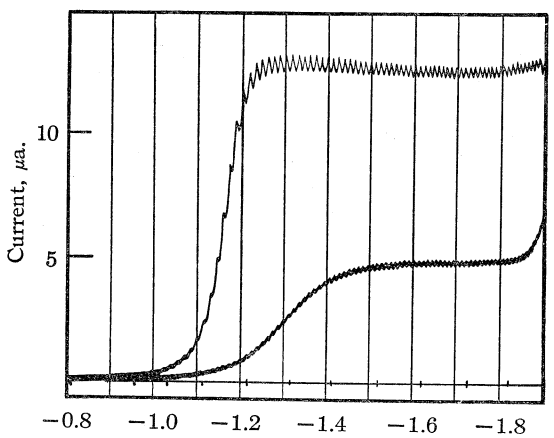



Fig. 1.—Polarograms of 0.002 *M* $CoCl_2$: upper curve in 0.1 *M* KCl; lower curve 1.0 *M* KCN.

No reduction of the cobalt complex could be observed prior to the discharge of potassium ion; the polarograms were identical with the residual current of the cyanide supporting electrolyte. The following experiments were therefore devised to determine the nature of the complex formed by solution of cobaltous salts in alkali cyanide.

A solution of 0.200 millimole of cobaltous chloride in 50 ml. of 1.0 *M* potassium cyanide was titrated amperometrically with 0.100 *M* potassium ferricyanide with exclusion of oxygen. After each addition of reagent and a wait of 2 or 3 minutes, the current at cathode potentials of −0.8 v. and −1.7 v. was measured. The cobalt is not reduced at −0.8 v. but gives a diffusion current at −1.7 v. Ferricyanide is reduced in cyanide medium at all attainable potentials of the dropping electrode, while ferrocyanide gives no wave. Hence any current at −0.8 v. must be due to unreacted ferricyanide. The result is shown in Fig. 2. The ferricyanide was consumed until one mole had been added per mole of cobalt. During the titration, the color of the solution changed from pale yellow-green to deep yellow and the diffusion current at −1.7 v. increased steadily, being approximately doubled by the end of the titration. The wave of the cobalt compound became more drawn-out and the half-wave potential shifted to more negative values (approximately −1.4 v.). The experiment clearly showed, therefore, that cobalt (II) chloride dissolved in excess potassium cyanide solution in the absence of air remains in the divalent state. Furthermore, the oxidized product obtained by treatment with ferricyanide is definitely not cobalt(III) hexacyanide ion, as the latter gives no wave.

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(1) Taken from a portion of the Doctorate thesis of David N. Hume, 1943. Presented in part at the Chicago Meeting of the American Chemical Society, September, 1946.

(2) Du Pont Fellow in Chemistry 1942-1943. Present address: Massachusetts Institute of Technology, Cambridge 39, Massachusetts.

(3) (a) G. Grube and P. Schächterle, *Z. Elektrochem.*, **32**, 565 (1926); (b) R. Peters, *Z. physik. Chem.*, **26**, 217 (1898); (c) T. M. Lowry, *Chem. Ind.*, **42**, 318 (1923); (d) N. V. Emelianova, *Rec. trav. chim.*, **44**, 529 (1925); (e) G. Sartori, *Gazz. chim. ital.*, **66**, 688 (1936).

(4) (a) E. Rupp and F. Pfenning, *Chem. Z.*, **34**, 322 (1910); (b) P. Edelmann, "Dissertation," Dresden T. H., 1915, p. 44; (c) E. Müller and H. Lauterbach, *Z. anal. Chem.*, **62**, 23 (1923); (d) E. Müller and W. Schlüttig, *Z. anorg. allgem. Chem.*, **134**, 327 (1924); (3) S. Glasstone and J. C. Speakman, *Analyst*, **55**, 93 (1930).

(5) D. N. Hume and I. M. Kolthoff, THIS JOURNAL, **65**, 1897 (1943).

(6) A. A. Benedetti-Pichler, *Z. anal. Chem.*, **50**, 257 (1927).

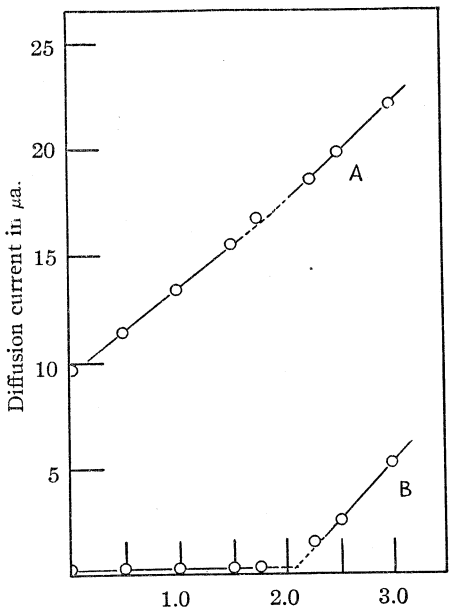



Fig. 2.—Amperometric titration of cobalt chloride with potassium ferricyanide in 1 *M* cyanide medium: (A) diffusion current at −1.7 v.; (B) diffusion current at −0.8 v.

Further experiments were performed in which 0.05 *M* cobaltous chloride solutions 1 *M* in potassium cyanide were heated in boiling water and samples taken in intervals for polarographic analysis. It was observed that the solutions first changed to an orange-yellow color while the polarographic wave decreased and became more drawn out. Amperometric titrations with ferricyanide showed that most of the cobalt had been oxidized after one hour. After three hours heating or standing overnight at room temperature, the solutions became almost colorless and yielded no polarographic wave. From this it was concluded that heating or standing in excess alkali cyanide ultimately converts the cobalt to the hexacyanocobalt(III)ate ion.

In order to establish the nature of the cobalt(II)cyanide complex first formed, experiments were performed in which cobalt chloride solutions were titrated with potassium cyanide, and *vice versa*. In agreement with previous investigators,[4] it was observed that good endpoints were obtained at a ratio of one cobalt to five cyanide ions regardless of whether the endpoint was located potentiometrically or by observation of the appearance or disappearance of the precipitate of cobalt cyanide. From this it would appear that the initial product obtained on dissolving cobalt(II) salts in excess potassium cyanide is the $[Co(H_2O)(CN)_5]^{=}$ ion. Since direct oxidation should result in the $[Co(H_2O)(CN)_5]^{-}$ ion, which can be obtained unambiguously by another method, proof of the identity of the two products would establish the structure of the cobalt(II) complex. A solution of pure potassium aquopentacyanocobalt(III)ate was therefore prepared. It was obtained without difficulty by the method of Ray[7] and Ray and Dutt[8] from cobaltous chloride through thiosulfato pentammine cobalt(III) chloride, potassium thiosulfato pentacyano cobalt(III) ate and silver aquopentacyanocobalt(III)ate, and found to have the properties described by them. In 1.0 *M* potassium cyanide as a supporting electrolyte, it gave a single wave, identical in shape with that obtained after oxidation of divalent cobalt with ferricyanide in the same medium (Fig. 3). The observed half wave potential of −1.45 v. is in satisfactory agreement with that obtained from the other product.

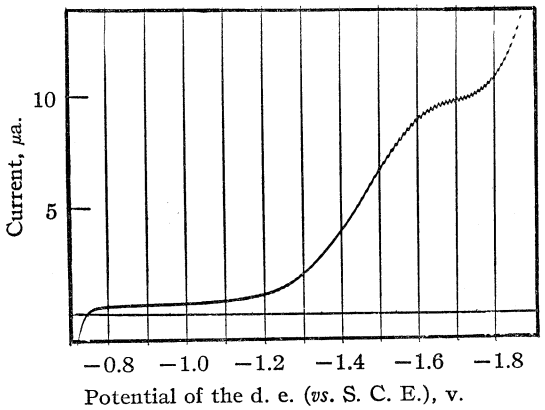



Fig. 3.—Polarogram of $[Co(H_2O)(CN)_5]^{-}$ ion in 1 *M* KCN.

An attempt was made to study the polarographic characteristics of the hexacyanocobalt(II)ate ion. Potassium hexacyanocobalt(II)ate was obtained as a finely crystalline violet precipitate by addition of a slight excess of potassium cyanide to a 0.1 *M* cobalt nitrate solution at −20°.[9] On transferring a sample of the solid to a 1 *M* potassium cyanide solution in the polarograph cell the solid immediately dissolved giving a clear pale yellow-green solution and the polarogram obtained was the same as that found on direct addition of cobalt nitrate to 1.0 *M* potassium cyanide.

The one-electron reduction of the cobalt(II) cyanide complex and the two-electron reduction of the cobalt (III) cyanide complex imply the existence of cobalt(I) as a cyanide complex formed at the surface of the dropping electrode. Grube and Schächterle[3a] in 1926 reported evidence for the formation of univalent cobalt by reduction of alkaline potassium hexacyanocobalt(III)ate solution at a cobalt cathode and with potassium amalgam. We observed a similar result when sodium amalgam was used as the reducing agent. The initially colorless solution slowly changed to red-orange with very little evolution of hydrogen. The same effect was observed when cobalt nitrate with five equivalents of cyanide added was used as the starting material. Samples of these reduced solutions were examined polarographically in 1.0 *M* potassium cyanide as a supporting electrolyte. In each case a small wave characteristic of the pentacyanocobalt(II)ate ion was observed. The height corresponded to only 5–10% of the total cobalt present. Addition of ferricyanide increased the height of the wave and gradually shifted it, ending with the characteristic wave of the pentacyanocobalt(III)ate ion. The cobalt(I) complex was not oxidizible anodically at the dropping electrode.

## Discussion

The most striking characteristic of the cobalt cyanide complexes is the irreversibility of the oxidation and reduction steps involved. None of the complex ions studied were reversibly reduced at the dropping electrode, and none were oxidized at all. The potential of a quiet mercury electrode in the cobalt(II) solutions was the same as that of a mercury electrode in a cyanide solution of the same concentration but with cobalt absent. For the measurement of the potential of cobalt(II)–cobalt(III) couple in cyanide medium, the mer-

(7) P. R. Ray, *J. Indian Chem. Soc.*, **4**, 64, 325 (1927).

(8) P. R. Ray and N. K. Dutt, *Z. anorg. allgem. Chem.*, **234**, 65 (1937).

(9) A. Descamps, *Ann. Chim. Phys.*, [5] **24**, 78 (1881).

cury electrode whether dropping or quiet is completely useless. The value commonly accepted[10] for the oxidation potential of that couple is due to Grube and Schächterle.[3a] From the potential of a platinized platinum electrode in a strongly alkaline solution of cobalt(III)hexacyanide partially reduced at a cobalt cathode, they calculated a result in terms of a hypothetical hexacyanocobalt(II)ate–hexacyanocobalt(III)ate electrode reaction. In addition to the error in formulation of the electrode reaction, a more serious difficulty exists. Both hydroxide ions and platinum are known to catalyze the water oxidation of the cobalt(II) cyanide complex. The potential which was measured differed from the potential of a hydrogen electrode in a solution of the same alkalinity by only a few millivolts: undoubtedly no more than experimental error. The potential which was reported (−0.81 v. on the hydrogen scale, European sign convention) must therefore be considered only as a lower limit on the reducing strength of the couple involved.

(10) W. M. Latimer, "Oxidation Potentials," Prentice-Hall, New York, N. Y., 1938.


## Summary

Polarographic investigation of the reduction of cobalt cyanide complexes has led to the following conclusions.

1. Addition of excess alkali cyanide to a solution of a cobalt(II) salt results in the immediate formation of the aquopentacyanocobalt(II)ate ion, reducible at the dropping electrode to a cobalt(I) complex.
2. Oxidation of the cobalt(II) complex yields aquopentacyanocobalt(III)ate, also reducible at the dropping electrode to a cobalt(I) complex.
3. Prolonged treatment of the aquopentacyano complexes with excess cyanide ultimately yields the hexacyanocobalt(III)ate ion, not reducible at the dropping electrode.
4. The cobalt(I) complex is neither reducible nor oxidizable at the dropping electrode.
5. The commonly accepted value for the potential of the cobalt(II)–cobalt(III) couple in cyanide medium cannot be considered valid.


CAMBRIDGE, MASSACHUSETTS
MINNEAPOLIS, MINNESOTA RECEIVED OCTOBER 28, 1948

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

# The Behavior of Oxygenated Organic Compounds in Acid Media[1]

BY MELVIN S. NEWMAN, RAYMOND A. CRAIG[2] AND ALFRED B. GARRETT

When oxygenated organic compounds are dissolved in strong protonic acids they generally accept a proton from the solvent to form a positively charged intermediate which may or may not undergo further change.[3] Evidence as to the fate of these conjugate acids has been obtained, among other sources, from the measurements of freezing point depression of solvent sulfuric acid[3,4] and from the nature of the reaction products isolated when the sulfuric acid solutions were poured into water or certain alcohols.[4] The further behavior of the species $BH^+$ forms the topic for the present discussion.

$$B + HA \longrightarrow BH^+ + A^- \qquad (1)$$

## Alcohols[5]

In the case of solutions of alcohols in sulfuric acid three types of cryoscopic behavior have been noted.

$$ROH + H_2SO_4 \rightleftharpoons ROH_2^+ + HSO_4^- \quad [i = 2][6] \qquad (2)$$

$$ROH + 2H_2SO_4 \rightleftharpoons RHSO_4 + H_3O^+ + HSO_4^- \quad [i = 3] \qquad (3)$$

$$ROH + 2H_2SO_4 \rightleftharpoons R^+ + H_3O^+ + 2HSO_4^- \quad [i = 4] \qquad (4)$$

For example, *i*-factors of 2 have reported for *t*-butyl and *t*-amyl alcohols[7]; *i*-factors of about 3 for several primary alcohols,[7] and an *i*-factor of 4 for triphenylcarbinol.[3,8] It appears reasonable to suppose that the first step in each of these cases involves a proton transfer to yield an oxonium compound, $ROH_2^+$. Two questions arose as to the further behavior of such oxonium compounds. (1) Why should an *i*-factor of only 2 be obtained with *t*-alcohols[7] when in reactions in acid media *t*-compounds often react most rapidly? (2) Are the conjugate acids of alcohols, $ROH_2^+$, thermally unstable at ordinary temperatures, or is some solvent effect operative?

In order to obtain information on the first topic, we have re-investigated the behavior of *t*-butyl alcohol in sulfuric acid and have also studied triethylcarbinol. When these alcohols are *carefully* (see Experimental Part for details) dissolved in sulfuric acid initial *i*-factors of slightly

(1) The work herein reported is taken from the Ph.D. thesis of R. A. Craig, The Ohio State University, March, 1948.

(2) Standard Oil Company of Indiana Fellow, 1946–1947. Present address: Experimental Station, du Pont, Wilmington, Delaware.

(3) For background discussion see Hammett "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, pp. 45–48, 53–56 and 277–285.

(4) (a) Newman, THIS JOURNAL, **63**, 2431 (1941); (b) Newman, Kuivila and Garrett, *ibid.*, **67**, 704 (1945); (c) Newman, *ibid.*, **64**, 2324 (1942).

(5) In this paper monofunctional compounds containing only carbon, hydrogen and oxygen and a few silicon organic compounds will be considered.

(6) The *i* refers to the van't Hoff *i* factor which means essentially the number of particles produced from one particle of solute.

(7) Oddo and Scandola, *Gazz. chim. ital.*, **39**, II, 1 (1909).

(8) Hammett and Deyrup, THIS JOURNAL, **55**, 1900 (1933).

over 2 are obtained. On standing, however, these values gradually increase and eventually go over 5. If roughly extrapolated back to zero time, *i*-factors of 2.1 and 2.4 are obtained. On standing, sulfuric acid solutions of these alcohols gradually develop a hydrocarbon layer. The presence of sulfur dioxide was also established. The above findings are interpreted further below.

As for the second question, we have found that *n*-propyl and *t*-butyl alcohols each give *i*-factors of about 1.7 in methanesulfonic acid.[9] We interpret this to mean that the reaction indicated in equation 5 is only partly complete and that the oxonium salts, $ROH_2^+$, are not unstable *per se*.

$$ROH + CH_3SO_3H \rightleftharpoons ROH_2^+ + CH_3SO_3^- \quad (5)$$

The importance of the solvent in the further reactions of the species $ROH_2^+$ is attested by the fact that the *i*-factor of 1.7 for *t*-butyl alcohol is only slightly increased by heating the solution in question to 60° for fifteen minutes[9] (compare the behavior of *t*-butyl alcohol in sulfuric acid).

It is interesting to note that, in their further reactions with sulfuric acid, the oxonium compounds, $ROH_2^+$, appear to react analogously to the corresponding alkyl halides, RX, in nucleophilic displacement reactions.[10] For example, most primary alkyl halides react by the $S_N2$ mechanism,[10] which involves a backside approach.[11] The *i*-factors of 3 generally observed for primary (and some secondary) alcohols may be explained by the backside approach of a bisulfate ion to displace a water molecule from the oxonium salt of the alcohol, followed by the further ionization of water in sulfuric acid, as shown below.

$$ROH + H_2SO_4 \rightleftharpoons ROH_2^+ + HSO_4^- \quad (6)$$

$$HSO_4^- + ROH_2^+ \rightleftharpoons RHSO_4 + H_2O \quad (7)$$

$$H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- \quad (8)$$

Summation of equations 6, 7, and 8 yields equation 3.

*t*-Halides undergo displacement reactions at an appreciable rate only by a first order mechanism (S1 type) in which the rate determining step involves ionization of the halide.[10] The rate is slow for *t*-butyl halides but quite rapid for triphenylmethyl halides. When *t*-butyl alcohol and triethylcarbinol are carefully dissolved in cold sulfuric acid, the first measurement of *i*-factor gives values of slightly over two. Successive measurements give increasing *i*-factors which eventually reach over 5. We interpret these results as evidence that the oxonium salts formed in accordance with equation 6 undergo a slow spontaneous ionization as shown in equation 9.

$$ROH_2^+ \rightleftharpoons R^+ + H_2O \quad (9)$$

If nothing further happened the summation of equations 6, 9, and 8 would yield equation 4 and an *i*-factor of 4 would result. In the case where R is triphenylmethyl, this is actually the case.[8]

However, complicating side reactions set in with the aliphatic *t*-alcohols. These side reactions include polymerization (*i*-factor lowering), general oxidation (*i*-factor raising) and possibly others. The fact that triphenylcarbinol gives an immediate *i*-factor of 4 is not surprizing in view of the fact that triarylcarbinyl halides ionize much more readily than trialkylcarbinyl halides. In this connection it is interesting to note that in methanesulfonic acid we have shown[9] that triphenylcarbinol gives an *i*-factor of 3.8.

The inability of *t*-halides to undergo $S_N2$ type reactions is commonly attributed to steric effects which hinder the approach of a substituting group from the face of the tetrahedron directly opposite to the carbon–halogen bond.[12] However, if the central atom involved were silicon instead of carbon, the steric effect should be less. We have found that triethylsilanol gives an *i*-factor of 3 in sulfuric acid and thus approximates the behavior of primary alcohols. We interpret this fact as support for the view that a bisulfate ion makes a backside attack to displace a water molecule from the initially formed silicon-containing oxonium salt, as shown below.

$$(R)_3SiOH + H_2SO_4 \rightleftharpoons (R)_3SiOH_2^+ + HSO_4^- \quad (9)$$

$$HSO_4^- + (R)_3SiOH_2^+ \rightleftharpoons (R)_3SiHSO_4 + H_2O \quad (10)$$

Summation of equations 9, 10, and 8 results in a calculated *i*-factor of 3.

In addition we have found that hexamethyldisiloxane,[13] hexaethyldisiloxane, and triethylethoxysilicon yield *i*-factors of about 4. The over-all equations are given below and may be derived by following the principles above outlined.

$$(R)_3SiOSi(R)_3 + 3H_2SO_4 \rightleftharpoons 2(R)_3SiHSO_4 + H_3O^+ + HSO_4^- \quad (11)$$

$$(C_2H_5)_3SiOC_2H_5 + 3H_2SO_4 \rightleftharpoons (C_2H_5)_3SiHSO_4 + C_2H_5HSO_4 + H_3O^+ + HSO_4^- \quad (12)$$

When added to water the trialkylsilicon bisulfate present in these solutions probably reacts with water as shown by the reverse of equation 10. In the acid medium the trialkylsilanols rapidly form disiloxanes and these compounds were obtained in high yield on pouring the sulfuric acid solutions above mentioned into water.[14]

The formation of trialkylsilicon chloride[15] by adding ammonium chloride to solutions which contain trialkylsilicon bisulfate probably involves the displacement of the bisulfate ion by a back-

(9) A more complete discussion of our work in methanesulfonic acid is being prepared for publication.

(10) Hughes, *J. Chem. Soc.*, 968 (1946).

(11) For an excellent review of the evidence see Hammett "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, Chapter VI.

(12) Evans, *Trans. Faraday Soc.*, **42**, 719 (1946); Hughes and Ingold, *ibid.*, **43**, 798 (1947).

(13) In agreement with Price, THIS JOURNAL, **70**, 871 (1948).

(14) Compare Ladenberg, *Ann.*, **164**, 320 (1872).

(15) Flood, THIS JOURNAL **55**, 1735 (1933).

side attack of chloride ion.[16] Because of the insolubility of the trialkylsilicon chlorides in sulfuric acid the reaction goes to completion and constitutes an excellent method of preparation for these chlorides.

$$Cl^- + (R)_3SiHSO_4 \rightleftharpoons (R)_3SiCl + HSO_4^- \quad (13)$$

## Esters[17]

Two types of behavior have been noted for solutions of methyl esters in sulfuric acid.

$$RCOOCH_3 + H_2SO_4 \rightleftharpoons RCO_2CH_3{\cdot}H^+ + HSO_4^- \; [i = 2] \quad (14)$$

$$RCOOCH_3 + 3H_2SO_4 \rightleftharpoons RC^+O + H_3O^+ + CH_3HSO_4 + 2HSO_4^- \; [i = 5] \quad (15)$$

Some factors tending to cause esters to behave according to either of these courses have been discussed.[4a,b] In seeking to determine the effect of heating the sulfuric acid solution of methyl benzoate, a new type of behavior has been noted, as shown in equation 16.

$$RCOOCH_3 + 2H_2SO_4 \rightleftharpoons RCO_2H_2^+ + CH_3HSO_4 + HSO_4^- \; [i = 3] \quad (16)$$

When solutions of methyl benzoate in sulfuric acid were heated to 45° or above for short times and then cooled for freezing point depression determinations, *i*-factors of about 3 were obtained. This behavior may be explained by postulating a backside attack of bisulfate ion on the conjugate acid of methyl benzoate as shown below.

$$RCOOCH_3 + H_2SO_4 \rightleftharpoons RCO_2CH_3H^+ + HSO_4^- \quad (17)$$

$$HSO_4^- + CH_3O_2CR{\cdot}H^+ \rightleftharpoons CH_3HSO_4 + RCOOH \quad (18)$$

$$RCOOH + H_2SO_4 \rightleftharpoons RCO_2H_2^+ + HSO_4^- \quad (19)$$

Summations of equations 17, 18, and 19 yields equation 16.

The conjugate acids of *t*-butyl esters undoubtedly undergo ionization as follows

$$RCO_2C(CH_3)_3{\cdot}H^+ \rightleftharpoons RCOOH + (CH_3)_3C^+ \quad (20)$$

Evidence for this type of reaction has been obtained in the formation of *t*-butyl methyl ether by the acid catalyzed decomposition of *t*-butyl esters in methanol.[18]

It is thus evident that the behavior of the conjugate acids of methyl and *t*-butyl esters in acid media can be compared to the behavior of the conjugate acids of methanol and *t*-butyl alcohol. How complete the analogy may be must await further experimentation.

It is a fact that *i*-factors of about 3 can be obtained from methyl benzoate on heating or on long standing at 25°. This might be explained by postulating an amount of ionization according to equation 15 sufficient to account for the *i*-factors observed. That such ionization does not occur is indicated by the fact that the amount of benzoic acid recovered on pouring the sulfuric acid solutions of methyl benzoate into water is far greater than that which would have been found if ionization according to equation 15 were taking place. Thus, when a solution of methyl benzoate in sulfuric acid was heated to 90° for fifteen minutes and then cooled, an *i*-factor of 3.32 was obtained. When an aliquot of this solution was poured into water 81% of the original ester was isolated as benzoic acid. If the benzoic acid had been formed by the reaction of the $C_6H_5CO^+$ ion (equation 15) with water, an *i*-factor of over 4 would have been expected. We have ruled out possible abnormalities derivable from the action of sulfuric acid on methanol by showing that *i*-factors of solutions of methanol in sulfuric acid do not change appreciably on heating to 90° for twenty minutes.

(16) In line with the above concept, it was predicted that the alkaline hydrolysis of trialkylsilicon halides should be first order with respect to the base used. This prediction appears to be confirmed by a statement of Dr. Gardner Swain of M. I. T. made at the Chicago meeting, April, 1948, to one of us (M.S.N.) that he had observed kinetics in such replacement reactions to be first order with respect to alkali.

(17) In this discussion only the behavior of methyl esters will be discussed.

(18) Cohen and Schneider, THIS JOURNAL, **63**, 3382 (1941).

## Experimental

### Reagents

**Sulfuric Acid.**—C. P. concentrated sulfuric acid and thirty per cent. fuming sulfuric acid were mixed in the ratio twenty to thirteen by weight and sufficient water added to make the solution slightly less than 100% sulfuric acid. Acid with a freezing point between 10.2 and 9.6° was used in cryoscopic determinations.

**Solutes.**—All solutes were carefully purified and dried before use. Where the material was not otherwise available, preparation was by previously reported procedures. Physical constants were as follows:

Benzoic acid: m.p. 122.1–122.3° (uncor.)
Hexaethyldisiloxane: b.p. 103° (11 mm.); $n^{20}D$ 1.4338
Hexamethyldisiloxane: $n^{20}D$ 1.3780. Received through the courtesy of General Electric Research Labs.
Methyl alcohol: $n^{20}D$ 1.3294
Methyl benzoate: b.p. 112.5° (53 mm.); $n^{20}D$ 1.5170
Triethylcarbinol: b.p. 80° (70 mm.); $n^{20}D$ 1.4300
Triethylethoxysilicon: b.p. 152° (740 mm.); $n^{20}D$ 1.4135
Triethylsilanol: b.p. 74.5° (26 mm.); $n^{20}D$ 1.4329
*t*-Butyl alcohol: m.p. 25.43° (cor.)

**Apparatus and Procedure.**—Except where indicated in the data section, the apparatus used and procedures followed are essentially those previously described.[4a]

## Data

**A. Tertiary Alcohols.**—Preliminary runs with *t*-butyl alcohol indicated that its *i*-factor rose rapidly with time, the rate of rise being temperature dependent. Care was taken in subsequent determinations to note the rate of this rise, making possible extrapolation of *i*-factor values to zero time. In all runs herein reported the solute was added after the freezing point apparatus and sulfuric acid had been in the cooling bath for some time, the addition being made when the temperature of the acid was about 13°. Use of this technique facilitated calculation of the *i*-factor at zero time since it not only cut the time that the alcohol was in the acid prior to the freezing

point determination, but also minimized the rate of *i*-factor change by maintaining a relatively constant low temperature.

The second column gives the time elapsing between addition of the solute and the time crystallization started in each run.

## I. Alcohols

### A. *t*-Butyl Alcohol (0.03509 Molal Solution)

Temperature of solution rose to a maximum of 180° between runs

| No. | Time, min. | F. p., °C. | *T* | *i* |
|---|---|---|---|---|
| 1 | Pure solvent | 10.024 | ... | .. |
| 2 | 20 | 9.473 | 0.551 | 2.56 |
| 3 | 76 | 9.322 | .702 | 3.27 |
| 4 | 205 | 9.168 | .856 | 3.99 |
| 5 | 1650 | 9.068 | .956 | 4.46 |

Highest *i*-value observed was 5.46. Rough extrapolation to zero time gives $i = 2.1$.

A second solution of *t*-butyl alcohol (0.3411 molal), in which the temperature never was above 14°, gave *i*-factors of 2.30, 3.08 and 3.85 for the time intervals of 15, 86 and 312 minutes, respectively.

### B. Triethylcarbinol (0.08017 Molal Solution)

Temperature was below 16° for runs 1–4; at room temperature for runs 5–7

| No. | Time | F. p., °C. | T | *i* |
|---|---|---|---|---|
| 1 | Pure solvent | 9.686 | ... | .. |
| 2 | 25 minutes | 8.432 | 1.254 | 2.55 |
| 3 | 63 minutes | 8.360 | 1.326 | 2.71 |
| 4 | 252 minutes | 8.201 | 1.485 | 3.04 |
| 5 | 27 hours | 7.759 | 1.927 | 3.96 |
| 6 | 40 hours | 7.412 | 2.274 | 4.68 |
| 7 | 160 hours | 6.902 | 2.784 | 5.74 |

Extrapolation to zero times gives $i = 2.4$.

## II. Organo-silicon Compounds

**A. Triethylethoxysilicon.**—The *i*-factors for 5 different increments of solute ranged in value from 3.98 to 4.44 with an average of 4.3. The time intervals ranged from a few minutes to fourteen hours and no drift in the value of *i* was noted with time.

**B. Hexamethyldisiloxane.**—The *i*-factors for 3 different increments of solute ranged in value from 3.98 to 4.23 with an average of 3.1. The time intervals ranged from a few minutes to twelve hours and no drift in the value of *i* was noted with time.

**C. Hexaethyldisiloxane.**—The *i*-factors for three different increments of solute ranged in value from 3.92 to 4.04 with an average of 4.0.

**D. Triethylsilanol.**—The *i* factors for 3 different increments of solute ranged in value from 2.84 to 3.10 with an average of 3.0. The time intervals ranged from a few minutes to three hours and no drift in the value of *i* was noted with time.

## III. Effect of Heating on the *i*-Factors

### A. Methyl Benzoate

| No. | *m* | F. p., °C. | *T* | |
|---|---|---|---|---|
| 1 | ..... | 9.638 | ... | .. |
| 2 | 0.07803 | 8.645 | 0.993 | 2.07 |
| 3 | At 14° for 40 minutes | 8.642 | 0.996 | 2.08 |
| 4 | At 45° for 15 minutes | 8.171 | 1.467 | 3.05 |
| 5 | At 45° for 50 minutes | 8.125 | 1.513 | 3.15 |
| 6 | At 45° for 35 minutes | 8.119 | 1.519 | 3.16 |
| 7 | New run | 9.802 | ... | .. |
| 8 | 0.07329 | 8.891 | 0.911 | 2.02 |
| 9 | At 65° for 15 minutes | 8.289 | 1.513 | 3.35 |
| 10 | At 65° for 35 minutes | 8.328 | 1.474 | 3.27 |
| 11 | At 25° for 10 hours | 8.344 | 1.458 | 3.23 |
| 12 | New run | 9.627 | ... | .. |
| 13 | 0.6282 | 8.840 | 0.787 | 2.04 |
| 14 | At 90° for 15 minutes | 8.344 | 1.283 | 3.32 |
| 15 | At 25° for 4 hours | 8.385 | 1.242 | 3.21 |
| 16 | At 45° for 30 minutes | 8.353 | 1.274 | 3.30 |

### B. Methyl Alcohol

| No. | *m* | F. p., °C. | *T* | |
|---|---|---|---|---|
| 1 | | 9.535 | | |
| 2 | 0.03682 | 8.895 | 0.640 | 2.85 |
| 3 | At 15° for 40 minutes | 8.913 | .622 | 2.77 |
| 4 | At 90° for 20 minutes | 8.888 | .647 | 2.88 |

### C. Benzoic Acid

| No. | *m* | F. p., °C. | T | |
|---|---|---|---|---|
| 1 | | 9.971 | | |
| 2 | 0.05385 | 9.304 | 0.667 | 2.10[a] |

[a] This freezing point was measured after the benzoic acid solution had been held at 70° for thirty minutes.

## Summary

*i*-Factors, calculated from measurements of the freezing point depression in sulfuric acid caused by solution of a number of organic compounds, have been determined.

The *i*-factors for *t*-butyl alcohol and triethylcarbinol are shown to change with time; extrapolation to zero time gives values of 2.1 and 2.4, respectively. An explanation of this phenomenon is proposed.

An hypothesis which attempts to correlate the behavior of oxonium salts, $ROH_2^+$, of alcohols in acid media with the nucleophilic displacement reactions of the analogous alkyl halides, RCl, is stated.

It is shown that the *i*-factor of a solution of methyl benzoate in sulfuric acid is raised from a value of 2 to 3 by heating at 90° for fifteen minutes. This *i*-factor is accounted for by postulating the following reaction

$$C_6H_5CO_2CH_3 + 2H_2SO_4 \rightleftharpoons C_6H_5CO_2H_2^+ + CH_3HSO_4 + HSO_4^-$$

Experimental evidence supporting this equation is presented.

Triethylethoxysilicon, hexamethyldisiloxane, hexaethyldisiloxane, and triethylsilanol were shown to give *i*-factors of about 4.3, 4.1, 3.9, and 3.0, respectively, in sulfuric acid.

COLUMBUS, OHIO RECEIVED SEPTEMBER 14, 1948

[CONTRIBUTION FROM THE FLIGHT PROPULSION RESEARCH LABORATORY OF THE NATIONAL ADVISORY COMMITTEE FOR AERONAUTICS]

# *o-*, *m-* and *p-t*-Butyltoluenes

BY KASPER T. SERIJAN, HAROLD F. HIPSHER AND LOUIS C. GIBBONS

The fuel evaluation program conducted at this Laboratory involving the synthesis and purification of aromatic hydrocarbons included the preparation of five-gallon quantities of *m-* and *p-t*-butyltoluenes. One reference was found in the literature on *o-t*-butyltoluene[1] and the physical properties attributed to this compound were not in accordance with expectations. Accordingly, a smaller scale preparation of this hydrocarbon was undertaken in order to obtain physical constants data for the three isomeric compounds, including a brief analysis of the infrared spectra.

The alkylation of monoalkylbenzenes by the alcohol–boron trifluoride method has been described in the preparation of some *p*-dialkylbenzenes.[2] This procedure was followed in the present work in several relatively large-scale runs and an analysis of the resulting product by careful fractionation using a distillation column rated above 100-theoretical plates indicated that nearly equal amounts of the *m-* and *p*-isomers were obtained. This result is not in agreement with the earlier work and the formation of the *m*-isomer may possibly be attributed to some slight deviation in the experimental conditions when applied on a larger scale. However, the refractive index value reported in the previous work for *p-t*-butyltoluene indicates a mixture of both isomers of nearly identical composition with that obtained in this investigation. The proximity of the boiling points of the two isomers as shown in Table I indicates that complete separation would require a precise fractionation.

The use of aluminum chloride in the alkylation of toluene with *t*-butyl alcohol[3] similarly resulted in mixtures which upon fractionation indicated the presence of both isomers. The total yield of dialkylbenzenes was nearly identical in both procedures as shown in Table I but the *m*-isomer was obtained in appreciably higher yield when aluminum chloride was used. Both procedures gave substantial yields of higher boiling material which was not investigated further at this time.

No trace of the *o*-isomer was apparent in the reaction products of these two methods of preparation. This compound was obtained by the condensation of *t*-butyl chloride with *o*-methylphenylmagnesium bromide and the physical properties of the three isomeric hydrocarbons are summarized in Table I. A high state of purity of each compound was indicated by the time–temperature freezing or melting curves. The physical properties were obtained by methods previously described[4] with the exception of the density values which were measured by means of apparatus described by Forziati, *et al.*[5]

TABLE I

PHYSICAL PROPERTIES, YIELDS AND ANALYSES OF *o-*, *m-* AND *p-t*-BUTYLTOLUENES

| Hydrocarbon | Butyltoluene *o-t-* | *m-t-* | *p-t-* |
|---|---|---|---|
| M. p., °C. | −50.32 | −41.39 | −52.49[a] |
| B. p., °C. (760 mm.) | 200.45 | 189.29 | 192.75 |
| Density, g./ml., 20°C. | 0.88976 | 0.86587 | 0.86115 |
| $n^{20}D$ | 1.50766 | 1.49456 | 1.49185 |
| Yield, % | 18 | 28[b] | 23[b] |
| | | 34[c] | 14[c] |
| *Anal.*, % Calcd.: Carbon | 89.11 | 89.11 | 89.11 |
| *Anal.*, % Calcd.: Hydrogen | 10.89 | 10.89 | 10.89 |
| *Anal.*, % Found: Carbon | 89.00 | 89.22 | 88.96 |
| *Anal.*, % Found: Hydrogen | 11.00 | 10.73 | 10.60 |

[a] Value obtained from freezing curve. [b] Reaction using boron trifluoride and calculated on basis of *t*-butyl alcohol after initial separation of product. [c] Reaction using aluminum chloride and calculated on basis of *t*-butyl alcohol after initial separation of product.

The physical properties of *o-t*-butyltoluene described in the previously cited reference[1] are the boiling point and the refractive index[6] and the values are seen to differ significantly from the corresponding values obtained in this investigation.

The hydrocarbons were oxidized to the corresponding *t*-butylbenzoic acids by the alkaline–permanganate method.[7] *o-t*-Butylbenzoic acid is reported for the first time and the analyses, neutral

TABLE II

DATA ON *t*-BUTYLBENZOIC ACIDS OBTAINED FROM ALKALINE-POTASSIUM PERMANGANATE OXIDATION OF *t*-BUTYLTOLUENES

| Oxidation product | Butylbenzoic Acid *o-t-* | *m-t-* | *p-t-* |
|---|---|---|---|
| M. p., °C. lit. | ..... | 127[a] | 164[b] |
| M. p., °C. obs.[c] | 80.3–80.8[d] | 127.0–127.6[e] | 165.0–165.6[e] |
| *Anal.*, % Calcd.: Carbon | 74.12 | 74.12 | 74.12 |
| *Anal.*, % Calcd.: Hydrogen | 7.91 | 7.91 | 7.91 |
| *Anal.*, % Found: Carbon | 73.74 | 73.82 | 73.97 |
| *Anal.*, % Found: Hydrogen | 7.66 | 7.72 | 7.54 |
| Neut. equiv. Calcd. | 178.2 | 178.2 | 178.2 |
| Neut. equiv. Found | 174.4 | 179.2 | 178.3 |

[a] Kelbe and Pfeiffer, *Ber.*, 19, 1726 (1886). [b] Kelbe and Pfeiffer, *ibid.*, 19, 1725 (1886); Bialobrzeski, *Ber.*, **30**, 1775 (1897). [c] Observed melting points are corrected. [d] Recrystallized out of neohexane. [e] Recrystallized out of ethyl alcohol. Identical acids also obtained by use of dilute nitric acid.

(1) Kozak, *Chem. Zentr.*, **78**, I, 1787 (1907).

(2) Welsh and Hennion, THIS JOURNAL, **63**, 2603 (1941).

(3) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry" Reinhold Publishing Corp., New York, N. Y., p. 621.

(4) Gibbons, *et al.*, THIS JOURNAL, **68**, 1130 (1946).

(5) Forziati, Mair and Rossini, *J. Research Natl. Bur. Standards*, **35**, 513 (1945).

(6) This compound is described as prepared by the condensation of *o*-bromo-*t*-butylbenzene with methyl bromide in the presence of sodium; b. p. 170° at 743 mm. and $n^{17}D$ 1.49423.

(7) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., p. 164.

equivalents and melting points of the acids are shown in Table II.

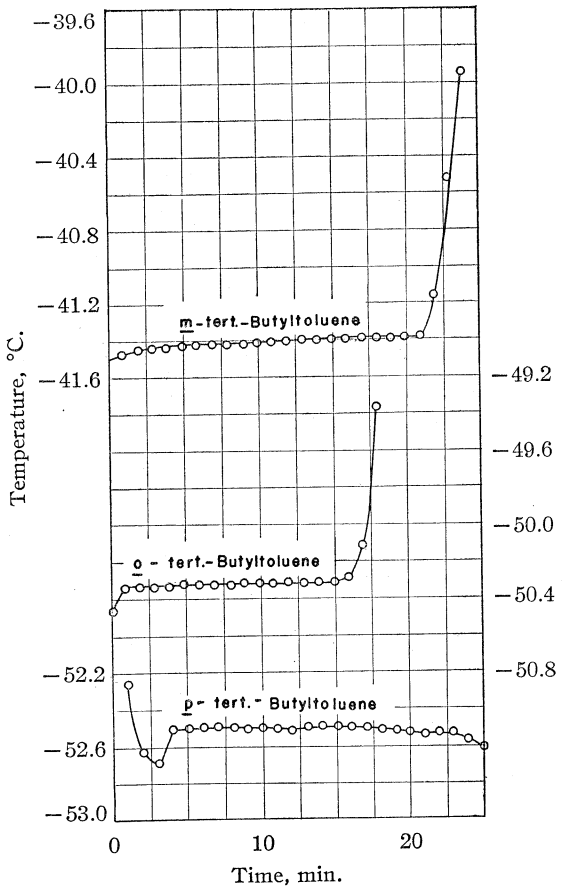



Fig. 1.—Time–temperature freezing or melting curves of *o*-, *m*- and *p*-*t*-butyltoluenes.

The infrared absorption spectra of the three hydrocarbons were obtained by the use of a spectrometer previously described[8] with the photoelectric amplifier of McAlister, *et al.*[9] The data are given in Table III with the intensity of absorption arbitrarily indicated as shown. The wave length certainty is estimated to be ±0.05 μ. Since the only purpose for the analysis of the absorption spectra of these compounds was to supplement the conclusions with respect to *o*-, *m*- and *p*-isomerism[10] a limited portion of the spectra is presented. The wave length regions 8.20–9.25 μ and 11.90–13.90 μ are of particular significance in the analysis of structure for the di-substituted aromatics[11] and Table IV is a summary from a portion of the data in the cited reference. The indicated wave length regions in the table are characterized by relatively high absorption for *o*-, *m*- and *p*-substituted compounds. The infrared data for the designated *t*-butyltoluenes show fairly good agreement as indicated by a comparison between Tables III and IV.

(8) Brattain, Rasmussen and Cravath, *J. Applied Phys.*, **14**, 418 (1943).

(9) McAlister, Matheson and Sweeney, *Review Scientific Instruments*, **12**, 314 (1941).

(10) Barnes, Liddel and Williams, *Ind. Eng. Chem., Anal. Ed.*, **15**, 659 (1943).

(11) Barnes, Gore, Stafford and Williams, *Anal. Chem.*, **20**, 402 (1948).

TABLE III

PARTIAL INFRARED SPECTRA OF THE ISOMERIC *t*-BUTYLTOLUENES

| Previously designated as *o*-*t*-butyltoluene λ, (μ) | Intensity of absorption[a] | Previously designated as *m*-*t*-butyltoluene λ, (μ) | Intensity of absorption | Previously designated as *p*-*t*-butyltoluene λ, (μ) | Intensity of absorption |
|---|---|---|---|---|---|
| 7.75 | W | 8.30 | M | 8.05 | W |
| 7.95 | M | 8.50 | W | 8.35 | M |
| 8.35 | W | 9.20 | M | 9.00 | S |
| 8.80 | W | 9.65 | W | 9.75 | S |
| 9.20 | M | 10.80 | W | 10.60 | W |
| 9.45 | M | 11.20 | S | 11.75 | W |
| 9.65 | W | 11.35 | W | 12.20 | S |
| 10.65 | M | 12.70 | S | 12.55 | W |
| 10.75 | W | | | 14.00 | M |
| 11.65 | W | | | | |
| 11.75 | W | | | | |
| 13.20 | S | | | | |
| 13.85 | S | | | | |

[a] W, M and S indicating weak, medium and strong intensities of absorption.

TABLE IV

CHARACTERISTIC INFRARED ABSORPTION BANDS FOR DI-SUBSTITUTED AROMATIC COMPOUNDS[11]

| Position of substituents | Wave length, (μ) | | |
|---|---|---|---|
| *o*- | 9.15 ± 0.10 | 13.60 ± 0.3 | |
| *m*- | 8.70 ± 0.10 | 12.80 ± 0.3 | |
| *p*- | 8.30 ± 0.10 | 9.05 ± 0.10 | 12.20 ± 0.3 |

## Experimental

**Alkylation of Toluene Using Boron Trifluoride.**—The reaction vessel consisted of a 10-gal., copper-lined reactor equipped with a stirrer, reflux condensor and a copper inlet tube in the form of a perforated coil submerged below the liquid level. An ice-chilled brine solution was circulated through the outer jacket of the reaction vessel by means of a pump. A typical run consisted of 25 moles of *t*-butyl alcohol and 100 moles of toluene cooled to approximately 5° after which 25 moles of boron trifluoride was bubbled through the coil in approximately two hours. The reaction mixture was stirred at 5–15° for four hours and then allowed to come to room temperature. The reaction product was then transferred to a stainless steel reactor and heated for six hours at 70–80°. After cooling, the hydrocarbon layer was separated off, washed twice with water, then with dilute sodium carbonate solution and again with water. The combined material from several such runs was dried by passage through alumina. The unreacted toluene was then stripped off and the remainder was fractionated on a Fenske-type column as previously mentioned.

**Alkylation of Toluene Using Aluminum Chloride.**—The Friedel–Crafts reaction was carried out in a 30-gal., glass-lined reactor. The quantities of reactants and reaction conditions closely followed the general procedure.[3] A mixture of 500 moles of toluene and 150 moles of aluminum chloride was cooled by cold water circulating through the jacket. To this was gradually added 150 moles of *t*-butyl alcohol dissolved in 250 moles of toluene, the total addition time being six hours. The reaction mixture was stirred for twelve hours and the complex was then hydrolyzed by passing it through a pipe to a second reactor which

was partially filled with water and ice and located one floor-level below. After a short period of stirring, the hydrocarbon layer was removed and worked up as in the previous procedure. Final purification was effected by a second fractionation of the individual isomers accumulated from both syntheses.

*o-t*-**Butyltoluene.**—The Grignard reagent was made using 85 moles of magnesium covered with 12 liters of dry ether to which was added over a period of five hours 80 moles of *o*-bromotoluene (f.p. −26.91° and $n^{20}D$ 1.5563) dissolved in 5 liters of dry ether. This was condensed with 72 moles of *t*-butyl chloride dissolved in 5 liters of dry ether and the reaction mixture was stirred overnight. After hydrolysis with dilute hydrochloric acid, the hydrocarbon layer was separated and the ether was evaporated.

The crude product was then dried over sodium sulfate and fractionated on a 15-theoretical plate column. Halogen impurities were removed by treatment with sodium in liquid ammonia. It was finally fractionated on a six-foot Podbielniak column and the yield of pure hydrocarbon based on the *t*-butyl chloride is shown in Table I.

**Oxidation of *t*-Butyltoluenes.**—No difficulty was encountered in the oxidation of the *m*- and *p*-isomers. The *t*-butylbenzoic acids obtained by the alkaline-permanganate method were found to be identical with those obtained by dilute nitric acid oxidation after maximum purity was attained by successive recrystallizations out of ethyl alcohol. Several attempted oxidations of the *o*-isomer using alkaline permanganate resulted in an oil which could not be crystallized. When the oil was purified by distillation at reduced pressure, a solid product was obtained which was recrystallized out of neohexane and found upon analysis to be *o-t*-butylbenzoic acid. The data on these acids are shown in Table II.

The oxidation of *o-t*-butyltoluene was also carried out in a sealed tube using dilute nitric acid and heating at 170° for twelve hours. Phthalic acid was precipitated out by the addition of chloroform to the oil resulting in this procedure and this was sublimed to phthalic anhydride, which gave no depression in melting point when mixed with an authentic sample (m.p. 130.8°).

**Acknowledgment.**—The authors wish to thank Mr. R. R. Hibbard for the infrared measurements, Mr. D. E. Grant for the carbon–hydrogen analyses and Mr. J. F. Thompson for the determination of the physical properties reported.

## Summary

1. The use of boron trifluoride as an alkylation catalyst has been shown to result in mixtures of *p*- and *m-t*-butyltoluenes in the reaction between toluene and *t*-butyl alcohol. The yield of each isomer is nearly the same but when aluminum chloride is used as the catalyst the *m*-isomer is appreciably greater with a corresponding decrease in yield of the *p*-compound.

2. The preparation and characterization of *o-t*-butyltoluene has been described. The physical properties have been shown to differ from those reported in the only earlier work on the synthesis of this hydrocarbon.

3. The physical properties of the three isomeric *t*-butyltoluenes in high purity have been described and time–temperature freezing or melting curves for these compounds are shown.

4. The oxidation of *o*-, *m*- and *p-t*-butyltoluenes to the corresponding *t*-butylbenzoic acids has been described and *o-t*-butylbenzoic acid has been reported for the first time.

5. Partial infrared absorption data for the *t*-butyltoluenes have been determined for purposes of gross structural analysis and the data have been shown to be in good agreement with previous work wherein characteristic absorption spectra for disubstituted aromatic compounds have been evaluated.

CLEVELAND, OHIO RECEIVED JULY 17, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# Erythrina Alkaloids. XVI. Studies on the Constitution of Erysodine, Erysovine and Erysopine[1]

BY FRANK KONIUSZY, PAUL F. WILEY AND KARL FOLKERS

Structure studies on erysodine, erysovine and erysopine have elucidated the functional groups and the number of rings of each alkaloid, and have shown that each has the same ring system.

These three *Erythrina* alkaloids[2,3,4] have interesting curare-like pharmacologic action.[5] Erysodine and erysovine have the same molecular formula, $C_{18}H_{21}NO_3$; each has two methoxyl groups and one phenolic hydroxyl group. Therefore, the functional groups containing all the oxygen atoms of erysodine and erysovine are known.[2] Erysopine[2] has the formula $C_{17}H_{19}NO_3$, one methoxyl group, and two phenolic hydroxyl groups which are ortho as indicated by a color reaction with ferric chloride. None of these three alkaloids showed the presence of an N-methyl group or a C-methyl group. The presence of methoxyl groups, and particularly the phenolic hydroxyl groups, implies the presence of at least one benzenoid nucleus in all three alkaloids.

A facile reaction between erysodine and methyl iodide to give the crystalline quaternary salt, erysodine methiodide, proved the tertiary nature of the nitrogen atom in erysodine.

Erysodine reacted with two molar equivalents of hydrogen with Adams platinum catalyst at atmospheric pressure. The ease of hydrogenation was

(1) Presented in part at the Meeting of the American Chemical Society in Atlantic City, N. J., September 10, 1941; Abstracts of Papers, Division of Organic Chemistry, p. 30.

(2) Folkers and Koniuszy, THIS JOURNAL, **62**, 1677 (1940).

(3) Gentile and Labriola, *J. Org. Chem.*, **7**, 136 (1942).

(4) Deulofeu, Labriola, Hug, Fondovila and Kauffman, *J. Org. Chem.*, **12**, 486 (1947).

(5) Unna and Greslin, *J. Pharmacol.*, **80**, 53 (1944).

typical of that of semi-saturated cyclic alkaloidal structures. The tetrahydroerysodine was isolated as a crystalline free base and hydrobromide. The fact that this hydrogenation reaction involved two >C=C< groups and not one >C=C< group and one >C=N— group was shown by the reaction of the tetrahydroerysodine with acetic anhydride to give crystalline O-acetyltetrahydroerysodine. The reduction of a >C=N— group to a >CH—NH— group would be expected to lead to an O-acetyl-N-acetyl derivative upon acetylation. On the basis of these data, the nitrogen atom of erysodine appears to be shared by two nuclei.

Erysopine was hydrogenated under similar conditions to give tetrahydroerysopine, which was isolated as a crystalline hydrobromide.

"Erysocine,"[6] which is a "complex" of erysodine and erysovine, absorbed two molar equivalents of hydrogen, similarly. The hydrogenation product yielded a crystalline tetrahydro-"erysocine" hydrobromide which did not separate into its components on crystallization.

It was observed[2] before that a characteristic property of erysodine, erysovine and erysopine is their weakly basic nature. For example, erysodine crystallizes from ethanol containing excess hydrogen chloride. Although erysodine dissolves in aqueous hydrochloric acid, it can be nearly completely removed by several chloroform extractions. Erysovine was converted into a crystalline hydrobromide and hydroiodide. Erysodine is also weakly acidic and could be removed from 2% aqueous sodium hydroxide solution by repeated chloroform extraction.

Since erysodine has two methoxyl groups, one phenolic hydroxyl group, a tertiary nitrogen atom shared by two nuclei, two "ethylenic" double bonds, and a benzenoid nucleus, it is now evident that erysodine has four nuclei in its ring system.

It appeared probable that erysodine, erysovine and erysopine have the same ring system, that the three oxygen atoms of each are in the same position and that each differs in the position or number of the O-methyl groups. This relationship between the alkaloids was investigated by methylation reactions.

Erysodine and erysopine reacted with dimethyl sulfate in alkaline aqueous solution to give identical crystalline products of the formula $C_{21}H_{29}NO_7S$. This composition corresponds to the methomethylsulfate of O-methylerysodine and O-dimethylerysopine, respectively. For simplicity of nomenclature, the fully oxygen-methylated alkaloid is designated "erysotrine"; hence, this new product, $C_{21}H_{29}NO_7S$, is erysotrine methomethylsulfate. As other data prove, this product should also be produced from erysovine.

It was desirable to methylate the free phenolic hydroxyl group of these *Erythrina* alkaloids without methylating the tertiary nitrogen atom. The methylation of the phenolic hydroxyl groups of alkaloids by dimethyl sulfate is frequently accompanied by methylation of the nitrogen atom. Thus, the reaction of morphine with dimethyl sulfate in sodium hydroxide solution gave codeine methomethylsulfate.[7] To circumvent this difficulty, morphine was methylated by reaction with phenyltrimethylammonium hydroxide in alcohol at 110° and codeine was obtained.[8] Our experiments with this method, including several modifications, for the methylation of erysodine were not satisfactory. Tetramethylammonium hydroxide has been used[9] for methylating sterically hindered acids, but treatment of erysodine with this reagent was unsatisfactory. The result of treating erysodine with diazomethane was also unsatisfactory since much erysodine was recovered.

The nitrogen atom of morphine was "protected" in the methylation of morphine N-oxide; codeine was obtained by reduction of the oxide with sulfurous acid.[10] We have found that the N-oxides of these *Erythrina* alkaloids could be made readily and, after methylation, reduction with zinc dust and hydrochloric acid gave the fully oxygen-methylated tertiary alkaloid which could be extracted readily from an ammoniacal solution. It was shown separately that erysodine N-oxide could be reduced to erysodine with zinc and hydrochloric acid.

Treatment of erysodine N-oxide with dimethyl sulfate gave a non-crystalline erysotrine N-oxide which was reduced with zinc and hydrochloric acid to erysotrine. This fully oxygen-methylated tertiary base did not crystallize, but it did sublime *in vacuo* to give a gum of the expected composition, $C_{19}H_{23}NO_3$, and it gave a crystalline picrate. It may be that some erysotrine was produced in the above-mentioned unsatisfactory methylation experiments, but was not isolated because of its non-crystalline character.

Conversion of both erysovine and erysopine into their N-oxides, followed by methylation, reduction, and treatment with picric acid, gave crystalline picrates which were identical with the one derived from erysodine.

Erysonine[11] has the molecular formula $C_{17}H_{19}NO_3$, which is the same as that of erysopine. Erysonine does not give a green color with ferric chloride in aqueous solution as does erysopine showing that erysonine apparently does not have two ortho phenolic hydroxyl groups. The series of reactions used to obtain erysotrine picrate was applied to erysonine. Although 20 mg. of gummy product was obtained from 127 mg. of erysonine, it did not give a crystalline picrate even after additional manipulation and storage.

(6) Folkers and Shavel, THIS JOURNAL, **64**, 1892 (1942).

(7) Pschorr and Dickhäuser, *Ber.*, **44**, 2633 (1911); German Patent, 261,588 (1910), *Frdl.*, **11**, 989.

(8) Rodionov, *Bull. soc. chim.*, **39**, 305 (1926).

(9) Fuson, Corse and Horning, THIS JOURNAL, **61**, 1290 (1939).

(10) German Patent 418,391 (1923), *Frdl.*, **15**, 1515.

(11) Folkers, Shavel and Koniuszy, THIS JOURNAL, **63**, 1544 (1941).

The conversion of erysodine and erysopine into erysotrine methomethylsulfate, and the conversion of erysodine, erysovine and erysopine into erysotrine picrate prove that all three alkaloids have the same oxygenated ring system and differ only in the position or number of O-methyl groups. Furthermore, all three alkaloids have four nuclei in their ring system.

## Experimental

**Erysodine Methiodide.**—A solution prepared from 150 mg. of erysodine, 1 ml. of methyl iodide, and 2 ml. of absolute methanol was refrigerated for twelve hours. The crystals, which were obtained, weighed 68 mg. and melted at 229–229.5°. Recrystallization of this product from 95% ethanol did not alter the melting point. The crystals were dried at 100° *in vacuo* for one hour.

*Anal.* Calcd. for $C_{18}H_{21}NO_3 \cdot CH_3I$: C, 51.70; H, 5.48; N, 3.18. Found: C, 51.82, 51.78; H, 5.62, 5.62; N, 3.27.

**Tetrahydroerysodine.**—A 508-mg. sample of erysodine was dissolved in 100 ml. of water to which 4 drops of concentrated hydrochloric acid had been previously added. The hydrogenation was carried out with 51 mg. of Adams platinum catalyst at atmospheric pressure and 2 moles of hydrogen was absorbed. After removal of the catalyst, the filtrate was made alkaline with sodium bicarbonate. The solution was extracted continuously with chloroform for eighteen hours. The chloroform extract was distilled under reduced pressure and 327 mg. of a gummy base was obtained; it crystallized after dissolving in 2 ml. of absolute ethanol. The crystals melted at 148–150°, and after three recrystallizations from ethanol, the melting point was constant at 152–153°. The tetrahydroerysodine was dried at 2 mm. and 25°.

*Anal.* Calcd. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.30; N, 4.61. Found: C, 71.10; H, 8.20; N, 4.78.

After a 2-g. sample of erysodine was hydrogenated, the chloroform residue of crude tetrahydroerysodine weighed 1.884 g. It was dissolved in 100 ml. of absolute ether and the solution was filtered to remove amorphous insoluble impurities. The filtrate was concentrated by distillation before crystallization, and 1.422 g. of tetrahydroerysodine was obtained; m. p. 150°. Recrystallization of this product from ether yielded crystals melting at 152–153° which is the same melting point observed for the product recrystallized from ethanol.

**Tetrahydroerysodine Hydrobromide.**—A 200-mg. sample of tetrahydroerysodine was dissolved in 2 ml. of absolute ethanol. After adding two drops of 40% aqueous hydrobromic acid, anhydrous ethyl ether (about ten drops) was added until incipient turbidity was observed. The crystals which were obtained melted at 247.5–248.5° and, after two recrystallizations from ethanol, the melting point was constant at 251–251.5° (dec.). The melting point was not changed by drying at 100° *in vacuo*.

*Anal.* Calcd. for $C_{18}H_{25}NO_3 \cdot HBr$: C, 56.25; H, 6.81. Found: C, 56.05; H, 6.65.

**O-Acetyltetrahydroerysodine.**—A 104-mg. sample of tetrahydroerysodine was added to 5 ml. of acetic anhydride and the solution was refluxed for ten minutes. After cooling, the solution was poured into 100 ml. of ice and water. When the excess anhydride had hydrolyzed, the solution was made alkaline with sodium bicarbonate and extracted six times with chloroform. Distillation of the chloroform extract yielded 109 mg. of colorless gum. A solution of this residue in 50 ml. of anhydrous ethyl ether was diluted with 5 ml. of petroleum ether, filtered, and concentrated to a volume of 12 ml. After refrigeration, 89 mg. of O-acetyltetrahydroerysodine, m. p. 135–136°, was obtained.

*Anal.* Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.87; $CH_3CO$-, 12.46. Found: C, 69.43, 69.63; H, 7.86, 7.91; $CH_3CO$-, 12.21.

**Tetrahydroerysopine Hydrobromide.**—One gram of erysopine was dissolved in a mixture of 25 ml. of water and 1.5 ml. of 40% aqueous hydrobromic acid. After the addition of 124 mg. of Adams platinum catalyst, the hydrogenation was carried out at atmospheric pressure, and 2 moles of hydrogen was absorbed. After removal of the catalyst, the filtrate was concentrated to dryness at 30° under reduced pressure in an atmosphere of nitrogen. The colorless gum was dissolved in 5 ml. of hot absolute ethanol and crystals quickly formed in the hot solution. The solution was cooled in the refrigerator. After the crystallization was complete, the yield of tetrahydroerysopine hydrobromide was 1.024 g.; m. p. 242–244°. Two recrystallizations of this product from ethanol yielded 900 mg. of tetrahydroerysopine hydrobromide which melted constantly at 244–245°.

*Anal.* Calcd. for $C_{17}H_{23}NO_3 \cdot HBr$: C, 55.15; H, 6.53. Found: C, 55.19; H, 6.50.

**Tetrahydro-"erysocine" Hydrobromide.**—A sample of "erysocine" was hydrogenated under conditions similar to that described for erysopine. The first crop of tetrahydro-"erysocine" hydrobromide melted at 223–224°. After recrystallization from absolute ethanol and ether, the melting point of the product was unchanged.

*Anal.* Calcd. for $C_{18}H_{25}NO_3 \cdot HBr$: C, 56.25; H, 6.91. Found: C, 56.11; H, 6.64.

It was interesting that this product showed no ready tendency to separate into tetrahydroerysodine hydrobromide and tetrahydroerysovine hydrobromide.

**Erysovine Hydrobromide Hemi-hydrate.**—To 5 ml. of absolute alcohol containing 300 mg. of erysovine was added 80 mg. of anhydrous gaseous hydrogen bromide in 2 ml. of alcohol. This solution was diluted with 4 ml. of anhydrous ethyl ether and refrigerated. Crystals separated slowly during three days; they weighed 197 mg. and melted at 150–151° (dec.). One recrystallization of this product did not alter the melting point.

*Anal.* Calcd for $C_{18}H_{21}NO_3 \cdot HBr \cdot 0.5H_2O$: C, 55.54; H, 5.95; N, 3.59. Found: C, 55.48; H, 6.06; N, 3.68.

**Erysovine Hydriodide Hydrate.**—A 300-mg. sample of erysovine was dissolved in 5 ml. of absolute ethanol and 150 mg. of sodium iodide was added. The solution was acidified with two drops of glacial acetic acid, diluted with 3 ml. of ethyl ether, and refrigerated. After one week, 121 mg. of crystals melting at 159–160° was obtained. Recrystallization of this product from ethanol and ether yielded 63 mg. of hydriodide melting at 162°.

*Anal.* Calcd. for $C_{18}H_{21}NO_3 \cdot HI \cdot H_2O$: C, 48.54; H, 5.43; N, 3.14. Found: C, 48.76; H, 5.52; N, 3.22.

**Conversion of Erysodine into Erysotrine Methomethylsulfate.**—A mixture of 20 ml. of 5% sodium hydroxide solution, 150 mg. of erysodine, and 1 ml. of dimethyl sulfate was shaken for five minutes at 25°. The excess dimethyl sulfate was hydrolyzed by warming the solution and the cooled clear alkaline solution was extracted four times with chloroform. Distillation of the solvent left 143 mg. of a clear gum which was dissolved in 1 ml. of absolute ethanol. The crystals, which formed during refrigeration, melted at 60°. The melting point was constant at 61° after two recrystallizations of the product from ethanol. The crystals were somewhat hygroscopic.

*Anal.* Calcd. for $C_{21}H_{29}NO_7S$: C, 57.39; H, 6.65; N, 3.16. Found: C, 57.46, 57.47; H, 6.96, 6.90; N, 3.15.

**Conversion of Erysopine into Erysotrine Methomethylsulfate.**—A 1.087-g. sample of erysopine was dissolved in 50 ml. of 10% sodium hydroxide solution and 2 ml. of dimethyl sulfate was added. After shaking the mixture vigorously for twenty-five minutes with cooling, the excess dimethyl sulfate was hydrolyzed by heating the solution to 50°. After cooling, the alkaline solution was extracted five times with chloroform. Distillation of the solvent left 1.313 g. of residue which crystallized when it was dissolved in 2 ml. of absolute ethanol. The crystals melted at 60–61° and when mixed with the substance de-

rived from erysodine, the melting point of the mixture was not depressed. A sample was dried four hours at 25° *in vacuo* for analyses.

*Anal.* Calcd. for $C_{21}H_{29}NO_7S$: C, 57.39; H, 6.65. Found: C, 57.75; H, 6.43.

**Conversion of Erysodine N-Oxide to Erysodine.**—A 470-mg. sample of erysodine was added to 5 ml. of superoxol and the mixture was heated forty-five minutes on the steam-bath. After standing overnight, the solution was concentrated *in vacuo*. The residue, 596 mg., was dissolved in 10 ml. of 15% hydrochloric acid. Two grams of zinc dust was added in small portions and after the reaction had subsided the solution was filtered. The filtrate was made alkaline with ammonium hydroxide and extracted five times with 10-ml. portions of chloroform. Distillation of the chloroform left 143 mg. (30%) of product, m. p. 189°. One recrystallization of this product from ether gave erysodine, m. p. 200–202°. A mixture of this product and the original erysodine showed no depression of melting point.

**Conversion of Erysodine into Erysotrine and Erysotrine Picrate.**—A 2-g. sample of erysodine was added to 20 ml. of superoxol (30% hydrogen peroxide), and the solution was heated for one hour on the steam-bath. Concentration of the solution at 18 mm. pressure yielded 3.093 g. of a thick oil. This crude N-oxide was dissolved in 50 ml. of 2% sodium hydroxide solution, and 5 ml. of dimethyl sulfate was added. The mixture was shaken for one hour, with occasional addition of alkali to keep the solution alkaline. The solution was extracted six times with chloroform, and distillation of the solvent *in vacuo* left 1.308 g. of crude erysotrine N-oxide. This product was dissolved in 50 ml. of 15% hydrochloric acid solution and reduced by gradual addition of 5 g. of zinc dust. After hydrogen evolution had practically ceased, the zinc sludge was collected on a filter and the filtrate was made alkaline with ammonium hydroxide. The solution was extracted six times with chloroform, and distillation of the solvent *in vacuo* left 963 mg. of crude erysotrine as a gum. This product did not crystallize from ether, so a 599-mg. portion was dissolved in 5 ml. of absolute ethanol and 500 mg. of picric acid was added. After standing, the clear yellow solution deposited crystals; m. p. 157°. Five recrystallizations from ethanol yielded pure erysotrine picrate, which melted constantly at 160–161°; $[\alpha]^{25}D$ + 138.1° (*c*, 0.35 in ethanol).

*Anal.* Calcd. for $C_{19}H_{23}NO_3 \cdot C_6H_3N_3O_7$: C, 55.39; H, 4.83; 3 $CH_3O$-, 17.17. Found: C, 55.48; H, 4.70; $CH_3O$-, 16.42.

The gummy erysotrine was sublimed in a molecular still at a bath temperature of 100–105° and a pressure of $2.5 \times 10^{-4}$ mm. The sublimate was gummy and showed no tendency to crystallize.

*Anal.* Calcd. for $C_{19}H_{23}NO_3$: C, 72.81; H, 7.39, 3 $CH_3O$-, 29.74. Found: C, 72.46; H, 7.64.

Resublimation gave a product of unaltered composition. Found: C, 72.46; H, 7.35; $CH_3O$-, 26.45.

**Conversion of Erysovine into Erysotrine Picrate.**—To 20 ml. of superoxol was added 276 mg. of erysovine and the solution was warmed to 90°. It was then cooled and maintained at 10° for six hours. After concentration *in vacuo*, 285 mg. of crude erysovine N-oxide remained. It was dissolved in 25 ml. of 4% sodium hydroxide solution and 5 ml. of dimethyl sulfate was added. The mixture was mechanically agitated for one hour; alkali was added to maintain an alkaline reaction. The solution was then extracted with chloroform ten times and distillation of the solvent left 270 mg. of crude erysotrine N-oxide. It was dissolved in 25 ml. of dilute hydrochloric acid and reduced by the gradual addition of 5 g. of zinc dust. When the reduction was complete, the zinc sludge was removed and the filtrate was made alkaline with ammonium hydroxide and extracted ten times with chloroform. Removal of the solvent *in vacuo* yielded 169 mg. of crude erysotrine. It was dissolved in 5 ml. of warm ethanol and treated with 5 ml. of warm ethanol containing 129 mg. of picric acid. The solution was maintained at 50–60° for six hours for crystallization. Filtration yielded 122 mg. of yellow crystals; m. p., 158–160°, $[\alpha]^{25}D$ + 137°. Recrystallization of this product yielded 65 mg. of erysotrine picrate, m. p. 160–161°. The melting point of a mixture of this picrate and the corresponding picrate derived from erysodine was not depressed. The rotation, $[\alpha]^{25}D$ + 139°, checked that of erysotrine picrate from erysodine.

**Conversion of Erysopine into Erysotrine Picrate.**—A 272-mg. sample of erysopine was added to 20 ml. of superoxol and the mixture was heated at 100° for thirty minutes. The insoluble alkaloid was filtered (32 mg.) and discarded. Concentration of the filtrate *in vacuo* left 282 mg. of crude erysopine N-oxide. It was dissolved in 50 ml. of 4% sodium hydroxide solution and after adding 5 ml. of dimethyl sulfate, the mixture was shaken one hour. After extraction eight times with chloroform, the combined extracts were concentrated *in vacuo;* 30.7 mg. of erysotrine N-oxide remained. Eight more extractions yielded only 6.5 mg. of oxide. The combined product was dissolved in 25 ml. of dilute hydrochloric acid, and reduced with 3 g. of zinc dust. The filtrate from the residual zinc was made ammoniacal and extracted eight times with chloroform. Distillation of the solvent *in vacuo* left 14 mg. of crude erysotrine, and further extractions yielded 4 mg. The 18 mg. of erysotrine was dissolved in 1 ml. of ethanol and treated with 15 mg. of picric acid dissolved in 1 ml. of ethanol. After addition of 2 drops of petroleum ether, crystals formed slowly and crystallization was allowed to continue overnight at 10°. The yield of crystals was 14 mg. and two recrystallizations from ethanol and petroleum ether gave 7 mg. of pure erysotrine picrate, m. p. 160–161°, $[\alpha]^{25}D$ + 138°. A mixture of this picrate and the one derived similarly from erysodine did not show a depressed melting point.

**Acknowledgment.**—We are indebted to Messrs. D. F. Hayman, W. Reiss, and H. C. Clark for the microanalytical data.

## Summary

Erysodine, erysovine and erysopine have the same four-nuclei ring system; each has three oxygen atoms at the same positions on the ring system, but each differs in the position or number of O-methyl groups. These deductions are based essentially upon the results of analytical, hydrogenation and methylation experiments.

RAHWAY, NEW JERSEY RECEIVED SEPTEMBER 29, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

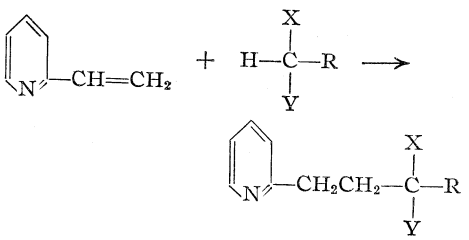
# Curariform Activity and Chemical Structure. V.[1] Syntheses in the Quinolizidine Series[2]

BY V. BOEKELHEIDE AND SEYMOUR ROTHCHILD[3]

An examination of the compounds possessing curariform activity reveals that a fused bicyclic ring system with nitrogen common to both rings is a structural feature present in many of the highly active compounds.[4] For example, such a ring system is present, or thought to be present, in members of the erythrina, calabash curare, and canadine alkaloids as well as in certain active synthetic compounds.[5] In view of this coincidence between curariform activity and the presence of a bicyclic, fused, nitrogen-containing ring system, model compounds based on the quinolizidine[6] nucleus have been prepared and tested to determine whether this structural unit, by itself, is sufficient for curariform activity. The results of testing the various derivatives, which are described in this paper, indicate that simple quinolizidines, either as tertiary or quaternary amine salts, do not possess appreciable curariform activity.

Although the simple quinolizidines did not have the desired physiological activity, the chemistry of their preparation proved to be quite interesting. Despite the number of syntheses of quinolizidine derivatives which have been reported,[7] particularly in investigations of the lupinane alkaloids, it seemed desirable to find a method which would be simpler and of more general applicability than those available. The development of such a method was facilitated by the discovery that 2-vinylpyridine can be employed effectively in the Michael reaction.[8a,b] It has now been found that the addition products of 2-vinylpyridine with active methylene compounds are particularly well suited for conversion to quinolizidines by reductive cyclization. Thus, the combination of Michael addition followed by reduction represents a two-step synthesis for a variety of quinolizidine derivatives.

In the present study the Michael additions of diethyl malonate, diethyl ethylmalonate, ethyl acetoacetate and acetylacetone to 2-vinylpyridine have been utilized to obtain I, II, III and IV, respectively. With the exception of acetylacetone, the additions proceeded readily and gave good yields of product.



I, X = $-CO_2Et$, Y = $-CO_2Et$, R = $-H$
II, X = $-CO_2Et$, Y = $-CO_2Et$, R = $-Et$
III, X = $-CO_2Et$, Y = $-COCH_3$, R = $-H$
IV, X = $-COCH_3$, Y = $-COCH_3$, R = $-H$
V, X = $-CO_2Et$, Y = $-H$, R = $-Et$
VI, X = $-COCH_3$, Y = $-H$, R = $-H$

The addition reactions of 2-vinylpyridine have been pictured by Doering and Weil[8a] as an attack by nucleophilic reagents on the electrophilic 2-vinylpyridine. In agreement with this picture it was found that the additions of the active methylene compounds, mentioned above, were most effectively catalyzed by bases, such as sodium or sodium ethoxide, which act by producing the nucleophilic anion of the active methylene compound. However, with ethyl acetoacetate, the addition could also be accomplished in good yield by the use of an acidic catalyst, dry hydrogen chloride. In this case the reaction probably involves an attack by the electrophilic 2-vinylpyridinium ion on the neutral ethyl acetoacetate molecule.

When basic catalysts were employed, it was necessary to control the reaction conditions carefully to avoid the side reactions typical of Michael additions. For example, the addition of diethyl ethylmalonate in the absence of solvent gave the expected adduct, II, but, when alcohol was employed as solvent, the main product was V. Apparently II is dissociated by base in the presence

(1) For paper IV in this series, see Craig and Tarbell, THIS JOURNAL, **71**, 465 (1949).

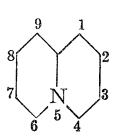
(2) Aided by a Grant from the National Foundation for Infantile Paralysis.

(3) Present address: Tracerlab, Inc., Boston, Massachusetts.

(4) For a summary on curariform activity and chemical structure, see Craig, *Chem. Rev.*, **42**, 285 (1948).

(5) Craig and Tarbell, THIS JOURNAL, **70**, 2783 (1948).

(6) The name quinolizidine is employed in this paper to designate the saturated compound shown at the right. This compound has been referred to in the literature by various names including octahydroquinolizine, quinolizidine, octahydropyridoccoline, norlupinane, and 1-azabicyclo-(0,4,4)decane. *Chemical Abstracts* lists both octahydroquinolizine and norlupinane. The name quinolizidine seems superior and has been chosen for the following reasons: (1) The corresponding unsaturated compound is generally called quinolizine, and so quinolizidine has a structural basis which norlupinane does not have. (2) Although octahydroquinolizine is indicative of structure, it is too unwieldy for referring to large numbers of compounds. (3) The use of quinolizidine is consistent with the use of pyrrolizidine, which is commonly accepted for 1-azabicyclo(0,3,3)octane. The system of numbering used for quinolizidine is that employed by *Chemical Abstracts*.



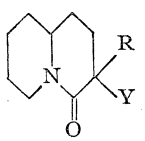
(7) See, for example, Clemo, Ramage and Raper, *J. Chem. Soc.*, 2959 (1932); Clemo, Morgan and Raper, *ibid.*, 965 (1937); Diels and Alder, *Ann.*, **498**, 16 (1932); Winterfeld and Holschneider, *ibid.*, **499**, 109 (1932); and Prelog and Bozicevic, *Ber.*, **72**, 1103 (1939).

(8) (a) Doering and Weil, THIS JOURNAL, **69**, 2461 (1947); (b) Boekelheide and Rothchild, *ibid.*, **69**, 3149 (1947).

of alcohol to give diethyl carbonate and V.[9] Likewise, the addition of acetylacetone gave both IV and VI, although under the proper conditions IV was the primary product. The formation of adducts, corresponding to two molecules of 2-vinylpyridine to one of active methylene compound, occurred to an appreciable extent only in the case when 2-vinylpyridine and diethyl malonate were employed in a 1:1 molar ratio.

The reductive cyclization of the addition products of 2-vinylpyridine to give quinolizidine derivatives was investigated under various conditions using as catalysts, Raney nickel, platinum oxide, and copper chromite, respectively. A few experiments were also carried out using lithium aluminum hydride. Inasmuch as the nature of the products differed under different catalytic conditions, the reductive cyclizations are discussed according to the catalyst employed.

**Raney Nickel Reductions.**—When substituted γ-(2′-pyridyl)-butyric esters were treated with Raney nickel catalyst at 125–150° under hydrogen pressures of one hundred atmospheres or more, it was found that reduction and cyclization occurred simultaneously to give the corresponding 4-ketoquinolizidines in high yields. By this method I, II, III, and V were converted to VII, VIII, IX and X, respectively, in yields ranging from 75 to 97%.



VII, R = —H, Y = —$CO_2Et$
VIII, R = —Et, Y = —$CO_2Et$
IX, R = —H, Y = —$CHOHCH_3$
X, R = —Et, Y = —H
XI, R = —H, Y = —H

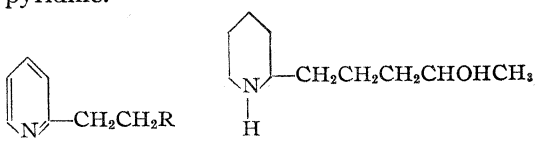
The structure of VII was established by its conversion on hydrolysis and decarboxylation to 4-ketoquinolizidine, XI, which was identified by the preparation of the hydrochloride[10] and also by its reduction with copper chromite to quinolizidine, XV. The structures of VIII, IX and X were assumed on the basis of analogy and because their subsequent reactions were consistent with these structures.

The reduction with Raney nickel of 1-(2′-pyridyl)-4-pentanone, VI, which was obtained from III by hydrolysis and decarboxylation, followed a different course at low temperatures than at high. At 120°, VI gave primarily XIV, whereas at 200° the product was almost entirely XVI. Since the reductive cyclization of 1-(2′-piperidyl)-4-pentanone would be expected to occur very readily, it can be concluded that the carbonyl group was reduced prior to the pyridine ring. The reaction must proceed by reduction of the intermediate 1-(2′-pyridyl)-4-pentanol, XII, to XIV, which at low temperatures is stable but which at higher temperatures undergoes cyclodehydration to give XVI.

(9) Similar reverse Claisen condensations have been frequently observed; see Cope and McElvain, THIS JOURNAL, **54**, 4319 (1932); and Connor, *ibid.*, **55**, 4597 (1933).

(10) For previous identifications of 4-ketoquinolizidine, see Ochiai, Tsuda and Yokoyama, *Ber.*, **68**, 2291 (1935), and ref. 8.

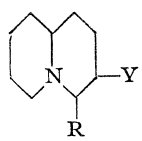
In support of this it was found that treatment of XIV with Raney nickel at 200° gave XVI. This is in agreement with the results previously found for the reductive cyclization of 2-(γ-hydroxypropyl)-pyridine.[11]

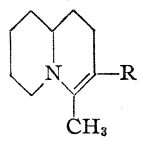


XII, R = —$CH_2CHOHCH_3$
XIII, R = —$CH(CH_2OH)_2$

XIV

Further evidence that the carbonyl group was reduced prior to the pyridine ring was obtained from a study of the reduction of III. If the pyridine ring were reduced first, it would be expected that cyclization would occur with the carbonyl group rather than the ester, and the product would be XVII. However, at 115°, III gave a 75% yield of IX and only 14% of XVII. The formation of XVII occurred in better yield at higher temperatures, though. At 200° there was obtained a 35% yield of XVII, a 15% yield of IX, and a small amount of XVI.





XV, R = —H, Y = —H
XVI, R = —$CH_3$, Y = —H
XVII, R = —$CH_3$, Y = —$CO_2Et$
XVIII, R = —H, Y = —Et
XIX, R = —$CH_3$, Y = —$CHOHCH_3$
XX, R = —$CH_3$, Y = —$CO_2H$
XXI, R = —$CH_3$, Y = —$CH_2OH$
XXII, R = —$CO_2Et$
XXIII, R = —$CHOHCH_3$

**Platinum Oxide Reductions.**—Since the pyridine ring is readily reduced in acid with platinum oxide at room temperature under an atmospheric pressure of hydrogen, this method was applied to several pyridyl ketones in an attempt to obtain cyclization of the pyridine ring with the carbonyl group. When III was reduced in this way, there was obtained a 42% yield of XVII plus a 38% yield of XXII.

The relationship of XXII to XVII was clearly established by the fact that XXII, on reduction in alcohol with platinum oxide catalyst, gave XVII in excellent yield. The presence of unsaturation in XXII was also shown by a test with permanganate solution. Since XXII is much less basic than XVII, the double bond must be adjacent to the nitrogen.

Although the structure of XVII was not rigorously established, there can be little doubt as to its correctness. XVII underwent the reactions to be expected of it and was readily shown to possess a carbethoxyl group. On hydrolysis, it gave the corresponding acid, XX, and by reduction with lithium aluminum hydride it was converted to the corresponding alcohol, XXI.

(11) Boekelheide and Rothchild, THIS JOURNAL, **70**, 864 (1948).

The formation of incompletely reduced products, such as XXII, during reductive cyclization with platinum oxide in acid is apparently a common behavior. When IV was reduced in acid solution, there was obtained in excellent yield an unsaturated compound, to which structure XXIII is assigned. In support of this structure, it was found that the compound reduced permanganate solution, did not react with carbonyl reagents, did not form a picrate, and decomposed on standing. Furthermore XXIII was readily reduced in neutral solution with platinum oxide to give the corresponding saturated derivative, XIX. As would be expected, XIX was a stable, colorless oil, which readily formed a picrate.

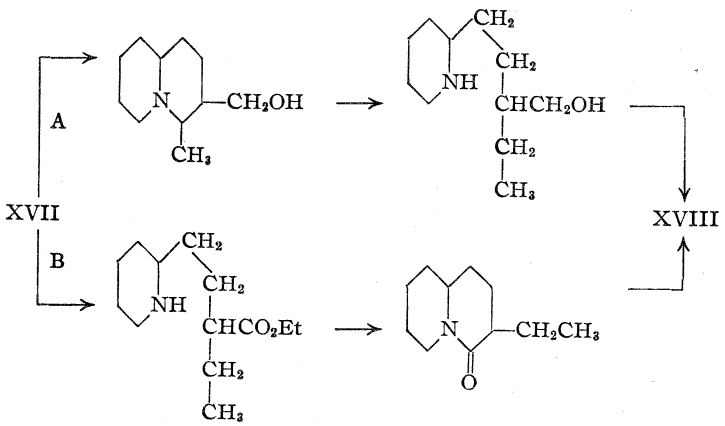
In agreement with the work of Galinovsky and Stern,[12] it was found that, with platinum oxide in acid, 4-ketoquinolizidines were reduced to the corresponding saturated derivatives. In this manner 3-ethyl-4-ketoquinolizidine, X, was reduced to 3-ethylquinolizidine, XVIII.

**Copper Chromite Reductions.**—The use of copper chromite at 250° was first attempted in order to convert the 4-ketoquinolizidines, obtained by Raney nickel reduction, to the corresponding saturated derivatives. In this way XI was readily reduced to quinolizidine, XV, in 75% yield. Also it was found that the reduction of V gave XVIII in good yield, illustrating that γ-pyridylbutyric esters can be converted in one step by copper chromite reduction to the corresponding saturated, cyclic derivatives. However, when the reduction of VII was attempted in the hope of preparing 3-hydroxymethylquinolizidine, an isomer of lupinine, there was obtained mainly quinolizidine plus a small amount of XI.

The loss of the carbethoxyl group in the reduction of VII is not surprising, though, in view of the well-known cleavages of substituted malonic esters by copper chromite.[13] Actually the copper chromite cleavage may be utilized for the preparation of quinolizidine on a practical scale.[8b] The direct copper chromite reduction of I gave a 65% yield of quinolizidine.

When reduction with copper chromite was tried with III, it was again found that cleavage occurred and from the reaction there was isolated quinolizidine and 3-ethylquinolizidine. However, the reaction product represented a complex mixture of which at least one of the components was not identified. In an attempt to simplify the number of reaction products, copper chromite reductions of IX and XVII, the intermediate cyclization products of III, were investigated. It was found that IX gave mainly 3-ethylquinolizidine plus some quinolizidine and a small amount of material which was not identified. On the other hand XVII was reduced with copper chromite to give a fair yield of 3-ethylquinolizidine.

Although the formation of 3-ethylquinolizidine would be expected from IX, its formation from XVII can only be accomplished by rearrangement. Two plausible routes for such a rearrangement are as follows:




The cleavage of a carbon to nitrogen bond during reduction of a β-amino ester, which is the essential step in route B, seems quite likely since Folkers and Adkins have found that this type of cleavage occurs during the reduction of ethyl N-ethyl nipecotate.[14] However, the reductive cleavage of a β-amino alcohol, which is the essential step in route A, has also been reported.[15] At present it is not possible to decide between the two routes.

**Lithium Aluminum Hydride.**—Lithium aluminum hydride was found to be of value chiefly for the reduction of esters to the corresponding carbinols. Thus, I with an excess of lithium aluminum hydride gave only the corresponding glycol, 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol (XIII). Reduction of the pyridine ring did not occur. Similarly, XVII on reduction with lithium aluminum hydride gave XXI in good yield.

When VII was treated with an excess of lithium aluminum hydride, the reaction took an unusual course and the only product to be isolated was XI. Apparently, lithium aluminum hydride can cause cleavages similar to those which occur during copper chromite reductions.

The compounds in this series were tested by intraperitoneal injection into mice. Compounds VII, VIII, IX and XXI were tested as aqueous emulsions, whereas the hydrochloride salts of XV, XVII, XIX, XXI, 5-methylquinolizidinium iodide and 5-benzyl-3-hydroxymethyl-4-methylquinolizidinium bromide were tested as aqueous solutions. None of these compounds exhibited curariform activity.

(12) Galinovsky and Stern, *Ber.*, **76**, 1034 (1943).

(13) Connor and Adkins, THIS JOURNAL, **54**, 4678 (1932); and Mozingo and Folkers, *ibid.*, **70**, 227 (1948).

(14) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

(15) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 88–89.

**Acknowledgment.**—We are indebted to F. M. Berger, M.D., of the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, for the pharmacological tests which have been reported.

## Experimental[16]

### Michael Additions to 2-Vinylpyridine

**Diethyl β-(2-Pyridyl)-ethylmalonate, I.**—Diethyl malonate (375 g., 2.35 moles) was added to a solution of sodium ethoxide (23 g. of sodium in 225 ml. of absolute alcohol) in a 1-liter flask equipped with condenser, drying tube, and a dropping funnel. To the boiling mixture, freshly distilled 2-vinylpyridine (106 g., 1.0 mole) in 175 ml. of absolute alcohol was added slowly. After the mixture had boiled under reflux for two hours, the alcohol was removed by distillation and the residue was acidified with dilute hydrochloric acid. The unreacted malonic ester was extracted with ether, the aqueous phase was made basic with dilute sodium hydroxide, and the basic organic layer was extracted with ether. After the ethereal solution had been dried over Drierite, the ether and recovered 2-vinylpyridine (b. p. 58° at 16 mm.) were removed *in vacuo*. The residue on distillation yielded 140 g. (53%) of a clear yellow oil; b. p. 135–140° at 0.02 mm.; $n^{25}D$ 1.4845.

*Anal.* Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.35; H, 7.26; N, 5.27.

The **picrate** of I formed slowly in ethanol over a period of several days and was obtained after recrystallization from ethanol as yellow needles, m. p. 85.0–85.5.

*Anal.* Calcd. for $C_{20}H_{22}O_{11}N_4$: C, 48.73; H, 4.24. Found: C, 48.58; H, 4.48.

**Diethyl Di-(β-(2-pyridyl)-ethyl)-malonate.**—When the preparation of I was carried out as above with equimolar quantities of 2-vinylpyridine and diethyl malonate, the maximum yield of I was only 15%. The major product was a dark viscous oil which was obtained by molecular distillation at above 190° at 1 mm. The dark oil formed a picrate in ethanol and, after crystallization from ethanol, the picrate was obtained as yellow crystals, m. p. 171–172°. The composition of the picrate, as revealed by analysis, agrees with that for the dipicrate of diethyl di-(β-(2-pyridyl)-ethyl)-malonate.

*Anal.* Calcd. for $C_{33}H_{32}N_8O_{18}$: C, 47.77; H, 3.89. Found: C, 47.95; H, 3.77.

**Diethyl Ethyl-β-(2-pyridyl)-ethylmalonate, II.**—A mixture of 2-vinylpyridine (31.5 g., 0.3 mole), diethyl ethylmalonate (84.7 g., 0.45 mole) and 2.3 g. of sodium was boiled under reflux for two hours. After the mixture had cooled, there was added 75 ml. of dilute hydrochloric acid. The product was then isolated according to the procedure given for the isolation of I, yielding 34.0 g. (39%) of a yellow oil; b. p., 138–150° at 0.2 mm.; $n^{20}D$ 1.4894.

*Anal.* Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.91. Found: C, 65.11; H, 7.97.

The **picrate** of II formed in ethanol over a period of several days and was obtained by recrystallization from ethanol as yellow crystals, m. p. 88.5–89.5°.

*Anal.* Calcd. for $C_{22}H_{26}N_4O_{11}$: C, 50.57; H, 5.02. Found: C, 50.58; H, 4.84.

When a small amount of II was boiled with concentrated hydrochloric acid, both hydrolysis and decarboxylation occurred. By careful neutralization of the acidic solution there was obtained a white granular solid. After crystallization from dilute ethanol, the white solid, α-ethyl-γ-(2-pyridyl)-butyric acid, was found to melt at 126.5–128°. A sample of the acid, when mixed with a sample of the acid obtained from V (see below), melted at 127–128°.

**Ethyl α-Ethyl-γ-(2-pyridyl)-butyrate, V.**—When the addition of diethyl ethylmalonate to 2-vinylpyridine was carried out according to the procedure given for the preparation of I, there were obtained two fractions on distillation of the product. The higher boiling fraction, obtained in 28% yield, was shown to be II by preparation of the picrate. The lower boiling fraction, V, was obtained in 47% yield as a yellow oil; b. p. 115–122° at 0.5 mm.; $n^{22}D$ 1.4851.

*Anal.* Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 69.85; H, 8.59.

**α-Ethyl-γ-(2-pyridyl)-butyric Acid.**—A solution of V (5.9 g.) in 10 ml. of concentrated hydrochloric was boiled under reflux for three hours. The reaction mixture was evaporated to dryness, the residue was taken up in dilute sodium hydroxide solution, and the basic solution was extracted with ether. When the aqueous phase was acidified with acetic acid, a white granular solid (2.6 g.) separated from the solution. After several recrystallizations from dilute ethanol, the acid was obtained as white crystals, m. p. 129–129.5°.

*Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.38; H, 7.83. Found: C, 67.88; H, 7.90.

**Ethyl β-(2-Pyridyl)-ethylacetoacetate, III.**—Dry hydrogen chloride was bubbled rapidly into a mixture of 2-vinylpyridine (26.0 g.) and ethyl acetoacetate (65.0 g.) for ten minutes. The mixture was then boiled under reflux for three hours. After the mixture had cooled, there was added 100 ml. of 3 *N* hydrochloric acid. The product was then isolated according to the procedure given for the isolation of I, yielding 29.0 g. (50%) of III; b. p. 138–150° at 1.0 mm.; $n^{22}D$ 1.500.

III was also prepared by the method of Doering and Weil.[8a] The yields by their procedure varied from 57 to 62%.

In the preparation of III by the method of Doering and Weil, there was also obtained a small yield of a white, needle-like solid, m. p. 172–173°. It is presumed that this is the same compound as that obtained by Collie and Chrystall[17] by heating ethyl acetoacetate with sodium ethoxide.

**3-Acetyl-1-(2′-pyridyl)-4-pentanone, IV.**—The addition of acetylacetone to 2-vinylpyridine was carried out according to the procedure described for the preparation of I using 31.5 g. of 2-vinylpyridine, 60.0 g. of acetylacetone, 2.3 g. of sodium and 50 ml. of absolute ethanol. Two fractions were obtained on distillation of the product. The lower boiling fraction consisted of 3.7 g. (7%) of a light yellow oil; b. p. 89–116° at 0.05 mm.; $n^{22}D$ 1.5062. This was shown to be 1-(2′-pyridyl)-4-pentanone, VI, by preparation of the picrate, m. p. 111–112°. A mixture of the picrate with the picrate of an authentic sample of VI showed no depression of melting point.

The higher boiling fraction, IV, consisted of 10.8 g. (16%) of a light yellow oil; b. p. 116–122° at 0.05 mm.; $n^{22}D$ 1.5228.

*Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.20; H, 7.37. Found: C, 70.07; H, 7.42.

The **picrate** of IV formed readily in ethanol and was obtained by recrystallization from ethanol as yellow clusters, m. p. 117–118°.

*Anal.* Calcd. for $C_{18}H_{18}N_4O_9$: C, 49.77, H, 4.18. Found: C, 49.53; H, 4.18.

When the preparation of IV was attempted according to the method of Doering and Weil for the preparation of III, the only product was a small yield of VI. Also, when the preparation of IV as given above was altered by employing larger amounts of sodium and ethanol, the yield of IV was markedly decreased and the yield of VI was increased.

**1-(2′-Pyridyl)-4-pentanone, VI.**—This was prepared by the hydrolysis and decarboxylation of III according to the procedure of Doering and Weil.[8a] VI was obtained in yields of 87 to 90%.

(16) Analyses by Mrs. G. L. Sauvage and the Micro-Tech Laboratories: all melting points are corrected.

(17) Collie and Chrystall, *J. Chem. Soc.*, **91**, 1802 (1907).

### Reductions with Raney Nickel

**3-Carbethoxy-4-ketoquinolizidine, VII.**—A mixture of 27.2 g. of I, 15 ml. of ethanol, and 5 g. of Raney nickel was heated at 145° for one hour under a hydrogen pressure of 200 atmospheres. After separation of the catalyst by filtration, the solvent was removed *in vacuo* and the residue was distilled. There was obtained 22.2 g. (97%) of a pale yellow oil; b. p. 145–155° at 0.5 mm.; $n^{22}D$ 1.5022.

*Anal.* Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.92; H, 8.47; N, 5.97.

**4-Ketoquinolizidine, XI.**—A solution of 13.4 g. of VII in 50 ml. of concentrated hydrochloric acid was boiled under reflux for three hours. The solution was evaporated to dryness, and the residue was treated according to the procedure which Ochiai, Tsuda and Yokoyama[10] employed for the conversion of γ-(2-pyridyl)-butyric acid hydrochloride to 4-ketoquinolizidine. On distillation there was obtained 5.2 g. (57%) of a colorless oil; b. p. 97° at 1.5 mm.

The identity of the 4-ketoquinolizidine was established by the preparation of the hydrochloride which melted at 143–145° (lit.,[10] m. p. 146–147°). Also the 4-ketoquinolizidine was reduced by copper chromite to quinolizidine (*vide infra*).

**3-Ethyl-3-carbethoxy-4-ketoquinolizidine, VIII.**—Following the procedure given above for the preparation of VII, the reductive cyclization of II was readily accomplished. Reduction was complete in three hours, and on working up the product there was obtained an 84% yield of a colorless oil; b. p. 140–145° at 0.8 mm.; $n^{22}D$ 1.4891.

*Anal.* Calcd. for $C_{14}H_{23}O_3N$: C, 66.38; H, 9.15. Found: C, 66.49; H, 9.06.

**3-Ethyl-4-ketoquinolizidine, X.**—The reductive cyclization of V was carried out according to the procedure given above for the preparation of VII. From 4.9 g. of V there was obtained 3.1 g. (78%) of a colorless oil; b. p. 125–128° at 0.5 mm.; $n^{23}D$ 1.4957.

*Anal.* Calcd. for $C_{11}H_{19}NO$: C, 72.87; H, 10.56. Found: C, 72.69; H, 10.54.

**Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate.**—The reduction of ethyl β-(2-pyridyl)-ethylacetoacetate, III, was carried out according to the procedure previously given for the preparation of VII. On distillation there were obtained two products: 3-(α-hydroxyethyl)-4-ketoquinolizidine, IX, and 3-carbethoxy-4-methylquinolizidine, XVII. The reduction was repeated several times to find the effect of temperature on the relative yields of IX and XVII. The results are shown in Table I.

TABLE I

| Temperature, °C. | % of IX | % of XVII | Total yield, % |
|---|---|---|---|
| 115 | 75 | 14 | 89 |
| 140 | 73 | 20 | 93 |
| 200 | 15 | 36 | 56[a,b] |

[a] This includes a 5% yield of 4-methylquinolizidine, XVI, which was identified by its picrate, m. p. 191–194°. A mixed melting point determination with the picrate of an authentic sample of XVI showed no depression. [b] Total yield is low because of mechanical loss.

IX and XVII were characterized as follows:

**3-Carbethoxy-4-methylquinolizidine,** XVII, was obtained as a colorless oil; b. p. 105–120° at 1.5 mm.; $n^{22}D$ 1.4820.

*Anal.* Calcd. for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29. Found: C, 69.41; H, 10.45.

The **picrate** of XVII formed readily in ethanol and was obtained by recrystallization from ethanol as a yellow granular solid, m. p. 127.5–128.5°.

*Anal.* Calcd. for $C_{19}H_{26}N_4O_9$: C, 50.22; H, 5.77. Found: C, 50.65; H, 5.69.

**3-Carboxy-4-methylquinolizidine,** XX, was readily obtained by hydrolysis of a small amount of XVII with dilute hydrochloric acid. An attempt to isolate the acid as the hydrochloride was unsucessful, but the picrate was readily prepared. After crystallization from ethanol, the picrate of XX was obtained as a yellow amorphous solid, m. p. 203–205°.

*Anal.* Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.20. Found: C, 48.08; H, 5.32.

**3-(α-Hydroxyethyl)-4-ketoquinolizidine,** IX, was obtained as a viscous, slightly yellow oil; b. p. 145–155° at 1.5 mm.; $n^{20}D$ 1.5090.

*Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.66. Found: C, 66.69; H, 9.26.

**Reduction of 1-(2′-Pyridyl)-4-pentanone.**—The reduction of 1-(2′-pyridyl)-4-pentanone, VI, was carried out according to the procedure previously given for the preparation of VII. On distillation there were obtained two products: 4-methylquinolizidine, XVI, and 1-(2′-piperidyl)-4-pentanol, XIV. The effect of temperature on the relative yields of XIV and XVI is shown in Table II.

TABLE II

| Temperature, °C. | % of XIV | % of XVI | Total yield, % |
|---|---|---|---|
| 125 | 67 | 9 | 76 |
| 150 | 55 | 26 | 81 |
| 200 | 15 | 69 | 84 |

XIV and XVI were characterized as follows:

**1-(2′-Piperidyl)-4-pentanol,** XIV, distilled as a colorless oil (b. p. 118° at 1.5 mm.) which crystallized in the receiver. After recrystallization from petroleum ether (60–70°), it was obtained as a hygroscopic, white solid, m. p. 64.5°.

*Anal.* Calcd. for $C_{10}H_{21}NO$: C, 70.11; H, 12.36. Found: C, 69.90; H, 12.31.

The **hydrochloride** of XIV was prepared in ether using dry hydrogen chloride. After recrystallization from a mixture of acetone and ethyl acetate, it was obtained as a white, crystalline solid, m. p. 107–108°.

*Anal.* Calcd. for $C_{10}H_{22}ClNO$: C, 57.81; H, 10.68. Found: C, 57.63; H, 10.74.

**4-Methylquinolizidine,** XVI, was obtained as a colorless oil; b. p. 79° at 13 mm.; $n^{19}D$ 1.4813.

*Anal.* Calcd. for $C_{10}H_{13}N$: C, 78.36; H, 12.50. Found: C, 78.21; H, 12.47.

The **picrate** of XVI formed readily in ethanol and was obtained by recrystallization from ethanol as yellow needles, m. p. 191–195°.

*Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80. Found: C, 50.29; H, 5.60.

Although there should be two diastereoisomeric forms of XVI, no other picrate was isolated. Similar results have been noted previously for compounds of this type.[18,19]

The cyclization of XIV to yield XVI was accomplished by heating 0.6 g. of XIV in 3 ml. of absolute alcohol in a bomb at 200° for one hour in an atmosphere of hydrogen and in the presence of Raney nickel catalyst. After removal of the catalyst, the product was isolated through the formation of the picrate. The picrate, which was isolated in good yield, was shown to be identical with the picrate of XVI by a mixed melting point determination.

### Reductions with Platinum Oxide

**Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate.**—A mixture of 47.1 g. of ethyl β-(2-pyridyl)-ethylaceto-

(18) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935).

(19) While correcting proof of this manuscript, the article by Lukes and Sorm, *Coll. Czechoslov. Chem. Commun.*, **12**, 356 (1947); *Chem. Abst.*, **42**, 7780 (1948), in which they describe two picrates of the possible diastereoisomeric racemates of 4-methylquinolizidine (allolupinane), became available to us. Our picrate appears to correspond to the picrate which they describe as melting at 195°. In view of their results and the fact that the crude preparation of our picrate melted at 188–192°, it would seem that essentially only one racemate was produced by the reductive cyclization.

acetate, III, 200 ml. of dilute hydrochloric acid and 0.89 g. of platinum oxide was reduced under a hydrogen pressure of 3 atm. at room temperature for one hour. The catalyst was removed by filtration, the solution was made basic, and the organic layer was extracted with ether. After the ethereal solution had been dried over anhydrous sodium carbonate, the ether was removed *in vacuo* and the residue was distilled. By careful distillation through a column packed with glass helices, there were obtained two fractions. The lower boiling fraction consisted of 19.0 g. (42%) of an oil which by its physical properties (b. p. 116–122° at 1.3 mm.; $n^{22}D$ 1.4820) and by formation of the picrate (m. p. 127–128°, mixed melting point determination with the picrate of an authentic sample of XVII showed no depression) was shown to be XVII.

The higher boiling fraction, **3-carbethoxy-3-ene-4-methylquinolizidine** (XXII), consisted of 17.2 g. (38%) of a semi-viscous, colorless oil; b. p. 129–132° at 0.8 mm.; $n^{20}D$ 1.5426.

*Anal.* Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.72; H, 9.72.

XXII readily decolorized a solution of potassium permanganate in acetone. Although no hydrogen absorption was observed when 5.6 g. of XXII in 20 ml. of ethanol was shaken under a pressure of 3 atm. of hydrogen at 50° in the presence of Raney nickel catalyst, reduction occurred rapidly when 0.10 g. of platinum oxide was added. The product was isolated in the usual manner and on distillation there was obtained 4.6 g. (82%) of a colorless oil. In the same manner as given above, this oil was shown to be XVII.

**3-(α-Hydroxyethyl)-3-ene-4-methylquinolizidine, XXIII.**—The reduction of IV with platinum oxide as catalyst was carried out according to the procedure given above for the reduction of III. From 6.2 g. of IV there was obtained on distillation of the residual oil 4.9 g. (85%) of a colorless oil; b. p. 92–100° at 0.5 mm.; $n^{21}D$ 1.4931.

*Anal.* Calcd. for $C_{12}H_{21}NO$: C, 73.79; H, 10.84. Found: C, 73.55, 73.70; H, 10.92, 11.04.

XXIII decolorized a solution of potassium permanganate, and it did not form a semi-carbazone, a 2,4-dinitrophenylhydrazone, or a picrate.

**3-(α-Hydroxyethyl)-4-methylquinolizidine, XIX.**—The reduction of 1.40 g. of XXIII in 10 cc. of ethanol in the presence of 0.093 g. of platinum oxide took place under an atmospheric pressure of hydrogen at room temperature. The uptake of hydrogen was complete in twelve hours. A colorless oil, about 1 g., was isolated by distillation; bath temp. 110–120° at 1.5 mm.; $n^{23}D$ 1.4920.

*Anal.* Calcd. for $C_{12}H_{23}ON$: C, 73.05; H, 11.75. Found: C, 73.27; H, 11.65.

**The picrate** of XIX was obtained, after recrystallization from ethanol, as yellow crystals, m. p. 198–201°.

*Anal.* Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15. Found: C, 50.78; H, 5.80.

**3-Ethylquinolizidine, XVIII.**—The reduction of X was carried out according to the procedure given by Galinovsky and Stern for the reduction of 4-ketoquinolizidine.[12] A mixture of 1.81 g. of X and 0.70 g. of platinum oxide in 50 ml. of a 1.5% solution of hydrochloric acid was shaken in an atmosphere of hydrogen at room temperature. After the mixture had been shaken for seventy-six hours, 88% of the calculated volume of hydrogen had been absorbed. The catalyst was removed and the solution was extracted with ether. The aqueous layer was then made basic and extracted again with ether. After the ethereal solution had been dried and the ether removed *in vacuo*, the residual oil was divided into two parts and converted directly to the corresponding picrate and hydrochloride. The picrate, after crystallization from ethanol, melted at 152–156°, and the hydrochloride, after crystallization from ethyl acetate, melted at 198–199°. The picrate and hydrochloride of 3-ethylquinolizidine were shown by the method of mixed melting points to be identical with the samples of these derivatives prepared previously (see the section on the copper chromite reduction of ethyl α-ethyl-γ-(2-pyridyl)-butyrate).

### Reductions with Copper Chromite

**Quinolizidine, XV, from 4-Ketoquinolizidine, XI.**—A mixture of 5.6 g. of XI and 1.5 g. of copper chromite in 20 cc. of ethanol was heated at 260° for five hours under a hydrogen pressure of 250 atm. After separation of the catalyst by filtration and removal of the ethanol *in vacuo*, the residual oil was distilled yielding 3.8 g. (75%) of a colorless oil; b. p. 79° at 18 mm.; $n^{20}D$ 1.4796. The oil was shown to be quinolizidine by the preparation of the picrate, which melted at 198–199° (lit.,[7,12] m. p. 194°, 196°; 199–200°), and the chloroaurate, which melted at 168–169° (lit.,[7] m. p. 171°).

The **methiodide** of XV formed readily and was obtained as white crystals, dec. 309–311° (lit.,[7,12] dec. 335°; 333°).

*Anal.* Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.17. Found: C, 42.50; H, 7.09.

The **hydrochloride** of XV formed readily in ether but it did not give a definite melting point.

*Anal.* Calcd. for $C_9H_{18}ClN$: C, 61.53; H, 10.32. Found: C, 61.20; H, 10.01.

**Quinolizidine, XV, from 3-Carbethoxy-4-ketoquinolizidine, VII.**—When the reduction of VII was carried out as given above for the reduction of XI, there was obtained on distillation a 76% yield of XV. The identity of XV was established through the preparation of the picrate, m. p. 198–199°, and the methiodide, dec. 309–311°. Mixtures of these derivatives with the corresponding derivatives of quinolizidine prepared previously (see above) showed no depression of melting point.

**Quinolizidine, XV, from Diethyl β-(2-Pyridyl)-ethylmalonate, I.**—The reduction of I was carried out on a 0.05 molar scale according to the procedure used for the reduction of XI. When the reduction was allowed to proceed overnight, there was obtained, on working up the product and distilling, a 65% yield of quinolizidine and a 13% yield of 4-ketoquinolizidine. The quinolizidine was identified in the same manner as described previously. The 4-ketoquinolizidine was identified by preparing the hydrochloride, m. p. 139–142°; no depression of melting point occurred when the hydrochloride was mixed with the hydrochloride of an authentic sample of 4-ketoquinolizidine. A sample of the 4-ketoquinolizidine was also converted by hydrolysis in dilute hydrochloric acid to the hydrochloride of γ-(2-piperidyl)-butyric acid, m. p. 191–192° (lit.,[10] m. p. 188–189°).

When the time of reduction was shortened to one-half hour, the yield of quinolizidine was only 42% but the yield of 4-ketoquinolizidine increased to 25%. In addition a small amount of a crystalline solid, m. p. 90–93°, separated during the distillation. The amount of solid was insufficient for further characterization.

**3-Ethylquinolizidine, XVIII, from Ethyl α-Ethyl-γ-(2-pyridyl)-butyrate, V.**—A mixture of 9.7 g. of V and 2.0 g. of copper chromite was heated at 250° for one hour under a hydrogen pressure of about 150 atm. After removal of the catalyst, the residual oil was fractionally distilled and there was obtained two fractions. The higher boiling fraction consisted of 2.8 g. (35%) of a colorless oil, which on the basis of its physical properties (b. p. 112–115° at 0.2 mm.; $n^{21}D$ 1.4933) must be 3-ethyl-4-ketoquinolizidine, a product which was obtained previously from the Raney nickel reduction of V.

The lower boiling fraction, XVIII, consisted of 3.1 g. (43%) of a colorless oil; b. p. 104–108° at 20 mm.; $n^{21}D$ 1.4735.

*Anal.* Calcd. for $C_{11}H_{21}N$: C, 78.97; H, 12.65. Found: C, 78.70; H, 12.65.

**The picrate** of XVIII was prepared in ethanol and, after several recrystallizations from ethanol, was obtained as yellow crystals, m. p. 156–157°.

*Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.10. Found: C, 51.62; H, 6.08.

The **hydrochloride** of XVIII was prepared in ether with

dry hydrogen chloride and, after several recrystallizations from ethyl acetate, was obtained as white crystals, m. p. 198–199°.

*Anal.* Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88. Found: C, 64.53; H, 10.72.

The picrate and hydrochloride of XVIII were shown by the method of mixed melting points to be identical with the corresponding derivatives of the oil obtained by the platinum oxide reduction of X. Since any sort of rearrangement during platinum oxide reduction at room temperature would be extremely unlikely, there can be little doubt that XVIII is 3-ethylquinolizidine. Even though isomerism due to the nitrogen atom is neglected, there should be two diastereoisomeric forms of XVIII. The presence of two such forms was indicated by the fact that the crude derivatives of XVIII melted over a wide range. However, no pure derivative corresponding to a second diastereoisomer was isolated, even though several attempts to do so were made.

**Reduction of Ethyl β-(2-Pyridyl)-ethylacetoacetate, III.**—A mixture of 21.2 g. of III and 5.0 g. of copper chromite in 26 ml. of ethanol was shaken at 250° under a pressure of 150 atm. of hydrogen for three hours. After removal of the catalyst and solvent, the residual oil was fractionally distilled and there was obtained three fractions.

The first fraction consisted of 3.4 g. (27%) of a colorless oil, b. p. 66–70° at 10 mm., which was shown to be quinolizidine by a comparison of the picrate and methiodide with the corresponding derivatives of an authentic sample of quinolizidine.

The second fraction consisted of 4.6 g. (31%) of a colorless oil, b. p. 80–87° at 10 mm., which was shown to be 3-ethylquinolizidine by the preparation of the picrate, m. p. 155–157°. A mixture of this picrate with the picrate of an authentic sample of 3-ethyl-quinolizidine (see above) showed no depression of melting point. Since mixtures of picrates of related compounds in this series were found to give marked depressions of melting point, the method of mixed melting points is assumed to be a valid test for identity.

The third fraction consisted of 6.3 g. of a colorless oil; b. p. 113–116° at 1.5 mm.; $n^{21}D$ 1.4956. The composition of the oil, as indicated by analysis, does not agree with any logical formula. A portion of the oil was converted to the picrate, m. p. 204–206°, but no further identification was carried out.

**Reduction of 3-(α-Hydroxyethyl)-4-ketoquinolizidine, IX.**—When the reduction of 5.0 g. of IX was carried out according to the procedure given previously for the reduction of III, there was obtained, on distillation, three fractions. The first two fractions, which weighed 0.6 g. and 1.2 g. respectively, were shown to be quinolizidine and 3-ethylquinolizidine in the same manner as described above. The third fraction consisted of 1.1 g. of a colorless oil; b. p. 102–108° at 1.5 mm.; $n^{20}D$ 1.4963. A portion of the oil from the third fraction was converted to the picrate, m. p. 158–160°, but further identification was not carried out. A mixture of the picrate of the oil from the third fraction with the picrate of 3-ethylquinolizidine showed a marked depression in melting point. The composition of the oil, as indicated by analysis, does not agree with any logical formula.

**Reduction of 3-Carbethoxy-4-methylquinolizidine, XVII.**—A mixture of 6.7 g. of XVII, 1.5 g. of copper chromite and 8 ml. of absolute alcohol was heated at 250° for two hours under a pressure of 200 atm. of hydrogen. When the reaction mixture was worked up in the usual fashion, there was obtained two fractions on distillation.

The lower boiling fraction consisted of 2.1 g. (42%) of a colorless oil, b. p. 83–90° at 8 mm., which was shown by the preparation of the corresponding picrate, m. p. 155–157°, and hydrochloride, m. p. 197–199, to be 3-ethylquinolizidine, XVIII. Neither the picrate nor the hydrochloride, when mixed with authentic samples of these derivatives previously prepared from 3-ethylquinolizidine, showed any depression of melting point. In one attempt to prepare the hydrochloride of the lower boiling fraction, there was obtained a sample of white crystals, m. p. 179–180°, whose melting point was not raised by further recrystallization from ethyl acetate. The composition of this hydrochloride (*Anal.* Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88. Found: C, 64.60; H, 11.07.) agrees with that for 3-ethylquinolizidine, and it was thought, at first, that this hydrochloride represented a diastereoisomer of the hydrochloride previously isolated. However, when a supersaturated solution of the hydrochloride melting at 179–180° was seeded with crystals from the hydrochloride melting at 198–199°, the crystals, which separated, melted at 183–187°, indicating that the two hydrochlorides are probably different polymorphic forms of the same diastereoisomer.

The higher boiling fraction consisted of 2.2 g. of a colorless oil, b. p. 105–110° at 1 mm. The composition of the oil, as indicated by analysis, did not agree with any logical formula, and the oil was not further identified.

### Reductions with Lithium Aluminum Hydride

**2-Hydroxymethyl-4-(2′-pyridyl)-1-butanol, XIII.**—A solution of 13.3 g. of I in 30 ml. of dry ether was added dropwise with stirring to 100 ml. of a 0.6 molar solution of lithium aluminum hydride in ether. The reaction mixture was decomposed with water and then hydrolyzed with dilute sulfuric acid. The ether layer was separated, and the aqueous layer was made strongly basic with sodium hydroxide solution. The organic layer was extracted from the basic solution with *s*-amyl alcohol, the amyl alcohol was removed from the extract *in vacuo*, and the residual oil was distilled. There was obtained 2.2 g. (24%) of a slightly green oil; b. p. 165–170° at 0.4 mm. When the oil was triturated with acetone, it crystallized to give a white solid, m. p. 57–59°.

*Anal.* Calcd. for $C_{10}H_{15}NO_2$: C, 66.28; H, 8.35. Found: C, 66.66; H, 8.20.

**3-Hydroxymethyl-4-methylquinolizidine, XXI.**—The reduction of 4.7 g. of XVII was carried out according to the procedure given above for the reduction of I. In this case the basic oil was extracted with ether instead of amyl alcohol. On distillation of the residual oil there was obtained 1.9 g. (50%) of a viscous, colorless oil; b.p. 98–110° at 0.8 mm.; $n^{19}D$ 1.5072.

*Anal.* Calcd. for $C_{11}H_{21}NO$: C, 72.12; H, 11.52. Found: C, 72.24; H, 11.40.

The **benzyl bromide salt** of XXI was readily formed by heating a sample of XXI with benzyl bromide. After recrystallization from an ethanol–acetone mixture, the benzyl bromide salt was obtained as white crystals, m. p. 179.5–180.5°.

*Anal.* Calcd. for $C_{18}H_{28}BrNO$: C, 61.02; H, 7.97. Found: C, 60.75; H, 7.95.

**Reduction of 3-Carbethoxy-4-ketoquinolizidine, VII.**—The reduction of 2.1 g. of VII was carried out according to the procedure given above for the reduction of I. Extraction of the basic aqueous solution was done with ether instead of amyl alcohol. On distillation of the residual oil there was obtained 0.3 g. of 4-ketoquinolizidine, b. p. 100–105° at 1 mm.; $n^{22}D$ 1.5131. The identity of the 4-ketoquinolizidine was established by the preparation of the hydrochloride, m. p. 143–145°. When a sample of this hydrochloride was mixed with an authentic sample of the hydrochloride of 4-ketoquinolizidine, there was no depression of melting point.

## Summary

The Michael addition of active methylene compounds to 2-vinylpyridine followed by reductive cyclization has been found to be an easy and practical method of synthesis for a variety of quinolizidine derivatives. Several methods of reductive cyclization have been employed, and, depending on the method of reduction used, either substituted quinolizidines or 4-ketoquinoli-

zidines may be obtained. When copper chromite was employed as catalyst for reductive cyclizations, examples of both skeletal cleavage and rearrangement were found.

Compounds, having the simple quinolizidine nucleus, were found not to possess appreciable curariform activity.

ROCHESTER, NEW YORK RECEIVED SEPTEMBER 13, 1948

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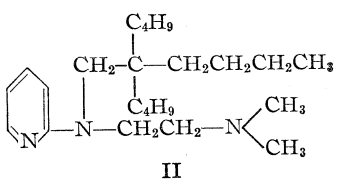
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

# Quaternary Carbon Compounds. II. N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine and the Diethyl Homolog

BY NATHAN SPERBER AND DOMENICK PAPA

In a publication[1] describing the synthesis of N′-benzyl-N′-(2-pyridyl)-N,N-dimethylethylenediamine (I) and related compounds, several substances in which the benzyl group of I was replaced by lower alkyl radicals such as ethyl, isopropyl and propyl are reported. The latter substances showed a low order of antihistaminic activity in experimental animals as compared with the benzyl compound.

In the course of studies on trialkyl-substituted compounds of pharmacological importance,[2] we have prepared a highly branched compound related to I, namely, N,N-dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine (II), in order to establish whether this type of substitution would show appreciably greater antihistaminic activity than the lower alkyl derivatives. In animal experiments, II has shown approximately $^1/_{250}$ the antihistaminic activity of I. The diethyl homolog (III) of II was also prepared and was $^1/_5$–$^1/_{10}$ as active as II.



II

The synthesis of II and the diethyl homolog was carried out in two steps. The condensation of 2-bromopyridine, (2,2-dibutylhexyl)-amine and anhydrous sodium carbonate in xylene or cymene yielded, after prolonged refluxing, N-(2,2-dibutylhexyl)-2-aminopyridine. The latter on alkylation with dimethylaminoethyl chloride or diethylaminoethyl chloride gave good yields of II and III, respectively.[3] Attempts to condense N,N-diethyl-N′-(2,2-dibutylhexyl)-ethylenediamine and 2-bromopyridine with sodamide were unsuccessful.

(1) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(2) (a) Junkmann and Allardt, U. S. 2,186,976, Jan. 16, 1940; (b) Allardt and Junkmann, U. S. 2,361,524, Oct. 31, 1944; (c) Sperber, Papa and Schwenk, Quaternary Carbon Compounds. I, THIS JOURNAL, **70**, 3091 (1948).

(3) These experiments were completed prior to the publication of Huttrer, *et al.*, and were based on the directions of Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

## Experimental

**(2,2-Dibutylhexyl)-amine.**—Capronitrile was dialkylated with butyl bromide and sodium amide according to the directions of Ziegler and Ohlinger.[4] The resulting 2,2-dibutylcapronitrile was reduced to (2,2-dibutylhexyl)-amine[2b]; yield 90%; b. p. 123–124° (4 mm.); hydrochloride m. p. 135°.

**N-(2,2-Dibutylhexyl)-2-aminopyridine.**[5]—A mixture of 32 g. of 2-bromopyridine, 50 g. of (2,2-dibutylhexyl)-amine and 21 g. of anhydrous sodium carbonate in 100 cc. of *p*-cymene was refluxed and stirred for sixty-seven hours. The mixture was poured into water, the cymene layer separated and, after drying, concentrated *in vacuo*. The residue was fractionated. After a forerun of 12.6 g., b. p. 95–163° (1 mm.), the substituted aminopyridine was obtained as a yellow viscous oil; yield 45 g., b. p. 172–174° (2 mm.); $n^{23}D$ 1.5045. Calcd. for $C_{19}H_{34}N_2$: N, 9.65. Found: N, 9.28.

**N,N-Dimethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.**—To a sodium amide suspension[6] (2.5 g. of sodium) in 75 cc. of dry toluene, was added 29 g. (0.1 mole) of N-(2,2-dibutylhexyl)-2-aminopyridine.[7] The mixture was heated with stirring for two hours on the steam-bath. A solution of 12 g. of dimethylaminoethyl chloride in 20 cc. of dry toluene was added dropwise to the stirred suspension and the reaction heated with stirring for twenty hours on the steam-bath. The reaction mixture was cooled and then decomposed with water. The organic layer was separated, dried and the solvent removed *in vacuo*. The residue distilled as a yellow viscous oil; yield 28.5 g., b. p. 175–177° (2 mm.), $n^{23}D$ 1.5002. Calcd. for $C_{23}H_{43}N_3$: C, 76.36; H, 11.99; N, 11.62. Found: C, 76.60; H, 11.99; N, 11.61.

**The dihydrochloride** was prepared as follows: A solution of 6 g. of the free base in 75 cc. of dry ethyl acetate was saturated with anhydrous hydrogen chloride. Upon cooling and scratching, a crystalline solid was obtained. Dry ether was added, the solid collected and washed with ether: recrystallized twice from alcohol–ether; yield 5.8 g.; m. p. 184.5–185.5°. Calcd. for $C_{23}H_{45}N_3Cl_2$: N, 9.67; Cl, 16.33. Found: N, 9.45; Cl, 16.00.

**N,N-Diethyl-N′-(2,2-dibutylhexyl)-N′-(2-pyridyl)-ethylenediamine.**—N-(2,2-Dibutylhexyl)-2-aminopyridine was alkylated with diethylaminoethyl chloride and sodium amide as described for the corresponding dimethyl compound; yield 70%; yellow viscous oil; b. p. 190–195° (2 mm.); $n^{21}D$ 1.5005. The free base was converted to

(4) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(5) The reaction of 16 g. of 2-bromopyridine, 39 g. of (2,2-dibutylhexyl)-amine and 50 cc. of pyridine for ten hours at 155–160° essentially as described by Whitmore[3] did not yield any of the substituted aminopyridine.

(6) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 99.

(7) Although King, King and Muir (*J. Chem. Soc.*, 5 (1946)) alkylated diphenylamine with diethylaminoethyl chloride by means of the Grignard reagent, N-(2,2-dibutylhexyl)-2-aminopyridine with methylmagnesium iodide and dimethylaminoethyl chloride yielded none of the expected tertiary amine.

the dihydrochloride in ethyl acetate and was recrystallized twice from a mixture of alcohol–ether; m. p. 205–205.5°. Calcd. for $C_{25}H_{49}N_3Cl_2$: N, 9.08; Cl, 15.34. Found: N, 9.18; Cl, 15.76.

**N,N-Diethyl-N′-(2,2-dibutylhexyl)-ethylenediamine.**—A mixture of 21 g. (0.1 mole) of 2,2-dibutylhexylamine, 14 g. (0.1 mole) of diethylaminoethyl chloride and 11 g. of anhydrous sodium carbonate in 50 cc. of dry xylene was refluxed with stirring for sixty-five hours. The cooled reaction product was poured into water, the xylene layer separated, and the solvent removed *in vacuo*. The brown oily residue was distilled; yield 29 g.; b. p. 155–156° (2 mm.); $n^{23}D$ 1.4540. The analytical sample showed the following constants: b. p. 151–152° (1.5 mm.); $n^{23}D$ 1.4513. Calcd. for $C_{20}H_{44}N_2$: C, 76.82; H, 14.20; N, 8.97. Found: C, 76.71; H, 13.74; N, 9.26.

**Acknowledgment.**—We wish to express our appreciation to Dr. Richard Tislow and Mrs. Annette LaBelle of our Pharmacology Laboratory for the pharmacological data reported herein.

## Summary

Replacement of the benzyl group in N′-benzyl-N′-(2-pyridyl)-N,N-dimethylethylenediamine by a highly branched aliphatic radical resulted in a considerable decrease in antihistaminic activity.

BLOOMFIELD, N. J. RECEIVED SEPTEMBER 9, 1948

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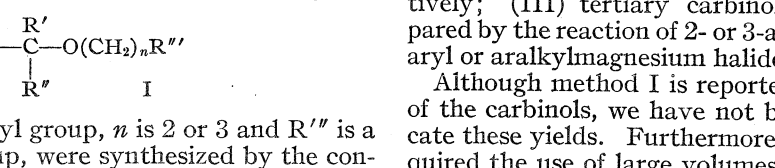
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

# Pyridyl-Substituted Alkamine Ethers as Antihistaminic Agents[1]

BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK AND MARGARET SHERLOCK

Although Fourneau and co-workers[2] demonstrated that dialkylaminoalkylaryl ethers[3] possessed antihistaminic activity, these substances proved too toxic for general clinical use. Recently, a series of dialkylaminoalkylbenzhydryl ethers[4] have been reported[5] to be potent antihistaminic agents. One of the latter type of compounds, β-dimethylaminoethyl benzhydryl ether, is employed at present in anti-allergic therapy.

The extremely favorable change in therapeutic index which resulted from the replacement of the phenyl group by a pyridyl group[6] in N′-phenyl-N′-benzyl-N,N-dimethylethylenediamine seemed of sufficient interest to warrant the study of a similar substitution in the benzhydrylalkamine ether series. A number of substituted dialkylaminoalkylpyridylmethyl ethers of the general formula I (Table II) wherein R is a pyridyl radical, R′ is alkyl, aryl or heterocyclic, R″ is hydrogen or a lower alkyl group, $n$ is 2 or 3 and R‴ is a dialkylamino group, were synthesized by the condensation of the appropriately substituted carbinols with dialkylaminoalkyl halides and sodium amide in toluene. In general, the yields of ethers varied from about 45–88%. In the case of (2-pyridyl)-(2-thienyl)-methylcarbinol, only 22% of the dimethylaminoethyl ether was obtained.



I

The requisite carbinols (Table I) were synthesized by the following three methods[7]: (I) the reaction of aldehydes with 2-pyridylmagnesium bromide as described by Overhoff and Proost[8]: (II) The condensation of picolinic acid and aromatic aldehydes and ketones to yield the secondary and tertiary pyridylarylcarbinols,[9] respectively; (III) tertiary carbinols were also prepared by the reaction of 2- or 3-acetylpyridine with aryl or aralkylmagnesium halides.

Although method I is reported to give 40–55% of the carbinols, we have not been able to duplicate these yields. Furthermore, this synthesis required the use of large volumes of solvent for extraction and, frequently, troublesome emulsions were encountered.

A more satisfactory method for the preparation of the secondary substituted 2-pyridylcarbinols is based on the decarboxylation of picolinic acid in the presence of an aromatic aldehyde at a temperature above 140° (Method II). The products of

(1) The major portion of this paper was presented in abstract before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, April 21, 1948. Similar amino ethers have been reported by Tilford, Van Campen and Shelton, abstract of Papers of 114th Meeting of the American Chemical Society, pg. 2K (August 31, 1948).

(2) Forneau and Bovet, *Arch. internat. de pharmacodyn. et de therap.*, **46**, 178 (1933); Staub, *Ann. Inst. Pasteur*, **63**, 400 (1939).

(3) 929F, 2-isopropyl-5-methylphenoxyethyldiethylamine; 1379F, 2-methyl-5-isopropylphenoxyethyldiethylamine; 1464F, 2-isopropyl-5-methylphenoxyethylpiperidine.

(4) Abstracts of the Atlantic City Meeting of the American Chemical Society, p. 50K (1946); Rieveschl, U. S. Patent 2,421,714, June 3, 1947.

(5) Loew, Kaiser and Moore, *J. Pharmacol. and Exp. Therap.*, **83**, 120 (1945); Loew and Kaiser, *Proc. Soc. Exper. Biol. and Med.*, **58**, 235 (1945).

(6) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(7) (a) Chichibabin oxidized 2-benzylpyridine to phenyl-2-pyridyl ketone (*J. Russ. Phys.-Chem. Soc.*, **33**, 701 (1901)). The latter was reduced to the corresponding carbinol with zinc dust and sodium ethoxide (*Ber.*, **37**, 1371 (1904)); (b) Emmert and Asendorf (*Ber.*, **72**, 1188 (1939)) have prepared several 2-pyridyl-substituted carbinols by the reaction of a ketone and mercuric chloride with pyridine and magnesium.

(8) Overhoff and Proost, *Rec. trav. chim.*, **57**, 179 (1938).

(9) Ashworth, Daffern and Hammick, *J. Chem. Soc.*, 809 (1939); Mislow, THIS JOURNAL, **69**, 2559 (1947).

TABLE I

CARBINOLS, RR'R"C—OH

| R | R' | R" | Method | Yield,[a] % | M. p., °C. | B. p., °C. | Mm. | Formula | N Analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 2-$C_5H_4N$ | $C_6H_5$ | H | I (II) | 35 (49) | 77–77.5[b] | 133–138 | 1 | | | |
| 2-$C_5H_4N$ | *p*-*i*-$C_3H_7C_6H_4$ | H | I (II) | 42.5 (24.5) | 102.5–103 | 166–170 | 2 | $C_{15}H_{17}ON$ | 6.16 | 6.35 |
| 2-$C_5H_4N$ | *p*-$CH_3C_6H_4$ | H | I (II) | 34 (49) | | 146–152 | 1 | $C_{13}H_{13}ON$ | 7.03 | 7.12 |
| 2-$C_5H_4N$ | *m*-$CH_3C_6H_4$ | H | I (II) | 25 (29) | 105–106 | | | $C_{13}H_{13}ON$ | 7.03 | 7.17 |
| 2-$C_5H_4N$ | *p*-$CH_3OC_6H_4$ | H | I (II) | 32 (33) | 133–134[c] | | | $C_{13}H_{13}O_2N$ | 6.51 | 6.68 |
| 2-$C_5H_4N$ | *p*-$(CH_3)_2NC_6H_4$ | H | I | 23 | | 146–152 | 0.5 | $C_{14}H_{16}ON_2$ | 12.27 | 12.75 |
| 2-$C_5H_4N$ | 3,4-$CH_2O_2C_6H_3$ | H | I (II) | 19 (26) | 142–142.5 | | | $C_{13}H_{11}O_3N$ | 6.11 | 6.27 |
| 2-$C_5H_4N$ | *o*-$ClC_6H_4$ | H | II | 45 | 63–64 | 136–140 | 1 | $C_{12}H_{10}ONCl$ | 6.38 | 6.39 |
| 2-$C_5H_4N$ | *p*-$ClC_6H_4$ | H | II | 37 | 80–81 | | | $C_{12}H_{10}ONCl$ | 6.38 | 6.28 |
| 2-$C_5H_4N$ | 3,4-$(OCH_3)_2C_6H_3$ | H | II | 2.5 | | 180–185 | 1.5 | $C_{14}H_{15}O_3N$ | 5.72 | 5.88 |
| 2-$C_5H_4N$ | $C_6H_5CH_2$ | H | I | 9 | 104–105 | | | $C_{13}H_{13}ON$ | 7.03 | 6 98 |
| 2-$C_5H_4N$ | $C_6H_5CH_2CH_2$ | H | I | 20 | | 148–152 | 1 | $C_{14}H_{15}ON$ | 6.57 | 6.81 |
| 2-$C_5H_4N$ | 2-$C_4H_3S$ | H | I | 16.5 | | 139 | 1 | $C_{10}H_9OSN$ | 7.33 | 7.41 |
| 2-$C_5H_4N$ | *n*-$C_3H_7$ | H | I | 34 | | 94–98 | 1 | $C_9H_{13}ON$ | 9.27 | 10.15 |
| 3-$C_5H_4N$ | $C_6H_5$ | H | I | 36 | | 180–182 | 2.5 | $C_{12}H_{11}ON$ | 7.56 | 7.70 |
| 2-$C_5H_4N$ | $C_6H_5$ | $CH_3$ | III (II) | 76.5 (17) | | 133–136 | 0.5[d] | $C_{13}H_{13}ON$ | 7.03 | 7.27 |
| 2-$C_5H_4N$ | *p*-$ClC_6H_4$ | $CH_3$ | II | 13 | | 134–138 | 0.5 | $C_{13}H_{12}ONCl$ | Cl, 15.18 | 15.15 |
| 2-$C_5H_4N$ | $C_6H_5$ | $C_6H_5$ | II | 14.5 | 105.5–106[e] | | | | | |
| 2-$C_5H_4N$ | 2-$C_5H_4N$ | $CH_3$ | II | 17 | 46–47 | 109–112 | 1 | $C_{12}H_{12}ON_2$ | 13.99 | 13.89 |
| 2-$C_5H_4N$ | 2-$C_4H_3S$ | $CH_3$ | II | 12 | 49–50 | | | $C_{11}H_{11}OSN$ | 6.82 | 6.88 |
| 3-$C_5H_4N$ | $C_6H_5CH_2$ | $CH_3$ | III | 47 | | 160–165 | 2 | $C_{14}H_{15}ON$ | 6.57 | 6.51 |
| 3-$C_5H_4N$ | $C_6H_5$ | $CH_3$ | III | 60.5 | 92–93 | | | $C_{13}H_{13}ON$ | 7.03 | 7.26 |

[a] Yields are based on a limited number of experiments and do not necessarily represent the maximum obtainable. [b] Ref. 9, m. p. 78°. [c] Ref. 9, m. p. 131.5°. [d] Ref. 9 described this compound as distilling at 152.5° (745 mm.); ref. 7b gives b. p. 301–303° and m. p. 32°. [e] Ref. 9, m. p. 105°.

this reaction are the desired carbinol, pyridine and carbon dioxide. Although the yields are reported to be rather low, the ease of operation and isolation of the carbinols renders the method a useful synthetic procedure. However, it appeared advisable to study the conditions for the preparation of a typical carbinol, since the published procedures make no mention of the effects of solvents or the ratio of reactants on yields.

Method I: $2BrC_5H_4N + C_2H_5Br + Mg \longrightarrow 2C_5H_4N—MgBr$

Method II: $2\text{-}C_5H_4N—COOH + RCHO \longrightarrow C_5H_4N—\underset{\displaystyle R}{\underset{|}{C}}HOH$ (RCHO)

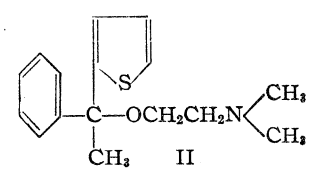
$2\text{-}C_5H_4N\text{-}COOH + RCOCH_3 \longrightarrow C_5H_4N—\underset{\displaystyle CH_2}{\underset{|}{\overset{\displaystyle R}{\overset{|}{C}}}}—OH$

Method III: $C_5H_4N—COCH_3 + RMgBr$

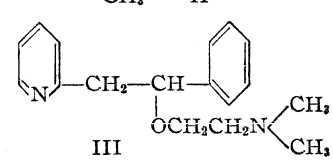
R = aryl or heterocyclic radical.

In the case of *p*-tolyl-2-pyridylcarbinol, the yield of carbinol is greatest when the ratio of aldehyde to picolinic acid is 6:1 and *p*-cymene at reflux temperature is used as solvent. Ashworth, *et al.*,[9] have used no solvent and a ratio of aldehyde to picolinic acid of 3:1 and 8:1 with no apparent increase in yield. It has been established that *p*-cymene is definitely superior to no solvent and to xylene. The optimum reaction time was found to be six hours and the yield of carbinol was not increased when the reaction was run for sixteen hours or when a nitrogen atmosphere was used.

In the course of this investigation, attempts to obtain 1-phenyl-1-(2-thienyl)-1-(β-dimethylaminoethoxy)-ethane (II) and 1-phenyl-1-(β-dimethylaminoethoxy)-2-(2-pyridyl)-ethane (III) were unsuccessful. In the case of II, instead of the expected tertiary carbinol, the Grignard reaction between bromobenzene and 2-acetylthiophene gave 1-phenyl-1-(2-thienyl)-ethylene, dehydration of the carbinol occurring notwithstanding precautions to remove traces of acid from the reaction product. The reaction of 1-phenyl-2-(2-pyridyl)-ethanol with β-dimethylaminoethyl chloride with sodium amide gave α-stilbazole and none of the expected ether, III.




II




III

**Pharmacology.**—The alkamine ethers listed in Table II have been tested for antihistaminic activity by the intravenous injections of lethal doses of histamine diphosphate one-half to one hour after the intravenous administration of the drug under test.

The most active compounds are the 2-pyridyl

TABLE II

ALKAMINE ETHERS $RR'R''—C(R''')_2—OCH_2CH_2N(R''')_2$

| No. | R | R′ | R″ | R‴ | Yield,[a] % | B. p. °C. | Mm. | Formula | N Analyses, % Calcd. | Found | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2-$C_5H_4N$ | $C_6H_5$ | H | $CH_3$ | 82 | 158–162 | 1.5 | $C_{16}H_{20}ON_2$ | 10.93 | 10.71 | |
| 2 | 3-$C_5H_4N$ | $C_6H_5$ | H | $CH_3$ | 69 | 149–153 | 1 | $C_{16}H_{20}ON_2$ | 10.93 | 11.02 | |
| 3 | 2-$C_5H_4N$ | *p*-*i*-$C_3H_7C_6H_4$ | H | $CH_3$ | 84 | 165–167 | 0.5 | $C_{19}H_{26}ON_2$ | 9.39 | 8.94 | |
| 4 | 2-$C_5H_4N$ | *p*-$CH_3C_6H_4$ | H | $CH_3$ | 88 | 156–160 | 1 | $C_{17}H_{22}ON_2$ | 10.36 | 10.35 | |
| 5 | 2-$C_5H_4N$ | *m*-$CH_3C_6H_4$ | H | $CH_3$ | 72 | 155–159 | 0.5 | $C_{17}H_{22}ON_2$ | 10.36 | 9.70 | 9.61[b] |
| 6 | 2-$C_5H_4N$ | *p*-$CH_3OC_6H_4$ | H | $CH_3$ | 86 | 168–172 | 0.5 | $C_{17}H_{22}O_2N_2$ | 9.78 | 9.71 | |
| 7 | 2-$C_5H_4N$ | *p*-$(CH_3)_2N$-$C_6H_4$ | H | $CH_3$ | 61 | 168–172 | 2.5 | $C_{18}H_{25}ON_3$ | 14.03 | 13.46 | 13.34[b] |
| 8 | 2-$C_5H_4N$ | 3,4-(—$OCH_2O$—)$C_6H_3$ | H | $CH_3$ | 45 | 176–180 | 1 | $C_{17}H_{20}O_3N_2$ | 9.34 | 9.05 | |
| 9 | 2-$C_5H_4N$ | *o*-$ClC_6H_4$ | H | $CH_3$ | 28 | 152–156 | 2 | $C_{16}H_{19}ON_2Cl$ | 9.64 | 8.98 | 8.94[b] |
| 10 | 2-$C_5H_4N$ | *p*-$ClC_6H_4$ | H | $CH_3$ | 47[c] | 164–167 | 2 | $C_{16}H_{19}ON_2Cl$ | 9.64 | 9.35 | |
| 11 | 2-$C_5H_4N$ | $C_6H_5CH_2$ | H | $CH_3$ | 63 | 138–142 | 0.5 | $C_{17}H_{22}ON_2$ | 10.36 | 10.14 | |
| 12 | 2-$C_5H_4N$ | $C_6H_5CH_2CH_2$ | H | $CH_3$ | 56 | 178–180 | 0.5 | $C_{18}H_{24}ON_2$ | 9.85 | 9.62 | |
| 13 | 2-$C_5H_4N$ | 2-$C_4H_3S$ | H | $CH_3$ | 22 | 145 | 1 | $C_{14}H_{18}ON_2$ | 10.68 | 11.03 | |
| 14 | 2-$C_5H_4N$ | *n*-$C_3H_7$ | H | $CH_3$ | 47 | 103–105 | 0.2 | $C_{13}H_{22}ON_2$ | 12.60 | 12.61 | |
| 15 | 2-$C_5H_4N$ | $C_6H_5$ | H | $C_2H_5$ | 82 | 147–150 | 0.5 | $C_{18}H_{24}ON_2$ | 9.85 | 9.97 | |
| 16 | 2-$C_5H_4N$ | *p*-$CH_3C_6H_4$ | H | $C_2H_5$ | 50[c] | 162–165 | 1 | $C_{19}H_{26}ON_2$ | 9.39 | 9.75 | |
| 17 | 2-$C_5H_4N$ | *p*-$CH_3C_6H_4$ | H | [e] | 70 | 143–147 | 0.5 | $C_{18}H_{24}ON_2$ | 9.88 | 9.80 | |
| 18 | 3-$C_5H_4N$ | $C_6H_5$ | $CH_3$ | $CH_3$ | 87 | 160–161 | 1.5 | $C_{17}H_{22}ON_2$ | 10.36 | 9.92 | |
| 19 | 2-$C_5H_4N$ | $C_6H_5$ | $CH_3$ | $CH_3$ | 46 | 137–141 | 0.5 | $C_{17}H_{22}ON_2$[d] | 10.36 | 10.93 | |
| 20 | 2-$C_5H_4N$ | *p*-$ClC_6H_4$ | $CH_3$ | $CH_3$ | 66 | 155–159 | 1 | $C_{17}H_{21}ON_2Cl$ | Cl, 11.63 | 11.24 | |
| 21 | 3-$C_5H_4N$ | $C_6H_5CH_2$ | $CH_3$ | $CH_3$ | 76 | 170–173 | 1 | $C_{18}H_{24}ON_2$ | 9.85 | 9.19 | 9.19[b] |

[a] The yields are not calculated on the basis of recovered carbinol. [b] Low nitrogen analyses are due to traces of unreacted carbinol which could not be removed by repeated fractionation. [c] Some decomposition occurred during distillation. [d] At present in clinical use under the trade name "Decapryn." [e] The dialkylaminoalkyl residue is either $—CHCH_2N(CH_3)_2$ | $CH_3$ or $—CH_2—CH(CH_3)—N(CH_3)_2$ | $CH_3$ or both. Compare Schultz, Robb and Sprague, THIS JOURNAL, 69, 188 (1947); 69, 2454 (1947).

derivatives in which R′ is phenyl or an alkoxy, alkyl, halogen or dimethylamino substituted phenyl group, R″ is hydrogen or a methyl group and R‴ is methyl. These compounds, group I, (1, 3, 4, 5, 6, 7, 10, 19 and 20) have exhibited antihistaminic activity comparable to that of the presently available preparations. The oral LD/50 in mice was approximately 300–400 mg./kg.

Lower antihistaminic activity is exhibited by the 3-pyridyl compounds (2, 18 and 21) and the 2-pyridyl compounds wherein R′ is 3,4-methylenedioxybenzene (8), benzyl (11), phenethyl (12), 2-thienyl (13), *n*-propyl (14); or wherein R″ is $C_2H_5$ (15 and 16). Variations in the length of the carbon chain of the ether also result in decreased potency (17). In general, these compounds possess $^1/_5$ to $^1/_{100}$ the activity of the group I compounds. A detailed pharmacological report will appear elsewhere.

## Experimental

**Method I. 2-Pyridyl-*p*-isopropylphenylcarbinol.**[8]—In a one-liter, three-necked flask equipped with a Hershberg tantalum stirrer, condenser and dropping funnel, there were placed 19.2 g. (0.8 mole) of magnesium turnings and 200 cc. of anhydrous ether. To the stirred mixture was added 20 g. (0.2 mole) of ethyl bromide. After the ethyl bromide had reacted, 64 g. (0.4 mole) of 2-bromopyridine was added dropwise at a rate which produced rapid reflux. The suspension was refluxed and stirred for an additional three hours. To the brown reaction mixture was added 89.5 g. (0.6 mole) of *p*-isopropylbenzaldehyde in 100 cc. of ether and the mixture was refluxed for ten hours. After decomposing the complex with cold, dilute hydrochloric acid, the aqueous acid layer was separated, made alkaline with gaseous ammonia and extracted with ether. The ether layer was dried over sodium sulfate, filtered, the ether removed and the residue distilled.

**Method II. 2-Pyridyl-*p*-tolylcarbinol**[9].—In a five-liter, three-necked flask equipped with a stirrer, condenser and nitrogen inlet tube, there were placed 100 g. of picolinic acid, 600 g. of *p*-tolualdehyde and 600 cc. of *p*-cymene. The reaction mixture was refluxed and stirred for six hours under nitrogen. The initial vigorous evolution of carbon dioxide subsided within a few hours. The solution was cooled and extracted with several portions of dilute hydrochloric acid. The aqueous acid layer was made alkaline with gaseous ammonia and the oil which separated was extracted with ether. The alkamine ether was isolated as described under Method I.

**Method III. 2-Pyridylphenylmethylcarbinol.**—In a 500-cc., three-necked flask, equipped with a stirrer, condenser and dropping funnel, there were placed 200 cc. of anhydrous ether and 4.4 g. (0.18 mole) of magnesium turnings. To the stirred mixture was added dropwise 28.2 g. (0.18 mole) of bromobenzene in 50 cc. of ether. The reaction mixture was then stirred and refluxed for one hour. After cooling the mixture, 20 g. (0.17 mole) of 2-acetylpyridine was added and a heavy white precipitate separated. After refluxing for several hours, the reaction mixture was decomposed with dilute hydrochloric acid and ice. The acid layer was separated, made alkaline with gaseous ammonia and extracted with ether. Isolation of the alkamine ether was carried out as described under Method I.

The alkamine ethers listed in Table II were prepared essentially as described for phenyl-2-pyridylmethyl-β-

N,N-dimethylaminoethyl ether (19): In a 500-cc., three-necked flask equipped with a stirrer, condenser and dropping funnel, containing a suspension of sodium amide (from 6.74 g. (0.29 mole) of sodium) in 250 cc. of dry xylene, there was added cautiously at 0° 53 g. (0.286 mole) of phenyl-2-pyridylmethylcarbinol. A vigorous evolution of ammonia occurred and the resulting deep blue reaction mixture was heated for several hours on the steam-bath. Then 32.5 g. (0.30 mole) of β-N,N-dimethylaminoethyl chloride was added and the reaction mixture heated for approximately eighteen hours on the steam-bath. During this time, the deep blue color of the sodium salt of the carbinol was discharged and a turbid brown mixture resulted. The excess sodium amide was decomposed with water, the xylene layer was separated and, after drying, was evaporated *in vacuo*. The crude alkamine ether was fractionated.

The following procedures were used in an attempt to secure ethers II and III. To phenylmagnesium bromide (48.7 g. bromobenzene) in 150 cc. ether, there was added 37.8 g. of 2-acetylthiophene. The reaction product yielded 23.3 g. of a pale yellow liquid, b. p. 100–108° (0.5 mm.).

*Anal.* Calcd. for $C_{12}H_{10}S$: C, 77.35; H, 5.41. Found: C, 77.26; H, 5.44. The residue from the distillation yielded 13.1 g. of a viscous material, b. p. 185–245 (0.5 mm.) which resinified on standing.

To a sodium amide suspension, from 1.2 g. of a sodium in 250 cc. of toluene, there was added at room temperature 10 g. of 1-phenyl-2-(2-pyridyl)-ethanol. The reaction mixture was heated with stirring on the steam-bath for two hours and then 9 g. of β-dimethylaminoethyl chloride was added. The condensation was carried out in the usual manner and the product distilled; yield 8.4 g.; b. p. 158–162° (2.5 mm.); m. p. 90–91° after recrystallization from aqueous ethanol, mixed m. p. with an authentic sample of α-stilbazole, 90–91°.

**Acknowledgment.**—We are grateful to Dr. Richard Tislow and Mrs. Annette LaBelle for the pharmacological data reported herein.

## Summary

A series of pyridyl-substituted alkamine ethers has been synthesized from pyridyl substituted carbinols and dialkylaminoalkyl halides. In general, the 2-pyridyl substituted alkamine ethers showed a high order of antihistaminic activity whereas the corresponding 3-pyridyl compounds were relatively less active.

BLOOMFIELD, N. J. RECEIVED SEPTEMBER 15, 1948

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Quinolines. VII. Some 3-Methylquinolines

BY EDGAR A. STECK AND LOUIS L. HALLOCK[1]

Potential antimalarials of the 4-amino-3-methylquinoline type have been the subject of considerable investigation in these laboratories.[2-6] The bulk of these studies[2,5] was concerned with the influence of the variation of substituents in the benzenoid moiety upon the schizontocidal action of 4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline derivatives. In the present contribution there are presented data relating to the preparation of 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline and certain experiences in the synthesis of other 3-methylquinolines which were terminated prior to completion because other work intervened.

The preparation of 4-chloro-7-ethoxy-3-methylquinoline, required for reaction with 4-diethylamino-1-methylbutylamine, was accomplished by a modification of the Conrad-Limpach synthesis.[2d] In the cyclization of the anil from 3-phenetidine and ethyl α-ethoxalylpropionate, only one quinoline ester appeared to be formed (*cf.* ref. 2c, d and 5), as in the case of the related methoxy series.[7] The structure of the series (notice Table I) could not be proved unequivocally, for several attempts to oxidize[2c,d] the ethoxy-4-hydroxy-3-methylquinoline or related 2-carboxylic acid gave only 3-phenetidine. There was no comment as to difficulty in the proof of structure of the 7-methoxy analog by oxidation,[7] but the facile decarboxylation of several anthranilic acids has been recorded in the literature recently,[8,9] including 4-methoxyanthranilic acid. The 7-position is assigned to the ethoxy group on the basis that only one product resulted from the pyrolytic cyclization (*cf.* ref. 7) and the ease with which the oxidation product decarboxylated to 3-phenetidine (*cf.* ref. 9).

The work on 3,5/7-dimethylquinoline derivatives was halted when it was learned that Hauser, *et al.*,[7] were engaged in similar studies. 3-Toluidine was employed as the starting material in the Conrad-Limpach synthesis, and the preparation discontinued at the 4-chloro-3,5/7-dimethylquinoline stage. The structure of the series, shown in Table I, was proven by the catalytic dehalogenation of one of the 4-chloroquinoline derivatives to the corresponding dimethylquinoline, previously prepared by Manske.[10] It was of interest that the lower-melting isomer of the 4-chloroquinoline type, here an oil, was the one bearing a methyl group in position 7 (*cf.* ref. 5).

(1) Present address: Commercial Solvents, Inc., Terre Haute, Ind.

(2) Steck, Hallock and Holland, THIS JOURNAL, **68**, (a) p. 129 (1946), (b) p. 132, (c) p. 380, (d) p. 1241.

(3) Huber, Bair, Laskowski, Jackman and Clinton, *ibid.*, **68**, 322 (1946).

(4) Kwartler and Lucas, *ibid.*, **68**, 2395 (1946).

(5) Steck, Hallock, Holland and Fletcher, *ibid.*, **70**, 1012 (1948).

(6) Steck, Hallock and Suter, *ibid.*, **70**, 4063 (1948).

(7) Hauser and co-workers, *ibid.*, **68**, 1232 (1946).

(8) Surrey and Cutler, *ibid.*, **68**, 2570 (1946).

(9) Stephen, Tonkin and Walker, *J. Chem. Soc.*, 1034 (1947).

(10) Manske, Marion and Leger, *Canadian J. Res.*, **20B**, 133 (1942).

TABLE I

SOME 3-METHYLQUINOLINE DERIVATIVES

| 3-Methyl-quinoline | Yield, %[a] | Appearance | Solvent[b] | M. p., °C.[c] | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| Ethyl 4-hydroxy-3-methylquinoline-2-carboxylates | | | | | | | | | | |
| 7-Ethoxy | 69[d] | White needles | E | 182.5–183 | 65.44 | 6.23 | 5.09 | 65.48 | 6.18 | 5.30 |
| 5-Methyl | 37 | White prismatic needles | E | 196.2–196.8 | 68.55 | 6.17 | 5.71 | 68.54 | 6.06 | 5.71 |
| 7-Methyl | 43 | Fine white needles | aAc | 159.5–160 | | | | 68.45 | 6.26 | 5.70 |
| 4-Hydroxy-3-methylquinoline-2-carboxylic Acids | | | | | | | | | | |
| 7-Ethoxy | 96 | Yellowish platelets | Pg | 245–245.5 d. | 63.15 | 5.30 | 5.67 | 63.23 | 5.00 | 5.64 |
| 5-Methyl | 95 | White needles | aE | 242–243 d. | 66.25 | 5.10 | 6.45 | 66.10 | 5.04 | 6.88 |
| 7-Methyl | 98 | Pale yellow needles | E | 231–232 d. | | | | 66.02 | 5.42 | 6.54 |
| 4-Hydroxy-3-methylquinolines | | | | | | | | | | |
| 7-Ethoxy | 86 | White needles | E | 254–254.5 | 70.92 | 6.45 | 6.89 | 70.69 | 6.54 | 7.05 |
| 5-Methyl | 81 | Fibrous white needles | aE | 270–271[e] | 76.27 | 6.40 | 8.09 | 76.16 | 6.28 | 8.25 |
| 7-Methyl | 88 | White microcrystals | aE | 217–218 | | | | 76.43 | 6.24 | 7.91 |
| 4-Chloro-3-methylquinolines | | | | | | | | | | |
| 7-Ethoxy | 84 | White prismatic needles | SA | 93.5–94 | 65.01 | 5.46 | 6.32 | 65.22 | 5.06 | 6.58 |
| 5-Methyl | 88 | White prisms | S, SA | 62–62.5[g] | 68.94 | 5.26 | 7.31 | 68.86 | 5.63 | 7.68 |
| 7-Methyl | *ca.* 85 | Oil[f] | | | | | | | | |

[a] Yield as employed in next step, being well-purified at ester stage. [b] Legend: Ac = acetone; E = ethanol; Pg = propylene glycol; S = sublimed; SA = Skellysolve A; a = aqueous. [c] Note reference 14; d. = decomposes. [d] Much tar formed during the cyclization. [e] Previously reported by Hauser, *et al.*; the 4-hydroxy compound was recorded as having m. p. 260–261° and the 4-chloro body had m. p. 59–60.5°. [f] Converted directly into the picrate, golden needles from acetone, m. p. 217–218°. *Anal.* Calcd. for $C_{11}H_{10}ClN$, $C_6H_3N_3O_6$: N, 13.36. Found: N, 13.10.

In the hope of obtaining some compounds bearing the 8-iodo-5-methoxy-3-methylquinoline nucleus, 3-amino-4-iodoanisole[11] was condensed with ethyl α-ethoxalylvalerate and cyclized in Dowtherm A.[12,2d] The loss of iodine was noted throughout all of the attempts to form the quinoline ring bearing the desired groups. Purification of the product of cyclization gave only ethyl 4-hydroxy-methoxy-3-methylquinoline-2-carboxylate, as indicated by analyses and comparison with a sample prepared after the method of Hauser.[7]

A re-examination of certain data relating to previous investigations on bz-iodo-3-methylquinolines[2d] was deemed of interest because the iodomethoxy type had a labile iodine atom. The compound formed by the action of 5% sodium hydroxide upon ethyl 4-hydroxy-5-iodo-3-methylquinoline-2-carboxylate was found to contain iodine when boiled with sodium and amyl alcohol. Analyses on this substance were not concordant, as earlier noted.[2d] When the acid was decarboxylated, a loss of iodine did occur, but the analyses indicated an impure substance. At last, treatment with phosphorus oxychloride gave a small amount of 4-chloro-3-methylquinoline[2a] after extensive purification by crystallization and sublimation.

The only compound herein reported which was screened as an antimalarial was 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline (SN-13,573[13]). This compound, although fairly low in activity, was superior to the related methoxy derivative (SN 10,566) and the 6- and 8-ethoxy-4(4-diethylamino-1-methylbutylamino)-3-methylquinolines[2a,b] (SN 9,082 and 12,348).

## Experimental[14]

**7-Ethoxy-3-methylquinolines.**—The application of the Conrad–Limpach synthesis to 3-phenetidine and ethyl α-ethoxalylpropionate followed the usual pattern, and data relating to the intermediates are presented in Table I. Several attempts to prove the structure of these compounds unequivocally by oxidative means[2c,d] failed because the resulting anthranilic acid decarboxylated readily to give only 3-phenetidine. The reaction of 4-chloro-7-ethoxy-3-methylquinoline with 4-diethylamino-1-methylbutylamine in phenol[2] at 170° led to a 76% yield of the 4-(4-diethylamino-1-methylbutylamino) compound. 4-(4-Diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline, SN-13,573, was obtained as a golden oil which boiled at 180–186° (0.05 mm.).

*Anal.* Calcd. for $C_{21}H_{33}N_3O$: C, 73.43; H, 9.68; N, 12.33. Found: C, 73.45; H, 9.58; N, 12.29.

**3,5/7-Dimethylquinolines.**—The synthesis of both the 3,5- and 3,7-dimethylquinolines here proceeded from 3-toluidine and ethyl α-ethoxalylpropionate in the customary manner. Hauser, *et al.*,[7] prepared several 3,5-dimethylquinoline derivatives through dehalogenation of 8-chloro-4-hydroxy-3,5-dimethylquinoline. In the present case, the isomeric ethyl 3,5- and 3,7-dimethyl-4-hydroxyquinoline-2-carboxylates proved to be rather recalcitrant of separation. The high-melting isomer, the 3,7-dimethyl compound, was less soluble in 70% acetone, while

(11) During the compilation of these data, the preparation of this compound was reported: Frank, Fanta and Tarbell, THIS JOURNAL, **70**, 2319 (1948).

(12) A commercial heat-transfer liquid consisting of 73.5% diphenyl ether and 26.5% diphenyl.

(13) All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey have been systematically tabulated, together with the antimalarial activities, in "Antimalarial Drugs, 1941–1945" (F. Y. Wiselogle, editor), Edwards Bros., Ann Arbor, Mich., 1946.

(14) The melting points and boiling points reported are uncorrected values.

the other was best crystallized from alcohol. In Table I are listed the properties of the compounds involved in proceeding to the 3,5- and 3,7-dimethyl-4-chloroquinolines. The structure of the two series was clarified by dehalogenation of the 4-chloro compound of m.p. 59.5–60° in alcohol containing one equivalent of sodium hydroxide employing Busch–Stöve catalyst[15] under 50 lb./sq. in. hydrogen pressure. The crude product was directly converted to the picrate, which melted at 221° after crystallization from acetone. Manske, *et al.*[10] have given the melting point of 3,5-dimethylquinoline picrate as 220° while that salt of 3,7-dimethylquinoline melted at 244°.

**3-Amino-4-iodoanisole in the Conrad–Limpach Synthesis.**—4-Amino-3-nitroanisole was diazotized and treated with potassium iodide after the manner of Reverdin[11,16,17] to give 4-iodo-3-nitroanisole in 86–92% crude yield. It crystallized from Skellysolve C or aqueous alcohol as orange needles, m.p. 62.5–63°. The reduction of the nitro group was best accomplished by the method of West[11,18] using aqueous ethanol as the solvent. Crude yields of 65–73% resulted, the 3-amino-4-iodoanisole being a reddish-brown oil. The crude material was used in subsequent work, for while a trial batch gave a fair recovery of a reddish liquid, b.p. *ca.* 90–115° (0.2 mm.), another sample exploded when distillation was attempted, much iodine vapor being noted afterward. This occurrence has also been witnessed recently by Tarbell, *et al.*[11]

The condensation of crude 3-amino-4-iodoanisole with ethyl α-ethoxalylpropionate was carried out in the usual manner, the product resulting in 69–80% yield. All attempts to cyclize the anil in Dowtherm A led to copious evolution of iodine vapor. When the crude reaction product was crystallized from ethanol and from acetone several times, using Darco G-60 liberally, fine white needles were obtained, m.p. 192–192.5°. Analysis and mixed melting point with an authentic sample (prepared from 3-anisidine by the method described by Hauser, *et al.*[7]) showed this compound to be ethyl 4-hydroxy-7-methoxy-3-methylquinoline-2-carboxylate. The yields obtained (from the anil) were 52–66%.

(15) Busch and Stöve, *Ber.*, **49**, 1064 (1916).

(16) Reverdin, *ibid.*, **29**, 2595 (1896).

(17) Hata, Tatematsu and Kubota, *Bull. Chem. Soc.* (*Japan*), **10**, 425 (1935).

(18) West, *J. Chem. Soc.*, 494 (1925).

*Anal.* Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; N, 5.37. Found: C, 64.45; H, 6.06; N, 5.36.

**Further Study of 5-Iodo-3-methylquinolines.**—In a previous contribution in this series,[2d] it was reported that a halogen-free compound, m.p. 251° dec., was obtained by the action of boiling 5% caustic upon ethyl 4-hydroxy-5-iodo-3-methylquinoline-2-carboxylate. This substance was re-examined and found to contain iodine when boiled with *n*-amyl alcohol and sodium for some while. The low solubility of the material in the common solvents led to the use of 2-methyl-2,4-pentanediol, but satisfactory analyses could not be obtained. Decarboxylation of the yellow acid in either Dowtherm A or mineral oil led to a white solid which melted vaguely around 286° after crystallization from alcohol. This alleged 4-hydroxy-5-iodo-3-methylquinoline failed to give concordant analyses, but merely indicated that more iodine was lost during the reaction. Ultimately, the 4-hydroxy-3-methylquinoline type so obtained was interacted with phosphorus oxychloride. The result of extensive purification of the product by crystallization from Skellysolve B and sublimation was a small quantity of white needles, m.p. 61.5–62.5°, which was free of iodine. A melting point of 60° has been reported for 4-chloro-3-methylquinoline.[2a]

**Acknowledgment.**—The authors wish to express their appreciation to Mrs. N. P. Gorman, Mr. E. V. Ryan and Mr. A. J. Holland for technical assistance. All analyses were carried out by the analytical staff of this Institute under the direction of Mr. M. E. Auerbach.

## Summary

The preparation of 4-(4-diethylamino-1-methylbutylamino)-7-ethoxy-3-methylquinoline from 3-phenetidine has been described.

The properties of a number of 3,5- and 3,7-dimethylquinoline derivatives have been reported and the structures proven. Certain experiences with iodinated compounds in the Conrad–Limpach synthesis have been described.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 20, 1948

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AND THE SCHOOL OF NUTRITION AT CORNELL UNIVERSITY]

# Pteridines. IV. Derivatives of 2,4-Diamino-6,7-diphenylpteridine[1]

BY C. K. CAIN, E. C. TAYLOR, JR., AND LOUISE J. DANIEL

In the course of a study of substituted pteridines, it was found that those compounds which have amino groups in both the 2- and 4-positions of the pteridine nucleus exhibit a high degree of antifolic acid activity against several bacteria.[2,3] However, the diaminopteridines studied showed very low solubility in water and in all of the common organic solvents tested. Since it appeared desirable to have available for biological testing compounds of this type which could be administered in aqueous solution, several experiments have been carried out to modify these compounds in such a way that solubility in water or alcohol would result with the retention of a high degree of antifolic acid activity.

Of the various pteridines previously reported,[4] 2,4-diaminophenanthro(9,10-e)pteridine had the maximum antifolic acid activity against *S. faecalis*. The preparation of a derivative of this compound having a sulfonic acid group on the phenanthrene nucleus has been carried out. The resulting compound is fairly soluble in aqueous sodium bicarbonate solution but shows very little antifolic acid activity. Since it was thought for a variety of reasons that 2,4-diamino-6,7-diphenyl-

(1) The work presented in this paper was undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and was aided by a grant to Cornell University by the Nutrition Foundation, Inc., New York City. It represents a part of a collaborative project on "Newer Members of the B Group of Vitamins."

(2) Daniel, Norris, Scott and Heuser, *J. Biol. Chem.*, **169**, 689 (1947).

(3) Daniel and Norris, *ibid.*, **170**, 747 (1947).

(4) Mallette, Taylor and Cain, THIS JOURNAL, **69**, 1814 (1947).

TABLE I

SOLUBILITY CHARACTERISTICS AND INHIBITORY INDICES OF SYNTHETIC PTERINS

| Compound | Name | Solubility[a] $H_2O$ | $C_2H_5OH$ | 0.1 *N* HCl | 0.1 *N* NaOH | Inhibitory index *vs. S. faecalis*[b] |
|---|---|---|---|---|---|---|
| 1 | 2,4-Diamino-6,7-diphenylpteridine | I | s | S | I | 10 |
| 2 | 2-Amino-4-acetamido-6,7-diphenylpteridine | I | SS | S | Hyd. | 30 |
| 3 | 2,4-Diacetamido-6,7-diphenylpteridine | I | S | I | Hyd. | 60 |
| 4 | 2-Amino-4-methylamino-6,7-diphenylpteridine | I | SS | S | s | 4500 |
| 5 | 2,4-Diamino-6,7-bis-(*p*-aminophenyl)-pteridine | I | S | SS | I | 3500 |
| 6 | 2,4-Diamino-6,7-bis-(*p*-acetamidophenyl)-pteridine | I | S | S | Hyd. | 10,000 |
| 7 | 2,4-Diamino-6,7-bis-(*p*-sulfitomethylaminophenyl)-pteridine, disodium salt | SS | I | s | SS | 8000 |
| 8 | 2,4-Diamino-6,7-bis-(*p*-sulfinomethylaminophenyl)-pteridine, disodium salt | SS | I | s | SS | 5000 |
| 9 | 2,4-Diacetamido-6,7-bis-(*p*-acetamidophenyl)-pteridine | I | SS | S | Hyd. | 150,000 |
| 10 | 2,4-Diamino-6,7-bis-(*p*-hydroxyphenyl)-pteridine | s | s | S | SS | 3500 |
| 11 | 2,4-Diamino-6,7-bis-(*m*-nitrophenyl)-pteridine | I | I | I | I | 70 |
| 12 | 2,4-Diamino-6,7-bis-(*m*-aminophenyl)-pteridine | I | S | SS | I | 500 |
| 13 | 2,4-Diamino-6,7-bis-(*m*-sulfinomethylaminophenyl)-pteridine, disodium salt | S | I | s | SS | 3000 |
| 14 | 2,4-Diaminophenanthro(9,10-e)pteridine-8(or 11)-sulfonic acid | s | s | I | SS | 50,000 |
| 15 | 2,4-Diaminophenanthro-(9,10-e)pteridine | I | I | I | I | 2 |

[a] Solubility expressed as follows: SS, greater than 10 mg./ml.; S, 1–10 mg./ml.; s, 0.1–1 mg./ml.; I, less than 0.1 mg./ml. [b] Ratio of concentration of inhibitor (pterin) to the concentration of metabolite (folic acid) at which complete inhibition of growth of the organism occurs.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF SYNTHETIC PTERINS

| Compound | | Maxima mμ | Maxima Log ε | Minima mμ | Minima Log ε |
|---|---|---|---|---|---|
| 1 | (d) | 267 | 4.25 | 250 | 4.14 |
| | | 370 | 4.19 | 318 | 3.54 |
| 2 | | 257 | 4.29 | 247 | 4.28 |
| | (a) | 288 | 4.26 | 279 | 4.25 |
| | | 370 | 4.08 | 332 | 3.76 |
| | (b) | 274 | 4.22 | 255 | 4.12 |
| | | 365 | 4.19 | 318 | 3.69 |
| 3 | (c) | 278 | 4.27 | 257 | 4.18 |
| | | 365 | 4.27 | 321 | 3.81 |
| 4 | (d) | 275 | 4.28 | 253 | 4.13 |
| | | 374 | 4.27 | 325 | 3.64 |
| | (e) | 285 | 4.37 | 257 | 4.13 |
| | | 395 | 4.15 | 336 | 3.48 |
| 5 | (d) | 267 | 4.29 | 247 | 4.13 |
| | | 367 | 4.22 | 315 | 3.59 |
| | | 235 | 4.35 | 247 | 4.31 |
| | (e) | 263 | 4.38 | 360 | 3.75 |
| | | 415 | 4.17 | | |
| 6 | | 268 | 4.44 | 240 | 4.31 |
| | (a) | 295 | 4.45 | 280 | 4.39 |
| | | 400 | 4.13 | 355 | 3.75 |
| | (b) | 274 | 4.22 | 255 | 4.21 |
| | | 370 | 4.12 | 330 | 3.80 |
| 7 | (d) | 267 | 4.07 | 247 | 3.94 |
| | | 365 | 3.97 | 315 | 3.43 |
| | | 230 | 4.17 | 225 | 4.16 |
| | (e) | 262 | 4.19 | 248 | 4.10 |
| | | 415 | 3.95 | 360 | 3.55 |
| 8 | (f) | 275 | 4.22 | 260 | 4.20 |
| | | 423 | 4.03 | 369 | 3.83 |
| | (e) | 265 | 4.25 | 248 | 4.21 |
| | | 415 | 4.03 | 363 | 3.76 |
| 9 | (a) | 265 | 4.53 | 235 | 4.41 |
| | | 400 | 4.25 | 353 | 3.81 |
| | (b) | 274 | 4.33 | 255 | 4.27 |
| | | 370 | 4.24 | 330 | 3.87 |
| 10 | (d) | Shoulder at 245–255 | 4.35 | 345 | 3.76 |
| | | 392 | 4.12 | | |
| | | 240 | 4.34 | 225 | 4.30 |
| | (e) | 275 | 4.32 | 258 | 4.30 |
| | | 432 | 4.13 | 370 | 3.84 |
| 11 | (g) | 268 | 4.54 | 245 | 4.39 |
| | | 365 | 4.26 | 320 | 3.83 |
| 12 | (d) | 294 | 4.08 | 288 | 3.92 |
| | | 369 | 4.15 | 321 | 3.70 |
| | (e) | 225 | 4.55 | 325 | 3.78 |
| | | Shoulder at 255–265 | 4.29 | | |
| | | 380 | 4.11 | | |
| 13 | (d) | 262 | 4.14 | 250 | 4.11 |
| | | 368 | 4.00 | 322 | 3.64 |
| | (e) | 230 | 4.35 | | |
| | | 390 | 3.90 | 340 | 3.67 |
| 14 | | Shoulder at 243–255 | 3.44 | | |
| | (e) | 265 | 3.46 | 355 | 3.42 |
| | | 428 | 4.01 | | |

Solvents for absorption spectra

[a] Methyl alcohol. [b] Methyl alcohol made 0.1 *N* in hydrochloric acid. [c] Ethylene glycol made 0.1 *N* in hydrochloric acid. [d] 0.1 *N* Hydrochloric acid. [e] 0.1 *N* Sodium hydroxide. [f] Water. [g] 1 *N* Hydrochloric acid.

pteridine would be a more suitable molecule to modify for solubility, several compounds have been prepared which might be considered as derivatives of this parent molecule. These compounds, together with their absorption spectra in solution, some solubility characteristics and antifolic acid activity against *S. faecalis*, are listed in Tables I and II.

Inspection of Table I leads to several interesting conclusions in regard to the relation of structure and antifolic acid activity. First, there seems to be no direct correlation between alcohol solubility, which we assume is related to lipid solubility, and antifolic acid activity. Extreme examples of this may be found in Compounds 2 and 9 of Table I. Second, acetylation of the amino groups in either the 4- or both the 2- and 4-positions of the pteridine ring has very little effect on the activity, the difference between the mono- and the diacetate probably being one of ease of hydrolysis by the organism. Third, substitution on the phenyl group, regardless of the nature of the substituting group, decreases the activity. Moreover, the position of the substituent on the phenyl group also has a marked effect on the activity, as shown by Compounds 5 and 12. Fourth, the introduction of any of the various water-solubilizing groups employed results in a considerable decrease in the activity, as shown by Compounds 7, 8 and 13. Fifth, replacement of the 4-amino group by a 4-methylamino group lowers the activity, as shown by Compounds 1 and 4.

It is also of interest to point out that the replacement of phenyl groups in the 6- and 7-positions of the pteridine nucleus by *p*-aminophenyl groups affects the reactivity of the amino groups in the 2- and 4-positions. As described in the Experimental Section, acetylation of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine under mild conditions gives the tetraacetyl derivative, all four of the amino groups present in the molecule being attacked. In contrast to this behavior, the acetylation of the 4-amino group of 2,4-diamino-6,7-diphenylpteridine requires rather vigorous conditions while the acetylation of both the 2- and 4-amino groups in this compound requires much more strenuous conditions.

The assignment of structure of the monoacetyl derivative of 2,4-diamino-6,7-diphenylpteridine as 2-amino-4-acetamido-6,7-diphenylpteridine is based upon a comparison of the absorption spectrum of this compound with that of 2-amino-4-methylamino-6,7-diphenylpteridine.

## Experimental

**2-Amino-4-acetamido-6,7-diphenylpteridine.**—A mixture of 1.0 g. of 2,4-diamino-6,7-diphenylpteridine and 50 ml. of acetic anhydride was heated under reflux for sixteen hours, the acetic anhydride removed by distillation under reduced pressure, and the residue taken up in 100 ml. of boiling alcohol and filtered. The dark orange filtrate was treated twice with Norit and the alcohol concentrated to 15 ml. on a steam-bath. Addition of 75 ml. of hot water and cooling gave 620 mg. (55%) of a light yellow microcrystalline solid. It was recrystallized by dissolving in alcohol, adding hot water to the point of precipitation, and allowing to cool slowly. On heating, the compound melts slowly at 140–150° to a clear red liquid.

*Anal.* Calcd. for $C_{20}H_{16}N_6O$: N, 23.6. Found: N, 23.6.

**2,4-Diacetamido-6,7-diphenylpteridine.**—A solution of 0.5 g. (0.0016 mole) of 2,4-diamino-6,7-diphenylpteridine in 3 ml. of concentrated sulfuric acid was treated with 10 ml. of acetic anhydride and the clear red solution heated on a steam-bath for one hour. It was then poured onto ice, diluted to 100 ml. with water and allowed to stand at 0° for one day. The light yellow solid was filtered off and washed first with water and then with alcohol. Recrystallization by dissolving in boiling dimethylformamide, adding hot water to precipitation and cooling gave 0.43 g. (68%) of a light yellow microcrystalline solid, which decomposed slowly on heating above 190°.

*Anal.* Calcd. for $C_{20}H_{18}N_6O_2$: C, 66.3; H, 4.6; N, 21.1. Found: C, 66.5; H, 4.8; N, 21.2.

**2-Amino-4-chloro-6,7-diphenylpteridine Hydrochloride.**—A suspension of 1.0 g. (0.0032 mole) of dry 2-amino-4-hydroxy-6,7-diphenylpteridine in 60 ml. of freshly distilled phosphorus oxychloride containing 5 g. of phosphorus pentachloride was refluxed for two hours in an oil-bath to give a clear red solution. After filtering through a sintered glass filter, the solvent was removed by distillation under diminished pressure and the excess phosphorus pentachloride destroyed by addition of ice. After standing for one-half hour, the bright yellow solid was filtered off and washed thoroughly with water to give 0.95 g. (81%). All attempts to recrystallize it resulted in the hydrolysis of the 4-chloro group to give 2-amino-4-hydroxy-6,7-diphenylpteridine.

**2-Amino-4-methylamino-6,7-diphenylpteridine.**—A mixture of 1.0 g. (0.002 mole) of 2-amino-4-chloro-6,7-diphenylpteridine hydrochloride, 30 ml. of alcohol, and 10 ml. of methylamine was heated in a glass bomb at 155° for sixteen hours. After cooling, the reaction mixture was filtered and the clear yellow filtrate evaporated to dryness under diminished pressure. The yellow residue was extracted with hot 0.5 *N* hydrochloric acid and filtered. The filtrate was treated with Norite and adjusted to *p*H 9 with ammonium hydroxide. The resulting precipitate was crystallized by dissolving in hot alcohol and adding hot water to the point of precipitation which gave 0.27 g. (27%) of bright yellow crystals in the form of rectangular platelets exhibiting parallel extinction and melting at 237–238° (cor.).

*Anal.* Calcd. for $C_{19}H_{16}N_6$: C, 69.5; H, 4.9; N, 25.6. Found: C, 69.6; H, 5.0; N, 25.8.

**2,4-Diamino-6,7-bis-(*p*-aminophenyl)-pteridine.**—To a solution of 2.00 g. (0.0084 mole) of 2,4,5,6-tetraminopyrimidine sulfate in 90 ml. of water was added 2.00 g. (0.0049 mole) of *p,p'*-diaminobenzil sulfate,[5] and the mixture refluxed for one hour to give a clear, cherry red solution. After treatment with Norit, it was poured into boiling dilute ammonium hydroxide of sufficient strength so that the final solution was distinctly alkaline (*p*H 11). Orange crystals of the desired product separated at once. After filtering, washing with water, and drying, 1.73 g. (quantitative) was obtained. Recrystallization from 50% ethanol gave bright orange prisms exhibiting parallel extinction, and decomposing sharply at 308–309° (cor.).

*Anal.* Calcd. for $C_{18}H_{16}N_8$: C, 62.8; H, 4.7; N, 32.6. Found: C, 63.0; H, 4.6; N, 32.6.

**2,4-Diamino-6,7-bis-(*p*-acetamidophenyl)-pteridine.**—A solution of 1.10 g. (0.00785 mole) of 2,4,5,6-tetraminopyrimidine in 75 ml. of water and a solution of 1.35 g. (0.00417 mole) of *p,p'*-diacetamidobenzil in 100 ml. of ethanol were mixed and refluxed for seven hours. After treatment with Norit, the ethanol was removed by dis-

(5) We should like to express our thanks to Calco Chemical Division of American Cyanamid Company for this material.

tillation under reduced pressure. Upon cooling and filtering, 1.46 g. (82%) of yellow crystals was obtained. Recrystallization from 50% aqueous acetic acid gave small, slender needles showing oblique extinction, m. p. 234–237° (cor.).

*Anal.* Calcd. for $C_{22}H_{20}N_8O_2$: C, 61.7; H, 4.7; N, 26.2. Found: C, 61.4; H, 4.8; N, 26.2.

**2,4-Diamino-6,7-bis-(*p*-hydroxymethylaminophenyl)-pteridine.**—To a suspension of 0.1 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in 4 ml. of boiling water, sufficient concentrated hydrochloric acid was added to cause solution, and then 0.2 ml. of 40% formaldehyde was added slowly. The addition product separated at once. The mixture was adjusted to *p*H 7.5 with sodium bicarbonate, cooled to 0°, filtered, and washed thoroughly with water to give 115 mg. (quantitative) of the bright orange product. The solid did not melt below 300°.

**2,4-Diamino-6,7-bis-(*p*-sulfitomethylaminophenyl)-pteridine Disodium Salt.**—The product obtained above was suspended in 30 ml. of water and 0.15 g. of sodium bisulfite added. The mixture was refluxed for three hours to give a clear, light red solution. Removal of three-quarters of the water by distillation under reduced pressure and addition of two volumes of acetone precipitated 0.148 g. (88%) of the orange product. The solid did not melt below 300°.

**2,4-Diamino-6,7-bis-(*p*-sulfinomethylaminophenyl)-pteridine Disodium Salt.**—To a solution of 0.8 g. (0.00232 mole) of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in 200 ml. of ethanol was added 0.65 g. of finely powdered sodium formaldehyde sulfoxylate and 50 mg. of sodium hydroxide, and the mixture heated under reflux on a steam-bath for six hours. During this time, the sulfoxylate gradually dissolved and a bright orange solid separated. The reaction mixture was cooled to 0° and the product filtered off and washed thoroughly with hot alcohol to yield 0.96 g. (76%). The solid did not melt below 300°. No satisfactory method of recrystallization could be found. The structure is assigned on the basis of absorption spectrum and ready solubility in water.

**2,4-Diacetamido-6,7-bis-(*p*-acetamidophenyl)-pteridine.**—A mixture of 0.2 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine, 1.9 ml. of glacial acetic acid, and 3.2 ml. of acetic anhydride was heated for forty-five minutes at 80°. Addition of 100 ml. of water caused the separation of a flocculent, light yellow solid, which was collected by filtration, washed with ice cold water, and recrystallized from water to give 0.18 g. (56%). The product was dried for analysis at 140° under vacuum over phosphorus pentoxide, but retained one molecule of water of recrystallization.

*Anal.* Calcd. for $C_{26}H_{24}N_8O_4 \cdot H_2O$: C, 58.9; H, 4.9; N, 21.1. Found: C, 59.0; H, 4.8; N, 20.8.

**2,4-Diamino-6,7-bis-(*p*-hydroxyphenyl)-pteridine.**—(a) To an ice-cold solution of 0.2 g. of 2,4-diamino-6,7-bis-(*p*-aminophenyl)-pteridine in a mixture of 7 ml. of water and 0.8 ml. of concentrated sulfuric acid was added slowly a solution of sodium nitrite in water until an excess of nitrous acid was present (starch–iodide paper). The excess nitrous acid was destroyed with urea and the reaction mixture was immersed in a water-bath at 60° for fifteen minutes and finally at 100° for one hour. Five ml. of water was added, and the yellow solid filtered off and washed with water to give 0.14 g. (71%). It was purified by dissolving in dilute sodium hydroxide, treating with Norite, and pouring into hot dilute hydrochloric acid, and was finally recrystallized from water to give a yellow microcrystalline solid. (b) A solution of 0.5 g. (0.002 mole) of *p,p'*-dihydroxybenzil, 1.0 g. (0.0045 mole) of 2,4,5,6-tetraminopyrimidine bisulfite, 20 ml. of ethyl methyl ketone, 20 ml. of ethanol, 40 ml. of water, and 6 ml. of concentrated hydrochloric acid was refluxed for sixteen hours. The clear yellow solution was then treated with Norit and concentrated by distillation under reduced pressure until a bright yellow product separated out. It was filtered off, washed with cold water, and recrystallized from water to give 0.6 g. (84%) of a light yellow microcrystalline solid. The absorption spectrum of this product was identical with that obtained by method (a) above.

*Anal.* Calcd. for $C_{18}H_{14}N_6O_2$: C, 62.4; H, 4.1. Found: C, 62.7; H 4.1.

**2,4-Diamino-6,7-bis-(*m*-nitrophenyl)-pteridine.**—A solution of 3.0 g. (0.0214 mole) of 2,4,5,6-tetraminopyrimidine and 2.0 g. (0.0066 mole) of 3,3'-dinitrobenzil in a mixture of 70 ml. of ethanol and 15 ml. of ethyl methyl ketone was refluxed for three hours. The heavy yellow solid which had separated from the reaction mixture was filtered off, washed with boiling water, and recrystallized by dissolving in a small amount of glacial acetic acid, treating with Norit, and pouring into a ten-fold excess of boiling water. The product weighed 2.3 g. (quantitative). After two additional recrystallizations, the product was obtained in the form of thin rods and sheets showing oblique extinction, m. p., 307–308° (cor.).

*Anal.* Calcd. for $C_{18}H_{12}N_8O_4$: N, 27.7. Found: N, 27.5.

**2,4-Diamino-6,7-bis-(*m*-aminophenyl)-pteridine.**—A solution of 1.0 g. (0.0025 mole) of 2,4-diamino-6,7-bis-(*m*-nitrophenyl)-pteridine in 75 ml. of ethanol containing 5 drops of concentrated hydrochloric acid was shaken with hydrogen at 2.5 atmospheres pressure with platinum oxide catalyst at room temperature. After one hour, reduction was complete, and the yellow reaction mixture was filtered and evaporated to dryness. The residue was dissolved in 15 ml. of water, treated with Norit, and the product precipitated by addition of ammonium hydroxide to give 0.55 g. (65%). After a partial purification by redissolving in dilute hydrochloric acid and precipitating by addition of ammonium hydroxide, the compound was recrystallized from dilute ammonium hydroxide to give an orange-yellow microcrystalline solid. It slowly decomposed on heating above 180°.

*Anal.* Calcd. for $C_{18}H_{16}N_8$: C, 62.8; H, 4.7; N, 32.6. Found: C, 62.6; H, 4.6; N, 32.7.

**2,4-Diamino-6,7-bis-(*m*-sulfinomethylaminophenyl)-pteridine Disodium Salt.**—A boiling solution of 0.04 g. (0.000116 mole) of 2,4-diamino-6,7-bis-(*m*-aminophenyl)-pteridine in 75 ml. of absolute alcohol was treated with 0.013 g. (0.00011 mole) of sodium formaldehyde sulfoxylate, and the mixture refluxed for two hours. The white sodium formaldehyde sulfoxylate gradually disappeared, while at the same time an orange solid deposited. After cooling, filtering, and washing with boiling absolute alcohol, 51 mg. (85%) of the desired product was obtained. The material was hygroscopic and rapidly formed the trihydrate in contact with air.

*Anal.* Calcd. for $C_{20}H_{18}N_8Na_2O_4S_2 \cdot 3H_2O$: C, 40.1; H, 4.0; N, 18.7. Found: C, 39.7; H, 4.5; N, 18.7.

**2,4-Diaminophenanthro(9,10-e)pteridine-8-(or 11)-sulfonic Acid.**—A solution of 5.0 g. (0.0225 mole) of 2,4,5,6-tetraminopyrimidine bisulfite in 20 ml. of 0.5% sodium hydroxide was added to a solution of 5.0 g. (0.0174 mole) of phenanthrenequinone-3-sulfonic acid in 130 ml. of water and the resulting deep green mixture refluxed for thirty minutes. At the end of this time the color had changed to a deep cherry red. The reaction mixture was treated with Norit and acidified to *p*H 5 with concentrated hydrochloric acid. The bright yellow solid which separated was collected by filtration and washed with water followed by acetone to give 6.0 g. (88%). The product was purified by dissolving in dilute alkali, treating with Norit, and adding an equal volume of 40% sodium hydroxide. The crystalline sodium salt so obtained was dissolved in water and poured into hot dilute hydrochloric acid to give a light yellow microcrystalline product. It does not melt below 360°.

*Anal.* Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.1; H, 3.1. Found: C, 55.2; H, 3.0.

## Summary

1. A number of derivatives of 2,4-diamino-6,7-

diphenylpteridine have been prepared for the purpose of finding a soluble derivative which would retain a high degree of antifolic acid activity.

The absorption spectra of these compounds in solution, some of their solubility characteristics and their inhibitory indices against *S. faecalis* are reported.

2. It has been found that a sulfinomethylamino group confers water solubility with the retention of antifolic acid activity. The introduction into the 2,4-diamino-6,7-diphenylpteridine molecule of any of the solubilizing groups investigated results in some lowering of antifolic acid activity.

3. Several conclusions have been drawn regarding the effect on antifolic acid activity of certain structural changes in the 2,4-diamino-6,7-diphenylpteridine molecule.

Ithaca, New York Received September 27, 1948

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[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

# Piperidine Derivatives. XX. The Preparation and Reactions of 1-Methyl-3-piperidone

By S. M. McElvain and John F. Vozza

The recent report[1] on the reactions of 1-methyl-4-piperidone, particularly those with a variety of aromatic aldehydes, indicated a study of similar reactions with the unsymmetrical isomer, 1-methyl-3-piperidone (VI). The preparation of this latter compound from 1-methyl-4-carbethoxy-3-piperidone (V), obtained by the cyclization of the diester (IV) was reported earlier[2] from this Laboratory. It seemed of special interest to determine the reactivity of VI in the presence of basic catalysts inasmuch as the previous workers[2] had shown that, due to the relative inertness of the α-aminomethylene group, the cyclization of IV produced the keto-ester V rather than the isomer, 1-methyl-2-carbethoxy-3-piperidone.

In the earlier work[2] the diester IV was prepared by the interaction of ethyl γ-bromobutyrate with sarcosine ester. In the present work a more satisfactory preparation of IV has been developed from butyrolactone, which is now commercially available.[3] The complete series of reactions from this lactone to the piperidone VI is

$$\underset{\text{OCH}_2\text{CH}_2\text{CH}_2\text{CO}}{\text{OCH}_2\text{CH}_2\text{CH}_2\text{CO}} \xrightarrow[280°]{\text{CH}_3\text{NH}_2} \underset{\text{I (90–93\%)}}{\text{CH}_3\text{NCH}_2\text{CH}_2\text{CH}_2\text{CO}} \xrightarrow{\text{HCl}}$$

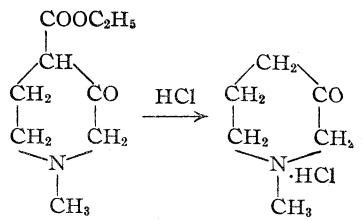
$$\text{HCl}\cdot\text{CH}_3\text{NHCH}_2\text{CH}_2\text{CH}_2\text{COOH} \xrightarrow{\text{KOH}}$$

$$\underset{\text{II (91\%)}}{\text{CH}_3\text{NHCH}_2\text{CH}_2\text{CH}_2\text{COOK}} \xrightarrow[\text{KOH}]{\text{ClCH}_2\text{COOK}}$$

$$\underset{\text{III}}{\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{COOK})(\text{CH}_2\text{COOK})} \xrightarrow[2.\ \text{NH}_3]{1.\ \text{C}_2\text{H}_5\text{OH} + \text{HCl}}$$

$$\text{CH}_3\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{COOC}_2\text{H}_5)(\text{CH}_2\text{COOC}_2\text{H}_5) \xrightarrow{\text{NaOC}_2\text{H}_5}$$

IV (37–46% from II)




V (74%) VI (100%)

The sequence from II to IV was found necessary, as it was not possible to obtain an ester of II; all attempts to prepare the ester gave the pyrrolidone (I). The amino-acid, however, is quite stable in the form of its salts II and III. The cyclization of IV was found to proceed most satisfactorily with sodium ethoxide; sodium hydride, which produced excellent yields of 1-methyl-3-carbethoxy-4-piperidone,[1] gave very poor yields (*ca.* 10%) of V.

The condensation of benzaldehyde with VI in alkaline, 60% ethanol was rapid and a crystalline product, which gave analytical values approximating an equimolecular mixture of the 4-carbinol (VII) and the 4-benzal derivative (VIII), was obtained in approximately 70% yield. No other products could be separated from this reaction. This mixture of VII and VIII could not be separated by recrystallization; a product with a constant melting range, 123–128°, was obtained. However, when this material was converted to the hydrochloride salts, the free bases liberated into ether, and the resulting solution concentrated, the benzal derivative VIII, m. p. 112–113°, separated. From the ether filtrate the carbinol VII was obtained as a glass, which gave a crystalline hydrochloride that melted at 192–202°, indicating that it was a mixture of the two possible racemates. Two other observations are worthy of note: (a) an ethereal solution of the carbinol VII containing a small amount of the benzal derivative (VIII) gave, on standing, a crystalline precipitate, m. p. 123–128°, and (b) this latter product also separated from an alkaline 60% ethanol solution of VII on

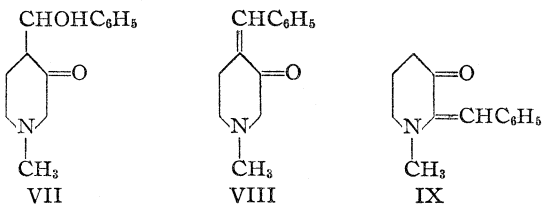
(1) McElvain and Rorig, This Journal, **70**, 1820 (1948).

(2) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(3) From the Cliffs Dow Chemical Company, Marquette, Michigan.

standing. These results lead to the conclusion that this reaction product is a molecular complex of VII and VIII, which is destroyed when the components are converted to their hydrochlorides, and which forms sufficiently slowly to permit separation of the components immediately after their liberation from the non-associated salts.

Both VII and VIII show a similar instability (as indicated by rapid darkening) to light and air as has been noted[2] for the free base of VI. The structures of VII and VIII were shown by their reduction to 1-methyl-4-benzylpiperidine, derivatives of which were compared to those obtained from an authentic sample prepared from 4-benzylpyridine.




VII VIII IX

The carbinols VII are as resistant to dehydration as are those obtained from 1-methyl-4-piperidone.[1] The 4-benzal derivative (VIII), however, is readily hydrated to VII, treatment of a moist ethereal solution of VIII with hydrogen chloride being sufficient to effect the reaction. This peculiar reactivity of the benzal linkage of VIII was noticeable in its hydrogenation: in alcohol solution it absorbed hydrogen very slowly and incompletely, while in dioxane solution it was rapidly, but incompletely, hydrogenated, possibly because of a complex formation between a hydroxylic reduction product and unchanged VIII.

The condensation of benzaldehyde with VI in an ethanolic solution of hydrogen chloride was much slower than the base catalyzed reaction. The dark-colored reaction product was readily recrystallized to colorless crystals, m. p. 165–166°, the analyses of which were corresponded to a monobenzal derivative of VI. This purified material was obtained in 43% yield, and no other product could be isolated from the reaction mixture. In spite of the narrow melting range of this salt it was shown to be a mixture of the hydrochlorides of VIII and the isomeric 2-benzal derivative IX by the following reactions: (a) conversion of the salt to the free base produced a pale-yellow oil that could not be induced to crystallize (VIII melts at 112–113°), but was reconverted to the original hydrochloride mixture, m. p. 164–165°, by hydrogen chloride; (b) reduction failed to give a single 1-methyl-benzylpiperidine, but a product, the methiodide of which had properties similar to a mixture of the methiodides of 1-methyl-2- and 1-methyl-4-benzylpiperidines; (c) the picrate of the reduction product behaved as a mixture of authentic picrates of 1-methyl-2- and -4-benzylpiperidines that contained a higher proportion of the 4-isomer.

The exclusive formation of the 4-derivatives of 1-methyl-3-piperidone with an alkaline catalyst indicates that the reactivity of the 2-methylene group is inhibited by the attached basic nitrogen as is the acetic ester–methylene group[2] of IV in the Dieckmann cyclization. In acid medium, however, some of the 2-derivative (IX) is formed, which indicates that a positive charge on the nitrogen of the piperidone promotes reaction at the 2-position. It is also of interest to note that none of the dibenzal derivative, which was the main or exclusive product with 1-methyl-4-piperidone,[1] could not be isolated from any of the reactions of benzaldehyde with VI.

It also seemed of interest to determine the behavior of the 3-piperidone toward such a Grignard reagent as phenylmagnesium bromide. With this reagent, the isomeric 1-methyl-2-piperidone is reported[4] to yield the dehydration product, 1-methyl-2-phenyl-1,4,5,6-tetrahydropyridine, of the expected tertiary carbinol when the initial Grignard reaction product is decomposed with acids. Under these conditions, however, the 1-methyl-4-phenyl-4-hydroxypiperidine may be obtained from the 4-piperidone.[5] The 3-piperidone (VI) behaves as does its 4-isomer with phenylmagnesium bromide. The carbinol, 1-methyl-3-phenyl-3-hydroxypiperidine, was obtained in 59% yield as a viscous oil, which, because of its sensitivity to air, was analyzed in the form of the methiodide. The hydrochloride of this compound was readily acetylated to the corresponding 3-acetoxy derivative.

## Experimental

**1-Methyl-2-pyrrolidone (I).**—A steel bomb containing 172 g. (2 moles) of butyrolactone[3] was placed in a bath of acetone and Dry Ice. After the bomb and its contents were thoroughly cooled, 124 g. (4 moles) of liquid methylamine was added, the bomb closed and heated at 280° for four hours. After removing the excess methylamine with the aspirator, the reaction mixture was distilled, yielding 175–185 g. (90–93%) of 1-methyl-2-pyrrolidone,[6] b. p. 201–202°.

The hydrochloride of I, precipitated from ether with hydrogen chloride and recrystallized from absolute ethanol,[2] melted at 86–88°.

**γ-N-Methylaminobutyric Acid Hydrochloride (II).**—A solution containing 179 g. (1.8 moles) of 1-methyl-2-pyrrolidone and 250 ml. of concentrated hydrochloric acid was refluxed in an oil-bath for eight hours. The water and excess acid then were removed at diminished pressure on the steam-bath. The solid residue was shaken with 250 ml. of cold, dry acetone, which does not dissolve the amino-acid hydrochloride but facilitates its subsequent crystallization from ethanol. Crystallization from ethanol yielded 250 g. (90%) of colorless crystals, m. p. 120–121°.[7]

Several attempts to esterify the secondary amino-acid hydrochloride (II) by heating it in the presence of ethanolic hydrogen chloride failed to yield the desired ester. Also various attempts to form the N-benzoyl derivative of II by the Schotten–Baumann reaction and modified versions of this general procedure failed to give the desired product.

(4) Lee, Ziering, Heineman and Berger, *J. Org. Chem.*, **12**, 885 (1947).

(5) Jensen and Lundquist, *Dansk. Tidsskr. Farm.*, **17**, 173 (1943). *C. A.*, **40**, 4086 (1946).

(6) Späth and Lintner, *Ber.*, **69**, 2727 (1936).

(7) Gansser, *Z. physiol. Chem.*, **61**, 59 (1909).

TABLE I

1-METHYL-2-BENZYLPIPERIDINE (A), 1-METHYL-4-BENZYLPIPERIDINE (B) AND DERIVATIVES

| Compound | B. p., °C. (mm.) | M. p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. I | Found C | Found H | Found I |
|---|---|---|---|---|---|---|---|---|---|
| A | 128–129 (13)[a,b,c] | ..... | ..... | ... | .. | .. | ... | .. | .. |
| Picrate of A | ..... | 180–181[b,c] | ..... | ... | .. | .. | ... | .. | .. |
| Methiodide of A | ..... | 225–226[d] | $C_{14}H_{22}IN$ | 50.75 | 6.65 | 38.4 | 50.65 | 6.52 | 38.1 |
| Hydriodide of A | ..... | 120–121 | $C_{13}H_{20}IN$ | ... | .. | 40.1 | ... | .. | 40.0 |
| B | 125–126 (7) | ..... | ..... | ... | .. | .. | ... | .. | .. |
| Picrate of B | ..... | 184–186 | $C_{19}H_{22}N_4O_7$ | 54.54 | 5.26 | .. | 54.24 | 5.46 | .. |
| Methiodide of B | ..... | 206–207 | $C_{14}H_{22}IN$ | 50.75 | 6.65 | 38.4 | 50.86 | 6.54 | 38.0 |
| Hydriodide of B | ..... | 128–129 | $C_{13}H_{20}IN$ | ... | .. | 40.1 | ... | .. | 40.2 |

[a] Anker, Cook and Heilbron, *J. Chem. Soc.*, 917 (1945). [b] Ref. 4. [c] Bryans and Pyman, *J. Chem. Soc.*, 549 (1929). [d] This compound was obtained also when an ethereal solution of 2-benzylpiperidine was treated with methyl iodide. Anker, *et al.*,[a] p. 918, report a similar product, but state that they obtained 1-methyl-2-benzylpiperidine (A) from it on treatment with sodium hydroxide. This is obviously an error, as the methiodide, m. p. 226°, is not converted to A by alkali as is the hydroiodide, m. p. 120–121°.

**Ethyl γ-(Methyl-N-carbethoxymethylamino)-butyrate (IV).**—To a 5-l. three-necked flask, equipped with a dropping funnel and mechanical stirrer and immersed in an ice–salt-bath, was added a solution of 358 g. (6.4 moles) of potassium hydroxide in 200 ml. of water. When the alkaline solution had cooled to 0°, a solution of 246 g. (1.6 moles) of II in 800 ml. of absolute ethanol was added slowly, and the temperature of the stirred mixture kept below 12°. A solution of 154 g. (1.6 moles) of monochloroacetic acid in 200 ml. of absolute ethanol then was added at such a rate that the temperature of the reaction mixture did not rise above 12°. The contents of the flask was allowed to warm slowly to room temperature as the ice melted, and stirring was continued for forty-eight hours. The reaction mixture then was made distinctly acid to congo red with hydrochloric acid and filtered to remove the potassium chloride that had separated from solution. The filtrate was taken to dryness under reduced pressure on the steam-bath, leaving a clear, light-brown, semi-solid material. This was dissolved in 500 ml. of absolute ethanol, and the solution was added to 1800 ml. of absolute ethanol that had been saturated with hydrogen chloride. The mixture was shaken vigorously and allowed to stand at room temperature for two days, after which it was refluxed on the steam-bath for *only* two hours, as it was found that a longer period of heating was unfavorable to the yield. After the reflux period, the alcohol and excess hydrogen chloride were removed under reduced pressure on the steam-bath until only a thick viscous mass remained in the flask. The flask and its contents then were cooled in an ice-bath and 200 ml. of ether added, after which a solution of liquid ammonia in ether was added slowly until a strong odor of ammonia persisted. Each addition of ammonia was accompanied by vigorous stirring and agitation in order to bring about intimate contact between the ether layer and the more dense lower layer. The liberation of IV was accompanied by the precipitation of ammonium chloride. After an excess of ammonia had been added, the liquid was decanted from the precipitated solid and the latter extracted with three 100-ml. portions of ether; it was necessary to centrifuge the ether–salt suspension to separate the ether in the last extraction. After removing the ether and residual alcohol, the product was distilled through a Vigreux column under reduced pressure. The forerun, principally 1-methyl-2-pyrrolidone (I), was collected up to 131° (10 mm.); it amounted to about 25% of the starting salt (II). The diester (IV) was collected at 133–137° (10 mm.); $n^{25}D$ 1.4380, and weighed 135 g. The residue in the flask was dissolved in ethanol and treated with excess hydrogen chloride. After separating a small amount of ammonium chloride, a white crystalline material was recovered from the ethanol solution. This material was found to be the hydrochloride of a half-ester of the dibasic acid of IV. Its melting point, 121–122°, was similar to that of II (120–121°), but a mixture of equal parts of these two salts melted at 92–103°.

*Anal.* Calcd. for $C_9H_{18}ClNO_4$: Cl, 14.8; N, 5.8. Found: Cl, 14.6; N, 5.2.

By re-esterifying this half-ester hydrochloride and processing the esterification mixture according to the procedure described above, an additional 35 g. of IV was obtained. The total amount, 170 g., represents a 46% yield.

The ethereal solution of ammonia was used to liberate IV from its hydrochloride, as it was found that aqueous solutions of alkali bases resulted in considerably lower yields of the product.

**1-Methyl-2- and 1-Methyl-4-benzylpiperidines.**—2-Benzylpiperidine and 4-benzylpiperidine were prepared by the hydrogenation[8] of the corresponding benzylpyridines.[9] These piperidines were N-methylated catalytically over copper–chromium oxide.[10] 4-Benzylpiperidine was also methylated with methyl iodide. The properties and analyses of these tertiary amines and their derivatives are listed in Table I.

**The Base-catalyzed Condensation of Benzaldehyde with 1-Methyl-3-piperidone (VI).**—To a solution of 10 g. (0.067 mole) of VI[2] in 70 ml. of 60% ethanol were added 7 g. (0.067 mole) of freshly purified benzaldehyde and 7.5 g. of solid potassium hydroxide. The mixture was shaken vigorously for fifteen minutes during which time a yellow, crystalline material separated. The reaction mixture then was allowed to stand in the dark at room temperature for four days. After separating the solid material by filtration, the filtrate was diluted with 100 ml. of water, causing a cloudiness to develop in the solution. As only a small amount of oil (0.1 g.) had separated after several days, it was discarded. The crude, yellow solid, m. p. 109–121° dec. was dissolved in ether to separate it from the potassium chloride which had crystallized from solution with it. After two recrystallizations from absolute ether, the yellow material attained a constant melting point range, 123–128° dec. and weighed 10.7 g.

*Anal.* Calcd. for $C_{13}H_{15}NO$ (VIII): C, 77.58; H, 7.51. Calcd. for $C_{13}H_{17}NO_2$ (VII): C, 71.20; H, 7.82. Found: C, 74.06; H, 7.65.

A solution of 9.2 g. of the product, m. p. 123–128°, from the preceding experiment in 300 ml. of absolute ether was treated with an excess of hydrogen chloride. This treatment caused the yellow color of the solution to disappear and a white solid separated, leaving a clear, colorless supernatant liquid. A solution of this hydrochloride in 25 ml. of water was treated with an excess of potassium carbonate and the liberated water-insoluble free base taken up in 50 ml. of ether. This solution was concentrated to the point where crystals began to separate from solution and then cooled for an hour in the refrigerator. The white, crystalline **1-methyl-4-benzal-3-piperidone (VIII)**, m. p. 112–113°, that separated weighed 4.0 g.

(8) Adkins, *et al.*, THIS JOURNAL, **56**, 2425 (1934).

(9) Crook, *ibid.*, **70**, 416 (1948).

(10) Schwoegler and Adkins, *ibid.*, **61**, 3499 (1939).

*Anal.* Calcd. for $C_{13}H_{15}NO$: C, 77.58; H. 7.51. Found: C, 77.68; H, 7.34.

The ether filtrate, from which VIII had been separated, was treated with hydrogen chloride. A white precipitate of 4.9 g. of **phenyl-4-(1-methyl-3-keto-piperidyl)-carbinol (VII) hydrochloride**, m. p. 192–202° dec., separated.

*Anal.* Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.06; Cl, 13.9. Found: C, 60.84; H, 6.88; Cl, 13.6.

This hydrochloride was also obtained from the monobenzal derivative (VIII). A solution of 100 mg. of VIII in 50 ml. of moist ether was treated with an excess of hydrogen chloride. A white solid, m. p. 176–197° dec., separated from solution. This product gave the following analysis: C, 61.21; H, 6.98.

**1-Methyl-4-benzal-3-piperidone (VIII) from VII.**—A solution of 0.8 g. of the hydrochloride of VII in 5 ml. of 60% ethanol was treated with 0.3 g. of solid potassium hydroxide. After shaking the mixture vigorously for fifteen minutes, it was allowed to stand in the dark for four days. From the reaction mixture 0.38 g. of the product, m. p. 124–128°, was obtained. The hydrochloride (0.4 g.) of this material, after conversion to the free base yielded 0.15 g. of VIII, m. p. 111–113°, by the procedure described above.

**Reduction of 1-Methyl-4-benzal-3-piperidone (VIII) to 1-Methyl-4-benzylpiperidine.**—A solution of 1.0 g. of VIII in 50 ml. of dixoane was hydrogenated over 0.5 g. of Raney nickel at room temperature and atmospheric pressure. The initial absorption of hydrogen was very rapid but became slower after the first five minutes. Addition of another portion (0.3 g.) of catalyst did not increase the rate of hydrogenation. At the end of thirty minutes, when 67% of the theoretical amount of hydrogen had been absorbed, the hydrogenation stopped. After removing the catalyst, the solution was taken to dryness under reduced pressure on the steam-bath. The residue was dissolved in 10 ml. of dilute hydrochloric acid and placed in a 50-ml. flask, which contained 2.0 g. of amalgamated zinc (prepared by shaking zinc with a solution of 0.1 g. of mercuric chloride in 10 ml. of water and 1 ml. of hydrochloric acid). The reaction mixture was refluxed for three hours during which time 8 ml. of hydrochloric acid was added in four 2-ml. portions. The solution then was decanted from the unreacted zinc amalgam and treated with excess solid potassium carbonate. The aqueous solution was shaken with ether and the supernatant liquids decanted from the inorganic salt. After shaking the suspension with 30 ml. of ether, the mixture was filtered and the precipitate washed several more times with ether. The aqueous solution was extracted twice more with ether and discarded. After drying the ether solution of the amine over anhydrous sodium sulfate, it was concentrated to 10 ml., a few drops of ethanol added, and then treated with methyl iodide. A solid, m. p. 158–208°, separated from solution. After four recrystallizations from ethanol, the product melted at 200–205°. A mixture of this material and an authentic sample of 1-methyl-4-benzylpiperidine methiodide (m. p. 206–207°) melted at 203–208°.

A solution of 4 g. of VIII in 35 ml. of dioxane absorbed two equivalents of hydrogen at 3000 p. s. i. of hydrogen at 250° over 1 g. of copper–chromium oxide. After separating the catalyst, the solvent was removed under reduced pressure on the steam-bath, leaving a light-brown, semi-solid material. A solution of 0.5 g. of this product in 15-ml. of colorless hydriodic acid was heated in a sealed tube at 250° from three hours. After cooling, the tube was opened and the reaction mixture was transferred to a 50-ml. flask. It was heated to about 50° and then treated with solid sodium sulfite until the solution became colorless and the water-insoluble material that had formed during the heating went into solution. The colorless solution then was treated with excess potassium hydroxide and extracted with two 25-ml. portions of ether. After drying the ether solution over anhydrous sodium sulfate, it was concentrated to 10 ml., a few drops of ethanol were added, and then it was treated with methyl iodide. An oil separated on standing; it was dissolved in a small amount of ethanol, and after adding a few drops of ether it was set aside. After several hours a solid, m. p. 185–197°, was deposited. After two crystallizations from an ethanol–ether mixture, it melted at 200–204°. A mixture of this product and the methiodide of 1-methyl-4-benzylpiperidine melted at 201–206°.

**Reduction of VII to 1-Methyl-4-benzylpiperidine.**—A solution of 0.5 g. of the carbinol (VII) hydrochloride in 20 ml. of ethanol and 16 ml. of hydrochloric acid was added to 2 g. of amalgamated tin. The mixture was refluxed gently for sixteen hours. After separating the unreacted metal, the alcohol and water were removed from the reaction mixture. The residue then was dissolved in 25 ml. of water and made basic to litmus paper with potassium hydroxide. The water-insoluble amine was extracted from the water with two 25-ml. portions of ether. After removing the ether, the amine was dissolved in 10 ml. of dilute hydrochloric acid and the solution was added to 2 g. of amalgamated zinc. The reaction mixture was refluxed for three hours during which time 10 ml. of hydrochloric acid was added in 2-ml. portions. After separating the unreacted metal, the reaction mixture was processed as described in the preceding procedure, yielding a crude methiodide, m. p. 192–203°. After two crystallizations from alcohol–ether, this product melted at 199–205°. A mixture of this material and the methiodide of 1-methyl-4-benzylpiperidine melted at 200–206°.

**The Acid-catalyzed Condensation of Benzaldehyde with 1-Methyl-3-piperidone (VI).**—A solution of 7.5 g. (0.05 mole) of VI and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde in 30 ml. of absolute ethanol was saturated with hydrogen chloride and allowed to stand in the dark at room temperature. No sign of reaction was observed for several hours when a red color began to develop. The following day a crystalline deposit was noticed in the reaction mixture, and the supernatant liquid was a blood-red. The reaction mixture was allowed to stand for three weeks before the solid was filtered. This material, m. p. 162–166°, became colorless after three crystallizations from ethanol. The purified product, m. p. 163–166°, weighed 5.1 g., and represented a 43% yield of hydrochloride of a monobenzal derivative.

*Anal.* Calcd. for $C_{13}H_{16}ClNO$: C, 65.77; H, 6.73; Cl, 15.0. Found: C, 65.40; H, 6.79; Cl, 14.6.

The filtrate was distilled under reduced pressure in a water-bath kept below 35° to remove the ethanol. After dissolving the residue in 100 ml. of water, the solution was shaken with ether to remove the residual benzaldehyde. On making the red aqueous solution basic to litmus paper with potassium carbonate, a dark brown color developed and a dark oil separated. The oil was extracted from the water with benzene and, after drying over anhydrous sodium sulfate, it was treated with hydrogen chloride; 3.0 g. of a dark amorphous solid, m. p. 60–73° dec., separated and the blood-red color reappeared in the solution. All attempts to isolate a pure product from this solid material were unsuccessful.

To further characterize the reaction product, a solution of 2.4 g. of the salt, m. p. 165–166°, in 30 ml. of ethanol and 40 ml. of water was hydrogenated over a previously reduced 5% palladium chloride–charcoal catalyst. The absorption of hydrogen was slightly more rapid at the outset, but then proceeded at a uniform rate until the theoretical amount was absorbed in seven hours. After separating the catalyst, the solution was taken to dryness under reduced pressure on the steam-bath, leaving a light-brown, glassy material. This product was dissolved in 15 ml. of water and after the addition of 6.0 g. of amalgamated zinc and 15 ml. of hydrochloric acid, the mixture was refluxed gently for four hours during which time another 15 ml. of hydrochloric acid was added. After decanting the solution from the unreacted metal, it was made basic to litmus paper with excess potassium carbonate. The water-insoluble amine was then extracted from the aqueous suspension of inorganic salts with three 25-ml. portions of ether. The ether solution of the amine was dried over anhydrous sodium sulfate and concentrated to 40 ml.

A 15-ml. aliquot of this ether solution was evaporated to remove the solvent and the residue dissolved in 10 ml. of ethanol. This solution was treated with a saturated ethanolic solution of picric acid. The crude picrate, m. p. 137–145°, after two crystallizations from ethanol, melted at 149–150°. It gave analytical values corresponding to those of a 1-methylbenzylpiperidine picrate and is subsequently designated as mixture A.

*Anal.* Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.26. Found: C, 54.58; H, 5.20.

A mixture of equal parts of the authentic picrates of 1-methyl-2-benzylpiperidine (m. p. 180.5–181.5°) and 1-methyl-4-benzylpiperidine (m. p. 184–186°) melted at 156–161°. A mixture of A and this known synthetic mixture melted at 133–143°. A solution of equal amounts of the two authentic picrates in ethanol yielded a product, m. p. 154–163°, which melted at 155–165° and 158–165° after two recrystallizations from ethanol. A mixture of the product from the second recrystallization and A melted at 138–149°. From the filtrates of the recrystallizations of the known mixture, a sample melting at 179–181° was obtained. This product depressed the melting point of the authentic picrate of 1-methyl-2-benzylpiperidine to 157–173°, but when mixed with the picrate of 1-methyl-4-benzylpiperidine the mixture melted at 181–185°. Similarly, the melting point of A (149–150°) was not depressed by either the sample obtained from the filtrate or by the authentic picrate of 1-methyl-4-benzylpiperidine; the latter combination melted at 152–169° and the former at 148–158°. However, the melting point of A was depressed to 140–152° by the picrate of 1-methyl-2-benzylpiperidine.

To the remainder of the ether solution containing the reduction products of benzalpiperidones was added 3 ml. of ethanol and 2 ml. of methyl iodide. A solid product X, m. p. 181–186°, was separated by filtration; from the filtrate another product Y, m. p. 185–191°, was obtained after standing in the refrigerator for thirty minutes. Both X and Y gave analytical values for the methiodide of a 1-methylbenzylpiperidine.

*Anal.* Calcd. for $C_{14}H_{22}IN$: C, 50.75; H, 6.65. Found: X, C, 50.68; H, 6.43; Y, C, 50.97; H, 6.44.

A solution containing equal parts of authentic samples of the methiodides of 1-methyl-2-benzylpiperidine (m. p. 225–226°) and 1-methyl-4-benzylpiperidine (m. p. 206–207°) in ethanol yielded a product, m. p. 171–178°. From a succession of crystallizations of this product from ethanol, samples melting at 187–196°, 184–188°, 183–187°, 181–186° and 183–188° were obtained. A mixture of X and Y melted at 182–185°. A mixture comprised of the product (m. p. 183–188°) obtained from the last crystallization of the known mixture and the mixture of X and Y melted at 179–185°.

From the above observations on the melting behavior of these picrates and methiodides, it may be concluded that a mixture of 1-methyl-2-benzyl- and 1-methyl-4-benzylpiperidines were obtained from the reduction of the product isolated from the acid-catalyzed condensation of VI with benzaldehyde.

**1-Methyl-3-hydroxy-3-phenylpiperidine Methiodide.**—To a suspension of 7.0 g. (0.05 mole) of 1-methyl-3-piperidone hydrochloride (VI) in 75 ml. of thiophene-free benzene was added 15 ml. of a saturated solution of potassium carbonate. The mixture was stirred vigorously until the evolution of carbon dioxide ceased. The aqueous layer was separated and extracted with three 15-ml. portions of benzene. The combined benzene solution was distilled on the steam-bath until the volume was reduced to approximately 80 ml. in order to remove all water. The dry benzene solution of the piperidone then was added dropwise to a Grignard reagent, which had been prepared under nitrogen from 1.5 g. (0.06 atom) of magnesium and 9.6 g. (0.06 mole) of freshly distilled bromobenzene. The reaction mixture was stirred during the addition of the piperidone and then for two hours while refluxing gently on the steam-bath. The flask and its contents then were immersed in an ice-bath, and a solution of 15 ml. of hydrochloric acid in 35 ml. of water added slowly. The mixture was transferred to a separatory funnel and shaken thoroughly and after separation, the aqueous layer extracted with ether. It then was made basic with potassium hydroxide and the water-insoluble oil extracted with chloroform. After removing the chloroform, the product was distilled and 5.3 g. (60%) of **1-methyl-3-hydroxy-3-phenylpiperidine**, b. p. 106–108° (0.4 mm.), was collected.

This product darkened quite rapidly on exposure to air. Consequently, it was converted to the methiodide by treating an ether–ethanol solution of the compound with methyl iodide. This salt, after one crystallization from ethanol, melted at 239.5–240.5°.

*Anal.* Calcd. for $C_{13}H_{20}INO$: C, 46.85; H, 6.00; I, 38.1. Found: C, 47.02; H, 6.09; I, 37.7.

The hydrochloride of the carbinol was prepared by passing hydrogen chloride into an ethereal solution of the compound. The resultant solid was hygroscopic; m. p. 134–136° dec. All attempts to purify this product sufficiently for consistent analyses were unsuccessful.

**1-Methyl-3-phenyl-3-acetoxypiperidine Hydrochloride.**—To a solution of 3.0 g. of the hydrochloride, obtained in the above procedure, in 15 ml. of glacial acetic acid was added 15 g. of acetyl chloride and the mixture refluxed gently for two hours. After removing the acetic acid and excess acetyl chloride under reduced pressure on the steam-bath, a white solid material remained in the flask. The product was crystallized from an alcohol–ether mixture, yielding 1.9 g. of white crystals of **1-methyl-3-phenyl-3-acetoxypiperidine hydrochloride**, m. p. 188–189°. A second crop of crystals, m. p. 179–182°, weighing 0.5 g. was recovered from the filtrate.

*Anal.* Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.34; H, 7.42; N, 5.19; Cl, 13.2. Found: C, 61.96; H, 7.70; N, 5.12; Cl, 13.2.

## Summary

An improved procedure for the preparation of ethyl γ-(N-methyl-N-carbethoxymethylamino)-butyrate (IV) from butyrolactone is described.

The condensation of 1-methyl-3-piperidone (VI) with benzaldehyde in basic medium yielded only the 4-substituted derivatives, 1-methyl-4-benzal-3-piperidone (VIII) and the corresponding carbinol VII. In acidic medium these reactants gave a mixture of VIII and its 2-benzal isomer (IX). None of the dibenzal derivative was obtained from either of these reactions.

The 3-piperidone (VI) reacts with phenylmagnesium bromide to yield 1-methyl-3-phenyl-3-hydroxypiperidine, which was isolated as the methiodide and as the 3-acetoxy derivative.

Madison, Wisconsin Received September 17, 1948

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

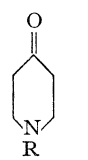
# Piperidine Derivatives. XXI. 4-Piperidone, 4-Piperidinol and Certain of their Derivatives

BY S. M. MCELVAIN AND ROBERT E. MCMAHON[1]

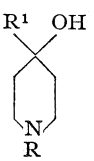
The preparation of 4-piperidinol (II) in 30% yield by the reduction of 4-hydroxypyridine with sodium in alcohol was reported[2] in 1915. A similar reduction of 4-methoxypyridine gave mainly piperidine together with a small amount of 4-methoxy-1,2,5,6-tetrahydropyridine, which was converted by hydrochloric acid to the hydrochloride of 4-piperidone (I).[2b] This piperidone could not be distilled, and on standing gradually underwent self-condensation to yield an odorless, amorphous solid.

Later a low yield of a crude hydrochloride of I was obtained by hydrolysis and decarboxylation of the reaction mixture resulting from the Dieckmann cyclization of di-($\beta$-carbethoxyethyl)-amine.[3] This hydrochloride was characterized as its 3,5-dibenzal derivative. Analyses of the self-condensation product of the free base (I) indicated that the condensation had involved a loss of water between amino hydrogen and the carbonyl oxygen, and the conclusion was drawn that the stability of such well known derivatives of I as nortropine (2,6-dimethylene), triacetoneamine (2,2,6,6-tetramethyl) and vinyldiacetoneamine (2,2,6-trimethyl) is the result of the steric inhibition of the reactivity of the secondary amino group by the 2,6-substituents.[3]

The Dieckmann cyclization of III with sodium ethoxide was later shown to yield only 10% of the 3-carbethoxy-4-piperidone (IV) and in view of the high yields of the 1-alkyl-3-carbethoxy-4-piperidones from IIIa, the low yield of IV was attributed to the high reactivity of the secondary amino group of III and/or its condensation product IV.[4]

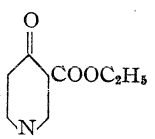


I, R = H
Ia, R = $C_6H_5CO$



II, R = $R^1$ = H
IIa, R = $C_6H_5CO$
$R^1$ = H
IIb, R = H
$R^1$ = $C_6H_5$
IIc, R = $C_6H_5CO$
$R^1$ = $CH_2COOC_2H_5$

$RN(CH_2CH_2COOC_2H_5)_2$
III, R = H
IIIa, R = alkyl
IIIb, R = $C_6H_5CO$



IV, R = H
IVa, R = $C_6H_5CO$

The recently reported[5] preparation of IIIb in high yield and its cyclization to IVa, which in the present work was found to proceed with sodium hydride in 92% yield, offered readily available material for the preparation and study of I and II and their derivatives.

Hydrolysis and decarboxylation of IVa yields the hydrochloride of I, which was reported[4] to crystallize from an alcohol–ether mixture with 1.5 molecules of alcohol of crystallization; this conclusion was based on the chloride analyses of the salt. However, the hydrogenation behavior of this salt in the present work indicated it to be the hydrochloride of the diethylketal of I, which, incidentally, has a chlorine content comparable to that originally found.[4] Analyses for the other elements of this molecule confirmed the ketal structure.[6]

This ketal hydrochloride could not be hydrogenated in alcohol solution over a platinum catalyst, but in an aqueous solution containing a trace of hydrochloric acid it was readily hydrogenated to the hydrochloride of II. The latter salt also was obtained by the hydrolysis of 1-benzoyl-4-piperidinol (IIa) resulting from the hydrogenation of Ia.

The 4-piperidone (I) was readily N-acylated, *e. g.*, the benzoyl derivative (Ia) was obtained in 70% yield from IVa *via* I. All attempts to remove the 3-carbethoxy group of IVa without simultaneously removing the 1-benzoyl group were not very successful. Mild hydrolysis of IVa with 2% aqueous potassium hydroxide followed by decarboxylation gave only a 30% yield of Ia; heating IVa with benzoic acid and a trace of *p*-toluenesulfonic acid gave a quantitative yield of carbon dioxide, but only 23% of Ia could be isolated from the resulting mixture.

In view of the experience with the condensation of 1-methyl-4-piperidone and a variety of aromatic aldehydes,[7] it seemed of interest to determine the behavior of Ia in such reactions. In an alcoholic solution of hydrogen chloride Ia reacted with two equivalents of benzaldehyde to give a quantitative yield of the 3,5-dibenzal derivative (VI), as did the corresponding 1-methyl derivative.[7] Alcoholysis of VI with alcoholic hydrogen chloride gave the hydrochloride of the diben-

(1) Eli Lilly and Company Fellow, 1947–1948.

(2) (a) Koenigs and Neumann, *Ber.*, **48**, 956 (1915); (b) Emmert and Dorn, *ibid.*, **48**, 688 (1915).

(3) Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920).

(4) Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).

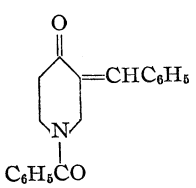
(5) McElvain and Stork, *ibid.*, **68**, 1049 (1946).

(6) It is of interest to note that the chlorine content reported for the hydrochloride of 1-phenylethyl-4-piperidone (Bolyard and McElvain, THIS JOURNAL, **51**, 922 (1929)) also corresponds to that of the hydrochloride of the diethylketal.

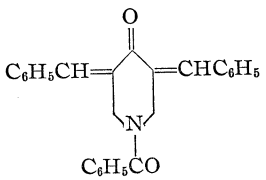
(7) McElvain and Rorig, *ibid.*, **70**, 1820 (1948).

zal derivative of I,[3,4] which on treatment with dilute alkali gave a stable free base. Apparently the 3,5-dibenzal substituents inhibit the reactivity of the carbonyl group of I as the previously noted[3] 2,6-substituents do for the amino group.

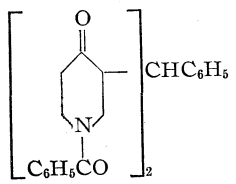
The course of the reaction of Ia with benzaldehyde in basic solution appeared even more complex than that of the 1-methyl analog.[7] A variety of conditions were tried and the procedure that produced the least complex mixture of reaction products is described in the experimental part. The products isolated from this condensation were: 16% of the monobenzal derivative (V), 29% of the phenyldipiperidylmethane (VII) and a trace of VI. The products V and VII precipitated from this reaction mixture as a complex that could not be separated by recrystallization from methanol. However, a solution of the complex in boiling ethyl acetate yielded the two components, *neither* of which would redissolve in this solvent.



V



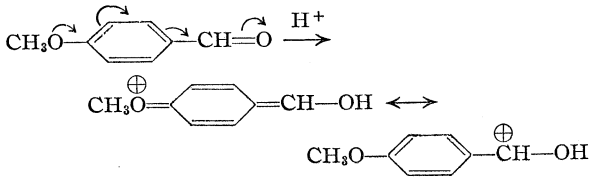
VI



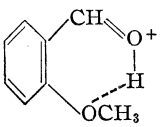
VII

To determine whether a weaker base would produce a less complex mixture of reaction products, sodium benzoate instead of potassium hydroxide was used to effect the condensation. The reaction was very slow: after a month, crystals of VI began to separate; they were removed periodically and after ten months a 65% yield of pure VI was obtained. A similar reaction mixture without the sodium benzoate gave no product.

If the proposed mechanisms[7] for the condensation of aromatic aldehydes with 1-methyl-4-piperidone in acidic and basic medium are valid, substituents in the aldehyde would be expected to show a more pronounced effect on the rate of the acid-catalyzed condensation than on the base-catalyzed reaction. A series of condensations of a variety of substituted benzaldehydes with Ia confirmed this conclusion. In acidic medium a tremendous variation in reaction rate (see Table I) was noted: anisaldehyde and piperonal reacted more rapidly than benzaldehyde, which showed a greater reactivity than *p*-chlorobenzaldehyde and a very much greater reactivity than *m*- and *p*-nitrobenzaldehydes; *o*-chloro- and *o*-methoxybenzaldehydes gave no reaction whatsoever. In each case the dibenzylidene derivatives corresponding to VI were the sole reaction products. It appears, therefore, that a group, *e. g.*, *p*-methoxy, capable of increasing the electron density around the carbonyl oxygen facilitates the coördination of the proton at this point and the consequent formation of the reactive (and resonance-stabilized) carbonium ion

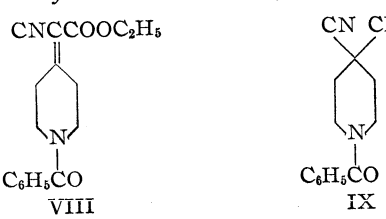


The failure of the *o*-substituted aldehydes, particularly the *o*-methoxy-benzaldehyde, to show any reaction is noteworthy and is probably related to the chelation (hydrogen bonding) between the oxonium hydroxyl and the adjacent methoxy group, which prevents formation of the carbonium ion necessary for the reaction

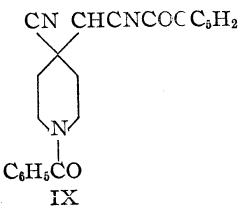


In contrast to their behavior in acidic medium, each of these aldehydes reacted quite rapidly with Ia in alkaline solution (see Table II). The small variations in the observed reaction rates indicate that those electron attracting substituents, *e. g.*, nitro and chloro, which have a retarding effect in acidic medium, definitely accelerate the reaction in basic solution. This behavior shows that the base-catalyzed condensation is relatively independent of the structure of the aldehyde, as the postulated mechanism[7] would indicate.

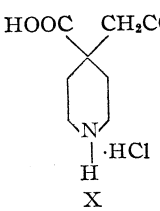
The condensation of the piperidone Ia with cyanoacetic ester[8] gave a 76% yield of the piperidylidene derivative VIII, the structure of which was shown by its reaction with aqueous potassium cyanide solution to form the dinitrile IX in 93% yield. The latter product was further characterized by hydrolysis to the dicarboxylic acid X.



VIII



IX



X

(8) Stork and McElvain, This Journal, **68**, 1053 (1946).

The $\alpha,\beta$-unsaturated cyanoester (VIII) reacted immediately with phenylmagnesium bromide to give a precipitate which appeared to be the magnesium enolate of VIII (with $\beta,\gamma$-unsaturation) as shown by the fact that 76% of the reaction product, after decomposition with acid, dissolved in cold, aqueous potassium cyanide; from another run 71% of VIII was recovered by adsorption on alumina. That portion of the reaction product which was insoluble in the cyanide solution could be evaporatively distilled, but the product so obtained did not give analytical data corresponding to those calculated for the product resulting from the 1,4-addition of the Grignard reagent to VIII. Methylmagnesium bromide gave even more of the enolate of VIII; 93% of this reaction product dissolved in aqueous potassium cyanide.[9]

Phenylmagnesium bromide reacted with the piperidone Ia to give the corresponding 4-phenyl-4-piperidinol, which was converted by alkaline hydrolysis to the piperidinol IIb.

The piperidone Ia and ethyl bromoacetate in the Reformatsky reaction gave a good yield of the piperidinol IIc, which proved to be remarkably resistant to dehydration: it was distilled without appreciable decomposition and also was recovered unchanged after heating in refluxing 90% formic acid.

## Experimental

**1-Benzoyl-3-carbethoxy-4-piperidone (IVa).**—A 3-liter three-neck flask was fitted with dropping funnel, a mercury-seal stirrer and a water-cooled condenser with a gas trap connected to the top. After filling the apparatus with nitrogen, the condenser was removed momentarily and 29.7 g. (1.24 mole) of sodium hydride added through a powder funnel; from the other neck of the flask 800 ml. of thiophene-free benzene was added through the dropping funnel.[10] After again flushing the system with nitrogen, stirring was started and 200 g. (0.62 mole) of N-benzoyl-di-($\beta$-carbethoxyethyl)-amine[5] (IIIb) was added. When 2 ml. of absolute alcohol was added, the reaction mixture became green in color and evolution of hydrogen started immediately. The rapidly stirred suspension was heated gently on a steam-bath for two and one-half hours, after which time it was cooled in an ice-bath and treated consecutively with 74.5 g. (1.24 moles) of glacial acetic acid and 67.0 g. (3.72 moles) of water. After the reaction mixture had stood for fifteen minutes, the crystalline sodium acetate trihydrate was removed by filtration and the filter cake washed with an additional 500 ml. of benzene.

The combined benzene filtrates were placed in a round-bottom flask and heated on a steam-bath at water-pump pressure until all of the solvent had been removed. The residue was 157 g. (92%) of IVa, a reddish oil, which crystallized after standing several days to give a solid melting at 56–59°.

(9) In contrast to these results, Kohler and collaborators (*Am. Chem. J.*, **33**, 21, 153 and 333 (1905); **35**, 386 (1906); **38**, 511 (1907)) reported the 1,4-addition of Grignard reagents to a variety of $\alpha,\beta$-unsaturated nitriles, aldehydes, ketones and esters. Birch and Robinson (*J. Chem. Soc.*, 501 (1943)) reported 1,4-addition of methylmagnesium bromide to ethyl cyclohexylidenecyanoacetate to the extent of 45%. More recently Widequist (*C. A.*, **41**, 1615 (1947)) reported good yields of the 1,4-addition products from isopropylidenemalonic ester and both methylmagnesium iodide and butylmagnesium bromide).

(10) These two materials were added from opposite necks of the flask to minimize the danger of fire, which once resulted from the sparking of a granule of sodium hydride when it and the benzene were added through the same neck.

**1-Benzoyl-4-piperidone (Ia).**—A mixture of 100 g. of IVa and 400 ml. of 6 *N* hydrochloric acid was refluxed for two hours. Extraction of the benzoic acid from the cooled reaction mixture with ether, followed by evaporation of the aqueous solution to dryness, gave the crude hydrochloride of I as a semi-solid mass. This material was dissolved in 30 ml. of water and to this stirred solution were added 50 g. of potassium carbonate, 500 ml. of chloroform, and then to this 51 g. of benzoyl chloride at a sufficient rate to maintain gentle reflux. The mixture was heated for four hours, after which time 30 ml. of alcohol was added and heating continued for an additional one-half hour. Then sufficient water to dissolve the precipitated salts was added to the cooled reaction mixture. The chloroform layer was separated and washed with 5% potassium carbonate solution, water, 5% hydrochloric acid, and with a saturated salt solution. After drying, the chloroform was removed by distillation and the residue distilled under reduced pressure to give 51 g. (70%) of Ia as a colorless liquid, b. p. 158–160° (0.2 mm.). Part of the product was allowed to stand in a closed flask and after several months it crystallized to a white solid, m. p. 49–52°. The succeeding batches of Ia could be crystallized readily by seeding with these crystals.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 71.17; H, 6.41.

The semicarbazone, which was prepared and crystallized from an ethyl acetate–ethyl alcohol mixture, melted at 193.5–195°,

*Anal.* Calcd. for $C_{13}H_{16}N_4O_2$: N, 21.55. Found: N, 21.77.

The 2,4-dinitrophenylhydrazone, after crystallization from methanol, melted at 196–198°.

*Anal.* Calcd. for $C_{18}H_{17}N_5O_5$: C, 56.39; H, 4.47. Found: C, 56.23; H, 4.48.

**1-Diphenylacetyl-4-piperidone.**—This compound was prepared by the procedure for Ia, except that diphenylacetyl chloride was substituted for benzoyl chloride. Recrystallization of the product from benzene gave fluffy white needles, m. p. 135–136°.

*Anal.* Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53. Found: C, 77.80; H, 6.62.

The 2,4-dinitrophenylhydrazone melted at 185–187°.

*Anal.* Calcd. for $C_{25}H_{23}N_5O_5$: C, 63.42; H, 4.90. Found: C, 63.18; H, 4.89.

**1-Acetyl-4-piperidone.**—The crude hydrochloride of I from 75 g. of IVa was dissolved in 250 ml. of glacial acetic acid and a solution of 22.4 g. of sodium acetate in 150 ml. of glacial acetic acid added with stirring. Following this, 36 g. of acetic anhydride was added and the reaction mixture heated with stirring on a steam-bath for ninety minutes, after which time 10 ml. of methanol was added and heating continued for fifteen minutes. The precipitated salt was filtered off and the acetic acid removed by distillation. The residue was fractionally distilled under reduced pressure through a short (15 mm.) Vigreux column to give 18.6 g. (49%) of 1-acetyl-4-piperidone as a water-white liquid; b. p. 124–128° (0.2 mm.); $n^{25}D$ 1.5023; $d^{25}_4$ 1.144, and $M_D$ 36.4 (calcd. 36.3). This compound is completely miscible with water, but insoluble in ether.

*Anal.* Calcd. for $C_7H_{11}NO_2$: C, 59.55; H, 7.85. Found: C, 59.43; H, 7.99.

The 2,4-dinitrophenylhydrazone, after crystallization from ethanol, melted at 212–213°.

*Anal.* Calcd. for $C_{13}H_{15}N_5O_5$: C, 48.59; H, 4.71. Found: C, 48.40; H, 4.95.

**4,4-Diethoxypiperidine (4-Piperidone Diethylketal) Hydrochloride.**—The crude hydrochloride of I, obtained from 50 g. of IVa was recrystallized three times from an absolute alcohol–ether mixture to give 8.0 g. (21%) of 4,4-diethoxypiperidine hydrochloride; m. p. 138–140° (Kuettel and McElvain[4] reported 138–140° for the hydrochloride of $I \cdot 1.5C_2H_5OH$).

Table I

Rates of Formation, Yields, Melting Points and Analyses of Various 3,5-Di-arylidene (RCH=) Derivatives of 1-Benzoyl-4-Piperidone

| R is | Time (hr.) for initial precipitation | Yield (%) in 5 hrs. | 24 hrs. | 72 hrs. | 340 hrs. | 670 hrs. | M. p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | 6 | .. | 75[a] | 97 | ... | .. | 165–167 | $C_{26}H_{21}NO_2$ | 82.29 | 5.58 | 82.02 | 5.47 |
| *p*-$CH_3OC_6H_4$ | 1 | 76 | 85 | 91 | ... | .. | 177–178 | $C_{28}H_{25}NO_4$ | 76.52 | 5.73 | 76.27 | 5.78 |
| *o*-$CH_3OC_6H_4$ | ... | | | | None | | | | | | | |
| 3,4-$OCH_2OC_6H_3$ | 0.5 | 76 | 89 | 99 | ... | .. | 196–197 | $C_{28}H_{21}NO_6$ | 71.94 | 4.53 | 71.90 | 4.53 |
| *p*-$ClC_6H_4$ | 11 | .. | 18 | 73 | ... | .. | 194–195 | $C_{26}H_{19}Cl_2NO_2$ | 69.65 | 4.27 | 69.73 | 4.43 |
| *o*-$ClC_6H_4$ | ... | | | | None | | | | | | | |
| *m*-$NO_2C_6H_4$ | 120 | .. | .. | .. | 30 | 61 | 205–207 | $C_{26}H_{19}N_3O_6$ | 66.52 | 4.08 | 66.57 | 4.24 |
| *p*-$NO_2C_6H_4$ | 168 | .. | .. | .. | 30 | 52 | 226–228 | $C_{26}H_{19}N_3O_6$ | 66.52 | 4.08 | 66.43 | 4.38 |

[a] After twelve hours the yield was 27%.

*Anal.* Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61; Cl, 16.9; $OC_2H_5$, 43.0. Found: C, 51.37; H, 9.64; Cl, 16.9; $OC_2H_5$, 43.2.

A higher melting form of this ketal salt was obtained as follows: 2 g. of the above salt, m. p. 138–140°, was dissolved in 50 ml. of alcohol and the solution stirred for several hours in a hydrogenation apparatus with hydrogen over previously reduced platinum oxide catalyst (Adams). At the end of this time there had been no appreciable uptake of hydrogen. The catalyst was removed by filtration, the filtrate warmed and dry ether added. After standing overnight, 1.0 g. of white crystals melting at 150° separated. Upon cooling and remelting this salt, a melting point of 140–141° was obtained. A mixed melting point with the salt, m. p. 138–140°, was 147–148°. Upon cooling and remelting, this mixture melted at 140–141°.

*Anal.* Found: C, 51.25; H, 9.44; Cl, 16.9.

**1-Benzoyl-4-piperidinol (IIa).**—In the glass liner of the hydrogenation bomb was placed 20 g. of 1-benzoyl-4-piperidone (Ia), 2 g. of Raney nickel and 80 ml. of alcohol. The liner was placed in the bomb and the latter filled with hydrogen to a pressure of 2200 p. s. i. After hydrogenation at 75° for two hours, the bomb was opened, the catalyst removed by filtration and the filtrate evaporated to dryness to give a quantitative yield of IIa as a colorless oil, which crystallized to a solid, m. p. 70–73°.

*Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 69.85; H, 7.42.

This compound also was prepared by reduction of Ia with Adams platinum-oxide catalyst.

**1-Benzoyl-4-piperidyl N-phenylcarbamate** was prepared by the action of phenyl isocyanate on IIa. After recrystallization from petroleum ether, it melted at 184–185°.

*Anal.* Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22. Found: C, 70.26; H, 6.37.

**4-Piperidinol (II) Hydrochloride.**—Ten grams of 1-benzoyl-4-piperidinol (IIa) was refluxed with 100 ml. of 20% aqueous hydrochloric acid for one hour and the resulting solution cooled to room temperature. The benzoic acid, some of which had crystallized, was removed by extraction with benzene and the aqueous solution evaporated to dryness. The crude hydrochloride thus obtained was recrystallized from alcohol–ether to give 3.4 g. (50%) of 4-piperidinol hydrochloride; m. p. 151–153° (reported,[2b] 146–148°).

*Anal.* Calcd. for $C_5H_{12}ClNO$: C, 43.63; H, 8.79; Cl, 25.8. Found: C, 43.48; H, 8.43; Cl, 25.3.

This compound was also prepared by the hydrogenation of the hydrochloride of 4,4-diethoxypiperidine over Adams platinum oxide catalyst in an aqueous solution containing a few drops of hydrochloric acid; twenty-four hours were required to hydrolyze and reduce 1 g. of the ketal. The product was recovered by filtering off the catalyst, evaporating to dryness and recrystallizing the crude hydrochloride from an alcohol–ether mixture. The yield of II, m. p. 148–149°, was 0.4 g. (43%)

**The Acid-catalyzed Condensation of 1-Benzoyl-4-piperidone (Ia) with Aromatic Aldehydes.**—The procedure used in these condensations is illustrated by the following preparation of 1-benzoyl-3,5-dibenzal-4-piperidone (VI). A solution of 0.5 g. of Ia and 0.52 g. (2 equivalents) of benzaldehyde in 30 ml. of absolute alcohol was cooled in an ice-bath and saturated with hydrogen chloride. The solution soon became very dark in color and after six hours crystals began to form. After one day of standing, the bright-yellow crystals were filtered off and dried. The yield was 0.70 g. (75%) of large yellow crystals, m. p. 162–164°. After two more days, 0.2 g. of a second crop, m. p. 162–163°, was obtained, bringing the total yield to 0.90 g. (97%). The melting point of this product was raised to 165–167° by recrystallization from either methyl or ethyl alcohol. It, as well as the other diarylidene derivatives listed in Table I, has extremely low solubilities in methyl and ethyl alcohols, acetone, ether, petroleum ether and benzene.

The rates of formation, yields, melting points and analyses of the various 3,5-diarylidene derivatives of Ia are summarized in Table I.

The dibenzal derivative (VI) was also prepared in the following manner. In 15 ml. of 65% aqueous alcohol were dissolved 1.0 g. of Ia, 1.06 g. of benzaldehyde and 0.30 g. of sodium benzoate, and the solution was allowed to stand. Crystals started to form after one month. The product was filtered off at intervals to give, after ten months, 1.2 g. (65%) of VI, m. p. 164–166°.

**1-Benzoyl-3,5-dibenzyl-4-piperidone.**—In 100 ml. of ethanol was suspended 2.0 g. of VI and 150 mg. of Adams catalyst. This suspension was stirred with hydrogen until two moles had been absorbed (two hours). The catalyst was removed by filtration and the filtrate evaporated to dryness to give a viscous oil. This oil was dissolved in petroleum ether (b. p. 90–100°); from this solution 0.8 g. (40%) of a 1-benzoyl-3,5-dibenzyl-4-piperidone, m. p. 127–129° separated. Further recrystallization from the same solvent raised the melting point to 130–131°.

*Anal.* Calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57. Found: C, 81.33; H, 6.49.

The semicarbazone, after recrystallization from alcohol–water, was obtained as white needles, m. p. 162–165°.

*Anal.* Calcd. for $C_{27}H_{28}N_4O_2$: N, 12.72. Found: N, 12.96.

**1-Benzoyl-3,5-dibenzyl-4-piperidinol.**—In 100 ml. of ethyl alcohol was suspended 2.0 g. of VI and 150 mg. of Adams catalyst and the mixture was stirred in the hydrogenation apparatus until no more hydrogen was absorbed (three hours). After removing the catalyst the solution was evaporated to dryness to give a colorless, viscous oil. Three successive crystallizations of this material from

petroleum ether (90–100°) gave 0.7 g. (45%) of a product, m. p. 111–114°.

*Anal.* Calcd. for $C_{26}H_{27}NO_2$: C, 81.00; H, 7.06. Found: C, 80.98; H, 7.23.

**3,5-Dibenzal-4-piperidone Hydrochloride.**—A solution of 0.5 g. of VI in 40 ml. of absolute alcohol was saturated with hydrogen chloride and the mixture refluxed two hours. Upon cooling, 0.25 g. (62%) of fluffy yellow crystals, m. p. 270–273°, separated. Recrystallization from alcohol raised the melting point to 274–276° (reported, 276–277°[4]; 275–277°[3]).

**3,5-Dibenzal-4-piperidone.**—In 25 ml. of 5% potassium carbonate was suspended 0.5 g. of 3,5-dibenzal-4-piperidone hydrochloride and the mixture was stirred at room temperature for two hours to insure complete reaction. The free base (0.45 g.) was filtered off and dried, m. p. 183–185°; recrystallization from alcohol gave lustrous, pale yellow crystals, m. p. 183–184°.

*Anal.* Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 82.82; H, 6.49.

**3,5-Dibenzyl-4-piperidinol Hydrochloride.**—In 80 ml. of alcohol was suspended 1.5 g. of 3,5-dibenzal-4-piperidone hydrochloride and 100 mg. of Adams catalyst. This suspension was stirred with hydrogen until hydrogen absorption ceased (4 hours), during which time, 105% of the theoretical amount of hydrogen was taken up. The catalyst was removed by filtration and the product recovered by evaporating the solution to a volume of 40 ml. and adding ether to start crystallization; 1.1 g. (73%) of **3,5-dibenzyl-4-piperidinol hydrochloride**, m. p. 288–291°, was obtained.

*Anal.* Calcd. for $C_{19}H_{24}ClNO$: C, 71.83; H, 7.62; Cl, 11.2. Found: C, 71.94; H, 7.53; Cl, 11.1.

**The Base-catalyzed Reaction of 1-Benzoyl-4-piperidone (Ia) with Benzaldehyde.**—In 130 ml. of 95% ethyl alcohol were dissolved 10.0 g. of Ia, 5.3 g. (one equivalent) of freshly distilled benzaldehyde and 1.0 g. of potassium hydroxide pellets. After standing for several days, a crop of yellow crystals started to form. After two weeks, these were removed by filtration, found to weigh 3.6 g., and to melt at 165–175°. This material was recrystallized from methanol to give 2.8 g. of lustrous, white crystals, m. p. 205–210°. Further recrystallization from methanol did not raise the melting point above 210–214°.

This material gave a red color with concentrated sulfuric acid, decolorized dilute potassium permanganate solution, and was found to contain 77.58% carbon and 6.04% hydrogen. It was dissolved readily in hot ethyl acetate; upon cooling, a crop of white crystals separated. These were removed by filtration, dried and found to weigh 2.6 g., m. p. 205–207°. When treated with hot ethyl acetate as before, most of the material was insoluble. The insoluble material (2.3 g.) was **1-benzoyl-3-benzal-4-piperidone (V)**, m. p. 236–240°.

*Anal.* Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.52; H, 5.92; N, 4.32.

From the ethyl acetate filtrates was obtained a second crop of crystals weighing 0.2 g. and melting at 228–240°. This material was recrystallized several times from ethanol to give **phenyl-bis-(1-benzoyl-4-keto-3-piperidyl)-methane (VII)** as a white powder, m. p. 272–274°. This compound gave no coloration with concentrated sulfuric acid and did not reduce dilute permanganate solution.

*Anal.* Calcd. for $C_{31}H_{30}N_2O_4$: C, 75.28; H, 6.11. Found: C, 75.07; H, 6.10.

After the original reaction mixture had stood an additional three weeks, a second crop of crystals, weighing 3.4 g., m. p. 215–230°, separated. Purification of this material showed it to be VII, bringing the total yield of this compound to 3.6 g. (29%).

From the mother liquors from the first recrystallization of both the first and the second crops of crystals from the original reaction mixture was obtained a trace (0.05 g.) of the dibenzal derivative (VI).

**The Rates of the Base-catalyzed Reaction of 1-Benzoyl-4-piperidone with Aromatic Aldehydes.**—In 6 ml. of 55% alcohol was dissolved 0.25 g. of Ia, two equivalents of the aldehyde and 0.05 g. of potassum hydroxide. The time required for the initial separation of a reaction product was noted; after two days the dry weight of this product was determined and expressed as the per cent. of the combined weight of the reactants. The results are summarized in Table II. No attempt was made to identify the reaction products.

TABLE II

BASE-CATALYZED CONDENSATIONS OF Ia AND AROMATIC ALDEHYDES, RCHO

| R | Time, (min.) for initial precipitation | Yield, % of combined wt. of reactants in 2 days | Nature of product |
|---|---|---|---|
| $C_6H_5$ | 11 | 28 | Oil |
| *o*-$ClC_6H_4$ | 0.25 | 83 | Oil |
| *p*-$ClC_6H_4$ | 2 | 92 | Oil |
| *m*-$NO_2C_6H_4$[a] | 0.25 | 89 | Oil |
| *p*-$NO_2C_6H_4$[b] | 1 | 97 | Yellow solid, m. p. 133–142° |
| *o*-$CH_3OC_6H_4$ | 3 | 92 | Oil |
| *p*-$CH_3OC_6H_4$ | 40 | 77 | Yellow solid, m. p. 115–123° |

[a] Because of insolubility of aldehyde 65% alcohol was used. [b] Because of insolubility of aldehyde 75% alcohol was used.

**Ethyl (1-Benzoyl-4-piperidylidene)-cyanoacetate (VIII).**—In a 50-ml. round-bottom flask were placed 10.0 g. of 1-benzoyl-4-piperidone (Ia), 5.65 g. of cyanoacetic ester, 1 g. of anhydrous ammonium acetate, 3 ml. of glacial acetic acid, 20 ml. of dry benzene and a porcelain chip. The flask, after attachment to a Cope separator[11] filled with benzene, was heated in an oil-bath for one hour at 125°. Titration of the resultant water layer in the separator with standard base showed that it contained 0.4 g. of acetic acid; the yield of water amounted to 0.8 g. (calcd. 0.9 g.).

The reaction mixture was diluted with benzene, extracted with water and saturated sodium bicarbonate solution, and the benzene solution dried. The solvent was removed from the dried solution to give 14.0 g. of a dark-red oil. This oil was extracted with a total of 300 ml. of boiling ether to give, after evaporation of the solvent and drying the residue at 80° under 0.5 mm. pressure, 9.4 g. of **ethyl (1-benzoyl-4-piperidylidene)-cyanoacetate (VIII)** as a pale-yellow oil. A benzene solution of the ether-insoluble material was treated with ether until no further precipitate formed; the resultant suspension was filtered and the filtrate evaporated to dryness. The residual red oil was extracted with ether to give an additional 1.7 g. of VIII, bringing the total yield to 11.1 g. (76%). After standing overnight, the product crystallized to a white solid melting at 84–86°.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08. Found: C, 68.49; H, 6.23.

**Ethyl (1-Benzoyl-4-cyano-4-piperidyl)-cyanoacetate (IX).**—The compound was made from VIII by the two following procedures.

(a)[12] A solution of 2.0 g. of VIII in 15 ml. of alcohol was treated with a solution of 0.87 g. of potassium cyanide in 5 ml. of water and the yellow solution cooled in an ice-bath. To this solution was added a mixture of 1.2 ml. of concentrated hydrochloric acid and 1 ml. of water and the reaction mixture allowed to stand twenty-five minutes at room temperature, before pouring into 50 ml. of cold 5% hydrochloric acid. The oily product that separated was taken up in benzene. After removal of the residual hydrogen cyanide by several extractions with water, the benzene was removed by distillation to give, after drying, 2.2 g. (96%) of IX as a colorless liquid, which crystallized

(11) Cope, *et al.*, THIS JOURNAL, **63**, 3452 (1941).

(12) *Cf.* Hope and Sheldon, *J. Chem. Soc.*, **121**, 2223 (1922).

to a solid melting at 110–113°. Recrystallization from benzene and petroleum ether (60–68°) gave white rosettes, m. p. 119–121°.

(b) A mixture of 10 ml. of 10% aqueous potassium cyanide solution and 0.2 g. of VIII was shaken for one-half hour and the resulting solution then carefully neutralized with 10% hydrochloric acid. Extraction with benzene gave 0.20 g. (93%) of IX after the benzene was removed and the residue dried.

*Anal.* Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89. Found: C, 66.62; H, 6.02.

**4-(4-Carboxypiperidyl)-acetic Acid Hydrochloride (X).**—A solution of 1 g. of IX in 25 ml. of 25% hydrochloric acid was refluxed for twenty-four hours. After cooling, the benzoic acid was extracted with benzene. The aqueous solution was evaporated to dryness, the residue treated with an excess of 30% potassium hydroxide and the solution heated until the evolution of ammonia ceased. The alkaline solution was acidified with concentrated hydrochloric acid and evaporated to dryness.

The residue of sodium chloride and the salt (X) was treated with two 50-ml. portions of boiling absolute alcohol. The alcohol solutions were combined, filtered, evaporated to 40 ml. and treated with dry ether to the point of cloudiness. The flocculent precipitate which formed was removed by filtration and the filtrate placed in the refrigerator overnight. The product (X) that separated was removed by filtration, dried and found to weigh 0.51 g. (76%). Its melting point, 207–212°, was raised to 217–219° by two recrystallizations from alcohol–ether.

*Anal.* Calcd. for $C_8H_{14}ClNO_4$: C, 42.96; H, 6.31; Cl, 15.9. Found: C, 42.63; H, 6.54; Cl, 15.7.

**The Reaction of VIII with Phenylmagnesium Bromide.**—A solution of 4.5 g. (0.015 mole) of VIII in a mixture of 25 ml. of dry benzene and 75 ml. of dry ether was placed in a three-neck flask equipped with stirrer, condenser and dropping funnel. After filling the system with dry nitrogen 0.016 mole of phenylmagnesium bromide in 50 ml. of ether was added; an immediate precipitate formed. After refluxing for one-half hour, the reaction mixture was cooled, diluted with 100 ml. of ether and treated with cold 10% hydrochloric acid until the mixture cleared. The organic layer was removed, dried and evaporated to give 5.1 g. of a yellow gum. This gum was dissolved in 100 ml. of dry benzene and the resulting solution poured through a 20 cm. column of alumina. The column then was eluted with an additional 300 ml. of benzene and the combined eluates evaporated to dryness. The residue (3.3 g.) crystallized to a white solid, m. p. 78–80°; mixed m. p. with VIII 80–84°. By elution with chloroform 0.2 g. of a dark colored, saturated gum was obtained.

The yellow gum from another similar reaction was treated with 5 ml. of benzene and stirred overnight with 150 ml. of 10% aqueous potassium cyanide solution. The mixture then was extracted twice with 75-ml. portions of benzene to give, after evaporation of the solvent, 1.3 g. of a dark-colored gum which did not decolorize dilute permanganate solution. When this gum was evaporatively distilled, biphenyl first sublimed far up the tube and then, at 215–230° (0.4 mm.), a yellow oil was collected. A considerable quantity of carbonaceous material remained in the bottom of the tube. The yellow oil was separated from the rest of the material and again evaporatively distilled as a clear yellow oil at 215–225° (0.5 mm.). The analytical values (C, 75.57; H, 6.88; $OC_2H_5$, 8.1) obtained for this compound, however, did not check with those (C, 73.38; H, 6.43; $OC_2H_5$, 12.0) calculated for ethyl 1-benzoyl-4-phenyl-4-piperidylacetate.

**Ethyl (1-Benzoyl-4-hydroxy-4-piperidyl)-acetate (IIc).**—In a 500-ml. three-neck flask, equipped with condenser, stirrer and addition funnel were placed 5.0 g. of 1-benzoyl-4-piperidone (Ia), 5 g. of well-cleaned zinc foil, 20 ml. of dry ether and 20 ml. of dry benzene. After flushing the flask with a stream of nitrogen, 7.5 ml. of ethyl bromoacetate and a crystal of iodine were added. Stirring and heating caused the reaction to start immediately. The stirred reaction mixture was heated at gentle reflux for two and one-half hours, during which time an additional 5 g. of zinc was added.

After cooling the reaction mixture, 5 ml. of methyl alcohol and 5 ml. of acetic acid were added and the clear solution decanted into 50 ml. of water. The mixture was then acidified with acetic acid and extracted with 50 ml. of benzene. The organic layer was washed several times with dilute ammonia, dried and the solvent removed to give 6.6 g. (92%) of IIc as a dark-red oil. A small amount of this oil was subjected to evaporative distillation and it was found that practically all of the material distilled as a yellow oil at a jacket temperature of 205–215° (0.2 mm.).

*Anal.* Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.48; H, 7.34.

**4-Phenyl-4-hydroxypiperidine (IIb) Hydrochloride.**—A solution of 12.0 g. (0.059 mole) of Ia in a mixture of 30 ml. of dry benzene and 60 ml. of dry ether was treated with a solution of 0.067 mole of phenylmagnesium bromide in 100 ml. of ether. After the addition, the mixture was refluxed for one hour, with stirring. The cooled mixture then was treated with saturated ammonium chloride solution until it cleared. The organic layer was removed by decantation, the salt washed with ether and the combined ether solutions evaporated to dryness.

The yellow gum thus obtained was refluxed for three hours with a solution of 8 g. of potassium hydroxide in a mixture of 40 ml. of alcohol and 60 ml. of water. After removal of most of the alcohol by distillation, 100 ml. of water was added and the resulting mixture extracted with a total of 750 ml. of ether. After drying the ether extract with anhydrous potassium carbonate and Drierite, it was treated with hydrogen chloride. This gave 5.2 g. (41%) of a brown solid melting at 180–185°. Recrystallization from alcohol–ether gave 2.0 g. (16%) of the hydrochloride of IIb as a white solid, m. p. 202–204°.

*Anal.* Calcd. for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; Cl, 16.6. Found: C, 61.73; H, 7.86; Cl, 16.4.

## Summary

A variety of derivatives of 4-piperidone and 4-piperidinol have been prepared from 1-benzoyl-4-piperidone and their properties reported.

The product obtained from the crystallization of 4-piperidone hydrochloride from alcohol is shown to be the ketal, 4,4-diethoxypiperidine hydrochloride.

The rates of the reactions of 1-benzoyl-4-piperidone with certain substituted benzaldehydes in acidic and basic media confirm the previously postulated mechanisms for such reactions.

The application of the Knoevenagel, Reformatsky and Grignard reactions to 1-benzoyl-4-piperidone are described. The product of the former reaction, ethyl (1-benzoyl-4-piperidylidene)-cyanoacetate, does not give significant amounts of 1,4-addition products with Grignard reagents, but reacts primarily as an acid to form a magnesium enolate.

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# Electrophoretic Analysis of Ovalbumin

BY JOHN R. CANN

## Introduction

Longsworth, Cannan and MacInnes[1] found that within the *p*H range of 5 to 10 crystalline ovalbumin is resolved electrophoretically into two components, $A_1$ and $A_2$, $A_2$ being the slower moving component. The relative concentration of $A_2$ in freshly prepared material is reported to vary from 15 to 25%. A third component, $A_3$, has also been found to be present in small amounts.[2] $A_3$ is less mobile than $A_1$ and $A_2$ at *p*H 6.8.

In connection with the program of protein fractionation by electophoresis-convection being carried out in this Laboratory,[3] it has been necessary to analyze a large number of samples of ovalbumin electrophoretically using the moving boundary technique of Tiselius[4] as modified by Longsworth.[5]

The moving boundary theory recently extended by Dole[6] and Svensson[7] indicates that appreciable error may be made in the usual electrophoretic analyses of proteins due to the superposition of foreign protein and buffer gradients on the concentration gradient of a given electrophoretic component. In the case of protein mixtures in alkaline solution these superimposed gradients would cause the relative concentration of the fastest moving component, *e. g.*, albumin in serum, to appear greater than its real value. Since electrophoretic distributions appear to approach actual distributions at high ionic strengths and low protein concentrations, Longsworth[8] recommends that the true distribution of components be obtained either by extrapolating the apparent electrophoretic distributions to infinite ionic strength at constant protein concentration or zero protein concentration at constant ionic strength. Other workers[9] have suggested extrapolating to zero value of the ratio of protein concentration to ionic strength.

Since the electrophoretic analysis of ovalbumin is complicated by the change of relative mobilities of the components with ionic strength, it appeared desirable to report the findings of this Laboratory with respect to the variations in apparent distribution of the components of ovalbumin as a function of the conditions of electrophoresis.

## Experimental

**Method.**—The electrophoresis apparatus described by Longsworth[5] for use in the analysis of proteins by the Tiselius moving boundary method was used in this investigation. The time and field strength employed are noted under the appropriate pattern in Fig. 1. Photographic records of the refractive index gradients in the boundaries were made by the schlieren scanning method.

The apparent concentrations of the components of ovalbumin were determined by finding the ratio, in each case, of the component area to the total area, exclusive of the $\epsilon$-boundary. The areas were measured on projected tracings of the descending patterns with a planimeter, resolution into components being carried out by the method of Pedersen.[10]

**Material.**—Crystalline ovalbumin was prepared by the method of Sorensen and Høyrup.[11] Analysis of a 1% solution of a representative preparation in phosphate buffer, *p*H 6.81 and ionic strength 0.1, yielded 76.0% $A_1$ ($-5.93 \times 10^{-5}$ cm.$^2$ sec.$^{-1}$ volt$^{-1}$), 18.2% $A_2$ ($-5.05 \times 10^{-5}$) and 5.8% $A_3$ ($-4.4 \times 10^{-5}$).

## Experimental Results and Discussion

Electrophoretic experiments were carried out in phosphate buffers, *p*H 6.8 and ionic strength 0.05 and 0.1, and in phosphate–chloride buffer, *p*H 6.7 and ionic strength 0.3. In these runs the protein concentration was 0.74%. The resultant electrophoretic patterns are shown in Fig. 1. It will be noted that a marked decrease in resolution into components parallels an increase in ionic strength. Thus, at ionic strength 0.05 excellent resolution into three components was obtained, while at ionic strength 0.3 the pattern consisted of a single asymmetric peak ($-4.3 \times 10^{-5}$). The apparent distribution of components at ionic strength 0.05 was 78.6% $A_1$ ($-7.08 \times 10^{-5}$), 15.2% $A_2$ ($-5.93 \times 10^{-5}$) and 6.2% $A_3$ ($-5.2 \times 10^{-5}$), and at ionic strength 0.1, 77.9% $A_1$ ($-6.24 \times 10^{-5}$), 17.6% $A_2$ ($-5.37 \times 10^{-5}$) and 4.5% $A_3$ ($-4.8 \times 10^{-5}$). A similar behavior was observed in the case of electrophoresis in acetate buffers. Patterns obtained in phosphate buffer, *p*H 6.8 and ionic strength 0.3, revealed the presence of three components,

(1) L. G. Longsworth, R. K. Cannan and D. A. MacInnes, THIS JOURNAL, **62**, 2580 (1940).

(2) C. F. C. MacPherson, D. H. Moore and L. G. Longsworth, *J. Biol. Chem.*, **156**, 381 (1944); R. A. Alberty, E. A. Anderson and J. W. Williams, *J. Phys. and Colloid Chem.*, **52**, 217 (1948).

(3) L. E. Nielsen and J. G. Kirkwood, THIS JOURNAL, **68**, 181 (1946).

(4) A. Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

(5) L. G. Longsworth, *Chem. Rev.*, **30**, 423 (1942); *Ind. and Eng. Chem., Anal. Ed.*, **18**, 219 (1946).

(6) V. P. Dole, THIS JOURNAL, **67**, 1119 (1945).

(7) H. Svensson, *Arkiv. Kemi, Mineral. Geol.*, **17A**, No. 14, 1 (1943); **21B**, No. 5, 1 (1945); **22A**, No. 10, 1 (1946).

(8) L. G. Longsworth, *J. Phys. and Colloid Chem.*, **51**, 171 (1947).

(9) G. E. Perlmann and D. Kaufman, THIS JOURNAL, **67**, 638 (1945); S. H. Armstrong, Jr., M. J. E. Budka, and K. C. Morrison, *ibid.*, **69**, 416 (1947).

(10) T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford Univ. Press, London, 1940, p. 296.

(11) S. P. L. Sorensen and M. Høyrup, *Compt. rend. trav. lab. Carlsburg*, **12**, 12 (1916).

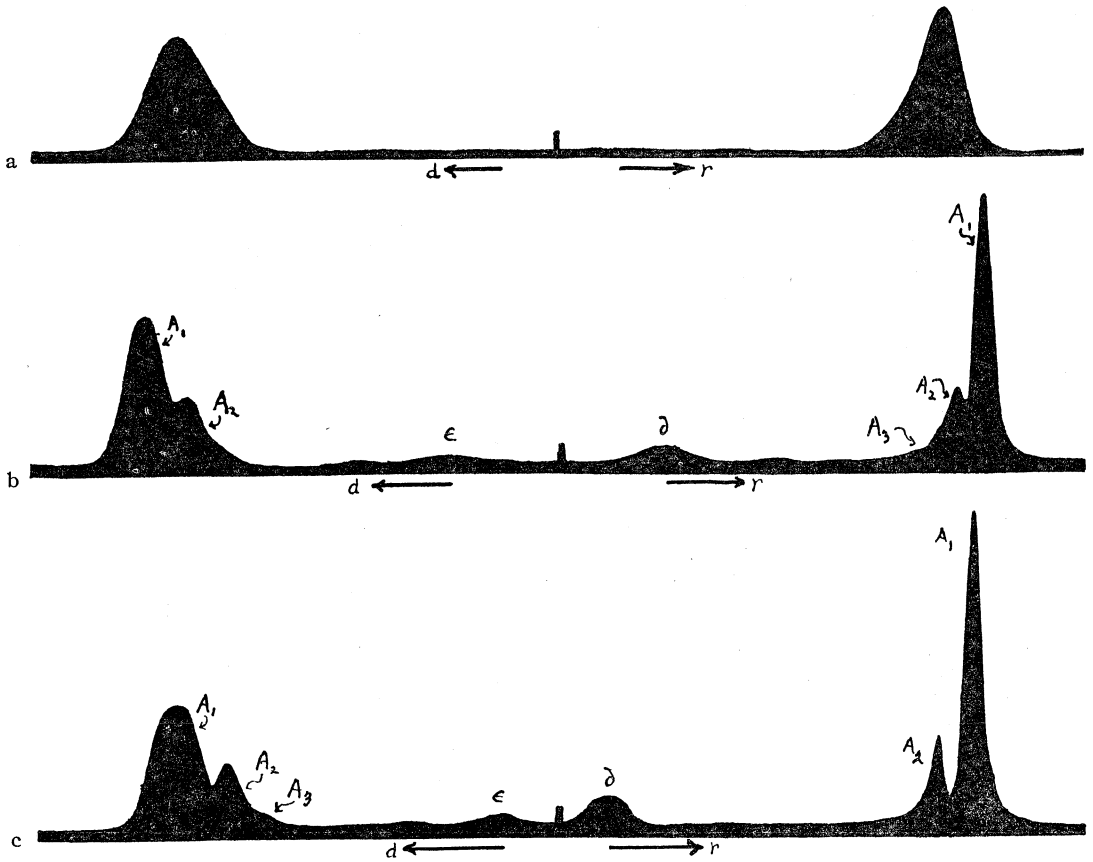



Fig. 1.—Electrophoretic patterns showing the effect of ionic strength on resolution of ovalbumin at a protein concentration of 0.74%; a, phosphate–chloride buffer of ionic strength 0.3, 28 hr. at a field strength of 1.1 volts cm.$^{-1}$; b, phosphate buffer of ionic strength 0.1, 4 hr. at a field strength of 5.0 volts cm.$^{-1}$; c, phosphate buffer of ionic strength 0.05, 2.2 hr. at a field strength of 8.9 volts cm.$^{-1}$.

although considerably less resolution was obtained than at ionic strength 0.1. In accordance with theory the $\epsilon$- and $\partial$-boundary anomalies were diminished and the enantiography of the patterns were increased as a result of increasing the ionic strength.

Because of the strong dependence of relative mobilities upon ionic strength, the "true"[12] electrophoretic distributions of components were determined by extrapolation of apparent distributions to zero protein concentration at constant ionic strength instead of to infinite ionic strength at constant protein concentration or to zero ratio of concentration to ionic strength. The apparent distributions were obtained by electrophoresis in phosphate buffer, *p*H 6.8 and ionic strength 0.1. A representative series of determinations is presented in Table I. The deviations of the apparent from extrapolated relative concentrations of component $A_1$ when plotted against the protein concentration fall on straight lines, arising from the origin. Theoretical deviations for ovalbumin samples containing 82.7 and 68.8% of $A_1$ were calculated by the equations of Dole, and are compared with experimental data in Fig. 2. The agreement between the computed and observed deviations is as good as can be expected considering the nature of the approximations made in the computations.[13] It would appear that Dole's the-

(12) It should be borne in mind that the extrapolated composition has not been shown to be the true value.

(13) The calculations were simplified by including the small contribution of component $A_3$ to the electrophoretic pattern with that of component $A_2$. Thus, the protein was considered as being composed of two components of mobilities $-6.45 \times 10^{-5}$ and $-5.88 \times 10^{-4}$, which correspond to the mobilities of $A_1$ and $A_2$, respectively, at zero protein concentration. These mobilities were obtained by extrapolation of the plot of the reciprocal of the mobility *vs.* the square root of the protein concentration, linear in the range of protein concentration 2 to 0.4%, to zero concentration. This method of extrapolation was suggested by Dr. A. Bueche, Baker Chemistry Laboratory, Cornell University.

In the calculations of the $V\sigma$ products for the boundaries (Dole,[6] equation 33) and of the component concentration ratios across them (Dole,[6] equation 31), (whose summations define the deviations of apparent from true electrophoretic distributions), the following relative mobilities were used: sodium + 1, monohydrogen phosphate −1.10, dihydrogen phosphate −0.66, component $A_1$ −0.322, component $A_2$ −0.293.

The equivalent concentration of component $A_1$ was arbitrarily taken from the net charge per g. of ovalbumin ($-2.7 \times 10^{-4}$ faraday equivalent per g. of protein) as given by the titration data of Cannan, Kibrick and Palmer (*Ann. N. Y. Acad. Sci.*, **41**, 243 (1941)). For component $A_2$ the net charge per gram was assigned the same ratio with that of $A_1$ as between its mobility and the mobility of $A_1$.

ory adequately accounts for the errors involved in ordinary electrophoretic analyses.

TABLE I

ELECTROPHORETIC ANALYSES OF OVALBUMIN

| Experiment | | Protein concentration, % by wt. | Apparent electrophoretic concentration of $A_1$, % | Deviation of apparent electrophoretic from extrapolated concentration of $A_1$, % |
|---|---|---|---|---|
| I | 1 | 1.41[a] | 88.4 | 5.7 |
| | 2 | 0.89[a] | 86.8 | 4.1 |
| | 3 | 0.72[a] | 85.5 | 2.8 |
| Extrapolation | | 0 | 82.7 | |
| II | 1 | 2.6[b] | 90.3 | 12.9 |
| | 2 | 17.[b] | 86.9 | 9.5 |
| | 3 | 1.2[b] | 83.2 | 5.8 |
| Extrapolation | | 0 | 77.4 | |
| III | 1 | 1.96[a] | 85.3 | 11.8 |
| | 2 | 0.95[a] | 79.2 | 5.7 |
| Extrapolation | | 0 | 73.5 | |
| IV | 1 | 1.4[b] | 81.1 | 9.4 |
| | 2 | 1.2[b] | 79.4 | 7.7 |
| | 3 | 0.8[b] | 76.8 | 5.1 |
| Extrapolation | | 0 | 71.7 | |
| V | 1 | 1.87[a] | 81.9 | 13.1 |
| | 2 | 1.05[a] | 76.1 | 7.3 |
| Extrapolation | | 0 | 68.8 | |

[a] From nitrogen determination. [b] From area of electrophoretic pattern. The relation between the protein concentration and the area of the electrophoretic pattern was determined empirically over the concentration range of 0.7 to 2%.

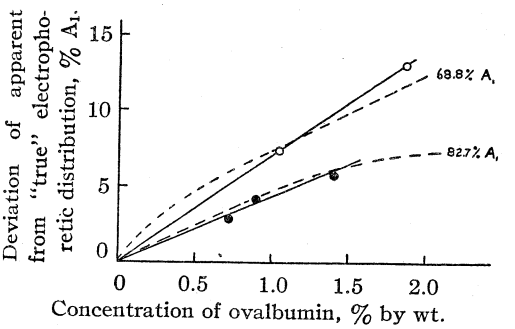



Fig. 2.—Deviations of apparent from "true" electrophoretic distributions: solid line, experimental deviations; broken curve, deviations calculated from the equations of Dole.

**Acknowledgment.**—The author is indebted to Dr. J. G. Kirkwood for his interest in this work and for his review of the manuscript.

## Summary

The electrophoretic analysis of ovalbumin is complicated by the fact that the change of relative mobilities of the components with ionic strength is such that, while resolution into components is obtained at *p*H 6.8 and ionic strength 0.1, only slight if any resolution is found at ionic strength 0.3. "True" electrophoretic distributions of components were obtained by extrapolation of apparent distributions to zero protein concentration at constant ionic strength of 0.1. The moving boundary theory of Dole adequately accounts for the deviations of apparent from "true" distributions.

PASADENA, CALIFORNIA RECEIVED JULY 28, 1948

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

# Spectrophotometric Studies of Complex Formation with Sulfosalicylic Acid. II. With Uranyl Ion

BY ROBERT T. FOLEY AND ROBBIN C. ANDERSON

As part of a series of studies on complex formation with sulfosalicyclic acid, it has been of interest to compare the reactions of uranium—as a member of another transition series of elements—with that of iron. Weil and Rozenblum[1] reported a solid compound of uranium and sulfosalicylate, $[C_6H_3(OH)(SO_3)(COO)]_2U$, but no observations in solution were made. Muller, Fernandes, Mai and Weinland and Hager[2] have reported complex formation between uranyl ion and salicylic acid or various salts.

In this particular investigation reactions of sulfosalicyclic acid in solutions containing uranium as uranyl ion have been studied.

(1) St. Weil and St. Rozenblum, *Bull. tran. inst. pharm. (Poland)*, **1**, 1 (1902).

(2) See R. Weinland and K. Hager, *Z. anorg. allgem. Chem.*, **160**, 193 (1927).

## Experimental

**Materials.**—Uranyl nitrate dihydrate was obtained by vacuum drying the hexahydrate (Eimer and Amend C. P grade) over sulfuric acid. A 0.005 *M* uranyl nitrate solution was prepared by dissolving the proper weight of the dihydrate in water at 25°.

Uranyl acetate dihydrate was also simply weighed and dissolved in water. The salt was Eimer and Amend C. P grade.

The sulfosalicylic acid was a special sample from Eastman Kodak Co. with melting point 112–120° (reported in literature, 108–113°.[3]) Analysis for sulfate gave 0.06%. Solutions of this acid were standarized by titration against a National Bureau of Standards sample of potassium acid phthalate.

**Apparatus.**—Measurements of optical density were made with a Beckmann Model DU Quartz Spectrophotometer, using a tungsten lamp and Corex cells of 10-mm. light path. The cells were held in a thermostatted cell

(3) Schulze, *Apoth. Ztg.*, **51**, 319 (1936).

compartment of design similar to that of Bell and Stryker.[4] Temperature measurements were made directly on the solution in the cells, and, unless otherwise specified, were at 25 ± 0.2° for all determinations.

*p*H measurements were made with a Beckmann *p*H meter, Model G. This was calibrated against a standard buffer.

**Procedure.**—After each solution was prepared, it was allowed to stand one hour in a thermostat at 25°. Preliminary experiments showed that the complex reached equilibrium within one hour and did not change appreciably in the next twenty-four hours. Each sample placed in the thermostatted absorption cells was allowed to stand at least fifteen minutes to reach thermal equilibrium before measurements were made.

## Results

**Absorption Spectra.**—In Fig. 1 are shown typical absorption curves for uranyl acetate solution and for a mixture of uranyl acetate and sulfosalicylic acid solutions.

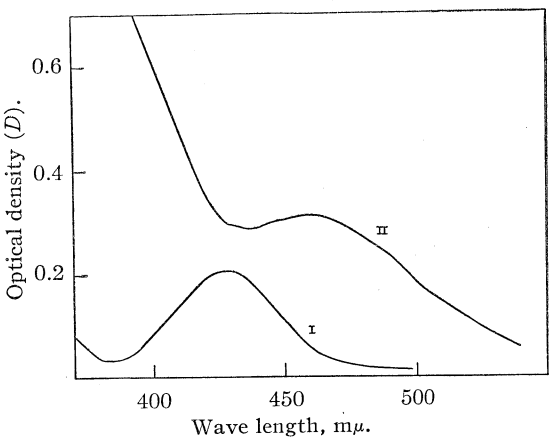



Fig. 1.

Curve I is for a solution 0.005 *M* in uranyl (II) acetate at a *p*H of 4.5. Curve II is for a solution 0.00075 *M* in uranyl acetate and 0.00425 *M* in sulfosalicyclic acid at a *p*H of 4.65. Sulfosalicyclic acid itself shows no appreciable absorption throughout this range. Since the concentration of uranyl salt is much less for curve II than for curve I, it is evident that a complex must be formed with sulfosalicyclic acid—a complex which absorbs much more strongly than uranyl acetate particularly in the region of 460 mμ and just below 400 mμ.

Uranyl nitrate solution showed essentially the same absorption curve as the uranyl acetate. (The peak at 430 mμ in absorption by these solutions possibly involves association with hydroxyl ions. Qualitative tests showed that increase in *p*H—*i. e.*, in hydroxyl ion concentration—causes an increase in intensity of the color in this wave length region. Although acetate also seems to form a complex, the complex does not absorb at this wave length).

**Composition of Complex.**—The composition of the complex was determined by Job's method of continuous variations.[5] In Fig. 2 are shown curves obtained when the quantity $\overline{D}$—the difference between the total optical density of the solution and that which would be shown by the uranyl salt alone if no reaction occurred—is plotted against the ratio

$$[UO_2^{++}]/[UO_2^{++}] + [C_6H_3OHCOOHSO_3H]$$

The curves in Fig. 2 are for mixtures of equimolar solutions of uranyl and sulfosalicylate at *p*H 4.65. The total molarity of uranyl plus sulfosalicylate is 0.005 throughout. Curve I is based on measurements at 400 mμ and Curve II at 460 mμ. Similar curves were obtained at 420 mμ and 440 mμ.

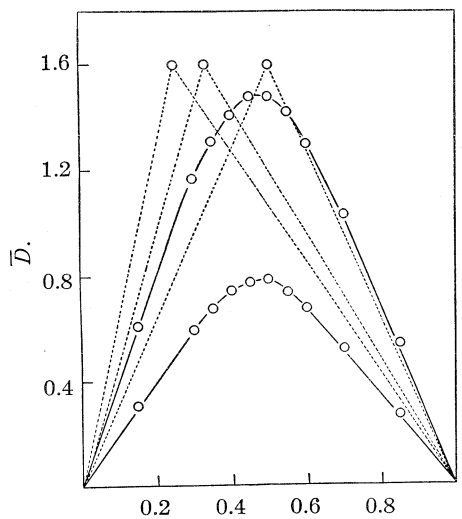



Fig. 2.

The dotted lines with peaks at ratios of 0.25, 0.33 and 0.5 represent theoretical curves which would be obtained for complexes having formulas $MR_3$, $MR_2$, and MR (where R might be sulfosalicylic acid or one of its ions), respectively—if the association reaction to form the complex were complete.

The experimental data clearly indicate that under these conditions a complex containing uranyl and sulfosalicylate in the ratio 1:1 is formed. The fact that the peak of the experimental curve is lower than that of the theoretical indicates that the association reaction is not complete, *i. e.*, that the complex is appreciably dissociated.

Measurements at *p*H 5.1 and 6.1, using acetate buffers, gave maxima at ratios between 0.45 and 0.5, thus indicating that the ratio of uranyl to sulfosalicylate is 1:1 in these regions also. However, measurements at higher *p*H values are more difficult because of the lower absorption.

**Effect of *p*H Change.**—The solution of the complex shows maximum absorption at a *p*H of about 4.5–4.7 and decreases markedly in absorption if the *p*H is increased or decreased, as shown in the curve of Fig. 3 (for $\lambda$ = 440 mμ).

(4) P. H. Bell and C. R. Stryker, *Science*, **105**, 415 (1947).

(5) P. Job, *Ann. chim.*, **9**, 113 (1928); **11**, 97 (1936); *cf.* also R. T. Foley and R. C. Anderson, THIS JOURNAL, **70**, 1195 (1948).

Since the $pK$ value for the second dissociation constant of sulfosalicylic acid is about 2.86 at 25°,[6] the effect of $p$H in the range 2 to 4.7 suggests complex formation must occur between $UO_2^{++}$ and $^-O_3SC_6H_4OHCOO^-$ ions. In this region increasing association to $^-O_3SC_6H_4OHCOOH$ might interfere with complex formation. The decreased complex formation at $p$H values above 4.67 may result from formation of a complex such as $UO_2OH^+$. The tendency of uranyl ion to form basic salts indicates this should be probable, but there is no conclusive evidence on this possibility at present.

**Effect of Acetate.**—It was noted in the experiments using acetate buffers that there was a marked decrease in color of the complex when the buffer was added. Such an effect might result from a change in the ionic strength or from a specific reaction of the acetate. Comparisons were made by adding acetate to one sample of a solution (0.002 $M$ in uranyl and sulfosalicylate) containing the complex and chloride to another so as to produce corresponding changes in ionic strength. These showed that the effect of the acetate is specific, being much greater than the effect of change in ionic strength as shown by the solutions containing chloride (see Table I).

TABLE I

ACETATE EFFECT

| Concn. added salt, moles/l. | Optical density at 460 mμ acetate added | chloride added |
|---|---|---|
| 0 | 0.643 | 0.643 |
| 0.18 | .242 | .620 |
| .36 | .103 | .607 |

Apparently the acetate ion competes with the sulfosalicylate in complex formation but forms a complex which does not absorb in this region of the spectrum. Ghosh and Mitter[7] have reported evidence from spectroscopic studies for the existence of such a complex.

**Dissociation Constant and Free Energy.**—Using optical densities for solutions containing a large excess (9:1 or more) of sulfosalicylic acid, so that as a first approximation the concentration of complex may be taken to be equal to that of uranyl added, one may determine values for the extinction coefficient of the complex.

Typical approximate values (for solutions 0.0005 $M$ in uranyl) are shown in Table II.

TABLE II

APPROXIMATE EXTINCTION COEFFICIENTS

| $T$, °C. | Coefficient, mμ 440 | 460 |
|---|---|---|
| 23.4 | 404 | 432 |
| 29.1 | 413 | 438 |
| 34.3 | 417 | 444 |

(6) Private communications, Dr. R. G. Bates, Nat. Bureau of Stds.

(7) J. C. Ghosh and B. N. Mitter, *J. Ind. Chem. Soc.*, **4**, 353 (1927).

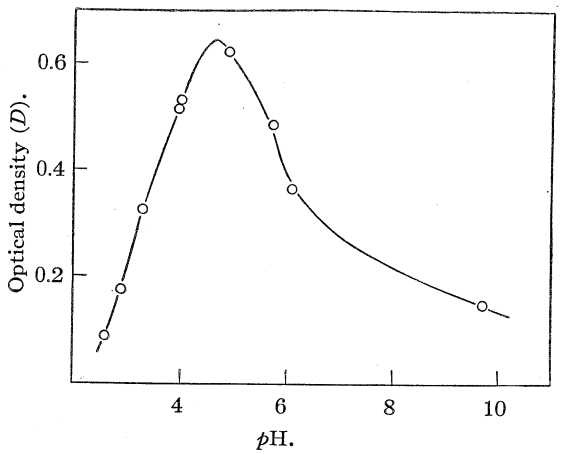



Fig. 3.

From these values one can calculate concentrations of the complex in various mixtures and thus calculate the dissociation constant. The concentration of uranyl ion is then calculated, and correction for its absorption gives a better value for the extinction coefficient of the complex. Successive approximations by this method from data for the various temperatures give for the extinction coefficient at 460 mμ, an average value of 451 (within ±2%). For 440 mμ the average value is 423. From determinations of the equilibrium constant calculated using equilibrium concentrations determined by this method an average value was obtained of

$$K = \frac{[UO_2^{++}][R]}{[UO_2^{++}R]} = 1.3 \times 10^{-4} \pm 0.8 \times 10^{-4}$$

The calculations above involve the initial assumption in each step that Beer's law may be applied for the color of the solution containing uranyl ion and the complex. This is an assumption which cannot be accurate except in very large excess of one of the reagents.[8] The variations in Table II show that it is not entirely accurate here.

A better method is to base calculations of equilibrium constants on comparisons made in solutions of equal or closely similar optical densities. A solution containing uranyl and sulfosalicylate in 1:1 ratio was diluted at constant ionic strength, until solutions were obtained having the same optical densities (after correction for $UO_2^{++}$ absorption by using the known approximate value of $K$ to determine $UO_2^{++}$ concentrations) as those at other ratios such as 2:8, 3:7, etc. In this manner pairs of solutions may be prepared which have the same optical density (from the complex) and thus contain equal concentrations of complex but different total concentrations of each reagent. Since the dissociation constant is the same for both members of a given pair, the concentration of

(8) *Cf.* for example, A. K. Babko, *Zavodskaya Lab.*, **23**, 9 (1947), or *Chem. Abs.*, **41**, 7175 (1947).

complex and thus the value of $K$ may be calculated from the relation

$$K = \frac{(a_1 - x)(b_1 - x)}{x} = \frac{(a_2 - x)(b_2 - x)}{x}$$

where the $a$'s and $b$'s denote initial concentration of uranyl and sulfosalicylate, respectively, and $x$ denotes the concentration of complex formed.

$K$ values calculated by this method are of the same order of magnitude as those obtained by the first method but show greater precision. The average $K$ from several determinations is

$$K = 1.93 \times 10^{-4} \pm 0.08 \times 10^{-4} \text{ (at } 25°)$$

The free energy of *formation* of the complex may be calculated readily from the relation $\Delta F = RT \ln K = -5060$ cal./mole (where $K$ denotes the *dissociation* constant as determined above).

**Temperature Effect and Heat of Reaction.**—From the data in Table II it may be seen that increased temperature tends to increase complex formation but that the effect is not pronounced. A determination of the dissociation constant at 33.2° gave an average value of $1.48 \times 10^{-4} \pm 0.6 \times 10^{-4}$.

It is apparent that the heat of reaction must be small. It can be calculated readily from standard relations, but since the difference in $K$ values is small the effect of experimental errors becomes very pronounced and can outweigh the temperature effect itself. Such a calculation is then of uncertain validity.

**Structure of Complex.**—None of the experiments using Job's method in the region of *p*H 4.6 indicate other than a 1:1 mole ratio in the complex. Since the color fades rapidly as the *p*H changes, there is no evidence for formation of more than one colored complex under the conditions of these experiments.

No attempt should be made to express a structural formula for this complex until more evidence is available, in particular concerning the presence or absence of hydrogen or hydroxide ions.

It may be noted, however, that the low free energy of formation indicates a weak association effect rather than a strong covalent bond. Extraction tests with various organic solvents such as benzene and carbon tetrachloride were unsuccessful, giving no positive evidence for the presence of any neutral, covalent grouping. The 1:1 ratio, the *p*H region in which the maximum effect occurs, and the rapid formation—without appreciable "aging" effect—indicate association of ions such as $UO_2^{++}$ and $^-O_3SC_6H_3OHCOO^-$. This would give an apparent charge of zero, but a "zwitterion" type of structure is possible. The *p*H effect and the apparently high reactivity of the complex with either increase or decrease in *p*H are suggestive of such a structure.

The authors wish to express their appreciation to the Pan American Refining Corporation for its generous support of this work by a fellowship grant (to R. T. F.).

## Summary

1. Spectrophotometric data for solutions with concentrations in the region of 0.005 $M$ and over a *p*H range of 2 to 10 indicate only one complex formed with uranyl ion and sulfosalicyclic acid. This involves a 1:1 mole ratio of uranyl and sulfosalicyclic acid.

2. The effects of changing *p*H, of temperature, and of acetate ion have been studied.

3. The dissociation constant and free energy of formation of the complex have been calculated.

RECEIVED JUNE 9, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

# Spectrophotometric Studies on Complex Formation with Sulfosalicylic Acid. III. With Copper(II)

BY STANLEY E. TURNER AND ROBBIN C. ANDERSON

As part of a series of experiments on complex formation by sulfosalicylic acid with various metal ions in solution[1] a study of its reaction with copper (II) ions has been made.

Spacu and Macarovici[2] reported formation of a deep olive-green complex of composition $[Cu(OC_6H_3CO_2 \cdot SO_3)_2]H_4$ in connection with experiments on copper-cobalt complex sulfosalicylates. Babko[3] has studied the copper-salicylate system and reports a complex of the type CuR from *p*H 3-5 and $CuR_2$ from *p*H 7–9.

## Experimental

The apparatus used was the same as that described previously.[1] Preliminary absorption measurements were made with a General Electric Hardy Recording Spectrophotometer. Data for determination of composition of the complex, temperature effects, etc., were taken with a Beckmann Model DU Spectrophotometer equipped with a thermostat for temperature control in the absorption cells.

*p*H measurements were made with a Beckman model G *p*H meter.

To avoid any interference from iron, Merck Reagent Grade copper sulfate was precipitated and redissolved in ammonium hydroxide. The solution was acidified with nitric acid and evaporated almost to dryness to remove

(1) Robt. T. Foley and Robbin C. Anderson, THIS JOURNAL, **70**, 1195 (1948).

(2) G. Spacu and G. Gh. Macarovici, *Bull. Soc. Stiintje Cluj*, **8**, 364 (1936); *cf. Chem. Abs.*, **31**, 3810 (1937).

(3) A. K. Babko, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 443 (1947), *cf. Chem. Abs.*, **42**, 475 (1948).

ammonium nitrate. The resulting sludge was heated with sulfuric acid to drive off the nitric acid and water. In this manner crystals of copper sulfate with a small amount of residual sulfuric acid were obtained. Solutions were prepared by dissolving this material in distilled water and standardizing electrolytically with a Fisher Scientific Co. Electroanalyzer.

Sulfosalicylic acid and sodium hydroxide were prepared as described earlier.[1]

For comparisons of various mixtures at constant *p*H, the copper(II) sulfate and sulfosalicylic acid were mixed in proportion such as to give the desired final concentration. The mixture was then adjusted to the desired *p*H by adding sodium hydroxide and diluted to final volume with water containing a little sulfuric acid or sodium hydroxide as needed to bring it to the same *p*H.

## Results

**Effect of *p*H.**—Since Babko had reported different complexes in different *p*H ranges with copper(II) and salicylic acid, the effect of *p*H on color of the sulfosalicylate system was first tested. In Fig. 1 are shown three typical transmittance curves taken on the recording spectrophotometer using solutions containing 0.0055 *M* copper(II) sulfate and 0.0075 *M* sulfosalicyclic acid at different *p*H values (5.3 for curve I, 6.8 for II, and 10.9 for III). From a series of such curves at values from *p*H 3.6 to 11.7 it was found that curves for solutions above *p*H 8.5 were of the type of III, with an absorption peak at 660 mμ. Those for solutions of *p*H less than 5.5 were of the type such as I, with maximum absorption at 700 mμ or above. Between *p*H 5.5 and 8.5 there was apparently a transition from type I to III, as illustrated by curve II.

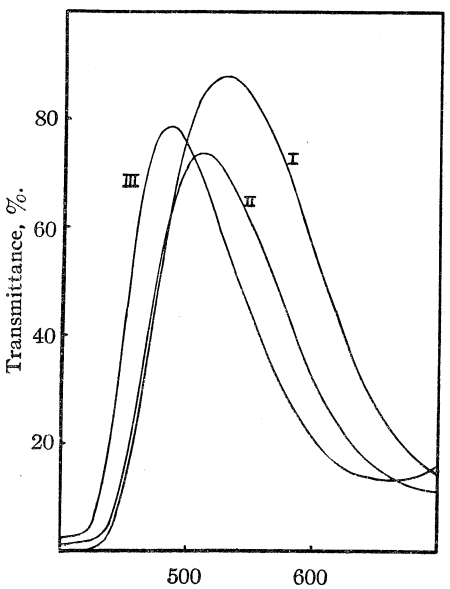



Fig. 1.

This suggested the existence of two different complexes, in this case also. Studies of composition were then made both at *p*H 5 and *p*H 9.

**Complex at *p*H 5.**—The ratio of copper(II) to sulfosalicylic acid in the complex was determined by Job's method of continuous variations.[4] A series of solutions was prepared with varying ratios of copper(II) and sulfosalicyclic acid, but with the total molarity of the two constant at 0.038 *M* and with the *p*H constant at 5. The difference ($\bar{D}$) between the observed optical density of each solution and that which would be given by the original reagents if no association occurred (in this case that of copper(II) since sulfosalicyclic acid is colorless) is plotted against the ratio $[Cu^{++}]/[Cu^{++}] + [HO_3SC_6H_3OHCOOH]$. This gives a curve which should rise to a maximum at a point corresponding to the ratio in which the reagents combine to form the complex.

The results are shown in Fig. 2, curves II and III. Curve II is for data taken at a wave length of 700 mμ and curve III at 630 mμ. The curves clearly indicate a complex of composition CuR (where R might be sulfosalicylic acid or one of its ions).

**Complex at *p*H 9.**—A similar determination by the Job method was made at *p*H 9. The result is shown in curve I of Fig. 2 (the total molarity of copper(II) plus sulfosalicylate being 0.038 *M*). The curve indicates that in this *p*H region the complex is of the type $CuR_2$.

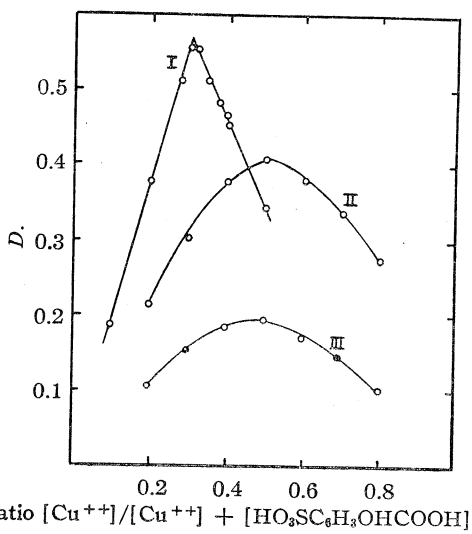



Fig. 2.—Method of continuous variations: I, *p*H 9, λ = 660 mμ; II, *p*H 5, λ = 700 mμ; III, *p*H 5, λ = 630 mμ.

**Effect of Temperature.**—Tests made over a range of 20 to 30°, showed only a small temperature effect practically within the range of experimental error. The tendency toward complex formation does show a slightly increasing trend with increase in temperature. Typical data are shown in Table I.

**Dissociation Constants.**—To determine the dissociation constant of the complex at *p*H 5 a mixture containing 0.019 *M* copper(II) and 0.019 *M* sulfosalicylate (corresponding to the

(4) P. Job, *Ann. chim.*, **11**, 97 (1936); *cf.* Vosburgh and Cooper, THIS JOURNAL, **63**, 436 (1941).

TABLE I

TEMPERATURE EFFECT, ($[Cu^{II}] = 0.019 = [HO_3SC_6H_3OHCOOH]$, $p$H = 5)

| Temp., °C. | Optical density 630 | Optical density 700 |
|---|---|---|
| 22 | 0.235 | 0.492 |
| 25 | .236 | .493 |
| 27 | .239 | .496 |
| 30 | .241 | .495 |

peak of curves II and III, Fig. 2) was diluted in successive stages—adding sodium sulfate as needed to keep the ionic strength constant. From this dilution curve and the data of Fig. 2 a series of pairs of solutions could be selected, having equal optical density (and thus essentially equal concentrations of complex) but different concentrations of reagents. From the equation

$$K = \frac{[Cu_1^{II} - X][R_1 - X]}{X} = \frac{[Cu_2^{II} - X][R_2 - X]}{X}$$

$X$ and $K$ could then be calculated since the values for $Cu^{II}$ and $R$ were known.

As a first approximation the effect of $Cu^{++}$ on the optical density was neglected, but, by using the value of $K$ so obtained, correction could be made for the optical density of unreacted $Cu^{++}$ and better values for $K$ determined. Results are shown in Table II for data at 630 mμ and 25°. A similar determination at 700 mμ gave a value in agreement with that at 630 mμ, but the variations are larger since much higher corrections have to be applied for absorption by copper(II) ions.

TABLE II

DISSOCIATION CONSTANT

| Total $[Cu^{++}$ | Total [R] | $K$ |
|---|---|---|
| 0.0076 | 0.0304 | $1.7 \times 10^{-3}$ |
| .0114 | .0266 | 2.3 |
| .0152 | .0228 | 2.0 |

Mean value = $2 \times 10^{-3}$

$K$ can also be determined by assuming that, in solutions containing large excess of sulfosalicyclic acid, association is complete. A value for the extinction coefficient can then be calculated and used to determine dissociation in other solutions. This method gives $K$ values showing wider variation than the data of Table II, but the average value is $1.8 \times 10^{-3}$—in agreement with the result above.

The approximate extinction coefficients as determined by this method were 16 at 630 mμ and 33 at 700 mμ.

The dissociation constant for the $CuR_2$ type complex cannot be determined so well because the data are not sufficiently accurate to permit correction for effects of precipitation, dissociation to the CuR type complex, and similar factors. However, the sharp peak at the maximum of curve I, Fig. 2 indicates that dissociation is small. Assumption that dissociation is negligible in the presence of fairly large excess of sulfosalicyclic acid (for example where the ratio $[Cu^{++}]/([Cu^{++}] + [R]$ is 0.1) should be reasonably well justified.

From the observed optical densities of such solutions, a value of 53 was obtained for the approximate extinction coefficient of the complex at 660 mμ. Using this extinction coefficient, the concentrations of complex in other solutions and the dissociation constant were determined. An average value of $8 \times 10^{-7}$ for $K$ at 25° was obtained. It should be noted that the results show some "drift," the $K$ value increasing somewhat as the proportion of sulfosalicyclic acid decreases. Such an effect must be expected since no correction could be made for the presence of the 1:1 complex.

From the dissociation constants above, one may calculate the free energies of formation: $\Delta F = RT \ln K$. This gives a value of −3700 cal./mole for the free energy of formation of the complex of type CuR and approximately −8000 cal./mole for the type $CuR_2$.

**Structure of the Complex.**—The close resemblance in reactions of copper(II) with salicylic and sulfosalicylic acids indicates that linkage occurs with the carboxyl and/or phenolic groups. Since at $p$H 5 the carboxyl group is largely dissociated, the 1:1 complex is probably a combination of $Cu^{++}$ and $^-O_3SC_6H_3OHCOO^-$ ions. At $p$H values in the region of 9, it seems likely that the phenolic group is also involved—the linkage with two carboxyl and two phenolic groups being in accord with the normal coördination number of 4 for the copper.

The authors wish to acknowledge the coöperation and assistance of Mr. L. L. Antes, Bureau of Engineering Research, in making the measurements with the recording spectrophotometer. This research was supported by a grant from the University of Texas Research Institute.

## Summary

Spectrophotometric measurements indicate copper(II) ions and sulfosalicylate ions react in a 1:1 ratio in the $p$H range 3–5.5 and a 1:2 ratio at $p$H values above 8.5, with mixtures of the two forming in the intermediate ranges.

Temperature changes within ordinary ranges were found to have little effect on the complexes.

Dissociation constants and approximate extinction coefficients for the two complexes have been determined.

RECEIVED AUGUST 30, 1948

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, CONTRIBUTION NO. 1239]

# Kinetics of the Oxidation of Hypophosphorous Acid by Iodate Ion

BY PHILIP HAYWARD AND DON M. YOST

**Introduction.**—The rates of oxidation of hypophosphorous acid, $H_3PO_2$, to phosphorous acid, $H_3PO_3$, with various oxidizing agents have been the subject of a number of investigations.[1,2] An interesting feature was found to be common to all these reactions, namely, that the rate of reaction became independent of the concentration of oxidizing agent when this was made sufficiently large. To explain this phenomenon, the hypothesis has been made that hypophosphorous acid in aqueous solution exists in both a "normal" and an "active" form, the latter being much more reactive, and that the conversion of the normal to the active form occurs at a measurable rate. These suppositions lead to a rate law which agrees well with experiment; however, the nature of the postulated active form is unknown, although the present consensus is that it contains a univalent phosphorus atom. It seemed of interest, however, to extend the range of investigations on hypophosphorous acid in the hope of gaining a better understanding of its reactions.

## Experimental

The choice of iodate as the oxidizing agent leads to a rather complicated system, from the kinetics point of view. After the initial iodate–hypophosphorous acid reaction (1) has begun, there may also take place; (2) the iodate–iodide reaction; (3) the iodate–phosphorous acid reaction; (4) the iodine–hypophosphorous acid reaction; (5) the iodine–phosphorous acid reaction. Reaction (2), being very rapid in acid solution, is the chief trouble-maker, and any scheme for suppressing it would of course also dispose of (4) and (5). Reaction (3) seems to be unavoidable, but fortunately was found to be of minor importance. Our attention was therefore devoted mainly to minimizing the contribution of the iodate–iodide reaction. Successive approaches to this problem consisted of (1) measuring initial rates, abandoning a run as soon as a definite iodine color had appeared; (2) stirring the reaction mixture with finely divided silver chloride (several grams in 200–300 ml. of solution), a procedure which served to keep down the iodide ion concentration; (3) carrying out the reaction in the presence of small amounts of *n*-propanol, a substance which apparently inhibits the iodate–iodide reaction.[3]

C. P. chemicals were used throughout, and solutions were made up using ordinary distilled water. For about half of the experiments, stock solutions of hypophosphorous acid were prepared, either by treating phosphorus with barium hydroxide and obtaining the acid from barium hypophosphite, or as was suggested by Professor L. C. Pauling, by converting sodium hypophosphite to the acid by means of an Amberlite ion-exchange column. These solutions contained various amounts of phosphorous acid, the mole percentage being in no case higher than 4. For the rest of the experiments, stock solutions of sodium hypophosphite were used; these always contained negligible amounts of phosphite. Sulfuric acid was used when additional acid was needed. On occasion, the ionic strengths of the reaction mixtures were varied by adding potassium nitrate.

The reactions were usually carried out in glass-stoppered flasks placed in a water-bath, the temperature of which was kept constant within 0.02°. Samples of the reaction mixture were analyzed for iodate by running them into acidified potassium iodide solution and immediately titrating the iodine liberated with thiosulfate. Experiment showed that the error caused by the iodine–hypophosphorous acid reaction in this procedure is negligible.

**Calculations.**—The rate law upon which calculations were based is of the form given by Mitchell[1]

$$-\mathrm{d}(IO_3^-)/\mathrm{d}t = \frac{k_1(H^+)(H_3PO_2)}{1 + k_2(H^+)/k_3(IO_3^-)}$$

where the constants $k_1$, $k_2$, $k_3$ refer to the reactions

$$(H_3PO_2)_I \underset{k_2}{\overset{k_1}{\rightleftarrows}} (H_3PO_2)_{II} \xrightarrow{k_3} \text{products}$$

Here $(H_3PO_2)_I$ denotes the normal form of hypophosphorous acid, $(H_3PO_2)_{II}$ the active form. It should be observed that since the $k_1$ and $k_2$ reactions have been shown to be subject to general acid catalysis,[2] the above rate law is really a special case of a more inclusive expression, which may be written

$$-\mathrm{d}(IO_3^-)/\mathrm{d}t = \frac{(\Sigma k[HA])(H_3PO_2)}{1 + \Sigma k_2^a[HA]/k_3(IO_3^-)}$$

Here HA is any substance capable of furnishing a proton, such as water, bisulfate ion, undissociated hypophosphorous acid, etc., and $k^a$ is the corresponding catalytic coefficient. The simpler form of the rate law, however, was found to express the results sufficiently well for our purpose.

The reaction rates in this discussion are all given with respect to iodate ion, the units being moles per liter and hours. For purposes of calculation, the iodate concentrations were plotted against time on a large scale, and a smooth curve was drawn through the points. From these graphically smoothed data the rates of reaction at various times were found by numerical differentiation. These rates were also smoothed graphically, and the smoothed values used in the calculation of rate constants.

The stoichiometry of the iodate–hypophosphorous acid reaction was found experimentally to be expressed by the equation

$$IO_3^- + 3H_3PO_2 = I^- + 3H_3PO_3$$

The concentration of hypophosphorous acid at any time could therefore be obtained from the corresponding iodate concentration, provided the hydrogen ion concentration and the dissocia-

(1) Mitchell, *J. Chem. Soc.*, **117**, 1322 (1920), and succeeding papers, 1921–1924.

(2) Griffith and McKeown, *Trans. Far. Soc.*, 530 (1934); Griffith, McKeown and Taylor, *ibid.*, **36**, 752 (1940).

(3) Neogi and Sen, *J. Ind. Chem. Soc.*, **8**, 725 (1931); *C. A.*, **26**, 1178 (1932).

tion constant of hypophosphorous acid were known. It is here that the calculations are subject to considerable error. Dissociation constants of the acid at various ionic strengths were taken from the paper of Griffith, McKeown and Taylor.[2] Where sulfuric acid of sulfate–bisulfate buffer solutions were used, the data of Harned and Hamer[4] were used to calculate dissociation constants of bisulfate ion. The acidity at any time was assumed to be due solely to the hypophosphorous and sulfuric acids present, no correction being made either for the production of phosphorous acid during a run or for possible incomplete dissociation of iodic acid. Neglect of the first factor is justified both because hypophosphorous and phosphorous acids are of approximately equal strengths and because actual *p*H measurements during the course of the reaction showed (with an exception to be mentioned later) no significant change in acidity.

**Results and Discussion. 1. Determination of Initial Rates.**—In these experiments the attempt was made to determine the order of the reaction with respect to the various reactants. Figure 1 gives the results of a set of experiments designed to test simultaneously the dependence of the order on the hydrogen ion concentration and the concentration of (undissociated) hypophosphorous acid. In these experiments, the iodate concentration and the total concentration of hypophosphorous acid (undissociated acid plus hypophosphite ion) were kept constant, and the acidity varied by adding sulfuric acid. If the rate were proportional to the first power of both hydrogen ion and hypophosphorous acid concentrations, a straight line should result from plotting initial rate against $(H^+)^2/(K + (H^+))$, where $K$ is the ionization constant of hypophosphorous acid. It is seen that there is a linear relationship at lower acidities, but evidence of a falling off from this linear increase in rate at higher acidities. This, of course, is to be expected if the rate law derived by Mitchell is adhered to in this case, for when the ratio $(H^+)/(IO_3^-)$ becomes sufficiently large, the rate becomes independent of $(H^+)$.

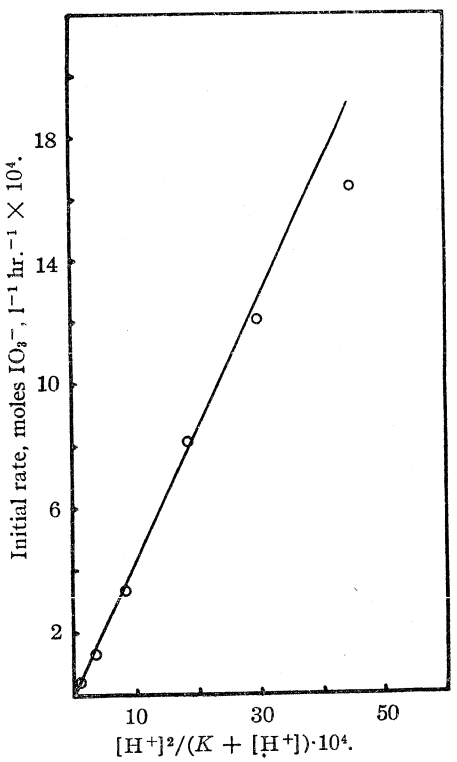



Fig. 1.—Dependence of initial rate on $[H^+][H_3PO_2]$ in the oxidation of hypophosphorous acid by iodate ion.

(4) Harned and Hamer, THIS JOURNAL, **57**, 27 (1935).

Another set of experiments, in which the iodate concentration was made small compared to the hypophosphorous acid concentration, was designed to test the dependence of rate on iodate concentration. Under such conditions, the assumed rate law can be written

$$\frac{1}{\text{initial rate}} = \frac{1}{k_1(H^+)(H_3PO_2)} + \frac{k_2}{k_3k_1(H_3PO_2)} \times \frac{1}{(IO_3^-)} = C + \frac{D}{(IO_3^-)}$$

where $C$ and $D$ are constants. Figure 2 shows the data plotted in conformity with this relation; the expected linearity is fairly apparent. However, it must be remarked that the subsequent evaluation of $k_1$ leads to a value of about $2.3 \times 10^3$ for the intercept $C$, instead of to a value of approximately zero, as shown in Fig. 2. In other words, the initial rates are higher than the rate law would predict. The major part of this discrepancy can probably be explained by the fact that the reaction mixtures were heavily buffered with phosphate, the catalytic effect of which in this case is considerably greater than that of hydrogen ion alone. Using the catalytic coefficients given by

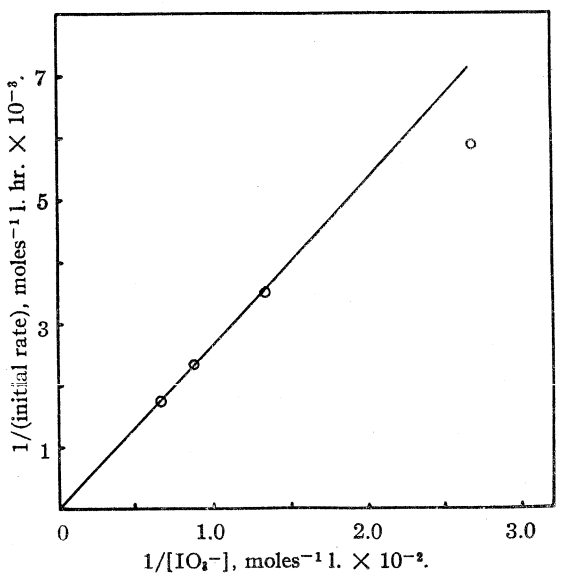



Fig. 2.—Dependence of initial rate on $[IO_3^-]$ in the rate of reduction of iodate ion by hypophosphorous acid.

Griffith, McKeown and Taylor,[2] we find the value of $C$ to be reduced to about $0.2 \times 10^3$, which, in view of the uncertainties in the initial rates, is now in reasonable agreement with the value found graphically. These phosphate buffers were not used in other experiments, which are therefore not subject to such a major correction.

The rate law can be written in the form

$$k_1 = \frac{\text{rate}}{(H^+)(H_3PO_2)} + \frac{\text{rate}}{(IO_3^-)(H_3PO_2)} \frac{k_2}{k_3} = A + B\frac{k_2}{k_3}$$

The experimentally determined quantities $A$ and $B$ determine the intercept and slope of a straight line, any point of which gives a pair of values of $k_1$ and $k_2/k_3$. Altering the experimental conditions should, by altering $A$ and $B$, give a family of straight lines which intersect in a point, the coördinates of which are the required values of $k_1$ and $k_2/k_3$. The results given by this procedure are presented in Table I.

TABLE I

"INTERACTION" VALUES OF $k_1$ AND $k_2/k_3$ AT 30°

| $k_1$, moles$^{-1}$ l. hr.$^{-1}$ | $k_2/k_3$ |
|---|---|
| 8.1 | 0.50 |
| 8.5 | .54 |
| 8.7 | .57 |
| 10.4 | .82 |
| 9.0 | .84 |
| 10.0 | .42 |
| 9.4 | .40 |
| 9.4 | .37 |
| 9.3 | .35 |
| 8.7 | .31 |
| 7.9 | .20 |
| Average 9.0 ± 0.7 | 0.48 ± 0.19 |

**2. The Reaction in the Presence of Silver Chloride.**—By stirring the reaction mixtures with silver chloride, it was found possible, if the acidity and iodate concentration were not too high, to prevent entirely the appearance of iodine. Blank experiments showed that oxidation of hypophosphorous acid by silver ion under these conditions was not appreciable, nor was there any evidence for precipitation of silver iodate. This procedure widened considerably the range of practicable initial conditions; also, since the reaction could now be followed through a greater portion of its course, $k_1$ and $k_2/k_3$ could be estimated from each experiment. From the rate law written in the form

$$(H_3PO_2)/\text{rate} = \frac{1}{k_1(H^+)} + \frac{k_2}{k_3k_1} \times \frac{1}{(IO_3^-)}$$

it can be seen that plotting the left-hand side against $1/(IO_3^-)$ should give a straight line from whose intercept and slope the values of $k_1$ and $k_2/k_3$ could be obtained.

This linearity was always found, at least during the first part of a run. Later on, the slopes of the curves often decreased markedly, an effect which is probably to be attributed to the iodate–phosphorous acid reaction, since the reaction mixtures usually began to give positive tests for phosphate at about the point where the curves began to drop off. It is possible that the phosphorous acid produced is responsible also because its catalytic effect is about twice that of hypophosphorous acid.[2] Table II and Fig. 3 give the results obtained from one of the best runs of this kind.

TABLE II

THE IODATE–HYPOPHOSPHITE REACTION AT 30.06° IN THE PRESENCE OF SILVER CHLORIDE

$[\Sigma H_3PO_2]_0 = 0.0525$, $K_{H_3PO_2} = 0.076$, $[H^+] = 0.037$, $\mu = 0.13$, temp., 30.06°

| Time, hours | $[IO_3^-]$, $\times 10^3$ | $[H_3PO_2]$, $\times 10^2$ | Rate, moles l$^{-1}$ hr.$^{-1}$, $\times 10^3$ |
|---|---|---|---|
| 0 | 11.59 | 1.73 | 3.38 |
| 0.25 | 10.72 | 1.64 | 3.12 |
| 0.50 | 9.95 | 1.56 | 2.85 |
| 0.75 | 9.23 | 1.49 | 2.60 |
| 1.0 | 8.51 | 1.42 | 2.37 |
| 1.25 | 7.90 | 1.36 | 2.15 |
| 1.50 | 7.35 | 1.31 | 1.96 |
| 1.75 | 6.83 | 1.26 | 1.79 |
| 2.0 | 6.35 | 1.21 | 1.65 |
| 2.25 | 5.93 | 1.17 | 1.53 |
| 2.50 | 5.55 | 1.13 | 1.43 |
| 2.75 | 5.17 | 1.09 | 1.32 |
| 3.0 | 4.86 | 1.06 | 1.23 |

The averages of thirty-nine determinations of $k_1$ and $k_2/k_3$, both by the method just indicated and by the "intersection" method previously described, are 12.2 ± 3.0 moles$^{-1}$ l. hr.$^{-1}$ and 0.48 ± 0.25, respectively.

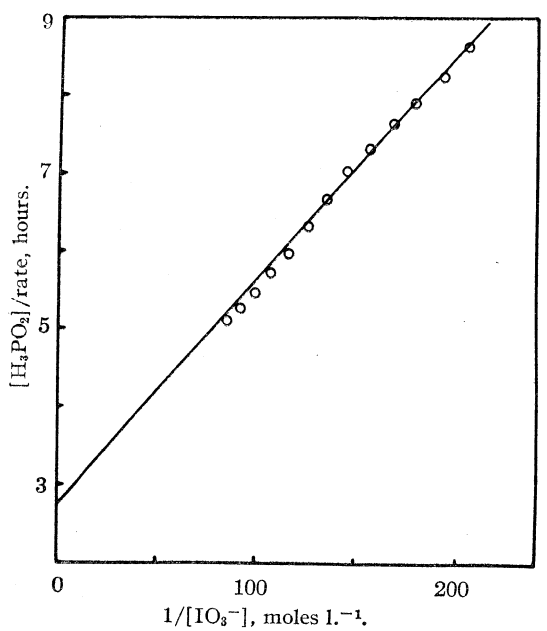



Fig. 3.—The rate of oxidation of hypophosphorous acid by iodate ion in the presence of solid AgCl.

**3. The Reaction in the Presence of *n*-Propanol.**—In these experiments small concentrations (never more than 7 volume per cent.) of

*n*-propanol were added to the reaction mixture. Tests showed that varying the concentration of alcohol in this range did not appear to have a significant influence on the rate, that there was no reaction between iodate and *n*-propanol, and that its presence did not interfere with the thiosulfate titrations. The dielectric constants of the solutions were lowered by as much as four per cent. by the addition of the alcohol,[5] but the error thus introduced into the calculations of hydrogen ion and hypophosphorous acid concentrations is hard to estimate quantitatively. At any rate, it was considered to be negligible, in view of the already considerable uncertainty in these quantities.

It was found that, while there was no apparent retardation of the reaction rate between iodate and hypophosphorous acid, the time of appearance of iodine was indeed delayed to an extent which, other things being equal, was quite accurately proportional to the amount of *n*-propanol added. It was noticed also that, while in previous experiments the acidity remained sensibly constant, in these experiments it dropped continuously, as shown by a *p*H meter. On this account, sodium sulfate–sodium bisulfate buffer solutions were used in some of the experiments designed to evaluate $k_2/k_3$; in other cases, when the acidity was not sufficiently well controlled, the calculated hydrogen ion concentrations were made proportional to their measured values.

It was now possible to work with such high iodate concentrations that a good first approximation to $k_1$ could be determined directly from the limiting form of the rate equation

$$k_1 = \text{rate}/(H^+)(H_3PO_2)$$

Using an average value of $k_1$ determined thus, values of $k_2/k_3$ could be found from experiments at lower iodate concentrations. These were used to correct the values of $k_1$, which in turn gave a final small correction in $k_2/k_3$. The values of the rate constants obtained using this technique agreed more closely among themselves than did those from the other experiments, and we therefore believe them to be the most reliable. Table III presents data from a representative experiment.

TABLE III

THE IODATE–HYPOPHOSPHITE REACTION AT 30.06° IN THE PRESENCE OF *n*-PROPANOL

$[\Sigma H_3PO_2]_0 = 0.0960$, $K_{H_3PO_2} = 0.078$, $[\Sigma H_2SO_4]_0 = 0.0172$, $\mu = 0.46$, concn. *n*-propanol = 7 vol. per cent.

| Time, hours | $[IO_3^-]$ | Rate, moles $l.^{-1}$ $hr.^{-1}$, $\times 10^3$ | $[H^+] \times 10^2$ | $[H_3PO_2]$, $\times 10^2$ | $k_1$ (uncor.) |
|---|---|---|---|---|---|
| 0.0 | 0.1433 | 2.70 | 1.60 | 1.63 | 10.35 |
| 0.25 | .1426 | 2.58 | 1.58 | 1.58 | 10.33 |
| 0.50 | .1420 | 2.45 | 1.55 | 1.53 | 10.32 |
| 0.75 | .1413 | 2.32 | 1.52 | 1.46 | 10.52 |
| 1.0 | .1407 | 2.19 | 1.49 | 1.41 | 10.42 |
| 1.25 | .1402 | 2.06 | 1.47 | 1.37 | 10.22 |
| 1.50 | .1396 | 1.93 | 1.45 | 1.33 | 10.00 |
| 1.75 | .1391 | 1.80 | 1.42 | 1.28 | 9.92 |
| 2.00 | .1387 | 1.67 | 1.40 | 1.25 | 9.55 |
| 2.25 | .1382 | 1.54 | 1.37 | 1.20 | 9.38 |

(5) Åkerlöf, THIS JOURNAL, **54**, 4125 (1932).

For $k_1$, the average value at 30.06° was found to be 9.7 ± 0.8 moles$^{-1}$ l. hr.$^{-1}$, and for $k_2/k_3$, 0.44 ± 0.03. These are to be compared with the values determined by Mitchell for the iodine reaction, which when adjusted to 30° and converted to these units amount to 9.0 and 0.012, respectively. The two values for $k_1$ are the same, within the limits of error, but $k_2/k_3$ is very different in the two cases. Recalling the interpretation of this constant, and assuming that $k_2$ has the same value in both reactions, we should conclude from this that the reaction of the active form of hypophosphorous acid with the halogens and mercuric ion is about thirty-five times faster than with iodate. It is interesting to point out in this connection that the iodate ion is unlike the other oxidizing agents studied in that it is not a simple neutral molecule or cation.

Increasing the ionic strength from 0.27 to 0.65 had no significant effect on the magnitude of $k_1$, and an increase from 0.66 to 1.29 cause $k_2/k_3$ to decrease from 0.47 to 0.42—a change which is also probably not significant, in view of the uncertain effects of changing ionic strength on the hydrogen ion and hypophosphorous acid concentrations. It is to be noted that the indifference of $k_2/k_3$ to changes in ionic strength is in accord with the postulated reaction-mechanism, in which both the $k_2$ and $k_3$ reactions involve a neutral molecule—*i. e.*, the active form of hypophosphorous acid.

The rate constants were also determined by means of similar experiments at 20.27°, the values being 3.66 for $k_1$ and 0.35 for $k_2/k_3$; these represent temperature coefficients of 2.7 and 1.3 per 10.4°, respectively. The corresponding activation energies are 17 and 4.5 kcal. The value for the temperature coefficient of the $k_1$ reaction is considerably below that of 3.14 per 10° found by Mitchell for the iodine reaction. Also, he states that the temperature coefficient of $k_2/k_3$ is "approximately unity"; lacking the data on which he based this statement, it may be that his value is compatible with the one found here.

**Acknowledgments.**—We wish to thank Professor E. H. Swift for help with analytical problems, Dr. Norman Davidson for general criticism, and Mr. Fred Ordway for the construction of a nomograph which materially shortened the labor of calculation. We also acknowledge the courtesy of the International Resin Corporation in supplying a sample of Amberlite IR-100 ion exchange resin for the preparation of hypophosphorous acid. The work was supported by a grant from The Research Corporation, and we are greatly indebted to them for this aid.

## Summary

The hypothesis that a normal and an active form of hypophosphorous acid coexist in aqueous

solution, and that the conversion of the normal to the active form can be a rate-determining step in its reactions with oxidizing agents, is supported by a study of the kinetics of its oxidation by iodate ion. The rate law

$$-d(IO_3^-)/dt = \frac{k_1(H^+)(H_3PO_2)}{(1 + k_2(H^+)/k_3(IO_3^-)}$$

is found to be in agreement with observation, the best values of the constants at 30° being 9.7 moles$^{-1}$ l. hr.$^{-1}$ for $k_1$ and 0.44 for $k_2/k_3$. The respective activation energies are 17 and 4.5 kcal.

It is probable that iodate ion reacts with the active form of hypophosphorus acid at a much slower rate than do other substances conforming to this rate law.

PASADENA, CALIFORNIA RECEIVED AUGUST 30, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# An Oxidation-Reduction Cycle in Emulsion Polymerization Systems[1]

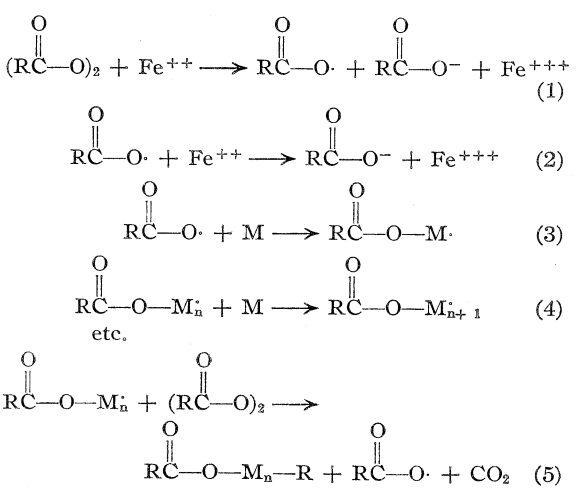
BY F. T. WALL AND T. J. SWOBODA[2]

## Introduction

The physical and chemical properties of synthetic polymers depend markedly upon the conditions under which they are made, particularly upon the temperature of polymerization.[3] In certain instances a superior product is obtained when the polymerization is carried out at low temperatures, but the rate of reaction may be so slow that the process is impractical. For this reason considerable effort has been directed toward activating polymerization catalyst systems to obtain substantial rates of polymerization at reduced temperatures.

For a polymerization taking place through a free radical mechanism, the over-all rate of reaction depends, among other things, upon the concentration of free radicals present. It would appear, therefore, that a high rate of polymerization might be attained at low temperatures if a sufficiently high concentration of free radicals could be realized. Unfortunately, the thermal decompositions of certain free radical producing compounds such as benzoyl peroxide are so slow[4] at reduced temperatures that they exhibit little or no catalytic effect under those conditions.[5] However, it is found that the formation of free radicals from benzoyl peroxide can be considerably hastened by the presence of ferrous iron. Since ferrous iron is a reducing agent and the peroxide an oxidizing agent, the combination is said to constitute a "Redox" system, and the increased catalytic effect of the peroxide is said to be the result of reduction activation.

The fundamental work of Haber and Weiss[6] on the reactions of iron with hydrogen peroxide forms the basis for the chemical aspects of reduction activation. Baxendale, Evans and Parks[7] made use of an iron–hydrogen peroxide system for the polymerization of acrylonitrile. If one employs an organic peroxide in place of hydrogen peroxide, the following reactions can be expected to occur in a polymerization system activated with ferrous iron



Reaction (1) involves the formation of one free radical and one acid ion, the latter being combined in some form of salt. (The use of the ionic nomenclature in this connection is for the purpose of designating the states of oxidation instead of the actual states of matter which are not necessarily in ionized form.) Reaction (2) represents the destruction of the initially formed free radicals by ferrous ions. It is clear that unless some other reaction intervenes to prevent (2) from occurring, the final result will simply be the complete reduction of the peroxide by the iron. If some polymerizable monomer is present, then reactions (3) and (4), which are precisely the polymer chain growth reactions, can occur. More-

(1) This investigation was carried out in part under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program, and was first reported on October 30, 1947. ADDED IN PROOF: Since the preparation of this manuscript, the authors have learned of some work by Werner Kern, "Die makromolekulare Chemie," **B1**, 199–268 (1948), dealing with topics closely related to those discussed in the present paper. Kern's findings are entirely compatible with those here indicated, although the cyclical aspect of the behavior was not emphasized.

(2) Firestone Tire and Rubber Company research fellow.

(3) Private communication from the Office of Rubber Reserve.

(4) McClure, Robertson and Cuthbertson, *Canadian J. Research*, **20B**, 103 (1942); Cass, THIS JOURNAL, **68**, 1976 (1946).

(5) Nozaki and Bartlett, *ibid.*, **68**, 1686 (1946).

(6) Haber and Weiss, *Proc. Roy. Soc. (London)*, **147A**, 332 (1934).

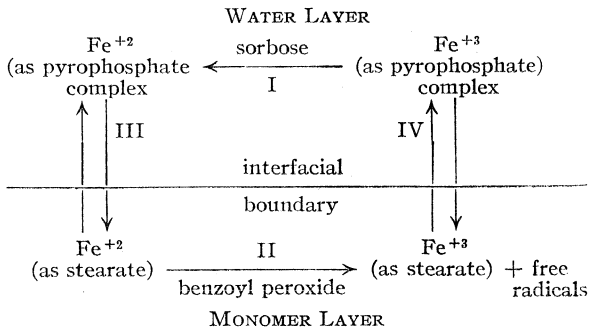
(7) Baxendale, Evans and Parks, *Trans. Far. Soc.*, **42**, 155 (1946).

over, once a monomer of the vinyl type has added to the initial free radical, the resulting free radical is no longer subject to the reaction represented by equation (2), since a stable salt can no longer be formed. However, a polymeric free radical can undergo reaction (5) which is equivalent to the induced free radical decomposition discussed by Nozaki and Bartlett.[5] Reaction (5) is also equivalent to chain transfer or modification so it is apparent that a peroxide can serve both as a catalyst and as a modifier[8] in a polymerization system.

If an appreciable amount of ferrous iron is brought into contact with an organic peroxide, reactions (1) and (2) take place so rapidly that the catalyst is soon spent. Accordingly, if reduction activation is to be of any use for promoting polymerization, some means must be found for controlling reaction (1) and for minimizing reaction (2) which does no good in a polymerization system. A solution to this problem can be found by keeping the iron concentration very low relative to the concentrations of the peroxide and of the monomer, since under these circumstances the rate of reaction (1) would be reduced to a reasonable value and reaction (3) would predominate over reaction (2). This pattern suggests that continuous addition of small amounts of ferrous iron to the polymerization recipe might give rise to the desired state of affairs. Although such addition by mechanical means is highly impractical, the same result can fortunately be accomplished in an emulsion system when appropriate auxiliary reagents are present. Thus certain highly effective "Redox recipes" for the preparation of a variety of polymers, such as the copolymer of butadiene and styrene, have actually been devised by polymerization technologists.[3] These recipes are complex reaction systems which involve a variety of substances in addition to the monomer, peroxide, and iron. The work reported here was undertaken to establish the role of each of the reagents in these recipes. It is our conclusion that a certain reaction cycle, to be called the "Redox Cycle," takes place, and that each of the reagents present in the simplest effective recipe serves a definite purpose in this cycle.

## The Emulsion "Redox" System

A typical recipe[9] for a "Redox" polymerization consisting only of those reagents which are necessary and sufficient is: 20 g. monomer, 40 g. water, 0.1 g. benzoyl peroxide, 0.1 g. ferric ammonium sulfate, 0.1 g. sorbose, 0.1 g. sodium pyrophosphate, 1.0 g. sodium stearate. In place of ferric ammonium sulfate, it is permissible to substitute ferrous ammonium sulfate for reasons which will be made clear presently. As we have already seen, if ferrous iron is present, such iron can react with benzoyl peroxide to form free radicals. Those free radicals then combine with monomer ultimately building up polymer molecules. It remains to be seen how the above recipe controls the decomposition of benzoyl peroxide to sustain a smooth and rapid polymerization at reduced temperature. As a result of this investigation, it appears that the following cycle properly describes the behavior of the system




The iron in the emulsion is originally present as ferric iron which is tied up for the most part as the pyrophosphate complex in the aqueous phase. But the ferric iron can be reduced by sorbose or some other reducing sugar to form ferrous iron, a large portion of which also remains as a pyrophosphate complex in the water layer. However, limited amounts of both ferrous and ferric iron will tend to pass into the oil phase, presumably as the stearate salts, since ferrous and ferric stearates are oil soluble compounds. The distribution between the phases will occur in accordance with the usual laws governing distribution of solutes between immiscible solvents. In the oil phase the ferrous iron can react with benzoyl peroxide to form free radicals and ferric iron. The free radicals start the polymerization going and the ferric iron ultimately passes back into the water layer to maintain distribution equilibrium. Since the iron finally returns to its original form, the net result of the whole process is the reduction and decomposition of benzoyl peroxide by sorbose.

Several factors contribute to the effectiveness of the cycle described above. First of all, the amount of iron present in a form capable of reacting with the peroxide is quite small. This means that reaction (1) will proceed at a moderate rate and will be followed almost exclusively by reaction (3), because of the large excess of monomer. Nevertheless, the total amount of iron in the system is appreciable, and hence can be readily controlled for reproducible results. The pyrophosphate serves to tie up most of the iron in complex form, thus providing a reservoir of iron to be drawn from as needed. If the pyrophosphate were not present, too much of the ferrous iron would be solubilized in the organic phase with the result that the peroxide would be decomposed too rapidly for sustained polymerization. Moreover, in the absence of pyrophosphate there would be little tendency for the ferric iron to be drawn into the water layer

(8) Snyder, Stewart, Allen and Dearborn, THIS JOURNAL, **68**, 1422 (1946); Wall, Banes and Sands, *ibid.*, **68**, 1429 (1946).

(9) Marvel, Deanin, Overberger and Kuhn, *J. Polymer Sci.*, **3**, 128 (1948).

TABLE I

DESCRIPTION OF EXPERIMENTS

| Experiment | Approximate concentrations of ingredients, moles per liter | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V[b] | VI | VII | VIII | IX |
| Chloroform phase[a] | | | | | | | | | |
| Benzoyl peroxide | 0.05 | 0.05 | 0.01 | 0.05 | | | 0.01 | 0.01 | 0.01 |
| Ferric stearate | | | | | | 0.01 | | | |
| Water phase[a] | | | | | | | | | |
| Ferrous ammonium sulfate | .05 | .05 | .01 | .05 | | | | | |
| Ferric ammonium sulfate | | | | | 0.01 | | .01 | .01 | .01 |
| Sorbose | | | | | .01 | .01 | .01 | .01 | .01 |
| Sodium pyrophosphate | | | | .10 | .02 | .02 | .02 | | .02 |
| Sodium stearate | .10 | .05 | [c] | .05 | .04 | .04 | .04 | .04 | [c] |
| Benzyltrimethylammonium hydroxide | | | .04 | | | | | | .04 |

[a] Equal volumes of two phases used. [b] No chloroform phase included in this experiment. [c] Sodium stearate added later during course of experiment.

where it can be reduced by the sorbose which is present for that purpose. If no sorbose is added, the system can still be made to function providing the original recipe contains a large amount of ferrous iron with sufficient pyrophosphate to handle it. The over-all operation under these conditions would lose its cyclical aspect, and the effective concentration of reducing iron would not be maintained at nearly as uniform a level.

The sodium stearate has a dual role in the "Redox" system, and it is largely because of this coincidence that the "Redox" system actually operates. Ordinarily sodium stearate would be added for emulsification purposes, and it does serve that function with the "Redox" recipe as well. Equally important, however, is the solubilization of the ferrous iron in the oil phase which is brought about by the formation of oil soluble ferrous stearate in the presence of soap. If the iron were not solubilized in the oil phase to a sufficient extent, then the entire cycle would break down. In fact, if certain cationic emulsifying agents such as the quaternary ammonium salts are substituted for sodium stearate without other changes in the recipe, the "Redox" system fails for the obvious reason that the iron is not brought into contact with the peroxide.

## Experimental

The validity of the cycle described above was established by a series of separate experiments which were designed to test every aspect of the cycle. To avoid the complications of actual polymerization, which would overshadow the reactions in the "Redox" cycle, chloroform was used in place of monomer. Thus there was obtained an emulsion system which simulated the polymerization system in all respects except that reaction (2) would take place instead of reactions (3), (4), and (5). Under these experimental circumstances, the stoichiometry of the cycle could be well established. Among the experiments carried out were the reaction of ferrous stearate with benzoyl peroxide, the reduction of ferric iron with sorbose, and the transfer of iron from one phase to the other. Other experiments involved the omission of one or more critical reagents. A description of the experiments which were performed is presented in Table I. Each experiment was carried out at room temperature in the absence of oxygen with vigorous agitation of the emulsion. The data for these experiments are given in Table II. The results of all the experiments were compatible with the cycle proposed, so the conclusions given above are considered correct.

Since the solubilization of ferrous iron in the oil phase of a reaction emulsion appears to be an important factor in the operation of the "Redox" system, several experiments were carried out to investigate this aspect of the system. The first experiments were of a qualitative nature designed to prepare ferrous stearate in chloroform or benzene solution and to observe its reaction with peroxide in such single phase oil systems. Solutions of ferrous stearate (0.01–0.02 molar) were simply prepared by adding, in the absence of oxygen, an aqueous solution of ferrous ammonium sulfate in slight excess to an agitated emulsion consisting of chloroform or benzene with water and sodium stearate. The phases were permitted to separate; then the water layer was discarded and the organic layer filtered. The experiments were continued by introducing benzoyl peroxide into these solutions of ferrous stearate. A very rapid decomposition of the peroxide with accompanying oxidation of the iron was observed.

After establishing the qualitative results described above, further quantitative experiments were carried out which involved the reaction of benzoyl peroxide with ferrous iron in an emulsion medium. For Experiment I an emulsion

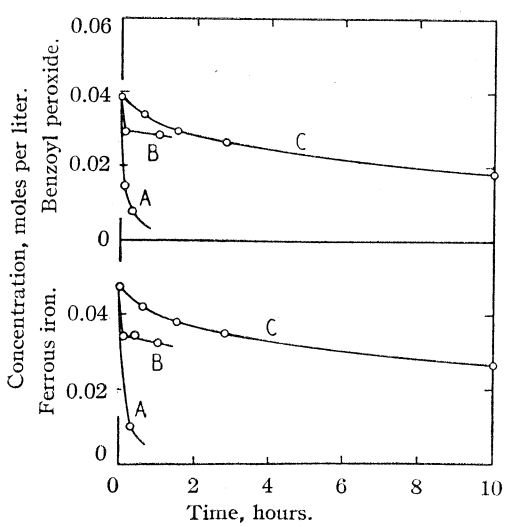



Fig. 1.—Peroxide–ferrous iron systems: curves A, equivalent amount of soap; curves B, half equivalent amount of soap; curves C, half equivalent amount of soap plus pyrophosphate.

TABLE II

SUMMARY OF RESULTS

| Expt. | Time, hr. | Concentrations: Benzoyl peroxide[a] | Ferrous iron[b] |
|---|---|---|---|
| I | 0 | 0.0389 | 0.0475 |
| | 0.1 | .0146 | ..... |
| | 0.3 | .0078 | .0100 |
| II | 0 | .0389 | .0475 |
| | 0.1 | .0293 | .0343 |
| | 0.4 | ..... | .0345 |
| | 1.0 | .0285 | .0323 |
| III | 0 | .01003 | |
| | 1.3 | .00990 | |
| | 4.6 | .00970 | |
| | 5.2 | added sodium stearate (40% equivalent of ferrous iron) | |
| | 5.3 | .00859 | |
| | 5.9 | .00720 | |
| | 6.8 | .00613 | |
| | 10.6 | .00460 | |
| | 11.4 | added sodium stearate (large excess) | |
| | 11.8 | .00355 | |
| IV | 0 | .0389 | 0.0475 |
| | 0.6 | .0340 | .0420 |
| | 1.5 | .0295 | .0380 |
| | 2.8 | .0264 | .0350 |
| | 10.0 | .0181 | .0265 |
| V | 0 | | 0 |
| | 2.3 | | 0.00124 |
| | 5.7 | | .00236 |
| | 9.8 | | .00320 |
| VI | 0 | | 0 |
| | 4.3 | | 0.00048 |
| | 6.7 | | .00088 |
| | 10.6 | | .00168 |
| | 22.4 | | .00360 |
| VII | 0 | .00925 | |
| | 6.0 | .00780 | |
| | 17.8 | .00573 | |
| | 27.2 | .00280 | |
| VIII | 0 | .01112 | |
| | 4.9 | .01063 | |
| | 9.0 | .01051 | |
| | 16.1 | .01020 | |
| IX | 0 | .01025 | 0[c] |
| | 1.3 | .01034 | ..... |
| | 1.6 | ..... | 0.0012 |
| | 2.7 | .01038 | ..... |
| | 3.0 | ..... | .0017 |
| | 3.1 | added sodium stearate (10% equivalent of ferric iron) | |
| | 3.2 | .00990 | ..... |
| | 3.3 | ..... | .0014 |
| | 4.2 | .00975 | ..... |
| | 4.3 | ..... | .0010 |
| | 5.6 | .00960 | ..... |
| | 5.7 | ..... | .0009 |
| | 8.1 | .00945 | ..... |
| | 8.2 | ..... | .0009 |

[a] Total moles calculated per liter of chloroform; obtained by iodometric titration. [b] Total moles calculated per liter of water; obtained by dichromate titration. [c] Initial ferric iron concentration, 0.01069; subsequent concentrations, as plotted in Fig. 5, obtained by difference.

was prepared consisting of chloroform, water, benzoyl peroxide, ferrous ammonium sulfate, and sodium stearate with the latter three substances present in stoichiometrically equivalent amounts. In this experiment, the results of which are illustrated in Fig. 1, a rapid decomposition of peroxide occurred, accompanied by a rapid oxidation of ferrous iron to the ferric state.

Experiment II was identical to Experiment I except that only one half the equivalent amount of sodium stearate was included. The results of this experiment, also illustrated in Fig. 1, show the same rapid initial reaction observed for Experiment I. But when one half the reactants were consumed, the rate of reaction abruptly decreased to a very small value. These experiments demonstrate conclusively that the iron must actually get into the organic phase to be truly effective as a reduction activator and that the sodium stearate serves as the solubilizing agent.

Further evidence supporting the conclusion drawn above was obtained in Experiment III which involved a similar emulsion, except that no sodium stearate was initially included. In its place there was substituted an equivalent amount of benzyltrimethylammonium hydroxide, which is a cationic emulsifying agent incapable of solubilizing iron. The data as shown in Fig. 2 show that no significant amount of reaction occurred with this system. However, after 5.2 hours a 40% equivalent of sodium stearate was added, whereupon the rate of reaction immediately became very rapid but then slowly diminished due to the insufficiency of sodium stearate. A further addition of a large excess of sodium stearate at 11.4 hours caused another surge of reaction. Thus the dual role of sodium stearate as emulsifier and solubilizer is established.

The undesirably rapid reaction which ensues between benzoyl peroxide and ferrous iron, as in Experiment I, is effectively controlled by holding a large part of the ferrous iron in the water phase in the form of the stable water soluble pyrophosphate complex,[10] $Fe_2(P_2O_7)_3^{-8}$. The effect of the addition of sodium pyrophosphate on the reaction is to be seen by comparing the results of Experiment II with those of Experiment IV given in Fig. 1. The experiments were identical except that in Experiment IV there was added an amount of sodium pyrophosphate 50% in excess of that required to hold all the ferrous iron in the pyrophosphate complex. The data show that, although the total amounts of reaction in the experiments are comparable, for Experiment IV the reaction between the benzoyl peroxide and ferrous iron proceeded at a more moderate rate and continued over a longer period of time.

The behavior exhibited by the reaction mixture of Experiment IV suggests that it would be capable of satisfactory polymerization initiation, a fact which is borne out by experience. However, the characteristics of the reaction between benzoyl peroxide and ferrous iron can be further improved by including in the system a means for generating ferrous iron as it is needed during the course of the reaction, and thus eliminating the need for a large water phase reservoir of ferrous iron. The water phase reduction of ferric iron by sorbose accomplishes this task and makes up the remainder of the "Redox" cycle, which will now be considered. First it should be noted that the behavior of ferric iron is quite similar to that of ferrous iron with respect to its solubilization in the organic phase of the emulsion as ferric stearate and its ability to form the stable water soluble pyrophosphate complex,[10] $Fe_2(P_2O_7)_3^{-6}$. Two experiments were performed which indicate the characteristics of the reaction between sorbose and ferric iron. In Experiment V, equivalent amounts of ferric iron and sorbose were permitted to react in a single phase water system containing sodium stearate and so-

(10) Freed and Kasper, THIS JOURNAL, **52**, 2632 (1930); Pascal, *Ann. chim. phys.*, [8] **16**, 359 (1909).

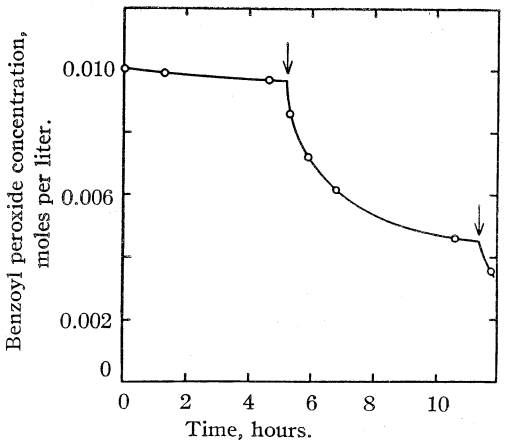



Fig. 2.—Peroxide–ferrous iron system with cationic emulsifier; soap added at times indicated by arrows.

dium pyrophosphate. (The composition of this reaction mixture is close to that of the water phase of a polymerization emulsion.) Experiment VI differed from Experiment V by the inclusion of a chloroform layer and the introduction of ferric iron as ferric stearate dissolved in the chloroform. The data for these experiments appear in Fig. 3. Both of these experiments show that the reaction between sorbose and ferric iron proceeds at a rate which is commensurate with the rate observed for the reaction between benzoyl peroxide and ferrous iron in the presence of pyrophosphate. The second of these two experiments demonstrates in particular the ability of the ferric iron to transfer from the organic to the water phase and to engage in the reaction with sorbose in an emulsion medium.

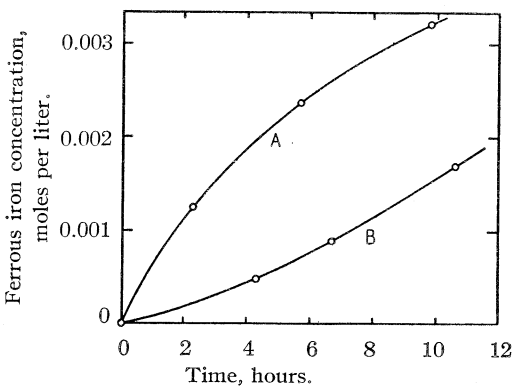



Fig. 3.—Sorbose–ferric iron systems: curve A, aqueous system; curve B, emulsion system.

With experimental verification of each step in the proposed "Redox" cycle completed, Experiment VII, involving the entire monomer free "Redox" system, was next considered. The reaction mixture of this experiment consisted of equal volumes of a chloroform phase, containing benzoyl peroxide and ferric stearate, and a water phase, containing sorbose, sodium stearate, and sodium pyrophosphate. The decomposition of benzoyl peroxide obtained in this experiment was moderate and uniform over an extended period, as shown by the data of Fig. 4. The desirability of this system is confirmed by its highly successful performance as a polymerization initiator.[9]

Two additional experiments involved interrupting certain steps in the "Redox" cycle to show that such interruptions result in almost complete breakdown of the mechanism leading to the decomposition of the benzoyl peroxide. Experiment VIII was equivalent to Experiment

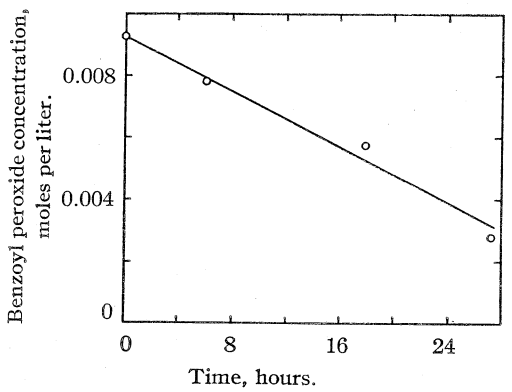



Fig. 4.—Peroxide decomposition for complete "Redox" system.

VII except that the pyrophosphate was eliminated. While this omission does not prevent the benzoyl peroxide–ferrous iron reaction from occurring, it renders difficult the transference of ferric iron from the organic to the water layer. The results of this experiment showed that, although some benzoyl peroxide did decompose, the rate of the decomposition was considerably reduced as compared with Experiment VII. Notwithstanding the small amount of benzoyl peroxide decomposition which occurred, the results are significant for the omission of the pyrophosphate does not positively assure the absence of small amounts of ferric iron in the water phase.

Experiment IX was also similar to Experiment VII, except that the reaction mixture initially contained a cationic emulsifying agent, benzyltrimethylammonium hydroxide, in place of sodium stearate. Here the only restriction placed on the system was to prevent the transfer of the ferrous iron from the water phase into the organic phase. The data for this experiment, appearing in Fig. 5, show that in the initial period no benzoyl peroxide decomposition occurred, even though the unrestricted sorbose–ferric iron reaction built up an appreciable ferrous iron concentration in the aqueous phase. At the end of 3.1 hours an amount of sodium stearate equivalent to 10% of the ferric iron originally present was added. Reaction immediately took place, giving rise to an abrupt drop in the benzoyl peroxide

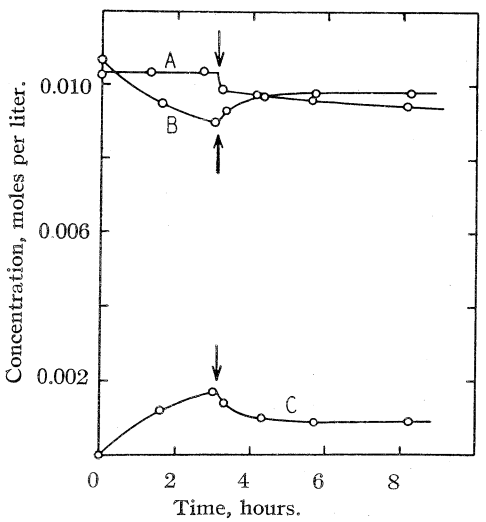



Fig. 5.—Peroxide–ferric iron–sorbose–pyrophosphate system with cationic emulsifier; soap added at time indicated by arrows: curve A, peroxide concn.; curve B, ferric iron concn.; curve C, ferrous iron concn.

concentration and an accompanying decrease in the ferrous iron concentration and increase in the ferric iron concentration. Following these adjustments the system approached a steady state in which the benzoyl peroxide concentration continued to decline at a slow rate while the ferrous and ferric iron concentrations became constant. This behavior can be readily interpreted in terms of the proposed "Redox" cycle. For given concentrations of benzoyl peroxide and sorbose, the rates of the various reactions will depend primarily upon the concentrations of the ferrous and ferric iron. But since the reaction which produces ferrous iron consumes ferric iron, and vice versa, it is obvious that the reaction system will approach a steady state in which the rates of the benzoyl peroxide–ferrous iron and the sorbose–ferric iron reactions become equal and the concentrations of the ferrous and ferric iron become constant.

## Summary

A mechanism is proposed for the reduction activation of polymerizations in emulsion systems. It is found that ferrous iron, solubilized in the oil phase as the stearate, promotes the decomposition of benzoyl peroxide into free radicals which are capable of initiating polymerization. In this process the ferrous iron is oxidized to the ferric form which is subsequently transferred to the aqueous phase where it exists as a pyrophosphate complex. The ferric iron is then reduced by an appropriate water soluble reducing agent such as sorbose. The reduced ferrous iron is ultimately transferred back to the oil phase to resume the cycle.

Sodium stearate is used as an emulsifying agent, but it does more than promote emulsification since it also renders the iron salts oil soluble. Omitting any of the reagents mentioned above or replacing the soap by a cationic emulsifying agent which is incapable of solubilizing the iron in oil, disrupts the smooth operation of the cycle. The net result of the entire cycle is the reduction of organic peroxides into free radicals and acid ions by a reducing sugar with iron serving as the effective intermediary.

URBANA, ILLINOIS RECEIVED AUGUST 12, 1948

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[CONTRIBUTION FROM GELATIN PRODUCTS DIV., R. P. SCHERER CORP.]

# Absorption Spectra of Steroid–Antimony Trichloride Reaction Products[1]

BY ALEXANDER MUELLER

It has been reported by numerous workers that sterols give color reactions with various reagents.[2] The employment of antimony trichloride has been shown to give a greater specificity for quantitative determinations.[3] Examinations in this laboratory[4,5] have revealed that the spectra of the colors developed with the widely used antimony trichloride reagent are highly characteristic and have reasonably high extinction coefficients with magnitudes at specific wave length maxima directly related to the structure of the steroid molecule. Measurements on thirty-four steroids, mostly cholesterol derivatives, to confine the study to a homologous series, are reported in this communication. The interrelationships between molecular groupings and resulting spectra are summarized and the applicability of the measurements in characterization of molecular structure is indicated.

## Experimental

A 1-ml. aliquot of the steroid[6] solution in purified chloroform was pipetted into a 25-ml., glass-stoppered cylinder, 10 ml. of antimony trichloride reagent[7] added, and the reaction mixture thoroughly shaken. The solution is poured into one pair of matched 10-mm. corex cells while the second or reference cell is filled with 1 ml. of chloroform and 10 ml. of antimony trichloride reagent. The absorption spectra were determined with a Beckman spectrophotometer, Model DU, using an incandescent lamp as the source of illumination and varying the slit width to accord with the region of the spectrum examined.

Throughout the measurements, reaction periods were determined with a stopwatch and optimum concentrations of steroid solutions were ascertained as the result of adjustments in preliminary trials. For additional manipulative details see reference.[5] From the optical densities determined for the solutions at the respective time intervals and wave length maxima, corresponding extinction coefficients, $E(1\%, 1\text{ cm.})$, were calculated. The values are summarized in the accompanying table and graphs.

## Discussion

The compounds in Table I are arranged according to the following order: (1) saturated hydrocarbons with one or more substituents (excepting hydrogen) on Rings I and II; (2) one double bond with no substituents on Rings I and II; (3) one double bond with one substituent (such as hydroxy, keto, ester or halogen) on Rings I and II; (4) one double bond with two substituents on Ring I or II; (5) two double bonds with no substituents on Ring I or II; (6) two double bonds with one substituent on Ring I or II; (7) unclassified (calciferol and sex hormones).

Comparing the magnitude of absorption intensities of the various antimony trichloride reaction products, calciferol (Fig. 8), with an exo-

(1) Presented in part before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, September 9 to 13, 1946.

(2) Sobotka "The Chemistry of the Steroids," The Williams and Wilkins Co., Baltimore, 1938) has reviewed applications of the qualitative aspects.

(3) G. Pincus, *Endocrinology*, **32**, 176 (1943).

(4) A. Mueller, *Ind. Eng. Chem. Anal Ed.*, **18**, 214 (1946).

(5) F. W. Lamb, A. Mueller and G. W. Beach, *ibid.*, **18**, 187 (1946).

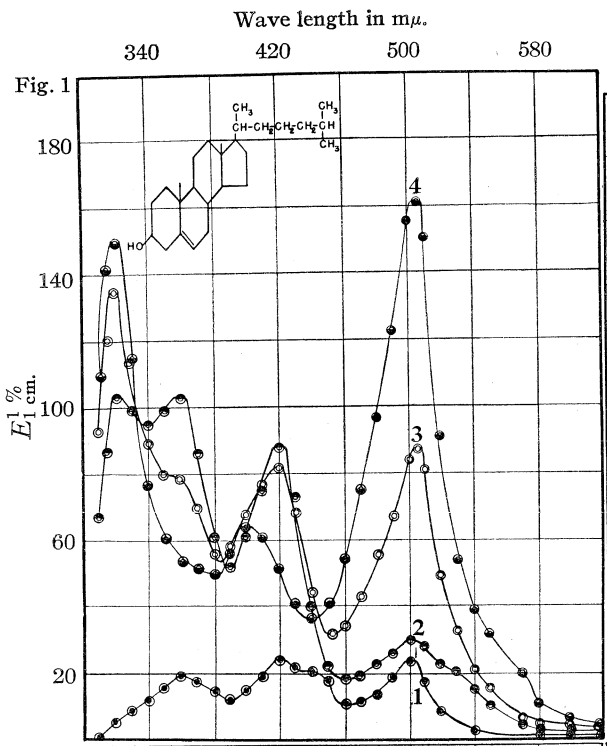
(6) The compounds examined were prepared in the Fine Chemicals Division of the R. P. Scherer Corp., and the purity verified by elemental analysis, melting point, optical rotation and ultraviolet absorption spectra.

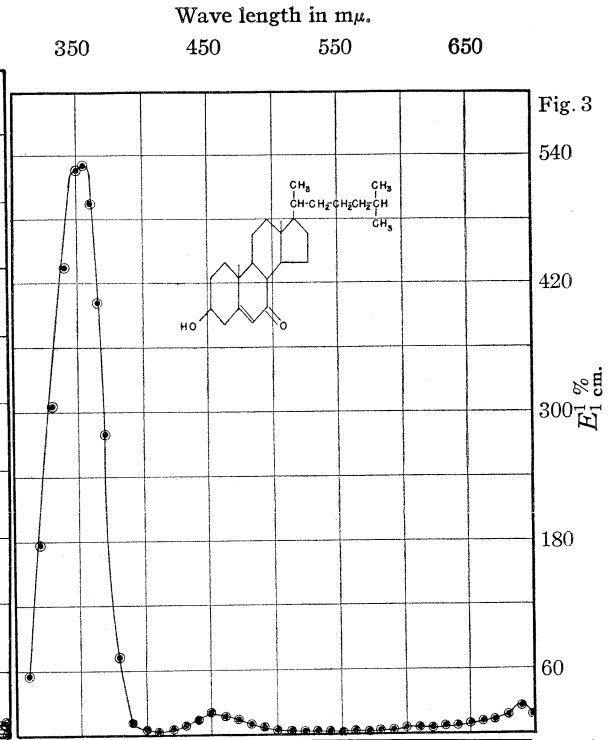
(7) The solvent and reagent were prepared according to D. T. Ewing, G. V. Kingsley, R. A. Brown and A. D. Emmett, *Ind. Eng. Chem. Anal. Ed.*, **15**, 301 (1943).

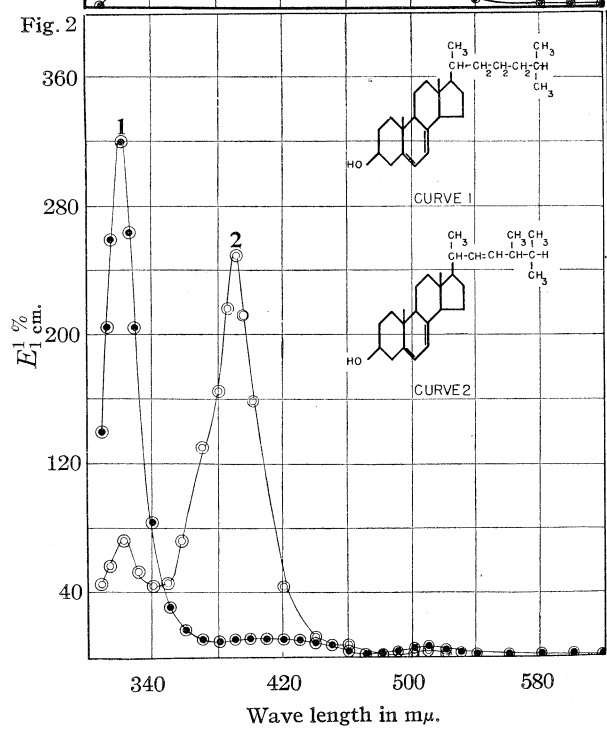
TABLE I

ABSORPTION PROPERTIES OF VARIOUS STEROID–ANTIMONY TRICHLORIDE REACTION PRODUCTS

| Compound | $\lambda_{max.}$, mμ | $E$ (1%, 1 cm.) | Time | Remarks |
|---|---|---|---|---|
| Cholestanone | 320 | 2.0 | 19 hr. | Slight maximum; continues to rise |
| Coprostanone | 320 | 24.3 | 44 hr. | Maxima develop very slowly, and are not sharp |
| | 415 | 6.0 | 20 hr. | |
| | 510 | 3.0 | 44 hr. | |
| 7-Keto-cholestanyl acetate | 355 | 11.4 | 1 hr. | Stable from 60 to 80 minutes |
| 6-Keto-cholestanyl acetate | 320 | 1.8 | 2 hr. | Very low absorption |
| | | 3.2 | 24 hr. | |
| 5,6-Dibromide cholestanyl acetate | 322 | 45.0 | 2 hr. | All maxima continue to rise |
| | 397 | 13.0 | 2 hr. | |
| | 490 | 6.0 | 2 hr. | Absorption similar to cholesteryl-α-oxide acetate (see Fig. 7) |
| $\Delta^4$-Cholestene | 320 | 5.0 | 30 min. | Absorption increases slowly |
| | 322 | 36.3 | 24 hr. | |
| | 424 | 19.5 | 30 min. | At 24 hr. 424 mμ max. has shifted to 450 mμ, and new max. is present at 525 mμ |
| | 450 | 15.0 | 24 hr. | |
| | 525 | 17.7 | 24 hr. | |
| $\Delta^5$-Cholestene | 322 | 7.0 | 30 min. | Absorption increases slowly |
| | 316 | 45.0 | 20 hr. | |
| | 420 | 24.0 | 30 min. | Both maxima are shifted at 20 hr. |
| | 430 | 33.0 | 20 hr. | |
| Cholesterol | 322 | 135.0 | 90 min. | Figure 1 (yellow color) |
| | 360 | 103.0 | 25 min. | |
| | 420 | 88.0 | 40 min. | |
| | 505 | 90.0 | 120 min. | |
| $\Delta^4$-Cholestenol-7 (pseudo-cholesterol) | 322 | 147.0 | 90 min. | Similar to cholesterol |
| | 360 | 106.0 | 25 min. | |
| | 420 | 45.0 | 40 min. | |
| | 505 | 36.0 | 120 min. | |
| Cholesteryl acetate | 322 | 107.0 | 90 min. | Similar to cholesterol |
| | 360 | 74.0 | 25 min. | |
| | 420 | 69.0 | 40 min. | |
| | 505 | 55.0 | 120 min. | |
| Cholesteryl benzoate | 322 | 95.0 | 90 min. | Similar to cholesterol |
| | 360 | 68.0 | 20 min. | |
| | 420 | 70.0 | 20 min. | |
| | 505 | 60.0 | 120 min. | |
| Cholesteryl chloride | 322 | 95.0 | 90 min. | Similar to cholesterol except reaction rate. $E$ (1%, 1 cm.) values continue to rise |
| | 360 | 49.0 | 35 min. | |
| | 420 | 35.0 | 35 min. | |
| | 505 | 87.0 | 90 min. | |
| Cholesteryl methyl ether | 322 | 114.6 | 90 min. | Similar to cholesterol except time reaction rate |
| | 360 | 69.4 | 40 min. | |
| | 420 | 63.6 | 60 min. | |
| | 505 | 82.2 | 120 min. | |
| *i*-Cholestanyl-6-methyl ether | 322 | 108.0 | 90 min. | Similar to cholesterol except time reaction rate |
| | 360 | 50.0 | 60 min. | |
| | 420 | 46.0 | 120 min. | |
| | 505 | 80.0 | 90 min. | |
| Cholesteryl-α-oxide acetate | 322 | 68.0 | 18 hr. | Figure 7. Maxima continue to rise |
| | 397 | 53.0 | 18 hr. | |
| | 480 | 28.0 | 18 hr. | |
| Cholestenone | 318 | 61.0 | 35 min. | Figure 4. Stable, then rises and shifts to 320 mμ, continues to rise |
| | 320 | 88.0 | 4 hr. | |
| | 320 | 116.0 | 24 hr. | |
| | 375 | 68.0 | 24 hr. | First observed at 24 hours |
| | 530 | 25.0 | 4 hr. | Maximum rises, then drops, then rises again |
| | 530 | 22.0 | 6 hr. | |
| | 530 | 40.0 | 24 hr. | Maximum shifts to 520 mμ at 24 hr. |
| | 650 | 7.0 | 4 hr. | |
| | | 12.0 | 6 hr. | Broad maximum, rises slowly shifts to 658, mμ |
| | | 15.0 | 24 hr. | |
| β-Sitosterol | 322 | 109.0 | 105 min. | Similar to cholesterol except time reaction rate |
| | 360 | 87.0 | 30 min. | |
| | 420 | 98.0 | 45 min. | |
| | 505 | 83.0 | 120 min. | |
| Stigmasteryl acetate | 322 | 48.0 | 30 min. | Similar to cholesterol except a marked change in time reaction rate and appearance of new maxima at 24 hours (green color) |
| | 360 | 72.0 | 20 min. | |
| | 420 | 114.0 | 50 min. | |
| | 505 | 67.0 | 120 min. | |
| | 640 | 30.0 | 24 hr. | |
| | 720 | 23.0 | 24 hr. | |
| 7-Keto-cholesterol | 355 | 533.0 | 50 min. | Figure 3 |
| | 460 | 22.0 | 2 hr. | |
| | 690 | 24.0 | 2 hr. | |
| 7-Keto-cholesteryl acetate | 355 | 593.0 | 50 min. | Similar to 7-keto-cholesterol |
| | 457 | 29.6 | 2 hr. | |
| | 695 | 25.6 | 2 hr. | |
| 7-Keto-cholesteryl benzoate | 355 | 450.0 | 50 min. | Similar to 7-keto-cholesterol except no 460 mμ maximum |
| | 685 | 36.0 | 90 min. | |
| 7-Hydroxy- | 590 | 159.0 | 1 min. | In usual $SbCl_3$ concentration |
| cholesteryl | 590 | 132.0 | 1 min. | In one-half usual $SbCl_3$ concentration |
| benzoate | 460 | 132.0 | 1 min. | In one-half usual $SbCl_3$ concentration |
| Cholesteryl dibenzoate | 590 | 138.0 | 1 min. | Figure 5. Similar to 7-hydroxycholesteryl benzoate (blue color) |
| | 460 | 125.0 | 1 min. | |
| | 590 | 181.0 | 5 min. | In one-half usual $SbCl_3$ concentration |
| $\Delta^3$, $\Delta^5$-Cholesterilene | 322 | 127.0 | 3 hr. | Figure 6 |
| | 360 | 141.0 | 5 min. | |
| | 420 | 268.0 | 3 min. | |
| | 500 | 100.0 | 3 hr. | |
| 7-Keto-cholesterilene | 355 | 655.0 | 1 min. | Stable from 1 to 25 minutes |
| | 450 | 11.0 | 2 hr. | Similar to 7-keto-cholesterol (see Fig. 3) |
| 6-Bromo-7-ketocholesterilene | 320 | 225.0 | 1 min. | Stable from 1 to 60 minutes (introduction of bromine changes entire character of absorption curve) |
| | 388 | 30.0 | 60 min. | |
| | 700 | 26.0 | 5 hr. | |
| | 700 | 68.0 | 22 hr. | |
| 7-Dehydro-cholesterol | 322 | 320.0 | 8 min. | Figure 2. The 322 mμ max. is stable from 4 to 10 min., then drops slowly |
| | 520 | 7.0 | 8 min. | |
| Ergosterol | 322 | 63.0 | 5 min. | Figure 2. The 393 mμ max. is stable from 5 to 10 min., then drops slowly |
| | 393 | 250.0 | 5 min. | |
| | 505 | 12.4 | 5 min. | |
| Androsterone | 320 | 110.0 | 48 hr. | Figure 9. Absorption rises very slowly |
| | 388 | 100.0 | 48 hr. | |
| | 455 | 22.0 | 48 hr. | |
| | 485 | 8.0 | 48 hr. | |
| | 570 | 16.0 | 48 hr. | |
| | 620 | 16.0 | 48 hr. | |
| Dehydro-iso-androsterone | 320 | 26.0 | 1 hr. | Figure 10 |
| | 388 | 142.0 | 6 hr. | |
| | 416 | 75.0 | 1 hr. | |
| | 510 | 86.0 | 6 hr. | |
| | 580 | 64.0 | 6 hr. | |
| | 615 | 65.0 | 6 hr. | |
| $\Delta^5$-Androstene-diol-(3β,17α) | 365 | 70.0 | 50 min. | Figure 12 |
| | 418 | 171.0 | 50 min. | |
| | 500 | 36.0 | 50 min. | |
| Testosterone | 320 | 83.0 | 5 min. | Figure 12 |
| | 320 | 108.0 | 2.5 hr. | |
| | 355 | 98.0 | 2.5 hr. | |
| | 355 | 59.0 | 2.5 hr. | |
| Estrone | 420 | 440.0 | 44 hr. | Figure 11 |
| | 510 | 95.0 | 44 hr. | |
| Calciferol | 500 | 1800.0 | 3 min. | Figure 8 |



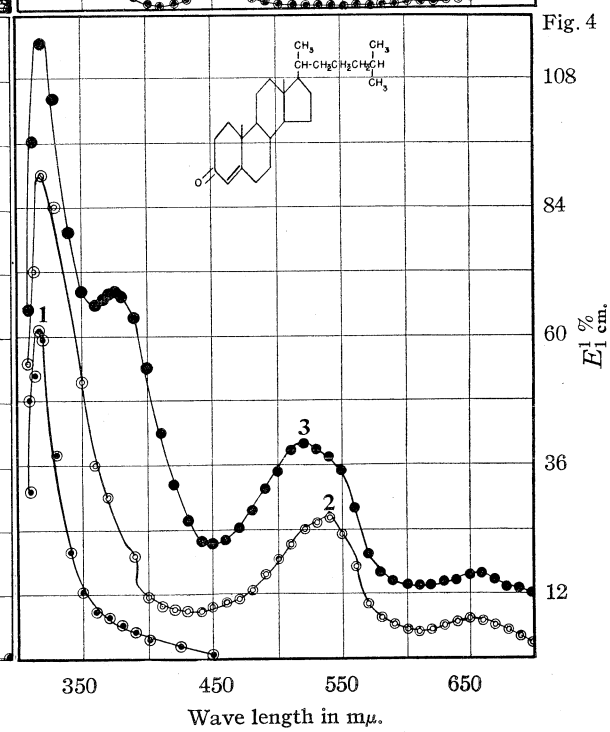






Fig. 1.—Absorption curves of cholesterol–antimony trichloride reaction products: 1, curve at five to fifteen minutes; 2, at thirty to forty minutes; 3, at ninety to one hundred minutes; 4, at twenty-four hours.

Fig. 2.—Absorption curves of 7-dehydrocholesterol and ergosterol–antimony trichloride reaction products: 1, 7-dehydrocholesterol at five to fifteen minutes; 2, ergosterol at one to ten minutes.

Fig. 3.—Absorption curve of 7-keto-cholesterol–antimony trichloride reaction product: (curve between 300–400 mμ at forty to fifty minutes, between 400–700 mμ at ninety to one hundred minutes).

Fig. 4.—Absorption curves of cholestenone–antimony trichloride reaction products: 1, curve at thirty to forty minutes; 2, at three and one-half to four hours; 3, at twenty-four hours.

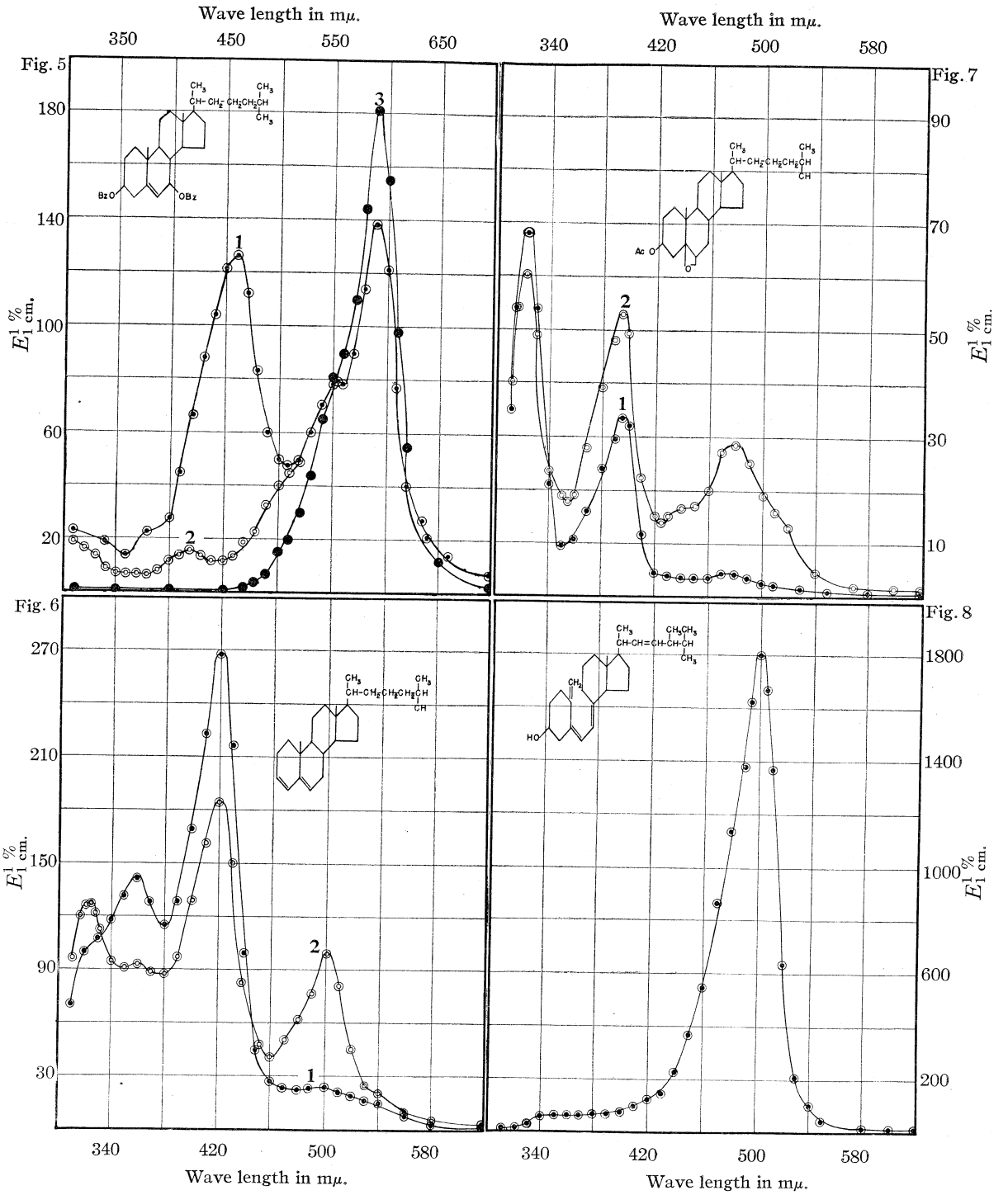



Fig. 5.—Absorption curves of cholesteryl dibenzoate–antimony trichloride reaction products: 1, curve at one to ten minutes; 2, at fifteen to twenty minutes (from 520–700 mμ, it is identical with curve 1); 3, at one to ten minutes with one-half the usual antimony trichloride concentration.

Fig. 6.—Absorption curves of $\Delta^3$, $\Delta^5$-cholesterilene–antimony trichloride reaction products: 1, curve at one to ten minutes; 2, at three hours.

Fig. 7.—Absorption curves of cholesteryl $\alpha$-oxide acetate–antimony trichloride reaction products: 1, curve at twenty to thirty minutes; 2, at eighteen hours.

Fig. 8.—Absorption curve of calciferol–antimony trichloride reaction product; curve at one to five minutes.

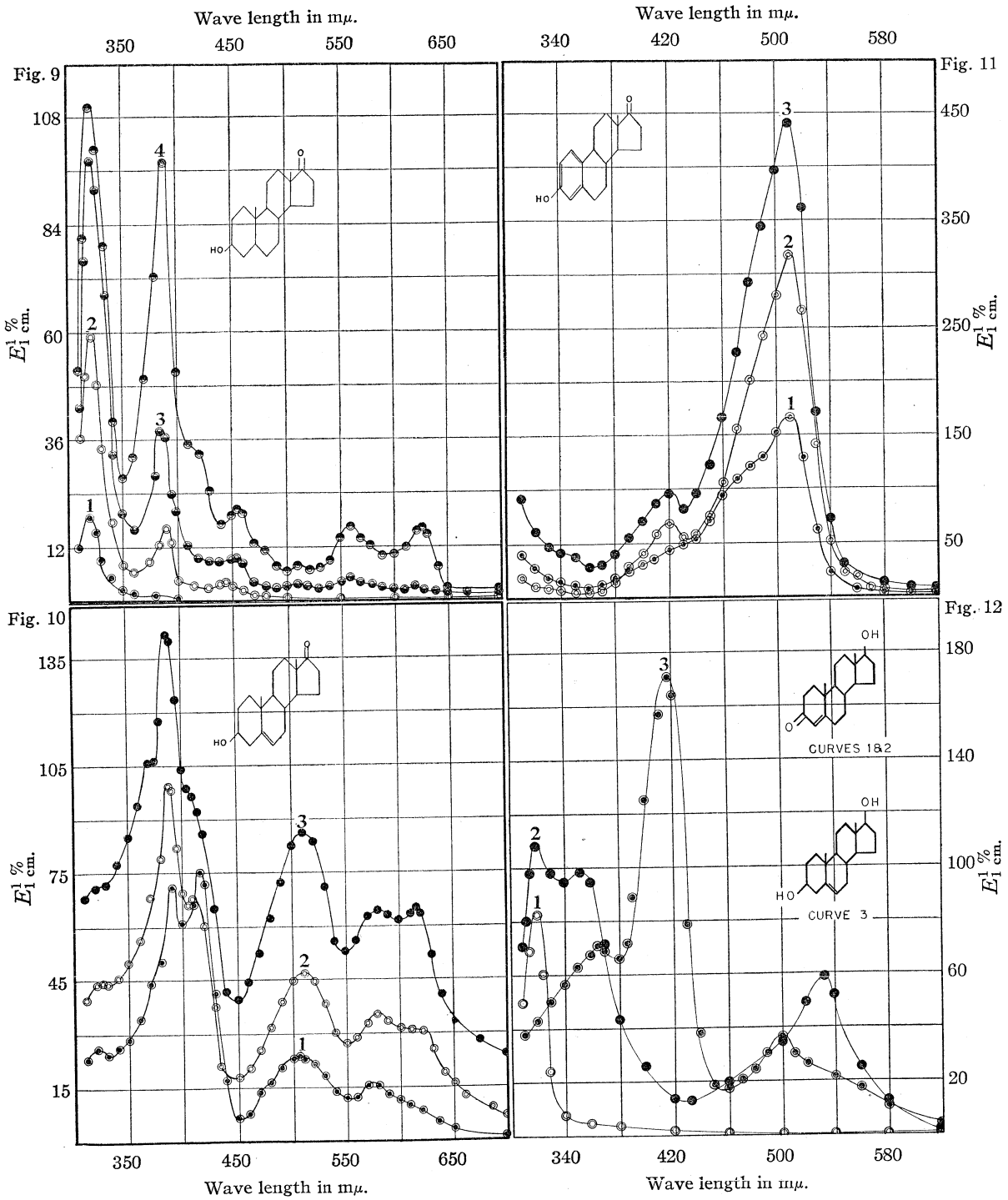



Fig. 9.—Absorption curves of androsterone–antimony trichloride reaction products: 1, curve at one hour; 2, curve at six hours; 3, curve at twenty-four hours; 4, at forty-eight hours.

Fig. 10.—Absorption curves of dehydro-isoandrosterone–antimony trichloride reaction products: 1, curve at one hour; 2, at two hours; 3, at six hours.

Fig. 11.—Absorption curves of estrone–antimony trichloride reaction products: 1, curve at twenty hours; 2, curve at twenty-seven hours; 3, curve at forty-four hours.

Fig. 12.—Absorption curves of testosterone– and $\Delta^5$-androstenediol-(3$\beta$,17$\alpha$)–antimony trichloride reaction products: 1, testosterone at one to five minutes; 2, testosterone at two to two and one-half hours; 3, $\Delta^5$-androstenediol-(3$\beta$,17$\alpha$) at fifty to sixty minutes.

cyclic, triply conjugated system, has the highest value. On the other hand, estrone (Fig. 11) with an endocyclic, triply conjugated system in Ring I has a contrastingly low absorption intensity. In general, the type of linkages which produces the highest absorption are the conjugated double bond, and the double bond in conjugation to a keto, hydroxy, or other polar grouping. Compounds having both endocyclic and exocyclic unsaturation produce high extinction coefficients (see 7-keto-cholesterilene, and 7-keto-cholesterol (Fig. 3)). The influence of exocyclic changes have little effect in the absence of endocyclic unsaturation, while endocyclic unsaturation in the absence of exocyclic groupings produces a spectrum of rather high intensity (see cholesterilene, Fig. 6). Generally, in a conjugated double bond system wherein there is one center of electronic interaction a single narrow absorption band is exhibited while a system having two or more locations of electron concentration exhibits more than one maximum. Comparing the antimony trichloride spectra of 7-dehydrocholesterol and ergosterol (Fig. 3) the difference apparently is due to the side chain double bond of ergosterol. 7-Dehydrocholesterol gives a single strong maximum, due to the single conjugated system in Ring II, while ergosterol with electronic interaction between the side chain and Ring II give two prominent bands. Conversely, calciferol (Fig. 8) with a double bond in the side chain gives a single absorption maximum. Possibly there is no interaction between the semicyclic, triply conjugated system in Ring II and the side chain double bond of calciferol. An interesting analogy exists in the comparison of the ultraviolet absorption of ergosterol and calciferol.[8]

(8) H. Dannenberg, *Abhandl. preuss. Acad. Wiss., Math. naturw. Klasse*, No. 21 (1939).

The nature of antimony trichloride reaction on a sterol was assumed (in the initial stages of this work) to be one of dehydration with subsequent shifting of double bonds, and possible introduction of an additional double bond. Preliminary experiments on the isolated reaction products of cholesterol, however, seem to indicate a cyclization product, probably forming a dicyclopentanoperhydrophenanthrene entity. A continuation of studies on this phase, as well as systematic investigations of a series are necessary before definite conclusions may be drawn.

**Acknowledgment.**—The writer wishes to express his appreciation to Sereck H. Fox for his criticism of this manuscript, and is very grateful to Gerard A. Fleisher for his interest and invaluable suggestions as well as for supplying most of the compounds investigated.

## Summary

The absorption spectra data of the antimony trichloride reaction products of thirty-four steroids are presented. Absorption curves are shown for fourteen representative compounds in the region from 310 to 700 mμ. The data indicate that the spectra are characteristic for specific molecular groupings or combination of groupings in the molecule. Generalizations of the influence of various groupings in the steroid molecule on the resulting spectra are summarized. The analysis of the data obtained from the spectra would indicate that the latter are particularly helpful in following the progress or change in a molecule during synthesis, degradation, or in its quantitative analysis for purity and concentration.

DETROIT, MICHIGAN RECEIVED FEBRUARY 24, 1948

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[CONTRIBUTION FROM MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND HARVARD UNIVERSITY]

# The Microwave Spectra of $CH_3NCS$ and $CH_3SCN$[1]

BY C. I. BEARD[2] AND B. P. DAILEY[3]

## Introduction

The use of microwave absorption spectroscopy in determining the structure of linear and symmetric top molecules is now well established. The application to asymmetric molecules, although of much importance in broadening the scope of the techniques, has been very slow because of the complexity of the spectra which are observed. These complexities arise not only from the pattern (or lack of one) of rotational energy levels for the asymmetric rotor, but from nuclear quadrupole coupling, rotational-vibrational interaction, internal free or hindered rotation, and from experimental difficulties in observing spectra in the microwave region. All of these complications, except the last, are potential sources of useful information provided an analysis can be carried out. The natural procedure would seem to be to select molecules for study, to begin with, which would exhibit only one or two of these complications. As an example sulfur dioxide,[4] for whose spectrum a preliminary analysis has appeared, has no quad-

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(4) B. P. Dailey, S. Golden and E. B. Wilson, Jr., *Phys. Rev.*, **72**, 871 (1947).

rupole interactions (except in molecules involving $S^{33}$), no internal rotation, and possesses a readily observable spectrum in the microwave region.

In this paper results of the investigation of the microwave spectra of the slightly asymmetric tops, methyl isothiocyanate ($CH_3NCS$) and methyl thiocyanate ($CH_3SCN$) will be presented. These are members of an interesting class of asymmetric molecules possessing internal rotating groups. Other members of this class whose microwave spectra have been studied are $CH_3NO_2$,[5] $CH_3NH_2$,[6] and $CH_3OH$.[6,7] $CH_3NCS$ would seem to be a favorable case for analysis since it has an easily observable spectrum in a convenient frequency range, has a negligible quadrupole coupling, and should be only slightly asymmetric. In addition the approximate dimensions of the NCS group are known from the microwave study of HNCS.[8]

## Experimental Details

The $CH_3NCS$ absorption spectrum has been studied in the frequency range from 20 to 30 kmc. using the Stark modulation spectrometer previously described.[9] The apparatus, shown in block diagram form in Fig. 1, used a waveguide absorption cell ten feet in length with a 100 kc./s. square wave Stark field. The $CH_3NCS$ was an Eastman Kodak Co. product used without further purification.

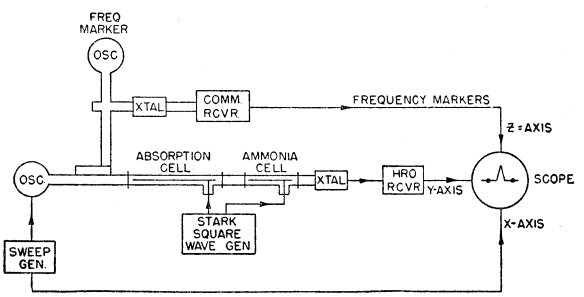



Fig. 1.—Arrangement of components in the microwave spectrometer.

With 100 v./cm. Stark field modulation and a vapor pressure ~0.05 mm. more than 29 $CH_3NCS$ absorption lines were found in the region from 19,440 to 29,800 mc./s. (Fig. 2 and Table I). Frequencies in most cases were determined using lines of the $N^{14}H_3$ and $N^{15}H_3$ inversion spectrum as secondary standards, measuring frequency differences by the method of Good and Coles.[10]

(5) B. P. Dailey and E. B. Wilson, Jr., paper presented at regional meeting of the American Physical Society, Amherst, Mass., May 31, 1947.

(6) W. D. Hershberger and J. Turkevitch, *Phys. Rev.*, **71**, 554 (1947).

(7) B. P. Dailey, *ibid.*, **72**, 84 (1947).

(8) C. I. Beard and B. P. Dailey, *J. Chem. Phys.*, **15**, 762 (1947).

(9) R. H. Hughes and E. B. Wilson, Jr., *Phys. Rev.*, **71**, 562 (1947).

(10) W. E. Good and D. K. Coles, *ibid.*, **71**, 383 (1947).

TABLE I

ASSIGNMENT OF LINES IN THE ROTATIONAL SPECTRUM OF $CH_3NCS$

| $\nu$ mc. | Relative intensity | Assignment |
|---|---|---|
| | | $J = 3 \rightarrow 4$ transition |
| 19700* | 5 | $CH_3NCS^{34}$; degenerate line, ground state |
| 19929* | 1 | $CH_3NCS^{34}$; degenerate line, J |
| 20020* | <1 | |
| 20140 | 10 | $CH_3NCS$: $+3_{1,3} \rightarrow 4_{1,4}$ ground state |
| 20216 | 100 | $CH_3NCS$; degenerate line, ground state |
| 20230 | <1 | |
| 20241 | 7 | $CH_3NCS$; degenerate line, E ? |
| 20350 | 20 | $CH_3NCS$; degenerate line, D |
| 20413 | <1 | |
| 20443 | 40 | $CH_3NCS$; degenerate line, J |
| | | $J = 4 \rightarrow 5$ transition |
| 24143* | <1 | $C^{13}H_3NCS$; degenerate line, ground state |
| 24609* | 5 | $CH_3NCS^{34}$; degenerate line, ground state |
| 24824 | 1 | |
| 24910 | 2 | $CH_3NCS^{34}$; degenerate line, J |
| 24930* | <1 | $CH_3NCS^{33}$; degenerate line, ground state |
| 24971* | 1 | |
| 25002* | <1 | $CH_3NC^{13}S$; degenerate line, ground state |
| 25077* | 1 | |
| 25100* | <1 | |
| 25161 | <1 | |
| 25195 | 10 | $CH_3NCS$; $4_{1,4} \rightarrow 5_{1,5}$, ground state |
| 25269 | 100 | $CH_3NCS$; degenerate line, ground state |
| 25306 | 7 | $CH_3NCS$; degenerate line, E ? |
| 25333 | 10 | $CH_3NCS$; $4_{1,3} \rightarrow 5_{1,4}$ ground state |
| 25390 | <1 | |
| 25409* | 1 | |
| 25442 | 25 | $CH_3NCS$; degenerate line, D |
| 25550 | 40 | $CH_3NCS$; degenerate line, J |
| 25653* | <1 | $CH_3NCS$; $4_{1,3} \rightarrow 5_{1,4}$, J |
| | | $J = 5 \rightarrow 6$ transition |
| 29700 | | $CH_3NCS^{34}$; degenerate line, ground state |

The frequencies of the lines marked by asterisks in Table I were determined only by cavity wavemeter readings. The approximate relative intensities reported represent observed signal strengths at the same power level incident on the terminal crystal detector. These relative intensities are comparable only within each group of lines and are not true relative intensities since they neglect the dependence upon the Stark effect of each line. Furthermore saturation effects tend to increase the apparent relative intensity of the weaker lines.

## Theoretical Spectrum

The analysis of the observed spectrum may be most conveniently discussed by setting up a probable structure for the molecule, calculating a theoretical spectrum and comparing with observed results. In view of the microwave data on HNCS, $CH_3NCS$ can with some confidence be pictured as being a resonance hybrid of the three structures shown in Fig. 3. If it is assumed that the structure of the NCS group suffers no major changes in

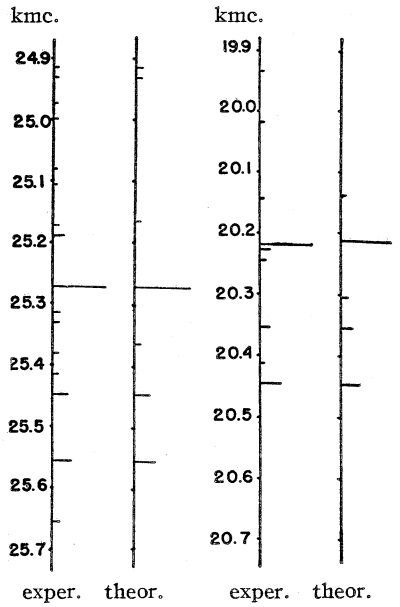
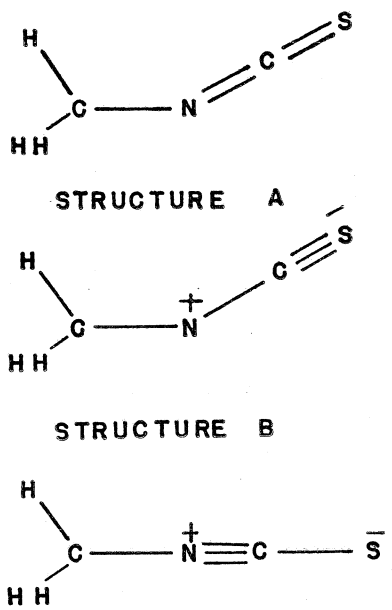



Fig. 2.—The experimental and calculated spectrum of $CH_3NCS$ in the microwave region.

going from the acid to the ester, and the dimensions of the methyl group are taken from the recent accurate work on the methyl halides[11] only a value for the $CH_3$–N–C angle need be chosen for a complete molecular model. For a first approximation the H–N–C angle could be used although it has been determined only roughly. The N–C distance in HNCS indicates a predominance of the structure involving the N≡C bond and suggests

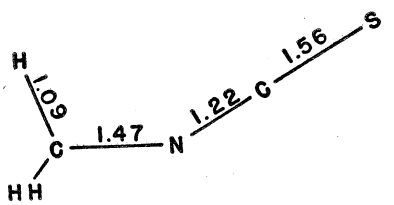



Structure C.

Fig. 3.—Resonating structures for $CH_3NCS$.

(11) J. W. Simmons, W. Gordy and A. G. Smith, *Phys. Rev.*, **74**, 243 (1948).

that an angle greater than the average for the resonating structures, 130°, may be the correct one. For the present purpose an angle of 142° has been chosen. The influence of hyperconjugation on the $CH_3$–$^+N{\equiv}C$–$S^-$ structure might lengthen the N–C bonds and shorten the $CH_3$–N bond but should leave the angle unchanged. The structure illustrated in Fig. 4 should roughly approximate the true molecular configuration and permit calculation of a theoretical spectrum correct in broad outline.




H–C–N angle 109°
C–N–C angle 142°

Fig. 4.—Approximate molecular configuration of $CH_3NCS$:

| | |
|---|---|
| $I_A$, $10.72 \times 10^{-40}$ g. cm.$^2$ | $A$, 2.61 cm.$^{-1}$ |
| $I_B$, 329.34 | $B$, 0.08498 |
| $I_C$, 334.85 | $C$, 0.08358 |

Using the formula given by Mecke[12] for the energy levels of a slightly asymmetric rotor (which, in view of the near degeneracy of the rotational constants $B$ and $C$, should apply in this case)

$$F(J,K)\ \text{cm.}^{-1} = \tfrac{1}{2}(B + C)J(J + 1) + [A - \tfrac{1}{2}(B + C)]K^2$$

where $A = h/8\pi^2cI_A$, $B = h/8\pi^2cI_B$, $C = h/8\pi^2cI_C$, the following formulas for observed frequencies may be obtained: For

$$\Delta J = +1,\ \Delta K = 0$$
$$\nu\text{cm.}^{-1} = (B + C)(J + 1)$$

For

$$\Delta J = 0,\ \Delta K = +1$$
$$\nu\text{cm.}^{-1} = [A - \tfrac{1}{2}(B + C)(2K + 1)$$

Using the calculated rotational constants based on the approximate molecular model, spectral lines would be predicted at the frequencies given in Table II. An inspection of this table permits the widely spaced groups of lines at 20,500 and 25,000

TABLE II

CALCULATED ROTATIONAL SPECTRUM FOR $CH_3NCS$ CONSIDERED AS A NEARLY SYMMETRIC ROTOR

| $J$ | $K$ | $J'$ | $K'$ | $\nu$, cm.$^{-1}$ | $\nu$, mc./s. |
|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | 0.16856 | 5,053 |
| 1 | 1 | 2 | 1 | .33712 | 10,106 |
| 2 | 2 | 3 | 2 | .50568 | 15,159 |
| 3 | 3 | 4 | 2 | .67424 | 20,212 |
| 4 | 4 | 5 | 4 | .84280 | 25,265 |
| 5 | 5 | 6 | 5 | 1.01136 | 30,319 |
| 0 | 0 | 0 | 1 | 2.5257 | 75,716 |
| 1 | 1 | 1 | 2 | 7.5772 | 227,148 |

(12) R. Mecke, *Z. Physik*, **81**, 313 (1933).

mc. to be identified as arising from the parallel type transitions $J = 3 \rightarrow 4$ and $J = 4 \rightarrow 5$. Detailed analysis to be presented later indicates that the lines at 29,800 are the beginning of the $J = 5 \rightarrow 6$ group. On the basis of these simple considerations, however, each of these transitions should consist of but a single line. Since there are more than 19 components in the $J = 4 \rightarrow 5$ group alone some explanation must be found for the extra lines.

### Removal of Degeneracies

Considering the various complicating factors in turn, the removal of degeneracies known to exist in the pattern of symmetric rotor energy levels by the asymmetry of the molecule and by the modulating field will be taken up first. Each $J$ level in the symmetric rotor is made up of $2J + 1$ degenerate levels corresponding to the individual values of $K$. In turn each $JK$ level is made up of $2J + 1$ levels, degenerate in the absence of an external field, corresponding to the individual values of the quantum number $M$. In the specific case of a molecule having the structure indicated in Fig. 4 the $K$ degeneracy is at least partially removed by the molecular asymmetry. The transition frequencies for such an asymmetric rotor have been calculated using third order perturbation theory and the coefficients tabulated by King, Hainer and Cross,[13] and are given in Table III. The single line predicted above for the $J = 4 \rightarrow 5$ transition, for example, has been replaced by a pattern of three lines. The lines corresponding to (in the KHC notation) the $4_{1,4;-3} \rightarrow 5_{1,5;-4}$ and $4_{1,3;-2} \rightarrow 5_{1,4;-3}$ transitions have split, not quite symmetrically, some 100 mc. away, on either side of the degenerate line.

TABLE III

CALCULATED ROTATIONAL SPECTRUM FOR $CH_3NCS$ CONSIDERED AS AN ASYMMETRIC ROTOR

| Transition | $\nu$, mc. |
|---|---|
| $3_{0,3;-3} \rightarrow 4_{0,4;-4}$ | 20,215 |
| $3_{1,3;-2} \rightarrow 4_{1,4;-3}$ | 20,131 |
| $3_{1,2;-1} \rightarrow 4_{1,3;-2}$ | 20,297 |
| $3_{2,2;0} \rightarrow 4_{2,3;-1}$ | 20,215 |
| $3_{2,1;+1} \rightarrow 4_{2,2;0}$ | 20,216 |
| $3_{3,1;+2} \rightarrow 4_{3,2;+1}$ | 20,215 |
| $3_{3,0;+3} \rightarrow 4_{3,1;+2}$ | 20,215 |
| $4_{0,4;-4} \rightarrow 5_{0,5;-5}$ | 25,262 |
| $4_{1,4;-3} \rightarrow 5_{1,5;-4}$ | 25,158 |
| $4_{1,3;-2} \rightarrow 5_{1,4;-3}$ | 25,364 |
| $4_{2,3;-1} \rightarrow 5_{2,4;-2}$ | 25,265 |
| $4_{2,2;0} \rightarrow 5_{2,3;-1}$ | 25,266 |
| $4_{3,2;+1} \rightarrow 5_{3,3;0}$ | 25,265 |
| $4_{3,1;+2} \rightarrow 5_{3,2;+1}$ | 25,265 |
| $4_{4,1;+3} \rightarrow 5_{4,2;+2}$ | 25,265 |
| $4_{4,0;+4} \rightarrow 5_{4,1;+3}$ | 25,265 |

Since the spectrometer employs an applied electric field for modulation, the spectrum actually observed is complicated by the presence of lines corresponding to the individual $M$ values. The experimental arrangement is such that the electric radiation vector and the applied electric field are parallel (except for negligible fringing effects near the edges of the waveguide absorption cell) and the selection rule $\Delta M = 0$ is obeyed. Analysis of this pattern of Stark components would allow calculation of the component of dipole moment along the approximate figure axis of the molecule but unfortunately the complexity of the not very intense spectrum was such that an analysis has not been carried out. In the reported spectrum Stark components have been omitted by eliminating all lines whose frequency varied with the electric field.

### Centrifugal Distortion

The foregoing calculations were based on the assumption that the molecule was rigid. The actual molecule is subject to centrifugal distortion which will have an effect on the pattern of rotational energy levels. Slawsky and Dennison[14] give an expression for the energy levels of a non-rigid symmetric rotor

$$F(J,K) = BJ(J+1) + (A-B)K^2 - D_J J^2(J+1)^2 - D_{JK}J(J+1)K^2 - D_K K^4$$

which leads to an expression

$$\nu = 2B(J+1) - D_J(J+1)^3 - D_{\bar{J}}(J+1) + D_{JK}K^2(J+1)$$

for the frequencies of the rotational transitions Slawsky and Dennison give the following calculated values of the constants for the case of $CH_3Cl$

$$D_J = 0.0036 \text{ mc/s.}$$
$$D_{\bar{J}} = 0.0414 \text{ mc/s.}$$
$$D_{JK} = 0.4020 \text{ mc/s.}$$

Gordy, Simmons, and Smith[9] report an experimental value of $D_{JK}$ for $CH_3Cl$ of 0.19 mc. The term involving $D_{JK}$ is much the largest and should lead to a separation between the $K = 0$ and $K = 4$ components of the degenerate transition of as much as 15 mc. In the experimental spectrum there is considerable evidence of fine structure on the high frequency side of the degenerate line but interference from the pattern of Stark components has prevented any accurate measurement of this centrifugal splitting. The term involving $D_J$ will cause deviations from the frequencies predicted using a linear relation between $\nu$ and $J(J+1)$. The example of $CH_3Cl$ makes it seem probable that this effect would be unobservable with the precision of frequency measurement available in this study.

### Excited Vibrational States

The interaction of vibration and rotation has so far been neglected. The rotational constant $B$ (and $A$ and $C$ as well) actually has different values in the different vibrational states. This de-

(13) G. W. King, R. M. Hainer and P. C. Cross, *J. Chem. Phys.*, **11**, 27 (1943).

(14) Z. I. Slawsky and D. M. Dennison, *J. Chem. Phys.*, **7**, 509 (1939).

pendence of $B$ on the vibrational quantum numbers is indicated by the following formula, taken from Herzberg[15] where the $\alpha_i$ are small compared

$$B_{[v]} = B_e - \sum_i \alpha_i^B (v_i + d_i/2)$$

to $B_e$, which is the rotational constant for the equilibrium position. $d_i$ is the degree of degeneracy of the vibration $v_i$. The summation extends over all vibrations. The constants $\alpha_i$ are usually positive for the non-degenerate vibrations of linear molecules, but may be positive or negative for the degenerate vibrations.

No complete vibrational study and resulting assignment of fundamentals has yet been published for $CH_3NCS$. However, Goubeau and Gott[16] have determined the stretching frequencies for the linear portion of the molecule and Eyster and Gillette[17] have made vibrational assignments for similar molecules including $CH_3NCO$. The approximate vibrational frequencies listed in Table IV should then be at least of the correct order of magnitude. The Boltzmann factors computed from these frequencies indicate roughly the expected ratio of relative intensities of spectral lines due to the same transition for molecules in the ground and excited vibrational states.

TABLE IV

APPROXIMATE VIBRATION FREQUENCIES FOR $CH_3NCS$

| Series | $CH_3NCO$ $\omega$ cm.$^{-1}$ | $CH_3NCS$ $\omega$ cm.$^{-1}$ | $CH_3NCS$ $e^{-h\nu/kT}$ |
|---|---|---|---|
| A | 870 | 850 | 0.0166 |
| B | 2232 | 2162 | < .0001 |
| C | 1412 | 1087 | .0052 |
| D | 353 | 300 | .2340 |
| E | 652 | 600 | .0550 |
| | 607 | 550 | .0699 |
| F | 2994 | 3000 | < .0001 |
| | 2951 | 2950 | < .0001 |
| G | 1453 | 1450 | .0009 |
| | | 1440 | .0009 |
| H | 1377 | 1375 | .0014 |
| I | 1181 | 1200 | .0030 |
| | 1107 | 1100 | .0049 |
| J | ? | 200 | .2982 |

The vibrations of series A correspond to $CH_3$–N stretching frequencies. Series B and C are stretching frequencies localized within the linear portion of the molecule. B is the N–C stretching and C the C–S stretching frequencies in $CH_3NCS$. The D vibration corresponds to the bending of the $CH_3$–N bond against the linear group. The E vibrations are the perpendicular bending vibrations of the linear group.

The vibrations F through H are the well known internal vibrations of the methyl group and the I vibrations correspond to the rocking frequencies of this group. The torsional oscillation frequency J requires further discussion.

## Internal Rotation

The features of the spectrum due to the internal rotation of the methyl group and isothiocyanate group independently about the molecular axis will depend upon the height of the barrier hindering the rotation. If the barrier is of a comparable (although probably somewhat smaller) magnitude to that in the roughly similar case of methanol[18] an appreciable number of molecules will occupy the first excited torsional vibration level. Indeed, if the figure 200 cm.$^{-1}$ for the height of this excited state above the ground level listed in Table IV is correct a line in the observed spectrum due to the second excited state might well appear. In methanol the ratio of populations for the ground state and first excited state of torsional vibration is 0.18; in the case of $CH_3NCS$ this ratio would probably be somewhat larger.

The torsional vibrational states, according to the analysis of the methyl alcohol problem presented by Koehler and Dennison,[18] are actually made up of a number of sublevels with a spread in energy which increases with the torsional vibration quantum number. In general there are three sublevels for each permitted $K$ value although certain degeneracies occur. For methyl alcohol the spread of the energy levels for the first excited state has been calculated to be 33 cm.$^{-1}$. Since this spread varies inversely with the barrier height an even wider separation of levels would be expected for $CH_3NCS$. It is difficult to predict whether the first excited torsional state will give rise to a single broad line in the pure rotation spectrum or will have a resolvable structure.

For low values of the barrier height, and in any case for torsional vibration states higher than the second or third, the internal rotation would be essentially free. If we apply the analysis of Koehler and Dennison[18] (which should fit only roughly because of the considerable asymmetry of the NCS group) the following expression for the frequencies of the lines in the $\Delta J = 0$ series may be used

$$\lambda = A_1 - B - 2BK + 2A_1K_1$$

$A_1$ is the rotational constant for the NCS group about the molecular axis (not the symmetry axis of the methyl group). Using the rotational constants given in Fig. 4 and a minimum value of $A_1$ of 3.0 cm.$^{-1}$ the frequencies for this series were calculated. All lie outside the experimental frequency range for this investigation.

A limit to the complexity introduced into the observed spectrum by excited vibrational states is set only by the available sensitivity of the spectrometer. If the observed spectrum is limited to those lines whose apparent intensity is at least

(15) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., New York, N. Y., 1945, p. 370.

(16) J. Goubeau and O. Gott, *Ber.*, **73B**, 127 (1940).

(17) E. H. Eyster and R. H. Gillette, *J. Chem. Phys.*, **8**, 369 (1940).

(18) J. S. Koehler and D. M. Dennison, *Phys. Rev.*, **57**, 1006 (1940).

0.005 of that for the most intense line in the spectrum the Boltzmann factors listed in Table IV should permit selection of the vibrations whose first excited states might give rise to lines. On this basis the most intense of the excited vibration lines should be due to the torsional vibration J. Next most intense would be the line corresponding to the first excited state of the $CH_3$–N bending vibration, D. Following in order of intensity would be the second excited levels for these two vibrations and the first excited levels for the nearly degenerate bending modes of the NCS group, E. Finally a line due to the first excited level for the $CH_3$–N stretching vibration, A, might be seen. The $\alpha$'s for these vibrational states cannot be easily calculated so that the lines due to excited vibrational states must be identified from their intensities and from the change of intensity with temperature. The experimental measurement of temperature coefficients of intensity was made rather difficult by the small temperature range over which measurements could be made for this molecule and with the present equipment. The rough values obtained, however, definitely serve to establish several of the fairly intense lines as being due to excited vibrational states.

## Isotopic Spectra

There should be, of course, separate and easily resolvable microwave spectra for each of the different isotopic varieties of the $CH_3NCS$ molecule. The relative intensities of lines due to the more abundant naturally occurring $CH_3NCS$ molecules have been calculated and are given in Table V.

TABLE V

RELATIVE ABUNDANCE OF ISOTOPIC VARIETIES OF $CH_3NCS$

| Molecule | Relative abundance |
|---|---|
| $C^{12}H_3N^{14}C^{12}S^{32}$ | 100.00 |
| $C^{12}H_3N^{14}C^{12}S^{34}$ | 4.40 |
| $C^{12}H_3N^{14}C^{12}S^{33}$ | 0.76 |
| $C^{13}H_3N^{14}C^{12}S^{32}$ | 1.08 |
| $C^{12}H_3N^{14}C^{13}S^{32}$ | 1.08 |
| $C^{12}H_3N^{15}C^{12}S^{32}$ | 0.38 |

If the same range of relative intensities is used here as was proposed earlier in the discussion of excited vibrational states any or all of these molecules might give rise to observable spectra. It is even probable that for the molecule involving $S^{34}$ lines due to both the ground and excited vibrational states would be seen.

## Nuclear Quadrupie Coupling

Two of the nuclei which are concerned in the $CH_3NCS$ molecular species have nuclear quadrupole moments—$N^{14}$ and $S^{33}$. In the latter case the intensity of the main transition must be so low that the quadrupole fine structure would be unobservable. For $N^{14}$, intensities of the fine structure components might be sufficient but it is doubtful that the spectrometer was operated with sufficient resolving power to separate the individual lines. In the closely similar case of N in $CH_3NC$[5] the quadrupole splitting has been reported as less than 1 mc. Line widths in this study were considerably larger than this figure. Lines were, in fact, unusually broad although extra width seems to be a feature of the microwave rotational spectral lines of symmetric rotors possessing large dipole moments.

## Other Asymmetric Rotor Transitions

In considering the molecule as an asymmetric rotor certain transitions become possible other than the ones so far dealt with, which correspond to the parallel type $\Delta J = 1$, $\Delta K = 0$ transitions of the prolate symmetric rotor, and in the KHC notation[19] are described as $ae_{R_0,1}$ or $ao_{R_0,1}$. For the most part, however, the intensities of other types of "a" transitions may be shown to be too small to be detected with the present equipment for all reasonable values of the asymmetry parameter $\kappa$. The only other "$a$" transition which might be observable are the $ao_{Q_{0,1}}$-transitions between the split components of each K level. Very high J values would be required to bring the frequencies of such lines into the observed region so that the resulting Boltzmann factors would reduce their intensities to a rather small figure. Such transitions would be so widely spaced that at most they could account for only two or three lines in the entire experimental frequency range.

Since there is no component of the dipole moment along the $I_C$ axis (perpendicular to the C–N–C–S plane) "$c$" type transitions will have zero intensity. While a small component of the dipole moment does exist along the $I_B$ axis, the intensities of "$b$" type transitions would be quite small since the intensity is proportional to the square of the dipole moment component. There are a number of lines of low intensity in the observed spectrum which have not been accounted for (as well as some for whose assignment there is at least a reasonable doubt), so this possibility cannot be completely ruled out.

## Analysis of Observed Spectrum

An analysis of the observed spectrum has been made in the light of the discussion above and the results are presented in Table I. The theoretical spectrum, calculated using the molecular model described in Fig. 4, and compared to the experimental spectrum in Fig. 2, reproduces the general features of the experimental spectrum quite well. The features of this spectrum which are advanced with the most confidence are the following: The average rotational constants, $^1/_2(B + C)$, for $CH_2NCS$ in the ground vibrational state have the value indicated in Table VI. Certain of the lines in different transition groups reveal by the ratio of their frequencies that they correspond to the

(19) P. C. Cross, R. M. Hainer and G. W. King, *J. Chem. Phys.*, **12**, 210 (1944).

same average rotational constant, which is different from the value assigned the most abundant isotopic variety in the ground vibrational state.

TABLE VI

| Molecule | $\nu$, mc. | $(B+C)^{1/2}$, cm.$^{-1}$ | Transition | Vib. state | $I_{av.}$, g. cm.$^2$ |
|---|---|---|---|---|---|
| $CH_3NCS$ | 20216 | 0.084295 | $J = 3 \rightarrow 4$ | Ground | $332.01 \times 10^{-40}$ |
| | 25269 | .084292 | $J = 4 \rightarrow 5$ | Ground | 332.02 |
| | 20443 | .085241 | $J = 3 \rightarrow 4$ | $J$ | 328.33 |
| | 25550 | .085223 | $J = 4 \rightarrow 5$ | $J$ | 328.40 |
| | 20350 | .084854 | $J = 3 \rightarrow 4$ | $D$ | 329.83 |
| | 25442 | .084869 | $J = 4 \rightarrow 5$ | $D$ | 329.77 |
| $CH_3NCS^{34}$ | 19700 | .082144 | $J = 3 \rightarrow 4$ | Ground | 340.71 |
| | 24609 | .082090 | $J = 4 \rightarrow 5$ | Ground | 340.93 |
| | 29540 | .082116 | $J = 5 \rightarrow 6$ | Ground | 340.82 |
| | 19929 | .083099 | $J = 3 \rightarrow 4$ | $J$ | 336.79 |
| | 24910 | .083094 | $J = 4 \rightarrow 5$ | $J$ | 336.81 |

The details of the assignment of these rotational constants to different isotopic varieties of the molecule in different vibrational states depends upon measurements of relative intensity and calculations of isotopic frequency shifts. The relative intensities are highly approximate because of difficulties encountered in their measurement. The calculated frequency shifts, of course, depend upon the assumed molecular model. However, in the case of the lines assigned to the first excited torsional vibration level the intensities are so large as to rule out most other possible assignments. For the lines assigned to $CH_3NCS^{34}$ both the frequency shifts and the intensities are of the right order of magnitude and their agreement tends to support the conclusion. The assignment of the next most intense set of lines to the first excited state of the $CH_3$–N bending mode seems reasonable since in the vibrational assignment for similar molecules this is much the lowest lying vibration exclusive of torsion. The assignment of lines to the nearly degenerate bending modes of the NCS group is much more doubtful but has been made simply on the basis of the relative intensities. Because of the complexity of the spectrum the interesting question of the effects of the near degeneracy and slight asymmetery on what would be $l$-type doubling in a linear molecule has not been pursued.

Because of the uncertainty in the degeneracy of the lines ascribed to the first excited torsional vibration level the assignment of the lines in the neighborhood of 25500 mc. is rather tentative. It is perhaps possible that this group of lines is made up of the resolved components of the degenerate line.

The designation of certain of the lines as components of the degenerate main transition split out by the molecular asymmetry is somewhat difficult because their spacing is quite sensitive to small changes in the rotational constants and their intensities are low enough to permit confusion with the excited vibrational lines. The spacing of the lines should be nearly symmetric about the degenerate line and should be greater for the $J = 4 \rightarrow 5$ transition than for $J = 3 \rightarrow 4$. The relative intensities should be in the calculated ratio. Most of these requirements are at least roughly met by the assignment given above.

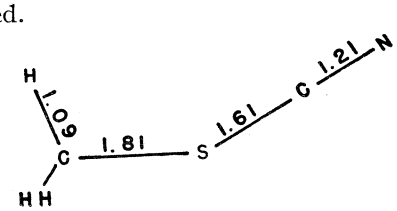
## $CH_3SCN$ Spectrum

With the same Stark modulation apparatus, the region from 20,000 to 30,000 mc. was searched for lines of methyl thiocyanate. The observed spectrum was similar in many respects to that for the tautomeric ester although, of course, occurring at different frequencies. Again the spectrum consisted of complex groups of lines. However, for methyl thiocyanate the intensities were so low that only the strongest lines could be properly studied. The two strongest lines, which by analogy with the tautomeric ester would be assigned to the degenerate transition of the ordinary isotopic form of the molecule, were found to have the frequencies given in the table.

| Frequency, mc. | Transition | Average rotational constant, cm.$^{-1}$ |
|---|---|---|
| 22,680 | $J = 3 \rightarrow 4$ | 0.09457 |
| 28,380 | $J = 4 \rightarrow 5$ | .09467 |

The frequencies were determined using a cavity wavemeter and are accurate only to $\pm 10$ mc.

The frequency ratio of these lines enables them to be identified as $\Delta J = 1$, $\Delta K = 0$ transitions of a slightly asymmetric rotor involving the $J$ values listed above. This conclusion is supported by calculations based on various probable structures of the $CH_3SCN$ molecule. By assuming probable values of the interatomic distances, the C–S–C angle corresponding to moments of inertia resulting from the observed value of $\frac{1}{2}(B + C)$ could be calculated. The $CH_3SCN$ structure shown in Fig. 5 is the one consistent with the above considerations. In order to determine the structure completely from the spectrum, independent of the above assumptions, spectra for several different isotopic varieties of the molecule, probably synthesized from enriched material, would have to be observed.




H–C–S angle 109°
C–S–C angle 142°

Fig. 5.—Approximate molecular configuration of $CH_3SCN$.

## Summary

Measurements of the pure rotational spectra of $CH_3NCS$ and $CH_3SCN$ have been made in the frequency range from 20,000 to 30,000 mc. Experimental techniques used and the interpretation of the spectra of these molecules are discussed. A theoretical spectrum for $CH_3NCS$ has been set up and the complicating effects of the removal of de-

generacies by asymmetry and by an external electric field, of centrifugal distortion, of the presence of excited vibrational states, of internal rotation, of isotopic varieties of the molecule, of nuclear quadrupole coupling, and of other allowed asymmetric rotor transitions are calculated. There is good general agreement between the theoretical and observed spectra for $CH_3NCS$. The spectrum of $CH_3SCN$ was too weak for detailed analysis but values of the average rotational constant $^1/_2$ $(B + C)$ are presented.

RECEIVED AUGUST 17, 1948

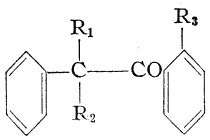
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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

# Steric Hindrance in the Stobbe Condensation[1]

BY MELVIN S. NEWMAN AND JACK LINSK[2]

The first step in the recently reported method for the synthesis of 1,2-benzanthracene[3] involves the Stobbe condensation (in 60% yield) of desoxybenzoin, I ($R_1 = R_2 = R_3 = H$), and methyl succinate. In order to apply this method to the synthesis of 1′,9-dimethyl-1,2-benzanthracene,




we prepared, *o*,α-dimethyldesoxybenzoin, II ($R_1 = R_3 = CH_3$, $R_2 = H$) and attempted to condense it with ethyl succinate. In spite of numerous attempts including the use of potassium *t*-butoxide[4] in place of sodium ethoxide and the substitution of methyl succinate, succinic anhydride, and *n*-methylsuccinimide for ethyl succinate, we were entirely unsuccessful. To test the suggestion that enolization of the ketone[5] might be responsible for this failure to condense, we prepared *o*,α,α-trimethyl-desoxybenzoin, III ($R_1 = R_2 = R_3 = CH_3$), and attempted the reaction, but without success. Hence it appeared that steric factors were involved.

Accordingly we prepared α-methyldesoxybenzoin, IV ($R_1 = R_3 = H$, $R_2 = CH_3$), α,α-dimethyldesoxybenzoin, V ($R_1 = R_2 = CH_3$, $R_3 = H$), and 2,5-dimethylphenyl benzyl ketone, VI (a compound analogous to *o*-methyldesoxybenzoin [$R_1 = R_2 = H$, $R_3 = CH_3$] but easier to prepare) and have tested these under similar conditions in the Stobbe reaction. All of these attempts failed except that with IV, which gave the expected product in about 60% yield. Thus, from a comparison of the reactions involving ketones IV and VI, it appears that the substitution of one methyl group in the ortho position of the phenyl group adjacent to the carbonyl is more effective in hindering reaction than the substitution of a methyl group in the methylene group. Substitution of a second methyl group in the methylene group (ketone V) effectively hinders reaction.

## Experimental[6]

**2-Phenyl-1-*o*-tolyl-1-propanol.**—A solution of 386 g. (2.87 mole) of hydratropaldehyde[7] in 600 cc. of dry ether was added dropwise during two hours to a well stirred solution containing the Grignard reagent prepared from 835 g. (3.83 mole) of *o*-iodotoluene in two liters of dry ether. After decomposition of the reaction mixture with iced hydrochloric acid, the alcohol was obtained as a colorless oil, b. p. 149–150° at 2 mm., in 65% yield. The *p*-nitrobenzoate melted at 112.1–113.4° after three recrystallizations from methanol.

*Anal.*[a] Calcd. for $C_{16}H_{18}O$: C, 84.9; H, 8.0. Found: C, 85.0; H, 8.1. Calcd. for $C_{23}H_{21}O_4N$: N, 4.0. Found: N, 4.2, 4.0.

**o,α-Dimethyldesoxybenzoin, II.**—In all attempts to oxidize the above alcohol using chromic oxide, potassium dichromate and sulfuric acid, or nitric acid, considerable cleavage into acetophenone and *o*-toluic acid occurred. In the best experiment 220 g. (0.98 mole) of the alcohol was added during ten minutes to a well-stirred two phase system composed of 100 cc. of benzene and a solution of 200 g. of potassium dichromate in 900 cc. of water and 90 cc. of concentrated sulfuric acid. The temperature slowly rose to 54° but did not go higher. After stirring for twelve hours, during which time the temperature fell to room, the reaction products were taken into ether. The acid was removed by an alkaline wash and the ketone was obtained in 65% yield as a colorless oil, b. p. 120–124° at 1 mm., which soon crystallized. A sample crystallized from methanol melted at 54.4–55.5°. The 2,4-dinitrophenylhydrazone formed small yellow needles, m. p. 136.0–137.0° after several crystallizations from ethyl acetate and from chloroform–alcohol. In all attempts to effect a Stobbe condensation, the ketone was recovered in high yield.

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found[a]: C, 85.7; H, 7.3. Calcd. for $C_{22}H_{20}O_4N_4$: C, 65.3; H, 5.0; N, 13.9. Found[c]: C, 65.2; H, 4.7; N, 13.5.

**o,α,α-Trimethyldesoxybenzoin, III.**—Ketone II was methylated with potassium *t*-butoxide and methyl iodide[8] to yield III as a solid, m. p. 37–38°, in 92% yield. A sample recrystallized for analysis melted at 38.6–39.6°. We were unable to prepare a 2,4-dinitrophenylhydrazone, semicarbazone, or oxime of this ketone, or to secure any acidic material after attempted Stobbe condensations.[4]

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(1) The material herein presented is taken from the Ph.D. thesis of Jack Linsk, Ohio State University, June, 1948. Present address: Standard Oil Company of Indiana, Whiting, Indiana.

(2) Abbott Laboratories Fellow, 1947–1948.

(3) Newman and Hart, THIS JOURNAL, **69**, 298 (1947).

(4) W. S. Johnson, A. Goldman and W. P. Schneider, *ibid.*, **67** 1367 (1945).

(5) Private communication from Dr. W. S. Johnson, University of Wisconsin.

(6) All melting points corrected. Analyses marked [a] by the Oakwold Laboratories, Alexandria, Va., [b] by James Polglase, Ohio State University, and [c] by Mrs. Edith Klotz, Ohio State University.

(7) Obtained from the Van Ameringen-Haebler Co., 417 Rosehill Place, Elizabeth, New Jersey.

(8) W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943).

*Anal.*[a] Calcd. for $C_{17}H_{18}O$: C, 85.6; H, 7.6. Found: C, 85.3; H, 7.4.

**α-Methyldesoxybenzoin, IV.**—To a solution of the Grignard reagent prepared from 157 g. (1 mole) of bromobenzene and 30 g. of magnesium in 400 cc. of ether was added dropwise during one hour a solution of 63 g. (0.48 mole) of hydratropanitrile[9] in 100 cc. of benzene. After replacing 200 cc. of ether, which was allowed to distil, with an equal volume of benzene, the mixture was refluxed for five hours. The complex was decomposed with dilute hydrochloric acid, 200 cc. of concentrated hydrochloric acid was added, and the mixture refluxed for two hours to hydrolyze the imine hydrochloride. The ketone, IV, was finally isolated in 57% yield as a colorless oil, b. p. 136–137° at 2 mm., which soon crystallized to a solid. On recrystallization this ketone was obtained as feathery needles, m. p. 52–53°.[10]

**3-Carboxy-4,5-diphenyl-4-hexenoic Acid.**[11]—A solution of 10.3 g. (0.05 mole) of IV and 15.5 g. (0.09 mole) of ethyl succinate in 30 cc. of *t*-butyl alcohol was added to a cooled stirred solution of 2.2 g. (0.055 mole) of potassium in 30 cc. of *t*-butyl alcohol maintained under nitrogen. After refluxing for one and three-quarters hours, the mixture was cooled and treated with 12 cc. of 6 *N* hydrochloric acid. Since the crude half ester did not crystallize, it was saponified and the acid obtained in 42% yield as colorless needles, m. p. 174–176°. More acid was present, but no attempt to isolate the maximum amount was made. The pure acid, obtained on recrystallization from aqueous methanol, melted at 174.6–175.7°. From the neutral reaction products, 19% of IV was recovered.

*Anal.*[c] Calcd. for $C_{19}H_{18}O_4$: C, 73.8; H, 6.0. Found: C, 74.0; H, 6.2.

**α,α-Dimethyldesoxybenzoin, V.**—On methylation[8] IV was converted into V in 84% yield. The product boiled at 137–138° at 2 mm. and crystallized on standing to give thin rods, m. p. 45–47°.[12] The attempted Stobbe condensation failed, 79% of V being recovered.

**2,5-Dimethylphenyl Benzyl Ketone, VI.**—To a stirred cooled solution of 77.3 g. (0.5 mole) of phenylacetyl chloride and 90 g. of pure *p*-xylene[1] in one pound of carbon disulfide was added 110 g. of aluminum chloride during one hour. After heating to reflux during one hour and stirring at room temperature for two more, the mixture was decomposed with ice and hydrochloric acid. The ketone, VI, obtained in 86% yield, boiled at 147–148° at 2 mm. and melted at 30.5–32.0°. The Stobbe reaction failed, an 82% yield of VI being recovered from the reaction mixture.

*Anal.*[c] Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.8; H, 7.4.

## Summary

Steric hindrance in the Stobbe condensation of several methylated desoxybenzoins has been observed. A methyl group ortho to the carbonyl effectively hinders the reaction as do two methyl groups in any positions adjacent to the carbonyl group.

(9) Newman and Closson, THIS JOURNAL, **66**, 1553 (1944).
(10) Kayser, *Ann. Chim.*, (11) **6**, 188 (1936).
(11) The position of the double bond in this acid is assumed.
(12) Bruzan, *Ann. chim.*, [11] **1**, 335 (1934), reports m. p. 46–47°.

COLUMBUS, OHIO RECEIVED OCTOBER 25, 1948

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[CONTRIBUTION FROM THE SMITH, KLINE AND FRENCH LABORATORIES]

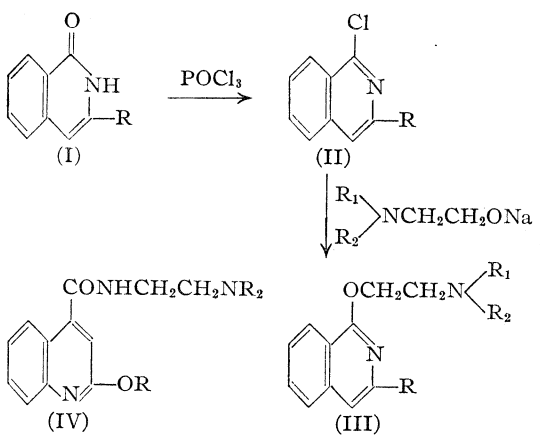
# Local Anesthetics. Aminoalkoxyisoquinoline Derivatives

BY JAMES W. WILSON, III, NORMAN D. DAWSON,[1] WALTER BROOKS[2] AND GLENN E. ULLYOT

Aminoalkyl ethers of phenols have been reported to possess local anesthetic activity.[3,4]

As far as we can find, however, no one has investigated the pharmacological properties of aminoalkoxy derivatives of isoquinolines. Previous work in this Laboratory[5] provided an excellent method for preparing a group of isocarbostyrils (I) from which a series of aminoalkoxy derivatives (III) has been obtained according to the procedure outlined by formulas I–III.

In order to be able to study the effect of modifying the lipophylic and hydrophylic character of the terminal groups of the molecule (III) on the pharmacological properties, we have varied the nature of the R, $R_1$ and $R_2$ groups as shown in Table I. That such factors play a role is demonstrated by the effect of varying the R groups in the known local anesthetics of the quinoline type (IV),[6] and by gradations in the local anesthetic activity among our compounds, as indicated in the last column of Table I.




The 1-chloroisoquinolines which are intermediates in our syntheses are listed in Table II.

## Experimental

**Preparation of 1-Chloroisoquinolines.**—All of these compounds were prepared from the corresponding isocarbostyrils by the action of phosphorus oxychloride[7] using essentially the same procedure in each case.

(1) Present address: Department of Chemistry, University of Virginia, University, Virginia.
(2) Present address: University of Pennsylvania, Philadelphia, Pennsylvania.
(3) Merck, German Patent 184,968 (1907).
(4) I. G. Farbenindustrie, Swiss Patents 135,890 (1929), 136,186 (1930).
(5) To be reported in a forthcoming paper.
(6) Miescher, *Helv. Chim. Acta*, **15**, 163 (1932).
(7) See Footnote [a], Table II.

TABLE I

AMINOETHOXYISOQUINOLINES (FORMULA III)

| | R | $R_1$ | $R_2$ | Formula | B. p. °C. | Mm. | $n_D$ | °C. | Yield, % | Analyses, % Calcd. C | Calcd. H | Found C | Found H | Duration of local anesthetic activity in min. by a 0.1% soln. on the rabbit's cornea[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | $CH_3$ | $C_{18}H_{16}N_2O$ | 133–134 | 2 | 1.5708 | 20 | 80 | 72.18 | 7.45 | 72.12 | 7.31 | 9.6 |
| 2 | H | $n$-$C_4H_9$ | $n$-$C_4H_9$ | $C_{19}H_{28}N_2O$ | 172–173 | 2 | 1.5355 | 20 | 76 | 75.96 | 9.39[a] | 76.16 | 9.59 | 27.8 |
| 3 | $CH_3$ | $C_2H_5$ | $C_2H_5$ | $C_{16}H_{22}N_2O$ | 153–154 | 1–2 | 1.5530 | 21 | 91 | 74.36 | 8.58 | 74.38 | 8.70 | 76.0 |
| 4 | $CH_3$ | —$(CH_2)_5$— | | $C_{17}H_{22}N_2O$ | 175–178 | 1 | 1.5715 | 21 | 83 | 75.51 | 8.20 | 75.60 | 8.32 | 26.4 |
| 5 | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | $C_{17}H_{24}N_2O$ | 154–157 | 1 | 1.5481 | 21 | 89 | 74.98 | 8.88 | 74.77 | 8.70 | 141.8 |
| 6 | $C_2H_5$ | —$(CH_2)_5$— | | $C_{18}H_{24}N_2O$ | 175–178 | 1 | 1.5654 | 21 | 93 | 76.01 | 8.51 | 75.86 | 8.44 | 180+ |
| 7 | $C_2H_5$ | H | $CH_2C_6H_5$ | $C_{20}H_{28}N_2OCl$[b] | | | | | 82 | 70.05 | 6.76 | 69.83 | 6.94 | 121 |
| 8 | $n$-$C_3H_7$ | $CH_3$ | $CH_3$ | $C_{16}H_{22}N_2O$[c] | 150–152 | 2 | 1.5525 | 21 | 92 | 74.36 | 8.58[d] | 74.38 | 8.55 | 72.0 |
| 9 | $n$-$C_4H_9$ | $CH_3$ | $CH_3$ | $C_{17}H_{24}N_2O$ | 155–157 | 3 | 1.5486 | 20 | 87 | 74.95 | 8.88 | 74.99 | 8.81 | 138+ |

[a] Calcd.: N, 9.33. Found: N, 9.07. [b] This product was isolated as the monohydrochloride, m. p. 154–155°. Calcd.: $Cl^-$, 10.34. Found: $Cl^-$, 10.22. [c] Forms a solid dihydrochloride which under prolonged vacuum drying loses one molecule of hydrogen chloride. This product melts at 113–116°. *Anal.* Calcd. for $C_{16}H_{23}N_2OCl$: $Cl^-$, 12.05. Found: $Cl^-$, 12.00. [d] Calcd.: N, 10.84. Found: N, 10.61. [e] Anesthetic activity was appraised after topical application to the rabbit's eye. For comparative purposes the durations of anesthesia produced by a 1.0% solution of cocaine or procaine were eighteen and two minutes, respectively.

TABLE II

1-CHLORO-3-SUBSTITUTED-ISOQUINOLINES

| 3-Substituent | Formula | B. p. °C. | Mm. | M. p., °C. | Yield, % |
|---|---|---|---|---|---|
| H | $C_9H_6NCl$ | 114–116[a] | 8–9 | 31 | 79 |
| $CH_3$ | $C_{10}H_8NCl$ | 108–110[b] | 1 | 32 | 94 |
| $C_2H_5$ | $C_{11}H_{10}NCl$ | 148–150[c] | 9–10 | 26 | 96 |
| $n$-$C_3H_7$ | $C_{12}H_{12}NCl$ | 157–161[d] | 9 | | 96[e] |
| $n$-$C_4H_9$ | $C_{13}H_{14}NCl$[f] | 155–158 | 6 | | 77 |

[a] Gabriel and Colman, *Ber.*, **33**, 985 (1900). [b] Gabriel and Neumann, *Ber.*, **25**, 3569 (1892). [c] Damerow, *Ber.*, **27**, 2236 (1894). [d] Albahary, *Ber.*, **29**, 2395 (1896). [e] $n^{21}D$ 1.5968. [f] Calcd.: C, 71.06; H, 6.42. Found: C, 71.23, H, 6.48.

**3-*n*-Butyl-1-chloroisoquinoline.**—A solution of 56 g. of 3-*n*-butylisocarbostyril in 86 g. of phosphorus oxychloride was refluxed for sixteen hours, cooled, and poured into 300 g. of cracked ice. The cold solution was carefully neutralized with 40% sodium hydroxide and the product extracted into ether. After drying over anhydrous sodium sulfate, the ether was removed, and the product distilled to yield 47 g. of colorless liquid.

**Preparation of Aminoalkyl Ethers.**—In each case a solution of the sodium derivative of the amino alcohol in toluene or xylene was condensed with the chloroisoquinoline. The ethers, with the exception of the 1-(β-benzylaminoethoxy)-3-ethylisoquinoline, were isolated by distillation.

**1-(β-Dimethylaminoethoxy)-3-propylisoquinoline.**—A mixture of 3.4 g. of finely divided sodium metal and 17.6 g. of β-dimethylaminoethanol in 100 ml. of dry xylene was heated at 60–80° with efficient stirring for three hours. While maintaining the resulting solution at 75–85°, 26 g. of 1-chloro-3-propylisoquinoline was added, with stirring, over a period of six hours. The heating was continued for an additional two hours, the sodium chloride was removed by filtration, the filtrate washed with water and the product extracted with 2 *N* hydrochloric acid. This acid solution was made alkaline and the product extracted with ether. After drying, the ether was removed and the product distilled to yield 29.4 g. of colorless oil, b. p. 150–152° (2 mm.).

**1-(β-Benzylaminoethoxy)-3-ethylisoquinoline Monohydrochloride.**—The initial condensation was carried out as described above, employing 2.3 g. of sodium, 18 g. of benzylaminoethanol, and 19.2 g. of 1-chloro-3-ethylisoquinoline. When this reaction mixture was extracted with acid, the hydrochloride of the product crystallized, yielding 28 g. (82%) of white solid. Crystallization from acetone–alcohol and vacuum drying gave 22 g., m. p. 154–155°.

**Pharmacological.**—We are indebted to Dr. Edwin J. Fellows of the Pharmacology Department of Temple University for the pharmacological results reported in Table I: the detailed results will be published elsewhere. Compounds (5), (6), and (9), were superior. Of these (9) appeared outstanding in that it exhibited local anesthetic activity in concentrations as low as 0.001%.

## Summary

The properties of five 1-chloroisoquinolines, including one not previously reported, are given.

Eight new 1-(β-dialkylaminoethoxy)-3-alkylisoquinolines and one secondary amine of the same type are described, and their local anesthetic activity is reported. The most effective agent in this series is the 3-butyl-1-(β-dimethylaminoethoxy)-isoquinoline.

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[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# The Partial Methylation of Methyl β-D-Xylopyranoside with Methyl Sulfate

BY O. WINTERSTEINER AND ANNA KLINGSBERG

In connection with our study of O-tetramethylstreptamine[1] methyl trimethyl-β-D-xylopyranoside was needed. Instead of preparing this compound from β-methyl-D-xylopyranoside by the usual multiple treatment with methyl iodide and silver oxide,[2] we explored the use of the method of Holden and West[3] with dimethyl sulfate and sodium hydroxide which in other instances studied in our laboratory had given excellent yields of fully methylated sugars. However, the chloroform-extractable material obtained in a trial run amounted to only 20% of the starting product and consisted for the most part of a crystalline methyl dimethylxyloside m. p. 78°. The fully methylated product had evidently been lost by volatilization during the later stages (70–100°) of the reaction. By conducting the methylation under somewhat milder conditions in a closed vessel fitted with a reflux condenser there was obtained in good yield a mixture of methylated products the crystallizable part of which consisted again of the methyl dimethylxyloside m. p. 78°. The remainder could be conveniently and quantitatively separated into methyl 2,3,4-trimethyl-β-D-xyloside and dimethylated methyl xylosides by steam distillation.

The compound m. p. 78° was identified as methyl 2,4-dimethyl-β-D-xylopyranoside by the following reactions: On tosylation it yielded a monotosylate m. p. 76°, and on acid hydrolysis a crystalline dimethylxylose m. p. 118° which showed $[\alpha]_D$ −26° in chloroform and in water mutarotated to an equilibrium value of +24°, which is in the neighborhood of those reported for the sirupy 2,3- and 3,4-dimethyl-D-xyloses,[4,5] and the crystalline 2,4-dimethyl-β-D-xylopyranose[6] to be mentioned later. The phenylosazone (m. p. 158°) obtained from the dimethyl sugar contained only one methoxyl group, proving that the methyl group eliminated in its formation occupied position 2. The sugar was further characterized by the preparation of an anilide m. p. 157°, $[\alpha]_D$ −40° in ethyl acetate, which in ethyl acetate containing acetic acid attained an equilibrium rotation value of +85°. The sirupy dimethylxylonic lactone formed by bromine oxidation showed the characteristic fast mutarotation of a pyranolactone, and moreover on Purdie methylation yielded 2,3,-4-trimethylxylonic lactone. The dimethyl lactone was converted into two crystalline derivatives of the corresponding xylonic acid, namely, an amide m. p. 100° and a phenylhydrazide m. p. 144°. The amide was only very gradually attacked by periodic acid under conditions under which 2-tosyl-5-desoxyarabonamide[7] was readily cleaved. The phenylhydrazide consumed in rapid reaction 2 moles of periodic acid, but since a simple hydrazide, N-acetylphenylhydrazine, behaved in the same manner, it is clear that the xylose portion had remained unaffected. These findings, and the additional fact that the dimethylxylose itself proved to be inert toward periodate, show conclusively that the second methyl group in this compound occupies position 4.

It should be mentioned that a result seemingly inconsistent with the above conclusion was obtained in the periodate titration of the monomethylxylosazone derived from the dimethyl sugar. Since it is known that the phenylosazone grouping in glucosazone protects the linkage between carbon atoms 2 and 3 from cleavage by periodic acid,[7a] 4-methylxylosazone should not be attacked at all by this oxidant. Actually, a rapid uptake of periodate, which came to a standstill at between 1 and 2 molar equivalents, was observed. However, as it could be demonstrated that no formaldehyde is produced in this reaction, the 4-methyl structure is secure, and the observed uptake must be ascribed to an anomalous type of oxidation.

The methyl dimethylxyloside fraction remaining after steam distillation usually yielded additional small amounts of methyl 2,4-dimethyl-β-D-xyloside, and, on occasion, lower-melting crystalline products which were obviously mixtures containing the position-isomeric compounds. In one run the non-crystallizable part of the steam distillation residue was converted to a mixture of dimethylated xylonolactones. From the mutarotation characteristics of one of the lactone fractions it appeared that considerable amounts of the highly dextro rotatory 2,3-dimethyl-D-xylono-γ-lactone[4] were present. This was borne out by the fact that the sirupy amides prepared from the lactone mixtures rapidly consumed periodic acid equivalent to the presence of about 20% of the 2,3-dimethyl isomer.

In 1934 Robertson and Speedie[5] described a methyl dimethylxyloside (m. p. 61°, $[\alpha]_D$ −82°), to which they likewise attributed the methyl 2,4-dimethyl-β-D-xylopyranoside structure. They prepared this compound by a sequence of reactions involving first monotritylation of methyl β-

(1) O. Wintersteiner and A. Klingsberg, THIS JOURNAL, **70**, 885 (1948).

(2) A. Carruthers and E. L. Hirst, *J. Chem. Soc.*, **121**, 2299 (1922); F. P. Phelps and C. B. Purves, THIS JOURNAL, **51**, 2443 (1929).

(3) R. F. Holden and E. S. West, *ibid.*, **56**, 930 (1934).

(4) H. A. Hampton, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 1739 (1929).

(5) G. J. Robertson and T. H. Speedie, *ibid.*, 824 (1934).

(6) C. C. Barker, E. L. Hirst and J. K. N. Jones, *ibid.*, 783 (1946).

(7) J. Fried and D. Walz, unpublished results from this Laboratory.

(7a) E. Chargaff and B. Magasanik, THIS JOURNAL, **69**, 1459 (1947).

D-xylopyranoside, acetylation of the other two hydroxyl groups, replacement of the trityl by a nitrate group, deacetylation first with sodium methylate and then dimethylaniline, methylation according to Purdie, and finally reductive removal of the nitrate group with sodium amalgam. None of the intermediates except the diacetyl nitrate derivative were crystalline. The 2,4-position of the methylated hydroxyl groups in the final product was inferred from the fact that the monotosylate (m. p. 88°, $[\alpha]_D$ −58.9° in chloroform) was not identical with either the monotosylate of the crystalline β-methyl-3,4-dimethylxylopyranoside described by the same authors, or with that of the sirupy methyl 2,3-dimethylxylopyranoside of Hampton, Haworth and Hirst.[4] Though it would appear from the rotation characteristics that the compound m. p. 61° belongs to the β-xylopyranoside series, a more direct proof for the location of the methylated hydroxyl groups would be desirable. Since neither the free sugar nor the lactone were prepared, any basis for correlating this product with compounds of known structure is lacking, so that the marked discrepancies between the melting points and rotations reported by Robertson and Speedie and those found by us cannot be explained at present. The possibility that our compound m. p. 78° is a mixture of dimethylated methyl xylopyranosides seems to be excluded by the fact that the lactone obtained from it directly by hydrolysis and oxidation, that is without isolation of the intermediate dimethylxylose, gave no evidence of being contaminated by either 2,3-dimethylxylono-γ-lactone[4] or 3,4-dimethylxylonolactone,[8] both of which exhibit quite different mutarotation characteristics.

On the other hand, there is little doubt that our dimethylxylose m. p. 118° is essentially identical with the 2,4-dimethylxylose m. p. 108° (equilibrium rotation in water +22°) which Barker, Hirst and Jones[6] obtained by methylation of methyl α,β-D-xylopyranoside with methyl iodide and thallous hydroxide. The structure of this product was deduced from the non-identity with the position-isomeric dimethylxyloses, the mutarotation of the lactone, and the negative Weerman test of the (sirupy) amide. The only other derivative reported by Barker, *et al.*, is the anilide, which showed a somewhat higher melting point (170°) and levorotation (−80°, in dioxane) than the anilide prepared by us. These differences are probably to be ascribed to the presence of a greater proportion of the α-anomer in our product, and the lower melting point of their dimethylxylose preparation can be similarly explained. On the other hand, the mutarotation data obtained on the respective lactones are in excellent agreement.

The findings of the British authors parallel ours also in that the 2,4-dimethyl isomer preponderated in the dimethylxyloside fraction. To explain the preferential formation of this isomer they reason that "the hydrogen atoms on the hydroxyl groups at $C_2$ and $C_4$ are most likely to be substituted since they are the greatest distance apart, and the thallium atoms in these positions are therefore least likely to interfere with each other." However, this concept is applicable only when, as in the procedure with thallous hydroxide, the metal salt of the starting glycoside is isolated prior to this reaction with the anhydrous methylating agent. In our case, where the reaction proceeded in aqueous sodium hydroxide solution and the hydroxyl groups of the glycoside were presumably in the charged anionic form, it is difficult to see how steric factors could have played any role in preventing salt formation at the third hydroxyl group in position 3. This group, since it is situated *trans* to the neighboring, more reactive, hydroxyl groups, does not appear to be subject to steric hindrance of any kind in the model. It would be interesting to ascertain by a similar study on methyl arabinoside whether the *cis* relationship of two hydroxyl groups in the pyranoside ring *per se* predisposes them to preferential attack by methylating agents.

(8) S. P. James and F. Smith, *J. Chem. Soc.* 739 (1945).

## Experimental

**Methylation of Methyl β-D-Xyloside.**—A solution of methyl β-D-xyloside (m.p. 155°, $[\alpha]^{26}_D$ −64.7° in water, 13.6 g.) in water (10 cc.) was placed into a 500-cc. 3-neck reaction flask equipped with a mercury-sealed stirrer, reflux condenser, thermometer and two dropping funnels. After the addition of methyl sulfate (36.8 cc.) and carbon tetrachloride (50 cc.) the mixture was warmed to 55°. During the following dropwise addition, with stirring, of 60% sodium hydroxide solution (163 cc.) this temperature was maintained by outside cooling and regulation of the dropping rate. After about half of this volume had been added, cooling could be dispensed with, and the remainder of the solution was added at a rate of 3 drops per second. (Toward the end slight warming may be necessary to maintain the temperature at 55°.) Methyl sulfate (65 cc.) was then added dropwise in such a manner that the temperature remained around 55° during this period also (cooling). After all of the reagent had been added stirring was continued for thirty minutes at 55°. The mixture was allowed to come to room temperature, and after addition of sufficient water (*ca.* 90 cc.) to dissolve the sodium sulfate, was extracted with 900 cc. of chloroform in ten portions. The combined extracts were dried and concentrated *in vacuo* to a small volume (*ca.* 15 cc.). Ligroin (b.p. 90–100°) was added in small portions to faint turbidity (50 cc.). The crystalline product obtained on standing in the refrigerator (2.64 g.) yielded on recrystallization from warm ligroin substantially pure **methyl 2,4-dimethyl-β-D-xyloside**, m.p. 76–78°[9]; yield 2.31 g. or 14.5%. One more recrystallization raised the melting point to 77.5–78.5° (constant); $[\alpha]^{24}_D$ −70 ± 1° (*c*, 1.0 in chloroform).

*Anal.* Calcd. for $C_8H_{16}O_5$: C, 49.99; H, 8.39; $OCH_3$, 48.4. Found: C, 50.20; H, 8.60; $OCH_3$, 48.4.

The combined mother liquors were taken to dryness. The residue (*ca.* 12 g.) was dissolved in water (150 cc.) and subjected to steam distillation.[10] Exhaustive extraction of the steam distillate (320 cc.) with chloroform yielded a partly crystalline product (7.9 g.) which on recrystallization from ligroin melted at 47–49°. Further recrystallization yielded **methyl 2,3,4-trimethyl-β-D-xylo-**

(9) All melting points were taken in the capillary and are corrected for stem exposure.

(10) Fractional distillation *in vacuo* was not practicable because the products crystallized in the efferent parts of the distillation vessel.

pyranoside[2] m.p. 49–50°, $[\alpha]^{24}D$ −73° (*c*, 0.765 in chloroform).

*Anal.* Calcd. for $C_9H_{18}O_5$: C, 52.41; H, 8.79; $OCH_3$, 60.2. Found: C, 52.57; H, 8.93; $OCH_3$, 59.9.

The glycoside was converted to **2,3,4-trimethyl-D-xylose**[2], m.p. 88–91°, $[\alpha]^{27}D$ + 62.5° (*c*, 1.0 in chloroform), and further to 2,3,4-trimethylxylonolactone[11] m.p. 52–53°.

The products not volatile with steam (3.1 g.) were recovered by extraction with chloroform. The oily residue on seeding gave an additional small amount (520 mg.) of impure methyl 2,4-dimethylxyloside (m.p. 67–71°). The remainder was distilled *in vacuo* (100–110° (0.5 mm.)), and yielded 2.33 g. of a sirup consisting of mixed methyl dimethylxylosides ($[\alpha]^{26}D$ − 69°; $OCH_3$, found, 48.0; calcd., 48.4) which was hydrolyzed and oxidized to the mixture of lactones described further below.

In another methylation experiment carried out as described above, in which the yield of methyl 2,4-dimethylxyloside was 17.4%, the non-steam distillable fraction of the mother liquor material afforded a crystalline mixture of methyl dimethylxylosides (m.p. 55–58°, $[\alpha]D$ −65°; $OCH_3$, 49.2) accounting for an additional 22% of the starting material. Hydrolysis of this material gave a crystalline product, from which, however, only a small amount of impure 2,4-dimethylxylose (m.p. 108°) could be eventually obtained.

An attempt to increase the yield of pure 2,4-dimethyl isomer by conducting the methylation at 35–40° failed, as all the crystalline products isolated from the dimethylated fractions consisted of inseparable mixtures.

**Methyl 2,4-Dimethyl-3-tosyl-β-D-xyloside.**—To an ice-cold solution of methyl 2,4-dimethyl-β-D-xyloside (192 mg.) in pyridine (2.5 cc.) tosyl chloride (380 mg.) dissolved in chloroform (1 cc.) was slowly added. After standing at room temperature for forty-eight hours the product was recovered by chloroform extraction in the usual way. Crystallization of the oily residue (306 mg.) from ethyl acetate–hexane yielded plates (200 mg., m.p. 74–75°). The pure substance melted at 75–76°; $[\alpha]^{28}D$ + 28.8° (*c*, 1.06 in chloroform).

*Anal.* Calcd. for $C_{15}H_{22}O_7S$: C, 52.02; H, 6.40; S, 9.25. Found: C, 52.04; H, 6.59; S, 9.48.

**2,4-Dimethyl-D-xylose.**—A solution of methyl 2,4-dimethyl-β-D-xyloside (0.50 g.) in 0.6 *N* hydrochloric acid (13 cc.) was heated on the steam-bath till $[\alpha]^{26}D$ became constant at +23° (six hours). After removal of the chlorine ions with silver carbonate and of excess silver with hydrogen sulfide the solution was lyophilized. The partly crystalline residue (335 mg.), was recrystallized to constant melting point from ethyl acetate. 2,4-Dimethylxylose forms long fine needles melting at 116–118°; $[\alpha]^{25}D$ −26° (*c*, 0.95 in chloroform). A 3.0% solution in water showed $[\alpha]^{25}D$ +9.4° after five minutes and +24.7° after fifty minutes (constant).

*Anal.* Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92; $OCH_3$, 34.8. Found: C, 47.04; H, 7.82; $OCH_3$, 35.7.

An aqueous solution of the compound did not consume any periodate within a four-hour period. (Potassium paraperiodate was used in this and all other titrations.)

**The anilide** was prepared by refluxing a solution of the sugar (89 mg.) with aniline (623 mg.) in absolute ethanol (3 cc.) for two and one-half hours. The residue obtained after removal of the solvents was crystallized from ethyl acetate (0.7 cc.) and a few drops of pentane (23 mg., m. p. 144–145°). Two recrystallizations raised the melting point to 155–157°; $[\alpha]^{27}D$ −40° (*c*, 0.695 in ethyl acetate).

*Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.77; H, 7.61; N, 5.28.

A 0.74% solution in ethyl acetate containing 4% acetic acid showed rapid mutarotation from $[\alpha]^{27}D$ −7° (five minutes) to the equilibrium value +87° (two hours). The corresponding figures for another, independently prepared sample (m. p. 148–151°), $[\alpha]^{26}D$ −40° in ethyl acetate) were −56 and +85°, respectively.

**4-Methyl-D-xylosazone.**—2,4-Dimethyl-D-xylose (180 mg.) was dissolved in water (5 cc.), and acetic acid (0.25 cc.) and phenylhydrazine (0.5 cc.) were added. The solution was heated on a steam-bath for one and one-half hours while a slow stream of carbon dioxide was passed through it, and the water lost by evaporation was replaced from time to time. After cooling, the solution was extracted with benzene. The red oil obtained on evaporation of the dried benzene extract (454 mg.) could not be crystallized. It was dissolved in benzene and chromatographed on a column of acetic acid–washed alumina (1 × 20 cm.). After elution of pigmented amorphous material with benzene (300 cc.) and of some colorless crystalline material, probably acetylphenylhydrazine, with benzene–ether 3:1 (350 cc.), the crude osazone (153 mg.) was recovered by washing with benzene containing 3% of ethanol (250 cc.). Several recrystallizations from ethyl acetate–hexane 2:1 yielded small yellow needles melting at 158–158.5°; $[\alpha]^{25}D$ +25° → 0° (constant) in twenty-one hours (*c*, 0.91 in pyridine–ethanol 2:3).

*Anal.* Calcd. for $C_{18}H_{22}O_3N_4$: C, 63.14; H, 6.47; N, 16.4; $OCH_3$, 9.06. Found: C, 63.32; H, 6.56; N, 16.6; $OCH_3$, 10.24, 9.94.

For measuring the periodate consumption, weighed samples (*ca.* 4 mg.) of the osazone were dissolved in ethanol (5 cc.), and 0.0128 *M* aqueous potassium paraperiodate (5 cc.) was added. Aliquots (2 cc.) were withdrawn at intervals for the determination of the residual oxidizing capacity with 0.01 *N* thiosulfate. The total oxidizing capacity of the reagent in 50% ethanol was determined at the same intervals to eliminate possible errors due to the presence of the alcohol. The figures obtained in two different runs were not consistent. Molar equivalents consumed: (1) 0.67 (four min.); 0.86 (twenty-five min.); 1.05 (one and one-half hours, constant to nineteen hours); (2) 1.52 (four min.); 1.69 (forty-five min., constant to nineteen hours).

In order to ascertain whether or not formaldehyde was produced in the reaction the osazone (60 mg.) was treated with paraperiodic acid and the volatile products were tested with dimedon as described by Karrer and Pfaehler.[12] A reaction occurred, as evidenced by the formation of a yellow precipitate, but no formal-dimedon was obtained. Glucosazone (60 mg.) subjected to the same procedure gave 48% of formal-dimedone, m. p. 186–187°.

**2,4-Dimethyl-xylonolactone.**—The procedure of Haworth and Westgarth[11] for the oxidation of 2,3,4-trimethylxylose was employed, as 2,4-dimethylxylose proved to be rather resistant to bromine oxidation at room temperature. Methyl 2,4-dimethyl-β-D-xyloside (2.31 g.) was hydrolyzed with 3% hydrobromic acid (24 cc.) at 85° for one hour. Heating was continued for a total of ten hours at 75° while bromine (3.0 cc.) was added in small portions. The Fehling reaction at this point was only slightly positive. The reaction mixture was worked up in the usual manner by removal of the excess bromine by aeration and of the bromide ions with silver carbonate. The residue of the filtered solution was repeatedly extracted with dry ether. The extracted material (1.82 g.) was heated for two hours on the steam-bath to complete lactone formation, and then distilled at 105–125° (0.1 mm.), yielding 1.23 g. of a sirup ($n^{27}D$ 1.4652; $OCH_3$: Found, 35.1; calcd., 35.2). Mutarotation in water (*c*, 1.02): −13.2° (seven min.), −9.3° (fifty min.), −5.8° (three hours), +26.8° (twenty-four hours), +29.5° (forty-eight hours, constant), in good agreement with the data of Barker, Hirst and Jones[6] (−15° → +30°).

A portion (150 mg.) of the lactone was methylated with methyl iodide (10 cc.) and silver oxide (0.98 g.) in the usual way. Removal of the reagent and extraction of the residue with chloroform yielded a sirup (162 mg.) from which on crystallization from benzene–pentane 2,3,4-

(11) W. N. Haworth and G. C. Westgarth, *J. Chem. Soc.*, 880 (1926).

(12) P. Karrer and K. Pfaehler, *Helv. Chim. Acta*, **17**, 766 (1934).

trimethylxylonolactone (99 mg., m. p. 50–52°) was obtained. The purified product melted at 52–54° and did not depress the melting point of an authentic specimen.

**2,4-Dimethyl-D-xylonamide.**—The amide was prepared from the lactone (331 mg.) with methanol (5.0 cc.) saturated at 0° with ammonia. After standing for three days at room temperature the mixture was taken to dryness. Since the sirupy product could not be induced to crystallize, it was dissolved in water and treated with charcoal. The filtered solution was lyophilized, and the residue (309 mg.) extracted with warm ethyl acetate (10 cc.). The extract on cooling to room temperature deposited crystals (160 mg., m. p. 95–97°) which were purified by recrystallization from the same solvent; rods, m. p. 98–100°, $[\alpha]^{26}D$ + 51° (*c*, 1.00 in water).

*Anal.* Calcd. for $C_7H_{15}O_5N$: C, 43.51; H, 7.82; N, 7.25; $OCH_3$, 32.1. Found: C, 43.41; H, 7.56; N, 6.95; $OCH_3$, 32.2.

The amide consumed no periodate over a two-hour period, but after this time was attacked at a slow rate (0.14 and 0.33 molar equivalents after five and one-half and twenty-four hours, respectively).

**2,4-Dimethyl-D-xylonic Acid Phenylhydrazide.**—A mixture of the lactone (320 mg.) and phenylhydrazine (197 mg.) was heated on the steam-bath for one hour. Since the orange-colored, viscous product failed to crystallize, it was dissolved in ethylene chloride (5 cc.) and chromatographed on a small column of alumina (1 × 15 cm.). While washing with ethylene chloride (200 cc.) removed only pigmented impurities, the subsequent eluates with the same solvent containing 3% ethanol (150 cc.) and 10% ethanol (100 cc.) yielded the phenylhydrazide, which crystallized on addition of ethyl acetate. The combined crystalline material (363 mg., m. p. 142–144°) was recrystallized twice from the same solvent, blocks, m. p. 143.5–144.5°, $[\alpha]^{26}D$ + 47° (*c*, 0.98 in ethanol).

*Anal.* Calcd. for $C_{13}H_{20}O_5N_2$: C, 54.92; H, 7.09; N, 9.85; $OCH_3$, 21.8. Found: C, 54.73; H, 6.79; N, 10.14; $OCH_3$, 21.7.

The consumption of periodate was as follows (in molar equivalents): five min., 1.44; fifteen min., 1.80; four and one-half hours, 1.85; twenty-two hours, 1.99. Acetylphenylhydrazine behaved in a similar manner: five min., 1.62; twenty min., 1.78; three hours, 1.85; twenty hours, 2.17.

**Lactone and Amide Fractions from Methyl Dimethylxyloside Mixture.**—A portion (2.0 g.) of the mixture of methyl dimethylxylosides remaining after steam distillation (see above) was hydrolyzed and oxidized with bromine as described for the pure 2,4-dimethyl isomer, except that it was found necessary to employ larger amounts of bromine (6.5 cc.) and a longer heating period (twenty-six hours). The material finally recovered by ether extraction (1.3 g.) was heated at 75–80° at 12 mm. for one hour and then distilled fractionally *in vacuo*. Two main fractions were collected: I, 533 mg., b. p. 105–110° (0.05 mm.) and II, 469 mg., b. p. 125–130° (0.05 mm.). The mutarotation data were as follows: Fraction I (*c*, 1.14 in water): ten min., −5.3°; one hour, −4.2°; seven hours, −2.0°; twenty-four hours, +8.9°; thirty-four hours, +15.5°; fifty-four hours, +13.7. Fraction II (*c*, 0.99 in water): one hour, + 10.6°; four hours, +15.6; twenty-five hours, +34°; ninety-eight hours, +41° (constant).

The sirupy amides were prepared from both fractions in the usual fashion. Amide mixture II, but not I, gave on seeding with 2,4-dimethylxylonamide a small amount of crystalline material, which after purification melted at 93–95°. Both amide mixtures consumed periodate at a rapid rate:

| Time | | 5 min. | 3 hours | 20 hours |
|---|---|---|---|---|
| Molar equivalents of | I | 0.11 | 0.18 | 0.19 |
| periodate consumed | II | .23 | .22 | .27 |

Since 2,3-dimethylxylonamide is the only isomer which should be attacked by periodate, the above figures may be taken as indicating the presence of about 20% of the corresponding methyl xyloside in the original mixture. This is also borne out by the high positive equilibrium rotation value of lactone fraction II, since 2,3-dimethyl-D-xylono-γ-lactone[4] is strongly dextrorotatory and mutarotates very slowly (+97° → + 86° (forty-eight hours) → +69° (384 hours)). Apparently Fraction II consisted mainly of a mixture of the 2,3- and 2,4-isomers (isolation of the amide of the latter), while the mutarotation data of Fraction I and the failure of the corresponding amide mixture to yield 2,4-dimethyl-xylonamide are consistent with the properties to be expected of a mixture containing mainly the 2,3- and 3,4-dimethyl isomers (3,4-dimethyl-D-xylonolactone[5] mutarotates from −56° to −27° in sixty-five hours).

**Acknowledgment.**—The microanalyses were performed by Mr. J. F. Alicino and his assistants.

## Summary

Methyl-β-D-xyloside on methylation with methyl sulfate yields besides methyl 2,3,4-trimethyl-β-D-xyloside a mixture of methyl dimethylxylosides, which can be conveniently separated from the trimethyl derivative by virtue of the fact that only the latter is volatile with steam. Methyl 2,4-dimethyl-β-D-xyloside m. p. 78°, which can be obtained in 15–20% yield directly from the reaction mixture, preponderates among the dimethylated compounds. It was identified by conversion, *via* the free sugar, to a monomethyl-D-xylosazone, and by the behavior toward periodate of the crystalline amide and phenylhydrazide of the corresponding xylonic acid. Indirect evidence for the occurrence also of the 2,3-dimethyl isomer in the dimethylated fraction is presented.

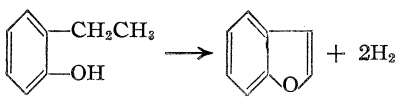
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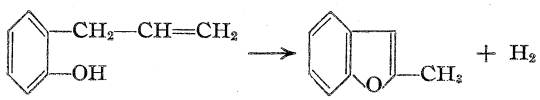
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE]

# Catalytic Synthesis of Heterocycles.[1] III. Benzofuran

BY CORWIN HANSCH, WILLIAM SALTONSTALL[2] AND JAMES SETTLE[3]

The successful synthesis of thianaphthene from *o*-ethylbenzenethiol[1] suggested the possibility of accomplishing the same type of ring closure with the oxygen analog. This paper discusses the vapor phase catalytic dehydrocyclization of *o*-ethylphenol and *o*-allylphenol to benzofuran and 2-methylbenzofuran according to the equations




## Experimental

The apparatus and the technique used for the catalytic reactions have been described previously.[1]

**Catalyst Preparations.**—The method of preparation for the platinum catalyst has been described.[1] For the preparation of palladium on charcoal,[4] 10 g. of palladium chloride was dissolved in 40 ml. of hot concd. hydrochloric acid. This solution was diluted to 187 ml. with distilled water and 30 g. of activated charcoal added. The mixture was heated to boiling and the charcoal separated by decantation. The catalyst was dried at 115° for two hours. Before using, it was reduced *in situ* with a slow stream of

TABLE I

CONVERSION OF *o*-ALLYLPHENOL TO 2-METHYLBENZOFURAN DISTILLATION

| Allyl-phenol, g. | Cat. | Temp.[f] °C. | S. V.[g] | Alkali insoluble fraction: Methylbenzofuran,[a] b. p. 190–196°, g. | Alkali insoluble fraction: (730 mm.),[d] % | Alkali insoluble fraction: Benzofuran,[b] b. p. 170–190°, g. | Alkali soluble fraction: Phenol and Cresol,[c] b. p. 175–200°, g. | Alkali soluble fraction: Allylphenol, b. p. 200–216°, g. |
|---|---|---|---|---|---|---|---|---|
| 53.5 | Pd | 525 | 815 | 7.9 | 15.0[e] | 2.7 | 2.9 | 18.1 |
| 49.5 | Pd | 550 | 544 | 14.9 | 31.0 | 5.5 | 3.8 | 9.8 |
| 50.2 | Pd | 550 | 773 | 14.6 | 29.5 | 3.2 | 3.7 | 9.4 |
| 40.0 | Pd | 550 | 1568 | 10.5 | 26.5 | 2.8 | Trace | 9.3 |
| 39.8 | Pd | 575 | 1470 | 11.0 | 28.0 | 2.2 | 3.5 | 9.9 |
| 48.9 | Pd | 600 | 1208 | 13.0 | 27.0 | 4.6 | 4.3 | 6.9 |
| 40.2 | Pd | 625 | 1407 | 10.5 | 26.5 | 7.4 | 7.5 | 0.0 |
| 51.1 | Pt | 550 | 788 | 14.4 | 28.6 | 6.9 | 4.7 | 11.0 |

[a] Redistillation of 120 g. of this material from several runs through a 20-plate column gave 98 g. of material, b. p. 195–196° (730 mm. cor.), $n^{24}D$ 1.5539. Adams and Rindfusz, THIS JOURNAL, **41**, 655 (1919), report b. p. (744 mm.) 196–197° and $n^{22}D$ 1.555. The material from this batch distillation and from the individual runs formed a picrate m. p. 72–74°. Stoermer and Barthelmer, *Ber.*, **48**, 67 (1915), report m. p. 72–74°. [b] This fraction consisted of mostly benzofuran with some 2-methylbenzofuran. These fractions were refractionated and the benzofuran identified by physical constants and by preparation of picrate. [c] These fractions also lumped together and refractionated and the phenol and *o*-cresol identified by means of the urethan derivatives. [d] The barometer varied on these experiments by ±2 mm.; however, this difference was ignored and the cuts taken at the temperatures listed above. [e] Calculated as per cent. conversion of allylphenol to methylbenzofuran. [f] The temperature of the catalyst varied from this average temperature by ±3 or 4°. [g] The space velocity was calculated as ml. of vapor at s. t. p. per ml. of catalyst per hour.

TABLE II

CONVERSION OF *o*-ETHYLPHENOL TO BENZOFURAN DISTILLATION

| Ethyl-phenol, g. | Cat. | Temp., °C.[g] | S. V.[g] | Alkali insoluble fraction: Crude benzofuran,[a] b. p. 140–169°, g. | Alkali insoluble fraction: (730 mm.),[d] % | Alkali insoluble fraction: Benzofuran,[b] b. p. 170–172° cor., g. | Alkali insoluble fraction: % | Alkali soluble fraction: Phenol,[c] b. p. 178–200°, g. | Alkali soluble fraction: Ethylphenol, b. p. 202–204°, g. |
|---|---|---|---|---|---|---|---|---|---|
| 28.2 | Pd | 600 | 1702 | 1.4 | 5.2[f] | 1.1 | 4.1[f] | 6.5 | 7.8 |
| 30.6 | Pd | 625 | 1768 | 1.3 | 4.4 | 1.7 | 5.8 | 9.6 | 5.8 |
| 26.8 | Pd | 625 | 622 | 3.6 | 13.9 | 2.2 | 8.5 | 9.8 | 0.0 |
| 54.8 | Pd | 625 | 927 | 1.1 | 2.1 | 4.6 | 8.7 | 15.6 | 11.4 |
| 51.4 | Pd[e] | 620 | 652 | 2.1 | 4.2 | 5.6 | 11.3 | 15.2 | 10.2 |

[a] This fraction consisted of benzofuran with some unidentified product. [b] The yield of pure benzofuran was somewhat higher than this would indicate because of about 1 to 2 g. holdback of material in the distilling column which contained considerable benzofuran. These fractions when mixed together had $n^{24}D$ 1.5631 and formed a picrate m. p. 102–103°. v. Auwers, *Ann.*, **408**, 271 (1915), reports $n^{22.7}D$ 1.565. Kramer and Spilker, *Ber.*, **23**, 79 (1890), report b. p. (758 mm.) 170–171° and *ibid.*, 3276, m. p. picrate 102–103°. [c] This fraction consisted of phenol along with some *o*-ethylphenol and probably some *o*-hydroxystyrene. [d] See Table I. [e] Fifteen ml. of catalyst used instead of usual 5 ml. [f] See Table I, *e*. [g] See Table I, *f* and *g*.

(1) For the preceding papers in this series, see Hansch and Blondon, THIS JOURNAL, **70**, 1561 (1948), and Hansch and Hawthorne, *ibid.*, **70**, 2495 (1948).

(2) Present address, Department of Chemistry, University of Notre Dame.

(3) Present address, Department of Chemistry, Northwestern University.

(4) The activated charcoal used in this work was Type B15P, 6–8 mesh, supplied through the courtesy of the Pittsburgh Coke and Chemical Company.

hydrogen saturated with formaldehyde by passing the hydrogen through aqueous 40% formalin. The reduction was carried out for forty-five minutes at 270° and then for forty-five minutes at temperatures slightly above those at which the dehydrogenation run was to be conducted.

**Catalytic Synthesis of 2-Methylbenzofuran.**—The following is an example of a typical dehydrogenation run for the preparation of 2-methylbenzofuran.

*o*-Allylphenol[5] (50.2 g.) was processed over 5 ml. of palladium catalyst at a temperature of 550 ± 4° over a period of one hundred thirty minutes. A total of 47.6 g. of condensate was collected and the catalyst tube gained 1.2 g. weight. About 0.3 g. of material remained in the seed system. A total of 3330 ml. of gas was given off during the course of the reaction as measured by a wet test meter. The rate of gas evolution was 40 ml./min. at the end of the first fifteen minutes at which time the catalyst reached a relatively steady activity. This rate gradually fell until it reached a constant value of 16 ml./min. at seventy minutes. This rate then held until the end of the reaction. On longer runs of four hours or more the rate sometimes fell as low as 12 ml./min.

The condensate was made alkaline with 20% sodium hydroxide and the 2-methylbenzofuran extracted with petroleum ether. After drying over sodium sulfate the extract was distilled through a 20-plate, 30″, "spinning band" distilling column. Distillation gave 14.6 g. of 2-methylbenzofuran, b. p. 190–196° (730 mm.), 3.3 g., 170–190° (730 mm.) which was mainly benzofuran, a residue and hold back of 1.7 g. remaining in the distilling flask.

The alkali-soluble portion of the condensate was acidified with hydrochloric acid, extracted with ether, the extract dried over calcium chloride and then distilled. Nine and four-tenths grams of material, mainly *o*-allylphenol, was collected between 200–216° (730 mm.). Three and seven-tenths grams was obtained, boiling at 175–200°, and consisting of a mixture of phenol, *o*-cresol and a trace of *o*-allylphenol.

Tables I and II summarize the results of the run with *o*-allylphenol and *o*-ethylphenol.[6] All of the runs were made and worked up as described above except where indicated.

(5) D. S. Tarbell, "Organic Reactions," John Wiley and Sons Inc., New York, N. Y., 1944, Vol. II, p. 26.

(6) The *o*-ethylphenol was supplied through the courtesy of Dale Robertson of this Laboratory. It was prepared by vapor-phase alkylation of phenol and had a b. p. of 203.1–205.1° (730 mm. cor.) after two distillations through a 20-plate distilling column.

## Discussion

In all of the catalytic runs made in this research using both *o*-ethylphenol and *o*-allylphenol, very little charring occurred on the catalyst or on the quartz chips used as preheater. The catalyst gained 0.6 g. to 1.2 g. depending on the size of the run and the temperature. The condensate was clear and light brown in color.

It should be noted that the catalyst activity as measured by the rate of gas evolution fell off after about the first hour to about 50% of the fifteen minute value. An attempt to use a chromium oxide on alumina catalyst was unsuccessful because of excessive decomposition of the phenols. At present work is in progress to find a more stable and more active catalyst. It was discovered that the activated charcoal[4] itself possessed considerable ability to bring about the dehydrocyclization. This may be due to the charcoal itself or possibly to impurities in it.

As noted in Table I, a considerable amount of benzofuran was formed in the preparation of 2-methylbenzofuran. This same phenomenon has been observed in the preliminary investigation of the preparation of other 2-methylbenzofurans and also with the corresponding sulfur analogs.

**Acknowledgment.**—The authors are indebted to the Research Corporation for a Frederick Gardner Cottrell grant-in-aid which supported this research.

## Summary

A vapor phase catalytic method for the dehydrogenation of *o*-ethylphenol to benzofuran and *o*-allylphenol to 2-methylbenzofuran is described.

CLAREMONT, CALIFORNIA RECEIVED AUGUST 4, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE VICK CHEMICAL COMPANY]

# Attempted Synthesis of β-2,6-Dihydroxybenzoyl- and β-2,4,6-Trihydroxybenzoyl-acrylic Acids

BY CHARLES I. JAROWSKI,[1a] WILLIAM J. MORAN[1b] AND BETTY JANE CRAMER[1c]

The most active bacteriostatic agent in a series of β-aroyl acrylic acids was β-2,4,6-triethylbenzoylacrylic acid.[2] The preparation of β-2,6-dihydroxy- (I) and β-2,4,6-trihydroxybenzoyl acrylic acid (II) was attempted to determine the effect of ortho hydroxyl groups. The formula chart shows the method used for I.

Condensation of III with diethyl oxalate in the presence of sodium ethoxide gave IV. The crude product was heated under reflux with a mixture of glacial acetic and concentrated hydrochloric acids to give V. This in turn was esterified and hydrogenated to VII.

It had been previously shown that 2-carbethoxy-γ-chromanone was easily converted to β-(*o*-hydroxybenzoyl)-acrylic acid by treatment with dilute alkali. Hence treatment of VII with alkali gave either I or VIII.

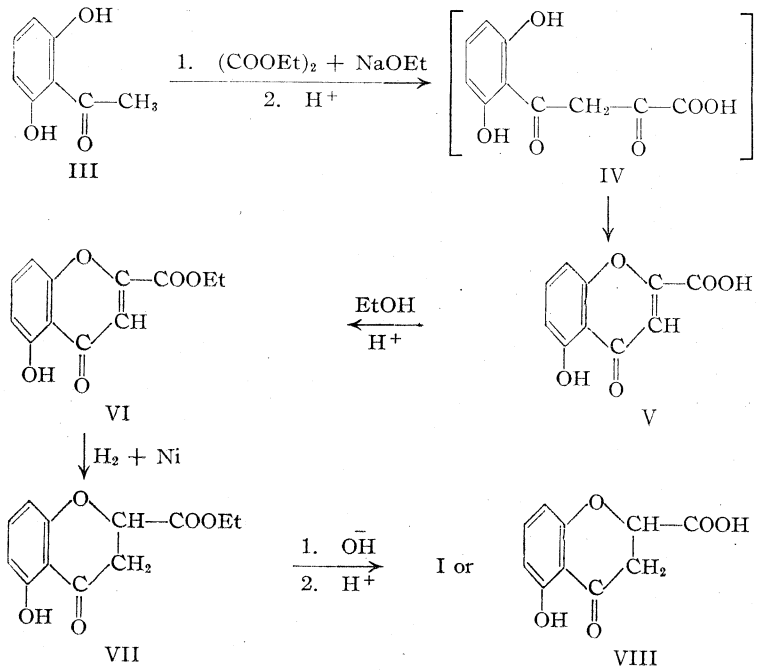
It was expected that the reaction between maleic anhydride and phloroglucinol would result in the formation of II and 2-carboxy-5,7-dihydroxy-γ-chromanone (IX), for a similar reaction using

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(1c) Present address: 151 Leroy St., Binghamton, N. Y.

(2) Cramer, Schroeder, Moran, Nield, Edwards, Jarowski and Puetzer, *J. Am. Pharm. Assoc.*, **37**, 439 (1948).




cinnamoyl chloride led to the formation of a mixture of a chalcone and γ-chromanone derivative.[3] When the reaction mixture was worked up however only one acid was isolated.

The two acids are almost white in color whereas all the other β-aroylacrylic acids prepared were highly colored. They both failed to abolish the nitroprusside reaction of cysteine, a test designed for the detection of α,β-unsaturated ketones.[4] All the β-aroylacrylic acids previously prepared readily added cysteine.[2] The two compounds were ineffective as antibacterial agents. Treatment of the supposed β-2,6-dihydroxybenzoylacrylic acid with excess diazomethane in ether gave the methyl ester exclusively. The failure to methylate the phenolic group was not surprising for more drastic conditions are needed as a general rule to alkylate such a group ortho to a carbonyl.[5] The complete absence of any pyrazoline derivative was an argument against I. According to the work of Lutz and Scott[6] diazomethane reacts with β-aroylacrylic acids to give substituted pyrazolines.

From the above it was felt that the correct structures of the two acids prepared are most likely VIII and IX.

## Experimental[7]

**2-Carboxy-5-hydroxy-γ-chromone (V).**—Alcohol-free sodium ethoxide was prepared by adding 25 cc. of absolute ethanol to 8 g. (0.345 gram atom) of metallic sodium sanded in 350 cc. of dry xylene at 105–115° and distilling off the excess alcohol. The stirred suspension was cooled to 20° and a mixture of 16.1 g. (0.11 mole) ethyl oxalate and 15.2 g. (0.1 mole) of 2,6-dihydroxyacetophenone in 75 cc. of anhydrous ether was added during 15 minutes. The mixture was kept at 20–25° for 0.5 hr., heated under reflux for 1.5 hr., cooled and filtered. The sodium salt was dissolved in cold water and extracted twice with 200 cc. of ether. The aqueous solution was acidified to congo paper with 10% hydrochloric acid and extracted with 500 cc. of ether. The dried ethereal extract (sodium sulfate) was deprived of solvent and the residual red oil was dissolved in 90 cc. of 5 to 1 glacial acetic–concentrated hydrochloric acid and heated under reflux one hour. The reaction mixture was cooled and the insoluble solid (12 g.) was collected. Recrystallization from 75% acetic acid gave 10.3 g. (46%) of bright yellow crystals of V with a melting point of 264°.

*Anal.* Calcd. for $C_{10}H_6O_5$: C, 58.3; H, 2.9; neut. eq., 206. Found: C, 58.15; H, 2.97; neut. eq., 202.

**2-Carbethoxy-5-hydroxy-γ-chromone (VI).**—Concentrated sulfuric acid (5 cc.) was added to a suspension of 7.3 g. (0.035 mole) of V in 50 cc. of absolute ethanol and heated under reflux on a steam-bath. The insoluble chromone acid gradually went into solution. After one hour the reaction mixture was poured into 300 cc. of ice water with stirring. The solid was filtered off and washed free of acid with cold sodium bicarbonate solution. The ester was recrystallized from benzene to give 6.3 g. (76%) of yellow crystals melting at 148°.

*Anal.* Calcd. for $C_{12}H_{10}O_5$: C, 61.6; H, 4.3. Found: C, 61.88; H, 4.42.

**2-Carbethoxy-5-hydroxy-γ-chromanone (VII).**—A mixture of 4.7 g. (0.02 mole) of VI, 100 cc. of absolute ethanol and one-half teaspoonfull of a suspension of freshly prepared nickel catalyst[8] was heated to 80° under hydrogen at 30 lb. pressure. In ten minutes the pressure fell two pounds (theory, 1.6 lb.). The catalyst was filtered off and the filtrate was concentrated to 50 cc. and cooled. The less soluble VI was filtered off and identified by a mixture melting point. The filtrate was further concentrated and cooled. The yellow crystals obtained were recrystallized from absolute ethanol; m. p. 72–74°; 2.1 g. (44%).

*Anal.* Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.23; H, 5.18.

**Alkaline Hydrolysis of VII.**—Two grams (0.0084 mole) of VII was added to 25 cc. of 10% sodium hydroxide and heated to 75° for five minutes. The solution was acidified with 10% sulfuric acid and cooled. The tan product was recrystallized from 95% ethanol; m. p. of gray acid 191°; yield 0.95 g. (54%).

*Anal.* Calcd. for $C_{10}H_8O_5$: C, 57.7; H, 3.87; neut. eq., 208; mol. wt., 208. Found: C, 57.49; H, 4.03; neut. eq., 214; mol. wt., 240 (Rast method).

**2-Carbomethoxy-5-hydroxy-γ-chromanone.**—To an ethereal solution of 1.1 g. (0.0053 mole) of VIII was added a 5-fold (0.0265 mole) molar concentration of diazomethane in ether. The solution was allowed to stand overnight at room temperature. The excess diazomethane and solvent were distilled off and the sirupy residue was washed with sodium bicarbonate solution. The insoluble material was dissolved in ether and dried (sodium sulfate). Removal of the ether left a solid which was recrystallized from methanol; m. p. 78.5°; 0.74 g. (63%). The compound still gave a positive test for the phenolic group with ferric chloride solution.

(3) Shinoda and Sato, *J. Pharm. Soc. Japan*, **48**, 791–801 (1928); *C. A.*, **23**, 836 (1929).

(4) Geiger and Conn, THIS JOURNAL, **67**, 112 (1945).

(5) Houben, "Die Methoden der organischen Chemie," Vol. III, G. Thieme, Leipzig, 153.

(6) Lutz and Scott, *Virginia Acad. Sci. Proc.*, **2**, 195 (1944).

(7) All melting points are uncorrected.

(8) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

*Anal.* Calcd. for $C_{11}H_{10}O_5$: C, 59.41; H, 4.53. Found: C, 59.17; H, 4.36.

**5,7-Dihydroxy-2-carboxy-γ-chromanone (IX).**—A mixture of 5.04 g. (0.022 mole) of phloroglucinol and 3.96 g. (0.04 mole) of maleic anhydride in 45 cc. of nitrobenzene was cooled to 10°. During the course of 15 minutes 17.42 g. (0.13 mole) of anhydrous aluminum chloride was introduced with mechanical stirring. External cooling was needed to keep the temperature at 30°. After 0.5 hr. the exothermic reaction subsided and the mixture was stirred at room temperature for 0.75 hr. The aluminum complex was decomposed in a mixture of ice and concentrated hydrochloric acid. The crude acid (4 g.) was recrystallized from water; m. p. of light colored acid 262.5° (dec.).

*Anal.* Calcd. for $C_{10}H_8O_6$: C, 53.56; H, 3.57; neut. eq., 224. Found: C, 53.14; H, 3.58; neut. eq., 230.

**Acknowledgments.**—The authors would like to express their thanks to Mr. Glenn B. Hess and Miss Celia Durham for their analytical results.

## Summary

An attempt was made to prepare β-(2,6-dihydroxybenzoyl)-acrylic acid and β-(2,4,6-trihydroxybenzoyl)-acrylic acid. The failure of these compounds to add cysteine and their almost white color indicate that cyclization has occurred to give the corresponding 2-carboxy-γ-chromanone.

RECEIVED JULY 2, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY AND PURDUE RESEARCH FOUNDATION]

# The Chemical Behavior of Hexachlorocyclopentadiene. I. Transformation to Octachloro-3a,4,7,7a-Tetrahydro-4,7-methanoindene-1,8-dione[1]

BY J. S. NEWCOMER[2] AND E. T. McBEE

During the course of extensive studies conducted in this Laboratory on the chlorination of organic compounds, it was discovered that the pentanes, with the exception of neopentane, can be readily converted to hexachlorocyclopentadiene. The results of preliminary investigations concerning the chemical behavior of this chlorocarbon are shown diagrammatically in Fig. 1.

In view of the recent publication of Prins,[3] the authors were prompted to report[4] the results of concurrent investigations on this versatile chemical intermediate. Since this report,[4] Krynitsky and Bost[5] have described the preparation of tetrachloro-5,5-diethoxycyclopentadiene by the reaction of hexachlorocyclopentadiene with sodium ethoxide.

Prins[3] reported the conversion of hexachlorocyclopentadiene to (a) nonachloromethylcyclopentene by the addition of chloroform, (b) a compound, $C_{10}Cl_{12}$, by the action of aluminum chloride, (c) 3,4,5-trichloro-3-cyclopentene-1,2-dione and 2,3,4,4,5-pentachloro-2-cyclopentenone by the action of sulfuric acid, and (d) octachlorocyclopentene by the addition of chlorine. Recently, Prill[6] described the use of hexachlorocyclopentadiene in the diene synthesis.

The ketals (II), tetrachloro-5,5-dimethoxy- and -diethoxycyclopentadiene, were prepared by the action of the appropriate sodium alkoxides or alcoholic potassium hydroxide on hexachlorocyclopentadiene (I). The ketals were shown to contain a diene system by effecting condensations with maleic anhydride. The adducts, 1,4,5,6-tetrachloro-7,7-dialkoxybicyclo(2.2.1)5-heptene-2,3-dicarboxylic acids (XIV), were converted to 4,5-dichlorobenzene-1,2,3-tricarboxylic acid (XV) upon treatment with sulfuric acid. The position of the two alkoxy groups on the same carbon atom was also established by hydrolysis of II with sulfuric acid to form tetrachlorocyclopentadienone, which immediately dimerized to form an indefinite hydrate of octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione. Recrystallization of the latter from aqueous acetic acid produced the tetrahydrate (III), which was identified by dehydration to the anhydrous form (IV) and by conversion to hexachloroindone (V) upon treatment with water. The anhydrous form (IV) was shown by the method of mixed melting points to be identical to that prepared as described by Zincke[7] and Meyer by the reduction of a hexachlorocyclopentenone (m. p. 28°) with stannous chloride. Although not reported by Zincke, the initial product isolated from the reaction mixture is an indefinite hydrate of IV. The hydrate is readily differentiated from the anhydrous form by the insolubility of the former in non-polar solvents at room temperature. However, if the hydrate is boiled with such solvents until solution is effected, the product obtained by cooling the solution is the anhydrous form. The reduction of an isomeric hexachlorocyclopentenone (m.p. 92°) with stannous chloride has been reported[5] to form a compound having the molecular formula $C_5H_2Cl_4O$. This material has now been found to be a hydrate of indefinite composition of IV, containing approximately two molecules of water.

Octachlorocyclopentene (VI) was prepared by the addition of chlorine to I at atmospheric pressure and in the presence of a catalytic amount of aluminum chloride. The rapid absorption of

(1) Abstracted from the doctoral thesis of J. S. Newcomer.

(2) Present address: Sharples Chemicals, Inc., Wyandotte, Michigan.

(3) H. J. Prins, *Rec. trav. chim.*, **65**, 455 (1946).

(4) Presented before the Division of Organic Chemistry at the 111th Meeting of the American Chemical Society, April, 1947.

(5) J. A. Krynitsky and R. W. Bost, THIS JOURNAL, **69**, 1918 (1947).

(6) E. A. Prill, *ibid.*, **69**, 62 (1947).

(7) T. Zincke and K. H. Meyer, *Ann.*, **367**, 9 (1909).

chlorine under these conditions provides a convenient method for preparing large quantities of VI in a short period of time.

Hexachlorocyclopentenone (m.p. 28°) used in this investigation was derived by the action of sulfuric acid on VI. The conversion of this ketone to (a) an isomeric hexachlorocyclopentenone (m.p. 92°) by the application of heat and (b) a pentachloropentadienoic acid (m.p. 124–125°) by treatment with alkali showed it to be identical to the ketone obtained from a hexachlorocyclohexenedione[8] through a series of reactions and also by the action of sulfuric acid on octachloropentadiene.[3] Considerable work has been performed[8,9,10] in attempts to determine the position of the ethylenic bond in the two isomeric hexachlorocyclopentenones (VIII) and (IX). van Brederode[11] states that "none of the reactions of the two ketones $C_5Cl_6O$ permits a definite choice between the two isomers." An attempt to identify the ketones by Raman spectra[11] was not decisive. The last attempt of Zincke[7] to establish the identity of the ketones was based upon the reduction of the isomer having a melting point of 28° to form a compound tentatively identified as 2,3,4,4,5-pentachloro-2-cyclopentenone, since it decomposed upon treatment with alkali. A more rigorous determination of the structure of the pentachlorocyclopentenone performed in this Laboratory has substantiated the proposed structure. It was assumed previously[7] that 2,3,4,4,5-pentachloro-2-cyclopentenone could be derived only from the conjugated hexachloroketone, apparently because (a) it was considered improbable that rearrangement might occur under similar treatment of the unconjugated hexachloroketone and (b) reduction of the hexachloroketone melting at 92° gave a compound $C_5H_2Cl_4O$ of unknown structure. Since this compound is now shown to be a hydrate of IV, rearrangement must have occurred upon reduction of the unconjugated ketone. Consequently, due to the lack of knowledge concerning the mechanisms of reduction and rearrangement of the unconjugated isomer, either hexachloroketone might have formed 2,3,4,4,5-pentachloro-2-cyclopentenone.

Based upon the data presented herein and further interpretation of published information, it seems probable that the ketone melting at 28° has the structure shown as compound VIII and that its isomer melting at 92° has the structure IX. It was known[12] that cleavage of the hexachloroketone melting at 28° produces a high yield of only one product, a pentachloropentadienoic acid (m.p. 124–125°), whereas cleavage of the isomeric ketone melting at 92° produces an isomeric acid (m.p. 96°) contaminated with a small quantity of the higher melting acid. Furthermore, separation of the two isomeric acids has been accomplished only by microscopic techniques. Investigations in this Laboratory show that pure pentachloropentadienoic acid (m.p. 124–125°) can be obtained in high yield by (a) treatment of octachlorocyclopentene with sodium methoxide to form a ketal of hexachlorocyclopentenone, (b) hydrolysis of the ketal to a hexachlorocyclopentenone, and (c) cleavage of the ketone with alkali to form the acid. The enhanced reactivity of chlorine atoms in a position allylic to a double bond is well known, and is used to establish the structure of the ketal as 1,2,4,4,5,5 - hexachloro - 3,3 - dimethoxycyclopentene. Hydrolysis of the ketal to form hexachloro-2-cyclopentenone may be readily explained. On the other hand, hexachloro-3-cyclopentenone could have been formed only through a rearrangement. Consideration of the equilibrium mixtures[10,11] of the two ketones at various temperatures shows that if a rearrangement had occurred upon hydrolysis of the ketal, the product would have been a mixture of the two ketones containing at least 5% of the isomer melting at 92°. Since the ketone melting at 28° was the only product, a rearrangement could not have taken place. Further evidence supporting structure VIII as that of the ketone melting at 28° is obtained by an interpretation of the results of Zincke and co-workers.[13,14,15,16] Whereas ammonia converted the higher melting ketone to an amide of a pentachloropentadienoic acid, the other ketone was converted to a pentachloro-3-iminocyclopentanone which was believed to be either 2,4,4,5,5-pentachloro-3-iminocyclopentanone or 2,2,4,5,5-pentachloro-3-iminocyclopentanone. The action of basic reagents on the lower melting ketone proceeds by two distinct modes of attack. Cleavage occurs by the action of aqueous potassium hydroxide to produce a pentachloropentadienoic acid. Addition to the conjugated system occurs by the action of both ammonia and aniline resulting in the ultimate formation of pentachloro-3-iminocyclopentanones. On the other hand, the higher melting ketone does not show the properties of a conjugated system, since both aqueous alkali and ammonia convert it to straight chain derivatives, while aniline reacts with it only on long standing to form an amorphous material.

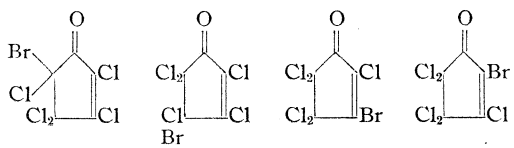
Prins[3] reported the preparation of a pentachlorocyclopentenone (m.p. 82–83°) by the action of sulfuric acid on hexachlorocyclopentadiene at 100–105°, "the lowest temperature at which reaction occurs." Under these conditions, or at

(8) T. Zincke and K. W. Kuster, *Ber.*, **21**, 2719 (1888).
(9) (a) T. Zincke and F. W. Kuster, *ibid.*, **22**, 486 (1899); (b) **23**, 820, 2200 (1890); (c) **26**, 2104 (1893).
(10) F. W. Kuster, *Z. physik. Chem.*, **18**, 161 (1895).
(11) H. van Brederode, *Rec. trav. chim.*, **65**, 174 (1946).
(12) T. Zincke and F. W. Kuster, *Ber.*, **26**, 2111 (1893).
(13) T. Zincke and F. Kuster, *Ber.*, **21**, 2728 (1888); **22**, 494 (1889); **23**, 2222 (1890); **26**, 2107 and 2116 (1893).
(14) T. Zincke, *ibid.*, **23**, 2208 (1890); **25**, 2230 (1892); **27**, 3364 (1894); **28**, 1644 (1895).
(15) T. Zincke and A. Rohde, *Ann.*, **299**, 367 (1897).
(16) T. Zincke and O. Fuchs, *Ber.*, **26**, 1680 (1893).

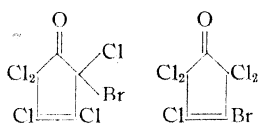
higher temperatures, the main product was 3,4,5-trichloro-3-cyclopentene-1,2-dione. It has been shown in this Laboratory that a compound $C_5HCl_5O$ (m.p. 82-83°) (X) can be obtained in 78% yield by performing the reaction at 80°. Both pentachlorocyclopentenones are identical to those obtained[7] by the reduction of VIII.

During the course of the identification of the pentachlorocyclopentenone, attempts were made to replace the hydrogen atom by a halogen atom. Although chlorination was not successful, bromination occurred readily to form a compound $C_5BrCl_5O$ (m.p. 3–4°). The identification of the bromo derivative as 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone (XI) and the reduction of the bromoketone to the original pentachloroketone provides evidence useful in establishing the structure of the pentachloroketone.

Of the six possible bromopentachlorocyclopentenones (XI-XIE), structures XIB and XIC

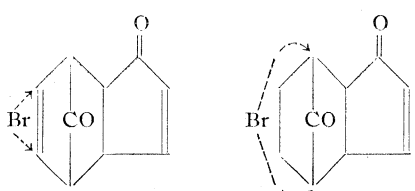


XI XIA XIB XIC

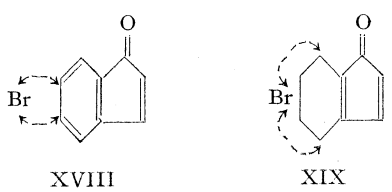


XID XIE

were readily eliminated, since treatment of the bromoketone with potassium iodide in acetone solution formed hexachloroindone (V). Structures XIB and XIC would have formed the intermediates XVI and XVII, in which a bromine atom is attached to either position 5 or 6 and 4 or 7, as indicated. The elimination of $COX_2$ from these intermediates would have formed bromoindone derivatives, represented by structures XVIII and XIX. The reduction of the bromo-



XVI XVII



XVIII XIX

ketone (XI) to form a stable pentachlorocyclopentenone eliminates structures XID and XIE. Structure XID would be expected to behave similarly to hexachloro-3-cyclopentenone, in which case an unstable intermediate, $C_5HCl_5O$, would immediately dehydrochlorinate and dimerize to form a hydrate of IV. Structure XIE is likewise improbable, since reduction with stannous chloride should form a bromocyclopentenone or the dimer of a tetrahalocyclopentadienone. Structure XIA, as well as XIB, XIC, and XIE was eliminated by cleavage of the bromoketone with aqueous alkali to form a bromotetrachloropentadienoic acid (XII), in which the bromine atom was shown to be on the terminal carbon atom. The salt solution obtained after removal of the acid was free of bromide ion. The bromo acid was identified by its synthesis from tetrachloro-5,5-dimethoxycyclopentadiene (II), involving (a) addition of bromine, (b) hydrolysis of the dibromoketal to a dibromotetrachlorocyclopentenone (XIIIA) or (XIIIB), and (c) cleavage of the dibromoketone with alkali. Irrespective of the structure of the dibromoketone, the resulting bromo acid, $C_4BrCl_4CO_2H$, must be 5-bromo-2,3,4,5-tetrachloropentadienoic acid. Since it is identical to the acid obtained by cleavage of the bromopentachlorocyclopentenone, only structure XI readily accounts for all the experimental results.

The reduction of hexachloro-2-cyclopentenone with stannous chloride to form a pentachlorocyclopentenone might be initiated at the carbonyl group, or at positions 4 or 5. Possible attack at the carbon to carbon double bond necessitates a consideration of allylic shifts involving carbon atoms 2, 3, and 4. On the other hand, the reduction of 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone to a pentachlorocyclopentenone could conceivably occur only at the carbonyl group or at position 5. The replacement of the bromine atom by a hydrogen atom is not concerned with the position allylic to the carbon to carbon double bond, and there is no reason to suspect an allylic shift involving carbon atoms 2, 3, and 4. Consequently, whether the reduction involves direct replacement of the bromine atom by a hydrogen atom, or conversion of the carbonyl group to an alcohol followed by dehydrobromination and ketolization, the only possible product is 2,3,4,4,5-pentachloro-2-cyclopentenone (X).

It is interesting to note that the reaction of hexachlorocyclopentadiene with sulfuric acid produces 2,3,4,4,5-pentachloro-2-cyclopentenone, whereas fluorosulfonic acid produces octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione, and chlorosulfonic acid produces a compound having the molecular formula $C_{10}H_2SCl_{12}O_3$, the identification of which is in progress.

## Experimental

**Materials.**—The hexachlorocyclopentadiene used in this investigation was supplied by the Hooker Electrochemical Company. Other reagents were obtained from the usual chemical supply houses.

**1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene.**—A solution containing 684 g. (12.2 moles) of potassium hydroxide dissolved in 3 liters of methanol was added to a

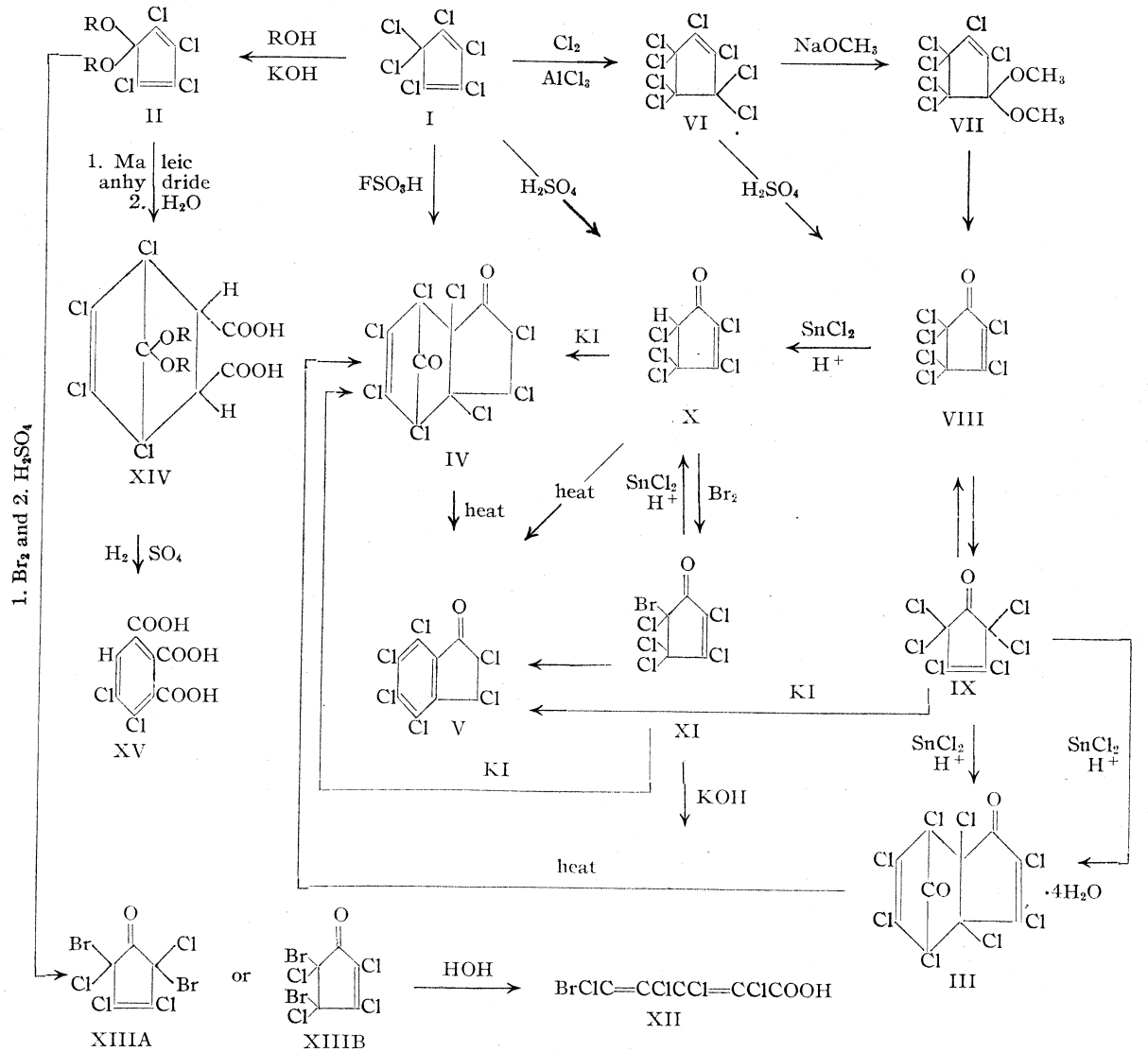



Fig. 1.

solution of 1270 g. (4.7 moles) of hexachlorocyclopentadiene in 4 liters of methanol during a period of four hours. The temperature increased from 48° at the beginning of the addition to 60° at the end. After dilution with water, the organic layer was separated, washed with water, dried, distilled, and rectified. There was obtained 841 g. (3.2 moles) of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, a yellow liquid having a sweet odor and the following physical properties: b. p. (11 mm.) 108–110°, $d^{20}_4$ 1.5010, $n^{20}D$ 1.5288.

*Anal.* Calcd. for $C_7H_6Cl_4O_2$: Cl, 53.8. Found: Cl, 53.8.

**1,2,3,4-Tetrachloro-5,5-diethoxycyclopentadiene.**—This acetal, b. p. (5 mm.) 101–103°, $d^{20}_4$ 1.3932, and $n^{20}D$ 1.5063, was prepared from hexachlorocyclopentadiene in a manner similar to that described for the dimethoxy derivative using ethanol as a solvent and reactant in place of methanol.

*Anal.* Calcd. for $C_9H_{10}Cl_4O_2$: Cl, 48.7; mol. wt., 292. Found: Cl, 49.2; mol. wt. (cryoscopic in benzene), 287.

**1,2,3,4,11,12,13,14-Octachloro-6,9,15,18-tetraoxadispiro(4.4.4.4)-1,3,11,13-octadecatetraene.**—Hexachlorocyclopentadiene (540 g., 2.0 moles) was added to a solution of potassium hydroxide (600 g., 10.7 moles) in ethylene glycol (750 g., 12.1 moles) at 50–60° during a period of two hours. After cooling, the reaction mixture was diluted with water and the organic layer separated and dissolved in petroleum ether. Upon cooling in a bath of Dry Ice and trichloroethylene, fine white needle-like crystals separated. Recrystallization of the solid from a mixture of acetone and benzene produced 63 g. of the octadecatetraene, m. p. 279–280°.

*Anal.* Calcd. for $C_{14}H_8Cl_8O_4$: Cl, 54.2; mol. wt., 524. Found: Cl, 54.1; mol. wt. (Rast), 511, 518.

**1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo(2.2.1)-5-heptene-2,3-dicarboxylic Acid and Anhydride.**—A solution containing 53 g. of tetrachloro-5,5-dimethoxycyclopentadiene, 19 g. of maleic anhydride, and 300 ml. of xylene was refluxed for 1.25 hours. During this period, the pale yellow solution became orange and a solid crystallized. The solvent was removed by steam distillation. Upon cooling, tan crystals separated from the water and collected on the orange residue. After filtration, the solid product was washed repeatedly with petroleum ether (90–100°) at room temperature. The resulting white product (62 g.) was recrystallized from water to produce 1,4,5,6-tetrachloro-7,7-dimethoxybicyclo(2.2.1)-5-heptene-2,3-dicarboxylic acid, m. p. 196–197°.

*Anal.* Calcd. for $C_{11}H_{10}Cl_4O_6$: Cl, 37.4; neut. equiv., 190. Found: Cl, 38.0; neut. equiv., 192.

The dibasic acid (14 g.) was heated at 220–225° until the evolution of gases ceased. The product was cooled, extracted with hot benzene, filtered, and recrystallized from benzene to obtain the anhydride, m. p. 192°.

*Anal.* Calcd. for $C_{11}H_3Cl_4O_5$: Cl, 39.2; neut. equiv. (in methanol), 362. Found: Cl, 39.7; neut. equiv., 360.

**4,5-Dichlorobenzene-1,2,3-tricarboxylic acid.**—1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo(2.2.1)-5-heptene-2,3-dicarboxylic acid (14 g.) was heated with concentrated sulfuric acid (150 g.) at 90° for twenty minutes. Upon cooling the resulting solution, crystals of 4,5-dichlorobenzene-1,2,3-tricarboxylic acid anhydride crystallized. The anhydride was filtered, dissolved in water, extracted with ether, and recrystallized from an ether–benzene mixture to produce 4 g. of 4,5-dichlorobenzene-1,2,3-tricarboxylic acid, m. p. 124–126°.

*Anal.* Calcd. for $C_9H_4Cl_2O_6$: Cl, 25.4; neut. equiv., 93. Found: Cl, 25.8; neut. equiv., 95.

**Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione. Method A.**—1,2,3,4-Tetrachloro-5,5-diethoxycyclopentadiene (11 g.) was added slowly to 45 g. of concentrated sulfuric acid at 0–5°. Immediately upon the addition of each drop of the acetal, a red color formed which disappeared with the simultaneous precipitation of a white solid. The mixture was poured onto cracked ice and the solid was washed repeatedly with water and "dried" by exposure to the atmosphere. There was obtained 8.9 g. of a hydrate of octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione. This material melted with decomposition at 157–163°.

*Anal.* Calcd. for $C_{10}Cl_8O_2 \cdot 2H_2O$: Cl, 60.2; mol. wt., 462. Found: Cl, 59.2; mol. wt. (cryoscopic in nitrobenzene), 455.

A hydrate of octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione was also obtained by the reduction of hexachloro-3-cyclopentenone with stannous chloride as described by Zincke,[5] who reported the product to have the formula $C_5H_2Cl_4O_2$. The hydrate was converted to the tetrahydrate by recrystallizing from aqueous acetic acid. The tetrahydrate was converted to the anhydrous material by recrystallizing from petroleum ether as well as by heating to constant weight at 90–95° at 20 mm.

*Anal.* Calcd. for $C_{10}Cl_8O_2 \cdot 4H_2O$: Cl, 55.9; mol. wt., 508. Found: Cl, 55.9; mol. wt. (cryoscopic in glacial acetic acid), 509, 482, 508.

*Anal.* Calcd. for $C_{10}Cl_8O_2$: Cl, 65.2. Found: Cl, 65.2.

**Method B.**—A mixture containing 30 g. of potassium iodide, 27 g. (0.11 mole) of 2,3,4,4,5-pentachloro-2-cyclopentenone and 1 liter of acetone was refluxed for thirty minutes, cooled, and poured into water. There was an immediate precipitation of a red solid followed by the separation of a flocculent orange solid. Separation by decantation gave 4 g. of hexachloroindone, orange in color, and a red solid which was washed with aqueous potassium iodide and water to remove the color. Recrystallization from petroleum ether (90–100°) gave 19 g. of anhydrous octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione. The yields were 11 and 88%, respectively.

**Method C.**—Fluorosulfonic acid (200 g., 2.0 moles) was added to hexachlorocyclopentadiene (544 g., 2.0 moles) at 120° during a period of twenty-five minutes. After addition of the fluorosulfonic acid was completed, the mixture was heated at 80–100° with vigorous stirring for one and one-fourth hours. The orange-red reaction mixture was poured onto cracked ice and the organic layer separated and washed with water. The semi-solid product was filtered and the solid recrystallized from petroleum ether (90–100°). There was obtained 146 g. of octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione.

**Octachlorocyclopentene.**—Chlorine was bubbled rapidly into a stirred mixture of 2580 g. (9.49 moles) of hexachlorocyclopentadiene and 40 g. of anhydrous aluminum chloride. The temperature of the reaction mixture was maintained at 40–45° by absorbing the heat of the rapidly occurring exothermic reaction in an ice–water-bath. The mixture was washed with warm water and then purified by crystallization from ethanol. The purified product weighed 3245 g. (9.46 moles) and melted at 39°.

*Anal.* Calcd. for $C_5Cl_8$: Cl, 82.6. Found: Cl, 82.3.

**Hexachloro-2-cyclopentenone.**—A mixture containing 1832 g. (5.3 moles) of octachlorocyclopentene and 2600 g. of concentrated sulfuric acid was heated with vigorous stirring for seven hours at 105°. After cooling to 25°, the pale yellow upper layer was separated, washed with water and recrystallized twice from *n*-pentane. There was obtained 1138 g. (3.9 moles) of hexachloro-2-cyclopentenone, m. p. 28°. This product was converted to hexachloro-3-cyclopentenone (m. p. 92°) and to pentachloropentadienoic acid (m. p. 124.5–125° cor.).[8]

**Pentachloropentadienoic Acid.**—Sixty-seven grams of sodium (2.9 moles) was added to 1.5 liters of methanol. The solution was added to a suspension of 548 g. (1.6 moles) of octachlorocyclopentene in 2 liters of methanol at 45–50° during a three and one-half-hour period. Water was added to the reaction mixture and the solid which precipitated was separated and recrystallized from pentane. A 95-g. portion of a crude product was stirred with concentrated sulfuric acid at 45° for ten minutes. The sulfuric acid mixture was poured onto cracked ice, the resulting liquid was washed with water, and then it was added to a solution of 50 g. of potassium hydroxide in 400 g. of water at 25°. After stirring for ten minutes, the mixture was filtered to obtain 23 g. of unreacted octachlorocyclopentene. The filtrate was acidified with dilute hydrochloric acid. The pentachloropentadienoic acid, which precipitated, melted at 118–120°. This acid was readily purified by recrystallizing from a mixture of carbon tetrachloride and pentane. After two recrystallizations, the acid melted at 124.5–125° (cor.). This material was shown by a method of mixed melting points to be identical with pentachloropentadienoic acid obtained by cleavage of hexachloro-2-cyclopentenone.

**2,3,4,4,5-Pentachloro-2-cyclopentenone. Method A.**—A mixture of 814 g. (3.0 moles) of hexachlorocyclopentadiene and 1600 g. of concentrated sulfuric acid was heated with vigorous stirring at 80° until the solution was complete. This required eleven hours. A portion (790 ml.) of the homogeneous reaction mixture (total volume 1270 ml.) was poured onto cracked ice and the resulting solid was separated by filtration. The crude material was purified by recrystallization from petroleum ether (90–100°). There was obtained 372 g. (1.5 moles) of 2,3,4,4,5-pentachloro-2-cyclopentenone, m. p. 82–83°, yield 78%. This material did not depress the melting point of the compound $C_5HCl_5O$ prepared previously.[7]

*Anal.* Calcd. for $C_5HCl_5O$: Cl, 69.7; mol. wt., 254. Found: Cl, 69.6; mol. wt. (cryoscopic in benzene), 257.

**Method B.**—Thirty-one grams (0.14 mole) of stannous chloride dihydrate was dissolved in a mixture of 62 g. of glacial acetic acid and 150 g. of concentrated hydrochloric acid. The resulting solution was added to a mixture of 30 g. (0.9 mole) of 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone in 300 g. of glacial acetic acid at 10–15° during a period of twenty minutes. The reaction mixture was diluted with water and the solid material which separated was recrystallized from a pentane-carbon tetrachloride mixture. Eighteen grams (0.07 mole) of 2,3,4,4,5-pentachloro-2-cyclopentenone, m. p. 82–83°, was obtained in a yield of 78%. Attempts to convert this material to hexachlorocyclopentenone by reaction with liquid chlorine at 30° and by reaction with gaseous chlorine at 70° (carbon tetrachloride solution) were unsuccessful.

**5-Bromo-2,3,4,4,5-pentachloro-2-cyclopentenone.**—Two hundred and ten grams of bromine (1.3 moles) and 275 g. (1.08 moles) of 2,3,4,4,5-pentachloro-2-cyclo-

pentenone were added to 1.5 liters of carbon tetrachloride. The mixture was allowed to stand at 25° for twenty-two hours in the presence of light from two 40-w. 360 B. L. lamps. Carbon tetrachloride, bromine, and dissolved gases were removed by heating on a steam-bath under reduced pressure. The liquid product which remained was crystallized from petroleum ether (90–100°) to obtain 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone (221 g., 0.66 mole), m. p. 3–4°, and 102 g. of starting material. The conversion and yield were 62 and 98%, respectively.

*Anal.* Calcd. for $C_5BrCl_6O$: total halogen (calculated chloride, grav. anal.) 63.9. Found: total halogen, 62.8.

**Dibromotetrachlorocyclopentenone.**—A mixture containing 150 g. (0.94 mole) of bromine, 200 g. (0.73 mole) of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene, and 500 g. of carbon tetrachloride was allowed to stand at room temperature for fifteen hours. The mixture was then heated on a steam-bath to remove excess bromine and carbon tetrachloride. The viscous liquid which remained was added slowly to 800 g. of concentrated sulfuric acid at 30°. The mixture was poured onto cracked ice and the organic product was crystallized from pentane. After repeated recrystallizations, a white solid melting at 156–157° was obtained. The odor of bromine was readily detected in the pure solid, and upon warming with water bromine vapors were evolved.

*Anal.* Calcd. for $C_5Br_2Cl_4O$: total halogen (calculated as chloride), 56.4. Found: total halogen, 56.4.

**5-Bromo-2,3,4,5-tetrachloropentadienoic Acid. Method A.**—Cleavage of 14 g. (0.042 mole) of 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone was accomplished by adding the ketone, with stirring, to 30 g. of potassium hydroxide in 270 ml. of water at 25°. The reaction mixture was diluted and filtered. A tan solid precipitated upon acidification of the filtrate with dilute hydrochloric acid. This solid was recrystallized from carbon tetrachloride to give 6 g. (0.02 mole) of 5 bromo 2,3,4,5-tetrachloropentadienoic acid: white solid, m. p. 118–119°.

*Anal.* Calcd. for $C_5HBrCl_4O_2$: total halogen (calculated as chloride), 56.4; neut. equiv., 315. Found: total halogen, 56.0; neut. equiv., 317.

**Method B.**—Excess bromine was added slowly to a few grams of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and the reaction mixture was allowed to stand until it cooled to room temperature. The mixture was dropped into concentrated sulfuric acid at room temperature, poured onto cracked ice, washed with water, and dissolved in 10% aqueous potassium hydroxide solution. After filtration and acidification, a white solid, m. p. 119°, was obtained. It did not depress the melting point of the acid obtained by Method A.

**Hexachloroindone.**—5-Bromo-2,3,4,4,5-pentachloro-2-cyclopentenone (60 g., 0.18 mole), potassium iodide (70 g., 0.42 mole) and acetone (1 liter) were mixed and refluxed for two and one-half hours. The reaction mixture was then cooled and diluted with water. The orange solid which precipitated was washed with aqueous potassium iodide and recrystallized from acetone to give 25 g. (0.074 mole) of hexachloroindone, m. p. 149°, yield 83%. This product is identical to that obtained by heating octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione with water.

*Anal.* Calcd. for $C_9Cl_6O$: Cl, 63.1. Found: Cl, 63.1.

**Reaction of Hexachlorocyclopentadiene with Chlorosulfonic Acid.**—A mixture of 1000 g. of hexachlorocyclopentadiene (3.68 moles) and 1000 g. (8.62 moles) of chlorosulfonic acid was stirred vigorously for two hours at 90°. Solid began to crystallize from the reaction mixture after one half hour. After cooling in an ice-bath, the thick slurry was filtered through a sintered glass funnel and the solid was washed with water, refiltered, and washed with petroleum ether (90–100°) saturated with the final product. The resulting product, 987 g., m. p. 143–147°, was a white, crystalline solid. Recrystallization from petroleum ether-benzene increased the melting point to 146–147°.

*Anal.* Calcd. for $C_{10}H_2Cl_{12}O_3S$: C, 19.11; H, 0.32; Cl, 67.8; S, 5.09; mol. wt., 627. Found: C, 19.02, 19.10; H, 0.26, 0.25; Cl, 67.6, 67.8, 67.8; S, 5.05, 5.12; mol. wt. (ebull. in benzene), 611, 639.

Distillation of the original filtrate produced 674 g. (5.81 moles) of chlorosulfonic acid and 130 g. of tar, whereas decomposition of the filtrate by dropping onto ice produced 97.5 g. of a mixture of hexachlorocyclopentadiene and the sulfur-containing product. The conversion and yield are 86 and 95%, respectively. The structure of the product is being investigated.

**Acknowledgment.**—The authors express their indebtedness to the Hooker Electrochemical Company for defraying the expenses of this investigation and for supplying the hexachlorocyclopentadiene used.

## Summary

Hexachlorocyclopentadiene reacts with alcoholic alkali to form the ketals, tetrachloro-5,5-dialkoxycyclopentadiene. The ketals react with dienophiles to form Diels–Alder adducts and undergo hydrolysis to give octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene-1,8-dione. The tricyclic ketone was also prepared by treatment of 2,3,4,4,5-pentachloro-2-cyclopentenone and 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone with potassium iodide in acetone solution, as well as by the reaction of hexachlorocyclopentadiene with fluorosulfonic acid.

The reaction of hexachlorocyclopentadiene with sulfuric acid may be controlled to produce a 78% yield of 2,3,4,4,5-pentachloro-2-cyclopentenone, which was identified by bromination to 5-bromo-2,3,4,4,5-pentachloro-2-cyclopentenone, reduction of the bromoketone to the same pentachloroketone, and conversion of the pentachloroketone to octachlorotetrahydromethanoindenedione. Identification of the bromoketone was based primarily upon cleavage to form 5-bromo-2,3,4,5-tetrachloropentadienoic acid, the structure of which was demonstrated by synthesis involving (a) addition of bromine to tetrachloro-5,5-dimethoxycyclopentadiene, (b) hydrolysis of the acetal linkage to form a dibromotetrachlorocyclopentenone, and (c) cleavage of the dibromoketone with alkali.

Octachlorocyclopentene, prepared by the catalytic addition of chlorine to hexachlorocyclopentadiene, was found to produce hexachloro-2-cyclopentenone by reaction with sulfuric acid. Strong chemical evidence is presented in regard to the aged controversy as to the structure of the isomeric hexachlorocyclopentenones (m. p. 28° and 92°). The former is believed to be hexachloro-2-cyclopentenone; the latter, hexachloro-3-cyclopentenone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY AND THE PURDUE RESEARCH FOUNDATION]

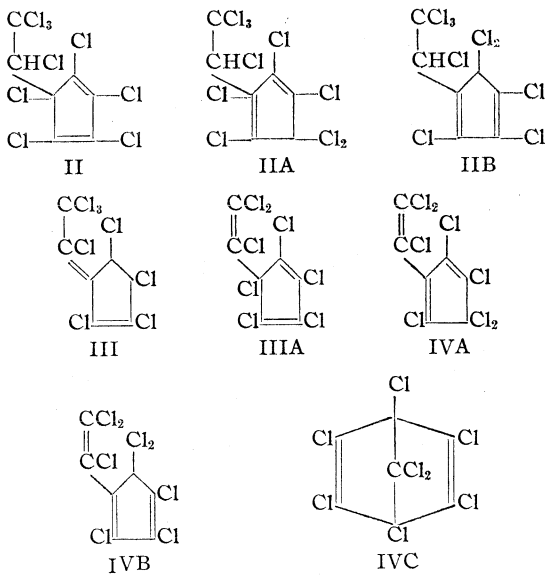
# The Chemical Behavior of Hexachlorocyclopentadiene. II. Condensation with Trichloroethylene[1]

BY J. S. NEWCOMER[2] AND E. T. McBEE

The exceptional reactivity of hexachlorocyclopentadiene (I) in the presence of aluminum chloride may be attributed to the pentachlorocyclopentadienyl cation, $C_5Cl_5^+$. The resonance forms of this ion provide a theoretical basis for the susceptibility of I toward addition reactions, either as an addend or augend. The former is illustrated by the addition of chloroform to I to produce a nonachloromethylcyclopentene[3] and by the addition of chlorine in the presence of aluminum chloride to form octachlorocyclopentene.[4] The latter is illustrated by the addition of I to trichloroethylene to form 5-(1,2,2,2-tetrachloroethyl)-pentachlorocyclopentadiene (II). Both processes are illustrated by the dimerization of I to form a compound $C_{10}Cl_{12}$ (XVI). A summary of the reactions reported in this paper is shown diagrammatically in Fig. 1.

Since the presentation of this paper,[4,5] Krynitsky and Bost[6] reported the preparation of a compound $C_7HCl_9$ by the condensation of I with trichloroethylene in the presence of aluminum chloride. These investigators also reported the preparation of a chlorocarbon $C_7Cl_8$ by the dehydrochlorination of $C_7HCl_9$ with alcoholic alkali. No proof of the structure of these materials was presented. Investigations in this Laboratory have shown that the condensation of I with trichloroethylene may be controlled to produce high yields of either $C_7HCl_9$ (II) or $C_7Cl_8$(l), octachloro-1 or 2-vinylcyclopentadiene (IV), with a small quantity of a dimer of I as a by-product. Although I readily dimerizes in the presence of aluminum chloride, the rate of dimerization at 80° is not as rapid as the rate of condensation with trichloroethylene. By performing the condensation at 80°, and then increasing the temperature to 110–115°, the aluminum chloride effects rearrangement and dehydrochlorination of II to form IV. On the other hand, the dehydrochlorination of II with alcoholic alkali occurs without rearrangement to form an isomeric solid chlorocarbon $C_7Cl_8$(s), octachloro-5-ethylidenecyclopentadiene (III).

It is highly improbable that dehydrochlorination of $C_7HCl_9$ with alcoholic alkali involves a rearrangement. Consequently, the corresponding chlorocarbon $C_7Cl_8$(s) may be represented by structure III or IIIA, IVA, IVB, or IVC, depending upon whether it was derived from the structure II, IIA, IIB, or the bicyclic compound.




The isomeric chlorocarbons, $C_7Cl_8$(l) and $C_7Cl_8$(s) display entirely different chemical properties. The former undergoes reactions analogous to those of hexachlorocyclopentadiene, corresponding to structures IVA and IVB. The latter undergoes reactions typical of polychlorinated compounds which contain a trichloromethyl group attached to a carbon atom of an ethylenic bond, thus corresponding to structure III.

The bicyclic structure IVC can account in no apparent manner for either of these two types of reactions. In addition, IVC is not in accord with molecular refraction data, nor with the observed reactivity of both chlorocarbons toward alcoholic silver nitrate as well as toward alcoholic alkali. Furthermore, the liquid chlorocarbon, which was produced by the more drastic conditions, was converted to the unsaturated derivatives of ethylcyclopentane (XIII and XIV) by treatment with antimony pentafluoride. Fluorination of XIII with silver difluoride formed a chlorotridecafluoroethylcyclopentane. If the liquid chlorocarbon is assumed to have structure IVC, then cleavage must have occurred during the formation of the unsaturated compounds XIII and XIV. It is improbable that cleavage of the bicyclic compound would produce unsaturated derivatives of ethylcyclopentane, but more plausible to expect the cleavage

(1) Abstracted from the doctoral thesis of J. S. Newcomer.

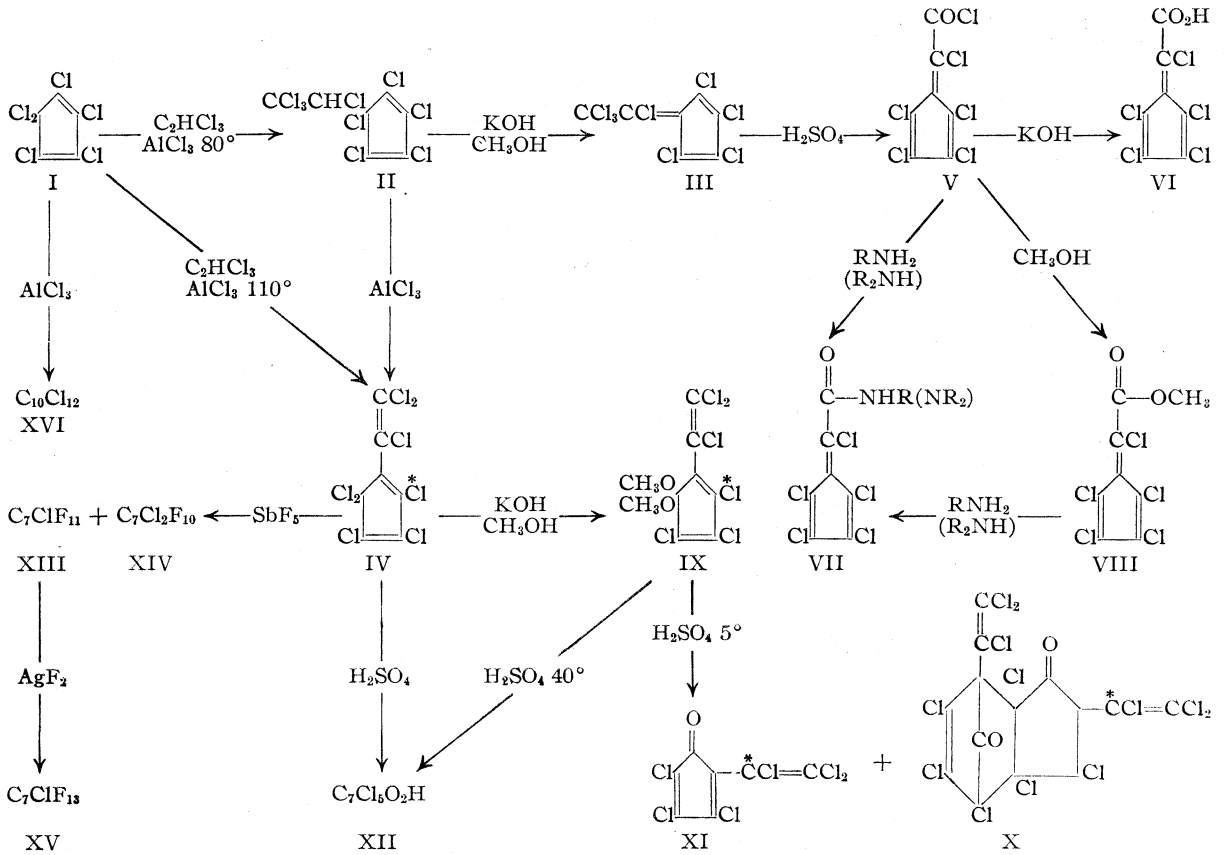
(2) Present address: Sharples Chemicals, Inc., Wyandotte, Michigan.

(3) H. J. Prins, *Rec. trav. chim.*, **65**, 455 (1946).

(4) J. S. Newcomer and E. T. McBee, THIS JOURNAL, **71**, 946 (1949).

(5) J. S. Newcomer and E. T. McBee, presented before the 111th Meeting of the Am. Chem. Soc., April 14–18, 1947.

(6) J. A. Krynitsky and R. W. Bost, THIS JOURNAL, **69**, 1918 (1947).




Chlorotridecafluoroethylcyclopentane. (*Position of trichlorovinyl group uncertain.)

to occur at a position allylic to the two ethylenic linkages to form unsaturated derivatives of methylcyclohexane, which might undergo further cleavage to form cyclohexene derivatives. However, no compound of these types of structures was obtained.

The fluorination of $C_7Cl_8$(l) (IV) with antimony pentafluoride to give high yields of the seven carbon atom compounds XIII and XIV may be contrasted with our previous investigations[7] in which it was shown that the fluorination of (tetrachlorophenyl) - pentachloroethane, (pentachlorophenyl)-dichlorotrifluoroethane, mixtures of polychloropolyfluoroethylbenzenes, pentachlorobenzotrifluoride, and hexachlorobenzene, under similar conditions, produced predominantly a six carbon atom compound, $C_6Cl_2F_8$.

The liquid chlorocarbon reacts rapidly with methanolic alkali to form an acetal, $C_7Cl_6(OCH_3)_2$ (IX), whereas the solid chlorocarbon reacts sluggishly to form a mixture of products. Structure III could form an acetal only by the elimination of a chloride ion to form an organic cation in which the charge could resonate from the terminal carbon atom of the side chain to one of the carbon atoms of the ring containing a chlorine atom. If this type of resonance were significant in the cation derived from structure III, then it should also be significant in the cations derived from structures IIIA, IVA, and IVB, since common resonance hybrids would be produced. Therefore, if III formed an acetal, IIIA, IVA, and IVB would also be expected to form acetals. The chlorocarbons $C_7Cl_8$(l) and $C_7Cl_8$(s) represent two of these four possible structures, but only the former forms an acetal. Hence, structure III cannot form an acetal and the structure of $C_7Cl_8$(l) is limited to IIIA, IVA, or IVB. Structure IIIA could form an acetal only by rearrangement, whereas IVA and IVB could form acetals with or without rearrangement. It seems highly improbable that IIIA would be converted to a completely conjugated system upon treatment with alcoholic alkali, but not in the presence of aluminum chloride for eleven hours at 110°, which are the conditions employed for the preparation of $C_7Cl_8$(l). The structure of this material is limited to octachloro-1 or 2-vinylcyclopentadiene (IVA or IVB). Further evidence supporting this contention is afforded by hydrolysis of the acetal with sulfuric acid at 5° to form a blood-red ketone, hexachloro-2 or 3-vinylcyclopentadienone (X) and its colorless Diels–Alder dimer (XI). In addition, reduction of $C_7Cl_8$(l) with zinc and acid resulted in the replacement of two chlorine atoms, and treatment with sulfuric acid formed a diketone $C_7HCl_5O_2$- (XII). This same diketone was obtained by hy-

(7) E. T. McBee, *et al.*, *Ind. Eng. Chem.*, **39**, 384 (1947).

drolysis of the acetal (IX) with sulfuric acid at 40°, thus illustrating the expected reaction of hexachloro-2 or 3-vinylcyclopentadienone (X) with sulfuric acid. These results are in accord with those expected of a simple derivative of hexachlorocyclopentadiene.[4]

There is no reason to expect structures IVA and IVB to behave differently toward alcoholic alkali. Therefore, the structure of $C_7Cl_8$(s) is limited to III or IIIA. Both of these compounds could have been derived only from structure II, thus establishing the compound $C_7HCl_9$ as 5-(1,2,-2,2-tetrachloroethyl)-pentachlorocyclopentadiene. The dehydrochlorination of II with alcoholic alkali to form IIIA would involve the removal of a primary chlorine atom which is not in an allylic position. Furthermore, the product of this type of dehydrochlorination results in the formation of an isolated double bond. On the other hand, it is more plausible to expect the dehydrochlorination of II to involve the removal of a tertiary chlorine atom which is also allylic to two double bonds. Furthermore, the product III contains a completely conjugated system of double bonds. In addition, III would be expected to react sluggishly with alcoholic alkali, as is the case, whereas IIIA should be exceedingly reactive. Contributing evidence that $C_7Cl_8$(s) has the structure III was obtained by its conversion to a white solid, pentachloro-2,4-cyclopentadienylideneacetyl chloride (V) by reaction with sulfuric acid. Although this material is an isomer of hexachloro-2 or 3-vinylcyclopentadienone (X), it has entirely different chemical and physical properties. It does not undergo Diels–Alder reactions, and can be distilled at atmospheric pressure with only slight decomposition. Also, it does not react with concentrated sulfuric acid at 100°, whereas X reacts readily at 40°. The acid chloride (V) is converted to methyl pentachloro-2,4-cyclopentadienylideneacetate (VIII) by refluxing with methanol or more rapidly by potassium hydroxide and methanol. Treatment of V with aqueous alkali forms the acid (VI). The amides (VII) were obtained by the action of the appropriate amines on both V and VIII.

Prill[8] has demonstrated the use of hexachlorocyclopentadiene in the diene synthesis. Derivatives of hexachlorocyclopentadiene in which the allylic chlorine atoms are replaced by methoxy and ethoxy groups have been found to react similarly.[4] The ease with which these highly chlorinated compounds undergo the diene synthesis may be attributed partially to the required *cis*-butadienoid configuration of the ring system. It is interesting to note, however, that III does not react with maleic anhydride under ordinary conditions. Another contrast is afforded by the dimerization of X at or below room temperature, as compared with the failure of IV to form an adduct with maleic anhydride in twenty hours at 135°.

(8) E. A. Prill, THIS JOURNAL, **69**, 62 (1947).

## Experimental

**Materials.**—Hexachlorocyclopentadiene was obtained through the courtesy of the Hooker Electrochemical Company. Other reagents were obtained from the usual chemical supply concerns.

**Dimer of Hexachlorocyclopentadiene (XVI).**—A mixture of I (397 g.) and anhydrous aluminum chloride (40 g.) was stirred for one hour at 90–95°. In order to decrease the viscosity, carbon tetrachloride (300 ml.) was added and the mixture was heated for an additional three hours at 75–80°. The cooled reaction mixture was poured onto cracked ice, washed by decantation, and steam-distilled to remove the solvent. The resulting tan solid was recrystallized from benzene to give XVI (268 g.), a white solid which sublimes without melting at temperatures above 240°.

*Anal.* Calcd. for $C_{10}Cl_{12}$: Cl, 77.9, mol. wt., 544. Found: Cl, 77.9, mol. wt. (cryoscopic in benzene), 508, 529, 543.

The dimer was also prepared using tetrachloroethylene as the solvent. Although an 88% conversion to the dimer was obtained in the absence of a solvent, this method is not preferred because of the difficulty in controlling the highly exothermic dimerization.

**5-(1,2,2,2-Tetrachloroethyl)-pentachlorocyclopentadiene (II).**—One-fifth of 2.0 moles of trichloroethylene was added to a mixture of I (1.97 moles) and aluminum chloride (0.3 mole) during a period of twenty minutes as the temperature was increased to 80°. The remainder of the trichloroethylene was added during a period of forty minutes at 80°. After allowing the reaction to continue for an additional 1.5 hours, the purple mixture was cooled and poured onto ice. Recrystallization of the resulting tan solid from methanol gave II (1.80 moles), a white solid having a melting point of 80–81°.

*Anal.* Calcd. for $C_7HCl_9$: Cl, 78.9. Found: Cl, 78.6.

**Octachloro-5-ethylidenecyclopentadiene (III).**—A solution of potassium hydroxide (1.5 moles) in methanol (1 l.) was added to a stirred suspension of II (1.5 moles) in methanol (1.5 l.) during a period of twenty-five minutes at 42–45°. After dilution of the cooled reaction mixture with water, the resulting liquid was crystallized from pentane to obtain III (1.38 moles), a white solid of m. p. 53°, b. p. 146° at 7 mm.

*Anal.* Calcd. for $C_7Cl_8$: Cl, 77.2; mol. wt., 368. Found: Cl, 77.4; mol. wt. (cryoscopic in benzene), 370, 372.

It is important to avoid the use of an excess of alkali in the dehydrochlorination, for when 180% excess alkali was used, the yield of desired product was decreased to 27%.

**Octachloro-1- or 2-vinylcyclopentadiene (IV).**—During a period of thirty-five minutes, commercial trichloroethylene (17.0 moles) was added to a stirred mixture of I (16.3 moles) and aluminum chloride (60 g.) as the temperature was increased from 30 to 84°. External cooling was necessary for one hour to maintain the temperature at 75–87°. Heat was then applied to keep the temperature at 80–85° for three hours, 102–104° for fifteen hours, and 111–114° for eight hours. The cooled reaction mixture was poured onto ice, diluted with carbon tetrachloride, washed, dried, and subjected to distillation in a Claisen flask to obtain 5000 g. of liquid of boiling range 110–175° at 6–8 mm. Rectification of the distillate gave 38 g. of unreacted I and 3853 g. (10.46 moles) of IV; yellow liquid, b. p. 148–149° (13 mm.), 138° (5 mm.), $d^{20}_4$ 1.736, $n^{20}D$ 1.5852, MD 70.9.

*Anal.* Calcd. for $C_7Cl_8$: Cl, 77.2. Found: Cl, 77.6.

A by-product from this reaction is a viscous yellow liquid; b. p. 168–171° at 3 mm., 79.2% Cl, $d^{20}_4$ 1.8129, $n^{20}D$ 1.6011.

**Pentachlorocyclopentadienylideneacetyl Chloride (V).**—A mixture of III (100 g.) and concd. sulfuric acid (800 g.) was heated with vigorous stirring for two hours at 90–95°. White needles sublimed to cooler portions of

the reactor during the reaction period. Upon cooling, light yellow solid separated from the reaction mixture. The slurry was poured onto ice, and the resulting solid was washed with water and recrystallized rapidly from methanol to give V (65 g.); white needles of m. p. 85.0–85.5°, b. p. 266–267° at 750 mm.

*Anal.* Calcd. for $C_7Cl_6O$: Cl, 68.1. Found: Cl, 68.0.

**N,N-Diethylpentachloro-(cyclopentadienylideneacetamide) (VII).**—During a period of five minutes, diethylamine (6.3 g.) was added at room temperature to a solution of V (17 g.) in *n*-pentane (100 ml.). The yellow precipitate was washed thoroughly with water and recrystallized from a mixture of carbon tetrachloride and *n*-pentane to give VII (10 g.); yellow crystals m. p. 107°.

*Anal.* Calcd. for $C_{11}H_{10}Cl_5NO$: Cl, 50.7; N, 4.1; mol. wt., 349. Found: Cl, 50.7, 50.9; N, 4.0; mol. wt. (Rast), 343.

By employing a similar procedure, the diethylamide was also prepared by the action of diethylamine on the methyl (pentachlorocyclopentadienylidene)-acetate (VIII).

N-Phenylpentachloro-(cyclopentadienylideneacetamide) was prepared by the action of aniline on V in pentane solution. This amide is a white solid, m. p. 220°.

*Anal.* Calcd. for $C_{13}H_6Cl_5NO$: Cl, 47.9. Found: Cl, 47.9.

**Methyl Pentachlorocyclopentadienylidene)-acetate (VIII). Method A.**—A solution of potassium hydroxide (0.18 mole) in methanol (100 ml.) was added to a solution of V (0.17 mole) in methanol (200 ml.) during a period of twenty minutes at 45–47°. The reaction mixture was allowed to cool, diluted with water and filtered to obtain a white solid (39 g., m. p. 80–88°). The clear filtrate was acidified with dilute hydrochloric acid to obtain an additional quantity of white solid (11 g., m. p. 116°). Recrystallization of the former material from a mixture of hexane and carbon tetrachloride produced white crystals (25 g., m. p. 116°), which did not depress the melting point of that obtained upon acidification of the filtrate.

*Anal.* Calcd. for $C_8H_3Cl_5O_2$: Cl, 57.5. Found: Cl, 57.1.

**Method B.**—A solution of V (30 g.) in methanol (400 ml.) was refluxed for three hours. The solution was cooled, diluted with water, and the resulting solid was filtered. After two recrystallizations from a mixture of pentane and carbon tetrachloride, the solid melted at 84–97°; after three recrystallizations, 108–113°; and after four recrystallizations, pure VIII (7 g., m. p. 116°) was obtained. The product did not depress the melting point of that obtained by the action of alcoholic alkali on V.

**Dimer of Hexachlorovinylcyclopentadienone (XI). Step 1.**—A solution of potassium hydroxide (280 g.) in methanol (1000 ml.) was added to a stirred solution of IV (100 g.) in methanol (500 ml.) during a period of forty-five minutes at 40–45°. The cooled reaction mixture was diluted with water to dissolve potassium chloride and the resulting organic layer was washed with water to obtain a tan liquid (84 g.) having a sweet odor characteristic of the acetals of tetrachlorocyclopentadienone. Four recrystallizations of the product gave a pale yellow or white solid (60 g.), hexachloro-5,5-dimethoxy-1- or 2-vinylcyclopentadiene; m. p. 39°.

**Step 2.**—During a period of forty minutes, the acetal, prepared in step 1, (132 g.) was added to vigorously stirred concentrated sulfuric acid (800 ml.) at 0–5°. The blood-red solution was dropped onto cracked ice and the resulting red oil was washed with water. The addition of ethyl alcohol (90 ml.) at room temperature resulted in the crystallization of long red needles, which were recrystallized twice from acetone to give XI (2.8 g.); long white needles, m. p. 207°. The dimer evolves carbon monoxide at temperatures above 250°.

*Anal.* Calcd. for $C_{14}Cl_{12}O_2$: Cl, 68.0; mol. wt., 626. Found: Cl, 68.0, 68.1, 67.8; mol. wt. (ebullioscopic in benzene), 633, 639.

A blood red oil was obtained by evaporation of the alcohol from the filtrate. The oil is probably hexachloro-2 or 3-vinylcyclopentadienone (X).

**Hexachlorovinylcyclopentenedione (XII): Method A.**—A mixture of IV (1000 g.) and concentrated sulfuric acid (4000 g.) was stirred vigorously for seven hours at 120–125°. The reaction mixture gradually becomes black and resolves into a one-phase system. The cooled solution was extracted five times with a total of five liters of carbon tetrachloride. Evaporation of the solvent gave orange needles, which after two recrystallizations from carbon tetrachloride gave the diketone $C_7HCl_5O_2$ (XII) (315 g.); yellow needles, m. p. 96°.

*Anal.* Calcd. for $C_7HCl_5O_2$: Cl, 60.2. Found: Cl, 60.1, 60.1.

The diketone is decomposed by 5% aqueous potassium carbonate at room temperature.

**Method B.**—During a period of five minutes, hexachloro-5,5-dimethoxy-1 or 2-vinylcyclopentadiene (50 g.) was added to concentrated sulfuric acid (300 g.) at 40°. The blood-red mixture was dropped onto cracked ice and the red organic layer was washed with water and crystallized from petroleum ether (35–37°) to give an orange-red solid. Three additional recrystallizations produced the diketone XII (1.5 g.); yellow needles, m. p. 96°.

**Fluorination of Octachloro-1 or 2-vinylcyclopentadiene.**—A three-necked flask containing liquid $C_7Cl_8$ (440 g., 1.19 moles) was equipped with a thermometer, stirrer, distilling arm, and a dropping funnel containing antimony pentafluoride (2650 g., 12 moles). The distillation arm was connected to a water condenser, receiver, a second condenser, and finally a receiver cocled by ice water. The chlorocarbon was heated to 130° before the addition of antimony pentafluoride was begun. The heat was then discontinued and the temperature was regulated at 120–135° by the rate of addition of antimony pentafluoride. It was necessary to supply heat to maintain this temperature range after 1200 g. of the antimony fluoride had been added. At the conclusion of the addition, the temperature was increased gradually up to 170° to continue the gentle distillation of organic product. All of the product was collected in the first receiver. The colorless liquid distillate was washed with concd. hydrochloric acid, water, and dried to obtain 268 g. of clear, colorless, fluorinated product. Rectification of the crude product from a 52 in. column packed with small glass helices gave two clear-cut fractions; $C_7ClF_{11}$, 153.5 g., b. p. 90–92°, $d^{20}_4$ 1.7009, $n^{20}D$ 1.3210, and $C_7Cl_2F_{10}$, 62.5 g., b. p. 116°, $d^{20}_4$ 1.7174, $n^{20}D$ 1.3482.

*Anal.* Calcd. for $C_7ClF_{11}$: Cl, 10.7; F, 63.7; mol. wt., 328. Found: Cl, 10.9, 10.7; F, 63.8, 62.7; mol. wt. (vapor density), 328, 330.

*Anal.* Calcd. for $C_7Cl_2F_{10}$: Cl, 20.6; F, 55.1; mol. wt., 345. Found: Cl, 21.0; F, 55.6, 55.7; mol. wt. (vapor density), 346, 349.

Both fractions gave positive tests with permanganate indicating the presence of unsaturated linkages, as well as positive tests with alcoholic alkali establishing the presence of active halogen.

**Chlorotridecafluoroethylcyclopentane.**—The unsaturated derivative of ethylcyclopentane, $C_7ClF_{11}$ (118 g., 0.36 mole), was passed over silver difluoride (20 moles) during a period of two and one-half hours at 295–300°. At the conclusion of the addition, the reactor was swept out with nitrogen for three hours. The product was collected in an ice-water trap followed by a dry ice trap. The crude product (115 g.) was washed twice with water and dried over Drierite. Rectification gave only one fraction, chlorotridecafluoroethylcyclopentane, $C_7ClF_{13}$; 67 g., b. p. 102°, $d^{20}_4$ 1.7999, $n^{20}D$ 1.3073.

*Anal.* Calcd. for $C_7ClF_{13}$: Cl, 9.6; F, 67.5; mol. wt., 366. Found: Cl, 9.8, 10.2; F, 67.8, 68.3; mol. wt. (vapor density), 369, 370.

The physical constants of the product are in close agreement with those of a compound $C_7ClF_{13}$ obtained by Perkin[9] and believed to be a chlorotridecafluoroethyl-

(9) Private communication, M. Perkin, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

cyclopentane, and differ appreciably from those of the four known chloroperfluoromethylcyclohexanes.[10]

**Acknowledgment.**—The authors express their indebtedness to the Hooker Electrochemical Company for defraying the expenses of this investigation and for supplying the hexachlorocyclopentadiene.

## Summary

The condensation of hexachlorocyclopentadiene with trichloroethylene in the presence of aluminum chloride produces 5-(1,2,2,2-tetrachloroethyl)-pentachlorocyclopentadiene, which undergoes dehydrohalogenation with aluminum chloride and alkali to form two isomeric chlorocarbons, $C_7Cl_8$, octachloro-1 or 2-vinylcyclopentadiene and octachloro-5-ethylidenecyclopentadiene, respectively. The former chlorocarbon was identified by its conversion to the unsaturated derivatives of ethylcyclopentane, $C_7ClF_{11}$ and $C_7Cl_2F_{10}$, chlorotridecafluoroethylcyclopentane, hexachloro-5,5-dimethoxy-1 or 2-vinylcyclopentadiene, hexachloro-2 or 3-vinylcyclopentadiene, hexachloro-2 or 3-vinylcyclopentadienone and its Diels–Alder dimer, and hexachlorovinylcyclopentenedione. The latter chlorocarbon was identified by its conversion to pentachlorocyclopentadienylideneacetyl chloride and functional derivatives thereof.

Whereas hexachlorocyclopentadiene readily undergoes the Diels–Alder reaction and also forms a dimer in the presence of aluminum chloride, the isomeric chlorocarbons $C_7Cl_8$ do not react with maleic anhydride under ordinary conditions. On the other hand, hexachloro-2 or 3-vinylcyclopentadienone dimerizes spontaneously via Diels–Alder.

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(10) B. W. Hotten, Ph.D. Dissertation, Purdue University, 1945; J. Davis, Ph.D. Dissertation, 1947.

(11) Original manuscript received May 17, 1948.

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[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY, PEORIA, ILLINOIS[1]]

# Interpretation of Lignin. III. The Synthesis and Polymerization of Stable Monomers[2]

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There have already been described syntheses of three polymeric materials; one of these had many of the properties of spruce lignin[5] and the others were methoxyl-free analogs.[6] The polymers resulted by chain-like intermolecular aldolization of certain aryl methylketoaldehydes. The monomeric units were prepared by the Fries rearrangement of the monoacetates of monohydroxyarylaldehydes and could not be isolated due to their reactivity under the anhydrous conditions of the rearrangement reaction—polymerization proceeding at once to give polydihydrobenzopyrones.

It would be of interest to demonstrate the existence of similar stable monomeric units and their separate polymerization. Such methylketoaldehydes should be available by two general methods, either nuclear acylation of *suitably chosen* hydroxyarylaldehydes or nuclear formylation of *suitably chosen* hydroxyaryl ketones. Inactivation of the carbonyl group in the initial material by any conventional method would most likely be ineffective because the acylated or formylated reaction product would likely polymerize as soon as the inactivated carbonyl group was liberated if it did not do so even before liberation of the protected group.

A much more elegant procedure is to prepare a monomer which, because of its configuration, cannot polymerize easily. This may be accomplished by selecting the starting material so that the carbonyl group already present is chelated with an hydroxyl group and the second carbonyl group enters ortho to another hydroxyl group. A second chelate ring will form at once and, at least in some cases, the monomer should be stable.

Six such schemes may be tried rather easily since the starting materials are accessible: the nuclear acylation of β-resorcylaldehyde or of pyrogallic aldehyde; the nuclear formylation of resacetophenone, 2,6-dihydroxyacetophenone, gallacetophenone and 2,4,6-trihydroxyacetophenone (phloracetophenone).

No success was had in acylation attempts and the application of the Gattermann procedure to gallacetophenone was equally futile. However, the formylation of the other three hydroxy ketones by the Gattermann procedure, modified in one instance, was entirely successful and satisfactory yields were obtained of the three methylketoaldehydes — 2,4 - dihydroxy - 3 - formylacetophenone, 2,6-dihydroxy-3-formylacetophenone and 2,4,6-trihydroxy-3-formylacetophenone. All three monomers are stable, easily crystalline with sharp melting points. All three are unchanged by 40% aqueous alkali and by 50% sodium methoxide in methanol, but may be polymerized to red or brown amorphous materials by

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(2) Article not copyrighted.

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(5) A. Russell, THIS JOURNAL, **70**, 1060 (1948).

(6) A. Russell, *ibid.*, **70**, 2864 (1948).

sufficiently strong alcoholic sulfuric acid. The polymers are inert alkali-soluble materials and have similar solubility characteristics in organic solvents to those previously described. Some part of the polymer from the trihydroxy compound is slightly water-soluble.

Although each ketoaldehyde has a more or less reactive nuclear position, it does not seem likely that the polymers are phenol–aldehyde condensation products because of steric effects. They are not polybenzopyrrilium salts for they contain no halogen after reprecipitation from alkaline solution with hydrochloric acid. They may be formulated as in previous cases.

## Experimental

**Polymerization of 2,4-Dihydroxy-3-formylacetophenone[7] to Poly(2,8)-7-Hydroxydihydrobenzopyrone.**—2,4-Dihydroxy-3-formylacetophenone (1 g.) was dissolved in ethanol (20 cc.) and concentrated sulfuric acid (7.5 cc.) added. The whole was refluxed for thirty minutes, cooled and the deep red reaction mixture poured into water (250 cc.). The red amorphous precipitate was collected and washed free from acid. It was dissolved in dilute sodium hydroxide (100 cc., 5%) and reprecipitated with ice-cold hydrochloric acid. It was collected, washed free from acid and divided empirically into two fractions: (1) ether–dioxane insoluble, (2) dioxane–water insoluble.

*Anal.*[8] Calcd. for $C_9H_8O_4$: C, 60.44; H, 4.44. $C_9H_6O_3$: C, 68.66; H, 4.94. Found for $C_9H_8O_4$: C, 64.4, 64.7; H, 4.86, 4.80. $C_9H_6O_3$: C, 66.5, 66.3; H, 4.84, 4.83.

**Formylation of 2,6-Dihydroxyacetophenone.**—2,6-Dihydroxyacetophenone[9] (15 g. 1 mol) was dissolved in anhydrous ether (250 cc.) and dry, freshly prepared zinc cyanide (23 g., 2 mol) added. Anhydrous hydrogen chloride was passed into the ice-cold solution to saturation (six to seven hours). The reaction mixture was allowed to stand overnight (sixteen hours) and the supernatant ether poured away from the dark brown oil which was washed twice with 50-cc. portions of dry ether. The washed oil was treated with water (200 cc.) and traces of ether evaporated. Upon steam distillation, 2,6-dihydroxy-3-formylacetophenone was collected as a colorless solid. Recrystallized from dilute ethanol it forms colorless needles m. p. 101–102°; yield, 6.2 g.

*Anal.* Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.44. Found: C, 60.1, 59.8; H, 4.19, 4.13.

**Polymerization of 2,6-Dihydroxy-3-formylacetophenone to Poly-(2,6)-5-Hydroxydihydrobenzopyrone.**—2,6-Dihydroxy-3-formylacetophenone (2 g.) was dissolved in ethanol (20 cc.) and alcoholic sulfuric acid (20 cc., 50%) added. The whole was refluxed for thirty minutes, cooled and poured into cold water. The precipitated amorphous brown solid was collected, dissolved in dilute sodium hydroxide (*ca.* 5%) and reprecipitated with ice-cold aqueous hydrochloric acid. The finely divided amorphous brown solid was collected, washed free from acid and dried.

*Anal.* Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.44. $C_9H_6O_3$: C, 66.66; H, 3.70. Found: C, 64.1, 64.0; H, 4.29, 4.47.

**2,4,6-Trihydroxy-3-formylacetophenone.**—Phloracetophenone (8.4 g., 1 mol) was dissolved in anhydrous ether (125 cc.) and dry zinc cyanide (12 g., 2 mols) added, followed by anhydrous aluminum chloride (13 g., 1 mol) dissolved in anhydrous ether (50 cc.). The reaction mixture was cooled in Dry Ice and saturated with dry hydrogen chloride (seven hours). An orange-yellow colored solid started to separate after about two hours. Separation was completed by allowing to stand overnight. The supernatant ether was poured away and the residue washed twice with 50-cc. portions of dry ether. Water (125 cc.) was added to the solid residue and traces of ether evaporated. Upon raising the temperature the reaction product dissolved and a yellowish-colored crystalline precipitate separated. The whole was cooled, the solid product collected and recrystallized from dilute ethanol (charcoal). 2,4,6-Trihydroxy-3-formylacetophenone forms pale yellow microcrystalline needles m. p. 176°. The yield was 7.1 g. (73%).

*Anal.* Calcd. for $C_9H_8O_5 \cdot H_2O$: C, 50.5; H, 4.7. Found: C, 50.8, 51.0, 50.5; H, 4.97, 4.84, 4.42.

**Polymerization of 2,4,6-Trihydroxy-3-formylacetophenone.**—2,4,6-Trihydroxy-3-formylacetophenone (2 g.) was dissolved in ethanol (20 cc.) and alcoholic sulfuric acid (20 cc., 50%) added. The whole was refluxed for thirty minutes, cooled and poured into water (200 cc.). The bright red flocculent precipitate was collected, dissolved in aqueous sodium hydroxide (*ca.* 5%) and reprecipitated by dilute aqueous hydrochloric acid. The bright red amorphous precipitate was collected, washed until free from acid and dried.

*Anal.* Calcd. for $C_9H_8O_5$: C, 55.10; H, 4.08. $C_9H_6O_4$: C, 60.7; H, 3.37. Found: C, 63.7, 62.8; H, 4.42, 4.20.

## Summary

To investigate further the polymerization reaction used in the synthesis of lignin-like materials, three stabilized monomeric units—2,4-dihydroxy-3-formylacetophenone, 2,6-dihydroxy-3-formylacetophenone and 2,4,6-trihydroxy-3-formylacetophenone have been prepared, and separately polymerized.

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(7) Shah and Shah, *J. Chem. Soc.*, 132 (1939).

(8) All analyses are microdeterminations by Mr. C. H. Van Etten and Mrs. M. B. Wiele of the laboratory.

(9) Russell and Frye, *Org. Syn.*, **22**, 81 (1941).

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

# The Photochemistry of Cellulose. Effects of Water Vapor and Oxygen in the Far and Near Ultraviolet Regions

BY HERBERT F. LAUNER[1] AND WILLIAM K. WILSON

In a current study of the photochemistry of cellulose it was observed that water vapor strongly inhibits photochemical changes in cellulose in the far ultraviolet at 254 millimicrons. Very dry cotton or wood celluloses were found to undergo greater changes in color, cuprammonium degree of polymerization and alpha cellulose than the same celluloses with normal moisture content. This result indicates that at least some of the water molecules are held by cellulose in a fundamental chemical combination, as contrasted with physical phenomena, such as condensation.

It was also observed that gaseous oxygen has no effect upon the rate of change in the far ultraviolet. These results are in strong contrast with those observed by the writers[1a] for the near ultraviolet, and with those observed by Stillings and Van Nostrand[2] in heterogeneous ultraviolet, and permit some new theories regarding the photochemical processes of the cellulose chain molecule.

## Experimental

**Methods of Analysis.**—Values for alpha cellulose and cuprammonium degree of polymerization of the celluloses were determined before, and within one to four hours after, irradiation, using standard methods.[3]

The degree of polymerization was calculated from viscosity, using the expression derived by Battista,[4] DP = 2160 [log (relative viscosity +1) − 0.267]. The values for DP, plotted against log (time of flow), give an almost straight line from DP = 50 to DP = 3000. Cuprammonium dispersions, 0.50% by weight in cellulose, exclusive of other substances present, were used for measurement. The writers use the concept of cuprammonium DP as a convenient comparison of extent of cellulose change at various levels, rather than as fundamental constants capable of rigorous proof.

Diffuse reflectance of the sheets was measured using a Beckman UV spectrophotometer, standardized against freshly smoked magnesium oxide.

**Samples Studied.**—Widely differing types of cellulose, derived from cotton and wood, in the form of specially made papers, were studied. The use of cellulose in sheet form permitted adequate temperature control during irradiation, and allowed accurate measurement of reflectance.

The papers were made in the paper mill at the National Bureau of Standards, and are described in Table I, in terms of origins of the fibers, added materials, and chemical characteristics. Further details are given elsewhere,[5] the cellulose sample number corresponding to that of the original paper.

TABLE I

CHARACTERISTICS OF CELLULOSES STUDIED

| Cellulose | Fiber origin, and other sheet components | Alpha cellulose content, % | Cuprammonium degree of polymerization (DP) |
|---|---|---|---|
| 1372 | Unused, unbleached cotton from cloth. No alum, rosin or clay | 96.6 | 1660 |
| 1178 | Unused, bleached cotton from cloth. Alum and clay | 92.4 | 695 |
| 1193 | Used, bleached cotton from cloth. Alum and clay | 87.7 | 575 |
| 1380 | Purified sulfite wood pulp. No rosin, alum or clay. Known commercially as alpha pulp | 91.8 | 1195 |
| 885 | Ordinary sulfite wood pulp. No rosin, alum or clay. No connection with No. 1380 | 77.2 | 645 |

**Apparatus.**—The apparatus consisted of special equipment, some of which has been previously described,[1,6] in which celluloses in paper sheet form were irradiated, with several light sources, without heat effects, in atmospheres of air or nitrogen of various moisture contents. Air was passed over anhydrous magnesium perchlorate, or over saturated solutions of lithium chloride or sodium bromide, producing relative humidities of 0.01,[6] 11 and 56%,[7] respectively. Nitrogen was passed over hot copper at 500° to remove oxygen, and was either dried by anhydrous magnesium perchlorate or moistened by alkaline pyrogallol solution. The desired atmospheres were continuously circulated at 5 liters/min. through these systems one and one-half hours before, and during, the irradiation. An electrically heated copper mirror,[8] and a weighed amount of magnesium perchlorate, present in the gas stream during irradiation, served as checks on oxygen and moisture contents when desirable.

During irradiation in the near ultraviolet, usually 92 hours, the sheets were held within 1–2° of 30° by sucking them against a thermostated metal backing, and by elimi-

(1) Now at Western Regional Research Laboratory, United States Department of Agriculture, Albany, California.

(1a) Herbert F. Launer and W. K. Wilson, *J. Research Natl. Bur. Standards*, **30**, 55 (Jan. 1943), (RP 1517).

(2) R. A. Stillings and R. J. Van Nostrand, THIS JOURNAL, **66**, 753 (1944).

(3) The methods were essentially those of the Technical Association of the Pulp and Paper Industry, 370 Lexington Ave., New York, N. Y. A minor difference lay in the use of 240 instead of 200 g. of ammonia per liter, in the cuprammonium test.

(4) O. A. Battista, *Ind. Eng. Chem., Anal. Ed.*, **16**, 351 (1944).

(5) Merle B. Shaw and Martin J. O'Leary, *et al.*, *J. Research Natl. Bur. Standards*, **21**, 671 (1938); **11**, 7 (1933), (RP 1149), (RP 574).

(6) Herbert F. Launer, *J. Research Natl. Bur. Standards*, **24**, 567 (1940), RP 1300.

(7) Institute of Paper Chemistry, Instrumentation Report No. 40 (Feb. 15, 1945).

(8) This consisted of pure sheet copper folded around a nichrome heater, fed by a Variac (a variable transformer), and included a thermojunction in contact with the copper. Oxygen concentration in a gas stream was determined by measuring the temperature at which the interference bluishness of the oxide was observable in five minutes, the instrument being standardized against gases of known oxygen content. The device appeared useful down to concentrations of oxygen near 0.01%; below that, the hydrogen, used to regenerate the copper, was apparently dissolved by the latter in sufficient amounts to render oxide formation erratic. This and other complications, such as the rate being dependent upon the nature of the carrier gas, discouraged further development of the device.

nating the infrared from a Fadeometer carbon arc, used as the light source, with a liquid filter, which also limited the spectrum to the region 330 to 750 millimicrons,[6] with the principal maximum at 388 and a minor one at 359 millimicrons.

For irradiation in the far ultraviolet, usually one-half hour, a General Electric 15-watt Germicidal mercury vapor lamp, operated at regulated 115 volts, was used. This type of lamp is a very convenient source of almost monochromatic ultraviolet at 254 millimicrons, thus avoiding the uncertainties introduced by other wave lengths. The energy output (manufacturers' data) consists of 55% ultraviolet, 2% visible and 43% heat, and of the ultraviolet, 97% is at 254 millimicrons. Since this type of lamp has a very low intensity it was found convenient to wrap the sheets tightly on its glass surface for irradiation. The lamp, which is a tube 15″ × 1″, was then slipped into a glass tube of 2-mm. greater diameter, maintained at 30°, so that the gases passed between the two tubes. The rubber stopper carrying the four lamp leads out of the system was located at the gas-exit end, so that the apparatus, from the conditioning tubes to the paper, was all-glass. Because of the small space between the tubes, the gases previously brought to 30°, streamed past the sheets at high velocity, thus removing considerable heat. By measurement with a thermojunction imbedded in a sheet of paper by a technique previously described,[6] the temperature inside the sheet during irradiation was found to be 40°.

The change in intensity of the lamp with use, and the uniformity of intensity along the central 12-inch portion was studied with light-sensitive paper.[9] The variation in uniformity of four 3-in. portions was found to be less than 3%.

## Results

The effects of gases upon the rates of photochemical change in cellulose varied greatly with the spectral energy distribution of the sources used and are presented accordingly. The types of cellulose, test methods, apparatus, gases, and significance of the terms used to differentiate the ultraviolet regions are described in the preceding sections.

**Effects of Water Vapor and Oxygen in the Far Ultraviolet.**—The effects of water vapor and oxygen in the far ultraviolet, shown in Table II, differed radically from any reported heretofore.[1,2] The effect of water vapor appeared to be decisive whereas that of oxygen, negligible.

TABLE II

EFFECT OF WATER VAPOR AND OXYGEN DURING IRRADIATION IN THE *Far* ULTRAVIOLET[a]

Decrease[b] in alpha cellulose percentage and DP (in parentheses) during irradiation in various atmospheres.

| Cellulose no. and type | Moist air | Dry air | Moist $N_2$ | Dry $N_2$ |
|---|---|---|---|---|
| 1372 | 1.0 | 5.0 | 1.3 | 5.7 |
| Cotton | (325) | (415) | (325) | (440) |
| 1380 | 2.3 | 6.4 | 2.3 | 7.0 |
| Wood | (200) | (260) | (225) | (260) |
| 885 | 2.5 | 6.2 | 2.4 | 4.5 |
| Wood | (50) | (65) | | |
| 1178 | 2.3 | 6.8 | 4.3 | 6.6 |
| Cotton | (80) | (85) | | |

[a] Irradiation for one-half hour at 254 millimicrons.
[b] Initial values of alpha cellulose and DP are given in Table I.

(9) Herbert F. Launer, *J. Research Natl. Bur. Standards*, **41**, 169 (1948), RP 1916.

For all types of celluloses studies, the drop in alpha cellulose was considerably greater in dry air and dry nitrogen, than in moist air and moist nitrogen, but practically the same in dry air and dry nitrogen or in moist air and moist nitrogen. These results are in agreement with those for DP when measured: for materials of low DP the test is insensitive and was not applied in all cases.

This effect of water vapor was not the result of absorption of ultraviolet by water vapor at this wave length. It can be calculated that even a 1-mm. thickness of liquid water will absorb only 0.1% at 254 millimicrons.[10]

The effect of water vapor was studied for intermediate values of relative humidity and for longer periods of irradiation, using cellulose 1372. The curves, given in Fig. 1, show that intermediate moisture content of the atmosphere during irradiation had an intermediate effect on the rate of decrease of alpha cellulose and DP. The curves in Fig. 1 also show that the effect of water vapor upon the rate persists until the cellulose has undergone considerable change (alpha cellulose = 85%, DP = 1150), after which the effect disappears, as seen from the fact that the curves tend to approach each other or become parallel, showing

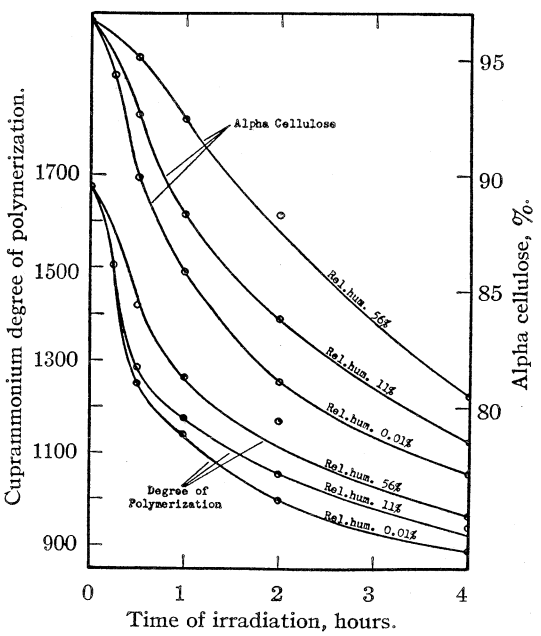



Fig. 1.—Effect of water vapor upon the rate of decrease of alpha cellulose percentage and degree of polymerization of cotton cellulose 1372 during irradiation in the far ultraviolet. The concentration of water vapor in each atmosphere is given in terms of per cent. relative humidity inscribed on each curve. Although the gases were at 30° the cellulose was at 40°. Using typical desorption isotherms, the calculated values for moisture content of the cellulose under the three conditions was 5.0, 2.0 and 0.002%.

(10) L. H. Dawson and E. O. Hulburt, *J. Optical Soc. Am.*, **24**, 175 (1934).

that the slopes and, therefore, the rates, reach common values.

The effect of oxygen was subjected to a similar detailed study for periods up to two hours of irradiation but no difference could be found between the rates in dry air and dry nitrogen. Experiments in pure, dry oxygen showed that DP, but not alpha cellulose values, were somewhat lower, by some 100 glucose units, after irradiation in pure oxygen than in air. Considering the small effect of the enormous differences in concentration, the role of oxygen, during irradiation in the far ultraviolet, can only be a minor one in the pure gas, and probably negligible in air.

The chemical results were borne out by reflectance measurements. The far ultraviolet was found to cause noticeable yellowing, the degree depending mainly upon water-vapor content. The yellowing was greater for dry air and dry nitrogen than for moist air and moist nitrogen. The reflectance curves over the region 360 to 500 millimicrons are shown in Fig. 2 for the typical example of cellulose 1380. The somewhat greater yellowing in dry and moist nitrogen than in dry and moist air is not believed to be due to an inhibitory effect of oxygen, but rather to a slight bleaching effect of ozone, the possibility of which must be considered when using lamps of this type in the presence of oxygen. Although the chemical results show no effect of ozone (with the possible exception of the results in pure oxygen, for which ozone might be held responsible), ozone being present only in the oxygen-containing atmospheres, it is not unreasonable to assume partial oxidation of the more readily oxidizable color bodies. Even so, such bleaching was not enough to reverse the curves for moist nitrogen and dry air.

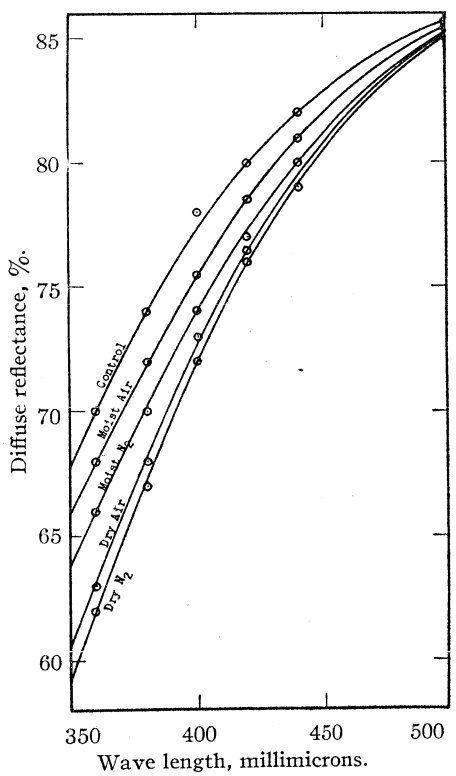



Fig. 2.—Effect of atmosphere upon the yellowing of wood cellulose no. 1380 during irradiation in the far ultraviolet for half an hour. The reflectances of sheets irradiated in the atmospheres as inscribed upon the curves are compared with the unexposed control.

The yellowing caused by far ultraviolet is of interest when compared to the effect of near ultraviolet, which the writers found bleaches cellulose.[1] It was shown that yellowing during irradiation in the near ultraviolet is the result of a thermal reaction which can be eliminated by control of cellulose temperatures.

It is not possible at present to state definitely that yellowing during irradiation in the far ultraviolet is a true photochemical reaction, although interior sheet temperatures during irradiation did not exceed 40°. Experiments were also conducted at 10, 20 and 30°, but no evidence of a temperature coefficient of yellowing was found. On the other hand, previously irradiated sheets yellowed extensively during storage in the dark, showing that yellowing does occur in the absence of light and must, therefore, be a thermal reaction. Such yellowing may, of course, be the result of another process. It is noteworthy that the yellowing during irradiation does not appear to be influenced by oxygen.

**Effects of Water Vapor and Oxygen in the *Near* Ultraviolet.**—The results for this region of the spectrum, given in Table III, confirm the writers' previous findings[1] for the effects of oxygen and water vapor, and those of others[2] for oxygen. The drop in alpha cellulose and in DP are considerably greater in the presence of oxygen than in its absence, for the various types of cellulose. In the presence of oxygen, water vapor promotes certain reactions and hinders others: the drop in DP of all of the celluloses is usually definitely greater in the presence of water vapor than in its

TABLE III

EFFECT OF OXYGEN AND WATER VAPOR DURING IRRADIATION IN THE *Near* ULTRAVIOLET[a]

Decreases in alpha cellulose percentage and DP (in parentheses) during irradiation in various atmospheres.

| Cellulose no. and type | Moist air | Dry air | Moist $N_2$ | Dry $N_2$ |
|---|---|---|---|---|
| 1372 | 0.4 | 1.1 | 0.0 | 0.2 |
| Cotton | (445) | (230) | (130) | (95) |
| 1380 | 4.0 | 2.8 | 0.8 | 1.1 |
| Wood | (385) | (250) | (115) | (120) |
| 885 | 5.9 | 4.5 | 1.5 | 1.4 |
| Wood | (110) | (55) | (50) | (40) |
| 1178 | 1.2 | 3.3 | 0.0 | 0.3 |
| Cotton | (65) | (20) | (0) | (0) |
| 1193 | 6.1 | 9.6 | 4.0 | 2.8 |
| Cotton | (75) | (75) | (0) | (0) |

[a] Irradiation for ninety-two hours with carbon arc.

absence, whereas the drop in alpha cellulose is greater in wood cellulose, and smaller in cotton cellulose, in the presence of water vapor, than in its absence. This confirms the previously found, more pronounced results[1] indicating a difference between wood and cotton celluloses. The results also illustrate that alpha cellulose and cuprammonium tests do not always coincide.

## Discussion

The lack of effect of oxygen and the inhibitory effect of water vapor show that oxidation and hydrolysis, the expected reactions, do not play a predominant part in the photochemical reactions of cellulose in the far ultraviolet. In the near ultraviolet, however, these reactions do play a dominant role.[1] When a light source including both of these regions is used, it is reasonable to expect a mixture of effects. This may explain why Stillings and Van Nostrand,[2] using a G.E. quartz Uviarc, model UA 26A2, which has about equal output in the near, middle and far ultraviolet regions,[11] did not observe the effects peculiar to each region. Upon decreasing the oxygen content in steps from 100 to 0.002% (the latter being the oxygen content of their purified nitrogen) they observed considerable decreases in the rate of change of cellulose. This apparently corresponded to the near ultraviolet portion of their spectrum, whereas some or all of the changes that persisted in purified nitrogen corresponded to the far ultraviolet, in which oxygen is without effect.

The differing mechanisms are explainable upon the basis of bond energies. Both the –C–C– and the –O–C– bonds, with dissociation energies near 80 kcal.,[12] are dissociable by a far-ultraviolet photon, corresponding to 112 kcal., without aid. However, the near-ultraviolet photons, in the cyanogen-band group at 388 to 385 millimicrons, corresponding to 73 to 74 kcal., lack the energy for such dissociation, and the deficit must be supplied by the exothermic reaction with oxygen, whose partial pressure thus becomes important in determining the rate in the near ultraviolet. The photons in the considerably weaker cyanogen band at 359 to 358 millimicrons, corresponding to 79 kcal., may barely have enough energy to cause disruption without the help of oxygen, in agreement with the writers' previous results[1] at low concentrations of oxygen, using the same carbon arc source.

The inhibitory effect of water vapor in the far ultraviolet indicates that some water molecules are in a fundamental chemical combination with cellulose. Such a combination is strongly indicated by the high heat of sorption and other departures from simple physical phenomena, as discussed by Valko[13] and is assumed to consist in bonds of –H–O–H– between proximate –OH groups along two or more molecular chains, producing a lateral, inter-chain "lacing," as discussed by Heuser.[14] These bonds are spontaneously formed, either at the expense of similar –H– bonds, than which they are more stable, as shown by the free energy decrease of water-bond formation, $-\Delta F = 3200$ cal./mole,[15] or they may be formed in addition to the existing –H– bonds with unsaturated –OH groups.[16] In either case it could be expected that the introduction of $H_2O$ molecules into the inter-chain spaces would result in decreased freedom of displacement for those C-atoms in the vicinity of a –H–O–H– bond. Thus, when a far-ultraviolet photon is absorbed, the deformation and disruption of a given glucose unit may be rendered less likely when such bonds exist nearby. The effect of deformability within the cellulose macro-molecule upon photochemical change has been indicated by the results of Mason and Rosevear.[17]

This explanation of the inhibition of the photochemical reaction by water vapor would indicate that the initial disruption occurs in the vicinity of C-atoms 2 or 3, rather than at the glycosidic linkage. This would in turn furnish a reasonable explanation for the instability of previously irradiated cellulose, observed by the writers[1] and confirmed by Heuser and his co-workers, Stillings, Van Nostrand and Chamberlin.[2,18] If, for example, the bond between C-atoms 1 and 2 were disrupted, this would not necessarily cause immediate rupture of the cellulose chain, but C-atom 1, attached now to three electronegative groups, would become sensitive to future thermal oxidation, thus disrupting the chain.

The –C–O– group is usually held responsible for the broad absorption band below 300 millimicrons, but such absorbed energy can migrate rapidly to another part of the molecule, as discussed by Frank and Teller.[19] Such transfer of absorbed energy to a more reactive group occurs even between discrete particles, as in photochemical sensitization.

It is of interest to note that the region of moisture content, 0 to 5%, for the results shown in Fig. 1, are essentially within the region found by Magne, Portas and Wakeham[20] to correspond to hydrogen-bonded water in cotton fibers.

Referring again to Fig. 1, it is of further interest to note that the first addition of water vapor to the dry cellulose has a smaller inhibitory effect upon

(11) L. B. Johnson and S. B. Webster, *Rev. Sci. Inst.*, **9**, 325 (1938).

(12) Kenneth S. Pitzer, THIS JOURNAL, **70**, 2140 (1948).

(13) E. I. Valko, "High Polymers V, Cellulose," Emil Ott, Ed., Interscience Publ. Inc., New York, p. 379.

(14) Emil Heuser, "Chemistry of Cellulose," Wiley and Sons, New York, 1944.

(15) Alfred J. Stamm and W. Karl Loughborough, *J. Phys. Chem.*, **39**, 121 (1935).

(16) S. M. Neale and W. A. Stringfellow, *Trans. Faraday Soc.*, **37**, 525 (1941).

(17) C. W. Mason and F. B. Rosevear, THIS JOURNAL, **61**, 2995 (1939).

(18) E. Heuser and George N. Chamberlin, *ibid.*, **68**, 80 (1946).

(19) James Frank and Edw. Teller, *J. Chem. Phys.*, **6**, 861 (1938).

(20) Frank C. Magne, H. J. Portas and Helmut Wakeham, THIS JOURNAL, **69**, 1896 (1947).

the chemical changes than the second addition of water vapor. This does not coincide with the known energy changes of hydration,[15] but a consideration of the molecular processes involved shows that no correlation is to be expected. When a photon is captured by dry, *i. e.*, 0.002%-moisture, cellulose, corresponding to one water-molecule per three cellulose chains of some 1700 glucose units each, the probability that the capture and C–C-bond rupture will occur near a water-bridge is very small. Even if the moisture content were increased 100-fold to 0.2%, corresponding to 30 water-molecules per chain of 1700 glucose units, the probability of a photon rupturing an adjacent C–C-bond is still very small. Thus, the first increments of water cannot be expected to exert much inhibitory effect, and proportionality of effect cannot obtain until a sizable fraction of the glucose units are water-bonded.

The depolymerizing action of water vapor observed during the ninety-two hours of irradiation in the near ultraviolet is a slow reaction which probably occurs to a slight extent in the one-half hour of irradiation in the far-ultraviolet, and which would probably manifest itself upon extensive irradiation in the latter region. This may partially explain the fact that the curves in Fig. 1 approach each other for longer periods. Such an approach would, furthermore, be a result of progressive depolymerization, inasmuch as water bonding probably decreases as the chains shorten and start to lose their high-polymeric character.

The differing effects of water vapor during irradiation in the near ultraviolet upon the alpha cellulose values of wood and cotton celluloses, as seen from Table III, appear to arise from unknown differences between these two types of cellulose.

Finally, it is of interest to attempt a calculation of the quantum efficiency, that is, the frequency with which cellulose chains are ruptured by captured photons at 254 millimicrons.

At this wave length the lamp radiates 2.9 watts (manufacturers' data) or $3.7 \times 10^{18}$ quanta/sec., over its arc length, 14 in. During one-half hour, one piece of paper, no. 1372, 3 in. wide, wrapped completely around the lamp, absorbs $1.4 \times 10^{21}$ quanta, assuming practically no loss by transmission through the paper (0.08 mm. thickness). This amount of paper corresponds to 0.5 g. cellulose or $1.9 \times 10^{21}$ glucose units. Since there are 1660 glucose units in an average chain (*i. e.*, DP = 1660) of this cellulose, there are $1.1 \times 10^{18}$ chains before irradiation. From the expression derived by Sakurada and Okamura[21] relating change in DP to the number of scissions, $s$, per chain

$$\frac{\text{DP final}}{\text{DP initial}} = \frac{2}{s^2}(s - 1 + e^{-s})$$

and from the final DP = 1245, after irradiation, in dry air, it may be calculated that, on the average, 0.93 scission per chain molecule, or $1.0 \times 10^{18}$ scissions occurred. Thus $1.4 \times 10^3$ quanta or photons were required per scission, or roughly every thousandth photon encountered conditions favorable for a rupture of a cellulose chain molecule. Actually, the number of successful encounters was probably larger than this, inasmuch as a disproportionately large number of scissions may have occurred in the leading layers of cellulose chains, without greatly affecting the cuprammonium DP values.

**Acknowledgment.**—The authors acknowledge with thanks the assistance and coöperation of Alice J. Padgett and Frances Dodge Gagliardi.

## Summary

1. Water vapor was found to retard, and oxygen was found to be without effect upon, the decrease in alpha cellulose and the depolymerization, of cotton and wood celluloses, during irradiation in the far ultraviolet. The reverse of both of these effects was confirmed for the near ultraviolet.

2. The contrasting behavior of cellulose in the two spectral regions is ascribed to bond energies in the molecular chain, in relation to the photon energies involved. Far ultraviolet photons have sufficient energy to disrupt the bond, whereas most near ultraviolet photons do not, and require participation of oxygen.

3. The retarding action of water vapor in the far ultraviolet is ascribed to inter-chain water bridging with the hydroxyl group on carbon atoms 2 or 3, thus interfering with the freedom of displacement of the carbon atom. This supports the theory that a part of the moisture in cellulose is in a fundamental chemical combination.

4. It was found that only one photon out of $10^3$, at 254 millimicrons, encounters conditions favorable for a rupture of the cellulose molecular chain.

WASHINGTON, D. C. RECEIVED JULY 28, 1948

(21) I. Sakurada and S. Okamura, *Z. physik. Chem.*, **A187**, 289 (1940).

[CONTRIBUTION OF THE RESEARCH LABORATORY, GENERAL ELECTRIC CO.]

# Polydimethylsilanes

BY CHARLES A. BURKHARD

Many publications dealing with the alkyl-substituted polysiloxanes have appeared in recent years,[1] but only very little interest has been shown in the alkyl-substituted polysilanes. An investigation of this latter type of compound has now been made. These new materials are the first alkyl-substituted polysilanes reported in which more than two silicon atoms are directly united. Hexamethyldisilane,[2] hexaethyldisilane,[2c,3] and hexa-*n*-propyldisilane[3e] have been prepared previously.

A similar investigation has been reported by Kipping[4] and co-workers in which the preparation and properties of aryl-substituted polysilanes are given. From diphenyldichlorosilane and molten sodium, Kipping was able to prepare several polydiphenylsilanes, which included a "*saturated*" $Si_4(C_6H_5)_8$ compound and a second $Si_4(C_6H_5)_8$ compound, which was reported to be an "*unsaturated*" compound. This apparent "*unsaturation*" was thought to be due to the presence of two tervalent silicon atoms in the $Si_4(C_6H_5)_8$ molecule. In addition to these materials, Kipping also isolated several $[Si(C_6H_5)_2]_n$ compounds in which $n$ varied from approximately six to eight as determined from chemical evidence. The extreme insolubility of these compounds made it impossible to obtain molecular weights. The majority of the product obtained from the reaction of sodium with diphenyldichlorosilane was soluble in the inert hydrocarbon solvent, and on evaporation of the solvent was found to be a glue-like or resinous mass.

In contrast to these results, it has now been found that dimethyldichlorosilane reacts with molten sodium to give a major quantity of hydrocarbon-insoluble material together with a minor quantity of hydrocarbon-soluble material. Analysis of the hydrocarbon-insoluble product (I) shows it to be a polymer of $[(CH_3)_2Si]$. Its extreme insolubility has made it difficult to make accurate molecular weight determinations. However, a molecular weight was obtained ebullioscopically in biphenyl and the results indicate an average degree of polymerization of approximately 55. X-Ray powder data indicate that this material is somewhat crystalline. It is unstable thermally; in fact, if heated in air at 200° for sixteen hours, a gel-like material is produced.

Isolation of hydrocarbon-soluble products by distillation at reduced pressure was difficult as evidenced by erratic heat-temperature readings in the column. However, it was possible to isolate a crystalline material, which when recrystallized from methanol and water, was shown by analytical and molecular weight data to be the cyclic hexamer, dodecamethylcyclohexasilane (II), $[(CH_3)_2Si]_6$.

After II was recovered, a high boiling residue (III) remained which is a grease-like solid at room temperature. Analytical data indicate that III is a copolymer of $[(CH_3)_2Si]$ and $[(CH_3)_2SiO]$ units. A small amount of chlorine is also present in this product. Analytical data indicate that on an average approximately three silicon atoms are directly united for each siloxane linkage present.

Martin[5] has reported hydrocarbon-insoluble polymers which contain both Si–Si and Si–O–Si linkages. These materials were prepared by the reaction of the methyl Grignard reagent with hexachlorodisilane followed by hydrolysis of the remaining silicon–halogen bonds. From a consideration of the method of preparation and the reported analytical data, it is seen that the polymers obtained by Martin have no more than two silicon atoms directly united and that the methyl to silicon ratio is less than two.

The blue color[4a] that develops when the arylchlorosilanes react with molten sodium is observed also when dimethyldihalogenosilanes are allowed to react with molten sodium. In both cases, the blue color is discharged by water. The development of this blue color recalls the reaction in which ketones, that are incapable of forming enols, form colored metal ketyls. For example, benzophenone reacts with sodium to form a blue derivative, which dimerizes to form a new carbon–carbon bond.[6] The blue color of the metallic ketyls is discharged by water.

$$(C_6H_5)_2CO + Na \longrightarrow (C_6H_5)_2C{-}O{-}Na \quad (1)$$

$$2(C_6H_5)_2C{-}O{-}Na \longrightarrow \begin{matrix}(C_6H_5)_2C{-}O{-}Na\\ |\\ (C_6H_5)_2C{-}O{-}Na\end{matrix} \quad (2)$$

From the similarity in behavior between the blue substances formed in the reaction of sodium with diorganodihalogenosilanes and the metallic

(1) Burkhard, Rochow, Booth and Hartt, *Chem. Rev.*, **41**, 97 (1947).

(2) (a) Bygden, *Ber.*, **45**, 707 (1912); (b) Blitz and Lemke, *Z. anorg. allgem. Chem.*, **186**, 387 (1930); (c) Dolgov and Volnov, *Zhur. Obshchei Khim. Ser.*, **1**, 91 (1931); (d) Brockway and Davidson, THIS JOURNAL, **63**, 3287 (1941).

(3) (a) Friedel and Ladenburg, *Compt. rend.*, **68**, 923 (1869); (b) *Ann.*, **203**, 241 (1880); (c) *Ann. chim. phys.*, **289**, 390 (1880); (d) Kraus and Nelson, THIS JOURNAL, **56**, 195 (1934); (e) Schumb and Saffer, *ibid.*, **61**, 363 (1939).

(4) (a) Kipping and Sands, *J. Chem. Soc.*, **119**, 830 (1921); (b) Kipping, *ibid.*, **123**, 2590 (1923); (c) **123**, 2598 (1923); (d) **125**, 2291 (1924); (e) 2719 (1927); (f) Kipping, *ibid.*, 2728 (1927); (g) Steele and Kipping, *ibid.*, 1431 (1928); (h) Kipping and Murray, *ibid.*, 360 (1929); (i) Kipping, Murray and Maltby, *ibid.*, 1180 (1929); (j) Kipping and Short, *ibid.*, 1029 (1930); (k) Kipping, Blackburn and Short, *ibid.*, 1290 (1931).

(5) (a) Martin, *Ber.*, **46**, 2442 (1913); (b) **46**, 3289 (1913).

(6) Bachman, THIS JOURNAL, **55**, 1179 (1933).

ketyls, it is reasonable to believe that a radical of the type $R_2Si-O-Na$ is formed which would be capable of forming Si–Si bonds by subsequent dimerization. The presence of oxygen can be explained by contact with air during the reaction or from the oxide film on the surface of the sodium.

$$R_2SiCl_2 \xrightarrow{Na + O_2} R_2Si(-O-Na)_2 \quad (3)$$

$$2R_2SiONa \longrightarrow \begin{matrix} R_2Si-O-Na \\ | \\ R_2Si-O-Na \end{matrix} \quad (4)$$

Further evidence in support of the structure for this intermediate radical is given by the fact that dimethyldibromo- and dimethyldichlorosilane both react with molten sodium to give this blue color. If sodium is to be expected to form a radical with the dimethylsiloxane unit which is similar to the radical that was formed with benzophenone, it is required that the "*enol*" form of the siloxane be incapable of existence.

The formation of the "*enol*" form of the siloxane requires the simultaneous formation of a carbon–silicon double bond; however, attempts to synthesize carbon–silicon double bonds have met with failure in spite of many diligent trials.[7] Thus it is reasonable to assume that the dimethylsiloxane unit differs from its carbon analog, acetone, in that it is incapable of existing in an enolic form. Therefore, the formation of the radical $R_2Si-O-Na$ in which R is methyl or phenyl is not considered unreasonable.

Kipping[8] experienced considerable difficulty in hydrolyzing the Si–Si bonds in the polydiphenylsilanes with aqueous and alcoholic alkali. Kipping found, however, that moist piperidine would hydrolyze these materials quantitatively. In contrast I is not hydrolyzed by aqueous caustic or by moist piperidine. In order to hydrolyze this compound, it was found necessary to heat it with alkali in hexanol.

## Experimental

**Reaction of Dimethyldihalogenosilanes with Sodium.**—As no reaction is obtained until the sodium is molten, it is necessary to use either a halogenosilane whose boiling point is greater than 98° or carry out the reaction in a sealed autoclave under elevated temperature and pressure. The products in either case appear to be the same. Dimethyldibromosilane, b. p. 112°, can be used when the reaction vessel is at atmospheric pressure; however, it was more advantageous to use dimethyldichlorosilane in a sealed autoclave.

Two preparations were made using the following charge of 1 lb. of sodium metal, from which most of the oxide film had been removed, 700 g. dimethyldichlorosilane (54.9% $Cl_2$) and 1 l. of dry benzene in each run. These materials were sealed in a 3 l. steel autoclave. The autoclave was heated and shaken. An exothermic reaction developed after the temperature had exceeded that of the melting point of the sodium. The pressure rose rapidly to 220 p. s. i. and the temperature to 200°. After cooling, the reaction vessel was again heated at 115° for approximately ten hours with continuous shaking. The extent of reaction as measured by titration of hydrolyzable halogen in the benzene solution was shown to vary between 95 and 99.6%.

The products were removed from the autoclave and filtered. A blue-colored residue and excess sodium were retained by the filter. The blue residue and excess sodium was added to a mixture (*ca.* 50–50) of glacial acetic acid and 95% ethanol to decompose the excess sodium. When the decomposition of the sodium had been completed, the entire mixture was added to water. By this time, the blue color had been discharged completely. The white powder, I, that formed was washed with water until free of acid and chloride ion. The resulting product was then dried at 75° *in vacuo*.

The benzene was removed from the combined filtrates leaving a solid product which yielded II on distillation. No definite boiling point of the fraction could be obtained as crystals of II formed, and the temperature was erratic. When the head temperature reached 170° at 2 mm., the distillation was stopped. A residue, III, remained which is grease-like. Products I and II are shown to be $[(CH_3)_2Si]_x$ polymers, and molecular weight determinations indicate that $x$ is approximately 55 for I and 6 for II. Compound II was recrystallized from methanol and water. Using a melting point block fitted with Nicol prisms, it was observed that II shows a change of its crystal form at 74°. This change is reversible if II is not heated to a temperature which is much greater than 74°, and at 100° II appears to sublime.

*Anal.* Calcd. for I, $C_2H_6Si$: C, 41.32; H, 10.41; Si, 48.72. Found: C, 40.1, 40.4; H, 10.1, 10.2; Si, 48.0; mol. wt.,[9] *ca.* 3200.

*Anal.* Calcd. for II, $C_{12}H_{36}Si_6$: C, 41.32; H, 10.41; Si, 48.72; mol. wt., 348. Found: C, 40.9, 41.2, 40.7; H, 10.6, 10.4, 10.2; Si, 47.2; mol. wt.,[10] 318.

*Anal.* Found for III: C, 38.6, 38.1; H, 9.4, 9.2; Si, 42.8, 42.2; Cl, 2.9, 2.8; mol. wt.,[11] 1700.

The yield of I from the two runs is 412 g. The yield of II and III is 237 g.

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## Summary

1. The reaction of molten sodium with dimethyldichlorosilane has been shown to give polydimethylsilanes as the major product.

2. Dodecamethylcyclohexasilane has been isolated and characterized.

3. A colored radical of the type $R_2Si-O-Na$, which appears to be similar to the metallic ketyls, is postulated as a by-product of the reaction of diorganodihalogenosilanes and sodium.

SCHENECTADY, N. Y. RECEIVED OCTOBER 25, 1948

(7) (a) Schlenk and Renning, *Ann.*, **394**, 221 (1912); (b) Kipping and Sands, *J. Chem. Soc.*, **119**, 831 (1921); (c) Kipping, *ibid.*, 104 (1927).

(8) Kipping and Sands, *ibid.*, **119**, 848 (1921). Schumb and Saffer also report that hexa-*p*-tolyldisilane and hexa-*n*-propyldisilane are stable toward hydrolysis with dilute aqueous alkali; see ref. 3e.

(9) Molecular weight determined ebulliscopically with diphenyl.

(10) Cyclohexane used in cryoscopic determination. Value obtained by extrapolation to zero concentration in four separate determinations.

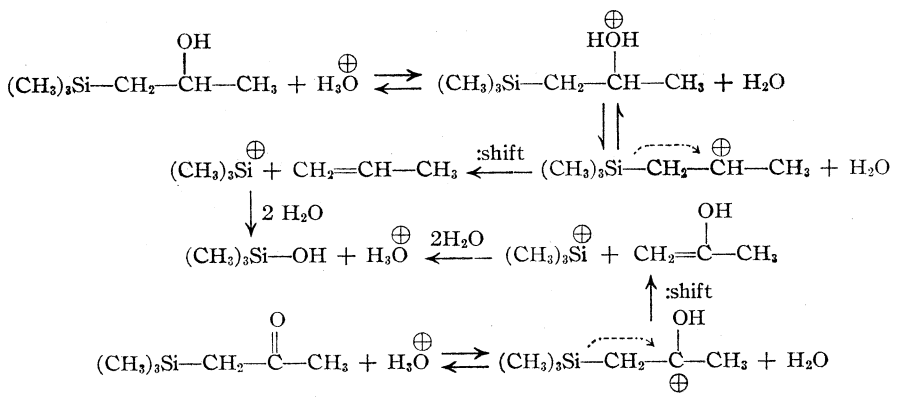
(11) Molecular weight determined using cyclohexane.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Organosilicon Chemistry: The Mechanisms of Hydrolysis of Triphenylsilyl Fluoride and Triphenylmethyl Fluoride in 50% Water–50% Acetone Solution[1]

BY C. GARDNER SWAIN, RAMON M. ESTEVE, JR., AND RICHARD H. JONES

Certain of the reactions of organosilicon compounds have been written by Whitmore and coworkers as proceeding through siliconium ion intermediates, analogous to the carbonium ion intermediates well established for similar reactions of carbon compounds. For example, the fission (cleavage) of trimethyl-$\beta$-hydroxypropylsilane by dilute acids or of trimethylsilylacetone even in neutral water have been represented with siliconium ion intermediates.[2] Siliconium ions have been used by these investigators primarily as *formal* ways of explaining the products obtained, since evidence was really not available to permit evaluation of their importance or stability as reaction intermediates. It is therefore of interest to determine how stable and how common are siliconium ion intermediates relative to analogous carbonium ions.



These intermediates with a positive charge on silicon might seem particularly likely, *a priori*, in view of the fact that silicon is a more electropositive element than carbon, and even has some of the properties of the metals.[3] Therefore, one might expect silicon to form a positive ion even more readily than carbon.

The carbonium ion intermediate in the hydrolysis of triphenylmethyl (trityl) halides is one of the stablest known carbonium ions.[4] The *formally analogous* hydrolysis of triphenylsilyl (hereafter referred to as "trisyl") halides was therefore studied to see whether the same mechanism (here involving a siliconium ion intermediate) really held. The results indicate that this is not the case. Parallel kinetic experiments have been carried out with trisyl fluoride and trityl fluoride to test the effect on the rate of hydrolysis caused by variations in *p*H, *p*-substituents, concentration of inert salt, and composition of the solvent.

**Data.**—The results of typical runs are summarized in Table I and detailed data are given for three runs with trisyl fluoride in Table II and Fig. 3 and for one run with trityl fluoride in Table III and Fig. 4.

Trisyl fluoride reacts more than a million times as rapidly with hydroxide ion (calculated for 1 *M*) as with water in 50% water–50% acetone solution (see experimental section on procedure), whereas trityl fluoride reacts at the same rate regardless of *p*H. Fluorosilanes have been reported[5] to react only slowly with strong alkali even when heated. We observed the same results with trisyl fluoride when working in a pure water solvent, but this was due to the existence of a heterogeneous system. In solution, reaction occurs very rapidly.

Substitution of three *p*-methyl groups in trisyl fluoride *decreases* the rate of reaction with water about five-fold, whereas *p*-alkyl substitution *increases* the rate of solvolysis of trityl halides.[6]

The salt and solvent effects are positive, *i. e.*, the rate increases with concentration of inert salt or increasing polarity of the solvent, for both trisyl fluoride and trityl fluoride, although the effects are much stronger with trityl fluoride.

The activation energy for hydrolysis of trisyl

(1) Paper presented at the St. Louis meeting of the American Chemical Society, September 6, 1948. This is paper III in the series, "Concerted Displacement Reactions"; for paper II, see Swain and Eddy, THIS JOURNAL, **70**, 2989 (1948).

(2) Whitmore, *Chem. Eng. News*, **26**, 672 (March 8, 1948); Whitmore, Sommer, Gold and Van Strien, THIS JOURNAL, **69**, 1551 (1947).

(3) Rochow, "Chemistry of the Silicones," Wiley and Sons, Inc., New York, N. Y., 1946, pp. 3–4. From the heats of formation of Si–Si, C–C, Si–C, Si–H, C–H, and H–H single bonds, it appears that the electronegativity of silicon is 1.8 compared to 2.1 for hydrogen and 2.5 for carbon (Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1945, pp. 58–70).

(4) From conductivity of halides in liquid sulfur dioxide it is clear that triphenylcarbonium ion is enormously stabler than trimethylcarbonium ion (Hantzsch, *Ber.*, **54**, 2573 (1921); Walden, *Z. physik. Chem.*, **43**, 454 (1903)), yet even the latter is stable enough to exist as a relatively free intermediate, as indicated by the noncorrelation of product composition with rate in the solvolysis of *t*-butyl halides in water-alcohol mixtures [Bateman, Hughes and Ingold, *J. Chem. Soc.*, 881 (1938); Cooper, Hughes and Ingold, *ibid.*, 1280 (1937)].

(5) Pearlson, Brice and Simons, THIS JOURNAL, **67**, 1769 (1945).

(6) Three *p*-*t*-butyl substituents increase the rate of methanolysis of trityl chloride in benzene solution at 25° thirty fold (Swain, THIS JOURNAL, **70**, 1119 (1948)). One *p*-methyl substituent increases the rate of ethanolysis of trityl chloride four-fold in 40% ethanol-60% ether at 25° (Nixon and Branch, *ibid.*, **58**, 496 (1936)).

TABLE I

REACTIONS OF TRIPHENYLSILYL AND TRIPHENYLMETHYL FLUORIDES

| Run | Fluoride | Concn., *M* | Water, %[a] | Temp., °C. | Method | $k$(min.$^{-1}$)[d] |
|---|---|---|---|---|---|---|
| 26 | $(C_6H_5)_3Si$ | 0.0186 | 16.6 | 45 | A | $0.52 \pm 0.05 \times 10^{-4}$ |
| 25 | $(C_6H_5)_3Si$ | .0186 | 33.3 | 45 | A | $2.4 \pm .3 \times 10^{-4}$ |
| 31 | $(C_6H_5)_3Si$ | .0186 | 33.3[b] | 45 | A | $2.9 \pm .3 \times 10^{-4}$ |
| 36 | $(C_6H_5)_3Si$ | .0110 | 40 | 25 | A | $0.87 \pm .09 \times 10^{-4}$ |
| 27 | $(C_6H_5)_3Si$ | .0186 | 41.7 | 45 | A | $3.5 \pm .4 \times 10^{-4}$ |
| 28 | $(C_6H_5)_3Si$ | .0093 | 50 | 45 | A | $7.0 \pm .7 \times 10^{-4}$ |
| 29 | $(C_6H_5)_3Si$ | .0093 | 50[b] | 45 | A | $9.1 \pm 1.0 \times 10^{-4}$ |
| 14, 20 | $(C_6H_5)_3Si$ | .00085 | 50 | 45 | C | $7.2 \pm 0.8 \times 10^{-4}$ |
| 32 | $(C_6H_5)_3Si$ | .0104 | 40 | 100 | B | $1.35 \pm .02 \times 10^{-2}$ |
| 33 | $(C_6H_5)_3Si$ | .0104 | 40[b] | 100 | B | $1.40 \pm .02 \times 10^{-2}$ |
| 34 | $(C_6H_5)_3Si$ | .0104 | 50 | 100 | B | $1.73 \pm .02 \times 10^{-2}$ |
| 35 | $(p\text{-}H_3C\text{–}C_6H_4)_3Si$ | .00918 | 40 | 100 | B | $3.0 \pm .3 \times 10^{-3}$ |
| 18 | $(p\text{-}H_3C\text{–}C_6H_4)_3Si$ | .00091 | 50 | 45 | C | $1.3 \pm .2 \times 10^{-4}$ |
| 45 | $(C_6H_5)_3C$ | .00124 | 40 | 25 | D | $1.25 \pm .13 \times 10^{-2}$ |
| 41 | $(C_6H_5)_3C$ | .00124 | 50 | 25 | E | $5.3 \pm .6 \times 10^{-2}$ |
| 46 | $(C_6H_5)_3C$ | .00124 | 50 | 25 | D | $5.2 \pm .6 \times 10^{-2}$ |
| 44 | $(C_6H_5)_3C$ | .00124 | 60 | 25 | D | $7.9 \pm .8 \times 10^{-1}$ |
| 54 | $(C_6H_5)_3O$ | .00100 | 50 | 45 | E | $2.3 \pm .3 \times 10^{-1}$ |
| 56 | $(C_6H_5)_3C$ | .00100 | 95[c] | 25 | E | $8.2 \pm .9 \times 10^{-3}$ |
| 55 | $(C_6H_5)_3C$ | .00100 | 95[c] | 45 | D | $4.2 \pm .4 \times 10^{-2}$ |
| 50 | $(C_6H_5)_3C$ | .00100 | 95[c] | 45 | E | $4.6 \pm .5 \times 10^{-2}$ |

[a] The part of the medium not indicated is acetone. [b] Sodium perchlorate was present to the extent of 0.52 *M*, 0.36 *M*, and 0.26 *M* in runs 31, 33, and 29, respectively. [c] 95% methanol, 5% acetone, no water present. [d] First order rate constant (equal to 0.693 divided by the half life).

TABLE II

HYDROLYSIS OF 0.0093 *M* TRIPHENYLSILYL FLUORIDE IN 50% WATER–50% ACETONE SOLUTION AT 45°, RUN 28, METHOD A

| Minutes | 0.0385 *N* cc. $Th(NO_3)_4$ | Reaction, % |
|---|---|---|
| 0.0 | 0.05 | 0.0 |
| 5.5 | 0.50 | 19.1 |
| 19.0 | 1.40 | 57.5 |
| 23.5 | 1.57 | 64.7 |
| 30.0 | 1.72 | 71.1 |
| 42.0 | 1.95 | 80.9 |
| 42.8 | 2.01 | 83.5 |
| 47.3 | 2.12 | 88.1 |
| 200 | 2.40 | 100.0 |

TABLE III

METHANOLYSIS OF 0.00100 *M* TRIPHENYLMETHYL FLUORIDE IN 95% METHANOL–5% ACETONE SOLUTION AT 25°. RUN 56, METHOD E

| Minutes | 0.0546 *M*, cc. $NaOCH_3$ | Reaction, % |
|---|---|---|
| 0.0 | 0.00 | 0.0 |
| 1.0 | .27 | 1.0 |
| 4.0 | .30 | 3.9 |
| 7.0 | .33 | 6.7 |
| 12.5 | .36 | 9.6 |
| 15.5 | .39 | 12.5 |
| 21.0 | .43 | 16.3 |
| 24.0 | .45 | 18.3 |
| 28.0 | .48 | 21.2 |
| 31.3 | .50 | 23.1 |
| 35.5 | .53 | 26.0 |
| 41.0 | .56 | 28.8 |
| 46.0 | .59 | 31.7 |
| 52.0 | .62 | 34.6 |
| 57.0 | .65 | 37.5 |
| 63.0 | .68 | 40.4 |
| 68.0 | .71 | 43.3 |
| 75.0 | .74 | 46.2 |
| 82.0 | .77 | 49.0 |
| 89.5 | .80 | 51.9 |
| 96.0 | .83 | 54.8 |
| 104 | .86 | 57.6 |
| 111 | .89 | 60.6 |
| 121 | .92 | 63.4 |
| 131 | .95 | 66.3 |
| 138 | .97 | 68.8 |
| 170 | 1.04 | 75.0 |
| 195 | 1.11 | 81.7 |
| 360 | 1.24 | 94.2 |
| 720 | 1.30 | 100.0 |

fluoride is 13.6 ± 0.5 kcal. in 50% water–50% acetone, 15.5 ± 0.5 kcal. in 40% water–60% acetone. For solvolysis of trityl fluoride the figures are 13.0 ± 0.6 kcal. in 50% water–50% acetone and 14.9 ± 0.5 kcal. in 95% methanol–5% acetone.

**Discussion.**—The mechanism of hydrolysis of trisyl fluoride is evidently quite different from that of trityl fluoride. The above experimental facts can be used to disprove all but one out of the following limited group of mechanisms[7] for

(7) This group includes the mechanisms commonly written. Other mechanisms can easily be written, but seem less probable, more complicated, or not really physically different from one of the five given. In these mechanisms all ions are understood to be hydrated and two (or more) solvent molecules are understood to play the role of reactants in solvating both anion and cation forming in each ionization step; these solvent molecules are omitted only to save space. The conjugate acid of silanol is the primary product of all these mechanisms. It will, of course, come into rapid equilibrium with silanol, water and oxonium ion, after its formation.

the hydrolysis of trisyl fluoride under our acid conditions.

$$(C_6H_5)_3SiF \xrightarrow{\text{slow}} (C_6H_5)_3Si^{\oplus} + F^{\ominus} \quad (1a)$$

$$(C_6H_5)_3Si^{\oplus} + H_2O \xrightarrow{\text{fast}} (C_6H_5)_3SiOH_2^{\oplus}$$

$$(C_6H_5)_3SiF \xrightleftharpoons{\text{fast}} (C_6H_5)_3Si^{\oplus} + F^{\ominus} \quad (1b)$$

$$(C_6H_5)_3Si^{\oplus} + H_2O \xrightarrow{\text{slow}} (C_6H_5)_3SiOH_2^{\oplus}$$

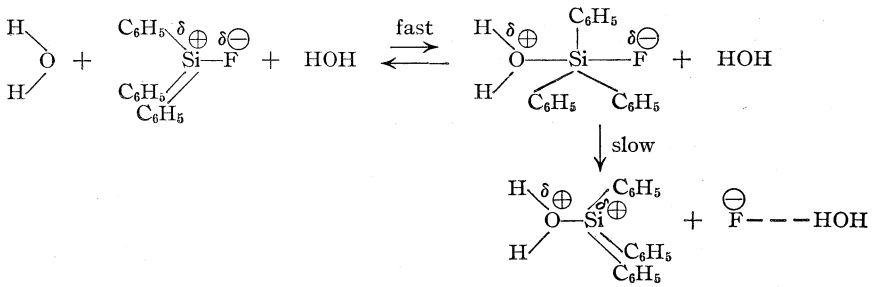
$$H_2O + (C_6H_5)_3SiF \xrightarrow{\text{slow}} H_2\overset{\oplus}{O}Si(C_6H_5)_3 + F^{\ominus} \quad (2)$$

$$H_2O + (C_6H_5)_3SiF \xrightarrow{\text{slow}} H_2OSi(C_6H_5)_3F \quad (3a)$$

$$H_2OSi(C_6H_5)_3F \xrightarrow{\text{fast}} H_2\overset{\oplus}{O}Si(C_6H_5)_3 + F^{\ominus}$$

$$H_2O + (C_6H_5)_3SiF \xrightleftharpoons{\text{fast}} H_2OSi(C_6H_5)_3F \quad (3b)$$

$$H_2OSi(C_6H_5)_3F \xrightarrow{\text{slow}} H_2\overset{\oplus}{O}Si(C_6H_5)_3 + F^{\ominus}$$



There are three general possibilities for the mechanism of hydrolysis of trisyl fluoride under our acid conditions.

(1) The old bond to fluorine may break *before* the new bond to oxygen forms. This would be a two-step mechanism involving a siliconium ion intermediate. (We have subdivided this possibility into mechanisms 1a and 1b, depending on which step is rate determining.)

(2) Breaking the old bond and making the new bond may be exactly *simultaneous*. This would be a one-step displacement (Mechanism 2).

(3) The old bond may break *after* the new bond forms. This would be a two-step mechanism involving a pentacovalent silicon compound as an intermediate. (We have subdivided this possibility into mechanisms 3a and 3b, depending on which step is rate determining.)

The retarding effect of *p*-methyl substituents in trisyl fluoride shows that the charge on the silicon atom in the transition state is less positive than in the ground state. This eliminates mechanisms 1a, 1b and 2. The silicon atom should be increasingly positive in the series trisyl fluoride (I), triphenylsilanol conjugate acid (II), triphenyl siliconium ion (III). Hence the silicon in the transition state would be more positive than in (I) regardless of whether the transition state were half way from I to III (mechanism 1a), III to II (mechanism 1b) or I to II (mechanism 2). Only mechanisms 3a and 3b predict a less positive silicon atom in the transition state.

By mechanism 3a one would expect trisyl fluoride to be more reactive than trisyl chloride, since fluorine is a stronger electron attractor than chlorine and should give a more positive or electrophilic silicon atom. Actually, the converse appears to hold,[8] leaving mechanism 3b as the only possibility out of this group of mechanisms.

The positive salt and solvent effects show that there is greater charge or charge separation in the transition state than in the ground state. This is also consistent with mechanism 3b, where the transition state would be half way from intermediate to product.



One cannot be sure from our experiments whether the charge on silicon in the transition state, and in the pentacovalent silicon intermediate, is slightly positive or slightly negative in an absolute sense, only that it is less positive in both states than in the starting material.

These observations permit one to draw the free energy diagram of Fig. 1 to represent qualitatively the free energy of the intermediate and

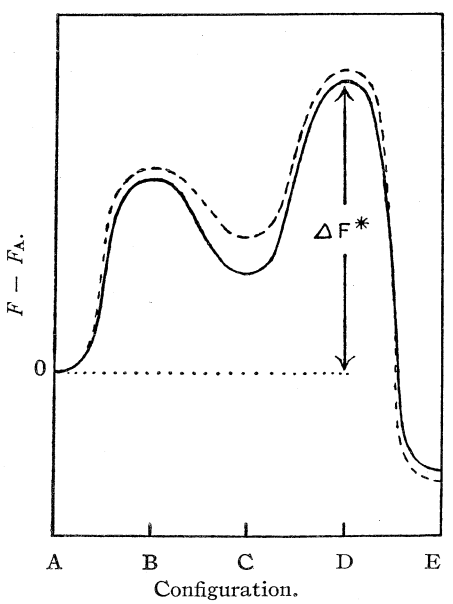



Fig. 1.—Free energy changes in the hydrolysis of triphenylsilyl fluoride: A, ground state of reactants; B, first activated state; C, pentacovalent silicon intermediate; D, second activated state; E, ground state of products.

(8) Burkhardt, Rochow, Booth and Hartt, *Chem. Rev.*, **41**, 121 (1947); Medoks and Kotelkov, *J. Gen. Chem.* (*USSR*), **7**, 2007 (1937); Gierut, Sowa and Nieuwland, THIS JOURNAL, **58**, 897 (1936).

activated states. The solid curve represents trisyl fluoride, the dashed curve the tri-*p*-methyl substituted compound. The spread between the two curves is at all points proportional to the magnitude of the increase or decrease of the charge on silicon relative to that in the ground state (A).

The plot for trityl fluoride would differ in the following ways. The intermediate (C) would have a more positive charge on the atom undergoing displacement than the ground state (A), rather than less positive. The first hill would represent chiefly bond breaking, the second bond making, rather than the reverse shown in Fig. 1. The first hill would be higher, not lower, than the second. The dashed curve would be everywhere below, not chiefly above, the solid curve. The separation between the curves would again be less for the activated states (B and D) than for the intermediate (C), but the separation at E would be comparable with that at C, rather than of reversed sign as in Fig. 1.

Mechanism 3 (a or b) has long been recognized as a possibility for the reaction of silicon compounds.[9] Not only are pentacovalent silicon intermediates possible and probable in view of the existence of the very stable fluosilicate ion, $SiF_6^=$, but $(C_6H_5)_3Si^{\oplus}$ or $(CH_3)_3Si^{\oplus}$ ions are improbable[10] relative to their carbon analogs because their resonance stabilization would require double bonds to silicon for which there is no stable example known. Mechanism 3 has also been advanced[9] as an attractive explanation for the remarkable ease of displacements on silicon, which are often much faster than analogous displacements on carbon, as in these examples[11]

$$HO:^{\ominus} + R_3SiH + H_2O \longrightarrow HO{-}SiR_3 + H_2 + :OH^{\ominus}$$

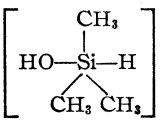
$$4HO:^{\ominus} + Cl_3SiCH_2CH_2Cl \xrightarrow[\text{dil. aq. NaOH}]{\text{titrate with}} (SiO_2)_n + CH_2{=}CH_2 + 4:Cl^{\ominus}$$

$$4CH_3MgBr + Cl_3SiCH_2CH_2Cl \xrightarrow{\text{ether}} (CH_3)_4Si + CH_2{=}CH_2 + 4MgBrCl$$

$$2(CH_3)_3SiOH \xrightarrow[\text{anhyd. } K_2CO_3]{\text{stand over}} CH_3{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}O{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}CH_3$$

$$(CH_3)_3SiNHCi(CH_3)_3 \xrightarrow[\text{dilute aq. HCl}]{\text{titrate with}} 2(CH_3)_3SiOH + NH_4Cl$$

Were a displacement like the first one above to occur on carbon, it would probably be through an unstable transition state with hydroxyl and hydrogen both only partly bonded. With silicon the following is a relatively much more stable structure due to the ability of silicon to expand its



valence shell to include more than eight electrons, and this should correspondingly lower the energy of the transition state separating this intermediate from the products.

## Experimental

**Reagents.**—Triphenylsilyl (trisyl) fluoride was prepared according to the procedure of Medoks and Kotelkov[8] by passing gaseous silicon tetrafluoride through 250 cc. of 2.8 *M*, phenylmagnesium bromide in ether for four hours at 25°. The silicon tetrafluoride was generated according to Nieuwland and Sowa[12] by adding 100 cc. of concd. sulfuric acid slowly to a mixture of 30 g. (0.16 mole) of sodium fluosilicate and 10 g. (0.17 mole) of silica (pumice) in a round-bottom glass flask while heating with a bunsen burner. After standing for a week at 25° the reaction mixture was hydrolyzed with acidified ice water and worked up as usual. The yield was 24 g. (0.086 mole, 36% based on sodium fluosilicate), b. p. 160–170° at 0.5 mm. (reported[8] 205° at 10 mm.) The distillate was crystallized twice from ether, once from acetone and again from ether, each time cooling finally with Dry Ice, to obtain a constant m. p., 61.4–61.6° (reported[8] 64°).

Tri-*p*-tolylsilyl fluoride (previously unreported) was similarly prepared starting with 29 g. (0.17 mole, b. p. 183–184°) of *p*-bromotoluene, 4.6 g. (0.19 atoms) of magnesium turnings, 200 cc. of dry ether, 7.5 g. (0.04 mole) of sodium fluosilicate, and 20 cc. of concd. sulfuric acid. The silicon tetrafluoride was passed through the Grignard solution for three hours, then the solution was allowed to stand for one hour at 25° before hydrolysis. The ether extracts were dried over sodium sulfate, evaporated on a water-bath and the residue cooled in a Dry Ice–acetone-bath to induce crystallization. The yield of crystals was 5.5 g. (0.017 mole, 28% based on sodium fluosilicate), m. p. 69–83°. This material was recrystallized from acetone by cooling with Dry Ice, then twice from petroleum ether, till a constant m. p. of 108–109° was obtained. The sample used for kinetic studies had the following analysis.

*Anal.* Calcd. for $C_{21}H_{21}SiF$, C, 78.71; H, 6.61. Found: 78.11; 6.69.

Triphenylmethyl (trityl) fluoride was prepared from acetyl fluoride and triphenylcarbinol (tritanol) by the procedure of Blicke.[13] The acetyl fluoride was prepared from zinc fluoride and acetyl chloride.[14] Zinc fluoride (technical grade) was heated at 150° for ten hours under oil-pump vacuum to remove all traces of water. Acetyl chloride (150 g., 2.1 moles) was added dropwise through a dropping funnel to 100 g. (0.96 mole) of the dried zinc fluoride in a well-cooled flask protected from moisture by calcium chloride tubes. After completing the addition, the water-bath around the reaction flask was warmed to 30°. All liquid boiling up to 30° was distilled through a Vigreux column and collected in a well cooled receiver. The distillate was poured into a flask containing a small amount of zinc fluoride and redistilled through the column, collecting 76 g. (1.2 moles, 63% yield), of b. p. 20–28°. In a subsequent preparation of acetyl fluoride, constant

(9) Sidgwick, "The Electronic Theory of Valency," Oxford University Press, London, 1927, pp. 159–160.

(10) It is, however, possible that siliconium ions may exist as intermediates in reactions with exceptionally electrophilic reagents such as aluminum chloride. To decide this, the effect of substituents on the rate of the reactions in question could be determined.

(11) F. Price, THIS JOURNAL, **69**, 2600 (1947); Sommer, Goldberg, Dorfman and Whitmore, *ibid.*, **68**, 1083 (1946); Sauer, *ibid.*, **66**, 1707 (1944).

(12) Nieuwland and Sowa, *ibid.*, **58**, 786 (1936).

(13) Blicke, *ibid.*, **46**, 1515 (1924).

(14) Meslans, *Ann. chim. phys.*, [7] **1**, 411 (1894).

mechanical stirring was found to increase the speed of reaction and ease of operation. To prepare the trityl fluoride 81 cc. (1.3 moles) of acetyl fluoride was added to a cold mixture of 80 g. (0.31 mole) of tritanol, m. p. 161–162°, and 400 cc. of benzene in a round-bottom flask, stoppered securely with a rubber stopper (wired in), and allowed to stand for four days at 25° with occasional shaking. The benzene was then distilled to reduce the volume to 100 cc., petroleum ether (100 cc.) was added and the solution was cooled. The crystals were collected and recrystallized from ligroin, yielding 48 g. (0.18 mole, 59%), of m. p. 99.5–101°. Five recrystallizations from ligroin, petroleum ether, carbon tetrachloride–ligroin and petroleum ether–ligroin and drying of the crystals *in vacuo* over soda lime and paraffin raised the m. p. to 102–103° (reported m. p., 102–104).[13] Kinetics showed that about 70% of this product was trityl fluoride and 30% tritanol. It appears to be very difficult to separate trityl fluoride from tritanol by recrystallization. Acetyl fluoride was badly occluded when the material was recrystallized in its presence. Further recrystallizations from thoroughly dried solvents, or crystallizations of the mother liquor, or preparations under slightly different conditions all gave less pure products. Therefore this material was used in the kinetic studies, since the presence of tritanol should not interfere with the analytical methods nor affect the rate of reaction of trityl fluoride.

The acetone was Merck reagent grade. Stock solutions (usually 0.02 *M*) were made by weighing out the fluorides and volumetrically dissolving them in Merck reagent acetone.

**Procedure.**—The approximate solubility of the fluorides in water–acetone mixtures is given in Table IV. This was determined by adding water from a buret to acetone solutions until turbidity appeared.

TABLE IV

SOLUBILITIES OF TRIPHENYLSILYL AND TRIPHENYLMETHYL FLUORIDES IN WATER–ACETONE MIXTURES

| Fluoride | Water, % | Solubility (*M*) at 25° | 45° | 100° |
|---|---|---|---|---|
| $(C_6H_5)_3Si$ | 40 | 0.01 | | |
| $(C_6H_5)_3Si$ | 50 | .002 | 0.02 | |
| $(C_6H_5)_3Si$ | 60 | .0005 | .01 | |
| $(C_6H_5)_3Si$ | 65 | .0002 | | |
| $(p\text{-}CH_3C_6H_4)_3Si$ | 30 | | .01 | |
| $(p\text{-}CH_3C_6H_4)_3Si$ | 40 | | | 0.01 |
| $(p\text{-}CH_3C_6H_4)_3Si$ | 50 | | .001 | |
| $(C_6H_5)_3C$ | 45 | .005 | | |
| $(C_6H_5)_3C$ | 60 | .002 | | |
| $(C_6H_5)_3C$ | 80 | .0005 | | |

Temperature control was ±0.02° at 25°, ±0.1° at 45° and ±0.5° at 100°. A steam-vapor-bath at atmospheric pressure was used at 100°.

Preliminary experiments demonstrated that the reaction of trisyl fluoride with hydroxide ion is so fast that one cannot titrate aliquot samples of 0.001 *M* solutions with dilute sodium hydroxide at 25° to determine the per cent. hydrolysis without hydrolyzing the remaining trisyl fluoride. The end-points were vague and indefinite. The reaction appears to have a half life of ten seconds or less at *p*H 11, corresponding to a rate constant for reaction with hydroxide ion of over $10^{+3}$ liters mole$^{-1}$ min.$^{-1}$, or ten million times that for reaction with water. This meant that the reaction with water had to be studied below *p*H 7 using analytical procedures in which aliquots were kept always below this *p*H. Methods A, B, and C served this function. The fact that good straight lines on a semi-log plot were obtained below *p*H 7 in spite of increasing acidity during the run shows that the reaction under these conditions was with water rather than with hydroxide ion.

Method A involved periodically titrating aliquot portions of the kinetic solution for fluoride ion with 0.0385 *N* thorium nitrate in acid solution using sodium alizarin sulfonate as indicator.[15] To 25 cc. of distilled water in a flask are added three drops of a saturated water solution of sodium alizarin sulfonate, two drops of 0.02 *M* nitric acid (which gives a yellow color), then 10 cc. of the solution to be titrated. The end-point is the change to a pink color. The method is accurate to ±2%. Time was counted from the moment of removal of the first aliquot, and the titer for this was used as a blank for all later aliquots. The final titer at ten times the half life was used as 100%. The thorium nitrate solution was standardized against a weighed sample of Merck reagent potassium fluoride. The blank in the standardization was 0.02 cc.

Method B used a separate sealed tube for each point, and was used for the runs at 100°. Into soft glass testtubes previously pulled out for easy sealing, 10-cc. aliquots of a water–acetone solution of fluoride were pipetted. The sealed tubes were placed in the 100° steam-bath simultaneously. On removal each was immediately placed in ice water and the time it was in the steam-bath was recorded. Each tube was opened, emptied into a flask and titrated as in method A. The first tube was used as a zero time point and blank for all the rest.

Method C involved following the increase in acidity by using a concentration cell.[16,17] Two 150 cc. extraction flasks fitted with rubber stoppers were used. In each stopper was fitted one arm of the salt bridge, a sleeve for the glass stirrer, and a shiny platinum wire electrode. In the stopper of the titrating (dummy) cell a 5-cc. buret was also inserted. The stirrers were fitted with rubber sleeves and lubricated with glycerol to cut down evaporation and keep the solutions carbon dioxide free. They were driven by one-inch pulleys on the same belt. The salt bridge was filled with 3% agar gel saturated with potassium chloride. The galvanometer was a Leeds and Northrup No. 2420-D enclosed scale type with a sensitivity of $3 \times 10^{-8}$ amp. mm.$^{-1}$ on a ground glass scale.

Initially 125 cc. of solution was placed in each cell. Quinhydrone (0.01 g.) was added to make the electrodes sensitive to *p*H. At zero time 5 cc. of the stock solution of fluoride was introduced into the reaction cell and 5 cc. of pure acetone into the dummy cell. To follow the reaction the cell was balanced by adding standard hydrofluoric acid to the dummy cell. The buret readings and times when the galvanometer swung through zero were recorded. The first titer was used as 0% and the final titer (at ten times the half life) as 100%.

This method is not as satisfactory for high concentrations because the platinum electrodes are gradually poisoned or desensitized by the organosilicon compounds after continued use (possibly due to coating over, although they remain bright and shiny in appearance). However, it will work with lower concentrations than the other methods.

Method D involved intermittent direct titration with sodium hydroxide of the acid liberated by the whole reacting solution.[18] This method is applicable to trityl halides since the rate of their hydrolysis is independent of the hydroxide ion concentration. Brom thymol blue was used as an indicator. The cell (Fig. 2) consisted of a 4.6 × 21 cm. test-tube, with a capillary side arm entering near the bottom for degassing with a stream of nitrogen. The shaft of a small glass stirrer rested in a depression blown in the bottom of the cell and passed through a glass sleeve in the rubber stopper in the top of the cell. It was driven at high speed by an electric motor. Small vanes, 4 cm. from the bottom, caught the gas bubbles issuing from the capillary tube, causing them to break and fill the whole solution. A thermometer graduated in 0.1° passed through a hole in the rubber stopper.

Standard sodium hydroxide solution (0.0480 *M*) was prepared from a 50% solution with freshly boiled distilled

(15) Huckaba, Welch and Metler, *Anal. Chem.*, **19**, 155 (1947).

(16) Swain and Ross, THIS JOURNAL, **68**, 658 (1946).

(17) Ross and Swain, *ibid.*, **69**, 1325 (1947).

(18) Technique developed by Peters and Walker, *Biochem. J.*, **17**, 260 (1923).

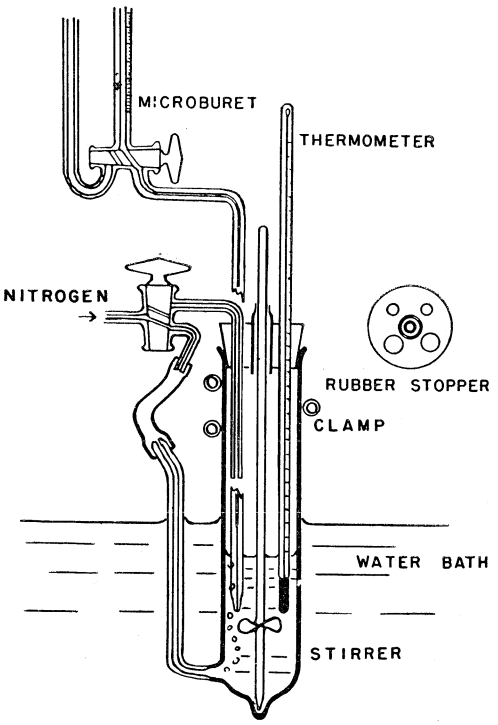



Fig. 2.—Cell used for intermittent titration in methods D and E.

water and protected from atsmospheric carbon dioxide. It was standardized against potassium acid phthalate. It was added from a 2-cc. microburet with a long fine capillary tip below the surface of the solution. For the runs in 95% methanol–5% acetone the methanol was dried over Drierite and distilled before use; in these a sodium methoxide (0.0546 *M*) solution in methanol (prepared by dissolving sodium) was used for titrating.

A cell containing the green shade of brom thymol blue to be matched was clamped in the thermostat bath next to the titration cell. A white porcelain plate was placed behind the two cells and good illumination was provided. The titration apparatus was mounted on a sliding assembly so that it could be easily raised out of the bath. By turning a stopcock the nitrogen stream could be introduced either through the solution or over the surface. Before entering the cell the nitrogen was passed through drying towers containing potassium hydroxide pellets to remove carbon dioxide and then saturated with the solvent by bubbling through two wash bottles each containing 100 cc. of 50% water–50% acetone mixture to prevent the evaporation of acetone from the reaction mixture. Before starting a run 50 cc. of water, 45 cc. of acetone, and 6 drops of 0.1% brom thymol blue were added to the cell. Nitrogen was bubbled through the solution with good motor stirring to remove carbon dioxide until the color of the kinetic cell matched the neutral green of the standard cell. Then the nitrogen stream was diverted over the surface of the liquid and 5 cc. of the stock solution of trityl fluoride was injected with a syringe pipet. The stopwatch was started when the pipet was half empty. It emptied within two seconds. The solution immediately turned yellow but excess base was added to make it blue. Each time when the solution reached a neutral green the time and buret reading were recorded and the solution immediately made basic again by adding excess base. Infinite or total hydrolysis was taken as the volume of base required at ten times the half life (99.9% hydrolysis). Dividing each volume by the total volume gave uncorrected per cent. reaction at a given time. Extrapolation back to zero time gave the initial per cent. reaction due to hydrogen fluoride

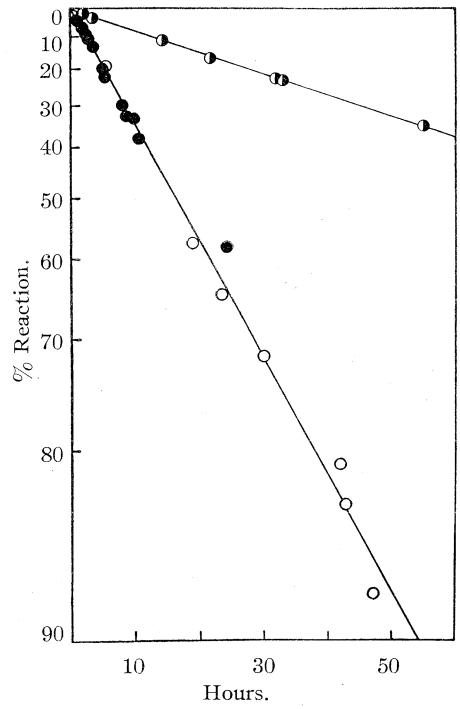



Fig. 3.—Hydrolysis of triarylsilyl fluorides in 50% water–50% acetone solution at 45°. ⊙, 0.0093 *M* triphenylsilyl fluoride, method A; ●, 0.00085 *M* triphenylsilyl fluoride, method C; ◑, 0.00091 *M* tri-*p*-tolylsilyl fluoride, method C.

impurity. This was subtracted out in obtaining corrected per cent. reaction, such as given in Table III or Fig. 4.

Method E was the same as Method D except that the solution was kept acid, rather than basic, except when taking end-points. The fact that methods D and E give

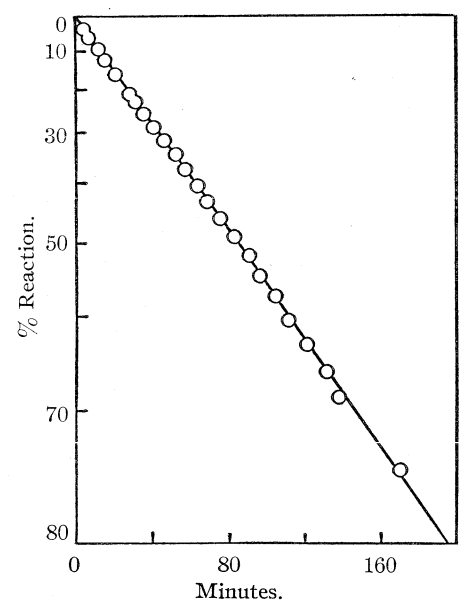


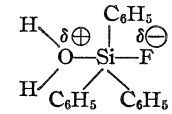

Fig. 4.—Methanolysis of 0.00100 *M* triphenylmethyl fluoride in 95% methanol–5% acetone solution at 25° by method E.

results which are identical within experimental error demonstrates that the rate of reaction of trityl fluoride is independent of *p*H.

## Summary

The hydrolysis of triphenylmethyl fluoride in 50% water–50% acetone is insensitive to *p*H, is aided by *p*-alkyl substituents, and is strongly accelerated by increasing the per cent. of water. This indicates an intermediate with a more positive charge on the central carbon atom than the starting material and only three groups attached to it by predominantly covalent bonds.

The hydrolysis of triphenylsilyl fluoride in 50% water–50% acetone is more than a million times faster with hydroxide ion than with water, is retarded by *p*-alkyl substituents, and is weakly accelerated by increasing concentration of inert salt or per cent. of water. These observations are not consistent with the idea of a siliconium ion intermediate with a positive charge on silicon analogous to the "carbonium ion" intermediate in the hydrolysis of triphenylmethyl fluoride above. They indicate instead that the intermediate in the reaction with water has a less positive charge on the silicon atom than the starting material and is more closely represented by the following structure with pentacovalent silicon.



It appears that many reactions of organosilicon compounds may proceed through similar pentacovalent silicon intermediates. This constitutes an easy reaction path for displacements on silicon which is not available to displacements on carbon, since carbon lacks the ability to expand its valence shell to include more than eight electrons.

CAMBRIDGE, MASS. RECEIVED JULY 22, 1948

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[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

# Methyldichlorosilane and its Fluorination Products[1]

BY HAROLD SIMMONS BOOTH AND ROGER LUCIEN JARRY

This investigation is a continuation of the work done in this Laboratory on the alkyl chloro silanes.[2–7] To the best of our knowledge no mention of the fluorination products, methylchlorofluorosilane and methyldifluorosilane, is made in the literature.

## Experimental

**Fluorination of Methyldichlorosilane.**—Purification of the methyldichlorosilane[7a] prior to fluorination was accomplished by fractional distillation in a column having a total condensation head, and take-off of the design used by Whitmore and Lux. The fluorination was carried out by the Swarts reaction using antimony trifluoride as the fluorination agent, but without the use of a catalyst. The decision not to use a catalyst was made after preliminary tests indicated the possibility of chlorination of the methyldichlorosilane by antimony pentachloride; the yields of the two products without the usual catalyst were in sufficient quantity for purification and study. The apparatus and procedure for the fluorination were essentially the same as those described in previous papers from this Laboratory[8,9] with the modification of the direct condensation described by Booth and Spessard.[2] This modification entailed direct condensation in liquid-nitrogen-cooled ampules instead of the previous procedure of passing the fluorination products through a stripping column and refluxing. Since the problem of producing the intermediate fluorination product in this case was not considered difficult, as subsequent fluorinations proved, the fluorination was carried out at room temperature and atmospheric pressure. The average yields were about fifty per cent. fluorinated products, of which methyldifluorosilane comprised 70% and methyl chlorofluorosilane comprised 30%. The unfluorinated methyl dichlorosilane was repurified and refluorinated. The threshold fluorination temperature is below 20°.

**Purification of the Fluorination Products.**—The products of fluorination, methylchlorofluorosilane and methyldifluorosilane, were fractionally distilled in a low temperature distillation column of the type previously described[8] with the exception that the packing was a single Podbielniak Heligrid. The pressure control was a modification of the anticipator previously described[10] and will be given in a future publication. The cooling agent used in the column head was acetone cooled by a Dry Ice–acetone-bath. The methylchlorofluorosilane was distilled at pressures of 740 mm. and 300 mm. approximately; the methyl difluorosilane at 740 mm. and 250 mm. approximately.

**Analysis.**—Samples for analysis were taken in small sealed-glass bulbs.[11] Chlorine was determined by the Volhard method and fluorine by hydrolysis with standard base and back-titrating with standard acid with correction for the hydrochloric acid produced in the hydrolysis. The analysis of the methyldichlorosilane by the Volhard method, after hydrolysis with sodium hydroxide, gave consistently low results. To avoid this a modified Chablay method[12] was used. The results are shown in Table I.

(1) From a thesis presented by Roger L. Jarry to the Graduate School of Western Reserve University, September, 1948, in partial fulfillment of the requirements for the degree of Master of Science, and based upon work done in connection with a research project sponsored by the Office of Naval Research.

(2) H. S. Booth and P. H. Carnell, THIS JOURNAL, **68**, 2650 (1946).

(3) H. S. Booth and H. S. Halbedel, *ibid.*, **68**, 2652 (1946).

(4) H. S. Booth and W. F. Martin, *ibid.*, **68**, 2655 (1946).

(5) H. S. Booth and J. F. Suttle, *ibid.*, **68**, 2658 (1946).

(6) H. S. Booth and D. R. Spessard, *ibid.*, **68**, 2660 (1946).

(7) H. S. Booth and A. A. Schwartz, *ibid.*, **68**, 2662 (1946).

(7a) Procured from the General Electric Company.

(8) H. S. Booth and A. R. Bozarth, *ibid.*, **61**, 2927 (1939); *Ind. Eng. Chem.*, **29**, 470 (1937).

(9) H. S. Booth and W. C. Morris, THIS JOURNAL, **58**, 90 (1936).

(10) H. S. Booth and R. McNabney, *Ind. Eng. Chem., Anal. Ed.*, **16**, 131 (1944).

(11) H. S. Booth and W. D. Stillwell, THIS JOURNAL, **56**, 1531 (1934).

(12) H. S. Booth, W. L. Mong and P. E. Burchfield, *Ind. Eng. Chem.*, **24**, 328 (1932).

TABLE I

| No. | | | 1 | 2 | 3 |
|---|---|---|---|---|---|
| Formula | | | $CH_3HSiCl_2$ | $CH_3HSiClF$ | $CH_3HSiF_2$ |
| Composition, % | Cl | Calcd. | 61.66 | 35.98 | ..... |
| | | Found | 61.30 61.60 | 35.80 35.80 | ..... |
| | F | Calcd. | ..... | 19.27 | 46.29 |
| | | Found | ..... | 19.28 19.29 | 45.80 45.94 |
| Mol. wts. | Calcd. | | 115.02 | 98.56 | 82.10 |
| | Found | | ..... | 99.2 | 83.2 |
| Freezing pt., °C. | | | 90.6 ± 0.5 | −120.2 ± 0.5 | −110.1 ± 0.5 |
| Boiling pt., °C. | | | +40.4 ± 0.1 | +1.2 ± 0.1 | −35.6 ± 0.1 |
| Liquid density, g./ml. at 0°C. | | | 1.135 | 1.059 | ..... |
| Heat of vapn., cal. | | | 6816 | 5933 | 5310 |
| Trouton const., cal./deg. | | | 21.7 | 21.6 | 22.3 |
| Vapor pressure, log $P$mm. = | | | (for 1) $-1489.4/T + 7.6304$ | | |
| | | | (for 2) $-1296.6/T + 7.6066$ | | |
| | | | (for 3) $-1160.4/T + 7.7655$ | | |
| Av. random dev., mm. | | | ±4.3 | ±2.2 | ±3.1 |
| Maximum dev., mm. | | | +8.7 | +6.2 | +5.5 |

**Determination of Physical Constants.**—Molecular weights of methylchlorofluorosilane and methyldifluorosilane were determined, during the course of distillation, by means of a gas density balance.[8]

The freezing points were determined as described by Booth and Martin.[13] Methyldichlorosilane supercooled about 3.6° the other two compounds showing no supercooling.

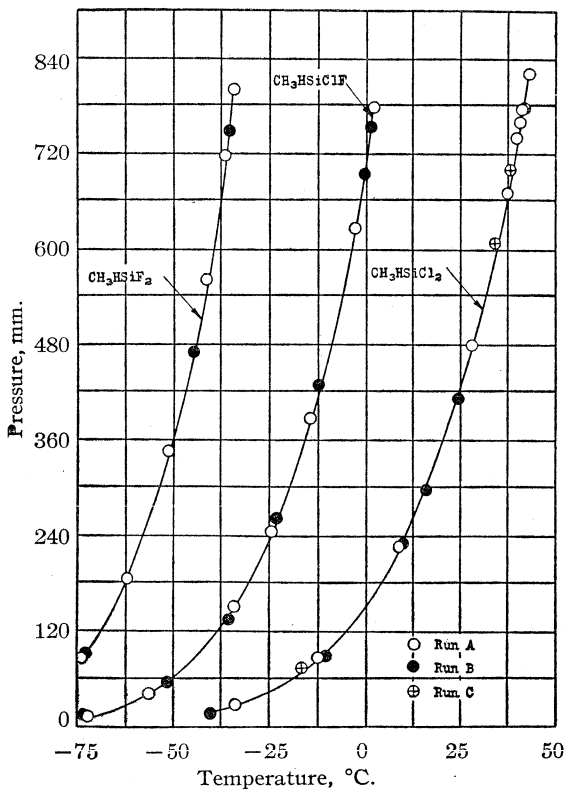



Fig. 1.—Plot of temperature *vs.* pressure for monomethyldichlorosilane and its fluorination products.

(13) H. S. Booth and D. R. Martin, *Chem. Rev.*, **33**, 2 (1943).

Liquid density of methyldichlorosilane and methylchlorofluorosilane were determined in a special type of pycnometer previously described.[14] The pycnometer was calibrated with freshly distilled mercury at 0° and the densities determined at the same temperature, allowance being made in the calculations for the free vapor space above the liquid.

Vapor pressures were determined as described by Booth, Elsey and Burchfield.[15]

The above determined physical properties are summarized in Table I. The vapor pressure data are given in the form of equations in Table I, and in Fig. 1 as a graph of the original data.[15a]

**Physical and Chemical Properties.**—These compounds fume in air and have sharp, irritating odors due to the hydrogen halides formed. They are readily hydrolyzed and dissolved by strong alkaline hydroxides with the evolution of hydrogen. They all smutted mercury, at room temperature, in time.

The lowering of the boiling point by the substitution of fluorine for chlorine followed the Swarts rule fairly closely; the substitution of the first fluorine lowered the boiling point by 39.3° while the substitution of the second fluorine lowered it 36.8°.

Trouton's constant showed an increase with increasing fluorine content which is to be expected with the more polar character of the fluorine.

## Summary

Methyldichlorosilane has been fluorinated with antimony fluoride at room temperature and atmospheric pressure to yield the new compounds methyl chlorofluorosilane and methyldifluorosilane. Certain of the physical constants and chemical properties have been determined.

CLEVELAND 6, OHIO RECEIVED SEPTEMBER 7, 1948

(14) H. S. Booth and C. Herrmann, THIS JOURNAL, **58**, 63 (1936).

(15) H. S. Booth, H. M. Elsey and P. E. Burchfield, *ibid.*, **57**, 2064 (1935).

(15a) For data for these vapor pressure curves consult original thesis at Western Reserve University Library.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

# Polarography of the Various Oxidation States of Tungsten

BY JAMES J. LINGANE AND LYNDON A. SMALL

The polarography of +6 tungsten in weakly acid solution and of the heteropoly acids, such as the phospho- and silico-tungstates has been studied by Souchay.[1] Stackelberg, *et al.*,[2] studied the polarography of tungsten(VI) in concentrated hydrochloric acid and they reported only a single reduction wave. No polarographic studies of tungsten in oxidation states lower than +6 have previously been reported.

No polarographic waves are found for tungsten (VI) in basic or neutral solution. Tungsten(VI) is insoluble in dilute strong acids, but is soluble in concentrated halogen acids. This paper presents the results of an investigation of the polarography of the various oxidation states of tungsten in hydrochloric acid, together with application of controlled potential electrolysis to the interpretation of the polarograms and the preparation of the lower oxidation states.

## Experimental

Standard solutions of tungsten(VI) were prepared from reagent quality sodium tungstate and standardized gravimetrically by the conventional tungstic acid precipitation with the aid of cinchonine.[3]

Polarographic measurements were made both by the resistance–potentiometer method,[4] and by use of a Heyrovsky–Shikata type photographic recording polarograph constructed in this Laboratory. An H-type cell[5] was used in most cases, with a saturated calomel electrode. Nitrogen, hydrogen or carbon dioxide purified by passage over copper gauze at 400°, or by passage through a solution of a chromous salt, was used for removal of dissolved oxygen and protection of air-sensitive solutions. All polarographic measurements were made at 25.0°; and all potentials are referred to the saturated calomel electrode at 25°. Appropriate corrections for residual current were made in calculating diffusion current constants. Electrolytic reductions at controlled potential were carried out according to the technique of Lingane, Swain and Fields,[6] with a cell of the same design as that used by those authors but with the rubber stopper replaced by a ground-glass joint and cap. The cell was constructed from a 250-ml. wide-mouth Erlenmeyer flask, with a 30-mm. medium porosity Pyrex sintered-glass disk as diaphragm. A mercury cathode and carbon anode were used. The potential of the mercury electrode was automatically controlled by a potentiostat[7] with respect to a saturated calomel reference electrode. Reduced solutions in the cell were protected by nitrogen or hydrogen, which was passed over rather than through the solution. Polarographic measurements on the cell contents were made by inserting the dropping electrode into the cell and using the mercury pool as anode.

Oxidation states were determined both by measurement with an oxygen–hydrogen coulometer of the current passed during reduction[8] and by an iodate titration. The latter was based on the Andrews iodine monochloride procedure.[9] According to Lang[10] iodate ion directly oxidizes tungsten (III) to tungsten(VI) only slowly, but reacts rapidly if catalyzed by ferric iron. Accordingly, an aliquot of the reduced solution was added to an air-free solution of excess of ferric iron in 4 to 6 *M* hydrochloric acid, and the ferrous iron produced was titrated potentiometrically with standard 0.01 *N* potassium iodate solution. The validity of this method was established by titration of samples of tungsten(III) prepared by reduction of tungsten(VI) in 12 *M* hydrochloric acid by saturated lead amalgam by the method of Someya.[11] Accuracy of about ±0.5% was obtained with 0.1 *N* iodate solutions. Deduction of a small blank (*ca.* 0.10 ml.) was found necessary in titrating with 0.01 *N* iodate.

Absorption spectra were recorded by use of the Beckman Model DU Photoelectric Quartz Spectrophotometer, with 1-cm. quartz cells. Some measure of protection of the solutions from air and of protection of the instrument from acid fumes was obtained by sealing the loose fitting glass cell covers with vaseline, and by providing the cell compartment with a cover fitted with tubulatures through which air was passed to provide ventilation. Slit widths of 0.02 to 0.2 mm. were used, corresponding to nominal band widths smaller than 5 millimicrons.

## Results and Discussion

**Tungsten(VI).**—It was found that tungsten (VI) in 12 *M* hydrochloric acid produces a double polarographic wave as shown in Fig. 1, one wave starting from zero applied e. m. f. and the second having a half-wave potential of −0.56 v. *vs.* S.C.E. In less concentrated acid, the half-

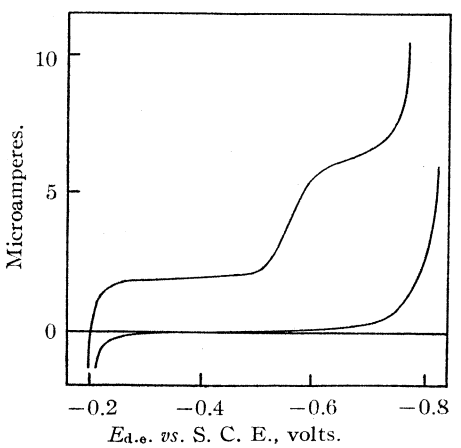



Fig. 1.—Polarogram of 1.00 millimolar tungsten(VI) in 12 *M* hydrochloric acid.

(1) P. Souchay, *Ann. chim.*, **18**, 61 (1943); **18**, 73 (1943); **18**, 169 (1943); **19**, 102 (1944); **20**, 73 (1945); **20**, 96 (1945); **1**, 232 (1946).

(2) M. v. Stackelberg, P. Klinger, W. Koch and E. Krath, *Forschungsberichte Tech. Mitt. Krupp, Essen*, **2**, 59 (1939).

(3) F. P. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1942.

(4) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

(5) J. J. Lingane and H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **11**, 504 (1939).

(6) J. J. Lingane, C. G. Swain and M. Fields, THIS JOURNAL, **65**, 1348 (1943).

(7) J. J. Lingane, *Ind. Eng. Chem., Anal. Ed.*, **17**, 332 (1945).

(8) J. J. Lingane, THIS JOURNAL, **67**, 1916 (1945).

(9) L. W. Andrews, *ibid.*, **25**, 756 (1903).

(10) Oesper, "Newer Methods of Volumetric Analysis," D. Van Nostrand Co., New York, N. Y., 1938.

(11) K. Someya, *Z. anorg. allgem. Chem.*, **145**, 168 (1925).

wave potential of the second wave is shifted somewhat in the negative direction. In both 10 *M* and 8 *M* hydrochloric acid, the half-wave potential was −0.62 v.; in 6 *M* acid −0.64 v.; in 4 *M* acid −0.66 v. *vs.* S.C.E. The solubility of tungsten (VI) in hydrochloric acid much less concentrated than 4 *M* is too small to allow the wave to be distinguished. Diffusion current constant data are given in Table I.

TABLE I

DIFFUSION CURRENT CONSTANTS OF TUNGSTEN(VI) IN HYDROCHLORIC ACID AT 25.0°

(a) 12 *M* Hydrochloric Acid. $m^{2/3}t^{1/6}$ = 1.61 mg.$^{2/3}$ sec.$^{-1/2}$ at −0.40 v. and 1.63 mg.$^{2/3}$ sec.$^{-1/2}$ at −0.67 v. *vs.* S. C. E.

| Tungsten(VI) millimolar | $i_d/Cm^{2/3}t^{1/6}$ at −0.40 v. | at −0.67 v. |
|---|---|---|
| 1.49 | 1.29 | 3.82 |
| 2.44 | 1.32 | 3.84 |
| 3.79 | 1.31 | 3.80 |
| 4.65 | 1.32 | .. |
| Av. | 1.31 ± 1 | 3.82 ± 2 |

(b) 10 *M* Hydrochloric Acid. $m^{2/3}t^{1/6}$ = 1.56 mg.$^{2/3}$ sec.$^{-1/2}$ at −0.40 v. and 1.59 mg.$^{2/3}$ sec.$^{-1/2}$ at −0.75 v. *vs.* S. C. E.

| Tungsten(VI) millimolar | $i_d/Cm^{2/3}t^{1/6}$ at −0.40 v. | at −0.75 v. |
|---|---|---|
| 1.00 | 1.42 | 4.35 |
| 1.97 | 1.42 | 4.32 |

(c) 8 *M* Hydrochloric Acid. $m^{2/3}t^{1/6}$ values as in (b)

| Tungsten(VI) millimolar | $i_d/Cm^{2/3}t^{1/6}$ at −0.40 v. | at −0.75 v. |
|---|---|---|
| 1.00 | 1.49 | 4.78 |
| 1.97 | 1.45 | 4.62 |

Since the ratio of the diffusion current constants is 1:3, reduction apparently proceeds to the +5 and +3 states, respectively. The alternative would be deposition of tungsten metal, which has never been achieved from such strongly acid solutions. Direct proof of the above interpretation is given below.

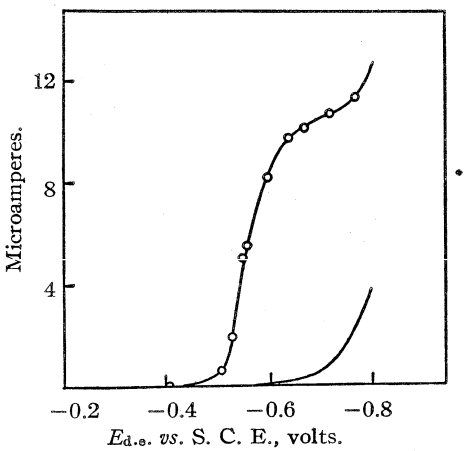



Fig. 2.—Polarogram of 2.61 millimolar tungsten(V) in 12 *M* hydrochloric acid.

**Tungsten(V).**—Reduction of solutions of tungsten(VI) in 12 *M* hydrochloric acid on the mercury cathode at −0.40 v. *vs.* S.C.E., *i. e.*, corresponding to the plateau of the first wave of the tungsten(VI) polarogram, produced blue solutions of tungsten(V). The identity of the product was established both by titration with iodate, which indicated an oxidation state of 5.00 in a typical case, and coulometric measurements during the controlled potential electrolysis, which indicated an oxidation state of 4.97. The +5 state has been obtained previously by Collenberg and Backer[12] by reduction of tungsten(VI) in concentrated hydrochloric acid on a platinum cathode without potential control.

As shown in a previous paper[13] the current in a controlled potential electrolysis in which diffusion is the controlling factor obeys the relation $i = i_0 \cdot 10^{-kt}$, where $k = 0.43\ DA/\delta V$, where $D$ is the diffusion coefficient, $A$ the electrode area, $V$ the solution volume, $\delta$ the diffusion layer thickness and $t$ is time. In reductions of 2, 4 and 8 millimolar tungsten(VI) in 12 *M* hydrochloric acid at −0.40 v. *vs.* S.C.E., the plots of log $i$ *vs.* time gave straight lines as required by the above equation, and the values of $k$ obtained were 0.049, 0.052 and 0.052 min.$^{-1}$, respectively. Under these conditions reduction to the +5 state was 99% complete in 2/0.051 or thirty-nine minutes.

The polarogram for the reduction of tungsten(V) to the +3 state is shown in Fig. 2. The slope of the wave corresponds to a reversible 2-electron reduction. The half-wave potential (0.56 v.) is identical with that of the second wave of the tungsten(VI) polarogram, and the diffusion current constant as shown in Table II agrees very well with the value 2.51 found for the difference between the two constants for the tungsten(VI) waves. No anodic wave is observed, showing that the potential of the tungsten(VI)–tungsten(V) couple has a value more positive than the oxidation potential of mercury.

TABLE II

DIFFUSION CURRENT CONSTANT OF TUNGSTEN(V) IN 12 *M* HYDROCHLORIC ACID AT 25°

| Tungsten(V) millimolar | $m^{2/3}t^{1/6}$ mg.$^{2/3}$ sec.$^{-1/2}$ | $i_d/Cm^{2/3}t^{1/6}$ at −0.67 v. *vs.* S. C. E. |
|---|---|---|
| 0.79 | 1.57 | 2.53 |
| 1.59 | 1.59 | 2.55 |
| 1.78 | 2.09 | 2.53 |
| 2.37 | 1.57 | 2.49 |
| | | Av. 2.53 ± 2 |

On dilution of a hydrochloric acid solution of tungsten(V) the blue color remains and the polarogram is qualitatively unchanged until the acid concentration is somewhat less than 6 *M*, but on further dilution the solution turns progressively more yellow, and the polarographic wave disappears.

(12) O. Collenberg and J. Backer, *Z. Elektrochem.*, **30**, 230 (1924).
(13) J. J. Lingane, *Anal. Chim. Acta*, **2**, in press (1948).

**Coulometric Reduction of Tungsten(V).**—The formation of tungsten(IV) in the reduction of tungsten in hydrochloric acid has previously been somewhat uncertain. The solid $K_2W(OH)Cl_5$ was isolated by Collenberg and Backer[12] from solutions of tungsten in concentrated hydrochloric acid after reduction on lead or mercury cathodes to below the +5 state, but these authors voiced the suspicion that the apparent tungsten(IV) might be only a compound between tungsten(V) and tungsten(III). The tungsten(VI) and tungsten(V) polarograms that we have studied indicate that reduction of tungsten(V) to tungsten(III) takes place directly, and that tungsten(IV) is unstable with respect to disproportionation into the higher and lower states.

Collenberg and Backer[12] isolated red $Rb_2WCl_5 \cdot H_2O$ containing tungsten(III) from solutions reduced on a mercury or lead cathode at temperatures below 18°; the red form was converted to the familiar green $Rb_3W_2Cl_9$ at higher temperatures.

In order to carry out the reaction corresponding to the tungsten(V) polarogram in Fig. 2, a solution of tungsten(VI) in 12 *M* hydrochloric acid was first reduced to tungsten(V) at −0.40 v. and then reduced further at −0.67 v. *vs.* S.C.E., a potential on the plateau of the tungsten(V) wave. The blue tungsten(V) solution first became purple, then red and finally yellow. After passing the +5 state and while the solution remained red the current consumption indicated by the coulometer was in close agreement with that indicated by iodate titration, *i. e.*, the current efficiency was 100%. The indicated oxidation state at one such point in the reduction of 0.01 *M* tungsten at 18° was 3.08 coulometrically and 3.09 by iodate titration. Since the solution was still red at this point, and turned yellow rather rapidly after the current had dropped to a nearly negligible value, it is clear that the red solution contained tungsten(III) rather than tungsten(IV). Immediately after completion of the electrolysis, iodate titration of the yellow solution indicated an oxidation state of 2.89, while the coulometer indicated 2.76. The latter value was lower due to a visible simultaneous reduction of a small amount of hydrogen ion near the end of the electrolysis. About fifteen minutes after completion, iodate titration indicated an oxidation state of 3.01. It thus appears possible that some lower state is formed, but is rapidly oxidized by hydrogen ion to the +3 state. All attempts to obtain reduction to a lower state failed. It is seen, therefore, that the reduction of tungsten(V) proceeds to red tungsten(III), which is spontaneously converted to the green or yellow form. The red form is presumably the reduction product involved in the polarographic wave.

We have obtained some evidence that either tungsten(IV) or a compound of tungsten(V) and tungsten(III) is produced transiently during the coulometric reduction of hydrochloric acid solutions of tungsten(V) when the concentration of the latter is relatively large. When 8 and 2 millimolar solutions of tungsten(V) were reduced, the red color produced after the quantity of electricity passed corresponded to the +4 state was much more intense with the larger concentration than could be accounted for by the ratio of the concentrations. Such intensification of color is commonly associated with compounds containing an element in two oxidation states. Further indication of an apparent +4 state was obtained by measurement of the oxidation potential at various stages during the reduction of a 2 millimolar and an 8 millimolar solution of tungsten(V). The potentials were measured against the saturated calomel electrode by interrupting the electrolysis and employing the large mercury cathode as indicator electrode. The data obtained are shown in Table III.

TABLE III

POTENTIAL CHANGES DURING REDUCTION OF TUNGSTEN (V) TO RED TUNGSTEN(III) IN 12 *M* HYDROCHLORIC ACID

The potentials are referred to the saturated calomel electrode.

(a) Total tungsten, 2.00 milimolar; 1 electron = 8.40 ml. hydrogen-oxygen at S. T. P.

| Coulometer reading, S.T.P., ml. | Apparent oxidation state | $E_{obs.}$ | $E^0$ |
|---|---|---|---|
| 0 | 5.00 | −0.350 | ..... |
| 2.50 | 4.70 | − .537 | −0.559 |
| 4.23 | 4.50 | − .541 | − .555 |
| 6.44 | 4.23 | − .549 | − .555 |
| 8.43 | 4.00 | − .554 | − .554 |
| 10.80 | 3.71 | − .562 | − .555 |
| 12.50 | 3.51 | − .568 | − .554 |
| 13.81 | 3.35 | − .575 | − .555 |
| 15.01 | 3.21 | − .583 | − .555 |
| 16.10 | 3.08 | − .595 | − .554[a] |
| 16.65 | 3.02 | − .606 | − .556[a] |
| | | Av. | −0.555 ± 1 |

[a] These solutions were beginning to turn yellow.

(b) Total tungsten, 8.00 millimolar; 1 electron = 33.6 ml. S. T. P.

| | | | |
|---|---|---|---|
| 0 | 5.00 | −0.343 | ..... |
| 3.38 | 4.90 | − .495 | − .533 |
| 9.95 | 4.70 | − .504 | − .526 |
| 15.91 | 4.53 | − .505 | − .520 |
| 21.25 | 4.37 | − .513 | − .523 |
| 27.80 | 4.17 | − .502 | − .506 |
| 35.8 | 3.92 | − .516 | − .514 |
| 44.4 | 3.68 | − .533 | − .524 |

The values of $E^0$ listed in the last column of Table III were computed by the equation $E_{obs.} = E^0 - (0.059/2) \log C_{III}/C_V$, where $C_{III}/C_V$ is the ratio of the concentrations of +3 and +5 tungsten calculated from the coulometer readings. With the 2 millimolar solution a very constant value of $E^0$ is obtained over the entire range of values of $C_{III}/C_V$, showing that the couple behaves reversibly at this concentration. Furthermore the $E^0$ value agrees with the half-wave po-

tential observed with tungsten(V) solutions (−0.56 v.), showing that the reduction of tungsten(V) to red tungsten(III) proceeds reversibly at the dropping electrode. With the 8 millimolar solution, on the other hand, the $E^0$ values are much too positive, and are not constant with varying values of $C_{III}/C_V$ but show a steady decrease down to an apparent oxidation state of +4, and then an increase with larger values of the $C_{III}/C_V$ ratio. Furthermore the observed potentials with the 8 millimolar solution were not steady but showed a continuous positive drift. Slow combination of tungsten(V) and tungsten(III) to produce a compound of the two states, or actual reaction to produce tungsten(IV), could account for this behavior.

**Red Tungsten(III).**—Solutions of the red form of tungsten(III) in 12 *M* hydrochloric acid were prepared by partial electrolytic reduction of tungsten(V) as described above. The reductions were not carried to completion because transformation of the red tungsten(III) to the yellow form occurs when this is done. The typical polarogram of such a mixture shown in Fig. 3 displays a well developed anodic diffusion current due to the oxidation of tungsten(III), as well as the cathodic wave of the remaining tungsten(V).

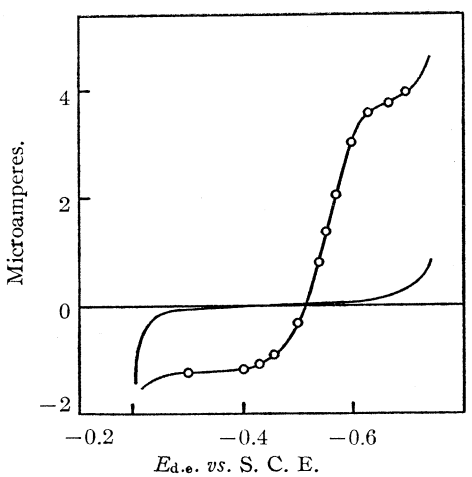



Fig. 3.—Polarogram of a mixture of 0.91 millimolar tungsten(V) and 0.67 millimolar red tungsten(III) in 12 *M* hydrochloric acid.

The fact that the composite cathodic–anodic wave shows no inflection at zero current is a commonly accepted criterion for reversibility of the electrode reactions but is misleading in this case because the anodic reaction is not the reverse of the cathodic reaction.

The anodic wave of red tungsten(III) actually corresponds to oxidation to the +4 state and not to the +5 state. With concentrations of red tungsten(III) between 0.3 and 0.7 millimolar the anodic diffusion current was directly proportional to concentration, and the average value of the diffusion current constant $i_d/Cm^{2/3}t^{1/6}$ was 1.10 ± 0.01 at 25° in 12 *M* hydrochloric acid. This is somewhat less than one-half the diffusion current constant (2.53) observed in the 2-electron reduction of tungsten(V), and slightly smaller than the diffusion current constant (1.31) observed in the 1-electron reduction of tungsten(VI) in 12 *M* hydrochloric acid. It is evident that the red tungsten(III) undergoes only a 1-electron oxidation to the +4 state. The alternative conclusion (oxidation to the +5 state) would require that the diffusion coefficient of tungsten(III) be about five times smaller than the diffusion coefficients of tungsten(V) and tungsten(VI), and this is very improbable.

This interesting result indicates that the rate of disproportionation of tungsten(IV) must be so small that no appreciable disproportionation occurs during the life of each mercury drop at the dropping electrode.

The absorption spectrum of red tungsten(III), which has not previously been reported, is shown as curve 1 in Fig. 4. This was obtained with a mixture of tungsten(III) and tungsten(V) and correction was applied for the small contribution of tungsten(V) to the measured optical density in calculating the extinction coefficient of the tungsten(III).

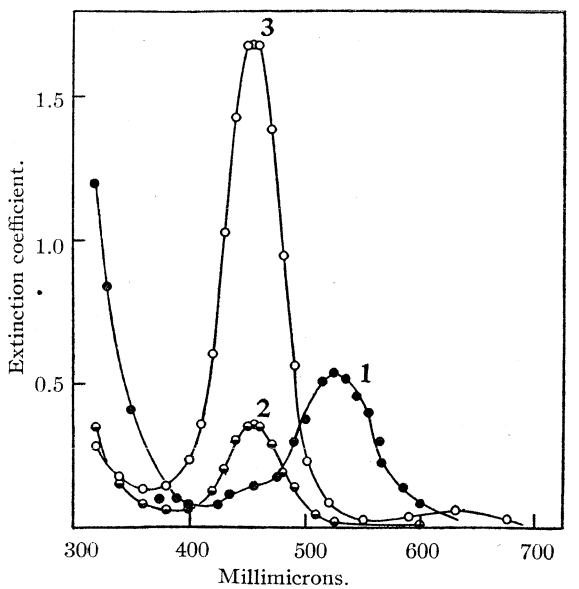



Fig. 4.—Absorption spectra of tungsten(III): (1), red form; (2), yellow form; (3), green form. Measured with Beckman UV Spectrophotometer with slit widths adjusted so that nominal band width was smaller than 4 millimicrons at all wave lengths.

**Yellow and Green Tungsten(III).**—Solutions of the red tungsten(III) turn yellow on standing, continued electrolysis or heating. A typical polarogram of the previously unreported yellow tungsten(III) is shown in Fig. 5. The well developed anodic wave has a half-wave potential of −0.53 v. *vs.* S.C.E., and thus nearly the same

as that of the red form. The anodic diffusion current is directly proportional to the concentration of yellow tungsten(III) only below about 4 millimolar, and with larger concentrations the diffusion current "constant" decreases significantly. The average value of $i_d/Cm^{2/3}t^{1/6}$ with 1 to 4 millimolar yellow tungsten(III) in 12 *M* hydrochloric acid was found to be 1.38 ± 0.06 at 25°. This is so nearly the same as that observed with red tungsten(III) that it is clear that the yellow form, like the red form, is oxidized only to the +4 state at the dropping electrode.

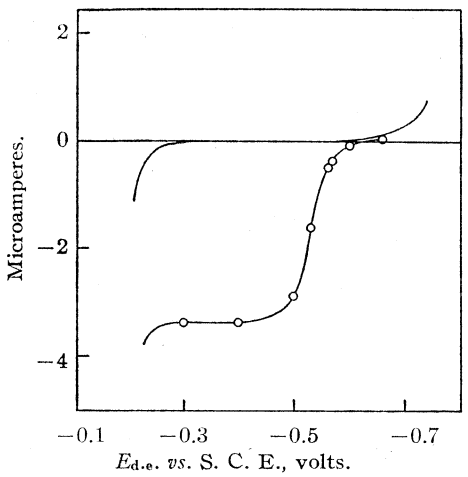



Fig. 5.—Polarogram of 1.59 millimolar yellow tungsten (III) in 12 *M* hydrochloric acid.

That the "yellow" form of tungsten(III) is actually distinct from the familiar "green" modification is demonstrated by the fact that solutions of the green $K_3W_2Cl_9$, prepared by the method of Olsson,[14] showed no anodic wave in either concentrated or dilute hydrochloric acid.

Absorption spectra of the "yellow" and "green" forms of tungsten(III) are shown in Fig. 4. The extinction of the green form at 455 millimicrons was found to obey Beer's law over a tenfold range of concentrations. The spectrum of the "yellow" form shows the same band at 455 millimicrons as the green form, but its extinction coefficient is very much smaller. Furthermore, solutions of the "yellow" form do not obey Beer's law; the extinction coefficient at 455 millimicrons was found to increase from 0.058 to 0.71 when the concentration was increased from 1 to 16 millimolar. The extinction coefficient of the green form is 1.64 at 455 millimicrons.

It seems very likely from these experiments that the "yellow" form may actually be a colorless modification of tungsten(III), and the apparent yellow color probably is caused by a small amount of the "green" form in the solutions used. This yellow or colorless form transforms to the "green" form, the rate and relative proportion of the "green" form increasing with increasing concentration.

(14) O. Olsson, *Z. anorg. allgem. Chem.*, **88**, 50 (1914).

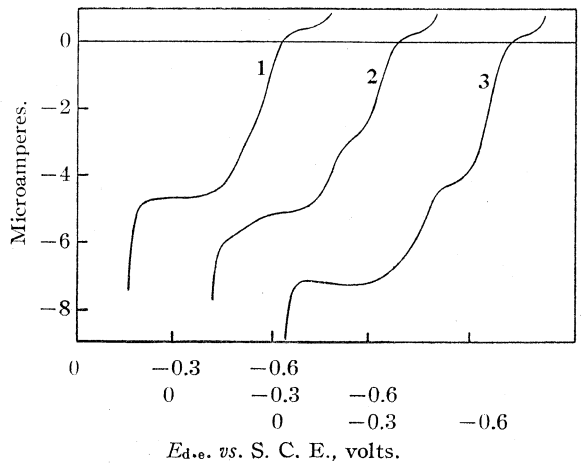



Fig. 6.—Polarogram of 1.33 millimolar yellow tungsten (III) in: (1) 9 *M*, (2) 6 *M*, and (3) 3 *M* hydrochloric acid.

Figure 6 shows polarograms of the same concentration of the "yellow" tungsten(III) in 9, 6 and 3 *M* hydrochloric acid. With decreasing concentration of hydrochloric acid the anodic wave divides into two parts and the total diffusion current increases markedly. The magnitude of the total diffusion current in 3 *M* hydrochloric acid, coupled with the fact that the two parts of the wave are of nearly equal height, indicates stepwise oxidation of the tungsten(III) to the +4 and +5 states. The other alternative is that the doublet wave results from the separate oxidation to the +4 state of two different molecular species of +3 tungsten in sluggish equilibrium, and the increase in the total diffusion current would then be attributed to an increased diffusion coefficient in 3 *M* hydrochloric acid. We believe, however, that this is unlikely.

**Controlled Potential Oxidation of "Yellow" Tungsten(III).**—Electrolytic oxidation of yellow solutions of tungsten(III) in 12 *M* hydrochloric acid was performed with the potential of the mercury electrode at −0.40 v. *vs.* S C.E., corresponding to the plateau of the anodic polarographic wave (compare Fig. 5). The oxidation was followed coulometrically. The results obtained with various concentrations of tungsten (III) at different temperatures are summarized in Table IV.

In all cases the current decreased to virtually zero at the end of the electrolysis, and the values of the average final oxidation state computed from the coulometer reading are listed in Table IV.

During the initial stages of the electrolysis the solutions tended to bleach slightly. For example, during the oxidation of a 4 millimolar solution the optical density at 455 millimicrons decreased from 0.197 to 0.186, and no other absorption band appeared, up to an apparent oxidation state of 3.50. On continued electrolysis

TABLE IV

FINAL OXIDATION STATE OF YELLOW TUNGSTEN(III) OXIDIZED AT −0.40 V. *vs.* S. C. E. IN 12 *M* HYDROCHLORIC ACID

Oxidation states determined by coulometric measurement.

| Tungsten, mg. atoms/l. | Temp. of oxidation, °C. | Oxidation state, av. |
|---|---|---|
| 1.00 | 25 | 4.49 |
| 2.00 | 10 | 4.48 |
| 2.00 | 25 | 4.56 |
| 2.00 | 25 | 4.64 |
| 2.00 | 30 | 4.52 |
| 4.00 | 12 | 4.80 |
| 4.00 | 20 | 4.51 |
| 4.00 | 20 | 4.48 |
| 4.00 | 20 | 4.65 |
| 4.00 | 25 | 4.76 |
| 4.00 | 25 | 4.70 |
| 4.00 | 30 | 4.20 |
| 4.00 | 30 | 4.37 |
| 8.00 | 13 | 3.99 |
| 8.00 | 12 | 4.08 |
| 8.00 | 20 | 4.37 |
| 8.00 | 20 | 4.38 |
| 8.00 | 25 | 4.35 |
| 8.00 | 25 | 4.33 |
| 8.00 | 33 | 4.12 |
| 16.0 | 25 | 3.86 |

the solution became red and the absorption band at 525 millimicrons of red tungsten(III) appeared. This band then faded out and the solution finally acquired a pale brownish-yellow color with a weak band at 455 millimicrons.

With the larger concentrations of tungsten (III) the final oxidation state is very close to +4, especially at the lower temperatures, but with small concentrations the final apparent oxidation state is consistently in the neighborhood of 4.5 and independent of the temperature between 10 and 30°.

These results furnish a clear indication that a fairly stable molecular species containing tungsten (IV) and tungsten(V) in a 1:1 ratio is formed in the more dilute solutions. Apparently the "yellow" tungsten(III) is first oxidized to a colorless species of tungsten(IV), which then slowly disproportionates to red tungsten(III) and tungsten(V). On continued electrolysis the red tungsten(III) is oxidized to tungsten (IV), and finally the tungsten(IV) and tungsten (V) combine to form a stable species with an apparent oxidation state of +4.5. The fact that with the larger concentrations the final oxidation state was closer to +4 than +4.5 was simply caused by the original presence in these solutions of a considerable proportion of the green tungsten(III) which, as the polarographic experiments demonstrate, is not easily oxidized at the mercury electrode. This interpretation is substantiated by the fact that the absorption spectra of the final solutions obtained with the larger concentrations showed the characteristic band of green tungsten(III) at 455 millimicrons. No other band is observed with the final solutions.

The final solutions containing the tungsten in an apparent oxidation state of +4.5 produce a polarogram which comprises a single cathodic wave with a half-wave potential of −0.56 v. *vs.* S.C.E., and is thus very similar to the wave of tungsten(V). The average diffusion current constant, measured with several solutions in which the apparent oxidation state of the tungsten was between 4.49 and 4.56, was 2.28 ± 0.04, which is consistent with reduction to the +3 state. This was confirmed by controlled potential reductions of the final solutions which yielded the "yellow" form of tungsten(III).

## Summary

The polarogram of tungsten(VI) in 12 *M* hydrochloric acid consists of two waves: one, reduction to tungsten(V), starting from the anodic dissolution potential of mercury, and the second, reduction to red tungsten(III), having a half-wave potential of −0.56 v. *vs.* S.C.E. Using these waves as guides, tungsten(VI) was reduced by controlled potential electrolysis with a large mercury cathode at −0.40 v. *vs.* S.C.E. to tungsten(V), the polarogram of which is identical with the second wave of the tungsten(VI) polarogram.

On reducing tungsten(V) at −0.67 v. *vs.* S.C.E. red tungsten(III) was found to be the primary product, with a deep red tungsten(IV) formed during reduction of 4 and 8 millimolar solutions but not of 2 millimolar. A mixture of tungsten(V) and red tungsten(III) gives a continuous anodic–cathodic polarographic wave at −0.55 v., with the anodic oxidation being to tungsten(IV) rather than to tungsten(V).

The standard reduction potential of the tungsten(V), red tungsten(III) couple in 12 *M* hydrochloric acid at 25° was found to be −0.555 ±5 v. *vs.* S.C.E.

Red tungsten(III) is spontaneously converted to a "yellow" tungsten (III) which displays an anodic polarographic wave at −0.53 v. *vs.* S.C.E. It was shown that in more concentrated solution, the familiar green tungsten (III), which gives no polarographic wave, is formed.

Electrolytic oxidation of yellow tungsten(III) at −0.40 v. *vs.* S.C.E. produced tungsten(IV) which disproportionates to red tungsten(III) and tungsten(V); tungsten(V) and tungsten (IV) then combine in dilute solution in a 1:1 ratio to form a species with an apparent oxidation state of +4.5. The polarogram of this species shows a cathodic wave at −0.56 v. *vs.* S.C.E., corresponding to reduction to the +3 state.

Absorption spectra of the red, yellow and green species of tungsten(III) are presented.

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# Synthesis of Chlorofluoropropanes

BY DONALD D. COFFMAN, RICHARD CRAMER AND G. W. RIGBY

Chloroform or carbon tetrachloride reacts with chloroethylenes in the presence of aluminum chloride to yield chloropropanes.[1] In seeking to extend this addition reaction to fluorinated methanes, Henne and co-workers[2] were deterred by the replacement of organic fluorine by chlorine from the aluminum chloride catalyst; to prepare the desired chlorofluoropropanes, they treated various chloropropanes with antimony fluoride.[2b,3]

We have now successfully brought about the aluminum chloride-catalyzed addition of chloromethanes and chlorofluoromethanes to tetrafluoroethylene as shown in Table I. In addition reactions with chlorotrifluoroethylene (see Table II), the yields were smaller and halogen exchange occurred with replacement of organic fluorine by chlorine.

TABLE I

PRODUCTS FROM HALOMETHANES AND TETRAFLUOROETHYLENE

| Halomethane | Primary adduct | % | Halogen replacement product |
|---|---|---|---|
| $CHCl_3$ | $CHCl_2CF_2CF_2Cl$ | 83 | |
| $CCl_4$ | $CCl_3CF_2CF_2Cl$ | 88 | |
| $CCl_3F$ | $CCl_2FCF_2CF_2Cl$ | 55 | |
| $CHCl_2F$ | $CHClFCF_2CF_2Cl$ | 50 | |
| $CHClF_2$ | | | $C_3Cl_2F_5H$ (14%) |
| $CHCl_2F$ | $CHClFCCl_2CCl_3$[a] | 58 | |

[a] Adduct from tetrachloroethylene. The authors are indebted to Dr. W. A. Hoffman for this experiment.

TABLE II

PRODUCTS FROM HALOMETHANES AND CHLOROTRIFLUOROETHYLENE

| Halomethane | Primary adduct | % | Halogen replacement product | % |
|---|---|---|---|---|
| $CHCl_3$ | $CHCl_2CF_2CFCl_2$ | 2 | $CHCl_2CF_2CCl_3$ | 20[a] |
| $CCl_4$ | $CCl_3CF_2CFCl_2$ | 14 | $CCl_3CF_2CCl_3$ | 30 |
| | | | $C_3Cl_4F_4$ | 18 |
| $CCl_3F$ | $CCl_2FCF_2CFCl_2$ | 30 | | |
| $CHCl_2F$ | $CHClFCF_2CFCl_2$ | 28 | | |
| $CHClF_2$ | | | $C_3Cl_3F_4H$ | 9 |

[a] The authors are indebted to Dr. T. A. Ford for this experiment.

Formation of the primary adducts without halogen exchange appears dependent on the use of a monofluoromethane. Thus dichlorofluoromethane and trichlorofluoromethane gave only the primary products in reactions with tetrafluoroethylene, chlorotrifluoroethylene or tetrachloroethylene. In a single instance, the replacement of chlorine by fluorine was observed. The product from carbon tetrachloride and chlorotrifluoroethylene contained a fraction $C_3Cl_4F_4$ which can be accounted for in this way.

The structures assigned in Table III to five of the chlorofluoropropanes are identical with structures previously proposed by Henne and coworkers for chlorofluoropropanes synthesized in a different way and of somewhat different properties. The structures designated in Table III can be inferred from the following facts. The product from carbon tetrachloride and tetrafluoroethylene corresponds in composition to the chlorofluoropropane formed by addition of one chlorine atom and one trichloromethyl group across the ethylenic bond. In reactions involving a chloromethane containing hydrogen or fluorine, the fragments which add must also be chlorine and its complementary halomethyl group, since neither carbon tetrafluoride nor trifluoromethane combines with tetrafluoroethylene and since the carbon–hydrogen bond of chloroform is not broken in Prins type reactions.[1b]

The synthesis of chlorofluoropropanes from chlorotrifluoroethylene apparently proceeds by a similar mechanism. The chlorine evidently attaches itself to chlorotrifluoroethylene at the carbon atom already bonded to chlorine, since none of the products could be dechlorinated by refluxing with zinc and alcohol. This indicates that adjacent carbon atoms are not chlorinated and therefore the central carbon atom of the propane must be completely fluorinated. This mechanism is similar to that established by Prins[1b] for the addition of chloromethanes to chloroethylenes.

In selected instances in which fluorine was replaced by chlorine, the halogen exchange *must* have taken place after formation of the chlorofluoropropane, while in other instances the exchange *may* have occurred before the Prins type reaction.

## Experimental

Most of the chlorofluoropropanes were synthesized in a silver-lined autoclave under their own pressures at 50–125° with aluminum chloride catalyst present in amounts ranging from 0.5 to 10.0% by weight of combined reactants. The reaction times varied from two to twenty-four hours. The reactants used and the yields and properties of the products are listed in Table III. The aluminum chloride, and halomethane if liquid at room temperature, were placed in the

(1) (a) Böeseken and Prins, *K. Akad. Weienschappen, Amsterdam*, **19**, 776 (1911); (b) Prins, *J. prakt. Chem.*, **89**, 414 (1914); (c) Prins, *Rec. trav. chim.*, **51**, 1065 (1932); (d) Prins and Engelhard, *ibid.*, **54**, 307 (1935).

(2) (a) Henne and Newman, THIS JOURNAL, **60**, 1697 (1938); (b) Henne and Ladd, *ibid.*, **60**, 2491 (1938).

(3) (a) Henne and Renoll, *ibid.*, **59**, 2434 (1937); (b) Henne and Renoll, *ibid.*, **61**, 2489 (1939); (c) McBee, Henne, Hass and Elmore, *ibid.*, **62**, 3340 (1940); (d) McBee, Truchan and Bolt, *ibid.*, **70**, 2023 (1948).

TABLE III

SYNTHESIS OF CHLOROFLUOROPROPANES

| Reactant[f] Methane | Reactant[f] Ethylene | Probable structure | Products Yield,[g] % | Products B. p., °C. | $n^{25}D$ | $d^{25}_4$ | Analyses, % C | Calcd. Cl | Calcd. F | Found C | Found Cl | Found F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CHCl_3$ | $C_2F_4$ | $CHCl_2CF_2CF_2Cl$[a] | 83 | 91.2 | 1.3704 | 1.6115 | | 48.6 | 34.6 | | 47.4 | 32.7 |
| $CCl_4$ | $C_2F_4$ | $CCl_3CF_2CF_2Cl$[b] | 88 | 114.5 | 1.3974 | 1.6927 | | 55.9 | 29.9 | | 56.1 | 30.4 |
| $CCl_3F$ | $C_2F_4$ | $CCl_2FCF_2CF_2Cl$ | 54 | 72–73 | 1.3578 | 1.6429 | 15.2 | 44.9 | | 16.1 | 44.7 | |
| $CHCl_2F$ | $C_2F_4$ | $CHClFCF_2CF_2Cl$ | 46 | 51–53 | 1.3262 | 1.5492 | 17.7 | 34.9 | 46.8 | 18.1 | 33.8 | 43.7 |
| $CHClF_2$ | $C_2F_4$ | $C_3Cl_2F_5H$ | 12 | 52–54 | | | 17.7 | 34.9 | | 17.8 | 33.1 | |
| $CHCl_2F$ | $C_2Cl_4$ | $CHClFCCl_2CCl_3$ | 38 | 209–211 | 1.5072 | | | 79.2 | | | 78.5 | |
| $CHCl_3$ | $C_2ClF_3$ | $CHCl_2CF_2CFCl_2$ | 2 | 127 | 1.4189 | 1.6704 | | 60.2 | 24.2 | | 60.8 | 23.6 |
| | | $CHCl_2CF_2CCl_3$[c] | 10 | 171–172 | 1.4621 | 1.7241 | | 70.3 | 15.1 | | 67.1 | 14.8 |
| $CCl_4$ | $C_2ClF_3$ | $CCl_3CF_2CFCl_2$[d] | 3 | 155.5–157 | 1.4399 | 1.7608 | 13.4 | 65.6 | 21.0 | 13.4 | 61.8 | 20.5 |
| | | $CCl_3CF_2CCl_3$[e] | 9 | 196.5–197 | 1.4777 | 1.7975 | 12.5 | 74.2 | 13.3 | 13.1 | 71.5 | 13.1 |
| | | $C_3Cl_4F_4$ | 6 | 114–115.5 | 1.4081 | | 14.2 | 55.9 | 29.9 | 14.4 | 54.1 | 24.7 |
| $CCl_3F$ | $C_2ClF_3$ | $CCl_2FCF_2CFCl_2$ | 24 | 112.5–115 | 1.3980 | 1.7006 | 14.2 | 55.9 | 29.9 | 14.0 | 54.0 | 26.1 |
| $CHCl_2F$ | $C_2ClF_3$ | $CHFClCF_2CFCl_2$ | 20 | 90–91 | 1.3712 | 1.6162 | 16.4 | 48.6 | 34.6 | 16.7 | 46.1 | 33.1 |
| $CHClF_2$ | $C_2ClF_3$ | $C_3Cl_3F_4H$ | 20 | 90–93 | 1.3710 | 1.6142 | 16.4 | 48.6 | 34.6 | 16.9 | 47.3 | 35.0 |

[a] Henne, *et al.*,[4c] have assigned this structure to a compound boiling at 91.7–91.9°; $n^{20}D$ 1.3750; $d^{20}_4$ 1.5877. [b] Henne, *et al.*,[4c] have described a compound of this structure, b. p. 112–112.5°; $n^{20}D$ 1.3961; $d^{20}_4$ 1.6992. [c] Henne, *et al.*,[4a] have described a compound of this structure, b. p. 174°; $n^{20}D$ 1.46410; $d^{20}_4$ 1.7557. [d] Melts at 55–56°. Henne, *et al.*,[4a] attribute this structure to a compound melting < −80°; b. p. 152–154°; $n^{20}D$ 1.43887; $d^{20}_4$ 1.7607. [e] Melts at −5°. Henne, *et al.*,[4a] have described a compound of this structure, b. p. 194–194.4°; m. p. −15.8°; $n^{20}D$ 1.48064; $d^{20}_4$ 1.8136. [f] When carbon tetrachloride or chloroform was one of the reactants the mole ratio of methane to olefin was about 2:1. In all other cases the mole ratio was 1:1. [g] Based on olefin used.

autoclave which was closed and chilled in Dry Ice–acetone. The halomethane if gaseous at room temperature and the haloethylene were forced in under pressure. The autoclave was clamped in a reciprocating shaker and heated. Following reaction, the gaseous compounds were bled off and liquified in a trap cooled with Dry Ice–acetone. The condensate was fractionally distilled. The liquid and solid remaining in the autoclave were removed by slurrying with ether. The slurry was shaken with hydrochloric acid containing crushed ice, and the ethereal extract was washed with water, dried over Drierite and fractionally distilled.

The reaction of dichlorofluoromethane with tetrachloroethylene was carried out at atmospheric pressure. A glass flask fitted with a reflux condenser and an efficient stirrer was charged with tetrachloroethylene and aluminum chloride at room temperature, and dichlorofluoromethane was distilled in slowly. The reaction was accompanied by the evolution of heat. When the reaction mixture had cooled to room temperature, the product was removed and washed with hydrochloric acid containing ice. After washing with water, the product was dried over calcium chloride and fractionated.

**Acknowledgment.**—The authors desire to express their appreciation to Dr. Paul R. Austin and to Dr. R. M. Joyce for helpful suggestions relating to this investigation.

## Summary

Chlorofluoropropanes, including several new ones, have been prepared by the reaction of halogenated methanes with haloethylenes in the presence of aluminum chloride.

Reactions of chloroform or carbon tetrachloride with tetrafluoroethylene, of dichlorofluoromethane or trichlorofluoromethane with tetrafluoroethylene or chlorotrifluoroethylene, and of dichlorofluoromethane with tetrachloroethylene, proceeded normally without appreciable replacement of fluorine by chlorine. Halogen replacement occurred in reactions involving chlorodifluoromethane.

WILMINGTON, DELAWARE RECEIVED JULY 27, 1948

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

# Diamides from Carboxylic Acids and their Nitriles

BY RICHARD H. WILEY AND W. B. GUERRANT

The formation of diamides on heating together an acid and its nitrile was first observed by Gau-

$$RCO_2H + RCN \longrightarrow (RCO)_2NH$$

tier[1a] and subsequently extended[1b-h] to a variety of acid–nitrile combinations. These studies, although not defining optimum reaction conditions, established that yields of diamide are increased by the presence of negative substituents on the $\alpha$-carbon atom. Trichloroacetic acid and nitrile gave a nearly quantitative yield and phenylacetic acid and its nitrile gave "good" yields of diamide. In the present study it has been shown that the phenylacetic acid–nitrile reaction is an equilibrium and that the yield is dependent upon reaction temperature and reaches a maximum of 45%. Also, it has been shown that the reaction of *p*-nitrophenylacetic acid with its nitrile to form the corresponding diamide, a new compound, takes place more rapidly than does the reaction of the unsubstituted phenylacetic type. Considerable decomposition accompanies the reaction of the nitro compounds.

## Experimental

Phenylacetic acid (Eastman Kodak Co.) was recrystallized from petroleum ether and vacuum dried over phosphorus pentoxide. Phenylacetonitrile (E. K. Co.) was redistilled from phosphorus pentoxide and a fraction b. p. 109–111° (4–6 mm.) collected. *p*-Nitrophenylacetic acid (E. K. Co.) was used and *p*-nitrophenylacetonitrile was prepared by nitration of phenylacetonitrile.[2]

The reaction between nitrile and acid was carried out by heating together equimolar amounts of acid and nitrile at the desired temperature. Since slightest exposure of the hot reaction mixture to air caused an immediate discoloration, all operations were conducted under oxygen-free nitrogen. The reaction mixture was sampled at time intervals and the composition of the phenylacetic acid–nitrile samples determined by one of the following methods.

A. The cooled, solidified sample (4–20 g.) was pulverized and thoroughly washed twice with 100 ml. of ether. The residue was dried and weighed as $\alpha,\alpha'$-diphenyldiacetamide, m. p. 189–191°, reported[1b] m. p. 192°. A typical sample gave the following analysis.

*Anal.* Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.88.

The ether solution was titrated with standard potassium hydroxide to a phenolphthalein end-point and the acidity expressed as yield of phenylacetic acid. With three samples the aqueous alkaline extract of the ether solution was acidified to precipitate phenylacetic acid. A typical sample of acid gave the following analysis.

*Anal.* Calcd. for $C_8H_9O_2$: neut. equiv., 142. Found: neut. equiv., 136.

The yield of acid isolated in this way was 90% of the amount calculated from the titration. The ether extracts after washing with aqueous alkali were evaporated to dryness and the residue weighed as phenylacetonitrile. A typical sample of nitrile gave the following analysis.

*Anal.* Calcd. for $C_8H_7N$: sapon. equiv., 117. Found: sapon. equiv., 119.

The total yield of isolated products in the three fractions accounted for 86–89% of the starting materials. A prepared mixture of the three products was separated by this technique with 95.2% accuracy.

B. This procedure, similar to that used by Colby and Dodge,[1b] was considered less reliable because of possible alcoholysis or hydrolysis of the diamides noted by Konig[1c] with phthalonitrile. A sample of $\alpha,\alpha'$-diphenyldiacetamide, subjected to this separation procedure, was recovered in 87% yield. The sample was washed with 5% aqueous sodium carbonate, then with 95% ethanol at 0°, and finally recrystallized from 95% ethanol. Prolonged heating in dissolving the diamide was avoided. The yield of diamide was taken as the amount of dried, recrystallized solid.

The composition of the reaction mixture using *p*-nitrophenylacetic acid and its nitrile was determined by the following procedure.

C. The sample was extracted with ether in an Underwriter's extraction apparatus. The extracted residue was $\alpha,\alpha'$-di-(*p*-nitrophenyl)-diacetamide, m. p. 215–219° dec. Recrystallization from nitrobenzene gave a product m. p. 219–221° dec. in 95% recovery.

*Anal.* Cacld. for $C_{16}H_{13}N_3O_6$: C, 55.86; H, 3.82; N, 12.24. Found: C, 55.75; H, 3.81; N, 12.38.

The weight of extracted residue was taken as yield of diamide. The extracts were titrated for acidity, which, calculated as *p*-nitrophenylacetic acid, was taken as unreacted acid. The acid isolated was found to be essentially that calculated by titration. The unreacted nitrile was not separated from nitrobenzene solvent left in the neutral residue. The ether insoluble residue obtained in runs made for periods of time much beyond those reported in Fig. 3 was contaminated with a brown impurity which made the estimation of yield of diamide unreliable. Trituration with ether gave similar amounts of extract and was used in most separations in place of the extraction.

The reaction temperature, at first supposed to be of secondary importance, was controlled manually within ±5° for the series reported in Fig. 1. When it became apparent that narrow temperature limits were required, the reaction was carried out in a thermostatically controlled bath at ±2°. The series reported in Figs. 2 and 3 were made thus.

The conversion of $\alpha,\alpha'$-diphenyldiacetamide to an equilibrium mixture was demonstrated by heating 10 g. of diamide at 200°, for one hour to melt, and then at 190° for eight hours. Separation of the reaction mixture by procedure A gave 35.9% yield of recovered diamide, 29.4% of acid by titration, and 29.9% of nitrile as neutral residue. Both $\alpha,\alpha'$-diphenyldiacetamide and $\alpha,\alpha'$-di-(*p*-nitrophenyl)-diacetamide were converted to tars, from which no acid or nitrile was isolated, when heated at 180° for eight to fifteen hours in nitrobenzene.

## Discussion

**Phenylacetic Acid–Nitrile Reaction.**—The data for two series of runs are given in Figs. 1 and 2. The data obtained at 225 and 250° (Fig. 1) show that the reaction produces about 25% of diamide within one to three hours and then on

(1) (a) Gautier, *Compt. rend.*, **67**, 1255 (1868); *Ann.*, **150**, 187 (1869); (b) Colby and Dodge, *Am. Chem. J.*, **13**, 1 (1891); (c) Konig, *J. prakt. Chem.*, [2] **69**, 1 (1904); (d) Miller, THIS JOURNAL, **16**, 433 (1894); (e) Seldner, *Am. Chem. J.*, **17**, 532 (1895); (f) Mathews, THIS JOURNAL, **20**, 648 (1898); (g) Hoogewerff and Van Dorp, *Rec. trav. chim.*, **11**, 91 (1892); (h) Liebermann, *Ber.*, **19**, 2281 (1886).

(2) Robertson, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 396.

prolonged heating the yield of diamide drops off presumably due to decomposition since there is considerable discoloration and tar formation. At 200°, the yield of diamide levels off at about 30% and there is no extensive discoloration and tar formation. At 175° (Fig. 1) and at 180 and 190° (Fig. 2) a constant yield of diamide is established at 35–46%. These data indicate the existence of an equilibrium reaction which was established by converting the melted diamide by heating at 190° for nine hours to a mixture similar in composition to that obtained from the nitrile–acid reaction at this temperature.

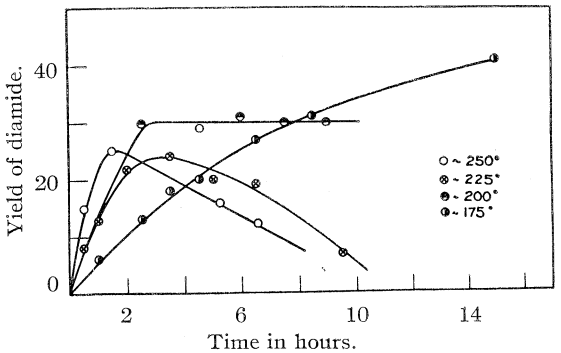



Fig. 1.—Yield of $\alpha,\alpha'$-diphenyldiacetamide at different temperatures; separation by procedure B.

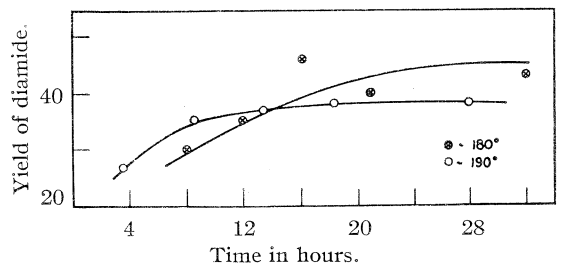



Fig. 2.—Yield of $\alpha,\alpha'$-diphenyldiacetamide at 180–190°; separation by procedure A.

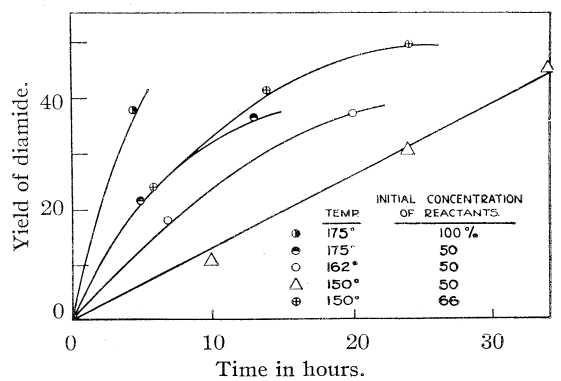



Fig. 3.—Yield of $\alpha,\alpha'$-di-($p$-nitrophenyl)-diacetamide at different temperatures and concentrations.

**$p$-Nitrophenylacetic Acid–Nitrile Reaction.**—The data for this series of runs are given in Fig. 3. Extensive decomposition takes place when the reaction is run at 160° or over. At 175° the reaction mixture solidifies after four hours with formation of 38% yield of diamide. A weight of nitrobenzene equal to or one-half that of the combined weight of nitrile and acid was added to the reaction mixture to give 50 and 66% concentration of total reactants and to keep the reaction mixture liquid in the other run. At the 50% concentration, the reaction rate increases as the temperature is raised from 150 to 175° but decomposition becomes extensive. At 66% concentration yields of 50 and 45% diamide are obtained at twenty-four and thirty-six hours, respectively. Under the conditions tried the maximum yield of diamide was 50% obtained at 66% concentration and 150° for twenty-four hours. The presence of an $\alpha$-$p$-nitrophenyl group increases the rate of reaction. High yields are not formed presumably because of side reactions caused by the oxidizing action of the nitro groups.

## Summary

The reaction between phenylacetic acid and phenylacetonitrile gives an equilibrium mixture containing 35–46% $\alpha,\alpha'$-diphenyldiacetamide at 180–190°.

The reaction between $p$-nitrophenylacetic acid and $p$-nitrophenylacetonitrile gives a 38% yield of $\alpha,\alpha'$-di-($p$-nitrophenyl)-diacetamide in four hours at 175°. With nitrobenzene as a solvent 50% of the diamide is formed at 150° in twenty-four hours.

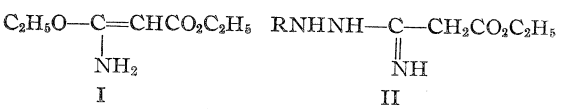
CHAPEL HILL, N. C. RECEIVED JUNE 28, 1948

[COMMUNICATION NO. 1198 FROM THE KODAK RESEARCH LABORATORIES]

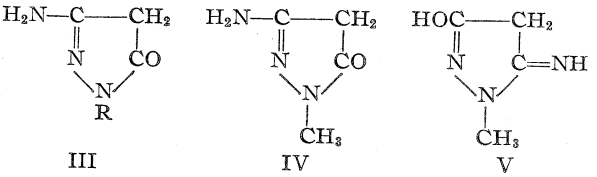
# Investigation of Pyrazole Compounds. VIII.[1] Synthesis and Acylation of Pyrazolones Derived from Hydrazine and Methylhydrazine

BY BRUCE GRAHAM, H. D. PORTER AND A. WEISSBERGER

Aromatic hydrazines and ethyl β-amino-β-ethoxyacrylate, I,[2] form the respective ethyl β-imino-β-(β-R-hydrazino)-propionates, II,[2] and/or 1-R-3-amino-5-pyrazolones, III.[3] The isolation of the intermediate, II, in high yields (80–90%) proves (1) that the $=C(NH_2)OC_2H_5$ group of I reacts in preference to the $-CO_2C_2H_5$ group, and (2) that the β-nitrogen atom of the aromatic hydrazines is much more reactive (basic) than the α-nitrogen atom. The latter observation agrees with the fact that aromatic hydrazines are acylated in the β-position exclusively.[4] However, aliphatic hydrazines are acylated[5] primarily at the more basic[6] α-nitrogen atom, although some acylation takes place in the β-position.[7] In a similar twofold reaction, *methylhydrazine* reacted with I to give two isomers: a compound melting at 180–182° in a yield of 47%, and another compound melting at 192–194° in a 6% yield. Both isomers analyze for the cyclized products, IV or V, and form soluble dyes in the oxidation film-strip test[8] and by condensation with *p*-nitrosodimethylaniline.[9] The formation of dye with both isomers in this latter test is unusual, because 1-aryl or 1-heterocyclic substituted 3-hydroxy-5-pyrazolone imides, *i. e.*, the isomers corresponding to V, give no dye in this test.[9] The fact that the higher-melting isomer obtained from methylhydrazine gives more dye with nitrosodimethylaniline than the lower-melting isomer, suggests[9] the structure *1-methyl-3-amino-5-pyrazolone*, IV, for the compound melting at 192–194°, and the structure *1-methyl-3-hydroxy-5-pyrazolone imide*, V, for the compound melting at 180–182°.



I II



III IV V

An attempt was made to prove the structure of the higher-melting compound to be IV by an unequivocal synthesis similar to that described in the first paper of this series.[10] 1-Methyl-3-carbethoxy-5-pyrazolone, VI, was prepared from methylhydrazine and ethyl oxalacetate. No intermediate methylhydrazone could be isolated in the reaction. However, the product couples in the film-strip test[8] which proves it to be VI and excludes the remotely possible structure, VII. Next, VI was converted to the hydrazide, VIII, and many attempts were made to obtain the azide, IX, from the latter. However, at best only a trace of the azide was isolated because nitrous acid reacted at the 4-position of the pyrazolone ring under the conditions of the experiments. Kufferath[11] got similar results when he treated 5-pyrazolone-3-acethydrazide with nitrous acid. The difference in reactivity between VIII and 1-phenyl-5-pyrazolone-3-carboxhydrazide[10] toward nitrous acid is noteworthy, since the 4-position of the latter is unaffected during the formation of the azide. Excess nitrous acid produced X in good yield. The compound gave uninviting products when subjected to the Curtius degradation.

In order to avoid nitrosation at the 4-position, VI was treated with *p*-methoxybenzenediazonium chloride to give XI. This was converted to the hydrazide, XII, which readily formed the azide, XIII. This azide was subjected to the Curtius degradation, producing 1-methyl-3-amino-4-(*p*-methoxyphenylazo)-5-pyrazolone, XVI, by way of the intermediates, XIV and XV. XVI is a red dye, melting at 172–174°.

The two products from the reaction of methylhydrazine with I were treated with *p*-methoxybenzenediazonium chloride to produce dyes for comparison with XVI. The higher-melting (192–194°) compound formed a red dye, melting at 172–174°, identical in every respect with XVI. The parent compound is, therefore, 1-methyl-3-amino-5-pyrazolone, IV. The lower-melting (180–182°) product formed a bright yellow dye, melting at 240–242°, XVII.

Upon benzoylation with two moles of benzoyl chloride in pyridine, IV and V yielded the dibenzoyl derivatives, XVIII, melting at 146–148°,

(1) Weissberger, Porter and Gregory, VII, THIS JOURNAL, **66**, 1851 (1944).

(2) This compound, previously[1] formulated as ethyl malonate monoimidoester, $C_2H_5OCCH_2CO_2C_2H_5$ (NH), was shown by Glickman and Cope [*ibid.*, **67**, 1017 (1945)] to be the tautomer, I. We continue to formulate the *hydrazine* derivative, II, as an imino compound without wishing to imply that this structure is more probable than other tautomeric forms.

(3) All derivatives of pyrazole, which, by prototropic shifts, could form pyrazolones are named pyrazolones [see Weissberger and Porter, *ibid.*, **64**, 2133 (1942)].

(4) Fischer, *Ann.*, **190**, 125 (1878).

(5) Michaelis and Hadanek, *Ber.*, **41**, 3286 (1909).

(6) Sidgwick, "The Organic Chemistry of Nitrogen," 2nd ed., Oxford Press, New York, N. Y., 1937, p. 378.

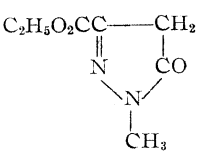
(7) Folpmers, *Rec. trav. chim.*, **34**, 34 (1915).

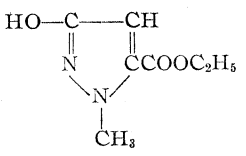
(8) Weissberger and Porter, THIS JOURNAL, **65**, 1495 (1943).

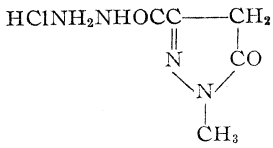
(9) Weissberger and Porter, *ibid.*, **65**, 732 (1943); **66**, 1849 (1944).

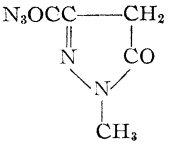
(10) Weissberger and Porter, *ibid.*, **65**, 1495 (1943).

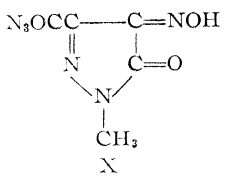
(11) Kufferath, *J. prakt. Chem.*, **65**, 336 (1901).

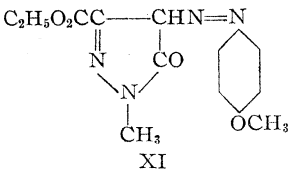

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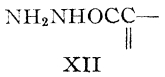

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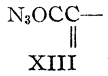

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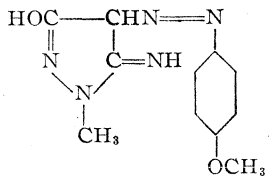

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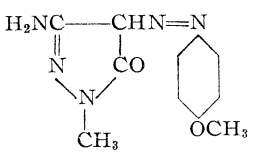

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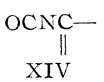

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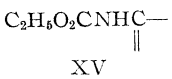

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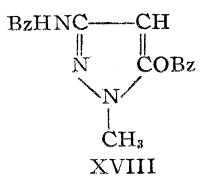

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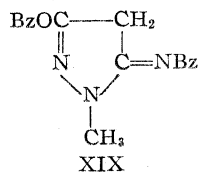

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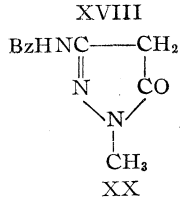

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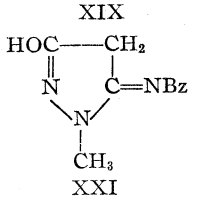

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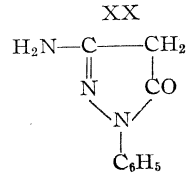
and XIX, melting at 150–153°, respectively. Both are insoluble in dilute sodium carbonate solution, but with alcoholic potassium hydroxide at room temperature, one benzoyl group was hydrolyzed from each of these compounds. The monobenzoyl derivative, XX, of IV formed in the film-strip test a magenta dye typical of 1-aryl-3-benzamido-5-pyrazolones. The corresponding derivative, XXI, of V formed no dye on the film strip but did form a very soluble blue dye in the test solution. It is noteworthy that the difference in the color test, which is pronounced[9] with the 1-phenyl derivatives, XXII and XXIII, and which is smaller with the 1-methyl derivatives, IV and V, becomes strong again if the 1-methyl pyrazolones bear a phenyl group on the 3-amino, XXIV, or the 5-imino nitrogen, XXV.[9] The relative yields of IV and V are those to be expected if the $=C(NH_2)OC_2H_5$ group of I reacts first and predominantly with that nitrogen which is more reactive in common acylations.[5,7]

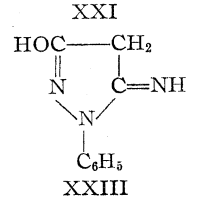

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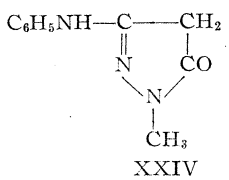

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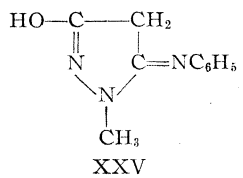

XX


XXI


XXII


XXIII


XXIV


XXV

Two isomers were also formed in the condensation of α-carbethoxyacetothioacetanilide with methylhydrazine,[9] *viz.*, 1-methyl-3-anilino-5-pyrazolone, XXIV, in 11% yield and 1-methyl-3-hydroxy-5-pyrazolone anil, XXV,[9] in 2% yield. If, as we assumed,[1] the $-CO_2C_2H_5$ group reacts first in this case, the relative yields agree with the higher reactivity of the α-nitrogen in methylhydrazine because XXIV is the result of primary reaction with the α-nitrogen atom, while XXV is the result of primary reaction at the β-nitrogen. However, the low total yield renders these observations rather inconclusive.

*Methylhydrazine* reacts with ethyl cyanoacetate under very mild conditions and *without alkali* to produce a mixture of IV and V. The yields are 29 and 26%, respectively. The high yield of *cyclized* products is rather surprising in view of the results obtained with hydrazine and with phenylhydrazine. When reacted with ethyl cyanoacetate *in the absence of alkali, hydrazine* produces only cyanoacethydrazide (quantitative),[12] and *phenylhydrazine* produces only cyanoacetphenylhydrazide[13] (10%, see Experimental). The cyanoacethydrazide and the cyanoacetphenylhydrazide can be cyclized in the presence of alkali to 3-amino-5-pyrazolone, XXVI,[14] and 1-phenyl-3-hydroxy-5-pyrazolone imide, XXIII,[13] respectively.

The same three hydrazines reacted with ethyl cyanoacetate *in the presence of two moles of sodium*

(12) Darapsky and Hillers, *J. prakt. Chem.*, **92**, 297 (1915).
(13) Weissberger and Porter, THIS JOURNAL, **65**, 52 (1943).
(14) Hepner and Fajersztejn, *Bull. soc. chim.*, **4**, 854 (1937).

*methylate. Methylhydrazine* and *hydrazine* gave no color-forming products so this reaction was not explored further. Phenylhydrazine formed 1-phenyl-3-amino-5-pyrazolone, XXII,[3] in 43% yield.

The different behavior of the three hydrazines in the absence of caustic alkali can be explained by the high basicity of the methylhydrazine. It appears that the latter takes over the role which, in the reaction of phenylhydrazine, is played by sodium methylate, and that methylhydrazine acts as its own condensing and cyclizing agent. The nitrile group probably reacts with the more reactive $\alpha$-nitrogen of methylhydrazine to produce the intermediate, $CH_3N(NH_2)C(NH)CH_2COOC_2H_5$, which immediately cyclizes, forming V. IV is probably produced by an initial reaction of the carbethoxy group at the $\alpha$-nitrogen of the methylhydrazine to form the intermediate, $CH_3N(NH_2)COCH_2CN$, which cyclizes to IV.

The formation of the two isomers, IV and V, might also be explained by a primary reaction of the nitrile group at the $\beta$-nitrogen and at the $\alpha$-nitrogen of the methylhydrazine, respectively. However, we are inclined to believe that the relative yields would then probably show a larger difference and would be in the opposite direction.

Hepner and Fajersztejn[14] prepared several acyl derivatives of 3-amino-5-pyrazolone. Acetylation with boiling acetic anhydride gave two isomeric triacetyl derivatives, melting at 190° and 130°. They considered them to be 1,4,4-triacetyl-3-imino-5-ketopyrazolidine, XXVII (R = $CH_3$), and 2,4,4-triacetyl-3-imino-5-ketopyrazolidine, XXVIII (R = $CH_3$), respectively, because neither compound reacted with nitrous acid, and boiling water hydrolyzed both to the parent compound. The same authors obtained a tribenzoyl derivative, melting at 183°, by a Schotten–Baumann reaction of XXVI with benzoyl chloride. They formulate this, by analogy, as 1,4,4-tribenzoyl-3-imino-5-ketopyrazolidine, XXVII (R = $C_6H_5$).

In our work, by using sodium methylate for the cyclization of cyanoacethydrazide we raised the melting point of XXVI by 10°. XXVI was also obtained by the reaction of I with hydrazine. On heating with acetic anhydride on the steam-bath and fractional crystallization, XXVI gave two triacetyl derivatives, melting at 202° and 130°. Not only the latter but probably also the higher-melting compound are identical with the products obtained by Hepner and Fajersztejn.

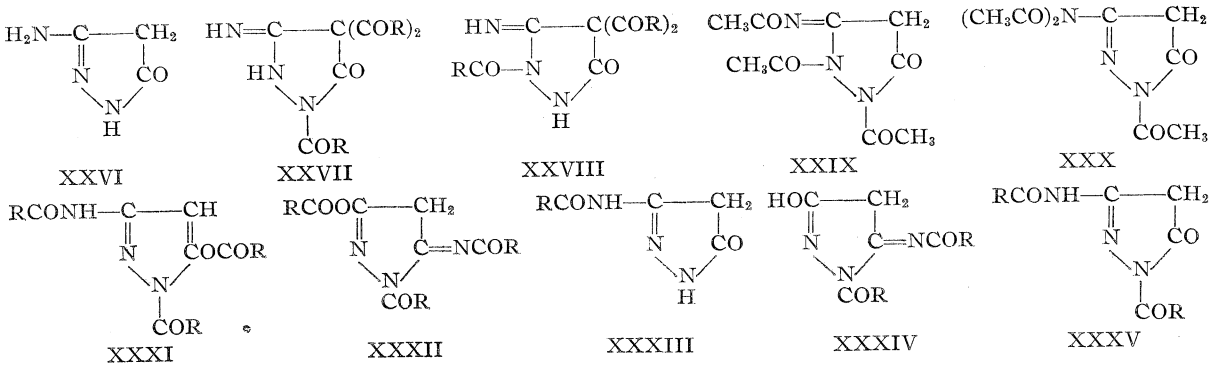
Both *triacetyl compounds* are insoluble in dilute sodium carbonate and do not couple with *p*-nitrosodimethylaniline.[9] On mild hydrolysis with dilute sodium hydroxide, both give the same *monoacetyl derivative*, melting at 227°, which is soluble in 3% sodium carbonate and couples with *p*-nitrosodimethylaniline. When the high-melting triacetyl compound is treated with one equivalent of piperidine, a *diacetyl* derivative, melting at 195°, is formed, which is soluble in 3% sodium carbonate and couples with *p*-nitrosodimethylaniline.[9] The lower-melting isomer gave the *monoacetyl* derivative, m. p. 227°, even under very mild conditions, *e. g.*, when the piperidine was added slowly at room temperature. Similar difficulties in selective deacylations have been noted before.[8]

The structures, XXVII and XXVIII (R = $CH_3$), which were given by Hepner and Fajersztejn to the triacetyl derivatives, are untenable because the ready hydrolysis of *all three acetyl* groups[14] excludes any 4-acetyl groups.[8] Moreover, the coupling action of the monoacetyl derivative, m. p. 227°, and the diacetyl derivative, m. p. 195°, excludes a 4-acetyl group in either of these compounds.[15] The structures, XXIX and XXX, are excluded because these compounds should be soluble in dilute carbonate and couple with *p*-nitrosodimethylaniline. This leaves for the two isomeric triacetyl compounds only structures XXXI and XXXII (R = $CH_3$). Inasmuch as both isomers hydrolyze to the same monoacetyl derivative, the latter compound, melting at 227°, is assigned the structure *3-acetamido-5-pyrazolone*, XXXIII (R = $CH_3$), because the other acetyl group which is common in XXXI and XXXII would be hydrolyzed[8,15] under the conditions for the preparation of XXXIII. The diacetyl compound, melting at 195°, is considered to be *1-acetyl-3-acetamido-5-pyrazolone*, XXXV (R = $CH_3$), because the isomeric compound, XXXIV, would not couple in the *p*-nitrosodimethylaniline test.[16] The triacetyl compound, melting at 202°, is therefore *1-acetyl-3-acetamido-5-acetoxypyrazole*, XXXI (R = $CH_3$), which leaves for the triacetyl compound, melting at 130°, the structure of *1-acetyl-3-acetoxy-5-pyrazolone acetylimide*, XXXII (R = $CH_3$).

By analogy with the determination of the structures of the acetyl derivatives, the structure of the tribenzoyl derivative (m. p. 185°), prepared as given in the literature was readily determined. It gives, on hydrolysis in dilute sodium hydroxide, a monobenzoyl derivative, melting at 205°. This is carbonate-soluble and couples in the *p*-nitrosodimethylaniline test and is, therefore, assigned the structure of *3-benzamido-5-pyrazolone*, XXXIII (R = $C_6H_5$). Reaction of the tribenzoyl compound with one equivalent of piperidine gives a dibenzoyl derivative, melting at 175°. Since this is soluble in carbonate and does not couple to form a dye even in the film-strip test,[15] it is assigned the structure *1-benzoyl-3-hydroxy-5-pyrazolone benzoylimide*, XXXIV (R = $C_6H_5$). This leaves only the structure *1-benzoyl-3-benzoyloxy-5-pyrazolone benzoylimide*, XXXII (R = $C_6H_5$), for the tribenzoyl compound (m. p. 185°) because of its insolubility in alkali.

If 3-amino-5-pyrazolone is benzoylated in pyridine solution, a different tribenzoyl derivative,

(15) Weissberger and Porter, THIS JOURNAL, **65**, 2180 (1943).
(16) *Cf.* XVII in ref. 8.



XXVI XXVII XXVIII XXIX XXX

XXXI XXXII XXXIII XXXIV XXXV

melting at 161°, is obtained. On hydrolysis with dilute sodium hydroxide, this also gives 3-benzamido-5-pyrazolone, XXXIII (R = $C_6H_5$). When the tribenzoyl derivative (m. p. 161°) is treated with one equivalent of piperidine, a dibenzoyl derivative, melting at 171°, is obtained. Since this is soluble in carbonate and couples in the film-strip test,[8] it is assigned the structure *1-benzoyl-3-benzamido-5-pyrazolone*, XXXV (R = $C_6H_5$). It follows that the tribenzoyl compound, melting at 161°, is *1-benzoyl-3-benzamido-5-benzoyloxypyrazole*, XXXI (R = $C_6H_5$).

## Experimental

**1-Methyl-3-amino-5-pyrazolone, IV, and 1-Methyl-3-hydroxy-5-pyrazolone Imide. V.**—(a) A solution of 21 g. (0.46 mole) of methylhydrazine in 75 ml. of absolute alcohol was added to a solution of 72.5 g. (0.46 mole) of ethyl β-amino-β-ethoxyacrylate I, in 75 ml. of absolute alcohol. The mixture warmed spontaneously to 60°. The solution was allowed to stand for twenty hours. Two easily distinguishable types of crystals separated. The crystals were large enough to be separated mechanically.

There were 24.3 g. (47%) of large prisms, 3.1 g. (6%) of needles, and 5 g. (10%) of mixed material. These fractions were carefully recrystallized to produce 14 g. of prisms, melting at 180–182°, and 1 g. of needles, melting at 192–194° in a sealed tube (190° if heated very slowly in an open tube). The needles were proved (by compound XVI) to be 1-methyl-3-amino-5-pyrazolone while the prisms were the 1-methyl-3-hydroxy-5-pyrazolone imide.

(b) Methylhydrazine (5 g., 0.11 mole) was dissolved in 10 ml. of water and the resulting solution was cooled. To this was added 12.3 g. (0.11 mole) of ethyl cyanoacetate. After a few minutes the ester dissolved, and the solution was placed in a vacuum desiccator for three days. Large prisms (some an inch long) formed but no needles were present. The prisms were collected and washed with 50 ml. of absolute alcohol; 3.2 g. (26%) melting at 180°. The mother liquor and washings were evaporated on a steam-bath. The residue was dissolved in 25 ml. of boiling absolute alcohol and cooled slowly. The needles were collected and washed with alcohol; 3.5 g. (29%), m. p. 190°. Recrystallization raised the melting point to 192–194° (in a sealed tube).

*Anal.* Calcd. for $C_4H_7N_3O$: C, 42.5; H, 6.2; N, 37.1. Found, for isomer melting at 180–182°: C, 42.4; H, 6.2; N, 36.9. Found, for isomer melting at 192–194°: C, 42.3; H, 6.2; N, 37.1.

**1-Methyl-3-carbethoxy-5-pyrazolone, VI.**—Freshly prepared methylhydrazine (2.3 g.) in 20 ml. of dry benzene was added to a solution of freshly prepared ethyl oxalacetate (9.4 g.) in 80 ml. of dry benzene. The temperature of the solution rose from 28° to 41°. After standing one hour at room temperature, the solution was refluxed for five minutes and cooled. The precipitate of sirupy crystals was collected and recrystallized from 50 ml. of water. The resulting white needles weighed 3.5 g. (41%) and melted at 148–150°.

The compound can also be prepared from the salts of the two starting materials. A solution of 14.4 g. of methylhydrazine sulfate in 20 ml. of water was diluted with 300 ml. of hot ethanol. To this was added a hot solution of 21.0 g. of sodium ethyl oxalacetate in 700 ml. of ethanol. Sufficient alcoholic potassium hydroxide was added to neutralize the solution. The inorganic salts were removed by filtration, and the alcoholic solution was concentrated under reduced pressure to near dryness. The residue was recrystallized from 200 ml. of water. The yield using this procedure was 11.5 g. (68%), m. p. 148–150°.

*Anal.* Calcd for $C_7H_{10}N_2O_3$: N, 16.5. Found: N, 16.6.

**1-Methyl-5-pyrazolone-3-carboxyhydrazide Hydrochloride, VIII.**—1-Methyl-3-carbethoxy-5-pyrazolone, VI, (6.9 g.) was suspended in 18 ml. of 42% hydrazine hydrate solution. After sixteen hours, the solution was acidified with 14 ml. of concentrated hydrochloric acid under cooling. The product was collected and washed with 30 ml. of water in three portions. It was recrystallized from 25 ml. of water. The product weighed 3.6 g. (46%) and melted at 253–255°.

*Anal.* Calcd. for $C_5H_8N_4O_2 \cdot HCl$: C, 31.3; H, 4.5; N, 28.3. Found: C, 31.2; H, 4.7; N, 29.1.

**1-Methyl-5-pyrazolone-3-carbazide, IX.**—1-Methyl-5-pyrazolone-3-carboxyhydrazide hydrochloride, VIII (0.90 g.) was suspended in 10 ml. of water. The slurry was layered with 20 ml. of ether and cooled to 0°. To this was added a solution of 0.33 g. of sodium nitrite in 5 ml. of water. The mixture was strongly agitated for ten minutes before the ether layer was removed. This ether layer yielded 0.05 g. of light yellow crystals after standing at 0° for one hour. The compound deflagrates at 113°.

*Anal.* Calcd. for $C_5H_5N_5O_2$: C, 35.9; H, 3.0. Found: C, 36.5; H, 2.9.

**1-Methyl-4-isonitroso-5-pyrazolone-3-carbazide, X.**—1-Methyl-5-pyrazolone-3-carboxyhydrazide hydrochloride, VIII (4.0 g., 0.021 mole), was suspended in 50 ml. of water, and the mixture was cooled in a salt–ice-bath.

A solution of 1.47 g. (0.021 mole) of sodium nitrite in 10 ml. of water was added to the slurry at such a rate that the temperature did not exceed 0°. The mixture was stirred for one hour. The yellow precipitate was collected, washed with water, and dried at room temperature. The yield was 2.1 g. The material explodes at 112° (slightly higher if heated rapidly).

*Anal.* Calcd. for $C_5H_4N_6O_3$: C, 30.6; H, 2.1; N, 42.6. Found: C, 30.1; H, 2.3; N, 42.6.

**1-Methyl-3-carbethoxy-4-(*p*-methoxyphenylazo)-5-pyrazolone, XI.**—1-Methyl-3-carbethoxy-5-pyrazolone, VI (5.0 g., 0.029 mole), was dissolved in 50 ml. of pyridine. The solution was cooled to 0° and treated with a cold solution of 0.029 mole of *p*-methoxybenzenediazonium chloride in 60 ml. of water. After ten minutes, 50 ml. of water was added to the mixture. The dye was

collected, washed with water, and recrystallized from 100 ml. of ethanol. There resulted 6.8 g. of orange dye, melting at 125–127°.

*Anal.* Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.3; H, 5.3; N, 18.4. Found: C, 55.7; H, 5.6; N, 18.7.

**1-Methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-carboxyhydrazide, XII.**—1-Methyl-3-carbethoxy-4-(*p*-methoxyphenylazo)-5-pyrazolone, XI (6.5 g.), was stirred into 80 ml. of 42% hydrazine hydrate solution. The stirring was continued for four hours. All the dye changed from orange to yellow. Water (100 ml.) was added, and the solution was filtered to remove a small amount of insoluble material. The clear solution was acidified with 50 ml. of acetic acid. The red dye was collected and washed with 100 ml. of boiling alcohol. The material weighed 3.8 g. (60%) and melted at 212–214°.

*Anal.* Calcd. for $C_{12}H_{14}N_6O_3$: C, 49.7; H, 4.9; N, 29.0. Found: C, 50.1, 49.9; H, 4.8, 4.9; N, 29.6.

**1-Methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-carbazide, XIII.**—1-Methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-carboxyhydrazide, XII (2.9 g.), was dissolved in a solution of 100 ml. of water, 100 ml. of dioxane, and 5 ml. of concentrated hydrochloric acid. The solution was cooled to 0°, and 0.70 g. of sodium nitrite in 30 ml. of water was added. The azide precipitated immediately. It was washed with water and ethanol. This process yielded 2.5 g. of the azide which explodes at 120°.

*Anal.* Calcd. for $C_{12}H_{11}N_7O_3$: N, 33.2. Found: N, 32.6.

**1-Methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-isocyanate, XIV.**—A suspension of 2.5 g. of 1-methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-carbazide, XIII, in 150 ml. of absolute alcohol was refluxed on a steam-bath for two hours. When all evolution of nitrogen had ceased, the insoluble product was collected and washed with ethanol. The product, 1.5 g., melted at 245–249°. A sample recrystallized from dioxane melted at 253–255°. Analysis proved it to be the isocyanate rather than the expected urethan.

*Anal.* Calcd. for $C_{12}H_{11}N_5O_3$: C, 52.8; H, 4.2; N, 25.7. Found: C, 52.5; H, 4.2; N, 24.9.

**1-Methyl-3-carbethoxyamino-4-(*p*-methoxyphenylazo)-5-pyrazolone, XV.**—A suspension of 0.35 g. of 1-methyl-4-(*p*-methoxyphenylazo)-5-pyrazolone-3-isocyanate, XIV, in 50 ml. of absolute alcohol was refluxed for twenty hours. The resulting solution was filtered and cooled. The precipitate was collected, washed with alcohol, and recrystallized from alcohol. The product was 0.20 g. of bright orange dye, melting at 181–182°.

*Anal.* Calcd. for $C_{14}H_{17}N_5O_4$: C, 52.7; H, 5.4; N, 21.9. Found: C, 52.4; H, 5.4; N, 22.1.

**1-Methyl-3-amino-4-(*p*-methoxyphenylazo)-5-pyrazolone, XVI.**—(a) A solution of 0.10 g. of 1-methyl-3-carbethoxyamino-4-(*p*-methoxyphenylazo)-5-pyrazolone, XV, in 4 ml. of 10% sodium hydroxide was warmed for two hours on a steam-bath. The solution was filtered, and acidified with 0.60 ml. of acetic acid. The precipitate was recrystallized from ethanol. It was a dull red dye, melting at 172–174°.

(b) A solution of 1.13 g. (0.01 mole) 1-methyl-3-amino-5-pyrazolone, IV, in 20 ml. of 5% sodium hydroxide solution at 0° was treated with (0.01 mole) of benzene diazonium chloride in 20 ml. of cold water. After fifteen minutes, the solution was acidified with acetic acid, and the dye was collected. It was washed with water and recrystallized from 20 ml. of ethanol. This procedure produced 1.0 g. of dull red dye, melting at 172–174°. The mixed melting point of (a) and (b) was 172–174°.

*Anal.* Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.5; H, 5.3; N, 28.4. Found: C, 53.4; H, 5.2; N, 28.3.

**1-Methyl-3-hydroxy-4-(*p*-methoxyphenylazo)-5-pyrazolone Imide, XVII.**—A solution of 1.13 g. (0.01 mole) of 1-methyl-3-hydroxy-5-pyrazolone imide, V, in 25 ml. of pyridine and 5 ml. of water was cooled to 0° and treated with a cold solution of 0.01 mole of benzenediazonium chloride in 15 ml. of water. After a few minutes, a yellow dye separated. It was collected, washed with water, and recrystallized from 50 ml. of ethanol. There resulted 0.9 g. of bright yellow dye, melting at 240–242°. A mixture of this material with XXIa melted at 167°.

*Anal.* Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.5; H, 5.3; N, 28.4. Found: C, 53.5; H, 5.7; N, 27.9.

**1-Methyl-3-benzamido-5-benzoyloxypyrazole, XVIII.**—Benzoyl chloride (3 g., 0.021 mole) was added dropwise to a solution of 1-methyl-3-amino-5-pyrazolone, IV (1.13 g., 0.010 mole) in 20 ml. of pyridine at room temperature. The mixture was warmed for one-half hour on a steam-bath, cooled, and drowned out with 20 ml. of water. The solid was collected, washed, dried, and recrystallized from 25 ml. of ethanol. This process yielded 1.9 g. (60%) of white powder, m. p. 146–148°.

*Anal.* Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.5, H, 4.9; N, 13.1. Found: C, 67.4; H, 4.6; N, 13.3.

**1-Methyl-3-benzoyloxy-5-pyrazolone Benzoylimide. XIX.**—1-Methyl-3-hydroxy-5-pyrazolone imide, V, was acylated, and the product was purified by the same procedure used in making XVIII. The yield was 1.9 g. (60%) of white powder, m. p. 150–153°. A mixture of XVIII and XIX melted above 130°.

*Anal.* Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.5; H, 4.9; N, 13.1. Found: C, 67.0; H, 4.8; N, 12.6.

**1-Methyl-3-benzamido-5-pyrazolone, XX.**—To a solution of 5 ml. of alcohol and 10 ml. of 5% sodium hydroxide was added 1.6 g. of 1-methyl-3-benzamido-5-benzoyloxypyrazole, XVIII. The solution was stirred for one hour, filtered, and acidified with acetic acid. The precipitate was collected, washed with alcohol, dried, and recrystallized from 40 ml. of ethanol; 0.7 g. (65%) of white crystals, which slowly melted, with decomposition, at 215°.

*Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.9; H, 5.1; N, 19.3. Found: C, 61.1; H, 5.1; N, 19.7.

**1-Methyl-3-hydroxy-5-pyrazolone Benzoylimide, XXI.**—1-Methyl-3-benzoyloxy-5-pyrazolone benzoylimide, XIX (3.2 g.) was added to a solution of 10 ml. of ethanol and 20 ml. of 5% sodium hydroxide. The solution was stirred for one hour, filtered, and acidified with acetic acid; 2.1 g. (96%), m. p. 243–249°. The material melted over the same range after recrystallization from ethanol.

*Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.9; H, 5.1; N, 19.3. Found: C, 60.5; H, 4.6; N, 19.2.

**Reaction of Phenylhydrazine with Methyl Cyanoacetate.**—A mixture of 10.8 g. of phenylhydrazine and 9.9 g. of methyl cyanoacetate in 20 ml. of dioxane was heated on the steam-bath for eighteen hours, cooled, drowned out with 100 ml. of water, and the solution decanted from the precipitated oil. The latter was triturated with ether, cooled, filtered, and the gummy product extracted with 100 ml. of benzene in four portions. The combined extracts, on cooling, gave 1.8 g. (10%)[17] of β-cyanoacetphenylhydrazide.

**3-Amino-5-pyrazolone, XXVI.**—Cyanoacethydrazide[8] (10 g.), in sodium methylate solution (4.6 g. of sodium in 50 ml. of methanol) was refluxed for one hour, cooled, and the sodium salt filtered off. The latter was dissolved in 35 ml. of water, acidified with 6 ml. of acetic acid, and the precipitated product was recrystallized from water; 7 g. (71%) of short, ivory needles, m. p. 214–215° dec. The compound deteriorates considerably on standing for more than a week at room temperature.

Ethyl β-amino-β-ethoxyacrylate, I (15.9 g.), and 5.9 g. of hydrazine hydrate (85%) in 25 ml. of absolute ethanol were brought to boiling on the steam-bath and the heat supply removed. Heat was evolved and crystals sepa-

(17) The low yield in the case of the phenylhydrazine is in agreement with low yields in the reaction of phenylhydrazine with other esters because of numerous side reactions. *Cf.* Baidowski and Slepak, *Chem. Zentr.*, **74**, I, 829 (1903).

rated. After standing at room temperature for one hour, the product was collected and washed with alcohol and ether; 7.0 g. (71%), m. p. 213–215° dec. When recrystallized from water, it formed short, ivory needles, m. p. 214–215° dec.

*Anal.* Calcd. for $C_3H_5N_3O$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.50; H, 5.12; N, 42.39.

**1-Acetyl-3-acetamido-5-acetoxypyrazole, XXXI** (R = $CH_3$).—A mixture of 2.3 g. of 3-amino-5-pyrazolone, XXVI, and 11 ml. of acetic anhydride was stirred on the steam-bath for twenty minutes. The resulting solution was cooled under the tap and filtered; 1.8 g. (36%), m. p. 192–196°. The product was recrystallized twice from *n*-propanol; it gave white, pearly flakes; m. p. 202–203°.

*Anal.* Calcd. for $C_9H_{11}N_3O_4$: C, 48.01; H, 4.92; N, 18.66. Found: C, 47.99; H, 5.02; N, 18.76.

Under the conditions for the hydrolysis of XXXII (R = $CH_3$) to XXXIII (R = $CH_3$), XXXI (R = $CH_3$) also gave XXXIII (R = $CH_3$) (60%) identified by melting point and mixed melting point. There was no evidence of rearrangement of XXXI into XXXII on heating in glacial acetic acid.

**1-Acetyl-3-acetoxy-5-pyrazolone Acetylimide, XXXII** (R = $CH_3$).—The filtrate from XXXI (above) was cooled in an ice–salt-bath, the mixture (m. p. 125–135°) which crystallized was filtered out, and the filtrate stirred with ice water and filtered; 0.45 g. (9%), m. p. 130–132°. Recrystallization from a 1:1 mixture of benzene and cyclohexane produced white needles, m. p. 131–132°.

*Anal.* Calcd. for $C_9H_{11}N_3O_4$: C, 48.01; H, 4.92; N, 18.66. Found: C, 48.25; H, 5.02; N, 18.64.

Under the conditions for the preparation of XXXV, XXXII gave XXXIII (81%).

**3-Acetamido-5-pyrazolone, XXXIII** (R = $CH_3$).—To a suspension of 1.8 g. of 1-acetyl-3-acetoxy-5-pyrazolone acetylimide, XXXII (R = $CH_3$), in 9 ml. of water was added dropwise 1.7 ml. of 40% sodium hydroxide diluted with 3 ml. of water, while stirring vigorously in an ice-bath. Ten minutes after addition was complete (five minutes), the solution was filtered from a slight insoluble portion, acidified with glacial acetic acid, and filtered; 0.85 g. (75%); m. p. 225–227°. Recrystallization from methanol produced short, white needles, m. p. 227–228° dec.

*Anal.* Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.79. Found: C, 42.64; H, 5.15; N, 29.58.

**1-Acetyl-3-acetamido-5-pyrazolone, XXXV** (R = $CH_3$). —To a solution of 0.7 g. of 1-acetyl-3-acetamido-5-acetoxypyrazole, XXXI (R = $CH_3$), in 25 ml. of 1-1 isopropyl alcohol–dioxane was added 0.3 ml. of piperidine in 5 ml. of isopropyl alcohol dropwise (twenty-five minutes) while stirring at room temperature. The solution was allowed to evaporate to dryness, the residue was triturated with *n*-propanol, and filtered; 0.5 g. (86%), m. p. 193–195°. Recrystallization from dioxane produced fine, white granules, m. p. 195–196°.

*Anal.* Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95, N, 22.93. Found: C, 46.02; H, 5.13; N, 22.57.

**1-Benzoyl-3-benzoyloxy-5-pyrazolone Benzoylimide, XXXII** (R = $C_6H_5$).—The directions in the literature[14] were followed, and the product was recrystallized from isopropyl alcohol. The yield was 25% of fine, white needles, m. p. 185–186°.

Hydrolysis of XXXII (R = $C_6H_5$) as of XXXI (R = $C_6H_5$) gave XXXIII (R = $C_6H_5$).

**1-Benzoyl-3-hydroxy-5-pyrazolone Benzoylimide, XXXIV** (R = $C_6H_5$).—To a solution of 0.6 g. of 1-benzoyl-3-benzoyloxy-5-pyrazolone benzoylimide XXXII (R = $C_6H_5$) in 6 ml. of dioxane, heated on the steam-bath, was added dropwise, with stirring, a solution of 0.15 ml. of piperidine in 1 ml. of dioxane. After heating for fifteen minutes, the solution was cooled to room temperature, diluted with 5 ml. water, cooled under the tap, and filtered; 0.3 g. (65%), sinters at 170°, m. p. 172–175°. Recrystallization from *n*-propanol gave fine, white, feathery crystals, m. p. 175–176°.

*Anal.* Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.23; N, 13.68. Found: C, 66.39; H, 4.44; N, 13.81.

**1-Benzoyl-3-benzamido-5-benzoyloxypyrazole, XXXI** (R = $C_6H_5$).—To a mixture of 2.5 g. of 3-amino-5-pyrazolone, XXVI (3 ml.), in 25 ml. of pyridine was added 10.5 g. of benzoyl chloride. The solution was heated one-half hour on the steam-bath. When cool, it was diluted with 5 ml. of water, cooled under the tap, filtered, rinsed with 50% ethanol, and recrystallized from 150 ml. of isopropyl alcohol; 5.9 g. (57%) of fine, white crystals, m. p. 161–163°.

*Anal.* Calcd. for $C_{24}H_{17}N_3O_4$: N, 10.21. Found: N, 9.92.

**3-Benzamido-5-pyrazolone, XXXIII** (R = $C_6H_5$).—A mixture of 3 g. of 1-benzoyl-3-benzamido-5-benzoyloxypyrazole, XXXI (R = $C_6H_5$), in 50 ml. of 2% sodium hydroxide and 20 ml. of 95% ethanol was stirred for one and one-half hours, filtered from a small amount of insoluble material, acidified with acetic acid, and concentrated *in vacuo* until the solution clouded. It was cooled and filtered. The product was digested with 8 ml. of methanol, cooled, and filtered; 1.2 g. (80%), m. p. 203–205°. Recrystallization from methanol gave a white powder, m. p. 205–206°.

*Anal.* Calcd. for $C_{19}H_9N_3O_2$: N, 20.68. Found: N, 20.84.

**1-Benzoyl-3-benzamido-5-pyrazolone, XXXV** (R = $C_6H_5$).—To a solution of 0.6 g. of 1-benzoyl-3-benzamido-5-benzoyloxypyrazole, XXXI (R = $C_6H_5$), in 12 ml. of boiling isopropyl alcohol was added dropwise 0.15 ml. of piperidine in 1 ml. of isopropyl alcohol. The solution was refluxed fifteen minutes, cooled, filtered, and the product was recrystallized from 95% ethanol; 0.2 g. (43%), white microcrystals, m. p. 171–172°.

*Anal.* Calcd. for $C_{17}H_{13}N_3O_3$: N, 13.68. Found: N, 13.26.

**1-Methyl-5-pyrazolone-3-carboxamide.**—1-Methyl-3-carbethoxy-5-pyrazolone, VI (10 g.), was dissolved in 100 ml. of 28% ammonium hydroxide. After three days, the solution was neutralized with acetic acid, the precipitate was collected, washed with water, and recrystallized from water. The yield was 5 g. of fine, white needles that sinter above 230°.

*Anal.* Calcd. for $C_5H_7N_3O_2$: C, 42.5; H, 5.0. Found: C, 42.7; H, 5.1.

This compound brominates readily so that no attempts were made to use it in a Hofmann degradation.

## Summary

1. Methylhydrazine, when reacting with either ethyl cyanoacetate or ethyl β-amino-β-ethoxyacrylate, yields two pyrazolones, namely, 1-methyl-3-hydroxy-5-pyrazolone imide and 1-methyl-3-amino-5-pyrazolone. The structure of the latter was proved unequivocally.

2. Acetylation of 3-amino-5-pyrazolone with boiling acetic anhydride produces 1-acetyl-3-acetamido-5-acetoxypyrazole and 1-acetyl-3-acetoxy-5-pyrazolone acetylimide rather than 1,4,4-triacetyl-3-imino-5-ketopyrazolidine and 2,4,4-triacetyl-3-imino-5-ketopyrazolidine suggested by Hepner and Fajersztejn.[12]

3. 1-Benzoyl-3-benzoyloxy-5-pyrazolone benzoylimide was obtained using benzoyl chloride in a Schotten–Baumann reaction on 3-amino-5-pyrazolone. 1-Benzoyl-3-benzamido-5-benzoyloxypyrazole was produced when the benzoylation was done in pyridine.

ROCHESTER 4, N. Y. RECEIVED MAY 15, 1948

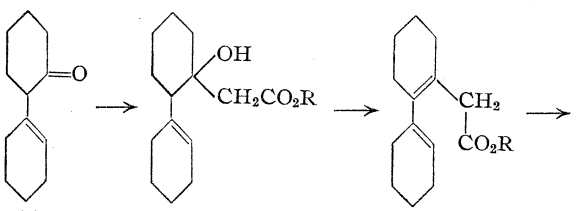
[CONTRIBUTION FROM THE POLYTECHNIC INSTITUTE OF BROOKLYN]

# A New Synthesis of 9-Hydroxy-*sym*-octahydrophenanthrene

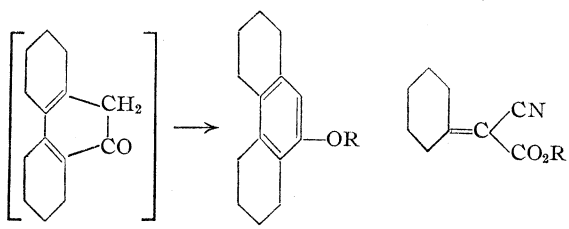
BY PHANINDRANATH BAGCHI,[1] FELIX BERGMANN[1a] AND D. K. BANNERJEE[2]

A common method for the synthesis of polycyclic ring systems consists in the cyclization of a saturated side-chain bearing a carboxyl group. This method has been applied to γ-aryl[3]- and γ-cyclohexenyl-butyric acids.[4] However, an old observation of Fittig[5] shows that unsaturated side chains may also be useful. β-Styrylacetic acid is converted thermally to α-naphthol, and a similar observation has been reported by Linstead[6] for 2-phenylcyclohexylidenecyanoacetic acid. It was, therefore, of interest to determine whether this type of reaction would apply also to dienic acids.

As a suitable system we intended to prepare 1,1′-dicyclohexenyl-2-acetic acid (IIIb),[6a] which we expected to cyclize to 9-hydroxy-*sym*-octahydrophenanthrene (IVa) according to the scheme




(I) (II) (a, R = $C_2H_5$; b, R = H) (III) (a, R = $C_2H_5$; b, R = H)




(IV) (a, R = H; b, R = $CH_3$) (V) (a, R = $C_2H_5$; b, R = H)

Reformatsky's method, when applied to the system cyclohexenylcyclohexanone (I) and ethyl bromoacetate, gave an 83% yield of the hydroxy ester (IIa). The latter could be dehydrated either by phosphorus pentoxide in benzene or by thionyl chloride in a pyridine-ether mixture (yield 76 and 78%, respectively). The dienic acid (IIIb) was cyclized by phosphorus pentoxide in benzene, after a number of other methods proved to be inferior. It was essential to sustain vigorous stirring throughout the cyclization and to add the dehydrating agent in small portions over an extended period. The phenol (IVa)[7,6] was obtained in 44% yield. The method was considerably simplified by saponifying the hydroxy ester (IIa) and treating the crude hydroxy-acid (IIb) directly with phosphorus pentoxide. The over-all yield (IIa → IVa) was 35% as compared to 30% in the more elaborate process described before.

The phenol (IVa), its acetate and its 10-bromo derivative (VIIIa) all showed properties identical with the corresponding compounds described in the literature, and the methyl ether (IVb) was found to be identical with the corresponding derivative of Bachmann[8] by direct comparison.

A second compound suitable for cyclization, was obtained by condensation of (I) with ethyl cyanoacetate. Three products were isolated from the reaction mixture: (i) ethyl cyclohexylidenecyanoacetate (Va)(26%); (ii) ethyl 2-(Δ¹-cyclohexenyl) - cyclohexylidene - cyanoacetate (VI) (44%); (iii) 9-hydroxy-10-cyano-1,2,3,4,5,6,7,8-octahydrophenanthrene (VIIa) (~1%). The first product (V) was obtained in each run, even when the starting material (I) was purified scrupulously and a constant boiling middle fraction was used for the reaction. It is thus beyond doubt that (V) originates from a reversed aldol condensation, occurring either before or after condensation with ethyl cyanoacetate.

The ratio of the yields of products varied according to the conditions employed during distillation. The higher the distillation temperature, the higher the proportion of (VIIa) formed. This could also be confirmed by direct conversion of (VI) into (VIIa) under the influence of heat (yield 50%) or in boiling acetamide as solvent (yield 72%). This type of cyclization is similar to the one observed by McRae,[9] Cope[10] and Linstead.[6]

The structure of (VII) was established in two ways: The nitrile (VII) was "denitrilated" to (IVa) by a mixture of zinc, zinc chloride and sodium chloride at 300°.[10] 9-Methoxy-10-bromo-octahydrophenanthrene (VIIIb) was converted into (VIIa) by cuprous cyanide. It is remarkable that this reaction was accompanied by demethylation. An analogous observation was made during "denitrilation" of (VIIb) by zinc dust.

(1) Government of India Overseas Scholar. From a thesis for the Masters degree, May, 1948.

(1a) On leave of absence from the Sieff Institute, Rechobot, Israel.

(2) Watumull Foundation Fellow.

(3) Kipping and Hill, *J. Chem. Soc.*, **75**, 144 (1899); Cook and Hewett, *ibid.*, 373 (1934).

(4) Cook and Lawrence, *ibid.*, 1637 (1935).

(5) Fittig and Erdman, *Ber.*, **16**, 43 (1883); *Ann.*, **227**, 242 (1838).

(6) Linstead, Whetstone and Levine, THIS JOURNAL, **64**, 2014 (1942).

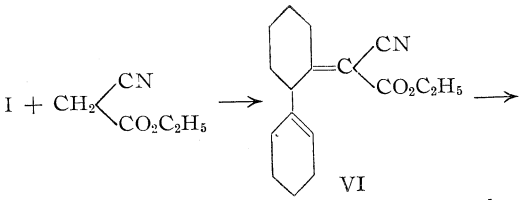
(6a) About the exact structure of this compound see the following discussion.

(7) v. Braun and Bayer, *Ber.*, **58**, 2667 (1925).

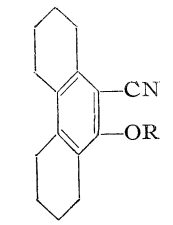
(8) Bachmann and Ness, THIS JOURNAL, **64**, 536 (1942). The authors wish to thank Prof. Bachmann, who kindly carried out the determination of mixed m. p.'s.

(9) McRae and Marrion, *Can. J. Res.*, **15B**, 480 (1937); **18B**, 265 (1940).

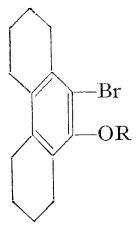
(10) Cope, Hofmann, Wyckoff and Hardenberg, THIS JOURNAL, **63**, 3452 (1941).



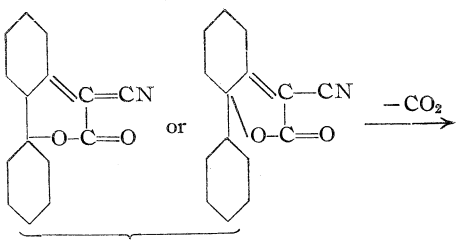
VI



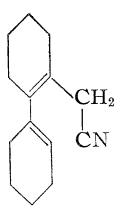
VII (a, R = H; b, R = $CH_3$)



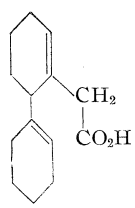
VIII (a, R = H; b, R = $CH_3$)



IX



X



(XI)

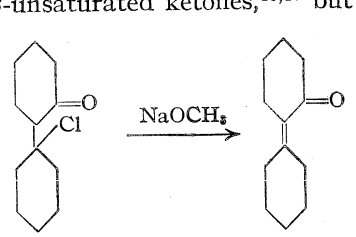
Acid hydrolysis of (VI) gave the lactone (IX), which was insoluble in sodium bicarbonate solution, but dissolved in warm sodium hydroxide solution, from which only the lactone could be recovered upon acidification. The lactonic structure was confirmed by decarboxylation to 1,1′-dicyclohexenyl-2-acetonitrile (X).

Ethyl cyclohexylidene-cyanoacetate, as shown by Kon and Nutland,[11] possesses the structure (Va) in view of its oxidative degradation to cyclohexanone and the exaltation shown by its molecular refraction. Decarboxylation of (Vb), however, gives a $\beta,\gamma$-unsaturated nitrile. In the case of compound (VI), it is possible that one or both of the double bonds are conjugated with the cyano-ester grouping. This problem was investigated by means of absorption spectra.

Although in $\alpha,\beta$-unsaturated acids and esters absorption bands are not as sharply defined as in $\alpha,\beta$-unsaturated ketones, it is possible, within a closely related group of compounds, to define the exact position of double bonds, *e. g.*, $\alpha$-cyanocrotonate shows a maximum at 2200 Å., the corresponding $\beta$-methyl derivative at 2300 Å. (log $\epsilon$ = 4.0). $\alpha$-Cyanosorbate and its $\delta$-methyl derivative have maxima at 2820 and 3020 Å., respectively.[12] Inspection of Fig. 1 demonstrates the close relationship between (Va), (Vb), (VI) and (IX) ($\lambda_{max.}$ at 2350 Å., log $\epsilon$ = 4.0–4.1). Furthermore, as all the three compounds are $\beta,\beta$-disubstituted carboxyl derivatives, their absorption maximum corresponds approximately to that of $\beta$-methyl-$\alpha$-cyanocrotonate. It is thus clear, that in (VI) only one double bond is conjugated with the ester group, the other being located inside the second ring.

The spectra of the acetic acids and acetonitriles are represented in Fig. 2. Cyclohexenylacetonitrile, acid (IIIb) and its ester again form a close group with absorption maxima < 2200 Å. In view of the fact that dicyclohexenyl itself has a maximum at 2360 Å. (log $\epsilon$ = 4.25)[13] and that acids of the abietic type, in which the butadienic structure is not conjugated with the carboxyl group, possess maxima at 2400–2500 Å.,[14] it is quite certain that the acid (IIIb) does not possess the expected 1,1′-dicyclohexenyl ring structure, but is to be represented rather as (XI). However, the nitrile(X), showing an appreciable absorption over the entire range of 2200–2700 Å. (log $\epsilon$ = 3.8–3.3), may contain partially conjugated structures.

In this connection, it is also of interest to discuss the structure of cyclohexenylcyclohexanone. Kon[11] assumed for this ketone the non-conjugated structure (I), in equilibrium with a small amount of cyclohexylidenecyclohexanone (XIII). Evans and Gillam[15] concluded from the fact that (I) shows an absorption of $\epsilon$ = 800 at $\lambda$ = 2540 Å. "This low intensity of absorption suggests the predominance of an unconjugated isomer." Recently Reese[16] prepared (XIII) in crystalline form by dehydrochlorination of (XII) by means of sodium methoxide in methanol. Therefore he ascribed to the "liquid isomer" the $\beta,\gamma$-unsaturated structure (I). The absorption spectrum of our preparation, obtained by dehydrochlorination of (XII) by means of methanolic potassium hydroxide, is given in Fig. 3. The liquid shows two absorption maxima, $\lambda_1$ < 2200 Å., $\lambda_2$ = 2450 Å. The value of $\lambda_2$ is near to that of $\alpha,\beta,\beta$-trisubstituted $\alpha,\beta$-unsaturated ketones,[15,17] but $\epsilon_2$ is only



XII XIII

(11) Kon and Nutland, *J. Chem. Soc.*, 3102 (1926).

(12) Andrews, Cristol, Lindenbaum and Young, THIS JOURNAL **67**, 715 (1945).

(13) Booker, Evans and Gillam, *J. Chem. Soc.*, 1453 (1940).

(14) Harris and Sanderson, THIS JOURNAL, **70**, 334 (1948).

(15) Evans and Gillam, *J. Chem. Soc.*, 815 (1941).

(16) Reese, *Ber.*, **75**, 384 (1942).

(17) Woodward, THIS JOURNAL, **63**, 1123 (1941).

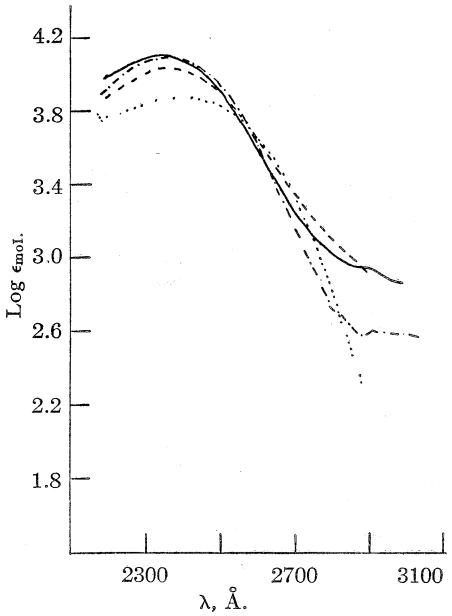



Fig. 1—Ultraviolet absorption spectra of cyclohexylidenecyanoacetic acid (Vb)———; ethyl cyclohexylidenecyanoacetate (Va)—·—·—·—; ethyl 2-cyclohexenylcyclohexylidenecyanoacetate (VI)- - - - - - - - -; lactone (IX) .....

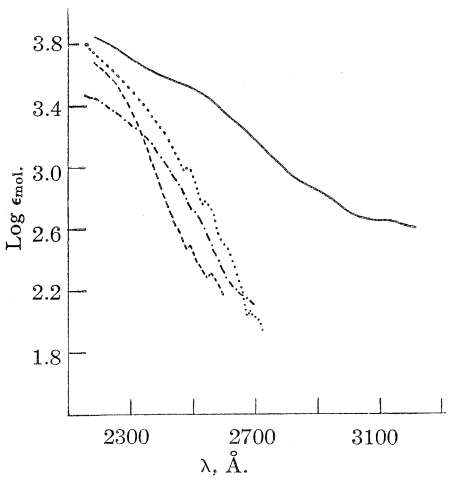



Fig. 2.—Ultraviolet absorption spectra of cyclohexenylacetonitrile- - - - - - - -; dicyclohexenylacetic acid (IIIB) .....; ethyl dicyclohexenylacetate (IIIa)·—·—·—; dicyclohexenylacetonitrile (X)———.

2.7, indicating that only part of the molecular species can be represented by (XIII).

## Experimental[18]

Cyclohexenylcyclohexanone (I) was prepared in 80% yield following essentially the procedure of Wallach,[19] methanolic caustic potash being used for dehydrochlorination of the intermediate chloroketone.

**Condensation of (I) with Ethyl Bromoacetate.**—Strips of zinc foil were activated by washing consecutively with

(18) All melting points are uncorrected.

(19) Wallach, *Ber.*, **40**, 70 (1907).

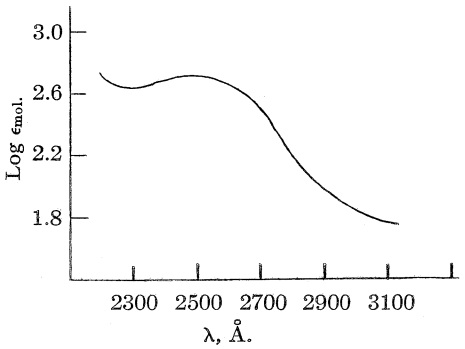



Fig. 3.—Ultraviolet absorption spectrum of cyclohexenylcyclohexanone (I).

5% sodium hydroxide, water, 2% hydrochloric acid, water, ethanol and finally with ether. When cyclohexenylcyclohexanone (22 g.), ethyl bromoacetate (30 g.) and zinc (11.5 g.) in benzene (90 cc.) were heated on a water-bath, a vigorous reaction set in. Thereafter the mixture was refluxed for one hour, the dark brown liquid decanted from the unreacted zinc and treated with cold dilute hydrochloric acid. The benzene solution was washed with water, dried over calcium chloride and fractionated. The yield of (IIa) was 83%; b. p. 144–146° (1.5 mm.); $n^{23.5}D$ 1.4960.

*Anal.* Calcd. for $C_{16}H_{26}O_2$: C, 72.2; H, 9.8. Found: C, 72.1; H, 9.6.

**Dehydration to Ethyl 1,1′-Dicyclohexenyl-2-acetate (IIIa): (a) Pyridine–Thionyl Chloride Method.**—To a stirred solution of the hydroxy ester (24.5 g.) in pyridine (18 cc.) and anhydrous ether (100 cc.), cooled to 0°, was added dropwise thionyl chloride (9 cc.). The mixture was left overnight and then decomposed with cold water containing a small amount of hydrochloric acid. The ether layer was washed with water and dried over calcium chloride. Distillation gave (IIIa) as a colorless oil of b. p. 114–115° (1.5 mm.) in 78% yield; $n^{23}D$ 1.5006.

*Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.3; H, 9.6.

(b) **Phosphorus Pentoxide Method.**—The hydroxy ester (24 g.) and phosphorus pentoxide (16 g.) in dry benzene (100 cc.) were refluxed for three and a half hours. The benzene layer was decanted, the sirupy pentoxide decomposed with water and extracted with benzene. The combined benzene layers were washed, dried and fractionated. The product (IIIa) obtained in 76% yield was identical with the one described before.

**Saponification to 1,1′-Dicyclohexenyl-2-acetic Acid (IIIb).**—The dienic ester (10 g.) and potassium hydroxide (4 g.) in methanol (20 cc.) were heated on a water-bath for three hours. After evaporation of the methanol, the residue was dissolved in water. After extracting any unsaponified matter with ether, the aqueous layer was acidified at 0°. A sticky, light brown precipitate was obtained, which crystallized on scratching. Two crystallizations from dilute methanol yielded the acid (IIIb) in the form of colorless prismatic blocks, m. p. 97°, yield 85%.

*Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.4; H, 9.1. Found: C, 75.9; H, 9.1.

**9-Hydroxy-1,2,3,4,5,6,7,8-octahydrophenanthrene (IVa): (a) From Acid (IIIb).**—To a boiling solution of the dienic acid (10 g.) in dry benzene (150 cc.), thoroughly stirred, was added phosphorus pentoxide (15 g.) in several portions during one and one-half hours. Thereafter the mixture was refluxed for one-half hour and worked up as usual. Distillation at 150–160° (3 mm.) gave a viscous, semi-solid mass, which was dissolved in petroleum ether (90–100°). The solution deposited crystals of m. p. 130–132°, yield 44%. Two crystallizations from the same solvent gave (IVa) as prismatic columns of m. p. 134–135°.

*Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.2; H, 8.9. Found: C, 83.2; H, 8.9.

From the mother liquor of the first crystallization some impure starting material was recovered.

The phenol (IVa) was obtained in only 8% yield, when (IIIb) was first converted into its acid chloride, treated with stannic chloride in dry carbon disulfide solution and the product dehydrochlorinated with dimethylaniline.[4]

(b) **From the Hydroxy Ester (IIa).**—The hydroxy ester (15 g.) and potassium hydroxide (5 g.) in water–methanol (1:2, 45 cc.) were heated on a water-bath for three hours. After removal of methanol and extraction of any unsaponified matter with ether, the solution was acidified with cold dilute hydrochloric acid. The precipitated oily acid was taken up in ether. After washing and drying, the ether was evaporated, the sirupy residue dried *in vacuo* and dissolved in dry benzene (100 cc.). To the boiling benzene solution phosphorus pentoxide (20 g.) was added portionwise during two hours, under vigorous stirring. After heating for one more hour, the mixture was worked up as before and yielded 35% of the phenol (IVa), m. p. and mixed m. p. 134–135°.

**9-Methoxyoctahydrophenanthrene (IVb).**—(a) The hydroxy compound (IVa) (2 g.) was warmed with 10% potassium hydroxide (20 cc.), when an insoluble potassium salt separated. It was dissolved by addition of methanol and warming. To the stirred solution dimethyl sulfate (2 cc.) was added. Upon heating an oil separated. Three more portions of potassium hydroxide (10 cc.) and dimethyl sulfate (1 cc.) were added. Upon cooling, the methyl ether (IVb) separated. Two crystallizations gave (IVb) in the form of prismatic columns, m. p. 92–93°; yield 70%.

This product did not depress the m. p. of the compound of Bachmann and Ness.[8]

(b) The phenol (IVa) (2 g.) was added to a solution of sodium (0.6 g.) in methanol (15 cc.) and methylated with methyl iodide (5 cc.) by refluxing for two hours; yield 65%.

**9-Methoxy-10-bromo-*sym*-octahydrophenanthrene (VIIIb).**—(a) 9-Hydroxy-*sym*-octahydrophenanthrene was brominated according to v. Braun and Bayer[7] and the 9-hydroxy-10-bromo derivative methylated by dimethyl sulfate as described above. (VIIIb) forms minute colorless prismatic plates from methanol, m. p. 99–100°; yield 70%.

*Anal.* Calcd. for $C_{15}H_{19}OBr$: C, 61.0; H, 6.5. Found: C, 61.2; H, 6.6.

(b) The same compound was obtained by bromination of the methyl ether (IVb) in glacial acetic acid; yield 66%.

**Condensation of (I) with Ethyl Cyanoacetate.**—A mixture of cyclohexenylcyclohexanone (17.8 g.), ethyl cyanoacetate (11.3 g.), ammonium acetate (1.5 g.), glacial acetic acid (10 cc.) and benzene (40 cc.) was refluxed for eight hours, and the water formed during the reaction was separated with the help of a separator. The light brown solution was washed with water, dried and fractionated at 1.5 mm.

Fraction 1. B. p. 112–114°; $n^{22}D$ 1.4970; yield, 5 g. of colorless oil (Va).

*Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.4; H, 7.8. Found: C, 68.1; H, 7.9.

Fraction 2: b. p. 146–148°; $n^{23}D$ 1.5180; yield 12 g. of a faintly yellow viscous liquid (VI).

*Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.7; H, 8.2. Found: C, 74.8; H, 8.5.

Fraction 3: residue; it was dissolved in benzene and left overnight, yielding 0.2 g. of crystals (VIIa). After repeated crystallizations from benzene or methanol, (VIIa) was obtained as colorless prismatic columns of m. p. 215–216°.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 79.3; H, 7.5. Found: C, 79.2; H, 7.4.

Like (IVa), this compound gave no color reaction with ferric chloride.

When fractionation was carried out at 7 mm. pressure, the yield of (VIIa) was 0.6 g. It was also obtained in 50% yield upon heating the ester (VI) to 210–215° for three hours and in 72% yield when (VI) was heated with an equal weight of acetamide to 200° for two hours.

The phenol (VIIa) was methylated as described above for (IVa) to give a 52% yield of (VIIb). On recrystallization from methanol prismatic columns were obtained, m. p. 105–106°.

*Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.7; H, 7.9. Found: C, 79.4; H, 7.9.

**Denitrilation.**—The hydroxy cyano compound (VIIa) (1 g.), zinc chloride (5 g.), zinc dust (1 g.) and sodium chloride (1 g.) were thoroughly mixed by grinding and the mixture heated to 215–225° for fifteen minutes. The mass was treated with dilute hydrochloric acid, and the residue recrystallized from methanol. The product had m. p. 212–224°, representing unchanged starting material. From the mother liquor a second crop of crystals was obtained which after repeated recrystallization from petroleum ether showed a m. p. of 133–134° and was identical with (IVa).

When the methoxy derivative (VIIb) was subjected to the same treatment, denitrilation was accompanied by demethylation to (IVa).

When 9-methoxy-10-bromo-*sym*-octahydrophenanthrene (VIIIb) (1.7 g.) was mixed with powdered cuprous cyanide (0.75 g.) and heated in pyridine (1 cc.) for ten hours to 215–225°, and the product directly sublimed in a high vacuum, 0.5 g. of a yellowish solid was obtained, which after repeated recrystallization from methanol showed a m. p. of 213–215°, not depressed by admixture of (VIIa).

**Lactonization of (VI).**—Ethyl cyclohexenylcyclohexylidene cyanoacetate (VI) (6 g.) in ethanol (60 cc.) was refluxed with concentrated hydrochloric acid (20 cc.) for four hours. Upon cooling crystals separated, which were recrystallized from methanol; prismatic plates of m. p. 171–172° (IX); yield 2 g.

*Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.5; H, 7.8; N, 5.7. Found: C, 73.4; H, 7.7; N, 5.8.

The lactone is insoluble in warm sodium carbonate solution, but dissolves in warm caustic soda or potash. Acidification reprecipitates the lactone.

When the lactone was heated to 200°, decarboxylation took place. The yellowish oil obtained in 90% yield, distilled at 114–117° (1.5 mm.) (X).

*Anal.* Calcd. for $C_{14}H_{19}N$: N, 7.0. Found: N, 7.4.

**Absorption Measurements.**—All absorption spectra were measured in 95% alcohol, using a Beckman quartz spectrophotometer.

## Summary

1,1′-Dicyclohexenyl-2-acetic acid is cyclized by phosphorus pentoxide to 9-hydroxy-*sym*-octahydrophenanthrene. Ethyl cyclohexenylcyclohexylidenecyanoacetate is cyclized thermally to 9-hydroxy-10-cyano-*sym*-octahydrophenanthrene. Spectrographical analysis shows that in the dicylohexenyl derivatives investigated usually the two double bonds are not conjugated.

BROOKLYN, N. Y. RECEIVED JUNE 26, 1948

[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

# Keto-Hemiacetal Tautomerism of Some N-Phenacyl-N-substituted Ethanolamines

BY NORMAN H. CROMWELL AND KWAN-CHUNG TSOU

In a previous communication[1] the syntheses of some N-benzohydryl-N-substituted ethanolamines and derivatives were reported. The present investigation was begun with the idea of extending the preparation of such compounds to the phenacyl series. The presence of the keto group in the latter series was expected to provide for further wide variation in the structures of the various derivative types.

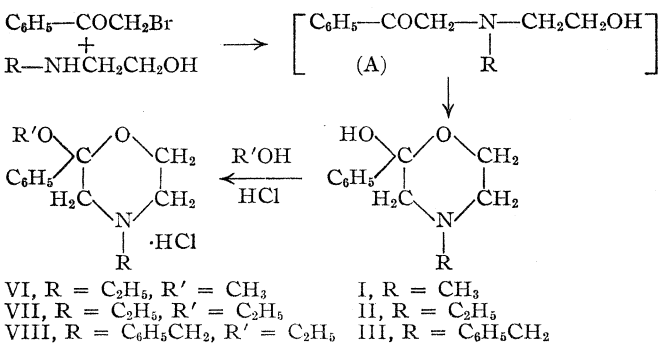
The reactions of the N-methyl, N-ethyl and N-benzyl ethanolamines with phenacyl bromide were investigated and the solid free bases, (I), (II) and (III) were isolated in fair yields. The behavior of the hydrochlorides of these bases upon attempted recrystallization from ethanol or methanol showed reaction with these solvents in such a manner as to indicate acetal formation. An inspection of the structure of an N-phenacyl-N-substituted ethanolamine (A) suggests the possibility of the formation of a six-membered ring, hemiacetal, which would, of course, be expected to form an acetal with reactive alcohols in the presence of hydrogen chloride. This phenomenon was not found for the previously investigated N-benzohydryl-N-substituted ethanolamine hydrochlorides.[1]

This problem then resolved itself into a study of the structures of the free bases (I), (II) and (III), their hydrochlorides, and their reaction products with ethanol and methanol. Helferich has made an extensive study of the analogous $\gamma$-hydroxy- and $\delta$-hydroxy aldehydes and ketones and has reported that they undergo such cyclization to give hemiacetals which react with methyl alcohol to form acetals.[2]

Recently, Hill and Powell[3] have reported a cyclization and dehydration of N-(3,4-dihydroxyphenacyl)-N-benzoylethanolamine hydrochloride to 2-(3′,4′-dihydroxyphenyl)-4-benzoyl-5,6-dihydro-1,4-oxazine. The former compound may actually exist in the hemiacetal form.[4]

The free bases (I), (II) and (III) did not readily form either phenylhydrazones or oximes. This was the first indication that they might not contain a keto group. All three of them gave an immediate Tollens test, which is not observed with either $\omega$-morpholinoacetophenone nor N-benzohydryl-N-benzylethanolamine.[1]

The hydrochlorides (IV) and (V) of (II) and (III), respectively, were obtained only when recrystallizations of the products were carried out very rapidly from cold methyl alcohol and dry ether, or from *t*-butyl alcohol and ether. When these hydrochlorides were dissolved in the hot alcohols the alkoxy derivatives, such as (VI), (VII) and (VIII) resulted. These latter compounds reduced Tollens solution only after warming.

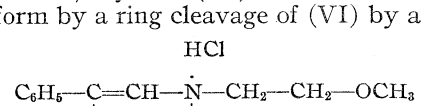



VI, R = $C_2H_5$, R′ = $CH_3$
VII, R = $C_2H_5$, R′ = $C_2H_5$
VIII, R = $C_6H_5CH_2$, R′ = $C_2H_5$

I, R = $CH_3$
II, R = $C_2H_5$
III, R = $C_6H_5CH_2$

Considerable difficulty was often experienced in repeating the preparation of (VI), (VII) and (VIII), in our numerous runs of these reactions. Further reaction with the alcohol often occurred, and compounds which analysis indicated might be of the nature of (IX), discussed below, resulted. Analyses of (VI), (VII) and (VIII), as well as for (IV) and (V) were difficult to obtain because the compounds often decomposed if the usual drying techniques were used. Such difficulties prevented us from obtaining analytically pure samples of the 2-phenyl-2-alkoxy-4-methylmorpholine hydrochlorides. Although acceptable chlorine and nitrogen analysis were not difficult to obtain in these various series, it was obvious that carbon and hydrogen analyses would be required here to establish definitely the identity of these compounds.

When a sample of the alkoxy compound (VI) was allowed to stand for some time in methanol before recovering a product, a further change took place to give a dialkoxy compound which possibly is $\alpha$-methoxy-$\beta$-(N-ethyl-N-($\beta'$-methoxyethyl)-amino)-styrene (IX). Such a compound could form by a ring cleavage of (VI) by a second




(IX)

(1) Cromwell and Fitzgibbon, THIS JOURNAL, **70**, 387 (1948).

(2) Helferich, *et al.*, *Ber.*, **52**, 1123 (1919); **55**, 702 (1922); **56**, 759, 2088 (1923); **57**, 1911 (1924); **58**, 1246 (1925).

(3) Hill and Powell, THIS JOURNAL, **67**, 1462 (1945).

(4) An interesting paper by Lutz, Freek and Murphey, *ibid.*, **70**, 2015 (1948), has recently appeared which reports that ring-chain tautomerism does result with various $\alpha$-(N-substituted-N-ethanolamino)-desoxybenzoins. The evidence cited was the non-reducibility of the carbonyl group in such compounds. These authors further indicated that they were studying such tautomerism in the related acetophenone series.

molecule of methanol, followed by the loss of water. This product (IX) did not react with Tollens solution until the reaction mixture was heated to boiling. After standing for several weeks (IX) underwent decomposition.

The absorption spectra studies (Table II and Fig. 1) of the free bases (I), (II) and (III), when compared with that of ω-dibenzylaminoacetophenone, offer convincing evidence that they exist almost wholly in the cyclic hemiacetal forms, as given by the 2-hydroxymorpholine structures. Acetophenone itself shows an absorption maximum of 2415–2430 Å. with a molar extinction coefficient of 12,600–16,200.[5] Thus it seems certain that if these compounds actually contained a benzoyl group ($C_6H_5$–CO–) they would show a strong absorption band near 2400 Å. with a molar extinction coefficient of at least 12,000.

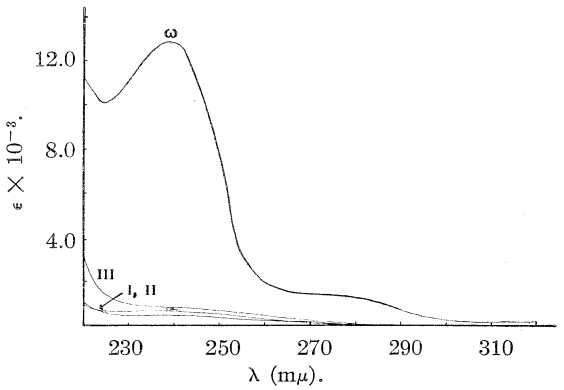



Fig. 1.—Absorption spectra of ω-dibenzyl-aminoacetophenone; of (I); of (II); and of (III) in heptane solution.

The fact that dilution had little effect on the absorption spectra (Table II, Fig. 2), indicated little tendency for (I) or (III) to exist in equilibrium with the open chain keto compounds (A) in heptane solution.

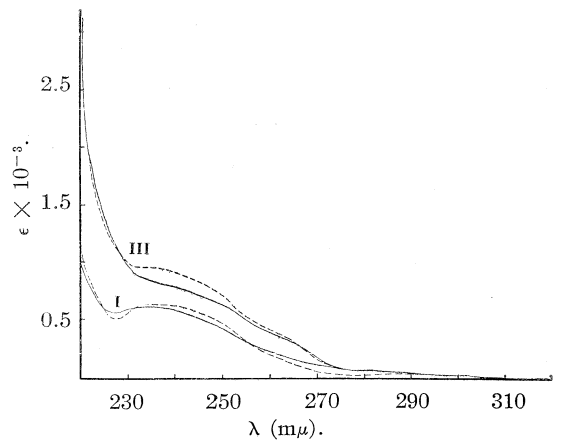



Fig. 2.—Absorption spectra dilution studies of (I) and (III): .... more dilute; — more concentrated; in heptane solution.

(5) Bielecki and Henri, *Ber.*, **47**, 1709 (1914); Morton and Sawires, *J. Chem. Soc.*, 1054 (1940).

The comparisons of the spectra of ω-morpholino- and ω-dibenzylaminoacetophenone hydrochlorides with those of the 2-hydroxymorpholine hydrochloride (V) and the 2-alkoxymorpholine hydrochlorides (VII) and (VIII), are equally convincing that these latter compounds do not contain a keto group (see Table III and Fig. 3).

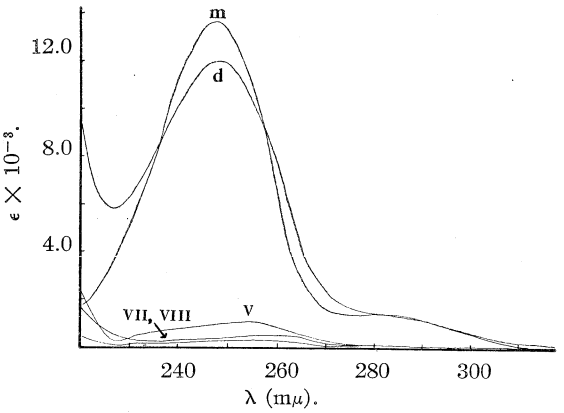



Fig. 3.—Absorption spectra in abs. ethanol: (m), ω-morpholinoacetophenone hydrochloride; (d), ω-dibenzylaminoacetophenone hydrochloride; (V); (VII); and (VIII).

The curves in Fig. 4 for the morpholine hydrochlorides (IV) and (VI) have been plotted on such a scale as to show more clearly the actual presence of weak bands for these compounds in the area expected for the keto structures. The magnitude of the molar extinction coefficients for these maxima are so low, however, that if the keto form actually exists in such solutions, it is present in very low concentrations (less than 10%). The absorption curve for the dialkoxy compound (IX) is given here, without comment, since no strictly analogous compounds were available for comparison. Styrene is known to have a maximum absorption band at 2450 A. with a molar extinction coefficient of 10,720.[6]

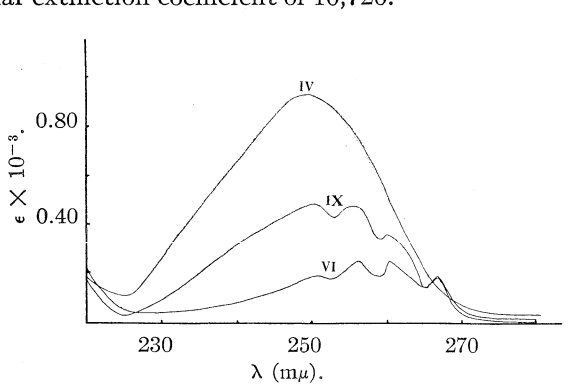



Fig. 4.—Absorption spectra in absolute methanol of (IV); (VI); and (IX).

(6) Ley and Dirking, *Ber.*, **67**, 1334 (1934).

TABLE I

PHYSICAL AND ANALYTICAL PROPERTIES

| 2-Phenyl-morpholines | No. | Yield, % | M. p., °C. | Formula | Percentage composition[a] Calcd. C | Calcd. H | Calcd. N | Calcd. Cl | Found C | Found H | Found N | Found Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-Hydroxy-4-methyl | (I) | 48 | 53 | $C_{11}H_{15}NO_2$ | 68.36 | 7.85 | 7.25 | ... | 68.20 | 8.00 | 7.30 | ... |
| 2-Hydroxy-4-ethyl | (II) | 70 | 54 | $C_{12}H_{17}NO_2$ | ... | .. | 6.75 | ... | ... | .. | 6.57 | ... |
| Hydrochloride | (IV) | 90 | 127 | $C_{12}H_{18}NO_2Cl$ | 59.13 | 7.45 | 5.74 | 14.55 | 59.35 | 7.59 | 5.54 | 14.59 |
| 2-Hydroxy-4-benzyl | (III) | 70 | 62 | $C_{17}H_{19}NO_2$ | 75.80 | 7.11 | 5.20 | ... | 75.88 | 7.05 | 5.08 | ... |
| Hydrochloride | (V) | 85 | 144 | $C_{17}H_{20}NO_2Cl$ | 66.77 | 6.59 | 4.58 | 11.60 | 66.33 | 6.79 | 4.54 | 11.67 |
| 2-Methoxy-4-ethyl Hydrochloride | (VI) | 50 | 148 | $C_{13}H_{20}NO_2Cl$ | 60.57 | 7.81 | 5.44 | 13.76 | 60.39 | 7.98 | 5.29 | 13.74 |
| 2-Ethoxy-4-ethyl Hydrochloride | (VII) | 50 | 143 | $C_{14}H_{22}NO_2Cl$ | 61.88 | 8.16 | 5.15 | 13.05 | 61.34 | 8.16 | 5.26 | 12.86 |
| 2-Ethoxy-4-benzyl Hydrochloride | (VIII) | 85 | 151 | $C_{19}H_{24}NO_2Cl$ | 68.35 | 7.24 | 4.19 | 10.62 | 68.70 | 7.40 | 4.15 | 10.58 |

[a] Micro analyses for carbon, hydrogen and nitrogen were carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

Herold has studied the ultraviolet absorption spectra of γ-hydroxybutyraldehyde in various solvents and has concluded that only about 10% of the free aldehyde is present.[7]

It seems evident that all of these compounds, (I) through (VIII), are essentially substituted morpholines.

## Experimental

**2-Hydroxy-2-phenyl-4-substituted Morpholines.**—Pure phenacyl bromide (0.20 mole) was dissolved in 400 ml. of dry ether and added dropwise with stirring to 0.40 mole of the corresponding N-substituted ethanolamine dissolved in 300 ml. of dry ether. The mixture was kept at near room temperature during the addition and then allowed to stand at this temperature for twenty-four hours. The supernatant liquid was decanted or filtered from the precipitated N-substituted ethanolamine hydrobromide and washed several times with saturated salt water, dried over anhydrous calcium sulfate and evaporated. The crude solid products were recrystallized from ether–petroleum ether mixtures to give almost colorless crystalline products.

In this way (I), (II) and (III) were obtained using, respectively, N-methylethanolamine,[8] N-ethylethanolamine,[9] and N-benzylethanolamine.[1]

These morpholines (I), (II) and (III) gave only slight tests with phenylhydrazine and no solid derivatives could be isolated. All three gave an immediate silver mirror formation with Tollens solution at room temperature. They did not give isolable products from reaction mixtures of hydroxylamine. An attempted hydrogenation of (III) in absolute alcohol at room temperature using platinum oxide catalyst and 50 lb. per square inch used up no hydrogen in three hours.[4] It was not possible to obtain a benzoate of (II) employing the usual methods with benzoyl chloride.

The compounds (I), (II) and (III) were each dissolved in dry ether and treated with one equivalent of dry hydrogen chloride gas in dry ether to give almost quantitative yields of the very hygroscopic hydrochlorides.

The hydrochloride of (I) could not be handled. The crude hydrochloride of (II) melted at 112–115° but rapid recrystallization, by dissolving in cold methyl alcohol followed by the immediate addition of dry ether, or solution in warm 85% *t*-butyl alcohol, followed by the addition of ether, gave the higher melting, pure hydrochloride (IV). The crude hydrochloride of (III) melted at 131–134° but recrystallization from 90% *t*-butyl alcohol and ether gave a higher-melting, pure product (V). These hydrochlorides, like the pure bases, gave an immediate, positive Tollens test at room temperature.

**2-Alkoxy-2-phenyl-4-substituted Morpholine Hydrochlorides.**—Dry ether solutions of the morpholines (II) and (III) were treated with dry hydrogen chloride by cooling the solutions in an ice-bath and bubbling in the dry gas. The flocculent precipitates were filtered off, washed with dry ether and dissolved in the corresponding hot absolute alcohols, methyl and ethyl. Dry ether was added and the solutions cooled to precipitate the alkoxy compounds which were again recrystallized from the corresponding alcohols and ether mixtures to give the pure alkoxy compounds (VI), (VII) and (VIII); see Table I. Samples of these compounds for analyses were dried under vacuum at room temperature for eight hours. An excess of ether was avoided in precipitating these products since it often carried down the dialkoxy compounds of type (IX) discussed below.

These compounds gave a positive test with Tollens reagent only after the solution was warmed.

**Reaction of (VI) with Methyl Alcohol.**—A 10-g. sample of (VI) was dissolved in 60 ml. of dry methyl alcohol at 50° and the solution allowed to stand at room temperature for twelve hours and in the ice-chest for three days. Dry ether was added to precipitate the product which was recrystallized again from methyl alcohol and dry ether; m.p. 142°, wt., 5.4 g. A fresh sample of (IX) did not react with warm Tollens solution, but upon boiling the mixture, reaction took place.

*Anal.* Calcd. for $C_{14}H_{22}NO_2Cl$: C, 61.88; H, 8.16; N, 5.15; Cl, 13.05. Found: C, 61.27; H, 7.86; N, 5.07; Cl, 13.07.

**Absorption Spectra Studies.**—These measurements were made with a Beckman Model DU Photoelectric Quartz Spectrophotometer. At the sensitivity used, the maximum band width was one millimicron with an accuracy of 0.1% for the density measurements. The solvents used were laboratory grade absolute ethanol, methanol, and heptane-from-petroleum, purified by the procedure recommended by Weissberger.[10]

The ultraviolet absorption spectra of (I), (II), (III) and ω-dibenzylaminoacetophenone[11] were observed using heptane as the solvent. These studies were made within two hours of the time

(7) Herold, *Z. physik. Chem.*, **16B**, 213 (1932).

(8) Generously supplied by the Carbide and Carbon Chemical Corp., New York.

(9) Kindly furnished by the Smith, Kline and French Laboratories, Philadelphia, Pa.

(10) Weissberger, "Physical Methods of Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946, p. 766.

(11) Busch and Hefele, *J. prakt. Chem.*, [2] **83**, 449 (1911).

the solutions were prepared. The results are tabulated in Table II and the complete curves shown in Fig. 1.

TABLE II

ABSORPTION SPECTRA OF THE 2-PHENYL-2-HYDROXYMORPHOLINES IN HEPTANE

| Morpholines | Molar Concn. × $10^4$ | Maxima λ,Å. | Maxima ε × $10^{-3}$ | Minima λ,Å. | Minima ε × $10^{-3}$ |
|---|---|---|---|---|---|
| (I) | 15.1 | 2350 | 0.63 | 2260 | 0.59 |
| | 0.60 | 2350 | .66 | 2260 | .55 |
| (II) | 2.67 | 2550 | .51 | 2300 | .49 |
| (III) | 2.47 | 2350 | .92 | 2340 | .91 |
| | 1.24 | 2350 | .98 | 2340 | .97 |
| ω-Dibenzylamino-acetophenone | 1.50 | 2390 | 12.96 | 2240 | 10.05 |

Using heptane as the solvent, the spectra of (I) and (III) were observed in more dilute solutions and compared with the previous results (see Table II and Fig. 2).

The spectra of the morpholine hydrochlorides (V), (VII), (VIII), and of ω-dibenzylaminoacetophenone hydrochloride,[11] and ω-morpholinoacetophenone hydrochloride[12] were examined in absolute ethanol solution (see Table III and Fig. 3).

TABLE III

ABSORPTION SPECTRA OF 2-HYDROXY AND 2-ETHOXY-2-PHENYLMORPHOLINE HYDROCHLORIDES IN ABSOLUTE ETHANOL

| Morpholines | Molar concn. × $10^4$ | Maxima λ,Å. | Maxima ε × $10^{-3}$ | Minima λ,Å. | Minima ε × $10^{-3}$ |
|---|---|---|---|---|---|
| V | 3.67 | 2500 | 1.05 | 2300 | 0.44 |
| VII | 3.37 | 2570 | 0.31 | 2300 | 0.13 |
| VIII | 1.45 | 2550 | 0.52 | 2340 | 0.25 |
| Acetophenones | | | | | |
| ω-Dibenzylamino-hydrochloride | 1.54 | 2480 | 11.89 | 2260 | 5.86 |
| ω-Morpholinohydrochloride | 1.00 | 2480 | 13.70 | .. | .. |

Using absolute methanol as a solvent, the spectra of the morpholine hydrochlorides (IV) and (VI) and the dimethoxy compound (IX) were examined. A summary of the results is given in Table IV and the complete curves are shown in Fig. 4.

TABLE IV

ABSORPTION SPECTRA OF 2-HYDROXY AND 2-METHOXYMORPHOLINE HYDROCHLORIDES IN ABSOLUTE METHANOL

| Morpholine | Molar concn. × $10^4$ | Maxima λ,Å. | Maxima ε × $10^{-3}$ | Minima λ,Å. | Minima ε × $10^{-3}$ |
|---|---|---|---|---|---|
| IV | 5.32 | 2500 | 0.93 | 2260 | 0.11 |
| VI | 3.53 | 2605 | . 26 | 2280 | .04 |
| IX | 4.16 | 2500 | .49 | 2240 | .02 |

## Summary

1. The reactions of phenacyl bromide with N-substituted ethanolamines have been studied and the desired N-phenacyl-N-substituted ethanolamines have been found to have tautomerized to their respective hemiacetal forms, the 2-phenyl-2-hydroxymorpholines.

2. Some acetal derivatives, or 2-phenyl-2-alkoxymorpholines, have been obtained from these hemiacetals.

3. Absorption spectra studies have aided in the elucidation of these structures.

4. These results confirm for the N-phenacyl-N-substituted ethanolamines the conclusions reached by Lutz, *et al.*, with the related α-(N-substituted-N-ethanolamino)-desoxybenzoins.[4]

(12) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

LINCOLN, NEBRASKA RECEIVED JULY 17, 1948

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

# Ring-Chain Tautomerism of α-(Ethylethanolamino)-acetophenone[1]

BY ROBERT E. LUTZ AND ROBERT H. JORDAN[2]

Because of the ring-chain tautomerism involved in the α-(ethylethanolamino)-desoxybenzoins,[3] and because of the interest in these compounds as possible tumor-necrotizing agents,[3,4] it seemed important to explore other series, especially simpler ones such as that based on acetophenone.[5] The present paper deals with preliminary work in this field.

α-(Ethylethanolamino)-acetophenone (I) (m. p. 52–53°) was made by condensing ethylethanolamine with phenacyl bromide.[6] It was readily con-

(1) This is the second paper dealing with ring-chain tautomerism of hydroxyalkylamino ketones. This work, except for the ultraviolet absorptions, was included in a doctorate dissertation by R. H. Jordan, University of Virginia, May, 1948. Some financial support for measurements and analyses, from a grant-in-aid by the National Cancer Institute, is acknowledged.

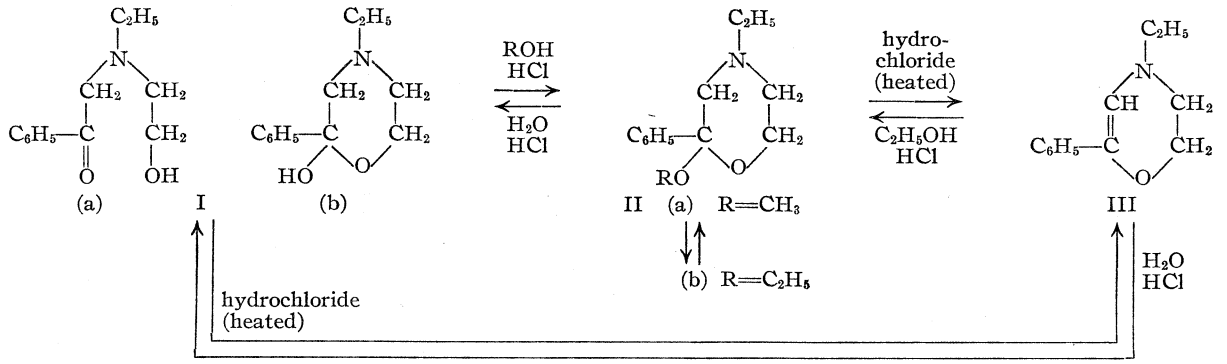
(2) Holder of Tennessee Eastman Company Fellowship, 1947–1948.

(3) (a) Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2015 (1948) [an error appears in Table I, page 2016, where $NR_2$ for compound 612 should read $NHC_6H_4N(C_2H_5)_2$-*p*. Another typographical error appears in the last sentence of the first column of page 2020, where "δ-hydroxyl" should read α-hydroxyl]. (b) Lutz and Murphey, *ibid.*, **71**, 478 (1949); (c) Lutz, Freek and Murphey, a paper presented at the Chicago meeting of the American Chemical Society, April 20, 1948.

(4) Unpublished work of Shear, Downing, MacCardle, Hartwell, *et al.*, at the National Cancer Institute.

(5) Prior work had already been under way on the 2,4-dichloro, 3,4,5- and 2,3,5-trichloro analogs (Lutz, Jordan and Ford; results to be published shortly; *cf.* also ref. 3c).

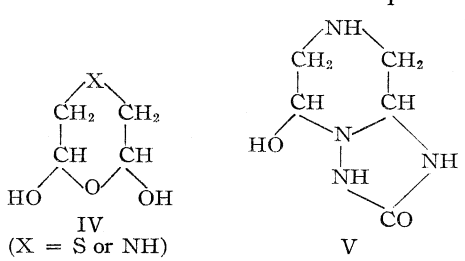
(6) (a) The hydrochloride of this compound (I) has recently been prepared by this method and converted into the *p*-ethoxybenzoyl derivative [Christiansen and Harris, U. S. Patent, 2,404,691 (July 1946); *C. A.*, **41**, 157*f* (1947)]; (b) *cf.* Brighton and Reid, THIS JOURNAL, **65**, 479 (1943).

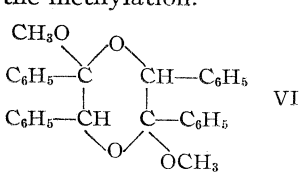



verted into the methyl and ethyl derivatives (IIa and b) by acid catalyzed alcoholysis. The conversion of the methoxy compound (IIa) into the ethoxy (IIb) was accomplished by means of ethanolic hydrogen chloride; and hydrolysis of both alkoxy compounds with dilute aqueous hydrochloric acid regenerated the original compound (I). Isopropyl alcohol did not react under these conditions.

It is noteworthy that the methoxy compound (IIa), which has not been obtained in crystalline form, was distillable under reduced pressure without loss of methanol. However, heating of either the methoxy or ethoxy compounds (II) or the parent compound itself (I), in the form of the hydrochloride or with a small amount of added hydrochloric acid, brought about elimination of the alcohol or water and gave the dehydromorpholine (the dihydro-1,4-oxazine, III). This compound was converted back into the original compound (I) by the action of hot dilute aqueous hydrochloric acid, and into the cyclic acetal (IIb) by ethanolic hydrogen chloride.[7] The reactivity of the dehydro compound in this series (III) is to be contrasted with the stability of the one obtained from α-(N-ethylethanolamino)-desoxybenzoin. The latter compound, with its stilbene double bond, seems to be stable under these conditions, is not readily hydrated to the cyclic hemiacetal nor does it react with alcohols to give the cyclic acetals.[7c]

The best known compounds showing this type of ring-chain tautomerism, of course, are the sugars and γ- and δ-hydroxyaldehydes and ketones; but special reference should be made to less well known analogs where the chain between the carbonyl group and the reacting hydroxyl is broken by an intervening hetero-element, nitrogen, oxygen or sulfur. The compounds of the type $R_2C(OH)CH_2–X–CH_2CHO$[8] and $HOCH_2CH_2–X–CH_2CHO$[9,8b] (where X = oxygen or sulfur), which doubtless involve ring-chain tautomerism, have not yet been studied adequately from this viewpoint. Related to these compounds is the dialdehydo thioethyl ether, $S(CH_2CHO)_2$, which apparently exists as the cyclic monohydrate, 2,6-dihydroxythioxane,[10] and forms the cyclic acetal, 2,6-diethoxythioxane (*cf.* IV).[11] The nitrogen analog, $NH(CH_2CHO)_2$, which appears to exist also as the cyclic monohydrate, 2,6-dihydroxymorpholine (IV),[12] is of particular interest because of the condensation with semicarbazide; the compound obtained, in view of its behavior,[13] is probably V, a possibility considered but not favored by the original authors.[12] The dimolecular product obtained from benzoin by the action of methanolic hydrogen chloride also is of interest here because it seems to be the cyclic diacetal (VI),[14] formed presumably through a benzoin hemiacetal or benzoin-methyl acetal of benzoin, cyclization and completion of the methylation.




In order to decide whether the ethylethanolamino ketones are cyclic or open-chain in simple solution [apart, for example, from possible stabilization as a complex with aluminum isopropoxide],

(7) (a) *Cf.* Hill and Powell, THIS JOURNAL, **67**, 1462 (1945); (b) Paul, *Bull. soc. chim.*, [5] **1**, 971 (1934). (c) In this connection a correction must be made to ref. 3(a and c); the supposed hydration of 3,4-dihydro-1,2-diphenyl-4-ethyl-1,4-oxazine, reported in the earlier paper, appears to be an experimental error; numerous attempts since then to repeat this experiment under a variety of conditions have failed and will be described in a later paper (Lutz and Truett).

(8) (a) Parham, THIS JOURNAL, **69**, 2449 (1947); *cf.* also (b) Fuson and Parham, *J. Org. Chem.*, **11**, 482 (1946).

(9) Palomaa and Aalto, *Ber.*, **66**, 468 (1933).

(10) Coghill, THIS JOURNAL, **59**, 801 (1937).

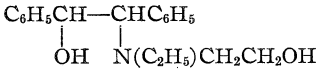
(11) Clark and Smiles, *Trans. Chem. Soc.*, **95**, 992 (1909).

(12) Wolff and Marburg, *Ann.*, **363**, 169 (1908).

(13) *Cf.* Dixon, *J. Chem. Soc.*, **61**, 509 (1892).

(14) Bergmann and Weil, *Ber.*, **63**, 1911 (1938); *cf.* also the work on dihydroxyacetone [Bertrand, *Compt. rend.*, **129**, 341 (1899); Herold, *Z. physik. Chem.*, **16**, 213 (1932)].

ultraviolet absorptions were carried out on the α-(ethylethanolamino) derivatives of acetophenone (I),[15a] desoxybenzoin[15b] and 5-chloro-2-methoxyacetophenone.[16] These compounds absorbed only very slightly in the region 240–250 mμ where ketones such as acetophenone,[17a] desoxybenzoin,[15,17b] and α-diethylaminodesoxybenzoin,[17c] show characteristic maxima. The ethyl derivative of I (the acetal IIb) and the amino-dialcohol corresponding to α-(ethylethanolamino)-desoxybenzoin (namely, VII),[15] neither of which possess a carbonyl group, show no significant absorption maxima in this range. From these facts it is to be concluded that the ethylethanolamino ketones under discussion are largely cyclic, and that the open-chain forms, if present in appreciable amounts in solution (in isoöctane), are there in concentrations probably below 3–5%.



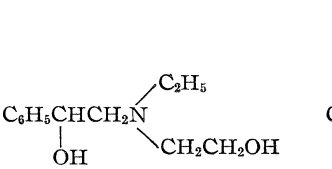
VII

It is of interest to contrast these results with those observed in the systems, —CHCH$_2$CH$_2$CH$_2$C—; the δ-hydroxyketone appears, on the basis of molar refraction, to be largely open-chain,[18a] and the δ-hydroxyaldehyde appears, on the basis of both molar refraction and ultraviolet absorption, to be largely cyclic.[7b,18b] As mentioned before[3a] the enhanced activity of the keto group in the present case (Ia) must be attributed to the heteroelement in the chain, amino nitrogen, which is at the same time alpha to the carbonyl group and comparable to the alpha hydroxyls in the ketone sugars.

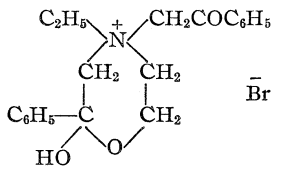
That the ethylethanolamino ketones studied so far,[3] including I, exist largely in the cyclic hemiacetal forms, is indicated[3] also by the fact that they are not reduced readily by the carbonyl-specific reagent, aluminum isopropoxide, under the usually effective conditions. If the open-chain form were present in small amounts, as is perhaps indicated by the ultraviolet absorption experiments, it is possible that the cyclization is actually promoted to some extent by combination with the reagent, because of the greater acidity of the hemiacetal hydroxyl (*cf.* Ib) as compared with the alcoholic hydroxyl of the open-chain form (Ia).

It is pertinent to note in this connection that in a preliminary experiment catalytic reduction of α-(ethylethanolamino)-desoxybenzoin[19] proceeds with far greater difficulty than it does with α-(piperidyl)-desoxybenzoin[3] which is necessarily open-chain.

The amino-dialcohol (VIII) which was desired for tests and for comparison with the corresponding ketone (I), was subsequently made by standard procedure through condensation of styrene bromohydrin with ethylethanolamine. It was not obtained in a crystalline form and was characterized as the picrate.



VIII



IX

As a minor by-product of the condensation of ethylethanolamine with phenacyl bromide, there was obtained the quaternary compound (IX), which is obtainable in good yield by the use of an excess of phenacyl bromide. It doubtless exists as the cyclic hemiacetal as formulated; it is easily converted by means of alcoholic hydrogen bromide into a monoethoxy derivative (the cyclic acetal). The compound (IX) is of interest in connection with the study of tumor-necrotizing agents in view of the known activity of certain phenacylpyridinium salts.[4]

The compounds I, IIb, III, VIII and IX, are being screened for pharmacological activity, and especially for tumor-necrotizing action.[4]

Further studies are in progress in the field of hydroxyalkylamino ketones and their reactions and derivatives, especially with respect to various aspects of the problem of ring-chain tautomerism. These include absorption spectral, reduction and polarographic studies.

**Acknowledgment.**—The ultraviolet absorption studies reported in this paper were carried out by Spencer M. King. Microanalyses were carried out by Mrs. Joyce Blume Caliga.

## Experimental[20a,b]

**α-(Ethylethanolamino)-acetophenone (I) [4-Ethyl-2-hydroxy-2-phenylmorpholine].**[6]—A solution of 60 g. (0.3 mole) of phenacyl bromide in 200 ml. of commercial absolute ether was slowly added under stirring to 60 g. (0.82 mole) of ethylethanolamine in 100 ml. of ether. After standing for two hours, filtering, washing, drying over sodium sulfate and evaporating, the residual oil was dissolved in 80 ml. of isoöctane, filtered from a small amount of the quaternary compound (IX) (see below), and was induced to crystallize by cooling in an ice–salt-bath; 43 g. (64%); m. p. 50–51°; m. p. after recrystallization from isoöctane, 52–53°. The compound was very sensitive, especially in contact with metals; on standing overnight the melting point dropped to 48–51°.

*Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.43; H, 8.26. Found: C, 69.41; H, 8.19. Ultraviolet abs. max. in isoöctane: λ 238–242 mμ ($\epsilon \times 10^3 = 0.28$; $c = 0.001$)[14].

(15) These determinations of ultraviolet absorption were carried out in this Laboratory by Spencer M. King. (a) λ (in isoöctane) 238–242 mμ ($\epsilon \times 10^{-3} = 0.28$; $c = 10^{-3}$). (b) λ (in isoöctane) 250–258 mμ ($\epsilon \times 10^{-3} = 0.44$; $c = 10^{-3}$).

(16) The work on this series was done in this Laboratory by Gilbert Ashburn (to be published shortly).

(17) (a) λ 246–249 mμ [Scheibe, *Ber.*, **59**, 2621 (1926)]; (b) λ (in isoöctane) 239–241 mμ ($\epsilon \times 10^{-4} = 1.2$; $c = 10^{-4}$). (c) λ (in isoöctane) 241–243 mμ ($\epsilon \times 10^{-4} = 1.2$; $c = 10^{-3}$).

(18) (a) Bergmann and Miekeley, *Ber.*, **55**, 1394 (1922); (b) Schniepp and Geller, THIS JOURNAL, **68**, 1646 (1946).

(19) Lutz and Truett, reduction studies in progress.

(20) (a) Melting points are corrected. (b) The ultraviolet absorptions reported were taken with a Beckman DU quartz spectrophotometer. The solvent used was isoöctane (2,2,4-trimethylpentane) (Phillips Petroleum Co.).

**The hydrochloride**[6] was precipitated from ether; m. p. 125–125.5°.

*Anal.* Calcd. for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.12; H, 7.44. Found: C, 59.18; H, 7.42.

Recrystallization from ethanol caused partial conversion to the ethoxy compound (IIb) (demonstrated by pyrolysis of the product and identification of the ethanol generated, by micro-boiling point).

Isopropyl alcohol was found not to react with I under the various conditions which were effective with ethanol and methanol.

**Treatment with aluminum isopropoxide** under the usual conditions,[3a] using a large excess of reagent, in isopropyl, alcohol refluxing for six hours, gave no test for evolved acetone; the recovery (crude, 80%) of pure material of melting point 51.5–52.5° was 40%.

**2-Ethoxy-4-ethyl-2-phenylmorpholine (IIb).**—Either of two procedures was effective. (A) A solution of I in 25:10 absolute ethanol–saturated ethereal hydrogen chloride was allowed to stand at room temperature for twelve days. The base was liberated and converted to the hydrochloride (yield 64%). (B) A solution of 24 g. of I-hydrochloride in 100 ml. of absolute ethanol with an added 5 ml. of saturated ethanolic hydrogen chloride, was refluxed for one and one-half hours. The volume was reduced to 50 ml. by distillation under reduced pressure and the hydrochloride was precipitated by ether; yield 22 g. (82.5%).

**The base** (liberated by alkali) crystallized on seeding. After recrystallization from petroleum ether it melted at 49–50°.

*Anal.* Calcd. for $C_{14}H_{21}NO_2$: C, 71.52; H, 9.00. Found: C, 71.25; H, 8.74.

The **hydrochloride** had to be handled under non-aqueous conditions to avoid the facile hydrolysis to I. It crystallized as rhombic plates from ethanol–ether mixtures; m. p. 144.5°.

*Anal.* Calcd. for $C_{14}H_{21}NO_2 \cdot HCl$: C, 61.86; H, 8.16. Found: C, 61.82; H, 8.01.

**Hydrolysis** to I was effected by 6 *N* hydrochloric acid (warmed, thirty min.); identified by mixture m. p.; yield 65%.

**4-Ethyl-2-methoxy-2-phenylmorpholine** (IIa) was prepared by (A) and (B) under IIb, using methanol. **The hydrochloride** was crystallized from isopropyl alcohol–ether mixture; it was hygroscopic; m. p. (dried *in vacuo*) 148–149°.

*Anal.* Calcd. for $C_{13}H_{19}NO_2 \cdot HCl$: N, 5.44. Found: N, 5.33.

**The base** did not crystallize, and was fractionated. The yield of the principal cuts was 42%; b. p. 112° (1.8 mm.); $n^{25}D$ 1.5151; $d^{25}_4$ 1.051; $(R)D$ 62.91.

*Anal.* Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.47; H, 8.61.

**Hydrolysis** (warm 6 *N* hydrochloric acid) gave I (yield 75%). **Ethanolysis** by method (B) under IIb, gave IIb (yield 64%).

**4-Ethyl-2-phenyl-5,6-dihydro-1,4-paroxazin (III).**—Micropyrolyses of less than 40-mg. samples of I and IIb hydrochlorides gave water and ethanol, respectively (identified by micro-boiling points[21]).

A mixture of 5 g. of I and 5 drops of concd. hydrochloric acid was heated at 175–180° until evolution of water ceased (*ca.* five minutes). The base could be distilled under reduced pressure, but a cloudy distillate was always obtained. There was evidence of change in the oil, even upon standing overnight. The hydrochloride was precipitated from an isoöctane solution of the base by ethereal hydrogen chloride; 3 g. (65%). After washing with a small quantity of acetone to remove some resinous material, it was recrystallized from acetone–ether mixture; m. p. 163.5–165.5° (dec.).

*Anal.* Calcd. for $C_{12}H_{15}NO \cdot HCl$; C, 63.85; H, 7.14. Found: C, 63.61; H, 7.24.

Pyrolysis of IIb under the above conditions gave III in similar yields.

**Hydrolysis** (hydration) by 6 *N* hydrochloric acid (warmed) gave I (60%). **Ethanolysis** (alcoholation) by (B) under IIb gave IIb (98%).

**4-Ethyl-2-hydroxy-4-phenacyl-2-phenylmorpholinium Bromide (IX).**—A mixture of 5 g. of I and 5 g. of phenacyl bromide was heated at 40–60° until the melt solidified (forty-five minutes); trituration and washing with ether gave 9.2 g. (94%); m. p. 183.5–184.5°. It crystallized from ethanol as short prisms; m. p. 189.5–190° (initial bath temperature 170°, heating rate 3° per minute).

*Anal.* Calcd. for $C_{20}H_{24}BrNO_3$: C, 59.11; N, 5.95. Found: C, 58.81; H, 5.84.

**2-Ethoxy-4-ethyl-4-phenacyl-2-phenylmorpholinium Bromide** was made from IX by the action of refluxing ethanolic hydrogen bromide (forty-five minutes) and precipitation by ether; yield 36% (on a 3-g. run). After recrystallization from absolute ethanol it melted at 181.5–182° (taken as above). A mixture melting point with IX showed a 5° depression below this point.

*Anal.* Calcd. for $C_{22}H_{28}BrNO_3$: C, 60.82; H, 6.49. Found: C, 61.05; H, 6.19.

**2-Ethylethanolamino-1-phenylethanol (VII).**—A solution of 24 g. (0.118 mole) of 2-bromo-1-phenylethanol (obtained in 65% yield by aluminum isopropoxide reduction of phenacyl bromide)[22] in 32 g. (0.35 mole) of ethylethanolamine, was heated at 100° for fifteen hours. The product was taken up in ether, washed, dried over sodium sulfate and obtained as an oil upon evaporation of the solvent.

**The hydrochloride** did not crystallize. The base was fractionated; the principal cuts of nearly constant refractive index totaled 15 g. (61%); b. p. 152–155° (1.8 mm.). Vacuum evaporation of the middle cut onto a cold-finger drip-condenser gave a pure fraction; $n^{25}D$ 1.5279.

*Anal.* Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15. Found: C, 68.69; H, 9.18.

**The picrate,** obtained from ethanol, was crystallized from ethanol–isoöctane mixture; m. p. 100.5–102°.

*Anal.* Calcd. for $C_{18}H_{22}N_4O_4$: C, 49.31; H, 5.06; N, 12.77. Found: C, 48.96; H, 5.38; N, 12.60.

## Summary

α-(Ethylethanolamino)-acetophenone shows typical ring-chain tautomerism. It is not reduced by aluminum isopropoxide. It is easily mono-alkylated under acid catalysis by methanol and ethanol but not by isopropyl alcohol. Pyrolysis of these compounds gives the dihydroparoxazine. The compounds are interconvertible.

The absence of significant ultraviolet absorption maxima in the region of 240–250° mμ shows this and other ethylethanolamino ketones to exist in the cyclic or hydroxymorpholine forms.

The corresponding amino-dialcohol, 2-ethylethanolamino-1-phenylethanol, was made through styrene bromohydrin.

The quaternary phenacyl derivative of α-(ethylethanolamino)-acetophenone was obtained; it gave a mono-ethyl derivative upon treatment with ethanol–hydrobromic acid.

CHARLOTTESVILLE, VA. RECEIVED AUGUST 10, 1948

(21) Morton, "Laboratory Technique in Organic Chemistry," Int. Chem. Series, 1938, p. 50.

(22) Lund, *Ber.*, **70**, 1520 (1937).

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

# The Ultraviolet Absorption Spectra of Steroidal Dinitrophenylhydrazones

BY CARL DJERASSI AND ELIZABETH RYAN

2,4-Dinitrophenylhydrazones are employed widely as carbonyl derivatives in view of their comparatively high melting points and easy crystallizability; furthermore, they are particularly useful in the chromatographic separation of a variety[1,2] of ketones including those of the steroid series.[3,4] Correlations between the ultraviolet absorption spectra of dinitrophenylhydrazones and the structure of the carbonyl compounds from which they are derived are therefore of obvious significance. Important contributions on this subject have been published recently by Braude and Jones,[5] and Roberts and Green,[6] who investigated the spectra of a considerable number of dinitrophenylhydrazones of representative saturated and unsaturated carbonyl compounds in both the aliphatic and aromatic series.

In connection with a study of the reaction of dinitrophenylhydrazine with steroidal bromo ketones,[7] it was necessary for comparison purposes to prepare authentic samples of a number of dinitrophenylhydrazones of steroid ketones with varying degrees of unsaturation and to determine their ultraviolet absorption curves. The present series of compounds is structurally more closely related than the hydrazones studied previously[5,6] and it was thus possible to examine the influence of relatively minor changes in the ketone moiety upon the absorption of the dinitrophenylhydrazone. Furthermore, precise absorption data for steroidal dinitrophenylhydrazones are lacking and in conjunction with the spectra of the carbonyl compounds should prove useful in the characterization of unknown steroid ketones or in the chromatographic separation of ketone mixtures *via* their dinitrophenylhydrazones.

## Experimental

In the present investigation all determinations were carried out in chloroform because of solubility considerations, although ethanol, employed by Roberts and Green,[6] has the considerable advantage that the effect of alkali on the spectrum can also be determined. The spectrum of each com-

TABLE I

ABSORPTION SPECTRA OF STEROIDAL DINITROPHENYLHYDRAZONES

| Dinitrophenylhydrazones of 3-ketosteroids | C-17 Substituents | λ max.,[a] mμ | λ max. of ketone,[b] mμ |
|---|---|---|---|
| Saturated, *allo* | $C_8H_{17}$, $COOCH_3$, $OCOC_6H_{11}$ | 367–369[c] | 280–286 |
| $\Delta^1$-Unsaturated, *allo* | $C_8H_{17}$, $COOCH_3$, $OCO_6H_{11}$ | 382–384 | 230–232 |
| 2-Bromo-$\Delta^1$-unsaturated, *allo* | $C_8H_{17}$, $OCO_6H_{11}$ | 375–376 | 254–256 |
| $\Delta^4$-Unsaturated | $C_8H_{17}$, (12-hydroxy)-cholenate | 390[d] | 240–242 |
| $\Delta^{1,4}$-Unsaturated | $C_8H_{17}$, $COOCH_3$, $OCO_6H_{11}$ | 400–402 | 243–244 |
| $\Delta^{4,6}$-Unsaturated | $C_8H_{17}$, $COOCH_3$, $OCOC_6H_5$ | 402–404 | 282–284 |

[a] The data refer to chloroform solutions and the typical log $E$ values can be obtained from Figs. 1 and 2. [b] In ethanol solution. [c] Sitostanone dinitrophenylhydrazone is reported (ref. 5) with max. at 368 mμ. [d] As in all other cases, all values refer only to data obtained by us on our compounds on a standardized Beckman spectrophotometer. Jones, *et al.*, ref. 4, give a max. at 391 mμ for $\Delta^4$-cholestenone and 392 mμ for the hydrazones of three other $\Delta^4$-3-ketosteroids. For the same ketones Braude and Jones, ref. 5, report maxima ranging from 393–395 mμ. We consider the values of Jones, *et al.*, more reliable.

TABLE II

ABSORPTION SPECTRA OF MISCELLANOUS HYDRAZONE DERIVATIVES

| No. | Compound[a] | λ max., mμ | Log $E_m$ (chloroform) |
|---|---|---|---|
| 1 | $\Delta^5$-Pregnen-3-ol-20-one DNPH | 368 | 4.46 |
| 2 | Progesterone bis-DNPH[b] | 383 | 4.72 |
| 3 | 4,4-Dimethyl-1-keto-1,2,3,4-tetrahydronaphthalene DNPH[c] | 385 | 4.49 |
| 4 | 4,4-Dimethyl-1-keto-1,4-dihydronaphthalene DNPH[c] | 404 | 4.55 |
| 5 | α-Ionone DNPH | 387 | 4.49 |
| 6 | β-Ionone DNPH | 392 | 4.46 |
| 7 | Benzalacetone DNPH | 305 396[d] | 4.16 4.53 |
| 8 | $\Delta^{1,1'}$-2'-Keto-3,4-dihydro-1,2-cyclopentenonaphthalene DNPH[e] | 312 404 | 4.17 4.70 |
| 9 | 3-(*p*-Methoxyphenyl)-cyclopenten-2-one-1 DNPH[e] | 315 414 | 4.19 4.64 |
| 10 | Cholestanone α-Methyl-DNPH | 387.5 | 4.25 |
| 11 | $\Delta^1$-Cholestenone α-Methyl-DNPH | 392.5 | 4.30 |
| 12 | $\Delta^1$-2-Bromocholestenone α-Methyl-DNPH | 392 | 4.22 |

[a] DNPH denotes dinitrophenylhydrazone. [b] The spectrum of this compound has already been discussed by Djerassi, *Anal. Chem.*, **20**, 880 (1948). [c] Both dinitrophenylhydrazones were kindly supplied by J. S. Buckley, Jr., of the University of Minnesota [Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947)]. [d] In ethanol solution the maxima were shifted to 302 mμ (log $E$ 4.23) and 393 mμ (log $E$ 4.57), respectively. [e] Compounds 8 and 9 were furnished by Prof. A. L. Wilds of the University of Wisconsin [Wilds, T. L. Johnson and J. A. Johnson, THIS JOURNAL, **67**, 286 (1945); **68**, 86 (1946)].

(1) See Roberts and Green, *Ind. Eng. Chem., Anal. Ed.*, **18**, 335 (1946), and White, *Anal. Chem.*, **20**, 726 (1948), for leading references.

(2) Gaddis and Butz, THIS JOURNAL, **69**, 117 (1947); Butz, Davis and Gaddis, *J. Org. Chem.*, **12**, 122 (1947).

(3) Johnston, *Science*, **106**, 91 (1947).

(4) Jones, Wilkinson and Kerlogue, *J. Chem. Soc.*, 391 (1942).

(5) Braude and Jones, *ibid.*, 498 (1945).

(6) Roberts and Green, THIS JOURNAL, **68**, 214 (1946).

(7) Djerassi, *ibid.*, **71**, 1003 (1949).

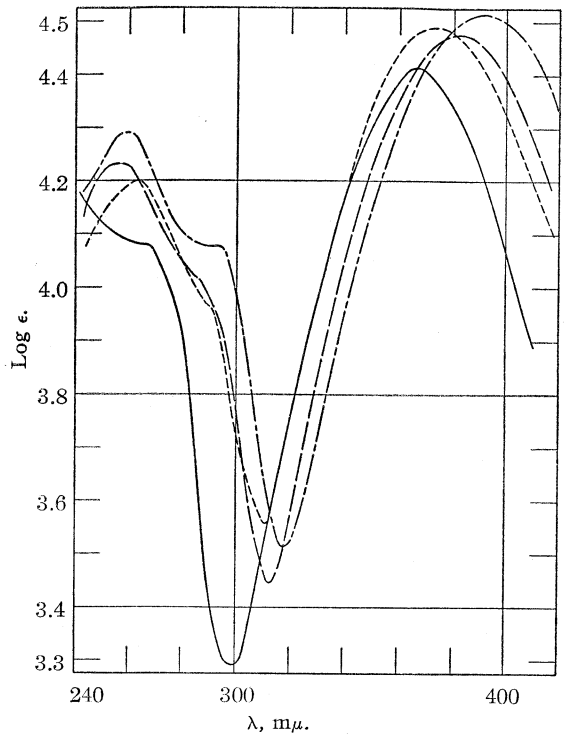



Fig. 1.—Ultraviolet absorption spectra in chloroform solution of dinitrophenylhydrazones of: — saturated 3-ketosteroids; — — — $\Delta^1$-3-ketosteroids; - - - - - - $\Delta^1$-2-bromo-3-ketosteroids; — · — · — · $\Delta^4$-3-ketosteroids.

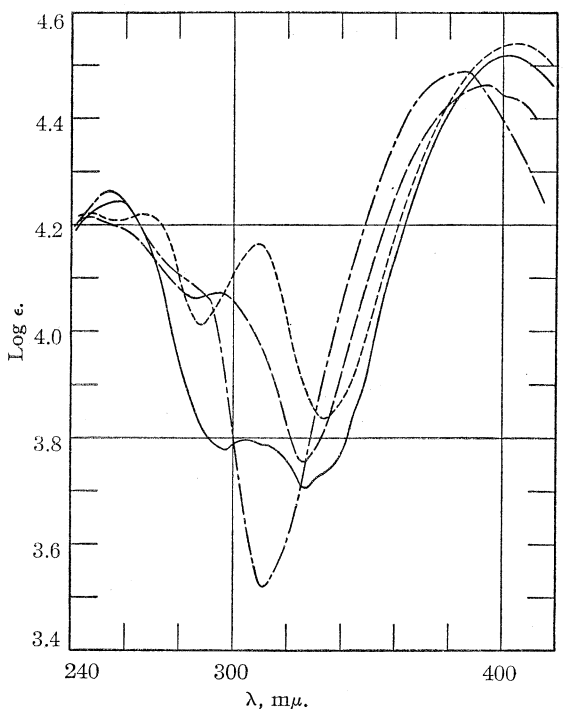



Fig. 2.—Ultraviolet absorption spectra in chloroform solution of dinitrophenylhydrazones of: — $\Delta^{1,4}$-3-ketosteroids; - - - - - - - $\Delta^{4,6}$-3-ketosteroids; — · — · — · — $\alpha$-ionone; — — — $\beta$-ionone.

pound was examined in a Beckman quartz spectrophotometer in the region 252 mμ to 415 mμ at 2.5 mμ intervals, except around maxima and minima where 1 mμ intervals were used; $E_m = 1/c \log I_0/I$, where $c$ is the concentration in moles per liter. All samples were of analytical purity and in most instances were prepared by two different methods as described elsewhere.[7]

## Discussion

It is apparent from an inspection of Table I and Figs. 1 and 2 that the main maxima of the dinitrophenylhydrazones of the various types of ketones in the steroid series do not overlap and differ sufficiently so that they may be correlated with the structure of the ketone from which the hydrazone is prepared. The various factors contributing to the absorption spectra of dinitrophenylhydrazones have already been discussed by earlier workers,[5,6] but it will be necessary to revise, or at least amplify somewhat, the position of the maxima as given by them for the various types of carbonyl derivatives. In the case of the wave length limits given by Roberts and Green,[6] a slight expansion is necessary to accommodate certain unsaturated ketones and to apply the data to chloroform solutions. It is suggested that this solvent should be used in preference to ethanol, since many dinitrophenylhydrazones are insoluble in the latter and no definite correction can be made for shifts in the two solvents.[8] The values of Braude and Jones[5] for compounds which we have checked, occasionally needed corrections ranging from 2–5 mμ,[9] either reflecting differences in the purity of the samples or in the spectrophotometers. These experimental differences as well as the fact that our narrow wave length limits given in Table I refer only to steroid ketones (cyclic six-membered), while those of the English workers include predominantly open-chain derivatives, account for the differences in our respective wave length ranges for unsaturated ketones.

While saturated 3-ketosteroids possess a low

(8) It should be noted that although no correction appears necessary in changing from ethanol to chloroform in the case of unsaturated ketones [Woodward, THIS JOURNAL, **63**, 1123 (1941)], erratic shifts are obtained in the case of dinitrophenylhydrazones as shown below (*cf.* ref. 5), thus making it desirable to employ only one solvent. The unpublished results of Roberts and Trimble were kindly supplied by Dr. John D. Roberts of M. I. T.

| | λmax (EtOH) (ref. 5) | λmax ($CHCl_3$) (ref. 5) | λmax (EtOH) (ref. 6) | λmax ($CHCl_3$) (Roberts and Trimble) |
|---|---|---|---|---|
| 2,4-Dinitrophenylhydrazine | 350 | 343.5 | 352 | 341 |
| Formaldehyde DNPH | 348 | 348 | 349 | 345 |
| Acetaldehyde DNPH | 360 | 360 | 356 | 356 |
| Crotonaldehyde DNPH | 373 | 372 | 377 | 374 |
| Chalcone DNPH | ... | ... | 395 | 398 |

We have confirmed Roberts' results for dinitrophenylhydrazine and the shift in the case of chalcone DNPH is quite similar to that observed in the case of benzalacetone DNPH (Table II).

(9) In that connection, see Jones, *et al.*, ref. 4, Barton and Jones, *J. Chem. Soc.*, 599 (1943), and the comparison with Roberts' results (footnote 8, this paper).

maximum at *ca.* 280–286 mμ (log *E ca.* 1.5),[10] the corresponding dinitrophenylhydrazones show a pronounced maximum (log *E* 4.4) at 367–369 mμ,[11] thus constituting a good diagnostic test for this type of carbonyl compound The introduction of one double bond results in a bathochromic shift of about 15–20 mμ, thus again permitting ready differentiation from the corresponding saturated derivatives. The dinitrophenylhydrazones of such singly unsaturated ketones can be separated into two classes on the basis of the absorption spectra although the difference (6–8 mμ) between the maxima of the hydrazones of the $\Delta^1$-ketones (one β-substituent and no exocyclic double bond) and the $\Delta^4$-ketones (two β-substituents and one exocyclic bond) is not as pronounced as in the corresponding ketones (10–15 mμ).[12] This is understandable since it has been noted already[5,6] that relatively minor changes in the carbonyl part of the molecule are not too readily transmitted over the =N–NH–bond. Of considerable interest is the fact that the introduction of an additional α,β-conjugated double bond next to the keto group exerts a pronounced bathochromic shift. Thus while $\Delta^4$-3-ketosteroids and the corresponding $\Delta^{1,4}$-dien-3-ones show practically the same selective absorption (*ca.* 242 mμ), the maxima of their dinitrophenylhydrazones differ markedly (390 mμ as compared to 404 mμ) and this should prove quite useful for purposes of differentiation between those two types of compounds (see Table I). It is also interesting to note that in the case of the hydrazones, both the cross-conjugated $\Delta^{1,4}$-dienone and the linear conjugated $\Delta^{4,6}$-dienone derivatives possess nearly the same maximum (around 404 mμ), whereas the spectra of the parent dienones differ very considerably (by about 40 mμ, see Table I). The hydrazones of those two types of dienones can be differentiated, however, by their spectra in the region 280–330 mμ,[13] since the dinitrophenylhydrazones of the $\Delta^{4,6}$-dienones exhibit a new and characteristic maximum at 309 mμ (Fig. 2).

It is of interest to note that the maximum of the $\Delta^1$-2-bromo-3-keto*allo*steroid dinitrophenylhydrazones occurs at an appreciably lower wave length (*cf.* Table I) than that of the $\Delta^1$- and $\Delta^4$-unsaturated hydrazones,[14] which is in contrast to the absorption spectra of the corresponding ketones, where the $\Delta^1$-2-bromo-3-ketones absorb at a higher wave length.[15]

The spectra of some miscellaneous dinitrophenylhydrazones are recorded in Table II. Through the kind coöperation of Drs. H. Sobotka and J. D. Chanley of the Mt. Sinai Hospital, New York City, we obtained authentic samples[16] of the dinitrophenylhydrazones of α- and β-ionone (compounds 5 and 6, Table II). Their spectra are reproduced in Fig. 2 and corroborate the previous report[5] that β-ionone dinitrophenylhydrazone lacks a definite maximum at 309 mμ in contrast to the hydrazones of ψ-ionone or the $\Delta^{4,6}$-3-ketosteroids discussed above, even though all three possess the same conjugated system. We did observe, however, that the β-isomer showed a slightly higher absorption maximum (392 mμ) than the α-isomer (387 mμ).[16a] It is probably not necessary to assume that some isomerization of the β-isomer had occurred during the preparation of its dinitrophenylhydrazone in glacial acetic acid, in order to explain the lowered maximum (392 as compared to *ca.* 404 mμ) and the absence of the maximum at 309 mμ, since β-ionone appears to be stable in acid solution.[17] It is simply a further instance of the anomalous spectral behavior of β-ionone, as exemplified by the ionone semicarbazones[17,18] and ionylideneacetones,[19] which has been ascribed[18] in part to a steric effect of the methyl group.

Qualitatively, a benzene ring adjacent to a carbonyl group can be considered equivalent (as a chromophore) to a double bond[20] and on that basis the two naphthalene derivatives 3 and 4 (Table II) represent a single unsaturated ketone and a cross-conjugated dienone, respectively. The spectra of their dinitrophenylhydrazones differ in the same manner as the comparable steroid derivatives discussed above.

The light absorption of the dinitrophenylhydra-

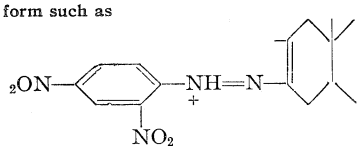
(10) *E. g.*, cholestanone, max. at 286 mμ (log *E ca.* 1.3) [Klotz, THIS JOURNAL, **66**, 90 (1944)] and dihydrotestosterone hexahydrobenzoate, max. at 280.5 mμ (log *E* 1.49) [Wilds and Djerassi, *ibid.*, **68**, 2128 (1946)].

(11) The maxima for the dinitrophenylhydrazones of cyclohexanone (366 mμ) and sitostanone (368 mμ) (ref. 5) are in agreement with this classification.

(12) *Cf.* Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942); and Gillam, *et al.*, *J. Chem. Soc.*, 815 (1941); 486 (1942), for correlation of absorption spectra and structure of ketones.

(13) This region cannot be employed for the characterization of the other hydrazones, since their spectra coincide almost completely with that of dinitrophenylhydrazine. This region of the spectrum of dinitrophenylhydrazine is discussed in detail by Braude and Jones (ref. 5).

(14) The influence of substituents in the carbonyl moiety of dinitrophenylhydrazones on the relative importance of contributing forms to the resonance hybrid has been discussed by Roberts and Green (ref. 6). It seems likely that the effect of the bromine atom is to favor a form such as



at the expense of quinoid structures with longer conjugated systems.

(15) It has been pointed out [Djerassi and Scholz, THIS JOURNAL, **69**, 2405 footnote 5 (1947)] that the $\Delta^1$-2-bromo-3-ketones do not follow Woodward's rules (ref. 12) with respect to their absorption maxima.

(16) Sobotka, Bloch and Glick, THIS JOURNAL, **65**, 1961 (1943).

(16a) NOTE ADDED IN PROOF: Since the submission of this manuscript, a paper by Naves and Ardizio [*Helv. Chim. Acta*, **31**, 1926 (1948)] appeared in which the ultraviolet absorption spectra of the dinitrophenylhydrazones of α-ionone (max. at 376 mμ) and β-ionone (max. at 385 mμ) were determined in ethanol solution. This serves as a furthes illustration of the irregular shifts observed in changing from ethanol to chloroform (*cf.* footnote 8).

(17) *Cf.* Young, Cristol, Andrews and Lindenbaum, *ibid.*, **66**, 855 (1944).

(18) Burawoy, *J. Chem. Soc.*, 20 (1941).

(19) Young and Linden, THIS JOURNAL, **69**, 2042 (1947) and references cited therein.

(20) See for instance Wilds, Beck, Close, Djerassi, Johnston, Johnson and Shunk, *ibid.*, **69**, 1991 (1947).

zones of benzalacetone (no. 7) and of the cyclopentenonaphthalene derivative 8 resembles that of linear conjugated dienones by exhibiting the characteristic maximum between 305–312 mμ in addition to the one at 396–404 mμ. The introduction of a *p*-methoxy group into such a system (no. 9) results in an expected bathochromic shift.[21] A considerable number of compounds would be required, however, to establish definite figures on the effect of a five-membered ring or ring substituents on the absorption of such aromatic dinitrophenylhydrazones.

In Table II are also listed the spectra of three α-(2,4-dinitrophenyl)-α-methylhydrazones of the steroid series. Although a slight bathochromic shift with respect to the corresponding dinitrophenylhydrazones was to be expected by analogy to the behavior of the methylsemicarbazones,[22] the pronounced shift (10–20 mμ) which was observed was not anticipated. These derivatives crystallize only poorly in the steroid series and thus do not lend themselves readily to the characterization of unknown carbonyl derivatives.

(21) A shift of the same magnitude was observed in the hydroxybenzaldehyde series (ref. 6).

## Summary

As an additional tool for the characterization of steroid ketones, the ultraviolet absorption spectra of a number of representative saturated and unsaturated steroid 2,4-dinitrophenylhydrazones have been determined. The position of their maxima is discussed on the basis of earlier work on the light absorption of such carbonyl derivatives.

The spectra of certain other dinitrophenylhydrazones are also recorded, including those of α- and β-ionone.

(22) Evans and Gillam, *J. Chem. Soc.*, 565 (1943).

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

# The Scope and Mechanism of the Reaction of Dinitrophenylhydrazine with Steroidal Bromo Ketones[1]

BY CARL DJERASSI

Most of the physiologically potent steroids in the androgenic, progestational and cortical hormone series possess a $\Delta^4$-3-keto grouping (IIa). Unless prepared from a steroid already possessing unsaturation in the 4-5 or 5-6 positions, the double bond is usually introduced by brominating the saturated 3-ketosteroid and dehydrobrominating the resulting bromo ketone, a method which is particularly important in the synthesis of the cortical hormones. Since 3-keto*allo*steroids (A:B ring juncture as in *trans* decalin) on monobromination give the 2-bromo derivative III,[2] in general only the ketones of the "normal" series (A:B juncture *cis*) have been employed for this purpose since they lead to 4-bromo-3- ketones I.[2,3] The dehydrobromination of the latter is usually accomplished by refluxing with pyridine for several hours[3,4] and it is believed[4] that frequently one of the factors responsible for the relatively poor yield is the formation of two diastereoisomeric 4-bromo derivatives, only one of which can undergo facile *trans*-elimination of hydrogen bromide. Recently, the mono- and dibromination products of the *allo* series have gained increased importance, since the 2,4-dibromo-3-ketosteroids (VII) on dehydrobromination yield the 1,4-dienones VIIIa, which represent the key intermediates in the partial synthesis of the estrogens.[5,6] Furthermore, partial dehydrobromination of the dibromo ketones (VII) leads to the 2-bromo-$\Delta^4$-3-ketosteroids (IX)[7,8] which can be converted to $\Delta^4$-3-ketosteroids (IIa). Even the 2-bromo-3-keto*allo*steroids (III) can be transformed partially to the $\Delta^4$-ketones[8,9] although the main product is the $\Delta^1$-isomer (IVa). Although Butenandt and co-workers[10] have shown that collidine is much more effective in the dehydrobromination of brominated derivatives of the *allo* series than is pyridine, the latter is still the base of choice for normal ketones. In spite of the importance of dehydrobrominations in steroid chemistry, even in the most thoroughly studied cases (both *allo* and normal series) using either collidine or pyridine, the yield in that step has never surpassed 60% which in turn has been a serious drawback in a number of syntheses.

A few months ago, Mattox and Kendall[11] in a preliminary communication recorded the interesting observation that when certain cortical hormone intermediates containing the 3-keto-4-bromo grouping (I) were treated in acetic acid solution with 1.2 moles of dinitrophenylhydrazine

(1) Presented in part on the program of the Division of Medicinal Chemistry at the Washington, D. C., meeting of the American Chemical Society, August 31, 1948.

(2) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935).

(3) Butenandt and Schmidt, *ibid.*, **67**, 1901 (1934).

(4) v. Euw and Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(5) Inhoffen, *Angew. Chem.*, **59A**, 207 (1947).

(6) Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946).

(7) Inhoffen and Zuehlsdorff, *Ber.*, **76**, 233 (1943).

(8) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947); *J. Org. Chem.*, **13**, 697 (1948).

(9) Ruzicka, Plattner and Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938); Marker, Wittle and Plambeck, THIS JOURNAL, **61**, 1333 (1939).

(10) Butenandt, Mamoli, Dannenberg, Masch and Paland, *Ber.* **72**,1617 (1939).

(11) Mattox and Kendall, THIS JOURNAL, **70**, 882 (1948).

with or without the addition of sodium acetate, the dinitrophenylhydrazone IIb of the corresponding $\Delta^4$-3-ketosteroid was obtained in excellent yield. Furthermore, on cleavage with pyruvic acid in the presence of hydrogen bromide, the unsaturated ketone could be regenerated almost quantitatively. Aside from the statement that "the reactivity of the bromine at $C_4$ is greatly increased through formation of a hydrazone at $C_3$," no mechanism was advanced, and no exact experimental details as to time or temperature were given. The purpose of the present paper is to record the results of an investigation of the scope of this reaction, particularly as applied to 3-keto*allo*steroids, and to suggest a reaction mechanism.

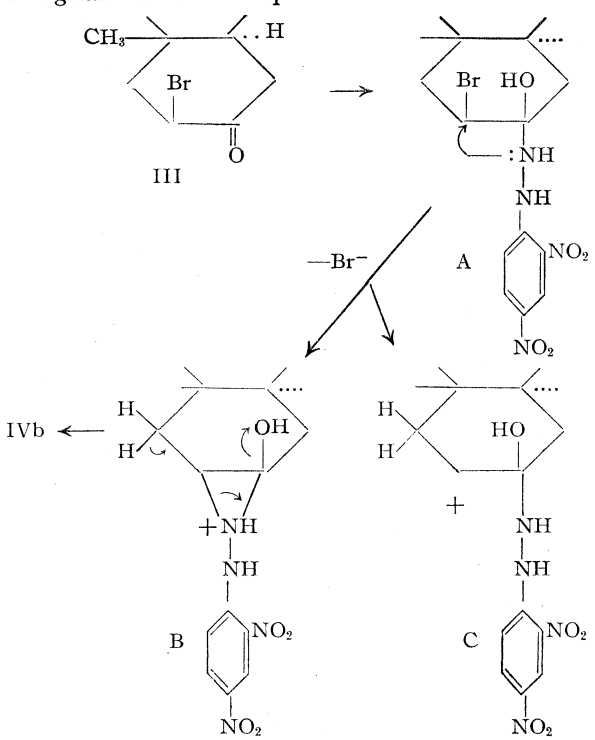
In the present investigation it was found that the reaction of the steroidal bromo ketone with 1.0–1.1 moles of dinitrophenylhydrazine was completed after heating for three to five minutes. Sodium acetate was not used so as not to introduce complications in a discussion of the reaction mechanism and those conditions were adhered to for all of the compounds described below.

Since 4-bromo-3-ketosteroids of the normal series (I) have already been studied by Mattox and Kendall,[11] only one additional example (methyl 3-keto-4-bromo-12-hydroxycholanate) was tested which gave nearly 90% of the dinitrophenylhydrazone IIb.

Three examples of 2-bromo-3-keto*allo*steroids (III) were investigated (R = $C_8H_{17}$, $COOCH_3$, $OCOC_6H_{11}$), all of which gave 80–90% of the dinitrophenylhydrazone IVb of the $\Delta^1$-3-ketone. Just as with collidine,[7,8] 2,2-dibromoketones V (R = $C_8H_{17}$, $OCOC_6H_{11}$) led to the $\Delta^1$-2-bromo derivatives VIb in 60% yield. In each case, the identity of the product was confirmed by analysis and direct comparison with authentic samples of the dinitrophenylhydrazones prepared from the known unsaturated ketones (Table I). Furthermore, cleavage of the ketone derivatives with pyruvic acid–hydrogen bromide by a slight modification of the Mattox-Kendall procedure[11] led to the unsaturated ketones. As described in detail in the experimental section the water content of the pyruvic acid apparently plays an important role in this cleavage. The regeneration of the carbonyl compound was nearly complete in the case of the $\Delta^4$- and $\Delta^1$-3-ketones (IIa and IVa), but only partial with $\Delta^1$-2-bromo compounds VIa (up to 30% of ketone, the remainder being recovered as hydrazone).

The remarkable fact about the dehydrobromination is that it is complete in a matter of minutes in acid solution in the presence of one mole of the very weak base[12] dinitrophenylhydrazine, while refluxing for fifteen minutes to four hours is required with a large excess of comparatively strong bases such as collidine or pyridine. Initial attack on the bromine by dinitrophenylhydrazine is quite unlikely, since under the same conditions (1.0–1.2 moles of base in glacial acetic acid) no comparable reaction is observed with benzylamine, aniline, ethylaniline or collidine. On the other hand, phenylhydrazine, $\alpha$-(2,4-dinitrophenyl)-$\alpha$-methylhydrazine, hydroxylamine and semicarbazide[13] produced essentially the same results as dinitrophenylhydrazine. Initial formation of a hydrazone of the bromo ketone as intimated by Mattox and Kendall[11] leaves no reasonable path for the elimination of hydrogen bromide, unless it is assumed that the bromine atom is so labilized by hydrazone formation as to be lost on warming for a few minutes in acetic acid.

It is suggested that the results are compatible with a reaction mechanism employing the concept of participation of neighboring groups in nucleophilic displacement reactions as developed by Winstein and co-workers in a brilliant series of papers,[14] and the reaction is depicted as proceeding as follows, a 2-bromo-3-keto*allo*steroid (III) being taken as an example




The initial attack of dinitrophenylhydrazine on the ketone III proceeds in the usual manner[15] to

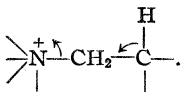
(12) See Davies, *J. Chem. Soc.*, 715 (1922) and Sidgwick, "Organic Chemistry of Nitrogen," Oxford, 1937, p. 395.

(13) All of the reagents (both successful and unsuccessful) were tried with 2-bromocholestanone. Phenylhydrazine and hydroxylamine hydrochloride did result in loss of hydrogen bromide but the product crystallized very poorly. Examples with the other two reagents are given in the experimental section. It should be noted however, that dinitrophenylhydrazine surpasses all reagents because of the ease with which the dinitrophenylhydrazones crystallize in the steroid series.

(14) See for instance Winstein, Grunwald, Buckles and Hanson, THIS JOURNAL, **70**, 816 (1948).

(15) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 334.

yield intermediate A, in which the nitrogen atom with its available electron pair represents a powerful neighboring group, thus leading to expulsion of a bromide ion and the formation of a cyclic imonium compound such as B, in which the carbonium ion C represents one of the extreme ionic forms contributing to the resonance hybrid. The hydroxy–imonium compound B is formally identical with quaternary ammonium salts in the Hofmann reaction where elimination of the β-hydrogen occurs as well as rupture of the N–C bond:



The mechanism of the Hofmann elimination is only incompletely understood[16] and the reaction is therefore written in the non-committal form B, even though it may proceed through the carbonium ion C. The strain of the positively charged three-membered ring and the tendency toward dehydration constitute a strong driving force in the expulsion of the proton and fission of the N–C bond with the resulting formation of the final product IVb. Furthermore it is necessary to ascribe an important function (possibly due to momentary formation of a second positive charge) to the adjoining second nitrogen atom in the Hofmann-type elimination which proceeds under such mild conditions in an acid medium, in contrast to the usual basic thermal treatment. This last assumption is a necessary corollary to the imonium ring mechanism, since otherwise primary and secondary amines, *e. g.*, ethylaniline or benzylamine, should also be effective in the dehydrobromination.[17]

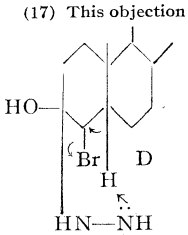
At this point it is necessary to consider the stereochemistry of the bromo compounds. As mentioned in the first paragraph, there exists some evidence[4] that 3-ketosteroids of the "normal" series on bromination often yield both stereoisomeric 4-bromo compounds, since only one form can be dehydrobrominated with ease. In the case of 2-bromo-3-keto*allo*steroids (III) such evidence is not available since *trans* elimination of hydrogen bromide is possible with either isomer. However, recent work[18] based on molecular rotation differences points toward the presence of both isomers in this series. On that basis the two bromo compounds (III, R = $C_8H_{17}$, and R = $COOCH_3$) represent different isomers at C-2 and yet both reacted equally fast with dinitrophenylhydrazine. Since the formation of the cyclic imonium compound B would require a *trans* relationship between the bromine atom and the dinitrophenylhydrazyl radical as in A in order to allow for rearward attack, it is necessary to postulate that in the case of the 4-bromo-normal (I) and 2-bromo-*allo* compounds (III) either the entrance of the dinitrophenylhydrazine molecule is always directed by steric factors of the steroid molecule in such a manner that a *trans* relation (A) is present, or more likely that a rapid equilibrium exists in which only one form (*trans*) reacts.

In the case of the 2,4-dibromo-3-keto*allo*steroids (VII), it is known that the 4-bromine atom has the (β)-configuration, since it can be eliminated with collidine[7,8] in less than one minute with the formation of the unsaturated bromo ketone IX. The configuration of the 2-bromine atom in VII is not known, but it is likely, again on the basis of rotation measurements,[18] that it has one and the same configuration in all of the *allo* compounds studied so far. It is conceivable that if a cyclic imonium ring mechanism operates, both bromines could be removed by one mole of dinitrophenylhydrazine, since a second ring could be formed after elimination of the first bromine atom, unless (a) dehydration to the hydrazone is an essential factor in that step, (b) both bromine atoms do not possess the same stereochemical configuration and (c) the hydroxyl group introduces steric hindrance. When the reaction was applied to 2,4-dibromo ketones (VII, R = $C_8H_{17}$, $COOCH_3$, $OCOC_6H_{11}$), a mixture was obtained, which by analysis still contained one mole of bromine, but which seemed to contain at least some of the $\Delta^{1,4}$-dien-3-one hydrazone VIIIb on the basis of the ultraviolet absorption spectra (Fig. 1). The hydrazone mixture could not be cleaved with pyruvic acid which was in agreement with experiments carried out on the hydrazones prepared from authentic dienones, and the results, therefore, are not conclusive.[19]

In order to elucidate further the action of dinitrophenylhydrazine on the 2,4-dibromo ketones VII, the 2-bromo-$\Delta^4$-3-ketones (IX) were investigated since they might be intermediates in the reaction of VII. The surprising observation was made that those ketones reacted with dinitro-

(16) *Cf.* Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(17) This objection has been brought up during a discussion at the University of California at Los Angeles. Drs. C. F. Koelsch and S. Winstein suggested as a possible alternative a mechanism, D, in which the α-nitrogen atom (which appears to be essential from our observations) assumes the dominant role by removing the proton on the β-carbon atom, the remaining steps being unexceptional. Such a suggestion, however, involves certain difficulties in the reaction of the $\Delta^4$-2-bromoketones (IX) leading to Xb, which incidentally could also be accomplished with semicarbazide hydrochloride.



(18) Djerassi, *J. Org. Chem.*, **12**, 823 (1947).

(19) Recently, an article appeared [Klein, Weiner and Gordon, *Anal. Chem.*, **20**, 174 (1948)] in which it was postulated that α,β-unsaturated steroid ketones such as progesterone reacted with dinitrophenylhydrazine to form a pyrazoline derivative, since the product could not be split with acid. It has since been shown [Djerassi, *Anal. Chem.*, **20**, 880 (1948)] that the product is in fact the bis-dinitrophenylhydrazone since it led to progesterone in 60% yield on cleavage with pyruvic acid. In view of the resistance of $\Delta^{1,4}$-dien-3-one hydrazones (VIIIb) even toward pyruvic acid, it might be suggested that they represent pyrazoline derivatives (according to ref. 26, pyrazolines are not affected by pyruvic acid), but the absorption spectra speak against such a supposition. By analogy to the ultraviolet absorption spectra of other steroid hydrazones (ref. 20), such pyrazolines would be expected to have maxima below 390 mμ, rather than at 402 mμ as observed for the reaction product.

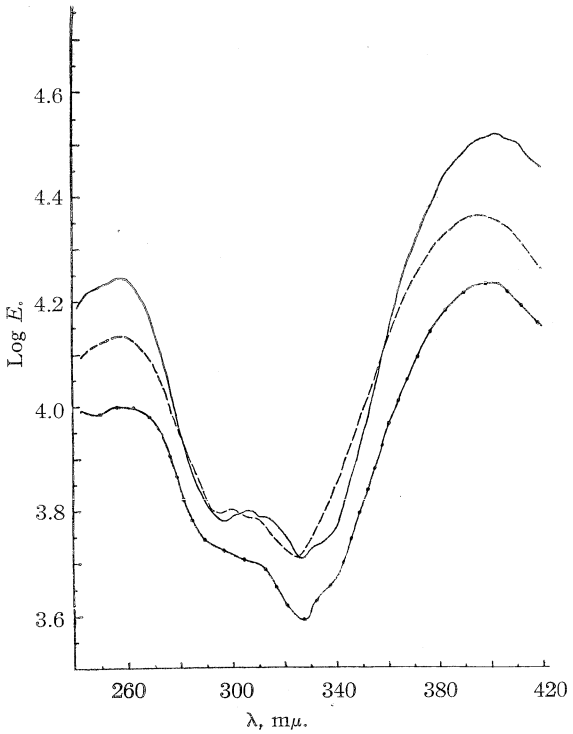
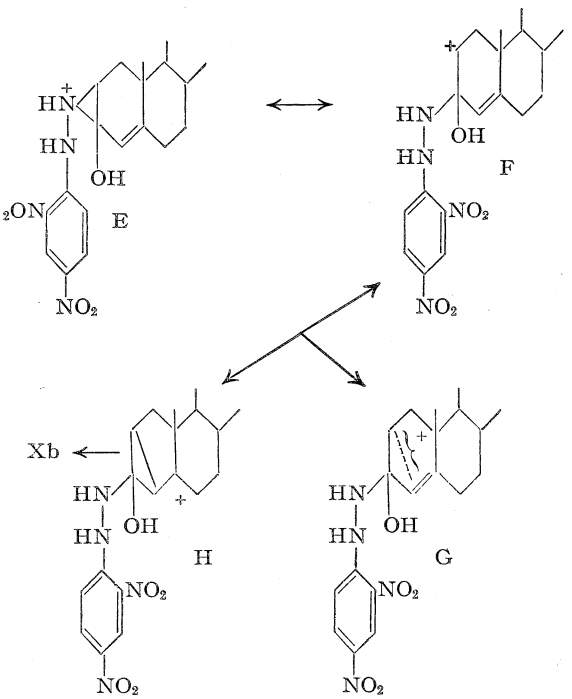
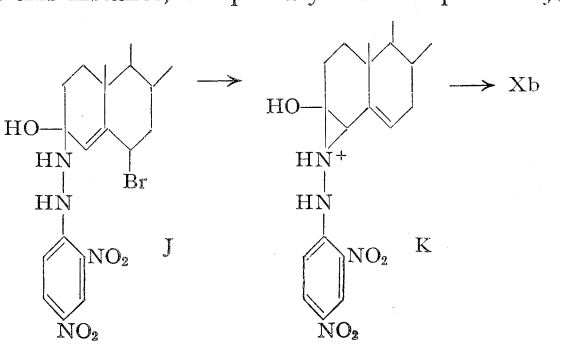



Fig. 1.—Ultraviolet absorption spectra in chloroform solution: — 1,4-androstadien-17-ol-3-one 17-hexahydrobenzoate dinitrophenylhydrazone; – – – – – product from reaction of 2,4-dibromoandrostan-17-ol-3-one 17-hexahydrobenzoate and 2,4-dinitrophenylhydrazine; —·—·— product from reaction of methyl 2,4-dibromo-3-keto*allo*etiocholanate and 2,4-dinitrophenylhydrazine.

phenylhydrazine to afford in about 45% yield the hydrazones of the corresponding $\Delta^{4,6}$-dien-3-one (Xb, R = $C_8H_{17}$, $COOCH_3$). The structure of the products was established by direct comparison with authentic samples (Table I) prepared from the known $\Delta^{4,6}$-dien-3-ones (Xa) as well as by their characteristic ultraviolet absorption spectra.[20] As was to be expected, the dinitrophenylhydrazones Xb were cleaved very incompletely with pyruvic acid but enough of the ketone was isolated to permit identification as the dienone Xa (m. p. and characteristic u. v. maximum at 282.5 mu). On applying the imonium-ring mechanism to this reaction, it is suggested that the primary intermediate is again a cyclic compound such as E. In this instance, the contributing carbonium ion form F, in contrast to C which lacks the double bond, is further stabilized by forms such as the hybrid carbonium ion G or the rearranged carbonium ion H. Forms F, G and H are somewhat comparable to the intermediates postulated in the *i*-steroid rearrangement.[21] It is realized that in this instance it is necessary to postulate a shift of hydrogen to C-2 in order to accommodate for structure Xb and the sequence of reactions from H leading to Xb is not depicted. Various explanations are possible for providing this shift, particularly since a proton donor is available in the solvent. It should be noted that if an alternate mechanism is considered in which the α-nitrogen atom is the essential factor,[17] it would be necessary to assume first that the bromine atom rearranged either to position 4 or 6, which could not be demonstrated (see experimental section), although it is conceivable that a very small amount of rearrangement product at any one time would be sufficient to drive the reaction to completion.




In view of the formation of the $\Delta^{4,6}$-derivative Xb from the $\Delta^4$-2-bromoketone IX it was of considerable interest to investigate the behavior of the $\Delta^4$-6-bromo-3-ketones XI (R = $COOCH_3$, $OCOC_6H_5$), where the bromine atom is not adjacent to the carbonyl group. As with the 2-bromo derivatives IX, the 6-bromo isomers XI also yielded the dinitrophenylhydrazones Xb although in appreciably higher yield. It is quite likely that in this instance, the primary reaction product J,

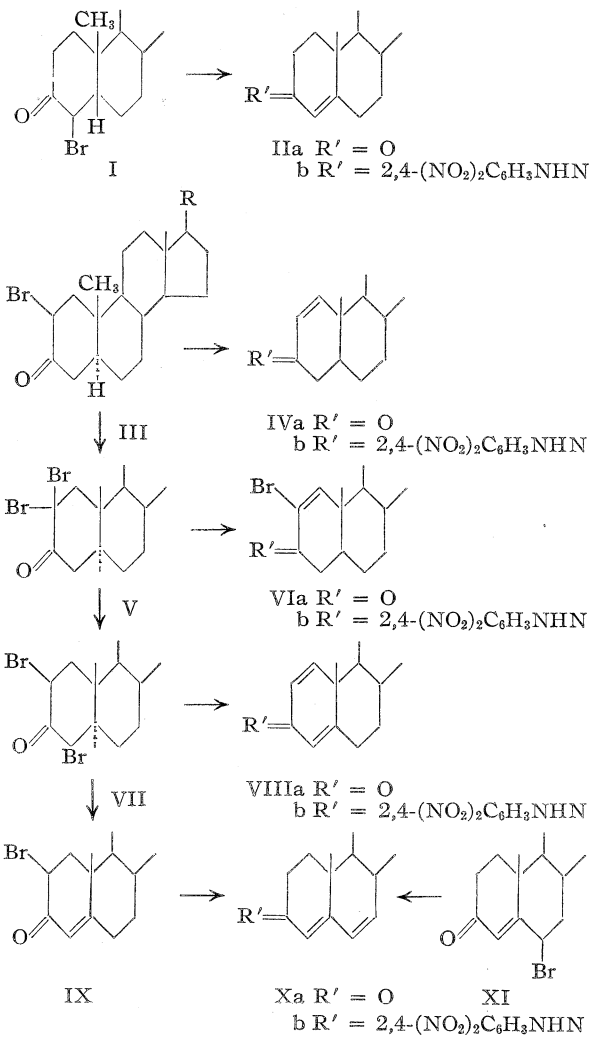



(20) Djerassi and Ryan, THIS JOURNAL, **71**, 1000 (1949).

(21) Winstein and Adams, *ibid.*, **70**, 838 (1948); Dodson and Riegel *J. Org. Chem.*, **13**, 424 (1948).

representing a particularly labile allylic system, undergoes simultaneous attack on position 4 by the nitrogen atom and shift of the double bond,[22] thus leading directly to the imonium compound K.

In conclusion, it can be stated that the Mattox–Kendall reaction[11] is useful for the dehydrobromination of 2-bromo-3-keto*allo*steroids and for 4-bromo-3-ketones of the normal series, particularly when employed on a small scale. The reaction has no practical applications in the other cases cited, unless a procedure is discovered for cleaving the dinitrophenylhydrazones of such poly-unsaturated ketones as the $\Delta^{4,6}$-dienones. It should be of interest to investigate this dehydrobromination procedure in simpler ketones other than steroids, where complicated steric factors do not enter and which may thus shed more light on the reaction mechanism.




**Acknowledgment.**—The author would like to express his gratitude to Dr. Gilbert Stork of Harvard University for the numerous stimulating discussions on the subject of this paper; furthermore, he is indebted to Dr. W. E. Doering of Columbia University for comments and to the Misses Helen Dudek and Jean Rogers for technical assistance. Since the completion of this work, the author has had the benefit of a critical discussion regarding the reaction mechanism with members of the summer staff of the University of California at Los Angeles, and he is thankful to Dr. S. Winstein for providing that opportunity.

(22) *Cf.* Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942).

## Experimental[23]

**General Procedure for Reaction of Steroid Ketones with 2,4-Dinitrophenylhydrazine.**—The following method was used for both the dehydrobromination of steroidal bromo ketones as well as for the preparation of comparison samples of dinitrophenylhydrazones from authentic saturated and unsaturated 3-ketosteroids.

Approximately 200 mg. of steroid was dissolved in 5–10 cc. of warm glacial acetic acid (depending on the solubility of the ketone) in an open Erlenmeyer flask while passing a slow current of nitrogen over the surface of the solution, 1.1 moles of dinitrophenylhydrazine was added, and the solution was heated on the hot-plate for five minutes in the open flask without condenser. In those instances where the hydrazone precipitated immediately, the heating time was reduced to three minutes. In practically all cases the hydrazone crystallized on cooling. Recrystallization was best effected from a mixture of ethanol and chloroform (all of the hydrazones were very soluble in chloroform) and all reactions involving solutions of hydrazone were carried out in an atmosphere of nitrogen. Experiments ranging from 25 mg. to 1.2 g. of steroid gave equally good results and required no modification except for variations in the amount of acetic acid. Remarks as to the applicability of this procedure to the dehydrobromination of the various classes of steroidal bromo ketones are given below in appropriate sections together with the physical constants of the products. In Table I are summarized the constants of some previously undescribed dinitrophenylhydrazones of both saturated and unsaturated steroid ketones which were prepared for one or more of the following purposes: Determination of the ultraviolet absorption spectra which are reported elsewhere,[20] preparation of authentic samples for comparison with the products arising from the dehydrobromination, and as model substances for determining conditions for the regeneration of the carbonyl compound from the hydrazone.

**General Procedure for the Cleavage of Steroidal Dinitrophenylhydrazones.**—The dehydrobromination procedure of Mattox and Kendall[11] is useful only if the unsaturated carbonyl compound can be regenerated from its dinitrophenylhydrazone. These workers indicated that the cleavage of the dinitrophenylhydrazones of $\Delta^4$-3-ketosteroids could be accomplished in nearly quantitative yield by warming for two and one-half hours at 45° in 20 cc. of chloroform, 30 cc. of pyruvic acid and 2.2 cc. of 2.3 *N* hydrogen bromide solution (in acetic acid), but they neglected to state the quantity of hydrazone which could thus be cleaved. Using the dinitrophenylhydrazones of $\Delta^1$- and $\Delta^4$-cholesten-3-one our initial experiments to confirm those results failed completely. The following variations also resulted in partial or complete recovery of the hydrazone: Refluxing the reaction mixture (containing hydrazone, pyruvic acid and chloroform) with either 4 *N* hydrogen bromide–acetic acid or hydrogen bromide–acetic acid–

(23) All melting points are uncorrected. The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J., and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

TABLE I

AUTHENTIC SAMPLES OF DINITROPHENYLHYDRAZONES OF SOME STEROID KETONES[a]

| Dinitrophenylhydrazone of | M. p., °C., (dec.) | Formula | Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|
| Cholestan-3-one | 228–230 | $C_{33}H_{50}O_4N_4$ | 69.93 | 8.89 | 9.89 | 69.74 | 8.99 | 9.70 |
| 2-Acetoxycholestan-3-one[b] | 173–175 | $C_{35}H_{52}O_6N_4$ | | | 8.97 | | | 8.60 |
| Dihydrotestosterone hexahydrobenzoate | 206–208 | $C_{32}H_{44}O_6N_4$ | 66.17 | 7.64 | 9.65 | 66.61 | 7.77 | 9.25 |
| Methyl 3-ketoetio*allo*cholanate | 225–228 | $C_{27}H_{36}O_6N_4$ | 63.26 | 7.08 | 10.93 | 63.11 | 7.46 | 10.84 |
| Methyl $\Delta^1$-3-ketoetio*allo*cholenate[c] | 270–272 | $C_{27}H_{34}O_6N_4$ | 63.51 | 6.71 | 10.97 | 63.36 | 6.46 | 11.31 |
| $\Delta^1$-Cholesten-3-one | 218–220 | $C_{33}H_{48}O_4N_4$ | 70.18 | 8.57 | 9.92 | 69.99 | 8.79 | 9.81 |
| $\Delta^4$-Cholesten-3-one | 232–235 | $C_{33}H_{48}O_4N_4$ | 70.18 | 8.57 | 9.92 | 69.76 | 8.63 | 9.52 |
| $\Delta^1$-2-Bromocholesten-3-one[d] | 265–267 | $C_{33}H_{47}O_4BrN_4$ | 61.57 | 7.36 | 8.71 | 61.36 | 7.57 | 8.97 |
| $\Delta^1$-2-Bromoandrosten-17-ol-3-one 17-hexahydrobenzoate[e] | 267–270 | $C_{32}H_{41}O_6BrN_4$ | 58.44 | 6.29 | 8.52 | 58.37 | 6.45 | 8.55 |
| $\Delta^{4,6}$-Cholestadien-3-one | 227–229 | $C_{33}H_{46}O_4N_4$ | 70.43 | 8.24 | 9.96 | 70.05 | 8.25 | 10.24 |
| Methyl $\Delta^{4,6}$-3-ketoetiocholadienate | 254–256 | $C_{27}H_{32}O_6N_4$ | 63.76 | 6.34 | 11.02 | 63.59 | 6.32 | 11.05 |
| Methyl $\Delta^{1,4}$-3-ketoetiocholadienate | 180–183 | $C_{27}H_{32}O_6N_4$ | 63.76 | 6.34 | 11.02 | 64.18 | 6.48 | 11.52 |
| $\Delta^{1,4}$-Cholestadien-3-one | 183–184 | $C_{33}H_{46}O_4N_4$ | 70.43 | 8.24 | 9.96 | 70.50 | 8.60 | 10.12 |
| $\Delta^{1,4}$-Androstadien-17-ol-3-one 17-hexahydrobenzoate | 263–264 | $C_{32}H_{40}O_6N_4$ | 66.64 | 6.99 | 9.72 | 66.80 | 6.92 | 9.56 |

[a] With one exception (preparation given in this paper) all of the ketones have been described in the literature. [b] Acetyl, calcd.: 6.89; found: 7.29. [c] Methoxyl, calcd.: 6.08; found: 5.85. [d] Bromine, calcd.: 12.42; found: 12.45. [e] Bromine, calcd.: 12.15; found: 11.92.

water,[24] using Hershberg's[25] pyruvic acid cleavage for semicarbazones, or that of Anchel and Schoenheimer[26] for splitting *p*-carboxyphenylhydrazones. Similarly, refluxing with pyruvic acid or biacetyl[27] alone resulted in recovery of the hydrazone. Finally, it was noted that the water content of the pyruvic acid greatly influenced the extent of cleavage and this unquestionably was the reason why Mattox and Kendall's procedure[11] could not be repeated originally. The following method gave fairly reproducible results:

A solution of 100 mg. of steroid dinitrophenylhydrazone in 5 cc. of chloroform is treated in a stoppered flask (air displaced by nitrogen) at 50–60° with 7.5 cc. of commercial pyruvic acid (83–85%) and 0.6 cc. of approximately 4 *N* anhydrous hydrogen bromide in acetic acid for three hours. It appears that pyruvic acid of neutral equivalent 105 or higher yields two layers under the conditions specified and hence continuous shaking is essential for cleavage. Pyruvic acid of neutral equivalent 102 or less gives a homogeneous solution, thus not requiring any shaking, and the yield of ketone seems to be higher. The completion of the reaction is usually indicated by appreciable lightening of the color of the solution. After dilution with chloroform and extraction with carbonate solution, the organic layer is dried and if the residue is still colored, it is recrystallized preferably from ethanol (using Norit), since any unchanged hydrazone is practically insoluble in that solvent.

This procedure has given satisfactory results in the cleavage of hydrazones of saturated as well as $\Delta^1$- and $\Delta^4$-unsaturated 3-ketosteroids,[28] where 60–70% of the pure ketone could be isolated. Losses in the purification of the ketone on such a small scale may be responsible for the lower yield as compared to that reported by Mattox and Kendall.[11] With $\Delta^1$-2-bromo-3-keto derivatives, the reaction proceeded to the extent of 20–30%, while in the case of the hydrazones of $\Delta^{4,6}$-dien-3-ones only about 5–10% of the ketone could be isolated, the rest being recovered as unchanged hydrazone. The derivatives of $\Delta^{1,4}$-dien-3-ones could not be split at all.[19] The $\alpha$-(dinitrophenyl)-$\alpha$-methylhydrazone of even a singly unsaturated ketone (such as $\Delta^1$-cholestenone) also were unaffected under those conditions.

**Preparation of Bromo Ketones.**—With a few exceptions the synthesis of the bromo ketones used below for the dehydrobrominations has been described in papers from this or other laboratories.[2,6,8,29,30] The following either are new compounds or require comment.

**$\Delta^4$-2-Bromocholesten-3-one (IX, R = $C_8H_{17}$).**—By analogy to related 2,4-dibromo ketones[7,8] 4 g. of 2,4-dibromocholestan-3-one[29] was refluxed for forty seconds with 18 cc. of redistilled collidine, which resulted in the loss of 1.2 moles of hydrogen bromide on the basis of collidine hydrobromide isolated. After working up as usual and recrystallizing from ethanol, there was obtained 1.17 g. (34%) of colorless, long needles melting at 117–119°, $[\alpha]^{29}D$ + 81° (chloroform), maximum at 243 mu, log *E* 4.15 (ethanol).

*Anal.* Calcd. for $C_{27}H_{44}OBr$: C, 69.80; H, 9.55; Br, 17.21. Found: C, 69.81; H, 9.22; Br, 17.05.

The structure of the compound was confirmed by further dehydrobromination to $\Delta^{1,4}$-cholestadien-3-one and dienone-phenol rearrangement of the latter to the corresponding 1-methylphenol.[29]

**Methyl $\Delta^4$-6-Bromo-3-ketoetiocholenate (XI, R = $COOCH_3$).**—The method of Ruzicka and Bosshard[30] for 6-bromotestosterone benzoate was applied to methyl $\Delta^5$-3-hydroxyetiocholenate by adding one mole of bromine, oxidizing with chromic anhydride and dehydrobrominating the crude 5,6-dibromo-3-ketone with anhydrous sodium acetate in ethanol. After recrystallization from hexane–acetone, there was obtained 59% of the desired unsaturated bromo ketone with m. p. 136–137°, $[\alpha]^{26}D$ + 30° (chloroform). Reich and Lardon[31] prepared the compound by the action of N-bromoacetamide on the enol acetate of the corresponding $\Delta^4$-3-ketone and reported m. p. 139–140°. The structure of the bromo ketone was proved by collidine dehydrobromination to methyl $\Delta^{4,6}$-3-ketoetiocholadienate with its characteristic maximum at 282.5 m$\mu$, and which gave no depression in m. p. on admixture with a sample prepared by the following method.

(24) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 75 (1947), described a mixture of acetic acid, 48% hydrobromic acid and water from which the hydrogen bromide was not lost on heating which was initially believed to be the reason why cleavage was unsuccessful on refluxing with anhydrous hydrogen bromide–acetic acid.

(25) Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(26) Anchel and Schoenheimer, *J. Biol. Chem.*, **114**, 539 (1936).

(27) Strain, THIS JOURNAL, **57**, 758 (1935).

(28) Even a 3,20-bis-dinitrophenylhydrazone (see ref. 19 for cleavage of progesterone bis-dinitrophenylhydrazone) can be split under those conditions.

(29) Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946).

(30) Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 328 (1937).

(31) Reich and Lardon, *ibid.*, **29**, 671 (1946).

**Methyl $\Delta^{4,6}$-3-Ketoetiocholadienate** (Xa, R = $COOCH_3$).—This previously unknown dienone was needed for comparison with the above sample prepared by dehydrobromination of the $\Delta^4$-6-bromo-3-ketone as well as for conversion to an authentic sample of dinitrophenylhydrazone. Wettstein's modification[32] of the Oppenauer oxidation presented a convenient one-step synthesis. Two grams of methyl $\Delta^5$-3-hydroxyetiocholenate was oxidized with quinone exactly as described for cholesterol[29] except that commercial aluminum isopropylate was substituted for the *t*-butoxide.[33] After chromatographing the crude, crystalline residue and recrystallizing from methanol, there was obtained 0.81 g. (41%) of colorless rosettes of prismatic needles with m. p. 165–165.5°, $[\alpha]^{26}D$ + 125° (chloroform), max. at 282.5 mμ (log *E* 4.49), and min. at 235 mμ., (log *E* 3.46 in ethanol).

*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 9.45. Found: C, 76.75; H, 8.48; methoxyl, 9.67.

**Dehydrobrominations with 2,4-Dinitrophenylhydrazine**

(a) **2-Bromo-3-keto*allo*steroids** (III).—The dehydrobromination of 2-bromocholestanone and methyl 2-bromo-3-ketoetio*allo*cholanate led in 80–90% yield to the hydrazones of the corresponding $\Delta^1$-3-ketones. These were found to be identical (m. p., u. v. spectrum, analysis) with authentic samples described in Table I and were further identified by pyruvic acid cleavage to the known[8] unsaturated ketones. 2-Bromoandrostan-17-ol-3-one 17-hexahydrobenzoate gave 83% of the corresponding $\Delta^1$-unsaturated dinitrophenylhydrazone, m. p. 237–239° (dec.), the analysis of which is reported since an authentic sample was not available.

*Anal.* Calcd. for $C_{32}H_{42}O_6N_4$: C, 66.41; H, 7.32; N, 9.68. Found: C, 66.69; H, 7.68; N, 9.93.

It is interesting to note that the last mentioned two 2-bromo compounds are believed[18] to possess a different configuration of the bromine atom as compared to 2-bromocholestanone, but that no difference in the rate of dehydrobromination was observed.

(b) **2,2-Dibromo-3-keto*allo*steroids** (V).—The general procedure for dehydrobromination was varied slightly in that the dinitrophenylhydrazine was dissolved in hot glacial acetic acid first and the dibromo ketones were then added, since it has been shown previously[8] that those ketones rearrange in a few minutes on heating in acetic acid to the 2,4-isomers. When applied to 2,2-dibromocholestan-3-one and 2,2-dibromoandrostan-17-ol-3-one 17-hexahydrobenzoate, 58–62% of the corresponding $\Delta^1$-2-bromo hydrazones was isolated on cooling. These products were identical with samples prepared from the known $\Delta^1$-2-bromo-ketones (*cf.* Table I).

(c) **4-Bromo-3-ketosteroids** (I).—These have already been investigated by Mattox and Kendall[11] and only one additional example was examined in order to demonstrate the applicability of our reaction conditions to such ketones. Methyl 3-keto-4-bromo-12-hydroxycholanate afforded 87% of methyl $\Delta^1$-3-keto-12-hydroxycholenate dinitrophenylhydrazone melting at 240–242° (dec.) after recrystallization from ethanol–chloroform. The ultraviolet absorption spectrum has already been reported.[20]

*Anal.* Calcd. for $C_{31}H_{42}O_7N_4$: C, 63.90; H, 7.27; N, 9.58. Found: C, 63.54; H, 7.35; N, 9.39.

Pyruvic acid cleavage of 70 mg. of this dinitrophenylhydrazone gave 35 mg. (72%) of methyl $\Delta^4$-3-keto-12-hydroxycholenate with m. p. 147–149°, $[\alpha]^{27}D$ + 78° (acetone), identical with a sample prepared by another method.[34]

(d) **2-Bromo-$\Delta^4$-3-ketosteroids** (IX).—Bromo ketones of this type have been reported[7] to be rearranged in the presence of hydrogen bromide to presumably the isomeric 6-bromo isomers. Since in the present dehydrobromination procedure, the ketone is heated first in acetic acid before dinitrophenylhydrazine is added, it was necessary to show that no rearrangement occurred during the initial heating period. This was tested in the case of methyl $\Delta^4$-2-bromo-3-ketoetiocholenate[35] which was recovered unchanged (melting point, bromine analysis, rotation) on heating for five minutes in glacial acetic acid. When this bromo ketone or 2-bromo-$\Delta^4$-cholesten-3-one was heated with dinitrophenylhydrazine in the usual manner, 44–46% of the dinitrophenylhydrazone (Xb) of the corresponding $\Delta^{4,6}$-dien-3-one was obtained. These compounds exhibited a shiny-red color and showed typical maxima at 309 mμ and 404 mμ as discussed elsewhere.[20] Furthermore, they were identical with samples prepared from authentic dienones (Table I) and on cleavage with pyruvic acid, 100 mg. of $\Delta^{4,6}$-cholestadien-3-one dinitrophenylhydrazone afforded 5 mg. of the ketone,[29] characterized by its selective absorption at 282.5 mμ and melting point. It is interesting to note that in the dehydrobomination of these compounds or the isomeric 6-bromo derivatives described below, occasionally on cooling the acetic acid solution yellowish-orange colored crystals appeared instead of bright red ones which, however, turned reddish on filtering and assumed the usual color on subsequent recrystallization. No obvious explanation seems evident for this behavior.

(e) **$\Delta^4$-6-Bromo-3-ketosteroids** (XI).—Methyl $\Delta^4$-6-bromo-3-ketoetiocholenate and 6-bromotestosterone benzoate[30] on dehydrobromination with dinitrophenylhydrazine behaved exactly as the above mentioned 4-bromo isomers, except that the yield of $\Delta^{4,6}$-dienone hydrazone (Xb) was appreciably higher (69–71%). 6-Dehydrotestosterone benzoate dinitrophenylhydrazone melted at 252–254° and showed ultraviolet absorption maxima at 309 mμ (log *E* 4.10) and 404 mμ (log *E* 4.49 in chloroform), typical of this type of conjugated system.[20]

*Anal.* Calcd. for $C_{32}H_{34}O_6N_4$: C, 67.35; H, 6.01; N, 9.82. Found: C, 66.94; H, 5.88; N, 9.88.

(f) **2,4-Dibromo-3-ketoallosteroids** (VII).—The behavior of 2,4-dibromocholestanone, methyl 2,4-dibromo-3-ketoetio*allo*cholanate and 2,4-dibromoandrostan-17-ol-3-one 17-hexahydrobenzoate with one mole of dinitrophenylhydrazine in glacial acetic acid was investigated and in each case it was necessary to add water to the reaction mixture in order to precipitate the products. They evidently consisted of a mixture which was not amenable to effective separation by recrystallization and which could not be cleaved with pyruvic acid, but which by analysis still contained approximately one bromine atom. On the basis of the ultraviolet absorption spectra (Fig. 1), it seems likely that some of the desired $\Delta^{1,4}$-dien-3-one dinitrophenylhydrazone was formed.

**Reaction of Steroid Ketones with α-(2,4-Dinitrophenyl)-α-methylhydrazine.**[36]—The reactions with this reagent were carried out in glacial acetic acid as described for dinitrophenylhydrazine. Unfortunately, the resulting hydrazones crystallized very poorly in nearly all cases (gelatinous solutions) and with the exception of cholestanone, no sharp melting points were obtained. No definite product could be isolated from the reaction of this reagent with $\Delta^4$-cholesten-3-one or methyl $\Delta^4$-2-bromo-3-ketoetiocholenate. It has been pointed out[20] that those derivatives exhibit an interesting shift in the ultraviolet absorption maxima.

**Cholestanone α-(2,4-dinitrophenyl)-α-methylhydrazone** was obtained as a yellow solid with m. p. 203–205° which crystallized directly from the reaction mixture.

*Anal.* Calcd. for $C_{34}H_{52}O_4N_4$: C, 70.31; H, 9.03; N, 9.65. Found: C, 69.99; H, 8.90; N, 9.58.

**$\Delta^1$-Cholestenone α-(2,4-dinitrophenyl)-α-methylhydrazone** was isolated in 66% yield as a greenish-yellow solid on diluting the reaction mixture from the dehydrobromina-

(32) Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

(33) A trial run with cholesterol using the earlier conditions (ref. 29), but employing the more readily available aluminum isopropylate gave the same yield of $\Delta^{4,6}$-cholestadien-3-one.

(34) Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

(35) The melting point of this compound was previously reported (ref. 8) as 162.5–163.5°. On repeating the synthesis, it was possible to raise the melting point to 167–167.5°, without, however, changing the rotation.

(36) Blanksma and Wackers, *Rec. trav. chim.*, **55**, 655 (1936).

tion of 2-bromocholestanone with this reagent, and recrystallizing from ethanol–chloroform (gelatinous solution); m. p. 166–177° (dec.).

*Anal.* Calcd. for $C_{34}H_{50}O_4N_4$: C, 70.55; H, 8.71; N, 9.68. Found: C, 70.23; H, 8.55; N, 9.57.

Methyl 2-bromo-3-ketoetio*allo*cholanate as well as 2,2-dibromocholestanone could be dehydrobrominated in a similar manner, but the products gave analytical figures which were always 2% too low in carbon content.

**Reaction of 2-Bromocholestanone with Semicarbazide Hydrochloride.**—A solution of 230 mg. of 2-bromocholestanone in 5 cc. of glacial acetic acid was heated with 60 mg. of finely crushed semicarbazide hydrochloride for six minutes. After dilution with water and recrystallization from ethanol–chloroform, there was obtained 170 mg. (78%) of $\Delta^1$-cholestenone semicarbazone with m. p. 233–235°, undepressed on admixture with an authentic specimen; the derivative showed the typical maximum at 266 mμ, log $E$ 4.41 (chloroform). The product gave a negative Beilstein test and was cleaved almost instantaneously with dioxane–43% sulfuric acid to yield 86% of $\Delta^1$-cholestenone. It should be noted that while dinitrophenylhydrazones are usually isolated and purified more readily than the corresponding semicarbazones, the latter are very easily split into their components.[25]


## Summary

The dehydrobromination of steroidal bromo ketones with dinitrophenylhydrazine, first discovered by Mattox and Kendall[11] in the case of 4-bromo-3-ketosteroids, has been examined critically. In addition to the 4-bromo ketones, the method is applicable to the dehydrobromination of 2-bromo- and 2,2-dibromo-3-keto*allo*steroids as well as 2-bromo- and 6-bromo-$\Delta^4$-3-ketosteroids. The last two compounds both yield the hydrazone of the $\Delta^{4,6}$-dien-3-one. A mechanism for the reaction is suggested which employs a cyclic imonium compound as the key intermediate.

The regeneration of the unsaturated carbonyl compounds from the dinitrophenylhydrazones was examined and was found to be feasible from a preparative standpoint only in the case of the $\Delta^1$- and $\Delta^4$-3-ketones, thus imposing somewhat of a limitation on the Mattox–Kendall reaction.


SUMMIT, NEW JERSEY RECEIVED SEPTEMBER 30, 1948

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[CONTRIBUTION NO. 152 FROM THE RESEARCH LABORATORIES OF HOFFMANN–LA ROCHE, INC.]

# Synthesis of 5,5′-Dibromosalicil and Related Compounds

BY JACOB FINKELSTEIN AND SEYMOUR M. LINDER

In reports distributed by the Office of The Publication Board, No. 20,466 (Bios Final Report No. 219) it was revealed that Kuhn, in 1943, at Heidelberg had prepared 2,2′-dihydroxy-5,5′-dibromobenzil (3065) and claimed it to be the first compound found to be effective against Rickettsia and Influenza virus strain A employing mice as test animals. The I.G. Laboratories at Elberfeld found this substance to be tolerated by man in ten-gram doses. However, they were disappointed in its action in bacterial infections when compared to the sulfa drugs of choice. The substance is extremely insoluble. Therefore, the solubilized form prepared in borax and soda was tested and showed a fatal dose in the mouse of 30 mg./kg. Nevertheless, the claim by another I.G. Laboratory of its activity against virus organisms served as a stimulus to prepare the substance for testing in our chemotherapeutic laboratories. Although we were unable to confirm Kuhn's chemotherapeutic findings for the compound, we continued the investigation by synthesizing closely related substances. However, none of the compounds prepared was active *in vivo*, but the chemistry involved is interesting and forms the subject of this paper.

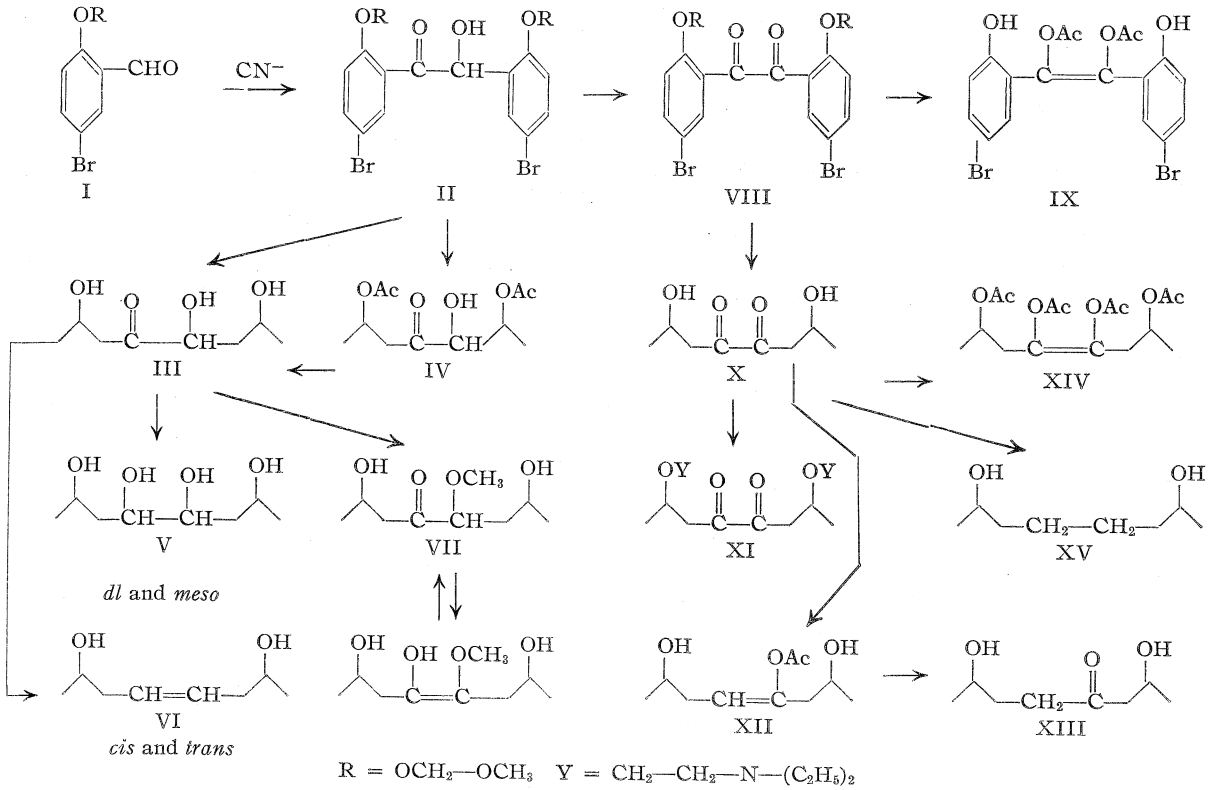
The methods of synthesizing the dibromosalicil are rather straight-forward. Kuhn, *et al.*[1] employed two closely related procedures. In one they started with 1,1′-dimethoxybenzil which was previously reported by Schonberger and Kraemer[2] and Irvine.[3] The compound was smoothly demethylated by aluminum chloride and then brominated in acetic acid. The other method by Perkin[4] starts with 2-methoxy-5-bromobenzaldehyde undergoing the benzoin condensation to produce the bromomethoxybenzoin. Another synthesis was outlined in the Department of Commerce Publication paralleling the latter method starting with 2-methoxymethoxy-5-bromobenzaldehyde (I). This methoxymethoxy substituent is ultimately removed by extremely mild conditions to produce the dibromosalicil.

For our investigation, the last method discussed was selected and the compound at each intermediate stage isolated and chemotherapeutically tested. In extending the problem to the preparation of closely related compounds, different compounds from those expected were isolated in several instances.

The first compound in the series capable of variation, 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin (II), was subjected to hydrolysis for two minutes to produce the 2,2′-dihydroxy derivative (III). However, under identical conditions and with the reaction time increased to thirty minutes, the expected phenolic compound was readily acetylated to form 2,2′-diacetoxy-5,5′-dibromobenzoin (IV). The structure of this compound was proven by a negative color reaction with ferric chloride and conversion to III by hydrolysis with 10% sodium hydroxide.

(1) Kuhn, *et al.*, *Ber.*, **76**, 900 (1943).
(2) Schonberger and Kraemer, *ibid.*, **55**, 1184 (1922).
(3) Irvine, *J. Chem. Soc.*, **79**, 670 (1901).
(4) Perkin, *Ann.*, **145**, 304 (1868).

FLOW SHEET




R = $OCH_2—OCH_3$ Y = $CH_2—CH_2—N—(C_2H_5)_2$

From the dihydroxybenzoin (III), five additional compounds were prepared. By reduction with sodium amalgam in wet ether in the manner of Irvine and Weir[5] as applied to benzoin, we were able to isolate the two possible hydrobenzoins (V), the *dl* and *meso* forms.

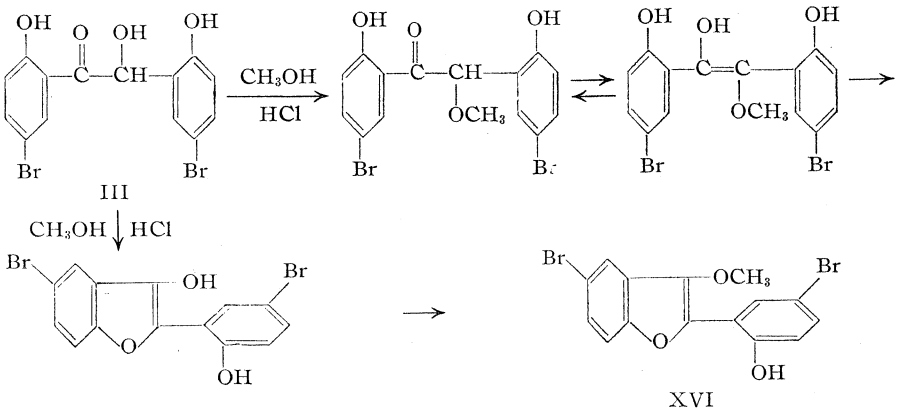
The stilbene derivative, 2,2′-dihydroxy-5,5′-dibromostilbene (VI) was prepared from the benzoin analog following the method of Ballard and Dehn[6] for the conversion of benzoin into stilbene. The two possible isomers were obtained.

Clemmensen[7] was able to convert benzoin or benzil to α,β-diphenylethane by reduction with zinc amalgam in dilute hydrochloric acid. Upon attempting to prepare 2,2′-dihydroxy-5,5′-dibromo-α,β-diphenylethane (XV), from the corresponding benzoin (III), a substance was obtained which is believed to be 2,2′-dihydroxy-5,5-dibromomethoxybenzoin monohydrate (VII). To account for such a substance, it would not be unreasonable to postulate the replacement of the alcoholic hydroxy group by a chlorine atom which when treated with methanol, as worked up, would produce the methyl ether. The location of the methoxy group was established by the negative reaction of the compound to Fehling solution.

To prove that the compound obtained is 2,2′-dihydroxy-5,5′-dibromomethoxybenzoin, an attempt was made to prepare it by another method for comparison purposes. Irvine[8] prepared methoxybenzoin by passing dry hydrogen chloride into a methanol solution of benzoin without controlling the temperature. When this was done with the benzoin (III), the compound isolated was alkali soluble and did not reduce Fehling solution. Thus phenolic methylation did not occur. The empirical formula, $C_{15}H_{10}O_3Br_2$, is that of the expected compound $C_{15}H_{12}O_4Br_2$, less the elements of water indicating the formation of a cyclic compound which could be 2-(2′-hydroxy - 5′ - bromophenyl) - 3 - methoxy - 5 - bromocoumarone (XVI). The possible courses of reaction may be graphically indicated as follows.

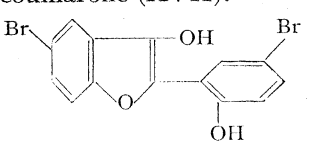
To obtain further information as to the course of reaction, 2,2′-dihydroxy-5,5′-dibromomethoxybenzoin monohydrate (VII) was treated with dry hydrogen chloride in methanol without any cooling. Under these conditions, the coumarone was not formed but a substance melting at 119–121° was obtained as compared to 173–175° for the starting compound. It gave an analysis which indicated no change in chemical formula and no reaction with Fehling solution. It is probable, therefore, that the compound VII was the *cis* form and the halogen acid catalyzed its conversion to the *trans* form. This conversion undoubtedly takes place more readily than ring closure. The melting point relationship is reversed from the usual and since the 119–121° iso-

(5) Irvine and Weir, *J. Chem. Soc.*, **91**, 1385 (1907).
(6) Ballard and Dehn, THIS JOURNAL, **54**, 3970 (1932).
(7) Clemmensen, *Ber.*, **47**, 683 (1914).
(8) Irvine, *J. Chem. Soc.*, 670 (1901).




mer did not undergo ring closure to form a coumarone it is therefore *trans*.

Pursuing the original objective to prepare the methoxybenzoin from the benzoin compound, the above experiment was repeated keeping the reaction temperature between −15 and 10°. The compound thus obtained gave a positive Fehling reaction and was alkali soluble. The analysis also indicated the elimination of a molecule of water and analogously must be the unmethylated coumarone (XVII).




XVII

The positive Fehling test is not surprising especially since it was shown by Friedländer and Neudörfer[9] that 3-hydroxycoumarone displays such a reaction. It was also found that the hydroxycoumarone could be obtained from the methoxymethoxybenzoin II when its methanol solution was saturated at 0° with dry hydrogen chloride. In this case, the methoxymethoxy ethers are readily cleaved and ring closure follows. The compounds obtained from each source are identical.

From all these observations, compound XVI is probably prepared *via* the hydroxycoumarone intermediate rather than through the methoxybenzoin since the latter did not undergo cyclization.

However, the desired diphenylethane derivative (XV) was obtained when 2,2′-dihydroxy-5,5′-dibromobenzil was reduced by zinc and concentrated hydrochloric acid in alcohol. The compound was extremely difficult to purify. Although its melting point indicated that it may have been the lower melting stilbene isomer VI, a mixed melting point gave a depression.

For another series of compounds, 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin II was first oxidized by Fehling solution to 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil (VIII).

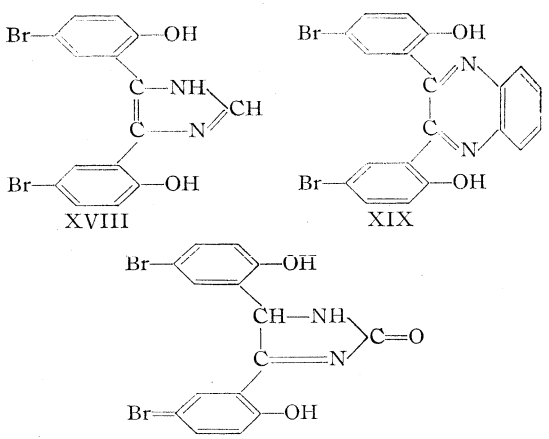
(9) Friedländer and Neudörfer, *Ber.*, **30**, 1081 (1897).

When VIII was subjected to reductive–acetylation below 40°, there was obtained 2,2′-dihydroxy-5,5′-dibromo-α,α′-diacetoxystilbene (IX).

Thus, during the reaction, the phenolic ethers were cleaved. However, when the ethers of VIII were removed by hydrolysis, 2,2′-dihydroxy-5,5′-dibromobenzil (5,5′-dibromosalicil) (X) was obtained. It agreed in all respects with the compound obtained by Kuhn. In an extension of the work several closely related compounds were synthesized. It was thought to be interesting to synthesize a derivative containing a basic water-soluble group. Therefore, 2,2′-bis-(β-diethylaminoethoxy)-5,5′-dibromobenzil (XI), was obtained as the free base and hydrochloride.

When Thiele's[10] procedure for reductive–acetylation was applied to dibromosalicil, 2,2′-dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII) was produced. The formation of this substance probably involved the dehydration of the intermediate di-hydroxy compound to the mono-hydroxy stilbene which was then acetylated. This compound, when hydrolyzed by 10% sodium hydroxide, yielded 2,2′-dihydroxy-5,5′-dibromodesoxybenzoin (XIII). Only by modification of the procedure for reductive-acetylation of dibromosalicil (X) could 2,2′,α,α′-tetraacetoxy-5,5′-dibromostilbene (XIV) be prepared.

Three cyclic derivatives of possible chemotherapeutic interest were also synthesized. These were 4,5-bis-(2-hydroxy-5-bromophenyl)-imidazole (XVIII), 2,3-bis-(2-hydroxy-5-bromophenyl)-quinoxaline (XIX) and 4,5-bis-(2-hydroxy-5-bromophenyl)-glyoxalone (XX). The imidazole was prepared from 2,2′-dihydroxy-5,5′-dibromobenzil




(10) Thiele, *Ann.*, **306**, 142 (1899).

(X) by the improved procedure of Davidson, *et al.*[11] The quinoxaline (XIX) was obtained from X and *o*-phenylenediamine. The glyoxalone (XX) was formed from 2,2′-dihydroxy-5,5′-dibromobenzoin (III) as in "Organic Syntheses."[12]

**Chemotherapeutic Results.**[13]—5,5′-Dibromosalicil, its water-soluble borate complex and the thirteen dibromo derivatives which constitute chemical variations of dibromosalicil were tested as to their toxicity for mice and their possible therapeutic effect in selected experimental infections.

**Toxicity.**—Since the majority of compounds were insoluble in water, they were administered by the oral route. Their LD50 was found to be higher than 5.0 g./kg., *i.e.*, that a 10% suspension given by gavage did not produce toxic symptoms. Compound VIII was injected by the subcutaneous route dissolved in peanut oil. A 5% solution was tolerated, corresponding to LD50 of more than 2.5 g./kg. The LD50 of 5,5′-dibromosalicil borate complex was 0.095 g./kg. for the subcutaneous injection.

**Chemotherapeutic Activity** *in vivo*.—All compounds were tested in experimental infections with a hemolytic streptococcus (group A, type 3), or a type 1 pneumococcus, but none of them exerted any therapeutic effect. Furthermore all compounds were tried in the infection with poliomyelitis virus (SK strain). Up to ten treatments were given during the incubation period, but no protective effect was noted. There was also no evidence of the alleged activity of dibromosalicil in experimental influenza infections of mice (intranasal infection with type A strain PR 8). Neither dibromosalicil nor its borate complex and none of the other compounds had any significant activity toward this viral infection.

Two compounds, VI, IX, were also tried in mice infected with *Trypanosoma equiperdum*. No trypanocidal effect was observed.

**Anti-bacterial Activity** *in vitro*.—The lack of solubility in water of most of the compounds did not allow determinations of the bacteriostatic activity *in vitro* at least not with the usual methods of the dilution test. Two compounds, the borate complex and III, were sufficiently soluble to permit *in vitro* testing. The results are shown in the Table I which gives the reciprocal figures of the minimal bacteriostatic concentrations after forty-eight hours of contact.

TABLE I

| Compound | Strepto-cocci | Pneumo-cocci | *Staph. aureus* | *E. coli* | *E. typhosa* |
|---|---|---|---|---|---|
| 5,5′-Dibromosalicil borate complex | 25,600 | 25,600 | 1,024,000 | 51,200 | 6400 |
| 2,2′-Bis-β-diethyl-aminoethoxy-5,5′-dibromo-benzil dihydro-chloride | 128,000 | 64,000 | 16,000 | 8,000 | 1000 |

The findings, as far as the soluble borate complex of 5,5′-dibromosalicil is concerned, confirm the figures recently given by Schales and Suthon[14] particularly the specific effect on *Staphylococcus aureus*. The substituted dibromobenzil derivative XI had a more marked limitation of activity to the group of gram-positive organisms.

## Experimental

**Chloromethyl Ether.**—This compound was prepared according to the method of Clarke, Cox and Mack.[15]

**5-Bromo-2-hydroxybenzaldehyde.**—This compound was prepared as per Avwers and Burger[16] by bromination of salicylaldehyde.

**2-(Methoxymethoxy)-5-bromobenzaldehyde (I).**—To a solution of 63.5 g. of sodium in methanol, 555 g. of 5-bromo-2-hydroxybenzaldehyde and 2.5 liters of dry toluene were added. The excess methanol was removed by distillation. After cooling to 0°, 220 g. of pure chloromethyl ether was added dropwise with stirring during one hour keeping the temperature between 0–10°. After the reaction was stirred and refluxed for one hour, the mixture was slightly acid. After cooling to room temperature, water was added to dissolve the sodium chloride and separated. The toluene layer was extracted with dilute sodium hydroxide until a test portion of the washings did not produce a precipitate upon acidification. Then, the toluene solution was washed with water until neutral and concentrated *in vacuo* from a water-bath to remove the solvent leaving a yellow oil, which was fractionated *in vacuo*. At 5 mm. the desired product was collected between 152–154°. The yield was 82%. *Anal.* Calcd. for $C_9H_9O_3Br$: C, 44.21; H, 3.70. Found: C, 43.55; H, 3.76.

**2,2′-Di-(methoxymethoxy)-5,5′-dibromobenzoin (II).**—A solution of 296 g. of 2-methoxymethoxy-5-bromobenzaldehyde in 320 cc. of alcohol was mixed with a solution of 31 g. of potassium cyanide in 100 cc. of water and refluxed for two hours. As much alcohol as possible was distilled off from the steam-bath and the heavy residual oil was poured into cold water. The organic product was extracted with ether which was washed with water. The small amount of solid interface was discarded. The ether solution was dried and concentrated *in vacuo*. The remaining oil was dissolved in 170 cc. of warm methanol. Upon cooling, the benzoin compound crystallized. After recrystallization it melted at 89–91°. *Anal.* Calcd. for $C_{18}H_{18}O_6Br_2$: C, 44.11; H, 3.70. Found: C, 43.87; H, 3.68.

**2,2′-Dihydroxy-5,5′-dibromobenzoin (III).**—To a solution of 100 g. of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin in 500 cc. of warm acetic acid, 40 cc. of 15% sulfuric acid was added, and the mixture then heated on the steam-bath for two minutes. It was poured into cold water and the resulting oil taken up into ether. The ethereal solution was washed with water, then with a sodium bicarbonate solution until the washings were alkaline and finally with water. After drying over sodium sulfate, the ether was distilled off. The residual oil was dissolved in benzene and the product induced to crystallize by scratching and seeding; m. p. 133–135°. This was sufficiently pure for the following reactions. Further purification when necessary was effected by several recrystallizations from benzene; m. p. 146–146.5°. *Anal.* Calcd. for $C_{14}H_{10}O_4Br_2$: C, 41.81; H, 2.51; Br, 39.74. Found: C, 41.72; H, 2.58; Br, 39.64.

**2,2′-Dihydroxy-5,5′-dibromodihydrobenzoin (V).**—A 5-g. solution of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) was prepared in 100 cc. of wet ether. While a stream of carbon dioxide was passed through the solution, 18 g.

(11) Davidson, *et al.*, *J. Org. Chem.*, **2**, 319 (1937).

(12) "Organic Synthesis," Coll. Vol. 2, p. 231.

(13) The authors are indebted to Drs. R. Schnitzer and E. Grunberg of the Chemotherapy Department for these results.

(14) Schales and Suthon, *Archives of Biochemistry*, **11**, 397 (1940).

(15) Clarke, Cox and Mack, THIS JOURNAL, **39**, 712 (1917).

(16) Avwers and Burger, *Ber.*, **37**, 3934 (1904).

of 3.3% sodium amalgam was added in small portions. The *p*H of the mixture was thus kept at 8 (or below). It was necessary to replace the ether lost by evaporation. Small amounts of water were added from time to time to replace that used in the reaction and to dissolve some of the salts formed. After two hours, the addition was completed. When hydrogen was no longer evolved, water was added to dissolve the sodium bicarbonate. The ether layer was separated, washed with water and dried. When the ether was removed, crystals were obtained which melted between 136–138°. When recrystallized from acetone–Skellysolve B mixture, m. p. 149–152°. This proved to be a mixture of the *dl*- and *meso*. Upon repeated crystallization, one product m. p. 225–229° was obtained and probably is the *dl* (racemic) mixture. *Anal.* Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.61; H, 2.99; Br, 39.59. Found: C, 41.60; H, 3.06; Br, 39.56.

To obtain the *meso* form, the above mother liquors were combined and concentrated to obtain a solid. Upon recrystallization from benzene, the *meso* form was obtained pure; m. p. 155–156°. *Anal.* Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.61; H, 2.99; Br, 39.59. Found: C, 41.73; H, 2.87; Br, 39.37.

**2,2′-Dihydroxy-5,5′-dibromostilbene (VI).**—To zinc amalgam prepared from 5 g. of mercuric chloride and 20 g. of zinc dust, a solution of 9 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) dissolved in 50 cc. of alcohol was added. While stirring and maintaining a reaction temperature of 15°, 40 cc. of concentrated hydrochloric acid was added dropwise over a period of two hours. After stirring for an additional hour, the mixture was diluted with a large volume of water and filtered. After washing with water, the residue was treated with ether to dissolve away the product from metal. The ether solution was dried and concentrated. The oil which was obtained soon crystallized. After three recrystallizations from xylene, the product was pure; m. p. 201–202°. This is the *trans* isomer. *Anal.* Calcd. for $C_{14}H_{10}O_2Br_2$: C, 45.41; H, 2.73; Br, 43.20. Found: C, 45.50; H, 2.64; Br, 43.03. The *cis* isomer was isolated from the xylene mother liquors and purified by recrystallization from benzene; m. p. 169–173°. *Anal.* Found: C, 45.18; H, 3.07.

**2,2′-Dihydroxy-5,5′-dibromomethoxybenzoin (VII).**—Zinc amalgam was prepared from 10 g. of mossy zinc, 1 g. of mercuric chloride, 0.5 cc. of concentrated hydrochloric acid and 15 cc. of water. To the amalgam, were added 5 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin, 20 cc. of water and 20 cc. of concentrated hydrochloric acid. Upon refluxing, a vigorous reaction took place and, to prevent the solids from coating the flask, 5 cc. of alcohol was added. The reaction mixture was refluxed for five hours and at each hour 2 cc. of concentrated hydrochloric acid was added. After cooling, filtering and washing with water, the product was taken up in ether to separate it from the metal, and dried. Upon removal of the ether, a greenish glassy substance was obtained. It was then triturated with methanol whereupon some crystals appeared. Another crop was obtained by concentrating the methanol. The second crop was recrystallized twice from xylene; m. p. 173–175°. *Anal.* Calcd. for $C_{14}H_{12}O_2Br_2$: C, 45.20; H, 3.25; Br, 42.95. Calcd. for $C_{15}H_{13}O_4Br_2 \cdot H_2O$: C, 41.54; H, 3.22; Br, 36.86. Found: C, 41.54; H, 2.23; Br, 36.89.

**2,2′-Diacetoxy-5,5′-dibromobenzoin (IV).**—Eighty grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin was dissolved in 300 cc. of glacial acetic acid with warming, and 32 cc. of 15% sulfuric acid was added. The solution was heated on the steam-bath for thirty minutes and worked up as for III above. The benzene solution did not produce any crystals and so was concentrated on the steam-bath to a smaller volume. After keeping in the refrigerator, a small amount of crystals appeared. These were collected and washed with benzene; m. p. 183–187°. For Compound III the m.p. 146–146.5°. By recrystallization from methanol, the pure compound was obtained; m. p. 199–201°; no color with ferric chloride. *Anal.* Calcd. for $C_{14}H_{10}O_4Br_2$ (free phenol): C, 41.81; H, 2.51. Calcd. for $C_{16}H_{12}O_5Br_2$ (mono-acetoxy): C, 43.28; H, 2.73. Calcd. for $C_{18}H_{14}O_6Br_2$ (di-acetoxy): C, 44.46; H, 2.90. Found: C, 44.77, 44.58; H, 2.65, 2.57.

**Conversion of IV to III.**—One-half gram of IV and 5 cc. of 10% sodium hydroxide were mixed. The solid turned yellow and, upon heating on the steam-bath, went into solution. Upon cooling, the yellow sodium salt precipitated out. The mixture was acidified with dilute hydrochloric acid and a colorless product was obtained. It was filtered, washed and purified; m. p. 143–145°; for III crystallized several times from benzene, m. p. 146–146.5°.

**2,2′-Di-(methoxymethoxy)-5,5′-dibromobenzil (VIII).**—To 64.5 g. of crude 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin in 75 cc. of alcohol, the following were added: A, 151 g. of $CuSO_4 \cdot 5H_2O$ in 600 cc. of water; B, 225 g. of $KNaC_4H_4O_6 4H_2O$ and 162 g. of potassium hydroxide dissolved in water to a volume of 860 cc. The reaction mixture was stirred at 75–80° for two hours. After cooling, the product was collected and freed from copper oxide by dissolving in hot alcohol and decolorized with Nuchar. The filtrate yielded practically colorless crystals. When recrystallized from alcohol, the compound was pure; m. p. 115–116°. A second crop can be obtained from the mother liquors. *Anal.* Calcd. for $C_{18}H_{16}O_6Br_2$: C, 44.28; H, 3.30. Found: C, 44.10; H, 3.43.

**2,2′-Dihydroxy-5,5′-dibromo-α,α-diacetoxystilbene (IX).**—Six grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil VIII was added to 10 cc. of acetic acid previously saturated with dry hydrogen chloride. Then, 60 cc. of acetic anhydride was added, and while stirring at 30°, zinc dust was added over one-half hour in several portions until 6 g. was added. The mixture was then stirred for an additional hour and a half and poured into 500 cc. of cold water. After standing overnight, the oil was extracted with ether, washed, first with water and then sodium bicarbonate and then water again. After drying over sodium sulfate, the ether was removed and the residual oil soon crystallized. It was purified by crystallization from butanol; m. p. 121–124°. *Anal.* Calcd. for $C_{18}H_{14}O_6Br_2$: C, 44.48; H, 2.90; Br, 32.88. Found: C, 44.27; H, 3.13; Br, 32.52.

**2,2′-Dihydroxy-5,5′-dibromobenzil (X).**—Fifty grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil (VIII) was dissolved in 250 cc. of glacial acetic acid. To the hot solution, 17 cc. of 15% sulfuric acid was added. Then, at once, 25 cc. of hot water was added and immediately crystals began to form. The heating was continued for one minute and the mixture cooled. The product was filtered, washed with methanol and dried at 90; m. p. 204–206°. Recrystallized from alcohol, the product was obtained pure; yield 95%; m. p. 209–210°; lit. m. p. 210°. *Anal.* Calcd. for $C_{14}H_8O_4Br_2$: C, 42.04; H, 2.03. Found: C, 42.44; H, 2.12.

**2,2′-Dihydroxy-5,5′-dibromodiphenylethane (XV).**—To a refluxing mixture of 2 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) dissolved in 60 cc. of alcohol, 3.5 g. of 30-mesh zinc and 5 cc. of concentrated hydrochloric acid was added. A vigorous reaction took place. At half-hour intervals, 5-cc. portions of acid were added. After one-half hour, the yellow color was discharged and after one and one-half hours, the refluxing ceased. After cooling, the solution was poured into water yielding an oil which soon crystallized. The product was filtered and dried at 100°; m. p. 153–160°. After recrystallization from benzene, the product melted at 172–173°. *Anal.* Calcd. for $C_{14}H_{12}O_2Br_2$: C, 45.20; H, 3.25; Br, 42.95. Found: C, 45.64; H, 2.54; Br, 43.22.

**2,2′-Di-(β-diethylaminoethoxy)-5,5′-dibromobenzil (XI).**—The disodium salt of 2,2′-dihydroxy-5,5′-dibromobenzil was prepared from 6.5 g. of the compound and 2 equivalents of sodium ethylate in alcohol and obtained dry by continuous concentration with benzene. It was then treated with excess β-diethylaminoethyl chloride in 100 cc. of dry toluene and refluxed for ten hours with continuous stirring. The sodium chloride was filtered off and the toluene solution was washed with alkali and then with water. The solution was dried over sodium sulfate and concentrated *in vacuo*. The oil soon crystallized. The free base so obtained melted at 82–84°. When recrystal-

lized from Skellysolve B, yellow crystals were obtained; m. p. 84–86°. *Anal.* Calcd. for $C_{26}H_{34}O_4Br_2N_2$: C, 52.18; H, 5.72; N, 4.68. Found: C, 52.18; H, 5.44; N, 4.72. The base was converted into the di-hydrochloride and recrystallized from isopropyl alcohol; m. p. 195–196°. *Anal.* Calcd. for $C_{26}H_{34}O_4Br_2N_2 \cdot 2HCl$: C, 46.53; H, 5.40; N, 4.17. Found: C, 46.67; H, 5.18; N, 4.36.

**5,5′-Dibromo-2,2′-α,α′-tetraacetoxystilbene (XIV).**—To 5 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) dissolved in 60 cc. of acetic anhydride, 10 cc. of acetic acid previously saturated with hydrogen chloride at 15° was added with stirring and cooling. Then, at 30–40°, 6 g. of zinc dust was gradually added. The reaction mixture turned green and then black. After one hour, the reaction mixture was poured into 500 cc. of cold water. The sticky solid thus produced was filtered and dissolved in ether. The ethereal solution was first washed with water then with sodium bicarbonate and water. When dried, the solution was concentrated leaving an oil. When treated with butanol, the product crystallized. It was then recrystallized from butanol several times to constant melting point; m. p. 155–157°. *Anal.* Calcd. for $C_{22}H_{18}O_8Br_2$: C, 46.31; H, 3.18; Br, 28.02. Found: C, 45.87; H, 3.27; Br, 28.22.

**2,2′-Dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII).**—To a suspension of 4.5 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) in 60 cc. of acetic anhydride, with cooling, a solution of 5 cc. of concentrated sulfuric acid in 10 cc. of acetic acid was slowly added to avoid undue rise in temperature. Then, at 30–40°, 6 g. of zinc dust was gradually added with good stirring. After one hour, white crystals appeared. The reaction mixture was diluted with water and filtered. To separate the zinc, the compound was extracted in a Soxhlet extractor with ether. The ether removed, the solid was recrystallized from butanol until pure; m. p. 145–147°. *Anal.* Calcd. for $C_{16}H_{12}O_4Br_2$: C, 44.85; H, 2.80; Br, 37.40; acetyl, 10.1. Found: C, 44.74; H, 2.61; Br, 37.25; acetyl, 10.9.

**2,2′-Dihydroxy-5,5′-dibromodesoxybenzoin (XIII).**—A solution of 1.8 g. of 2,2′-dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII) in 18 cc. of 10% sodium hydroxide was warmed for fifteen minutes on the steam-bath. After neutralization with dilute hydrochloric acid, the product crystallized. It was filtered, washed and recrystallized from benzene until it melted at 209–211°. *Anal.* Calcd. for $C_{14}H_{10}O_3Br_2 \cdot {}^1/_2H_2O$: C, 42.55; H, 2.78; Br, 40.51. Found: C, 42.24; H, 2.64; Br, 40.59.

**2-(2′-Hydroxy-5′-bromophenyl)-3-methoxy-5-bromocoumarone (XVI).**—A solution of 3.5 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) in 50 cc. of methanol was saturated with dry hydrogen chloride without any cooling. The temperature rose sufficiently to cause refluxing. After saturation and cooling, the product crystallized out. It was recrystallized from methanol, m. p. 103–104°. The Fehling test is negative. *Anal.* Calcd. for the coumarone $C_{15}H_{10}O_3Br_2$: C, 45.25; H, 2.53; Br, 40.12. Found: C, 45.78; H, 2.69; Br, 40.15.

**2-(2′-Hydroxy-5′-bromophenyl)-3-hydroxy-5-bromocoumarone (XVII).**—A. A solution of 3 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) in 100 cc. of methanol was cooled to −15° and saturated with dry hydrogen chloride. During the reaction, the temperature rose to 10°, before it could be checked, and then kept at 0°. The saturated solution was poured into 500 cc. of ice-water and the resultant precipitate filtered, washed with water and dissolved in ether. The ether solution was extracted with dilute sodium hydroxide and the combined alkali extracts were acidified. The solid was collected and recrystallized from toluene, m. p. 155–156°. The Fehling test was positive. *Anal.* Calcd. for the coumarone $C_{14}H_8O_3Br_2$: C, 43.80; H, 2.10. Found: C, 44.06; H, 1.94. B. A solution of 4 g. of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin (II) in 100 cc. of methanol at −25° was saturated with dry hydrogen chloride keeping the temperature below 0°. The yellow precipitate obtained when the reaction mixture was poured into ice-water was collected and recrystallized from toluene; m. p. 158–159°. When mixed with the compound obtained in A, there was no depression. It also gave a positive Fehling test. *Anal.* Calcd. for $C_{14}H_8O_3Br_2$: C, 43.80; H, 2.10; Br, 41.61. Found: C, 43.96; H, 2.17; Br, 41.33.

**Conversion of *cis*-2,2′-Dihydroxy-5,5′-dibromo-α-methoxybenzoin to *trans* Form.**—Ninety mg. of *cis*-2,2′-dihydroxy-5,5′-dibromo-α-methoxybenzoin was dissolved in 5 cc. of methanol and saturated with dry hydrogen chloride without cooling. Then, after refluxing for fifteen minutes, it was cooled and crystals separated. After filtering and recrystallizing from methanol, it melted at 119–121°. *Anal.* Calcd. for $C_{15}H_{10}O_3Br_2$ (coumarone): C, 45.28; H, 2.53; Br, 40.12. Calcd. for $C_{15}H_{12}O_4Br_2 \cdot H_2O$ (starting compound): C, 41.50; H, 3.22; Br, 36.86. Found: C, 42.22; H, 2.79; Br, 36.83.

**4,5-bis-(2-Hydroxy-5-bromophenyl)-imidazole (XVIII).**—A mixture of 3.0 g. of 5,5′-dibromosalicil (X), 0.2 g. of hexamethylenetetramine, 4.5 g. of ammonium acetate and 95 cc. of glacial acetic acid was refluxed for one hour. After *dilution* with 900 cc. of water and clarification by filtration, the solution was made alkaline with ammonia. The precipitate was collected and recrystallized from dilute alcohol twice and dried at 100°; m. p. 235–237°. *Anal.* Calcd. for $C_{15}H_{10}N_2O_2Br_2$: N, 6.83. Found: N, 7.05.

**2,3-bis-(2-Hydroxy-5-bromophenyl)-quinoxaline (XIX).**—A solution of 4 g. of 5,5′-dibromosalicil (X), 1 g. of *o*-phenylenediamine in 125 cc. of acetic acid was refluxed for three hours and poured into ice. The crystallized product was dried by distillation of a benzene solution and recrystallized from small amounts of benzene; m. p. 216–219°. With 5,5′-dibromosalicil, the melting point was depressed. This compound does not form a hydrochloride. *Anal.* Calcd. for $C_{20}H_{12}O_2N_2Br_2$: C, 50.85; H, 2.56; N, 5.94. Found: C, 50.68; H, 2.67; N, 5.85.

**4,5-bis-(2-Hydroxy-5-bromophenyl)-glyoxalone (XX).**—A solution of 3 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III), 0.81 g. of urea in 20 cc. of glacial acetic acid was refluxed for seven hours, during which time crystallization started. After standing, the product was filtered and washed with ether to remove starting material. The compound was purified by recrystallization from aqueous pyridine; m. p. 272–273°. *Anal.* Calcd. for $C_{15}H_{10}N_2O_3Br_2$: C, 42.30; H, 2.37; N, 6.58. Found: C, 42.50; H, 2.75; N, 6.41.

**Acknowledgment.**—The authors wish to thank Dr. John Lee for his interest, advice and helpful discussions during the course of this research and also Dr. Al Steyermark and his associates for the microanalyses.

## Summary

The 2,2′-dihydroxy-5,5′-dibromosalicil (5,5′-dibromosalicil) compound of Kuhn was synthesized and his claims for its activity toward virus infections could not be substantiated.

Many closely related compounds were synthesized and tested *in vitro* against hemolytic streptococcus, pneumococcus, poliomyelitis, trypanosoma, and gram-positive organisms without revealing any marked activity.

It was shown that benzoins substituted on the adjacent carbon atom with a hydroxy group can be converted into a coumarone upon treatment with dry hydrogen chloride.

The keto-alcohol part of the substituted benzoin molecule is capable of reaction to produce a cyclic compound as a glyoxalone.

The di-keto part of the substituted benzil molecule is capable of reaction to produce cyclic derivatives as the imidazole and quinoxaline.

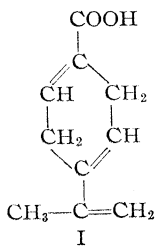
NUTLEY, N. J. RECEIVED SEPTEMBER 24, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Reactions of Dehydroperillic Acid

BY CHARLES D. HURD AND O. E. EDWARDS[1]

A crystalline acid, m.p. 88°, obtainable from the heartwood of Western Red Cedar was studied by Anderson and Sherrard.[2] It was named dehydroperillic acid and was assigned structure I.



I

Some of this compound was prepared for the present study through the courtesy of W. G. Van Beckum of Weyerhaeuser Timber Company.

It was found that the acyl chloride could be prepared by use of thionyl chloride and pyridine but not by thionyl chloride alone, since alkaline hydrolysis of the latter product gave rise to a mixture of carboxylic acids melting over a wide range. Anderson and Sherrard noted that dehydroperillic acid underwent isomerization into cuminic (*p*-isopropylbenzoic) acid when heated with mineral acids. The dehydroperillyl chloride formed in the presence of a little pyridine, however, was readily hydrolyzed to dehydroperillic acid of reasonable purity. Treatment of the acyl halide with ethanol, ammonia or aniline caused conversion to the ethyl ester, amide and anilide, respectively.

The isoprene-like structure of dehydroperillic acid made it seem reasonable to expect ease of polymerization but any such tendency was found to be slight. Attempts to polymerize the ester or the acid by heating with benzoyl peroxide were negative. The butyl-rubber type of polymerization procedure was also unsatisfactory. For these tests we are indebted to P. J. Frolich and W. J. Sparks of Esso Laboratories, Linden, New Jersey. They tested the acid, ester and anilide and found that although resinous products or oils could be obtained both at −23 or −97°, the degree of polymerization was low. Copolymerization experiments with isobutylene were unsuccessful also, since small quantities of dehydroperillic acid or its derivatives inhibited the reaction to such an extent that the only polymers formed were much too low in molecular weight for adequate vulcanizability. If the two double bonds in the ring of structure I were changed so as not to be conjugated with the double bond of the side chain, the present data would then become more understandable. The unconjugated, terminal methylene group seems necessary, however, to explain formaldehyde on ozonolysis[2] of I.

(1) Weyerhaeuser Timber Company Fellow, 1943.

(2) Anderson and Sherrard, THIS JOURNAL, **55**, 3813 (1933). In a private communication Dr. Anderson advises that Dr. H. Erdtman and associates of the Royal Institute of Technology, Stockholm, are investigating this acid with a view toward more complete elucidation of its structure.

## Experimental

Crude dehydroperillic acid was purified by crystallization from alcohol. Colorless needles were obtained melting at 85–86.5°.

**Dehydroperillyl Chloride.**—Five grams of the acid was added gradually into a mixture of 8 g. of thionyl chloride and five drops of pyridine. The temperature dropped rapidly to 10–15° as sulfur dioxide and hydrogen chloride were evolved. The reaction mixture was left at room temperature for twenty minutes after the acid was all added. Gas evolution had ceased at this time. The product was used directly for the preparation of the anilide.

**Dehydroperillanilide.**—The above crude acyl chloride was added slowly into a mixture of aniline (10 g., an excess) and benzene (60 cc.). A vigorous reaction ensued. The aniline hydrochloride was separated and any excess of aniline in the benzene layer was removed by washing with dilute hydrochloric acid, then with dilute alkali. The crude anilide (6.5 g.) remaining on evaporation of the solvent was crystallized from 75% alcohol; m.p. 97–98°.

*Anal.* (by T. S. Ma). Calcd. for $C_{16}H_{17}NO$: N, 5.86. Found: N, 5.68.

**Dehydroperillamide.**—Five grams of the acid was converted to the acyl chloride as before, and to the latter, dissolved in ether, was added powdered ammonium carbonate until gas was no longer evolved. Water was then added and the ether layer was separated, washed with concentrated ammonium hydroxide, then processed for the amide. Crystallization from 50% alcohol yielded colorless plates of m.p. 95–96°; yield 2 g.

*Anal.* (by M. Hines). Calcd. for $C_{10}H_{13}NO$: C, 73.58; H, 8.03. Found: C, 73.43; H, 8.03.

**Ethyl Dehydroperillate.**—The acid chloride, prepared from 16 g. of acid, was poured slowly into a mixture of 24 g. of absolute alcohol and 14 g. of dry pyridine. After warming the solution for ten minutes on the steam-bath, it was poured into water and the ester was taken up in ether. As finally purified, the ester was collected at 88° (4 mm.); yield, 13 g. or 70%; $d^{25}_{25}$ 0.999. On alkaline hydrolysis, it gave a 95% yield of pure dehydroperillic acid.

*Anal.* (by T. S. Ma). Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 73.77; H, 8.26.

**Heating with Benzoyl Peroxide.**—No polymeric material resulted on heating a mixture of 0.05 g. of benzoyl peroxide and 1.5 g. of dehydroperillic acid at 95° for one day. Similarly, 1.5 g. of the ethyl ester was not changed by heating at 70° with 0.07 g. of the peroxide.

It is of interest to note that when the acid was heated alone at 110° for half an hour, no pyrolysis was evident. The melt crystallized on cooling, m.p. 85–88°.

## Summary

Derivatives of dehydroperillic acid are reported. The conjugate unsaturation in the structure of these compounds suggests ready polymerizability which was not experienced in practice.

EVANSTON, ILLINOIS RECEIVED AUGUST 13, 1948

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

# *p*-Toluenesulfonyl and Iodo Derivatives of the Three Lower Polyethylene Glycol Monoethyl Ethers[1]

BY CLINTON W. TASKER AND C. B. PURVES[2]

As a prelude to a study of the hydroxyethyl ethers of cellulose,[3] it seemed advisable to check the physical properties of the *p*-toluenesulfonyl (tosyl) esters of simple monoethyl ethers in the polyethylene glycol series, and to examine the reactivities of the tosyloxy group during solvolysis and toward sodium iodide. The general formula of the compounds studied was $C_2H_5(OCH_2CH_2)_xR$, where $x$ was 1, 2 or 3, and R was OH, OTs or I. The marked tendency of some of the derivatives to undergo autoxidation during brief storage was noted, and the products formed in the thermal decomposition of the two higher tosylates were identified. A knowledge of these peculiarities made it possible to prepare the hitherto missing members of the above series.

Wurtz[4] noticed in 1859 that ethylene oxide slowly condensed with hydroxylic substances, and the employment of metallic catalysts by later investigators[5,6,7] to hasten such condensations resulted in a general method of preparing the monoalkyl ethers of polyethylene glycols. Another general method depended on the condensation of an appropriate sodium alcoholate with an appropriate alkyl halide.[8,9,10,11] The physical constants of lower members of the series, collected by Davidson,[12] revealed the interesting fact that the boiling points of the monoethyl ethers were very close to those of the next lower, unsubstituted polyethylene glycol. Unfortunately, this fact was overlooked until 1941, when Seikel[13] found that the monoethyl ether of diethylene glycol (x, 2; R, OH) could not be satisfactorily freed from ethylene glycol by fractional distillation. The observation that commercial samples of the monoether contained up to 28% of glycol explained in some degree the variable values quoted in the literature for the physical constants of this substance, and the many failures encountered in attempts to obtain crystalline derivatives.[14,15,16,17,18] The use of a sample adequately purified from glycol enabled Shupe[19] to crystallize the xanthate of diethylene glycol monoethyl ether, and recent workers[20] isolated crystalline tri-iodobenzoates of various monoethers of ethylene glycol and diethylene glycol without undue difficulty.

Cretcher and his collaborators[21,22] prepared the tosyl esters of a large number of the monoalkyl ethers of ethylene glycol, including that of the monoethyl ether (x, 1; R, OTs). The side reactions liable to occur during such tosylations were carefully investigated by Tipson,[23] who was able to improve the method of preparation. Although some of these esters were oils that decomposed on distillation,[22,24] the tosyl group was sufficiently resistant to hydrolysis to permit of their purification by thorough washing in cold water. The higher members of the series (x, 2 and 3; R, OTs) do not seem to have been accurately characterized, although presumably they were included in a patent by Adams,[24] which described the series in general terms as heavy, viscous oils, insoluble in water but soluble in organic liquids.

The action of sodium iodide in a ketone solvent would be expected to substitute an iodine atom for the tosyloxy group in the above esters, since all of the latter are derived from primary alcohol units.[25] β-Iodoethyl ether (x, 1; R, I), the product from the lowest member of the series, was first encountered in a preparation of ethylene di-iodide from ethylene and an alcoholic solution of iodine.[26] Later syntheses, which established the correct structure, involved the action of phosphorus tri-iodide on ethylene glycol monoethyl ether,[27,28] and of sodium iodide on β-chloroethyl ether.[29] Although decomposed by sodium ethylate at 150°[26,27] and by alcoholic silver nitrate,[30]

(1) Abstracted from a Thesis presented to the Faculty of McGill University in June, 1947, by C. W. Tasker in partial fulfilment of the requirements for the Ph.D. degree.

(2) At above address.

(3) Tasker and Purves, THIS JOURNAL, **71**, 1023 (1949).

(4) Wurtz, *Compt. rend.*, **49**, 813 (1859); *Ann. chim.*, [3] **69**, 331 (1863).

(5) Altman and Kedrinskii, *Trans. Exptl. Research Lab. Kemgas. Materials on Cracking and Chemical Treatment of Cracking Products*, (U. S. S. R.), **3**, 341, 351; *C. A.*, **31**, 6196 (1936).

(6) Stanley and Youell, British Patent, 467,228 (June 3, 1937); *C. A.*, **31**, 7886 (1937); **33**, 2536 (1939).

(7) Zimakov and Churakov, *Org. Chem. Ind. (U. S. S. R.)*, **1**, 329 (1936); *C. A.*, **30**, 7540 (1936).

(8) Paloma, *Ber.*, **35**, 3299 (1902); **42**, 3873 (1909).

(9) Berggärdh, *Finska Kemistsam, fundet. Medd.*, **44**, 80 (1935); *C. A.*, **30**, 5559 (1936).

(10) Capinjola, THIS JOURNAL, **67**, 1615 (1945).

(11) Perry and Hibbert, *Can. J. Research*, **14B**, 77 (1936).

(12) Davidson, *Ind. Eng. Chem.*, **18**, 669 (1926).

(13) Seikel, *Ind. Eng. Chem., Anal. Ed.*, **13**, 388 (1941).

(14) Conn, Collett and Lazzell, THIS JOURNAL, **54**, 4370 (1932).

(15) Whitmore and Lieber, *Ind. Eng. Chem., Anal. Ed.*, **7**, 127 (1935).

(16) Veraguth and Diehl, THIS JOURNAL, **62**, 233 (1940).

(17) Mason and Manning, *ibid.*, **62**, 1635 (1940). This article reviews all attempts to prepare crystalline derivatives of ethylene and diethylene glycol monoethers.

(18) Manning and Mason, *ibid.*, **62**, 3136 (1940).

(19) Shupe, *J. Assoc. Official Agr. Chem.*, **24**, 936 (1941).

(20) O'Connell and Carey, THIS JOURNAL, **68**, 1865 (1946).

(21) Butler, Nelson, Renfrew and Cretcher, *ibid.*, **57**, 575 (1935).

(22) Butler, Renfrew, Cretcher and Souther, *ibid.*, **59**, 227 (1937).

(23) Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(24) Adams, U. S. Patent 2,266,141 (Dec. 16, 1942); *C. A.*, **36**, 2270 (1942).

(25) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932).

(26) Baumstark, *Ber.*, **7**, 1172 (1874).

(27) Demole, *ibid.*, **9**, 746 (1876).

(28) Henry, *Bull. soc. chim.*, **44**, 459 (1885).

(29) Swallen and Boord, THIS JOURNAL, **52**, 651 (1930).

(30) Karvonen, *Ber.*, **42**, 687 (1909).

β-iodoethyl ether was stable to solid potassium hydroxide at 150°,[26,27] to tripropylamine at 100° for one hour,[30] and was affected neither by sodium amalgam,[26,27] nor by distillation (b.p. 155°) from pulverized silver[28] or metallic sodium.[30] The halogen atom in β-iodoethyl ether therefore has the low reactivity that is a general characteristic of β-, as opposed to α-halogen substituted ethers.[29] No reference has been found to the higher members of the iodinated ethers under consideration (x, 2 or 3; R, I).

## Experimental

**Materials and Reagents.**—Technical ethylene glycol monoethyl ether was thoroughly dried over anhydrous calcium sulfate and fractionally distilled through a Vigreux column. The fraction, free from aldehydes and peroxide, boiling correctly at 134.5° and with the correct refractive index of $n^{20}D$ 1.4073, was collected.[31] A benzene solution of technical diethylene glycol monoethyl ether was selectively extracted with water, by Seikel's[13] procedure, to remove ethylene glycol. It was not found necessary to remove any residual traces of the glycol from the dried benzene solution by a subsequent selective oxidation with lead tetraacetate,[32] a reagent which, indeed, slowly oxidized the monoether. Care was taken to fractionate repeatedly until all traces of peroxide oxygen and aldehydes were absent from the product, which had the correct b. p. of 196° (760 mm.) and $n^{20}D$ 1.4273.

Technical ethylene chlorohydrin was dried over anhydrous sodium sulfate and vacuum distilled. To avoid thermal decomposition,[33] a stream of dry carbon dioxide was passed through the still to prevent bumping. The fraction collected boiled constantly at 38.5–39.0° (10 mm.) and samples had the recorded constants b. p. 128.7° (760 mm.), and $n^{15}D$ 1.4438.[34]

Ethyl *p*-toluenesulfonate, prepared by Tipson's[23] method in a crude yield of 73%, gave 49% of recrystallized material melting correctly at 33 to 34°. A similar preparation[23] gave an 83% yield of analytically pure ethylene glycol monoethyl ether *p*-toluenesulfonate, melting correctly at 18.5°. The tosyl chloride used in such preparations, together with all organic solvents, was carefully purified by standard procedures.

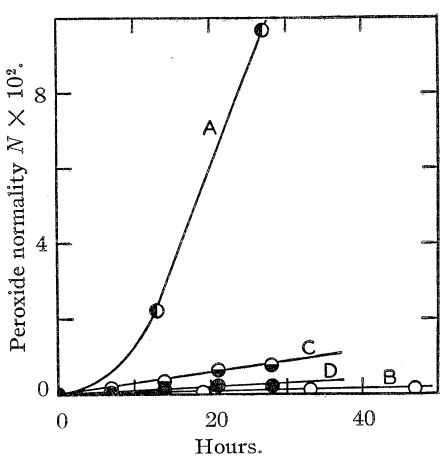



Fig. 1.—Peroxide formation: plot A, diethylene glycol monoethyl ether stored in light and air; plot B, the same in dark and nitrogen; plot C, ethylene glycol monoethyl ether in light and air; plot D, the same in dark and nitrogen.

**Analytical Methods.**—Combustion and other analyses were on the semimicro scale. Attempts were made to determine sulfur by a sodium peroxide fusion followed by a barium chloride titration with tetrahydroquinone as an internal indicator.[35] These attempts were discontinued because of difficulties with the end-point, and all sulfur analyses reported were by a standard Carius method employing barium chloride instead of silver nitrate.[36] Decomposition of the β-iodoethers by alcoholic caustic soda was quite inadequate to serve as a basis for rapid iodine estimations[37] and so the gravimetric Carius method[36] was used.

The fact that ethoxy estimations with hydriodic acid gave erratic and high results in the polyethylene oxide series[38,39,40,41] was thoroughly confirmed, but Morgan's[42] estimation for the ethylene as well as the ethyl iodide evolved from these substances was published too late for adoption in the present work.

**Peroxides and Autoxidation.**—Peroxides were detected by adding 1 cc. of the sample to 1 cc. of a 50% solution of aldehyde-free acetic acid. After shaking, a few mg. of potassium iodide was added and the mixture, together with a blank, was kept in the dark for five minutes. Even small traces of peroxide were sufficient to develop the deep color of free iodine. Quantitative estimations (Fig. 1) required a solution of potassium iodide in a glacial acetic acid–sodium bicarbonate mixture.[43] After discharging the slight yellow color of the mixture with 0.01 *N* sodium thiosulfate, better to a visual than to a starch end-point, the iodine liberated by the addition of the sample was titrated with the thiosulfate. This titration had to be carried out in stages at ten-second intervals, since the reaction was not instantaneous. With 5-cc. samples, the volume in cc. of peroxide oxygen per liter was 11.2 times the consumption of 0.01 *N* thiosulfate in cc.[44] The data were corrected for a blank which was usually 0.1 cc., and the limit of error of about 0.1 cc. corresponded to $2 \times 10^{-4}$ *N* peroxide.

Aldehydes were detected by Brady's 2,4-dinitrophenylhydrazine reagent[45] and were identified by Allen's[46] modification of the method. A red-orange 2,4-dinitrophenylhydrazone was obtained as small needles from samples of ethylene and diethylene glycol monoethyl ethers which contained peroxides. After recrystallization from glacial acetic acid or nitrobenzene, the hydrazone melted at 332° (cor.) and a mixed m. p., with authentic glyoxal-bis-2,4-dinitrophenylhydrazone (m. p. 330°[47]) was not depressed. Wieland and Wingler's work[48] was adapted for estimations of acidity caused by peroxide formation.

(31) Tallman, THIS JOURNAL, **56**, 126 (1934).

(32) Hockett and McClenahan, *ibid.*, **60**, 2061 (1938); **61**, 1667 (1939).

(33) Bozza and Gallarati, *Giorn. chim. ind. applicata*, **13**, 163 (1931).

(34) Timmermans and Martin, *J. chim. phys.*, **25**, 411 (1928).

(35) Mahoney and Mitchell, *Ind. Eng. Chem., Anal. Ed.*, **14**, 97 (1942).

(36) Niederl and Niederl, "Micromethods of Quantitative Organic Analyses," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1942.

(37) Mahoney and Purves, THIS JOURNAL, **64**, 9 (1942).

(38) Meisenheimer, *Ber.*, **41**, 1015 (1908).

(39) Grün and Bockisch, *ibid.*, **41**, 3477 (1908).

(40) Davis, Ph.D. Thesis, New York State College of Forestry, Syracuse, N. Y., 1941.

(41) Lawrie, Reynolds and Ward, *J. Soc. Dyers Colourists*, **56**, 7 (1940). These authors did not report on the reproducibility of their ethoxy estimations.

(42) Morgan, *Ind. Eng. Chem., Anal. Ed.*, **18**, 500 (1946).

(43) Liebhafsky and Sharkey, THIS JOURNAL, **62**, 190 (1940).

(44) Lindgren and Vesterberg, *Svensk Farm. Tids.*, **47**, 17 (1943); *C. A.*, **38**, 2167 (1944).

(45) Brady, *J. Chem. Soc.*, 756 (1931). See also Brady and Elsmie, *Analyst*, **51**, 77 (1926).

(46) Allen, THIS JOURNAL, **52**, 2955 (1930).

(47) Glasstone and Hickling, *J. Chem. Soc.*, 824 (1936).

(48) Wieland and Wingler, *Ann.*, **431**, 301 (1923).

**Density and Molecular Refraction.**—Standard directions[49] were followed, densities being determined in 1.0 cc. and 0.1 cc. pycnometers and refractive indices with an Abbé refractometer kept to ±0.1° of the desired temperature and re-calibrated frequently. The Lorenz and Lorentz function was used to calculate molecular refractions from observed densities and refractive indices. Molecular refractions were also calculated from a table of atomic refractivities.[49] The results are collected in Table I.

**Triethylene Glycol Monoethyl Ether (x, 3; R, OH).**—A three-necked, round-bottomed, glass-jointed flask was equipped with a capillary bubbling tube, a mechanical stirrer with mercury seal and a reflux condenser closed by a calcium chloride drying tube. After adding 175 cc. of anhydrous methanol, the air in the system was thoroughly displaced by a stream of dry, oxygen-free nitrogen introduced through the capillary below the level of the methanol. Clean sodium (16.2 g., 0.704 mole) was then added piece by piece through the condenser and, when all had dissolved, 105 g. (0.784 mole) of pure diethylene glycol monoethyl ether was introduced. Keeping a large flow of nitrogen passing through the system, the stirrer was replaced by a plug, and the reflux condenser was turned downward for distillation. The methanol was then removed by gradually increasing the bath temperature to 100° and decreasing the pressure to 20 mm. The viscous, deep red-brown residue of the sodium alcoholate of the monoether was diluted with enough of the pure monoether to bring the molar excess over the sodium to 45%, and traces of methanol were eliminated by two to three days' heating at 100° (15 mm.).

A dropping funnel was attached while nitrogen perfused the system and 63 g. (0.774 mole or 10% excess) of pure ethylene chlorohydrin was slowly added, with vigorous stirring and heating under reflux at 70 to 80° for twelve hours. No volatile matter passed through the water-cooled condenser. The contents of the reaction flask were diluted with dry ether and filtered to recover 39.7 g. (95.6%) of sodium chloride. Evaporation of the ether and fractional distillation up to 95° at 15 mm. recovered some chlorohydrin and 33.3 g. of diethylene glycol monoethyl ether; refractionation of a higher-boiling fraction gave 48 g. of the same monoethyl ether and 38 g. of a fraction of b. p. 85–90° (0.5 mm.). Careful refractionation of the latter from a 50-cc. Widmer flask left 36 g. of pure triethylene glycol monoethyl ether having b. p. 86–91° (0.5 mm.).

*Anal.* Calcd. for $C_8H_{18}O_4$: C, 53.9; H, 10.2. Found: C, 53.7; H, 10.5.

The yield was 29% based on the sodium and 48% on the unrecovered monoethyl ether. An earlier run gave a 15% yield on the sodium, and another, using a larger excess of chlorohydrin, gave none of the desired product.

**Tosylate of Diethyleneglycol Monoethyl Ether (x, 2; R, OTs).**—A freshly purified, peroxide- and aldehyde-free sample of the monoethyl ether (30 g., 0.224 mole) was tosylated in anhydrous pyridine according to Tipson's procedure.[23] Four 100-cc. volumes of chloroform were used to extract the product from the final aqueous pyridine solution, and pyridine was removed from the extract by successive washing with ice-water, dilute sulfuric acid, ice-water and sodium bicarbonate solution. The chloroform was removed from the dried extract, using a capillary bubbler and pure dry nitrogen, by warming for ten hours at 42° (23 mm.), and finally for seven hours at 42–45° (0.1 mm.). The 51.1 g. (79.2%) of slightly yellow, viscous oil was analyzed without being fractionally distilled, since distillation caused decomposition.

*Anal.* Calcd. for $C_{13}H_{20}O_5S$: C, 54.2; H, 7.0; S, 11.1. Found: C, 53.8; H, 7.1; S, 11.1.

The substance was difficult to burn, for its sudden decomposition sent a rush of gas through the train. Other preparations resulted in yields of 84, 84 and 74%.

(49) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940.

**Tosylate of Triethylene Glycol Monoethyl Ether (x, 3; R, OTs).**—Tipson's procedure,[23] employing 0.056 mole (10g.) of the pure ether, 0.067 mole of tosyl chloride and 100 cc. of dry pyridine, gave 13.1 g. or 71% of a slightly yellow viscous oil. This oil was decolorized in hot benzene solution with adsorbent charcoal and, after recovery, was somewhat low in sulfur content but was halogen-free. Chilling caused the product to separate into two oily layers, but the fraction deposited from a hot, concentrated solution of petroleum ether (b. p. 30 to 60°) remained homogeneous when cooled, and was accepted as pure.

*Anal.* Calcd. for $C_{15}H_{24}O_6S$: C, 54.2; H, 7.3; S, 9.6. Found: C, 53.8; H, 7.4; S, 9.6.

Combustion difficulties were as encountered with the lower homolog. Other preparations gave 77% yields.

**β-Iodoethyl Ethyl Ether (x, 1; R, I).**—A solution of 0.0205 mole of pure ethylene glycol monoethyl ether tosylate and 0.05 mole of dry C. P. sodium iodide in 75 cc. of pure acetone was heated at 115° for two hours in a stainless steel bomb.[25] Filtration removed the crystalline deposit of sodium *p*-toluenesulfonate, and, after recovery, the residual slightly yellow oil was repeatedly distilled from solid sodium hydroxide.[30] The pure product, b. p. 154° (754 mm.), was isolated in 81% yield.

*Anal.* Calcd. for $C_4H_9OI$: I, 63.5. Found: I, 63.5.

**β-Iodo-β′-ethoxy Diethyl Ether (x, 2; R, I).**—A solution of 0.0626 mole of pure tosylated diethylene glycol monoethyl ether and 0.187 mole of sodium iodide in 625 cc. of dry acetone was kept for sixty hours at 22 to 23°. The filtrate from the precipitated sodium *p*-toluenesulfonate was concentrated *in vacuo* at 30° to a volume of 100 cc., and 200 cc. of dry ethyl ether was then added to precipitate residual sodium iodide. The ethereal solution and washings were extracted with 100 cc. of aqueous sodium thiosulfate to remove some free iodine, and after two extractions with ice-water were dried over anhydrous potassium carbonate. Removal of the ether, finally at 30° (0.06 mm.), and fractional distillation of the residue resulted in an 88% yield of a colorless oil, b. p. 42° (0.4 mm.).

*Anal.* Calcd. for $C_6H_{12}O_2I$: C, 29.5; H, 5.4; I, 52.0. Found: C, 29.8; H, 5.6; I, 51.5.

The pure substance was stable enough to undergo no change beyond slight discoloration when stored in a cool dark place for five months.

**β-Iodo-β′-ethoxyethoxy Diethyl Ether (x, 3; R, I).**—A solution of the corresponding pure tosylate, 0.042 mole, and sodium iodide, 0.141 mole, in 625 cc. of acetone was kept for five days at 20 to 25°. After recovering 96.7% of the theoretical amount of sodium *p*-toluenesulfonate, the product was isolated from the mother liquors as just described for the lower homolog. Distillation of the crude red oil gave a 73% yield of a clear, very slightly yellow oil, b.p. 97 to 98° (0.15 mm.).

*Anal.* Calcd. for $C_8H_{17}O_3I$: C, 33.3; H, 6.0; I, 44.1. Found: C, 33.4; H, 6.0; I, 44.0.

**Thermal Decomposition of Higher Tosylates.**—(a) Tosylated Diethylene Glycol Monoethyl Ether: The pure ester (22.6 g., 0.0786 mole) was slowly heated up to 160° in a 50-cc. distilling flask filled with glass wool and evacuated to 0.13 mm. pressure. The side arm of the flask was connected to another, which served as an air-cooled receiver, and then to a trap cooled in chloroform–Dry Ice. Slow, even distillation took place at 125° (0.13 mm.) with no increase in pressure, and some of the distillate kept solidifying at the entrance to the Dry Ice trap. The air-cooled receiver eventually contained 15.33 g. (97.4%) of a slightly yellow, slightly acid oil whose m. p. of 30 to 33° was increased to m. p. 34 to 35° by recrystallization from petroleum ether. The elementary composition, the refractive index of $n^{40}D$ 1.5050, and the m. p. were those of ethyl *p*-toluenesulfonate and a mixed m. p. with an authentic sample was not depressed.

A clear colorless solid, 6.65 g. (97%), b. p. 100°, m. p. 6 to 9°, $n^{25}D$, 1.4190, collected in the Dry Ice trap, was

slightly impure 1,4-dioxane, which when pure has the constants $n^{25}D$ 1.4198 and m. p. 11.8°.[50a] This conclusion was confirmed by the preparation of the crystalline bromine addition compound with the proper m. p. 65 to 66°, undepressed by admixture with an authentic specimen.

(b) Tosylated Triethylene Glycol Monoethyl Ether: The pure ester (3.6 g., 0.011 mole) was heated at 0.03 mm. pressure in equipment as described in (a), but made from 10-cc. flasks. Even, smooth distillation occurred at 133 to 135° with no increase in pressure. The air-cooled receiver contained 2.03 g. (76.6%) of a slightly yellow, slightly acidic oil, $n^{25}D$ 1.5010, which after recrystallization melted at 18 to 19° and had $n^{25}D$ 1.5030. These were the constants of pure tosylated ethylene glycol monoethyl ether and a mixed m. p. was not depressed.

The Dry Ice trap contained 0.94 g. of a slightly unsaturated liquid that on distillation yielded 0.6 g. (62.8%) of nearly pure 1,4-dioxane with the constants b. p. 100°, $n^{25}D$ 1.4190, m. p. 8 to 10°. The identity was confirmed by preparing the orange-yellow bromine addition compound, m. p. 65 to 66°.

**Rate of Solvolysis of the Tosylates.**—In all cases 0.0015 mole of the tosylate was washed with anhydrous methanol into a 250-cc. volumetric flask to which 25 cc. of water was added. After being made up to the mark with anhydrous methanol at 25°, the solution was transferred to a 500-cc. flask equipped with a water-cooled reflux condenser and drying tube. Samples removed after various periods of heating at 65 ± 1° were rapidly cooled to 25° and 10-cc. aliquots were titrated with 0.1 *N* sodium hydroxide, using a microburet. Since the molar ratio of water to tosylate was 1.557 to 0.0015, the amount of water remained practically constant and the solvolysis was assumed to follow a first order rate course given by $kt = 2.303 \log a/(a - x)$, where $a$ was the initial concentration of tosyl ester and $(a - x)$ the concentration remaining after any time $t$. The quantity $(a - x)$ was readily calculated from the titrations. Table II and Fig. 2 summarize the results.

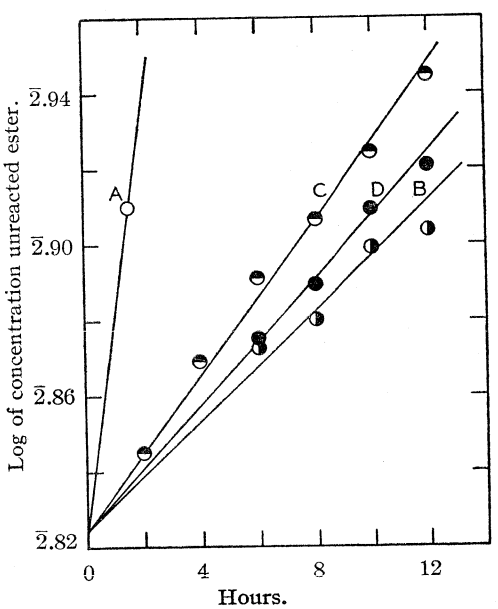



Fig. 2.—First order solvolyses of various *p*-toluenesulfonates in excess 90% aqueous methanol at 65°: plot A, ethyl; plot B, β-ethoxy ethyl; plot C, 2-(β-ethoxyethoxy)-ethyl; plot D, 2-(β-ethoxyethoxyethoxy)-ethyl *p*-toluenesulfonate.

(50) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1st ed., 1941 (a) p. 457; (b) p. 428.

**Rate of Iodination of the Tosylates.**—The tosyl ester, 0.0025 mole, and 0.0075 mole of dry, C. P. sodium iodide were completely dissolved in exactly 25 cc. of pure acetonylacetone by shaking the mixture for about five minutes in a 50-cc. glass-stoppered flask. The refractive index of the solution was promptly noted on an Abbe refractometer. The solution was then kept in the dark at 22 ± 0.5° and at intervals of two hours samples were removed by a capillary pipet and transferred directly into the refractometer for measurement. This technique was possible because the sodium *p*-toluenesulfonate separated as large crystals that settled readily. When the change in refractive index became slow, the solution was kept at 100° under a reflux condenser for two hours in order to complete the iodination. After making the final measurement at 22°, the sodium salt was recovered, washed, dried and weighed as a check on the completeness of the reaction. The recovery was 95.4 to 99.4%.

In order to calculate rate of iodination constants, the assumption was made that the refractive index varied linearly with the replacement of tosyloxy groups by iodine atoms. The moles of tosylate, $x$, converted at any time $t$ was then given by the change in refractive index at that time divided by the over-all change observed after the iodination was complete. This over-all decrease varied from $n^{22}D$ 0.0033 to $n^{22}D$ 0.0040 with different tosylates. If $a$ was the initial concentration of tosyl ester, 0.1 mole per liter, and $b$ that of sodium iodide, 0.3 mole per liter, the rate of iodination was given by the second order relation

$$k_2t = \frac{2.303}{(a - b)} \log \frac{b}{a} \frac{(a - x)}{(b - x)}$$

The results are summarized in Table II and Fig. 3, the former of which includes runs with tosylated ethanol and ethylene glycol monoethyl ether in which $a = b = 0.15$ mole per liter. In these cases the rate equation reduced to $k_2t = x/a(a - x)$.

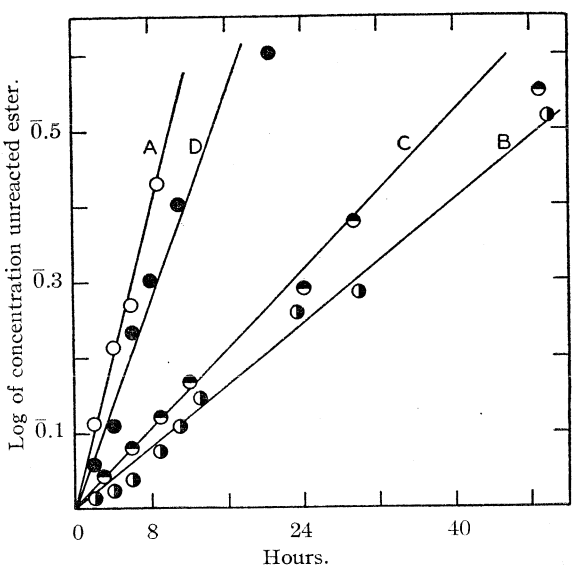



Fig. 3.—Second order iodination of various *p*-toluenesulfonates with sodium iodide in acetonylacetone at 22°: plot A, ethyl; plot B, β-ethoxy ethyl; plot C, 2-(β-ethoxyethoxy)-ethyl; plot D, 2-(β-ethoxyethoxyethoxy)-ethyl *p*-toluenesulfonate.

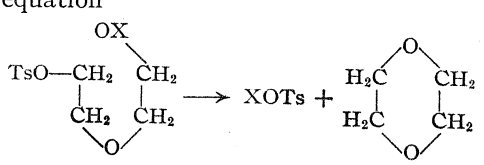
## Results and Discussion

The monoethyl ethers of both ethylene glycol and diethylene glycol readily formed peroxides and acidic products, the peroxide oxygen or acidic normalities sometimes exceeding 0.2 *N*

after storage in diffuse daylight and over a drying agent for prolonged periods. Storage even for one or two weeks was quite capable of producing peroxide oxygen normalities of the order of 0.04 *N* without causing a significant change in refractive index, a correct value of which was in consequence no decisive test of purity. Since both monoethyl ethers were practically odorless when quite pure,[12] the "fruity" odor they usually possess was tentatively attributed to aldehydes and other contaminants resulting from autoxidation.

The experiment summarized in Fig. 1, plots A and C, showed that very carefully purified diethylene glycol monoethyl ether greatly exceeded its lower homolog in ability to accumulate peroxide when kept in Erlenmeyer flasks exposed to diffuse daylight. Plots D and B record the great decrease in peroxide formation observed when aliquots of the same pure samples were stored under nitrogen in dark, glass-stoppered bottles. This result was to be expected, but for unknown reasons the monoethyl ether of triethylene glycol in all conditions tried gave negative tests for peroxide. Peroxide-containing ethylene glycol monoethyl ether yielded the crystalline bis-2,4-dinitrophenylhydrazone of glyoxal, which no doubt arose from glycolic aldehyde. Aldehydes are known to be primary decomposition products of peroxides[48,51] and, indeed, Milas[52] clearly showed that glycolic aldehyde was formed in the autoxidation of 1,4-dioxane. The same dinitrophenylhydrazone was isolated from peroxide-containing diethylene glycol monoethyl ether but failure to detect ethoxyacetaldehyde or hydroxyethoxyacetaldehyde, $HO-CH_2-CH_2-O-CH_2-CHO$, either as such or as dinitrophenylhydrazones, suggested that in this monoether both ether oxygen atoms acted as centers for peroxide formation. Ethoxy groups presumably produced acetic acid, since no acetaldehyde could be detected.

It was observed that tosylated diethylene glycol monoethyl ether appeared to distil smoothly at 125° (0.13 mm.), but the distillate consisted of 1,4-dioxane and ethyl *p*-toluenesulfonate, each recovered in 97% yield. The tosyl ester of triethylene glycol monoethyl ether decomposed similarly at 134° (0.03 mm.) to 1,4-dioxane (63%) and the crystalline tosylated monoether of ethylene glycol (76%), together with a somewhat unsaturated, acidic mixture that was not further examined. In both cases, therefore, the dominant reaction was a thermal cleavage represented by the equation




Structure I

in which X is $C_2H_5$ or $C_2H_5O-CH_2-CH_2-$. Ethyl *p*-toluenesulfonate and tosylated ethylene glycol monoethyl ether were stable to the cracking temperature, in accord with Tipson's observation that both could be purified by distillation under diminished pressure.[23] The thermal breakdown of the higher tosylates to 1,4-dioxane was not inconsistent with the fact that β,β'-dichloroethyl ether, when heated with aqueous caustic soda at 200°, yielded principally 1,4-dioxane and β-chloroethyl vinyl ether, rather than the divinyl derivative expected.[53] Cretcher and his coworkers[22] found that decomposition occurred during the high vacuum distillation of the tosylated monochlorohydrin of diethylene glycol; corresponding diethers yielded low-boiling fractions on distillation,[54] and only 30 to 40% of the original diether. Gallaugher and Hibbert[55c] noted that polyethylene glycols and their derivatives gave volatile, sweet-smelling distillates, sometimes at very low temperatures, and that the monochlorohydrin of tetraethylene glycol decomposed at 140°.

Such observations suggested that the OTs and X groups in Structure I might be replaceable in certain cases by hydroxyl, alkoxyl, halogen or similar units without abolishing the tendency of the polyethylene oxide chain to yield dioxane when heated. Anomalous physical properties, indeed, led to the inference[55b] that an intramolecular attraction existing between the hydroxyl groups of diethylene glycol maintained the molecule in a conformation approximating that of 1,4-dioxane. A more usual mode of decomposition was revealed in a recent careful study,[56] which showed that monoethers of ethylene and diethylene glycols were partially interconvertible when heated at 105 to 130° in presence of 1.5% sulfuric acid.

Although diethylene glycol readily yielded a white, crystalline monosodium salt when treated with metallic sodium or sodium methylate,[11] the monoethyl ether of the same glycol decomposed in part to very dark red-brown viscous materials under similar circumstances. Condensation of the resulting crude mixture with ethylene chlorohydrin gave the monoethyl ether of triethylene glycol in a yield whose small amount might possibly be attributed in part to thermal decomposition during the fractional distillation. The preparation of the corresponding tosylate was uneventful, but the thermal instability of this compound, and also of tosylated diethylene glycol monoethyl ether, made it prudent to conduct the double decompositions with sodium iodide near 23°,[57] instead of at the more usual temperature of

(51) Clover, THIS JOURNAL, **44**, 1107 (1922).
(52) Milas, *ibid.*, **53**, 221 (1931).
(53) Cretcher, Koch and Pittenger, *ibid.*, **47**, 1173 (1925).
(54) Liston and Dehn, *ibid.*, **60**, 1264 (1938).
(55) Gallaugher and Hibbert, *ibid.*, (a) **58**, 813 (1936); (b) **59**, 2514; (c) **59**, 2521 (1937).
(56) Dolgopolev, Melnikow and Nametkin, *J. Applied Chem.* (*U. S. S. R.*), **20**, 486 (1947).
(57) Tipson, Clapp and Cretcher, *J. Org. Chem.*, **12**, 133 (1947), also used room temperature when iodinating the *p*-toluenesulfonates of ethanol, glycol and other alcohols with sodium iodide in acetone.

100 to 110°. The resulting β-iodoethers, like other members of the class,[28,29,58] were quite stable when distilled.

TABLE I

DENSITIES, SPECIFIC AND MOLECULAR REFRACTIONS OF SERIES $C_2H_5(OCH_2CH_2)_xR$

| Series | Refractive index $n_D$ | °C. | $d^a$ | Molecular refraction Obs. | Calcd.[b] | Diff. |
|---|---|---|---|---|---|---|
| **Alcohols, R = OH** | | | | | | |
| $x = 0$ | 1.3610 | 20 | 0.7894[d] | 12.92 | 12.96 | −0.04 |
| 1 | 1.4074 | 20 | .9297[d] | 23.88 | 23.84 | +0.04 |
| 2 | 1.4273 | 20 | | | | |
| | 1.4254 | 25 | .9855 | 34.88 | 34.72 | +0.16 |
| 3 | 1.4380 | 20 | 1.0211[d] | 45.78 | 45.60 | +0.18 |
| **Tosylates, R = OTs** | | | | | | |
| $x = 0$ | 1.5067 | 35 | | | | |
| | 1.5050 | 40 | 1.1637[h] | 51.04 | 40.16[j] | 10.88[k] |
| 1 | 1.5032[f] | 25 | 1.1677 | 61.79 | 51.04[j] | 10.75[k] |
| | 1.5000 | 35 | | | | |
| | 1.4981 | 40 | | | | |
| 2 | 1.4976 | 25 | 1.1599 | 72.80 | 61.92[j] | 10.88[k] |
| 3 | 1.4959 | 25 | 1.1698 | 82.99 | 72.80[j] | 10.17[k] |
| **Iodides, R = I** | | | | | | |
| $x = 0$ | 1.5133 | 18.5 | 1.930[m] | 24.30 | 24.24 | +0.06 |
| 1[n] | 1.4996 | 15 | 1.6698[o] | 35.21 | 35.12 | +0.09 |
| | 1.4965 | 20 | | | | |
| 2 | 1.4908 | 20 | | | | |
| | 1.4881 | 25 | 1.5210 | 46.24 | 45.99 | +0.25 |
| 3 | 1.4889 | 20 | | | | |
| | 1.4870 | 25 | 1.4557 | 56.93 | 56.87 | +0.06 |

[a] Densities at 25–25° unless otherwise mentioned. [b] From tables of atomic refractivity, ref. 49. [c] Ref. 50 b. [d] At 20°/20°. [e] Ref. 31. [f] Ref. 13. [g] Davidson's value of $n^{26}D$ 1.4389 (ref. 12) was high, probably because of contamination with diethylene glycol, $n^{20}D$ 1.4475. [h] At 40°/40°. [i] Contribution of $-O-SO_2$ group omitted. [k] Contribution of $-O-SO_2$ group. [l] Tipson (ref. 23) found $n^{25}D$ 1.5026. [m] At 18.5°/4°. Quoted from Beilstein. [n] Ref. 30. [o] At 15°/4°.

Table I, column 5, records the molar refractions of compounds rigorously purified for the first time during this research, together with relevant data from the literature. The fact that values in the ethylene glycol monoethyl ether and in the β-iodoether series agreed closely with those calculated from a table of atomic refractivities (column 6) argued for the purity of the samples examined. In the first and second of these series the average increments occasioned by addition of an ethylene oxide unit were 10.95 and 10.88, respectively, in good agreement with the theoretical value of 10.88.[59] Since the observed increments in the tosylates, $10.98 \pm 0.21$, were also in good agreement, it followed that the tosylates were probably pure and that the presence of the sulfonic group occasioned no marked change in the molecular refraction of the remaining atoms. Column 7, giving the difference between the calculated molecular refraction of these atoms and that observed for the tosylate, therefore represents the molecular refraction of the $O-SO_2$ group. The result, $10.53 \pm 0.35$, was somewhat higher than the molecular refraction of $9.7 \pm 0.2$ found for the $O-SO_2$ group in several esters of ethylene sulfonic acid,[60] perhaps because of different amounts of optical exaltation.

Inspection of column 2, Table I, reveals that specific refractive indices in the series R–OH increased with $x$ but that the increment decreased. This tendency was true of the polyethylene glycol series[55a] and was included in a generalization about specific refraction by Smiles.[61] The values for tosylated and iodinated derivatives in Table I, however, decreased as each series was ascended and were in opposition to the generalization. Conn and his co-workers,[14] on the other hand, found no regular trend in refractive index in passing from the benzoates and *p*-nitrobenzoates of a number of ethylene glycol monoethers to the corresponding diethylene glycol derivatives. It is probable that in this and in much other work in the polyoxyethylene series,[14,18,62] the accuracy of the recorded physical constants was often impaired by the presence of impurities originating in autoxidation, incomplete fractional distillation or in thermal cracking.

Figures 2 and 3 record the relative rates of solvolysis of the tosylates in a large excess of aqueous methanol (1:9) at 65°, and their relative reactivities toward sodium iodide. The solvolyses followed a first order course and all the observations fell, within the experimental error, on the lines shown in Fig. 2. This error reflected the uncertainty of ±0.05 cc. in the titrations of acidity, and corresponded to 14 to 8% in the log $(a-x)$ values for solvolysis up to 10% completion. Between 10 and 20% completion the errors in log $(a-x)$ were 8 to 4%, being least for the fastest reaction. Iodinations (Fig. 3) were carried out with sodium iodide in acetonylacetone and the progress of the reaction was followed by the change in refractive index of the solution. Since the error in the refractometer readings was about $\pm 10^{-4}$, the extent of iodination was in serious doubt in the initial stages, and by 5 to 7.5% in the later stages of the reactions. Within these limits all observations fell upon straight lines passing through the origin, when second order kinetics were assumed,[63] but did not define the slope of the lines within 15%. Second order kinetics also applied to the reaction of ethyl *p*-toluenesulfonate, and other substituted benzene sulfonates, with sodium ethylate in absolute ethanol.[64]

The rate constants (Table II) refer only to the over-all kinetics of solvolysis and iodination since actual reaction mechanisms and possible side-reactions were not determined. Ethyl *p*-

(58) Cretcher and Pittenger, THIS JOURNAL, **47**, 163 (1925).

(59) Zimakov, *J. Phys. Chem.* (*U. S. S. R.*), **21**, 913 (1947), decided that the possession of the same molecular refraction by ethylene oxide itself could be attributed to a chance cancellation of theoretical errors.

(60) Whitmore and Landau, THIS JOURNAL, **68**, 1797 (1946).

(61) Smiles, "Relations between Physical Properties and Chemical Constitution," Longmans, Green and Co., London, 1910, p. 267.

(62) McKinley and Nibarger, THIS JOURNAL, **61**, 373 (1939).

(63) McCleary and Hammett, *ibid.*, **63**, 2254 (1941).

(64) Morgan and Cretcher, *ibid.*, **70**, 375 (1948).

TABLE II

APPROXIMATE RATE CONSTANTS FOR SOLVOLYSIS AND IODINATION OF THE TOSYLATES

| Tolsylate $C_2H_5(OCH_2CH_2)_xOTs$ | Solvolysis $k_1$[a] | Iodination $k_2$[b] | Iodination $k_2$[c] |
|---|---|---|---|
| x = 0 | 0.124 | 0.56 | 0.66 |
| 1 | .017 | .12 | .06 |
| 2 | .023 | .15 | |
| 3 | .019 | .36 | |

[a] In aqueous methanol (1:9) at 65 ± 1°; first order; unit, hours$^{-1}$. [b] With 0.1 mole of tosylate and 0.3 mole of iodide per liter at 22 ± 0.5°; second order; units, liters, moles$^{-1}$, hours$^{-1}$. [c] With 0.15 mole per liter both of tosylate and of iodide.

toluenesulfonate ($x = 0$) obviously was most reactive, as might have been expected from the known depressing effect of a β-ether group on the reactivity of organic halides, and from the similarity between halides and sulfonates.[57] Tosylated ethylene glycol, for example, hydrolyzed twelve times more slowly than tosylated ethanol.[65] The differences between the solvolysis rate constants for the higher tosylates ($x = 1$, 2 and 3, Table II) probably fell within the experimental error, and the same remark was true of the iodination rate constants for the tosylates with $x = 1$ and 2. The results in general suggest that the tosylation–iodination reaction as applied to cellulose acetates and ethers is valid for research on hydroxyethylcelluloses.

**Acknowledgment.**—The authors greatly appreciate the interest that Dr. R. T. K. Cornwell, of the Sylvania Division, American Viscose Corporation (formerly Sylvania Industrial Corporation), showed in the research. One of us (C. W. T.) also wishes to thank the same organization for the Fellowship, and the Canadian Pulp and Paper Association for the summer stipend, awarded to him for the period of the work (1945–1946).

(65) Foster and Hammett, THIS JOURNAL, **68**, 1736 (1946).

## Summary

1. The following compounds were obtained pure: triethylene glycol monoethyl ether, its *p*-toluenesulfonate, the *p*-toluenesulfonate of diethylene glycol monoethyl ether, β-ethoxyethoxy-β′-iododiethyl ether and β-ethoxy-β′-iododiethyl ether. A new preparation of β-iodoethyl ether was described.

2. Diethylene glycol monoethyl ether was particularly liable to peroxide formation, was partly decomposed by sodium methylate, and yielded a tosylate decomposing at 125° (0.13 mm.) to equimolar amounts of 1,4-dioxane and ethyl *p*-toluenesulfonate. The latter product was replaced by tosylated ethylene glycol monoethyl ether when tosylated triethylene glycol monoethyl ether was thermally decomposed at 134° (0.03 mm.). Ethyl *p*-toluenesulfonate was more reactive toward solvolysis in 90% methanol, and toward iodination with sodium iodide in acetonylacetone, than the higher tosylates.

3. Data for the molar refractivities of the above series of compounds were completed, and the molar refraction of the O–$SO_2$ group in *p*-toluenesulfonates was found to be 10.5 ± 0.35.

MONTREAL, CANADA RECEIVED AUGUST 3, 1948

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

# *p*-Toluenesulfonyl Chloro and Iodo Derivatives of an Alkali-Soluble Hydroxyethylcellulose[1]

BY CLINTON W. TASKER AND C. B. PURVES[2]

Hydroxyethyl ethers of cellulose were first described by Hubert[3] in 1920, but excited no general interest until 1933, when the publications of Shorygin and Rymaschewskaja[4] commenced. These articles, together with those of Sönnerskog,[5] and Schorger and Shoemaker,[6] and also the relevant patents[7–19] showed that hydroxyethyl-

(1) Presented at the Chicago meeting of the American Chemical Society, April, 1948. Abstracted from a Thesis presented to the Faculty of McGill University in June 1947, by C. W. Tasker in partial fulfilment of the requirements for the Ph.D. degree.

(2) At above address.

(3) Hubert, *J. Soc. Chem. Ind.*, **42**, 348A (1923); German Patent 363,192 (1920).

(4) Shorygin and Rymaschewskaja, (a) *Ber.*, **66**, 1014 (1933); (b) *J. Gen. Chem.* (*U. S. S. R.*), **7**, 2428 (1937); (c) *ibid.*, **8**, 1903 (1938).

(5) Sönnerskog, *Svensk. Papperstidn.*, (a) **48**, 413 (1945); (b) **49**, 409 (1946).

(6) Schorger and Shoemaker, *Ind. Eng. Chem.*, **29**, 114 (1937).

(7) Schorger, U. S. Patent (a) 1,863,208 (June 14, 1932); (b) 1,914,172 (June 13, 1933); (c) 1,941,277; (d) 1,941,278 (Dec. 26, 1933).

(8) Powers, Bock and Houk, U. S. Patent 2,087,549 (July 20, 1937).

(9) Berger and Bidaud, U. S. Patent 2,047,189 (July 14, 1936).

(10) Ellis, British Patent 408,730 (April 19, 1934).

(11) Seymour and Salvin, U. S. Patent 2,134,895 (Nov. 1, 1938).

(12) I. G. Farbenindustrie Aktiengesellschaft, British Patent (a) 383,612 (Feb. 12); (b) 383,617 (Feb. 13, 1931).

(13) Lilienfeld, U. S. Patent (a) 1,589,606 (June 22, 1926); (b) 1,722,927 (July 30, 1929); (c) 2,265,919 (Dec. 9, 1941).

(14) Richter, U. S. Patent 2,054,299 (Sept. 15, 1936).

(15) Broderick, U. S. Patent (a) 2,173,470; (b) 2,173,471 (Sept. 19, 1939).

(16) Thomas and Oxley, British Patent 463,317 (March 23, 1937).

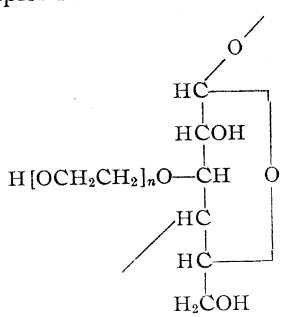
(17) Levesley and Craik, U. S. Patent 2,046,174 (June 30, 1936).

(18) Oxley, Thomas and Downing, U. S. Patent 2,184,564 (Dec. 26, 1939).

(19) Dreyfus, (a) U. S. Patent 1,502,379 (July 22, 1924); (b) British Patent 478,259 (Jan. 17, 1938).

celluloses were obtained by condensing cellulose, either aged or pretreated or not, with ethylene chlorohydrin in the presence of alkali,[6,7,13b,18,19a] or with ethylene oxide, usually in the presence of caustic soda or a wide variety of other inorganic bases and salts.[7,10,15,19b] Control over the experimental conditions and the relative amounts of the reactants made it possible to prepare substantially similar products either by the chlorohydrin or the ethylene oxide route.[7] Hydroxyethylcelluloses thought to average substantially less than one hydroxyethyl group per glucose unit[7] were usually soluble in cold 10% caustic soda, while solubility in weaker alkali and in water increased as the substitution increased from more than unity to three. Acetates,[4a] benzoates,[6,7,20] stearates, xanthates[6] and mixed methyl and ethyl ethers[5,6] were prepared, but Sönnerskog[5] could not correlate their properties accurately with the degree or the uniformity of substitution.

The existence of hydroxyethylcelluloses averaging four,[21] or even six[22] substituent groups per glucose residue made it clear that some of the substitution occurred at previously formed hydroxyethyl groups rather than at the free hydroxyl groups of the cellulose itself. It followed that such products contained structures of type I in which $n$ was an integer greater than unity, although simpler structures with $n$ equal to unity



I, $n$ an integer

were not excluded. With the possible exception of preparations made from cellulose dissolved in a quaternary ammonium base,[23] hydroxyethylcelluloses resulted from condensations between cellulose and ethylene oxide carried out in heterogeneous, or at best in quasihomogeneous, systems. Even samples of low average hydroxyethyl content might therefore contain local substitutions so high that units of type I, $n > 1$ might be present. Type I, $n > 1$ would also result, even in a homogeneous system, if ethylene oxide condensed preferentially with hydroxyethyl units. Consideration of structure I also shows that substitution in the sixth position of a glucose residue in cellulose failed to alter the number of primary alcohol groups from the original value of unity. Substitution in the second or third positions, however, replaced a secondary alcohol by the primary hydroxyethyl unit. If the total number of primary hydroxyl groups was $1 + x$ per glucose residue, it followed that the number of hydroxyethyl groups attached to secondary positions was $x$, or an integral multiple thereof. One of the objects of the present research was to determine the value of $x$.

The preceding article[24] showed that the primary hydroxyl groups in the series $C_2H_5[OCH_2CH_2]_nOH$ were esterified at the normal rapid rate by excess *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine. Although the resulting tosylates hydrolyzed with some rapidity and the higher members ($n$, 2 and 3) underwent quantitative decomposition during distillation *in vacuo*, all reacted normally with sodium iodide in acetonylacetone and yielded the corresponding β-halogen ethers. These experiments have now been extended to a commercial, alkali-soluble hydroxyethyl ether of cellulose of average substitution 0.44 and the molar amount of halogen in the final products has been assumed to be a measure of the moles of primary alcohol in the starting material. Although this method sharply differentiated unsubstituted primary from secondary hydroxyl groups in certain partly substituted glucose[25] and cellulose[26,27] derivatives, Malm and his collaborators[28] lately showed that with drastic conditions of halogenation, or with highly tosylated celluloses, the replacement extended to some secondary alcohol positions. The method has therefore to be used with discretion.

The hydroxyethyl content of hydroxyethylcelluloses has in the past been estimated from the gain in weight caused by the addition of ethylene oxide, and from the increase in carbon content,[20,22] but both methods are insensitive to appreciable changes in the substitution. Use was also made of the standard alkoxy estimation[20] because the hydroxyethyl group evolved ethyl iodide when heated with hydriodic acid. The recognition in 1946 by Morgan,[21] that ethylene was also evolved in this reaction and had to be included in the estimation, made it possible for him to devise the first reliable determination for the hydroxyethyl group. This valuable advance rendered the present work feasible.

## Experimental

**Materials and Analytical Methods.**—The commercial hydroxyethylcellulose (Ceglin E. S. type H,[29] moisture 5.9%; ash 0.12%; substitution 0.443) consisted of white flocks that were freely soluble in cold caustic soda, that swelled in water, but were only incompletely gelatinized by prolonged steeping in pyridine.

After being ground in a Wiley mill to pass a 60-mesh

(20) Nikitin and Rudneva, *J. Applied Chem.* (*U. S. S. R.*), **8**, 1023 (1935).

(21) Morgan, *Ind. Eng. Chem., Anal. Ed.*, **18**, 500 (1946).

(22) Davis, Ph.D. Thesis, New York State College of Forestry, Syracuse, N. Y. (1941).

(23) Bock, *Ind. Eng. Chem.*, **29**, 985 (1937).

(24) Tasker and Purves, THIS JOURNAL, **71**, 1017 (1949).

(25) Oldham and Rutherford, *ibid.*, **54**, 366 (1932).

(26) Mahoney and Purves, *ibid.*, **64**, 9, 15 (1942).

(27) Gardner and Purves, *ibid.*, **64**, 1539 (1942).

(28) Malm, Tanghe and Laird, *ibid.*, **70**, 2740 (1948).

(29) The authors thank Dr. R. T. K. Cornwell and the Sylvania Division, American Viscose Corporation, for donating this material.

sieve, the material was carefully tested for peroxide oxygen by the ferrous–cyanate,[30] the benzidine–copper sulfate[31] and the acetic acid–potassium iodide[32] procedures, with uniformly negative results. Indeed, in the latter method the samples often failed to liberate the minute amount of iodine found in the blanks. Oxidations with 0.03 *M* iodine in a borate buffer at *p*H 9.2 and 25°, as recommended for the estimation of aldehyde groups in celluloses[33] revealed consumptions equivalent to 0.66, 1.31, 1.97 and 2.46 cc. of 0.1 *N* iodine per gram sample (iodine no.) after six, twelve, eighteen and twenty-four hours. The hydroxyethyl ether group was intrinsically unstable to hypoiodite because an iodine number greater than 4 was recorded for highly purified ethylene glycol monoethyl ether after twenty-four hours.

The sulfur and halogen analyses were by the semi-micro Carius method, with 20 to 30 mg. samples and 0.5 cc. of nitric acid. Over ninety consecutive analyses were made in this way without incident, but when the stated amount of nitric acid was exceeded, explosion of the glass Carius tube almost always resulted. Morgan's modified alkoxyl method[21] was used for all estimations of the ethylene oxide (hydroxyethyl) group, using 20 cc. of freshly distilled hydriodic acid for each 0.2 to 0.4 g. sample. If the sample contained a, b, c, and d moles of hydroxyethyl, tosyl, chlorine and iodine, respectively, per glucose unit, the base molecular weight, *Z*, was $162.14 + 44.04a + 154b + 18.5c + 110d$. The individual substitutions were found by solving the simultaneous equations, % $OCH_2CH_2$ = $4404\ a/Z$; % S = $3206\ b/Z$, % Cl = $3550\ c/Z$; and % I = $1274\ d/Z$. Either *b*, *c*, or *d*, of course, was often known to be zero. All percentages used in these calculations were the average of closely concordant duplicate or triplicate analyses.

All reagents and solvents were carefully purified as previously described,[24] and all equipment was connected through ground glass joints.

**Tosylation of the Hydroxyethylcellulose.**—The sample, 14.88 g. air dry or 14.0 g. oven dry, corresponded to 0.077 mole containing 0.231 mole of free hydroxyl groups. After being dissolved in 350 g. of 5% sodium hydroxide by stirring under nitrogen at −10°, the hydroxyethylcellulose was reprecipitated in ribbons and pellets of highly swollen gel by pouring the solution into 1.5 liters of gently stirred 50% aqueous acetic acid. After complete coagulation had taken place it was possible to stir the mixture vigorously for twenty minutes without producing a system so dispersed that easy separation was impossible. The gel was recovered and washed in a well-laundered muslin bag until the effluent had the same *p*H (5.7) as the water used. The weight of the dry bag before and after use showed no significant change. The gel was then transferred to a tared 2-liter flask and the water it contained was eliminated by the continous addition and evaporation of dry pyridine into a vacuum so regulated that the bath temperature never exceeded 60°. Distillation was stopped when the distillate had regained the refractive index, $n^{20}D$, 1.5090, of pure dry pyridine and was miscible without turbidity with petroleum ether. The resulting transparent hydroxyethylcellulose–pyridine gel was cooled to 5°, and 274.1 g. (1.44 moles) of tosyl chloride, dissolved in enough cold pyridine to give a total weight of 1540 g. (19.46 moles) of pyridine, was added. Thereafter the tightly stoppered flask was kept at 25 ± 0.1° and was periodically shaken vigorously by hand. All gel particles disappeared after about twelve hours and for a few hours subsequently the system appeared homogeneous, but after fifteen to twenty-one hours separated into a highly swollen gel and a slightly yellow supernatant liquid phase.

In contrast to the earlier state, it was possible, from twenty-one hours onward, to disperse the gel uniformly by shaking and to withdraw representative aliquots of 100 to 150 cc. at various times. Each of these aliquots was slowly poured into 1.5 liters of chilled, rapidly stirred water, and the fibrous tosylate that precipitated was washed by decantation with 500 cc. of water, recovered quantitatively on a sintered glass funnel, and washed thoroughly until free from chlorine ions and pyridine. The fibers from the earlier aliquots were white, but those isolated from the later red-brown aliquots were tan in color. They were dried through methanol and ether and finally *in vacuo* over phosphorus pentoxide for at least two days at room temperature prior to analysis. Since reliable aliquots could not be obtained from the tosylation mixture prior to about twenty-one hours, separate 2-g. samples (dry weight) of the original hydroxyethylcellulose were precipitated from caustic soda, exchanged into pyridine and tosylated for varying brief times exactly as described, but using one-seventh quantities of reagents. Precipitation of each entire tosylation mixture into 2.5 liters of cold water yielded hard white pellets gradually giving place to white fibers as the time of tosylation increased. The percentage analyses of these products, isolated exactly as described, are included in Table I, the corresponding substitutions being in Figs. 1 and 2.

TABLE I

ANALYSES OF HYDROXYETHYLCELLULOSE TOSYLATED FOR INCREASING TIMES

| Tosylation,[a] hours[b] | S, % | Cl, % | $CH_2CH_2O$, % | Yield,[d] % |
|---|---|---|---|---|
| 0 | 0 | 0 | 10.76 | |
| 1 | 9.21 | Trace | | 95.3 |
| 3 | 10.68 | 0.14 | | 93.8 |
| 5 | 10.90 | 0.11 | 4.18 | 91.7 |
| 7 | 10.92 | 0.26 | | 94.4 |
| 9 | 11.02 | 0.33 | | 92.3 |
| 12 | 10.95 | 0.43 | | 95.1 |
| 21.5 | 11.68 | 0.70 | 2.93 | |
| Days[c] | | | | |
| 2 | 11.94 | 1.14 | 2.00 | |
| 3 | 11.95 | 1.38 | | |
| 5 | 12.02 | 1.83 | | |
| 8 | 12.17 | 2.38 | | |
| 12 | 11.88 | 2.87 | | |
| 20 | 11.84 | 3.65 | 1.57 | |
| 40 | 11.64 | 4.52 | 1.49 | |

[a] With excess tosyl chloride in pyridine at 25°. [b] Individual runs. [c] Aliquots from one large run. [d] Corrected for substitutions.

**Partial Replacement of Tosyloxy Group by Chlorine.**—A 1.2 g. (0.003 mole) sample of the product from twenty days of tosylation, dissolved in 20 cc. of dry pyridine, was mixed with 1.5 g. (0.041 mole) of dry hydrogen chloride gas dissolved in 30 cc. of the same solvent. After being heated under reflux at 85° for four hours, the mixture was cooled and poured into 200 cc. of dry, redistilled petroleum ether (b. p. 30 to 50°). The granular, light-tan precipitate together with pyridine salts was recovered as a filter cake which was macerated and thoroughly washed with water until free from chloride ion and pyridine. This product, 0.985 g. after drying as described above, did not swell or dissolve in water or in common organic liquids, even when the latter contained some water. *Anal.* Found: S, 9.30, 9.40; Cl, 8.51, 8.65; $OCH_2CH_2$, 1.99, 1.74, 1.68. The composition corresponded to cellulose substituted with 0.819 chlorine atom, 0.982 tosyl and 0.132 ethylene oxide groups per glucose unit, and the yield to 100%.

The tosylates obtained after seven hours and two days were submitted to the above reaction, but the chlorinated products were soluble, or so highly dispersed in water, aqueous pyridine and common organic liquids that they

(30) Trust, *Petroleum Engr.*, **13**, 58 (1942).

(31) Allen, "Commercial Organic Analyses," Churchill, London, 1924, Vol. I, p. 302.

(32) Liebhafsky and Sharkey, THIS JOURNAL, **62**, 190 (1940).

(33) Rutherford, Minor, Martin and Harris, *J. Research Natl. Bureau Standards*, **29**, 131 (1942).

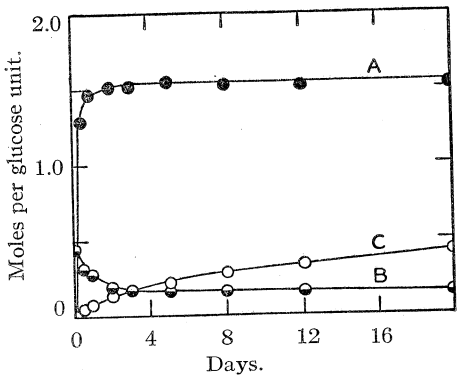



Fig. 1.—Changes in substitution of a hydroxyethyl cellulose during tosylation at 25°: plot A, tosyl; plot B, hydroxyethyl; plot C, chlorine substitution.

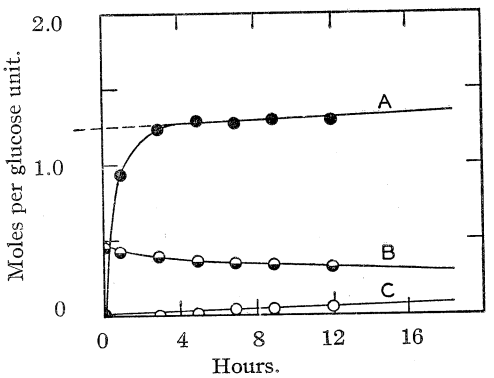



Fig. 2.—Initial changes in substitution of a hydroxyethyl cellulose during tosylation at 25°: plot A, tosyl; plot B, hydroxyethyl; plot C, chlorine substitution.

could not be isolated in good yield or adequately purified. A sample of the original hydroxyethylcelluose, when heated with a similar pyridine hydrochloride solution at 85° for four hours, was recovered chlorine-free and with the original hydroxyethyl content. Found: $CH_2CH_2O$, 10.69, 10.77; substitution, 0.44.

**Partial Replacement of Tosyloxy Group by Iodine.**—A 250-cc. flask containing 200 cc. of pure, dry acetonylacetone, 4 g. (0.027 mole) of sodium iodide and 2.42 g. (0.007 mole) of the three-hour tosylated hydroxyethylcellulose was heated under reflux for twelve hours at 115 to 120°. The ester was not completely soluble in the mixture, which developed a deep red color. Precipitation of the entire mixture into 1.8 liters of rapidly stirred ice-water yielded a granular, slightly yellow product that was repeatedly washed with water, then with 0.1 *N* sodium thiosulfate and again with water until all traces of iodide ion, free iodine and acetonylacetone had been removed. The iodinated product, 1.84 g., was dried *in vacuo* over phosphorus pentoxide for two days at room temperature. *Anal.* Found: S, 1.19, 1.15; I, 41.3, 41.4; $CH_2CH_2O$, 5.43, 5.44, 5.29. When the original trace of chlorine (0.14%) was neglected, these data corresponded to iodine, tosyl and ethylene oxide substitutions of 0.996, 0.114 and 0.373, respectively, and to a yield of 92%.

## Results and Discussion

Although the pure monoethyl ethers of diethylene and triethylene glycol readily formed peroxides,[24] three different tests for peroxides were negative with the commercial hydroxyethylcellulose, of unknown age, that was used. The observation that the latter, like the simpler analogs, slowly reduced alkaline hypoiodite discredited the use of the iodine number as a measure of average molecular weight[7,19b,22] in the hydroxyethylcellulose series.

Experiment showed that precipitation from alkali followed by careful solvent-exchange from water to dry pyridine converted the hydroxyethylcellulose to a uniform, highly swollen, completely translucent gel that seemed physically suitable for the tosylation with excess tosyl chloride and pyridine at 25°. This reaction was followed by the analyses of intermediate products (Table I) and from these data it was easy to calculate the corresponding changes in the tosyl, chlorine and ethylene oxide substitutions recorded in Figs. 1 and 2. The smooth nature of the plots, the high yields of the intermediate products, and the proved reliability of the analytical methods with simple analogs,[24] made it likely that these calculations were accurate to within ±0.02 mole per glucose unit. Figure 1, plot B shows that about half of the original 0.44 hydroxyethyl groups were eliminated during the first two days of tosylation but that the subsequent decrease was very slow, about one third remaining after twenty and also after forty days. Although pyridine hydrochloride was formed as a by-product of the tosylation and was used by Prey,[34] as an ether-cleaving agent, the original material was stable when heated at 85° with this substance in pyridine solution. It followed that the loss of hydroxyethyl groups occurred after, and not before, their tosylation and that these groups consisted of two distinct kinds, about one-third yielding stable, and the other two-thirds unstable, tosylates. When it was recalled that ethyl and β-ethoxyethyl *p*-toluenesulfonates were stable to vacuum distillation[35] but that the tosylates of higher homologs were nearly quantitatively cleaved to 1,4-dioxane and a stable lower tosylate,[24] it seemed likely that in the hydroxyethylcellulose one-third of the substituent was united as individual groups to the cellulose (structure I, $n = 1$) whereas the remaining two-thirds was present as polyethylene oxide chains (structure I, $n > 1$). The decomposition of an even-membered chain in the way suggested would transfer the tosyl group to the cellulose skeleton and would alter its nature from primary to secondary if the original chain was attached to a secondary alcohol position. An odd-membered chain, on the other hand, would yield a stable, tosylated, monomeric substituent and the ratio of primary to secondary tosyl groups would not be altered. Nothing in this mechanism would necessarily involve the permanent loss of tosyl units.

Plot C records a rather rapid chlorination, which probably resulted in the conventional way by the interaction of primary tosyl groups with by-product pyridine hydrochloride. The difference in reaction rates in plots B and C suggested

(34) Prey, *Ber.*, **75**, 350, 445 (1942).
(35) Tipson, *J. Org. Chem.*, **9**, 235 (1944).

that the loss of hydroxyethyl units and the gain in chlorine were independent side-reactions, and this inference was supported by the fact that the sum of the tosyl (plot A) and chlorine substituents increased steadily as hydroxyethyl groups decreased. Since both side reactions were insignificant during the early hours of the tosylation (Fig. 2, plots B and C), it seemed legitimate to determine the extent of the initial rapid tosylation by extrapolating the latter portion of plot A to zero time. The result, 1.22 moles, was taken as equal to the number of primary alcohol groups in the original hydroxyethylcellulose because their rate of reaction was comparable to that displayed by primary alcohol groups in cellulose ethers[27] and cellulose acetate[26] tosylated in closely similar circumstances. It then followed from the argument in the Introduction that 0.22 mole represented hydroxyethyl units substituted in the secondary alcohol positions of the cellulose, the actual number of such units being greater if they included polymers.

The fact that hydroxyethylcellulose tosylated for only three hours contained a negligible substitution (0.01 mole) of chlorine (Table II, line 2) made it possible to check the content of primary tosyl groups by the iodination method. Although the sample was heated with excess sodium iodide in acetonylacetone for twelve, instead of the usual two or four,[26] hours at 115 to 120°, and the replacement proceeded in over 90% yield, the product contained only 1.00 instead of the expected 1.22 moles of iodine (line 3), and the over-all substitution (tosyl plus halogen) decreased from 1.24 to 1.11 moles. According to Malm and his collaborators[28] the iodination method sometimes overestimated, but never underestimated, the content of primary tosyl groups. The replacement of primary tosyl by chlorine in the sample tosylated for twenty days (line 4) was completed by heating with pyridine hydrochloride in pyridine, the yield of the granular light tan product being nearly quantitative. A decrease in tosyl plus chlorine substitution from 1.93 to 1.80 moles, or of 0.13 mole, corresponded exactly to the similar decrease occasioned by iodination but the final chlorine content was only 0.82 mole. Halogenation, therefore, revealed only 1.00 and 0.82 mole of primary hydroxyl groups, whereas the minimum number possible was 1.0 for cellulose, or any hydroxyethylcellulose, and the number probable in the present case was 1.22. This large discrepancy, which could not be attributed to inadequate conditions of halogenation, suggested that another side-reaction occurred. No significant loss of the hydroxyethyl group was involved (Table II, lines 2 and 3, 4 and 5) but the reaction occasioned a decrease of 0.13 mole in the tosyl plus halogen substitution and another of at least 0.18 mole in primary tosyl. Although no direct evidence was obtained, this side-reaction was perhaps connected with the well-known ability of alkyl *p*-toluenesulfonates to act as alkylating agents in basic media.[36] Let it be assumed that the 0.15 mole of hydroxyethyl group stable throughout the tosylation quickly became esterified and then slowly alkylated unsubstituted hydroxyl groups of the cellulose at some stage in the reactions. As structures II and III show, such an alkylation might involve either the tosyl or halogen group and would result in the formation of a cyclic ether of ethylene glycol, the ethylene oxide unit being retained while 0.15 mole of primary alcohol group was eliminated. Although structures II and III are quite arbitrary as to detail, the iodinated and halogenated derivatives were soluble in some organic liquids and therefore were not likely to contain glycol ether cross-links between different glucose residues.

TABLE II

CHANGES IN SUBSTITUTIONS CAUSED BY HALOGENATION OF TOSYLATED HYDROXYETHYLCELLULOSES

| Sample | Moles per glucose residue $-OCH_2-CH_2$ | Tosyl | Halogen | Primary hydroxyl | Secondary tosyl |
|---|---|---|---|---|---|
| Original | 0.44 | 1.22[a] | 0.0 | 1.22[a] | 0.0 |
| Three-hour ester | .39 | 1.23 | 0.01 Cl | | |
| Iodinated | .37 | 0.11 | 1.00 I | 1.00 | .11 |
| Twenty-day ester | .15 | 1.51 | 0.42 Cl | | |
| Chlorinated | .13 | 0.98 | 0.82 Cl | 0.82 | .98 |

[a] Later tosylation rate plot extrapolated to zero time.

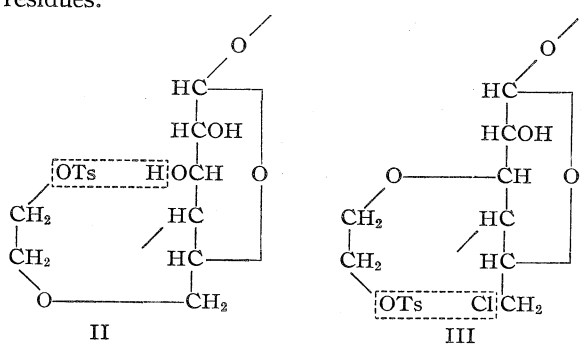



Table III contains an arbitrary distribution of monomeric and dimeric substituents in the primary and secondary positions of the hydroxyethylcellulose. The distribution was found by trial and error and its only merit is to summarize the experimental data and the series of unproved *ad hoc* assumptions outlined above.

The original material was assumed to have 0.05 primary plus 0.10 secondary position substituted by the dimeric unit, $-O-CH_2CH_2-O-CH_2-CH_2OH$, which during tosylation was gradually eliminated. This elimination reduced the ethylene oxide substitution from 0.44 to 0.38 and finally to 0.14 mole, and involved the transfer first of 0.02 and then of 0.10 mole of primary tosyl group to secondary positions on the cellulose. The monomeric hydroxyethyl substituents (0.02 plus 0.12 mole) were retained by the cellulose but the alkylating action of their tosylates converted them to cyclic

(36) Morgan and Cretcher, THIS JOURNAL, **70**, 375 (1948).

ether units. The same action caused the loss of at least 0.16 mole of primary tosyl or hydroxyl positions (structures II and III).

TABLE III

ARBITRARY DISTRIBUTION OF SUBSTITUENT IN AN ALKALI-SOLUBLE HYDROXYETHYLCELLULOSE

| Sample | Moles $CH_2CH_2O$ per glucose unit: Primary position, Monomer | Primary position, Dimer | Secondary position, Monomer | Secondary position, Dimer | Total | Primary OH |
|---|---|---|---|---|---|---|
| Original | 0.02 | 0.05 | 0.12 | 0.10 | 0.44 | 1.22 |
| | | | Found | | .44 | 1.22[a] |
| Three-hour tosylate | .02 | .04 | .12 | .08 | .38 | 1.06[b] |
| | | | Found | | .39 | 1.00 |
| Twenty-day tosylate | .02 | .0 | .12 | .0 | .14 | 0.86[b] |
| | | | Found | | .15 | 0.82 |

[a] By extrapolation of tosylation rate plot. [b] All tosylated monomers (0.02 + 0.12 mole) assumed to have become alkylated at primary hydroxyl positions, with elimination of the tosyl group.

**Acknowledgments.**—The authors are greatly indebted to Dr. R. T. K. Cornwell, of the Sylvania Division, American Viscose Corporation (formerly the Sylvania Industrial Corporation) for literature references, for several valuable suggestions, and for his sustained interest in the work. One of us (C. W. T.) also wishes to thank the same organization for the Fellowship, and the Canadian Pulp and Paper Association for the summer stipend, awarded to him for the period of the research (1946–1947).

## Summary

1. A commercial alkali-soluble hydroxyethylcellulose of substitution 0.44 was esterified at 25° with excess *p*-toluenesulfonyl chloride in pyridine. The rapid initial reaction was attributed to a primary hydroxyl content of 1.22 moles per glucose residue and in consequence at least 0.22 mole of the hydroxyethyl substituent was tentatively assigned to secondary positions in the cellulose.

2. When the tosylation was prolonged for twenty to forty days, only 0.14 mole of hydroxyethyl group remained in the product. The elimination of 0.30 mole might be a measure of the polyethylene oxide units originally present as even-membered chains. The residual 0.14 mole might be attached to the cellulose directly, either as a monomer or as the initial unit of an odd-membered polyethylene oxide chain.

3. Partial replacement of tosyloxy groups by halogen, using sodium iodide or pyridine hydrochloride, had little effect on the hydroxyethyl substitution, but decreased the combined tosyl plus halogen substitution by 0.13 mole. Iodine, 1.0 mole per glucose unit, was introduced into one sample and 0.82 mole of chlorine into another, the substitution in both cases presumably occurring in the primary alcohol positions remaining in the two samples. Possible causes for the apparent decrease from the original 1.22 moles of primary alcohol units were suggested.

MONTREAL, P. Q., CANADA RECEIVED AUGUST 4, 1948

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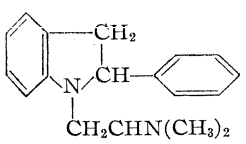
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

# Histamine Antagonists. IV. Indole and Carbazole Derivatives

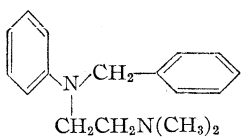
BY JOHN B. WRIGHT

In conjunction with a broad study of histamine antagonists under way in this Laboratory a number of 1-(dialkylaminoethyl)-indole and 9-(dialkylaminoethyl)-carbazole derivatives have been prepared and tested for antihistaminic activity.

A degree of similarity of structure exists between certain of these derivatives, such as 1-dimethylaminoethyl-2-phenylindoline (I), and N,-N - dimethyl - N′ - benzyl - N′ - phenylethylenediamine ("Antergan") (II). Because of this resemblance and the comparative ease with




I




II

which indole and carbazole derivatives may be prepared by means of the Fischer synthesis it seemed of interest to investigate compounds of this type. In this work β-(1-pyrrolidyl)-ethyl and β-dimethylaminoethyl were chosen as substituting groups in the indole or carbazole nucleus. The former grouping was chosen because of the promise that it has shown with other nuclei.[1,2]

The preparation of these compounds was carried out by forming the sodium salt of the indole or carbazole derivative by heating with either sodium or sodium amide in toluene or xylene solution, followed by heating of the resulting mixture under reflux with the dialkylaminoethyl chloride, either as the free base or as the hydrochloride salt. The yields ranged from 34–96%. The method of preparation outlined is essentially that of Eisleb[3] who prepared 9-(β-diethylaminoethyl)-carbazole and 1-(β-diethylaminoethyl)-2-methylindole by this method.

The indole and carbazole nuclei that were used in this work were indole, indoline, 2-phenylindole,

(1) Wright, Kolloff and Hunter, THIS JOURNAL, **70**, 3098 (1948).
(2) Reid, Wright, Kolloff and Hunter, *ibid.*, **70**, 3100 (1948).
(3) Eisleb, *Ber.*, **74B**, 1433 (1941).

2-phenylindoline, carbazole,[4] 1,2,3,4-tetrahydrocarbazole and 1,2,3,4,10,11-hexahydrocarbazole.

Preliminary pharmacological tests[5] indicate that these compounds possess weak to moderate antihistaminic activity. The results of these tests are indicated in Table I.

TABLE I

ANTIHISTAMINE ACTIVITY

| Name of compound[a] | Activity[b] |
|---|---|
| 1-[β-(1-Pyrrolidyl)-ethyl]-indole | [c] |
| 1-[β-(1-Pyrrolidyl)-ethyl]-indoline | 1/100–1/10 |
| 1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindole | 1/100–1/10 |
| 1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindoline | *ca.* 1/2 |
| 1-(β-Dimethylaminoethyl)-2-phenylindoline | 1/8–1/2 |
| 9-[β-(1-Pyrrolidyl)-ethyl]-carbazole | 1/100–1/10 |
| 9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole | 1/100–1/10 |
| 9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole | 1/6–1/3 |

[a] The pharmacological tests in all cases were carried out on aqueous solutions of the hydrochloride salts. [b] Activity is expressed in terms of β-dimethylaminoethyl benzhydryl ether hydrochloride as the unit of activity. These tests were carried out on isolated guinea pig small intestine. [c] Pharmacological results not yet available.

## Experimental[6,7]

**1-[β-(1-Pyrrolidyl)-ethyl]-indole.**—A mixture of 29.3 g. (0.25 mole) of indole and 5.76 g. (0.25 mole) of sodium was heated for two hours, with stirring, in an oil-bath at 180–200°. The mixture was allowed to cool somewhat, 100 cc. of dry xylene was added to the very viscous dark material and the mixture stirred and heated under reflux for fifteen minutes. The mixture was allowed to cool and 33.4 g. (0.25 mole) of β-(1-pyrrolidyl)-ethyl chloride[1] was added all at once. The mixture was stirred and heated under reflux for six hours. After the mixture had cooled to room temperature, the sodium chloride was filtered and washed with a small amount of xylene. The salt was dissolved in water and the aqueous solution extracted with about 250 cc. of xylene. The combined xylene solutions were extracted with a 3% hydrochloric acid solution, the acid extracts basified by the addition of solid potassium carbonate and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled *in vacuo* through a Vigreux column. There was obtained 29.9 g. (56%) of a colorless liquid, boiling at 128–129° (0.25 mm.), which darkened on standing.

**The picrate**, after two recrystallizations from ethyl acetate, consisted of reddish-orange flat needles melting at 142–142.5°.

*Anal.* Calcd. for $C_{14}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 54.17; H, 4.77; N, 15.80. Found: C, 54.34; H, 4.51; N, 15.62.

**1-[β-(1-Pyrrolidyl)-ethyl]-indoline.**—Sodamide was prepared from 1.9 g. (0.083 mole) of sodium according to the method of Vaughn, Vogt and Nieuwland.[8] To a mixture of the sodamide in 75 cc. of dry toluene was added, dropwise, 8.93 g. (0.075 mole) of indoline.[9] The mixture was stirred and heated under reflux for two and one-half hours. After cooling somewhat, 10.0 g. (0.075 mole) of β-(1-pyrrolidyl)-ethyl chloride was added and the mixture stirred and heated under reflux for fifteen hours. The mixture was filtered and the precipitate dissolved in 100 cc. of water and the aqueous phase extracted with toluene. The toluene extracts were combined with the toluene filtrate and the solution dried over anhydrous magnesium sulfate. The toluene was removed at atmospheric pressure and the residue distilled *in vacuo* through a Vigreux column. After a small amount of forerun, the main fraction boiled at 102–105° (0.2 mm.); yield, 11.3 g. (70%). The free base when freshly distilled is colorless but turns yellow slowly on standing.

*Anal.* Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 78.03; H, 9.05; N, 12.89.

**1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindole.**—The procedure given above for 1-[β-(1-pyrrolidyl)-ethyl]-indoline was followed using 5.06 g. (0.22 mole) of sodium, 19.3 g. (0.1 mole) of 2-phenylindole[10] and 17.0 g. (0.1 mole) of β-(1-pyrrolidyl)-ethyl chloride hydrochloride.[1] Xylene was used as the solvent in place of toluene. The reaction mixture was filtered, the precipitate dissolved in water and the resulting solution extracted with xylene. The combined xylene extracts and filtrate were extracted with a 3% hydrochloric acid solution. The acid extract was basified with potassium carbonate and the resulting mixture extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled *in vacuo* through a short Vigreux column. There was obtained 19.1 g. (66%) of a light-yellow viscous oil boiling at 187–189° (0.9 mm.). Upon standing the distillate solidified. Two recrystallizations of the crude product from methanol gave colorless needles melting at 78–78.5°.

*Anal.* Calcd. for $C_{20}H_{22}N_2$: C, 82.71; H, 7.64; N, 9.65. Found: C, 83.04; H, 7.36; N, 9.71.

**2-Phenylindoline** was prepared by the reduction of 2-phenylindole[10] with zinc dust and hydrochloric acid, according to the method of Fischer and Schmitt.[11] From 17.1 g. (0.087 mole) of 2-phenylindole there was obtained 14.4 g. (83%) of 2-phenylindoline boiling at 148–149° (1.4 mm.) and melting at 46–47.5°.

**1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindoline Hydrochloride.**—The procedure given for 1-[β-(1-pyrrolidyl)-ethyl]-2-phenylindole was followed with the exception that the crude undistilled product of the reaction was heated on a steam-bath for one hour with an excess of acetic anhydride. The solution, when cool, was poured into water. When the excess acetic anhydride had hydrolyzed completely the solution was neutralized with potassium carbonate and extracted with ether. The ethereal solution was extracted with dilute (3%) hydrochloric acid solution, the aqueous phase basified by the addition of solid potassium carbonate and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo* through a short Vigreux column. The product was obtained as a light-yellow viscous liquid boiling at 162–165° (0.2 mm.); yield, 34%.

**The hydrochloride** was prepared by adding the theoretical amount of a 2.96 *N* alcoholic hydrogen chloride solution to a solution of the free base in anhydrous ethanol and then adding an excess of anhydrous ether to precipitate the hydrochloride salt. Four recrystallizations of the crude material from an isopropyl alcohol–ethyl acetate mixture (1:1) gave clusters of small needles melting at 189.5–191.5°.

*Anal.* Calcd. for $C_{20}H_{24}N_2 \cdot HCl$: C, 73.04; H, 7.66; N, 8.52; Cl, 10.78. Found: C, 72.99; H, 7.48; N, 8.56; Cl, 10.88.

(4) 9-(β-Dimethylaminoethyl)-carbazole has recently been tested for antihistaminic activity by Freese, Hambourger and Michiels [*Federation Proc.*, **7**, 219 (1948)]. This compound has been reported also by Viaud [*Technologie Produits Pharmaceutiques*, **2**, 53 (1947)].

(5) For these results grateful acknowledgment is made to Dr. Milton J. VanderBrook of the Division of Pharmacology and Endocrinology of these laboratories.

(6) All melting points are corrected.

(7) For the analyses reported in this paper we are indebted to Mr. Harold C. Emerson and his staff of our Microchemical Division.

(8) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(9) King, Barltrop and Walley, *J. Chem. Soc.*, 280 (1945).

(10) "Organic Syntheses," **22**, 98 (1942).

(11) Fischer and Schmitt, *Ber.*, **21**, 1075 (1888).

**1-(β-Dimethylaminoethyl)-2-phenylindoline Hydrochloride.**—The procedure described above was employed, using an equivalent amount of β-dimethylaminoethyl chloride hydrochloride. From 12.9 g. (0.66 mole) of 2-phenylindoline there was obtained 12.6 g. (71.5%) of the free base. The free base is a colorless liquid boiling at 183–184° at 3.8 mm. The hydrochloride, prepared as described above, after four recrystallizations from absolute ethanol consisted of fine colorless needles melting at 210.5–212.5°.

*Anal.* Calcd. for $C_{18}H_{22}N_2$·HCl: C, 71.38; H, 7.65; N, 9.25. Found: C, 71.38; H, 7.50; N, 9.00.

**9-[β-(1-Pyrrolidyl)-ethyl]-carbazole.**—Sodamide[8] was prepared from 3.8 g. (0.17 mole) of sodium. A mixture of sodamide, 150 cc. of dry xylene and 25.1 g. (0.15 mole) of carbazole was stirred and heated in an oil-bath at 130° for three hours. To the mixture was added 20.0 g. (0.15 mole) of β-(1-pyrrolidyl)-ethyl chloride and the mixture stirred and heated under reflux for eight hours. The mixture was filtered and the precipitate washed with about 200 cc. of xylene. The xylene filtrate was extracted with dilute hydrochloric acid, the acid extracts made basic by the addition of a cold solution of sodium hydroxide, whereupon a light brown precipitate formed. This was filtered and dried in air. The weight of crude product was 38.4 g. (96%); m. p. 80–81°. Two recrystallizations from petroleum ether (Skelly B) after treatment with charcoal gave light yellow needles melting at 80.5–81.0°.

*Anal.* Calcd. for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: C, 81.80; H, 7.47; N, 10.51.

**9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole Hydrochloride.**—The procedure given above for 9-[β-(1-pyrrolidyl)-ethyl]-carbazole was followed using 25.6 g. (0.15 mole) of 1,2,3,4-tetrahydrocarbazole.[12] The product, which separated as an oil, was taken up in ether and the ethereal solution dried over anhydrous magnesium sulfate. The drying agent was filtered off and the hydrochloride precipitated by bubbling dry hydrogen chloride through the solution. The yield of crude product, melting at 211–220°, was 38.1 g. (83%). Three recrystallizations from an ethyl acetate–absolute ethanol mixture (3:1) using decolorizing carbon gave light yellow needles melting at 232.5–233.0°.

*Anal.* Calcd. for $C_{18}H_{24}N_2$·HCl: C, 70.91; H, 8.27; N, 9.19. Found: C, 70.74; H, 8.01; N, 9.42.

**9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole Hydrochloride.**—The procedure given above for 1-[β-(1-pyrrolidyl)-ethyl]-2-phenylindoline was followed using the appropriate quantity of 1,2,3,4,10,11-hexahydrocarbazole.[13] The free base was obtained as a light yellow, slightly fluorescent liquid boiling at 147–149° (0.5 mm.); yield 62%.

**The hydrochloride** was prepared as described in the same procedure. The crude product, upon five recrystallizations from ethyl acetate, in the presence of decolorizing charcoal, gave light yellow needles melting at 135–137.5°. The hydrochloride darkens upon standing.

*Anal.* Calcd. for $C_{18}H_{26}N_2$·HCl: C, 70.45; H, 8.87; N, 9.13; Cl, 11.55. Found: C, 70.40; H, 8.67; N, 9.07; Cl, 11.55.

## Summary

1. Four new 1-[β-(1-pyrrolidyl-ethyl]-indole derivatives, three new 9-[β-(1-pyrrolidyl)-ethyl]-carbazole derivatives, and 1-β-(dimethylaminoethyl)-2-phenylindoline hydrochloride have been prepared.

2. The results of preliminary pharmacological tests on these compounds for antihistaminic activity is reported.

(12) Rogers and Corson, THIS JOURNAL, **69**, 2910 (1947).

(13) Borsche, Witte and Bothe, *Ann.*, **359**, 70 (1908).

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 20, 1948

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[CONTRIBUTION FROM THE LABORATORIES OF GORDON A. ALLES, PH.D.]

# Characterization of Certain Alkaloids from *Fagara coco*

BY C. ERNST REDEMANN, BURNETT B. WISEGARVER AND GORDON A. ALLES

Stuckert[1] and co-workers in 1925 began the isolation and separation of the alkaloids of *Fagara coco* (Gill.) Engl. Six alkaloids were listed, only four of which, α-, β-, γ-, and δ-fagarine, were sufficiently well characterized to be considered discrete compounds. Merck and Company of Darmstadt subsequently carried out the isolation of the fagara alkaloids on a large scale and reported only two alkaloids, designated fagarine I, m.p. 163°, and fagarine II, m.p. 202°. Fagarine I is to be identified with α-fagarine, but fagarine II appears to be a new alkaloid. Later Deulofeu[2] and co-workers isolated α-, β-, and γ-fagarine from a sample of *Fagara coco* supplied by Stuckert. β-Fagarine has been identified[2] as skimmianine[3,4] and γ-fagarine as 8-methoxydictamnine.[5]

The structure of α-fagarine has been of interest since the report of Stuckert and Sartori[6] that it exerts a depressant action upon cardiac function, and the subsequent finding of Moisset de Espanés[7] that it raises the threshold for both auricular and ventricular fibrillation arising from faradic stimulation. It has more recently been reported as a superior substitute[8] for quinidine for controlling cardiac arrythmias. Stuckert[1] arrived at the empirical formula $C_{19}H_{22}NO_4$ for α-fagarine, while Merck[1] gave $C_{19}H_{23}NO_5$. Deulofeu[2,8,9] and co-workers concluded that the empirical formula is $C_{19}H_{23}NO_4$ and suggest a provisional structure.

Dried ground leaves and twigs of *Fagara coco* were extracted by the method of Deulofeu.[2]

(1) "Investigaciones del Laboratorio de Química Biológica, Cordoba, Argentina," Vol. I, 1933, and Vol. II, 1938.

(2) Deulofeu, Labriola and de Langhe, THIS JOURNAL, **64**, 2326 (1942).

(3) Honda, *Arch. exp. Path. Pharmakol.*, **52**, 83 (1904).

(4) Asahina and Inubuse, *Ber.*, **63**, 2052 (1930).

(5) Berinzaghi, Muruzabal, Labriola and Deulofeu, *J. Org. Chem.*, **10**, 181 (1945).

(6) Stuckert and Sartori, *Rev., Univ. Nac. Cordoba, Argent.*, **19**, 12 (1932).

(7) Moisset de Espanés and Navarro, *Rev. Soc. Arg. Biol.*, **12**, 137 (1936); **13**, 112 (1937); **13**, 259 (1937).

(8) Deulofeu, Labriola, Orias, Moisset de Espanés and Taquini, *Science*, **102**, 69 (1945).

(9) Deulofeu, Labriola and Berinzaghi, *J. Org. Chem.*, **12**, 217 (1947).

The α-fagarine thus obtained melted at 159–160° instead of either 163° or 169–170°, both values having been reported by Deulofeu. Analyses and molecular weight determination of our α-fagarine[10] indicated an empirical formula $C_{21}H_{23}NO_5$. The failure of Deulofeu and co-workers to determine neutral equivalent weights of the base and halogen analyses of the halogen acid salts of α-fagarine is probably responsible for the erroneous empirical formula they reported, for had they determined these quantities it would have been apparent that some of their analytical values were in error. Treatment of α-fagarine with phosphorus oxychloride gave an anhydromethochloride which is impossible with a compound having the provisional structure given by Deulofeu. In addition a careful repetition of Deulofeu's oxidative degradation in acid medium confirmed the presence of methanal, but failed to show any *m*-methoxybenzaldehyde. The identity of our α-fagarine with that described by Deulofeu is based upon the fact that five derivatives of our α-fagarine had melting points in agreement with the corresponding derivatives reported by Deulofeu.

α-Fagarine and α-allocryptopine[11] were found to be identical. Schmidt and co-workers[12] have shown that allocryptopine exists in two isomeric modifications, the α-melting at 160°, and the β-melting at 169–170°, which they were able to interconvert,[13] thus suggesting that these two modifications may arise from dimorphism. The melting points of α-allocryptopine and the α-fagarine we isolated are the same, while the higher melting point of β-allocryptopine is the same as that recently reported by Deulofeu[9] and co-workers for their α-fagarine. Deulofeu in an earlier paper[2] reported the m.p. of α-fagarine as 163°, which he subsequently attributed to a solvate. Jowett and Pyman[14] have isolated β-allocryptopine (γ-homochelidonine) from a closely related species of Fagara, *Xanthoxylum brachyacanthum*, F. Muell., more recently classified as *Fagara brachyacanthum* (F. Muell.) Engl.

α-Fagarine hydrochloride melted at 190–192° dec. which is in agreement with the dec. temperature of 190° reported by Haworth and Perkin[15] for α-allocryptopine hydrochloride. α-Fagarine aurichloride melted at 187° dec. in agreement with that given by Schmidt and Wintgen[12b] for α-allocryptopine aurichloride. When treated with phosphorus oxychloride α-fagarine gave an anhydromethochloride, m.p. 205°, which is close to the m.p. 200–201° reported by Gadamer[16] for the anhydromethochloride produced from α-allocryptopine by similar treatment.

An authentic sample of α-allocryptopine isolated from another plant source was kindly supplied by Dr. R. H. F. Manske. After recrystallizing both his α-allocryptopine sample and our α-fagarine from the same solvent a determination of the mixed melting point showed no depression. A comparison of crystal forms showed the two substances to be identical in crystal habit. The ultraviolet absorption spectra of α-fagarine and α-allocryptopine (Fig. 1) are identical, the two curves falling upon each other so exactly as to be indistinguishable. Our α-fagarine was shown to be identical with the α-fagarine commercially available in Argentina by direct comparison with an authentic sample purchased from the Laboratories Apotarg, Cordoba, Argentina. Both samples melted at 159–160° and in admixture showed no depression in m.p.

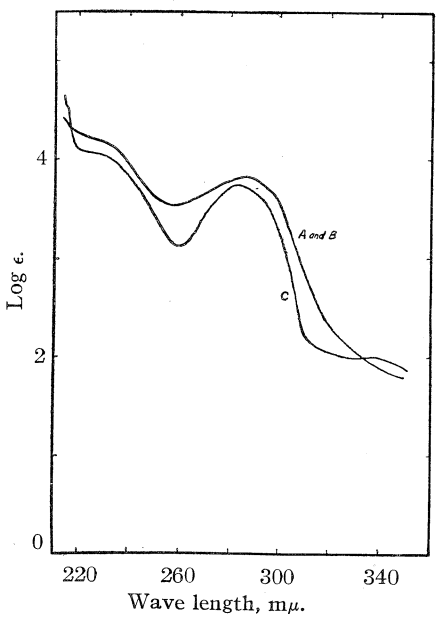



Fig. 1.—A, α-Allocryptopine; B, α-fagarine; C, α-fagarine hydrochloride.

It was found that a small quantity of hydrochlorides crystallized upon cooling a hot aqueous solution of the crude fagarine in dilute hydrochloric acid. The bases obtained from the crystalline hydrochlorides were separated into two fractions, one melting at 181–183° and the other at 198–199°. The base melting at 198–199° is to be identified with Merck fagarine II, while that melting at 181–183° appears to be new and will be referred to as fagarine III in this paper.

(10) Much difficulty was experienced in obtaining correct analyses of α-fagarine. Analyses were run by three commercial microanalytical laboratories and in our own laboratory before it was possible to get consistent analytical values.

(11) Stuckert annotated on p. 199 of his later report[1] that Merck suggested that α-fagarine was similar to α-allocryptopine, but this suggestion does not seem to have been followed. α-Allocryptopine is also called β-homochelidonine.

(12) (a) Schmidt and Fischer, *Arch. Pharm.*, **239**, 409 (1901); (b) Schmidt and Wintgen, *ibid.*, **239**, 438 (1901).

(13) We attempted the innerconversion following their directions, but all attempts were unsuccessful, probably because we had no seed crystals of the β-allocryptopine. The same difficulty is encountered with many polymorphic organic compounds.

(14) Jowett and Pyman, *J. Chem. Soc.*, **103**, 290 (1913).

(15) Haworth and Perkin, *ibid.*, 445 (1926).

(16) Gadamer, *Arch. Pharm.*, **258**, 148 (1919).

Analyses of fagarine II, its hydrochloride, hydrobromide, aurichloride and methiodide indicate an empirical formula of $C_{21}H_{23}NO_5$ for the base, with a methylimide, a methylenedioxy and two methoxy groups present. The lack of optical activity would indicate either the absence of an asymmetric carbon atom, or easy isomerization. Treatment with phosphorus oxychloride gave an anhydromethochloride. The ultraviolet absorption spectra of fagarine II and its hydrochloride (Fig. 2) are very similar to those of α-fagarine. The two molecules probably differ only in the positions occupied by the methylenedioxy and methoxy groups.

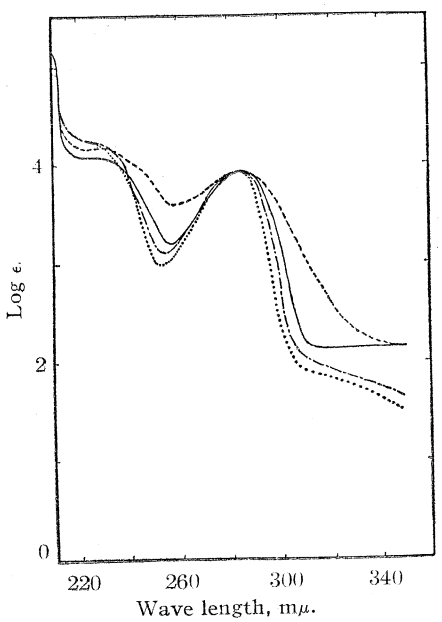



Fig. 2.— – – – –, Fagarine II; ——, fagarine II hydrochloride; – – – –, fagarine III; . . . . . , fagarine III hydrochloride.

The amount of fagarine III obtained has been too small for an extensive study of its properties and derivatives. This alkaloid gives no color with concentrated sulfuric acid, a negative Labat test for a methylenedioxy group, and is strongly levo-rotatory. Its ultraviolet absorption spectrum (Fig. 2) is similar to that of α-fagarine and fagarine II.

## Experimental[17,18]

**Purification of Crude α-Fagarine.**—Crude α-fagarine, extracted from ground *Fagara coco* by the method of Deulofeu,[2] was reprecipitated from its hydrochloride solution and then crystallized from ethanol giving pure α-fagarine, m. p. 159–160°. Samples of purified α-fagarine were crystallized from ethyl acetate, acetone, benzene and chloroform–petroleum ether, with no change in m. p. A sample of α-fagarine crystallized from ethyl acetate and dried at 100° *in vacuo* over phosphorus pentoxide at 2 mm. for nine hours was analyzed.

*Anal.* Calcd. for $C_{21}H_{23}NO_5$: C, 68.27, H, 6.27; N, 3.79; $CH_3O$, 16.80; mol. wt., 369.4; neut. eq., 369.4. Found: C, 68.47, 68.37; H, 6.18, 6.20; N, 3.37, 3.71; $CH_3O$, 16.93, 16.96; mol. wt., 362, 368, 370 (ebullioscopic in benzene); neut. eq., 368.5, 368.5, 369.5.

**α-Fagarine Hydrochloride.**—The hydrochloride was obtained from absolute ethanol solution in nearly the theoretical yield as a crystalline powder, m. p. 190–192° dec.; Deulofeu[9] gave the m. p. 192–193°. A sample of this hydrochloride was dried at 100° over phosphorus pentoxide at 2 mm. for six hours before analysis.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot C_2H_5OH \cdot HCl$: C, 61.1; H, 6.64; Cl, 7.87, $CH_3O$, 20.33. Found: C, 60.76, 60.78; H, 6.56, 6.60; Cl, 7.85, 7.89; $CH_3O$, 18.96, 19.17. (The ethyl alcohol of crystallization would be estimated as a methoxyl group, thus giving the equivalent of three methoxyl groups.)

The presence of ethanol in the analytical sample of α-fagarine hydrochloride was shown by distilling 5 g. with 20 ml. of 2 *N* hydrochloric acid and then redistilling the first 5 ml. of distillate. The first 0.5 ml. from the second distillation (b. p. 78°) was treated with 3 ml. of pyridine and 0.5 g. of 3,5-dinitrobenzoyl chloride, giving a 3,5-dinitrobenzoate, m. p. 92.5°, which is the melting point of ethyl 3,5-dinitrobenzoate. Concentration of the aqueous boiler residue from the first distillation gave a white crystalline product which turned slightly yellow when dried at 130° over phosphorus pentoxide at 2 mm. for two hours.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot HCl \cdot 0.5H_2O$: Cl, 8.54. Found: Cl, 8.54, 8.56.

The ionization constant of α-fagarine was estimated from the hydrolysis of its hydrochloride in aqueous solution. A 0.022 *M* solution of the hydrochloride in doubly distilled water had a *p*H of 5.38 at 25° from which the basic ionization constant, $K_b$, was calculated to be $1.3 \times 10^{-5}$.

**α-Fagarine Hydrobromide.**—This was prepared in ethanol by the procedure of Deulofeu.[9] The crystals were collected and dried at 100° over phosphorus pentoxide at 2 mm. for two hours; m. p. 185–188° dec.; Deulofeu gave 186–188° dec.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot HBr \cdot 0.5C_2H_5OH$: C; 55.7; H, 5.75; Br, 17.05. Found: C, 55.55; H, 5.77, Br, 16.95.

**α-Fagarine Hydroiodide.**—A solution of 300 mg. of α-fagarine in 5 ml. of ethanol and 0.5 ml. of freshly distilled hydroiodic acid (d. 1.57) was prepared by warming. Two crystal forms were observed after standing overnight. These were thought to be different solvates, since after drying they showed identical melting points, m. p. 192–194° dec. Deulofeu[9] gave 190–192° dec.

*Anal.* (A) Sample dried at 50° in air. Calcd. for $C_{21}H_{23}NO_5 \cdot HI \cdot C_2H_5OH$: I, 23.4. Found: I, 23.4. (B) Sample dried at 100° *in vacuo* over phosphorus pentoxide for three hours. Calcd. for $C_{21}H_{23}NO_5 \cdot HI$: C, 50.7; H, 5.52; I, 25.5. Found: C, 50.6; H, 5.52; I, 24.84, 24.95.

**α-Fagarine Methiodide.**—This was obtained by a slight variation of Deulofeu's procedure as a fine crystalline powder, m. p. 205–206°. Deulofeu gave 205°.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot CH_3I$: C, 51.6; H, 5.08; I, 24.84. Found: C, 51.77; H, 5.27; I, 24.82.

**α-Fagarine Picrate.**—This was prepared by the procedure of Deulofeu[9]; observed m. p. 207–208°; Deulofeu gave 208–209°.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot C_6H_3N_3O_7$: C, 54.1; H, 4.34. Found: C, 53.9; H, 4.45.

**α-Fagarine Aurichloride.**—A solution of 74 mg. of α-fagarine, 80 mg. of gold chloride, a few drops of diluted hydrochloric acid and 3 ml. of ethanol was prepared by warming slightly. Water was added to the warm solution, a few drops at a time, until just turbid. Garnet-red, warty, crystal masses gradually formed; m. p. 187° dec.

*Anal.* (A) Sample dried at 50° in air. Calcd. for $C_{21}H_{23}NO_5 \cdot HAuCl_4 \cdot H_2O$: Au, 27.0. Found: Au, 27.0.

(17) All melting points are uncorrected.

(18) The methoxy and methylimide determinations were made by the Elek Micro Analytical Laboratories, Los Angeles.

(B) Sample dried at 100° over phosphorus pentoxide *in vacuo* for three hours. Calcd. for $C_{21}H_{23}NO_5 \cdot HAuCl_4$: Au, 27.80. Found: Au, 27.82.

**Oxidation of α-Fagarine with Acid Permanganate.**—One gram of α-fagarine was oxidized by the procedure of Deulofeu.[9] An excess of a solution of 2,4-dinitrophenylhydrazine in 6 *N* hydrochloric acid was added to the steam distillate and the solution allowed to stand until precipitation was complete, in place of the ether extraction used by Deulofeu. The precipitate was collected and recrystallized from ethanol, giving yellow crystals, m.p. 165°, whose m.p. was not lowered in admixture with an authentic sample of formaldehyde 2,4-dinitrophenylhydrazone. The alcoholic mother liquor was evaporated to dryness leaving 30 mg. of a dinitrophenylhydrazone, m.p. 160–164°, whose m.p. was not depressed in admixture with formaldehyde 2,4-dinitrophenylhydrazone. In addition, Deulofeu[9] reported isolating *m*-methoxybenzaldehyde 2,4-dinitrophenylhydrazone, m.p. 220°, but we were not able to find any trace of such a substance.

The adequacy of our isolation procedure was demonstrated by a model experiment with 20 mg. of *m*-methoxybenzaldehyde which gave a copious yield of its 2,4-dinitrophenylhydrazone, m.p. 220°.

**Treatment of α-Fagarine with Phosphorus Oxychloride.**—A mixture of 2 g. of α-fagarine and 2 ml. of phosphorus oxychloride was allowed to stand without external heating for ten minutes, after which the mixture was heated in an 110° oil-bath for forty-five minutes. The excess phosphorus oxychloride was removed *in vacuo* and the residue was dissolved in hot water from which it crystallized upon cooling as very small needle crystals. Recrystallization from 2% hydrochloric acid gave crystals, m.p. 205° with previous browning and dec. A sample dried *in vacuo* at 130° decomposed.

*Anal.* (A) Dried at 50° in the air. Calcd. for $C_{21}H_{22}NO_4 \cdot HCl \cdot 3H_2O$: Cl, 8.01. Found: Cl, 8.04. (B) Dried at 65° for eight hours *in vacuo* over phosphorus pentoxide. Calcd. for $C_{21}H_{22}NO_4 \cdot HCl \cdot H_2O$: Cl, 8.71. Found: Cl, 8.63.

**Mixed Melting Point of α-Allocryptopine and α-Fagarine.**—A sample of authentic α-allocryptopine was kindly furnished by Dr. Manske. Both his sample and our α-fagarine were recrystallized from ethyl acetate. Each sample melted at 159–160° and no depression was shown in the melting point of their mixture.

**Isolation of Fagarines II and III.**—While working up a composite lot of 200 g. of crude α-fagarine from the first precipitation at *p*H 12–13, the dark-brown granular mass was dissolved in 2 l. of hot 1 *N* hydrochloric acid and the filtered solution was allowed to stand overnight at room temperature. The 43 g. of sparingly soluble hydrochloride which separated was dissolved in 2 l. of boiling water and the base liberated with sodium hydroxide. The crude base (26.5 g.) which separated was crystallized from "Cellosolve" and then from ethanol, giving 13.8 g. of fine white needles, m.p. 198–199°, of crude fagarine II. From the mother liquors 1.6 g. of another base, fagarine III, was obtained by taking advantage of its much smaller rate of crystallization. Fagarine III separated as large, pale yellow octahedral prisms, m.p. 181–183°.

**Fagarine II.**—Pure fagarine II was obtained by repeated crystallization of the crude fagarine II from "Cellosolve," ethanol, ethyl acetate and benzene. The melting point of the long fine white needles remained constant at 198–199°. This base showed no optical activity in chloroform solution, had a bitter taste and gave a red-violet color with concd. sulfuric acid which slowly changed to a purple color. The Labat test[19] for the methylenedioxy group was strongly positive.

*Anal.* Calcd. for $C_{21}H_{23}NO_5$: C, 68.27: H, 6.27; N, 3.79; 2 $CH_3O$, 16.80; mol. wt., 369.4; neut. eq., 369.4: 1 $CH_3N$, 7.8. Found: C, 68.4, 68.2; H, 6.31, 6.38; N, 3.61, 3.71; $CH_3O$, 15.29; mol. wt., 374 (ebullioscopic in benzene); neut. eq., 373, 374; $CH_3N$, 5.6.

(19) Labat, *Bull. soc. chim.*, [4] **5**, 745 (1909).

**Fagarine II Aurichloride.**—A solution of 160 mg. of fagarine II, 160 mg. of gold chloride trihydrate, 5 ml. of water and a few drops of hydrochloric acid was prepared by heating moderately. The aurichloride separated as a granular orange-colored solid, m.p. 218–219°. After boiling with ethanol and drying *in vacuo* at 130° this solid was analyzed.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot HAuCl_4$: Au, 27.80. Found: Au, 27.97, 27.49, 27.80.

**Fagarine II Methiodide.**—A suspension of 1.0 g. of fagarine II in 10 ml. of absolute ethyl acetate and 2 ml. of methyl iodide was heated in a sealed tube at 80° for four hours. The fine crystalline powder was collected and dried at 60°; weight 1.37 g. (99% yield); m.p. 234° dec.; sparingly soluble in hot water and hot ethanol.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot CH_3I$: C, 51.66; H, 5.13; I, 24.82. Found: C, 51.5; H, 5.18; I, 24.91, 24.78.

**Fagarine II Anhydromethochloride.**—A mixture of 1.0 g. of fagarine II and 2 ml. of phosphorus oxychloride was allowed to stand for ten minutes at room temp. During this time the solid dissolved with slight evolution of heat. After heating in an oil-bath at 110° for forty-five minutes the excess phosphorus oxychloride was distilled under reduced pressure and the residue was dissolved in 60 ml. of boiling water. The crystals which separated were recrystallized from 200 ml. of boiling 2% hydrochloric acid, giving pale yellow scales which turned red upon exposure to light. These crystals were dried in the dark at 50° and then in a brown glass vial at 65° for four hours *in vacuo* over phosphous pentoxide, weight 0.8 g.; m.p. 210–215° with previous sintering and browning.

*Anal.* Calcd. for $C_{21}H_{22}ClNO_4$: C, 65.01; H, 5.72; Cl, 9.14. Found: C, 64.5, 64.5; H, 6.05, 6.08; Cl, 8.57.

There may have been a slight contamination of unreacted fagarine II hydrochloride present in this material since the hydrochloride is much less soluble than the anhydromethochloride.

**Fagarine II Hydrochloride.**—A solution of 2.3 g. of fagarine II dissolved in a slight excess of hot dilute hydrochloric acid was evaporated to dryness. The residue was crystallized from ethanol–ether, giving 1.9 g. of microscopic needle crystals, m.p. 200–202° dec., but on rapid heating a m.p. as high as 215° dec. was observed. The sample for analysis was dried for four hours at 100° *in vacuo* over phosphorus pentoxide.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot HCl \cdot 0.5H_2O$: C, 60.79; H, 6.07; Cl, 8.54. Found: C, 60.5, 60.8; H, 6.29, 6.33; Cl, 8.47, 8.52.

**Fagarine II Hydrobromide.**—A suspension of 1.0 g. of fagarine II in 15 ml. of warm ethanol was treated dropwise with 48% aqueous hydrobromic acid until the solid dissolved and the solution was acidic. Ether was added to incipient turbidity and after standing for some time the crystalline hydrobromide was collected and dried four hours at 130° *in vacuo* over phosphorus pentoxide; weight 0.8 g.; m.p. 208–210° dec.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot HBr \cdot 0.5H_2O$: C, 54.91; H, 5.49; Br, 17.40. Found: C, 54.55, 54.30; H, 5.66, 5.73; Br, 17.60, 17.67.

**Fagarine II Picrate.**—A solution of 37 mg. of fagarine II in 25 ml. of hot ethanol was treated with 25 mg. of picric acid in 10 ml. of ethanol. Upon cooling, the bright yellow picrate crystallized as microscopic needles, m.p. 214°.

*Anal.* Calcd. for $C_{21}H_{23}NO_5 \cdot C_6H_3N_3O_7$: C, 54.2; H, 4.38. Found: C, 54.4; H, 4.65.

**Fagarine III.**—After recrystallizing from ethanol, pure fagarine III was obtained as almost colorless large octahedral prisms, m.p. 181–183°. This melting range could not be reduced by repeated crystallization from ethanol. $[\alpha]^{27}D$ −300° (112.4 mg. made up to 10.00 ml. with chloroform, $[\alpha]^{27}D$ −3.37°, *l*, 1 dm.). Fagarine III is tasteless, gives a colorless solution with concd. sulfuric acid, even when heated, and a negative Labat test[18] for a methylenedioxy group.

*Anal.* Calcd. for $C_{22}H_{26}NO_4$: C, 71.7; H, 7.07; N, 3.80. Found: C, 71.5, 71.6; H, 7.11, 7.17; N, 2.98, 3.03.

**Fagarine III Hydrochloride.**—Upon dissolving 1.6 g. of fagarine III in 200 ml. of dilute hydrochloric acid and cooling, very fine needle crystals of the hydrochloride separated. These were collected and dried at 130° *in vacuo* over phosphorus pentoxide; m.p. 232–234° dec.

*Anal.* Calcd. for $C_{22}H_{26}NO_4 \cdot HCl$: C, 65.2; H, 6.68; Cl, 8.77. Found: C, 64.4, 64.6; H, 6.87, 6.93; Cl, 9.15.

**Ultraviolet Absorption Spectra.**—The ultraviolet absorption spectra were determined using a Beckman model DU quartz spectrophotometer. The solvent was 99% ethanol for the bases, and 0.1 *N* aqueous hydrochloric acid for the hydrochlorides. Minimum slit widths were used with a 1.00 cm. quartz cell. All measurements were made against a blank of an identical sample of the pure solvent to eliminate its absorption.

**Acknowledgment.**—The authors wish to express their gratitude to Dr. R. H. F. Manske for supplying us with an authentic sample of α-allocryptopine.

## Summary

1. A re-investigation of α-fagarine and its derivatives has shown it to be identical with α-allocryptopine.

2. A second alkaloid, fagarine II, has been isolated and several derivatives have been prepared and analyzed. These data would suggest that fagarine II is isomeric with α-fagarine, differing only in the positions of the substituents.

3. Fagarine III has been isolated in very small amount. The ultraviolet absorption spectra of this alkaloid and its hydrochloride would suggest that it, also, belongs to the cryptopine group of alkaloids.

PASADENA 2, CALIFORNIA RECEIVED SEPTEMBER 7, 1948

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[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

# The Action of Ultraviolet Light on DDT

BY ELMER E. FLECK

The prolonged residual action of DDT (I) is due to its low vapor pressure[1] and to its stability toward oxidation.[2] Recently evidence has been accumulating to show that DDT is not so stable when exposed to direct sunlight in solution as when it is exposed in the solid state.[3]

Attempts have been made to explain this phenomenon by isolating the decomposition products of DDT produced by ultraviolet light. The isolation of 4,4′-dichlorobenzophenone (IV) was accomplished during 1945 in this laboratory by irradiating DDT dissolved in γ-valerolactone in an open Petri dish with ultraviolet light from a 100-watt mercury-vapor lamp. Since that time Wichmann, *et al.*,[4] have confirmed the formation of this compound by isolating the 2,4-dinitrophenylhydrazone of 4,4′-dichlorobenzophenone from the products obtained by irradiation of a benzene solution of DDT in an open Petri dish with ultraviolet light.

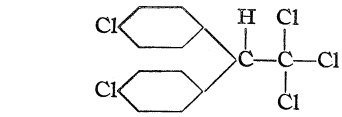
The formation of 4,4′-dichlorobenzophenone from DDT has been assumed to proceed first by elimination of hydrogen chloride from the trichloroethane group and then by oxidation of the resulting double bond. This mechanism of reaction was tested by irradiation of solutions of DDT in completely filled quartz cells. A wide variety of solvents were tried, and in every case hydrogen chloride was evolved but dehydrochlorinated DDT could not be isolated.

When a solution of DDT in ethyl alcohol was irradiated with a 360-watt mercury-vapor lamp for sixteen hours, about 1 mole of hydrogen chloride was evolved. A strong odor of acetaldehyde was present, and cooling the solution yielded about 10% of a crystalline compound which melted at 230–231°. This was shown to be 2,3-dichloro-1,1,4,4-tetrakis-(*p*-chlorophenyl)-2-butene (II) by analysis and by mixed melting point determinations with authentic material made by the method of Brand and Bausch.[5] These authors prepared II by hydrogenation of DDT in the presence of Pd–$CaCO_3$ catalyst. The identity of the two compounds was further substantiated by conversion of the irradiation product into 1,1,4,4-tetrakis-(*p*-chlorophenyl)-1,-2,3-butatriene (III) by refluxing with alcoholic sodium hydroxide. This procedure eliminated 2 moles of hydrogen chloride from II and resulted in a yellow crystalline product which melted with decomposition at 286°. Brand and Bausch give 288° with decomposition for this same compound. Mixed melting points of the two preparations showed no depression.

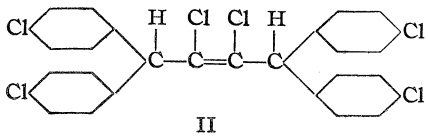
The butatriene (III), obtained by irradiation and reaction with alkali, was oxidized with chromic anhydride to form IV. This is in accordance with the oxidation of III prepared by the method of Brand and Bausch.[5]

In order to eliminate the possibility of an unknown impurity being present in the *p,p′*-DDT, the irradiation was repeated with a second preparation of *p,p′*-DDT made from DDT produced by a different manufacturer. The same yield of II was obtained.

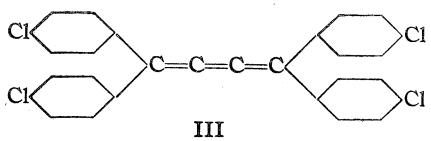
(1) E. E. Fleck, *J. Econ. Entomol.*, **37**, 853 (1944).
(2) O. Zeidler, *Ber.*, **7**, 1181 (1874).
(3) E. E. Fleck, *Ind. Eng. Chem.*, **40**, 707 (1948).
(4) H. J. Wichmann, W. I. Patterson, P. A. Clifford, A. K. Klein and H. V. Claborn, *J. Assoc. Offic. Agr. Chem.*, **29**, 222 (1946).
(5) K. Brand and W. Bausch, *J. prakt. Chem.*, **127**, 219 (1930).



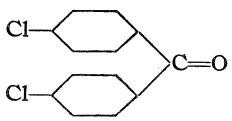
I



II



III



IV

Irradiation of dehydrochlorinated DDT and also of 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethane (TDE) in alcohol solution in quartz cells, under the same conditions that were used for DDT, resulted in recovery of the unchanged starting material.

The conversion of DDT into II by ultraviolet light provides a second and perhaps more probable mechanism by which sunlight may decompose DDT. The presence of another compound that can serve as a reactor with chlorine would tend to increase the speed of the reaction. In the case where alcohol is used as a solvent the chlorine oxidizes it to form acetaldehyde. When hydrocarbons are present the chlorine may react to form substitution products, or unsaturated groups in the molecule may serve as acceptors of chlorine to form addition compounds. These and other similar reactions may account for the more rapid decomposition of DDT in solution than in the solid state.

Although a large proportion of II would probably not exist at any one time in a DDT spray deposit, its presence can be detected by the yellow color of III formed by heating with alcoholic alkali. By contrast, the dehydrochlorinated DDT is colorless. When II is subjected to the colorimetric test of Schechter and Haller,[6] a wine-red color is produced. This is in contrast to the blue color produced by *p,p'*-DDT.

## Experimental

**Description of Apparatus.**—The quartz cell used was cylindrical in shape. The diameter was 40 mm. and the height 40 mm. A four × fifty mm. side tube was sealed on halfway up the side of the cylinder. This side tube was connected with a small rubber tube to a glass tube which was drawn down to a capillary. The rubber tube was shielded with a small piece of aluminum foil. The cell and side tubes were completely filled with liquid at the start of the experiment. As the solution warmed under the ultraviolet light, the excess liquid escaped through the capillary. The capacity of the cell was 42 ml.

In the early experiments a 100-watt Mazda mercury-vapor lamp was used. The light source was 25 cm. above the surface of the irradiated liquid. In the experiments with the quartz cell a 360-watt Uviarc lamp was used. It was fitted with an aluminum reflector and mounted so that the source of light was 25 cm. above the surface of the quartz cell. The cell was placed on a filter paper and was cooled by a strong current of air from an 8-inch fan. The temperature of the solution was between 35 and 40° during the experiments.

**Irradiation of DDT in Presence of Air.**—A solution of 1 g. of *p,p'*-DDT (m. p. 108–109°) in 10 ml. of γ-valerolactone was placed in a 100-mm. Petri dish. The irradiation was carried out for forty hours with the 100-watt mercury-vapor lamp. At the end of this period the solution had acquired a yellowish cast, and some of the DDT had crystallized on the side of the Petri dish. The liquid was pipetted out of the dish into water. The oil that separated crystallized when stirred. The mixture was extracted with ether and the ether solution washed with water until the wash was neutral to congo red. The ether was evaporated on the steam-bath, and the residue was taken up in 20 ml. of alcohol. When this solution was held at 0°, crystals separated which proved to be DDT (m. p. 107–108°, yield 0.4 g.).

The mother liquor from this separation was held at −30° for several days. The crystals that separated were recrystallized from alcohol to a constant melting point of 144–145°, yield 0.1 g. No depression of melting point could be observed when the sample was mixed with authentic 4,4'-dichlorobenzophenone.

**Irradiation of DDT in Absence of Air.**—A solution of 1 g. of *p,p'*-DDT (m. p. 108–109°) in 30 ml. of boiling alcohol was washed into the quartz cell with alcohol. The cell was cooled to room temperature and completely filled with alcohol. The capillary side tube was filled with alcohol and attached to the cell. The cell was placed with a flat surface up and irradiated for four hours with a 360-watt mercury-vapor lamp. The cell was then reversed and irradiated for four hours through the other window. This was followed by four hours of irradiation on each side of the cell with the side tube as a pivot. This change of surface is necessary, as small amounts of decomposition products deposit on the inside of the window and thereby reduce the yield. Between runs it was necessary to clean the cell with boiling ethyl acetate and also with boiling acetone.

The alcoholic solution irradiated in this manner acquired a yellowish cast. It sometimes contained a small amount of crystalline material. The product of irradiation was removed from the cell and cooled to −30° for several days. Four such runs were combined and filtered. A yield of 0.4 g. of crystalline material of melting point around 200° was obtained. Recrystallization from benzene gave prisms which melted at 230–231°. No yellow color was developed when a carbon tetrachloride solution was treated with tetranitromethane.

*Anal.* Calcd. for $C_{28}H_{18}Cl_6$: C, 59.29; H, 3.20; Cl, 37.51. Found: C, 59.59, 59.81; H, 3.38, 3.36[7]; Cl, 37.56.

No depression of melting point could be observed when this material was mixed with II prepared by the catalytic reduction of *p,p'*-DDT.[5]

II is insoluble in water, but very slightly soluble in methanol and ethanol. It is slightly soluble in ethyl acetate and acetic acid, and soluble in hot benzene, toluene, and chloroform.

**Hydrogen Chloride Produced by Irradiation of DDT.**—Alcoholic solutions of 1 g. of *p,p'*-DDT were irradiated as above for four-, eight- and sixteen-hour periods. Each alcoholic solution was poured into 200 ml. of water to which 3 ml. of concentrated nitric acid had been added. When precipitation was complete, the mixture was filtered

(6) M. S. Schechter, S. B. Soloway, R. A. Hayes and H. L. Haller, *Ind. Eng. Chem., Anal. Ed.*, **17**, 704 (1945).

(7) Analysis by N. Green.

by gravity and the filter paper washed with water. The filtrate was titrated with silver nitrate by means of an electrometric titrimeter.

*Anal.* Calcd. as moles of hydrochloric acid per mole of DDT: 4-hour irradiation, 0.39; 8-hour irradiation, 0.67; 16-hour irradiation, 0.88.

**1,1,4,4-Tetrakis-(*p*-chlorophenyl)-1,2,3-butatriene (III).**—A suspension of 100 mg. of II (from irradiated DDT) in 50 ml. of 2 *N* alcoholic potassium hydroxide was refluxed for two hours. The mixture was poured into 150 ml. of water and filtered by gravity when precipitation was completed. The yellow reaction product was washed with water, and the washings were added to the filtrate. The reaction product was dissolved in 50 ml. of benzene and shaken with water. The aqueous extracts were added to the filtrate.

The benzene solution was concentrated to 5 ml. on the steam-bath, and the yellow-orange needles that separated were recrystallized and dried in vacuum at room temperature. The product melted at 288° with decomposition, and no lowering of melting point could be observed when it was mixed with III prepared in accordance with Brand and Bausch.[5]

The filtrate from the original precipitation together with the washings was neutralized with concentrated nitric acid, and then a 3-ml. excess was added. The solution was titrated with 0.1 *N* silver nitrate with an electrometric titrimeter.

*Anal.* Calcd. for $C_{28}H_{18}Cl_6$: 2 moles Cl, 13.40 mg. Cl. Found: 13.65 mg. Cl.

**4,4′-Dichlorobenzophenone (IV).**—A solution of 45 mg. of III (from irradiated DDT) and 50 mg. of chromic anhydride in 5 ml. of acetic acid was refluxed for two hours. The solution was poured into 50 ml. of water and the reaction product filtered and recrystallized from alcohol. The product weighed 27 mg. and melted at 145–146°. No depression of melting point was observed when the product was mixed with authentic 4,4′-dichlorobenzophenone.

The ketone yielded an oxime of melting point 134–135°. Dittrich[8] gives the melting point as 135°.

## Summary

It has been shown that ultraviolet light catalyzes the decomposition of DDT.

One of the decomposition products is 4,4′-dichlorobenzophenone when air is present. In the absence of air 2,3-dichloro-1,1,4,4-tetrakis-(*p*-chlorophenyl)-2-butene is formed. This compound, through loss of hydrogen chloride and subsequent oxidation, may be converted into 4,4′-dichlorobenzophenone.

(8) M. Dittrich, *Ann.*, **264**, 177 (1891).

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

# Catalytic Reduction of Aromatic Ketones

BY E. C. HORNING AND D. B. REISNER[1]

The problem of reducing β-aroylpropionic acids to the corresponding γ-arylbutyric acids in convenient fashion and in good yield has led to continued investigation of classical chemical methods for the reduction of an aryl keto group to a methylene group. This work has led to the development of greatly improved procedures in the form of the Clemmensen–Martin–Sherman procedure[2] and the Wolff–Kishner–Huang method.[3] Modifications of these procedures can be applied to the reduction of aliphatic and alicyclic carbonyl groups as well, and these methods are of particular value because of this degree of generality.

The reduction of a carbonyl group adjacent to an aromatic nucleus does not present a difficult problem in terms of reactivity; the conversion of keto groups of this kind to the corresponding alcohols has been observed under a variety of mild catalytic hydrogenation conditions, and it is known that compounds of the benzyl alcohol type will undergo catalytic hydrogenolysis with ease to yield a fully reduced system. The fact that catalytic methods are not widely used for the reduction of such carbonyl groups to methylene groups is apparently due to the circumstance that appropriate catalytic conditions have not been established in many instances. We have found that certain types of carbonyl compounds can be reduced easily and in good yield by catalytic means, but that it is not always possible to predict in advance what effect structural changes will have upon the reduction. For example, 6-acetoxycoumaran-3-one can be reduced easily to 6-acetoxycoumaran, but under the same conditions the reduction of 6-hydroxycoumaran-3-one proceeds very slowly to give a mixture which includes products resulting from reduction of the aromatic ring.[4]

In the case of ketoacids, catalytic reduction with a palladium–carbon catalyst appears to proceed with particular ease in acetic acid at 65°. Two examples of the reduction of β-aroylpropionic acids are described; on a scale of about 0.1 mole the reduction was completed in about thirty or forty minutes, and the product was isolated easily in good yield. There was no apparent change in the rate of reduction during this period, and no attempt was made to isolate an intermediate reduction stage. For acids of this kind, this method may be superior to the procedures now in general use.

The reduction of *o*-benzoylbenzoic acid proceeded smoothly and rapidly to give *o*-benzylbenzoic aid in 95% yield.

The reduction of benzoin, under the same conditions, occurred very much less readily. The rate of reduction was rapid at first, but the time required for completion was much longer (about eight hours) and slightly less than the theoretical

(1) Research Corporation Research Assistant, 1948.

(2) Fieser, *et al.*, THIS JOURNAL, **70**, 3197 (1948).

(3) Huang, *ibid.*, **68**, 2487 (1946).

(4) Horning and Reisner, *ibid.*, **70**, 3619 (1948).

amount of hydrogen was taken up. The product, 1,2-diphenylethane, was isolated easily in crystalline form by dilution of the solvent with water. In this case, both oxygenated functional groups were converted to methylene groups.

**Acknowledgment.**—We are indebted to the Research Corporation for a grant-in-aid of this work.

## Experimental

All melting points are corrected.

**Palladium–Carbon Catalyst.**—A 5% palladium–carbon catalyst was prepared according to the general method of Hartung.[5] The palladium was obtained from J. Bishop and Company, in a 10% solution, and was deposited on Norit.

**γ-(*p*-Tolyl)-butyric Acid.**—A mixture of 20.0 g. of β-(*p*-toluyl)-propionic acid,[6] 3.0 g. of 5% palladium–carbon catalyst, and 40 ml. of acetic acid was shaken with hydrogen (initial pressure, 40 lb.) in a Parr hydrogenation apparatus at approximately 65°. The reduction (100% absorption) was completed in about twenty-five minutes. No further absorption occurred on continued shaking. The catalyst was removed by filtration and washed with acetic acid. The solvent was removed by distillation at atmospheric pressure; the distillation was continued under reduced pressure to yield 14.7 g. (79%) of γ-(*p*-tolyl)-butyric acid, b. p. 124–134° (0.3–0.5 mm.), m. p. 54–56° (reported, m. p. 61–62°, 92%, Clemmensen–Martin method).[7]

**γ-(*p*-Anisyl)-butyric Acid.**—The reduction of 20.8 g. of β-(*p*-anisoyl)-propionic acid[8] was carried out in 125 ml. of acetic acid with 3.0 g. of 5% palladium–carbon catalyst at approximately 65°. About forty minutes was required for the reduction (100% absorption). After removal of the catalyst, the solution was added to 200 ml. of water. The mixture was chilled and filtered to provide 14.5 g. (75%) of colorless γ-(*p*-anisyl)-butyric acid, m. p. 61–62° (reported, Clemmensen–Martin method, m. p. 59–60°, 65%[9]; m. p. 60–61°, 85%[7]; Wolff–Kishner–Huang method, 75%.[10]

***o*-Benzylbenzoic Acid.**—The reduction of 27.6 g. of *o*-benzoylbenzoic acid was carried out in 40 ml. of acetic acid with 3.0 g. of palladium–carbon catalyst at approximately 65°. About seventy-five minutes was required for completion of the reaction. After removal of the catalyst, the solution was poured into 200 ml. of water, and the mixture chilled for twelve hours. Filtration and drying *in vacuo* yielded 24.5 g. (95%) of colorless *o*-benzylbenzoic acid, m. p. 111–113° (reported, m. p. 113–114.2°, 75%, Clemmensen method).[11] The product was completely soluble in warm sodium bicarbonate solution.

**1,2-Diphenylethane.**—The reduction of 21.2 g. of benzoin was carried out in 200 ml. of acetic acid with 3.0 g. of 5% palladium–carbon catalyst at 65°; the rate of hydrogen absorption slowed gradually and stopped after about eight hours at 92% of completion. The catalyst was removed and the solution was poured into 300 ml. of water. The product crystallized immediately; after chilling, filtration yielded 13.5 g. (74%) of 1,2-diphenylethane, m. p. 49–50° (reported,[12] 51.5–52.5°).

## Summary

A method for the catalytic reduction of certain aryl ketones is described. The keto group is reduced to a methylene group in acetic acid solution at 65° with a palladium–carbon catalyst.

(5) "Organic Syntheses," **26**, 77 (1946).
(6) "Organic Syntheses," Coll. Vol. II, 82 (1943).
(7) Martin, THIS JOURNAL, **58**, 1438 (1936).
(8) Fieser and Hershberg, *ibid.*, **58**, 2314 (1936).
(9) Fieser, *et al.*, *ibid.*, **70**, 3200 (1948).
(10) Dauben and Adams, *ibid.*, **70**, 1759 (1948).
(11) Bradlow and VanderWerf, *ibid.*, **69**, 1254 (1947).
(12) Cannizzaro and Rossi, *Ann.*, **121**, 251 (1862).

PHILADELPHIA 4, PENNSYLVANIA
RECEIVED NOVEMBER 22, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# Allylic Chlorides. V. Relative Reactivities with Sodium Ethoxide in Ethanol

BY LEWIS F. HATCH AND HAROLD E. ALEXANDER

The relative reactivities of various allylic chlorides with potassium iodide in acetone have been reported[1,2] which indicate that both position isomerism and geometrical configuration have an effect on the rate of reaction. Although the reaction between sodium ethoxide and several allylic chlorides has been reported,[1,3] no effort had been made to ascertain if this reaction is influenced by geometrical configuration until the recent work of Andrews and Kepner.[4] Young and Andrews[3] had, however, suggested that this might be the case.

The present study was made to extend previously reported investigations on the sodium ethoxide reaction to determine the effects of substituents on the rate of reaction, and also to confirm the observation of Andrews and Kepner pertaining to the lack of influence of geometrical isomerism.

(1) Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).
(2) Hatch, Gordon and Russ, THIS JOURNAL, **70**, 1093 (1948).
(3) Young and Andrews, *ibid.*, **66**, 421 (1944).
(4) Andrews and Kepner, *ibid.*, **70**, 3456 (1948).

## Materials

**1-Chloro-1-propene.**—A mixture of *cis* and *trans* 1-chloro-1-propene (Research Chemicals, San Jose, California) was distilled to obtain a fraction with a boiling range of 34–35°. This fraction, being intermediate in boiling range between the two isomers (*cis* 32.0–32.2°; *trans* 36.7°), was assumed to contain both isomers.

**Allyl chloride**[5] boiling at 44.3° was used without further purification; $n^{25}D$ 1.4109.

**Methallyl chloride**[5] was redistilled and a fraction boiling at 70.9–71.0° was used.

**2-Bromo-3-chloro-1-propene** obtained from Halogen Chemicals of Columbia, S. C., was distilled at 150 mm. pressure. The fraction used boiled at 61.5°; $n^{25}D$ 1.4967.

**2,3-Dichloro-1-propene**[5] was distilled at 150 mm. pressure and a fraction boiling at 48° was used: $n^{25}D$ 1.4578; $d^{25}_4$ 1.2004; *MR* (calcd.) 25.32, (obsd.) 25.16.

**1,3-Dichloropropene.**—A mixture of the two isomers of 1,3-dichloropropene[5] was fractionated. The low boiling

(5) Furnished by Shell Chemical Co., San Francisco, California.

isomer boiled at 103.3°: $n^{25}D$ 1.4653. The high boiling isomer boiled at 111.5–111.9°: $n^{20}D$ 1.4742.

**1,3-Dichloro-2-methyl-1-propene.**—The isomeric 1,3-dichloro-2-methyl-1-propenes were prepared from methallyl chloride.[6] The methallyl chloride was chlorinated to 1,2,3-trichloro-2-methylpropane using sulfuryl chloride. The trichloride was dehydrochlorinated and hydrolyzed to a mixture of the 3-chloro-2-methyl-2-propen-1-ols from which the two alcohols were separated by means of a Podbielniak Hypercal distillation column. The chloroalcohols were converted to the corresponding dichlorides using concentrated hydrochloric acid. The low boiling isomer boiled at 130°: $n^{25}D$ 1.4702. The high boiling isomer boiled at 132°: $n^{25}D$ 1.4745.

**1,1,3-Trichloro-2-methyl-1-propene** was obtained from Halogen and Perfume Chemicals, Columbia, S. C., and was distilled at 150 mm. The fraction used boiled at 101°: $n^{25}D$ 1.4932.

## Experimental

The rates of reaction were obtained at 50.0 ± 0.1° using the procedure described by Tamele, *et al.*[1] The molar concentration of the chloride was 0.0998 ± 0.0018 and of the sodium ethoxide 0.0984. The data obtained are given in Table I. For each chloride at least four measurements were made covering the range of about 25 to 60% conversion. The individual values showed little or no drift and were constant as indicated in column 3 of Table I wherein the mean values of $k$ are given along with the average deviation of the individual measurements from them.

## Discussion

Table I lists the various allylic chlorides studied in the increasing order of their relative reactivity. The rate constant of allyl chloride was taken as unity, because all the other allylic chlorides may be considered as derivatives of allyl chloride, and also for a comparison between this reaction and that with potassium iodide.[2] A mixture of *cis* and *trans* 1-chloro-1-propene was tested to determine if a vinyl chlorine would react under the conditions of the rate determinations. There was no measurable reaction in twenty-four hours at 50°.

TABLE I

RELATIVE REACTIVITIES OF ALLYLIC CHLORIDES

| Compound | $k$ for $NaOC_2H_5$ 50° | Rel. reactivity $NaOC_2H_5$ 50° | Rel. reactivity KI 20°[a] |
|---|---|---|---|
| $CHCl{=}CH{-}CH_3$[b] | 0.00 | 0.00 | 0.00 |
| $CH_2{=}CCl{-}CH_2Cl$ | 0.56 ± 0.005 | 0.47 | 0.72 |
| $CH_2{=}CBr{-}CH_2Cl$ | 0.97 ± 0.06 | 0.82 | 0.87 |
| $CH_2{=}CH{-}CH_2Cl$ | 1.18 ± 0.01 | 1.00 | 1.00 |
| $CH_2{=}C(CH_3){-}CH_2Cl$ | 1.22 ± 0.03 | 1.03 | 1.58 |
| $CHCl{=}CH{-}CH_2Cl$[d] | 3.28 ± 0.06 | 2.78 | 8.58 |
| $CHCl{=}CH{-}CH_2Cl$[e] | 4.10 ± 0.06 | 3.47 | 2.90 |
| $CHCl{=}C(CH_3){-}CH_2Cl$[d] | 3.11 ± 0.13 | 2.64 | 32.8 |
| $CHCl{=}C(CH_3){-}CH_2Cl$[e] | 3.22 ± 0.11 | 2.73 | 8.45 |
| $CCl_2{=}C(CH_3){-}CH_2Cl$ | 8.75 ± 0.15 | 7.42 | 33 |
| $CH_3CH{=}CH{-}CH_2Cl$[c] | | 3.71[c] | 2.37[c] |

[a] Hatch, Gordon and Russ, THIS JOURNAL, **70**, 1093 (1948). [b] A mixture of *cis* and *trans* isomers. [c] Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941). This may be the *trans* isomer. [d] Low boiling. [e] High boiling.

The influence of the relative electronegativity of the atom or group on the number 2 carbon apparently is not as pronounced nor as consistent as it is for the reaction with potassium iodide. The effect of replacing the number 2 hydrogen with chlorine is more pronounced than in the potassium iodide reaction, but the bromine compound has essentially the same relative reactivity. Replacing the hydrogen with a methyl group increases the reactivity very slightly in contrast to a definite increase in reactivity toward potassium iodide. There is a slight inhibiting effect of the methyl group noted between the 1,3-dichloropropenes and the 1,3-dichloro-2-methyl-1-propenes.

A chlorine atom on the number 1 carbon causes a definite increase in the reaction rate, while a second chlorine atom in the same position (1,1,3-trichloro-2-methyl-1-propene) more than doubles the relative reactivity. Tamele, *et al.*, found that crotyl chloride (probably either *trans* or predominantly *trans*) had a relative reactivity of 3.71 at 35° compared to allyl chloride at the same temperature. This would indicate that a methyl group on the number 1 carbon has a greater activating effect than chlorine in the same position. Previous work[1,2] has indicated that with potassium iodide, chlorine has a greater activating effect than a methyl group.

The effect of geometrical configuration is much less pronounced and in the opposite direction from that shown in the reaction with potassium iodide. It is of interest to note that the high boiling isomer of 1,3-dichloropropene has nearly the same relative reactivity for both reactions. The relative reactivities of both isomers of 1,3-dichloro-2-methyl-1-propene, however, are much less than with potassium iodide. This reduced reactivity with sodium ethoxide may be caused by the lack of the activating effect of a methyl group in the number 2 position, an activation which is present with the potassium iodide reaction.

From these observations it is suggested that the reactions of allylic chlorides with sodium ethoxide and with potassium iodide may go by different mechanisms. It has been postulated[2] that the reaction with potassium iodide takes place through a negative iodide ion attack on the carbon atom holding the allylic chlorine. It may be that the reaction with sodium ethoxide is through an electrophilic attack on the allylic chlorine by the sodium ethoxide molecule. A reaction of this type should not be influenced appreciably by geometrical configuration, but should respond to inductive effects.

**Acknowledgment.**—This investigation was supported by a Grant-in-Aid from the Research Corporation for "Research on Allylic Chlorides." The authors wish to express their appreciation.

## Summary

A study has been made of the effect of both substituents and geometrical configuration on the relative reactivity of allylic chlorides with sodium ethoxide in ethanol at 50°.

(6) Hatch, Russ and Gordon, THIS JOURNAL, **69**, 2614 (1947).

The replacement of the hydrogen on the number 2 carbon by chlorine or bromine decreases the reactivity of the allylic chlorine. The effect of a methyl group in this position is very slight.

The replacement of the hydrogen on the number 1 carbon by chlorine causes a marked increase in reactivity.

It has been confirmed that geometrical configuration has only a slight effect on this reaction. It is suggested that the reaction mechanism for the reaction with sodium ethoxide is different from that in the reaction between allylic chlorides and potassium iodide.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# Allylic Chlorides. VI. Preparation of the 1,3-Dichloro-2-butenes

BY LEWIS F. HATCH AND STUART G. BALLIN

Several investigators have reported the preparation of 1,3-dichloro-2-butene from either vinylacetylene[1,2] or methyl vinyl ketone,[3] but no attempt was reported of the isolation and characterization of its two geometrical isomers. This is understandable, because the two isomers boil within 2 degrees of one another, and the higher boiling isomer rearranges to the lower boiling isomer rather readily.

Recently, 1,3-dichloro-2-butene has become available commercially and is called DCB.[4] It was possible, however, to obtain only the lower boiling isomer from this material probably because previous heating had rearranged the higher boiling isomer to the lower.

The two isomers of 1,3-dichloro-2-butene have now been prepared by the addition of hydrogen chloride to chloroprene. The isomers have been separated and various physical constants obtained. The same constants were also obtained for the corresponding isomeric chloro-alcohols (3-chloro-2-buten-1-ol). These data, together with available data from the literature, are given in Table I.

The 3,5-dinitrobenzoates were prepared from the dichlorides by use of silver 3,5-dinitrobenzoate and from the chloro-alcohols using 3,5-dinitrobenzoyl chloride. The high boiling chloro-alcohol gave a derivative of each isomer, probably because the hydrogen chloride (produced in the reaction) brought about interconversion.[5] This interconversion was also observed in the regeneration of the dichlorides from the corresponding chloro-alcohols. These interconversions of the high boiling isomer to the low boiling isomer would indicate that the high boiling isomer had the *cis* configuration. The geometrical configuration of the two isomers as indicated by their relative reactivities with potassium iodide,[6] cuprous chloride catalyzed hydrolysis[7] and sodium ethoxide[8] is discussed in the following paper.[9]

## Experimental

**Attempt to Obtain the Geometrical Isomers of 1,3-Dichloro-2-butene from Commercial Sources.**—Only the low boiling isomer of 1,3-dichloro-2-butenes ($n^{25}D$ 1.4695) was isolated from DCB[4] by distillation at various pressures down to 20 mm.

**Hydrochlorination of Chloroprene.**—Two moles of chloroprene distilled from a chloroprene solution[10] containing 50% xylene and 0.1% catechol by weight was shaken for twelve hours in a pressure bottle at room temperature with 37% hydrochloric acid (4 moles), 50 g. of cuprous chloride, and 20 g. of ammonium chloride. The reaction mixture was then cooled and the organic layer was separated and distilled at 20 mm. pressure through a 40-cm. vacuum-jacketed column without packing. A 58% yield of relatively pure high boiling 1,3-dichloro-2-butene ($n^{25}D$ 1.4708 to 1.4712) was obtained together with some unreacted chloroprene and polymers. Repeated distillations of the center cut at 20 mm. pressure caused no change in the refractive index of $n^{25}D$ 1.4711 if the kettle temperatures were no higher than 35–40°.

Attempts to cause hydrogen chloride to add to chloroprene at room temperature without the use of cuprous chloride or under anhydrous conditions were unsuccessful.

**Separation of the Isomeric 1,3-Dichloro-2-butenes.**—When the products from the hydrochlorination of chloroprene were distilled through a 4-ft. glass-helices packed column at atmospheric pressure with kettle temperatures in the range of 130–135° a 30–40% yield of relatively pure low boiling 1,3-dichloro-2-butene ($n^{25}D$ 1.4692–1.4699) was obtained. Further distillations at pressures of 1 atmosphere or less caused no further change in the refractive index of $n^{25}D$ 1.4695. Moreover, when the higher boiling isomer was distilled at atmospheric pressure, or even at pressures of 150 and 100 mm., only the lower boiling isomer could be obtained in appreciable quantities.

Apparently the high boiling isomer is the labile form and can readily be converted to the stable isomer by heat. Attempts to demonstrate this by maintaining the two isomers at 100° were unsuccessful primarily because polymerization occurred with both isomers, and the resulting products could not be identified. The rate of polymerization of the high boiling isomer exceeded that of the low boiling isomer, as indicated by changes in index of refraction.

Small quantities of each isomer were stored in dark bottles at 0° and at 27° for five months; no change of the index of refraction was observed, but a discoloration developed in each case.

(1) Carothers, Collins and Berchet, THIS JOURNAL, **54**, 4066 (1932).

(2) Carothers and Collins, U. S. Patent 2,102,611.

(3) Churbakov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 977 (1940).

(4) From E. I. du Pont de Nemours & Co., Wilmington, Delaware.

(5) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 454.

(6) Hatch, Gordon and Russ, THIS JOURNAL, **70**, 1093 (1948).

(7) Hatch and Roberts, *ibid.*, **68**, 1196 (1946).

(8) Hatch and Alexander, *ibid.*, **71**, 1037 (1949).

(9) Hatch and Ballin, *ibid.*, **71**, 1041 (1949).

(10) Commercial grade of chloroprene solution was furnished us for this work by the du Pont de Nemours Co., Wilmington, Delaware.

TABLE I

1,3-DICHLORO-2-BUTENE AND 3-CHLORO-2-BUTEN-1-OL

| | 1,3-Dichloro-2-butene (Low boiling) (alpha) | 1,3-Dichloro-2-butene (High boiling) (beta) | 3-Chloro-2-buten-1-ol (Low boiling) (alpha) | 3-Chloro-2-buten-1-ol (High boiling) (beta) |
|---|---|---|---|---|
| Boiling point, °C. (mm.) | 127.9 (745) | 129.9[f] (745) | 164.0[f] (738) | 166.0[f] (745) |
| | 127–128.5[a] | | 161–162[c] | |
| | 127–129[b] | | 115.5 (150) | |
| | 79 (150) | | 91.5 (50) | |
| | 53 (50) | | 92[d] (50) | |
| | 53–54[b] (50) | | | |
| | 33.3 (20) | 34.0 (20) | 72 (20) | 75.0 (20) |
| Freezing point, °C. | Below −75 | Below −75 | −40 | −47 |
| Index of refract. $n^{20}D$ | 1.4719 | 1.4735 | 1.4651 | 1.4673 |
| | 1.4695[a] | | 1.4678[c] | |
| | 1.4724[b] | | 1.4652[d] | |
| $n^{25}D$ | 1.4695 | 1.4711 | 1.4630 | 1.4653 |
| $n^{30}D$ | 1.4670 | 1.4687 | 1.4610 | 1.4633 |
| Density $d^{20}_4$ | 1.1585 | 1.1605 | 1.1099 | 1.1128 |
| | 1.1582[a] | | 1.1139[c] | |
| | 1.1591[b] | | 1.106[d] | |
| | 1.1952[e] | | | |
| $d^{25}_4$ | 1.1528 | 1.1542 | 1.1058 | 1.1085 |
| $d^{30}_4$ | 1.1465 | 1.1473 | 1.1014 | 1.1049 |
| Molecular refract. Calcd. | 29.94 | 29.94 | 26.60 | 26.60 |
| Molecular refract. Found | 30.21 | 30.24 | 26.53 | 26.52 |
| *Anal.*, % Cl Calcd. | 56.8 | 56.8 | 33.3 | 33.3 |
| *Anal.*, % Cl Found | 56.5, 57.0 | 56.6, 56.6 | 33.1 | 33.2 |
| 3,5-Dinitrobenzoate melting point °C. (cor.) | 75–76 | 58–59 | 75–76 | [g] |

[a] Churbakov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 977 (1940). [b] Carothers, Collins and Berchet, THIS JOURNAL, **54**, 4066 (1932). [c] Petrov, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1418–1424 (1940). [d] Klebanskii and Chevuichalova, *Sintet. Kauchuk* (1935) No. 6 (16–21) (1935), (*Chem. Abst.*, **30**, 1024 (1936)). [e] Tishchenko, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 658 (1937). Maybe this should have been 1.1592. [f] Determined by using a semimicro ebulliometer. [g] Apparently interconversion—both derivatives were isolated.

Various physical data for these dichlorides are given in Table I.

**3,5-Dinitrobenzoxy Derivative of the 1,3-Dichloro-2-butenes.**—The silver salt of 3,5-dinitrobenzoic acid was prepared by dissolving 4 g. of the acid in 80 ml. of 5% sodium hydrogen carbonate at room temperature. After filtration the solution was acidified with 10% nitric acid until the first permanent cloudiness of the free acid appeared. A 10% silver nitrate solution was added dropwise until no further silver salt precipitated. The product was filtered with suction, washed successively with hot water, ethanol, and ethyl ether, and dried in a vacuum desiccator. A 2-g. yield of a very light, flaky, white solid melting at 315° was obtained. Silver 3,5-dinitrobenzoate is very insoluble in water and all common organic solvents, but it dissolves readily in pyridine. It burns with a flame leaving a silver residue.

One gram of silver 3,5-dinitrobenzoate (0.0031 mole) was refluxed in 3 ml. of 95% ethanol with 0.3 ml. (0.0028 mole) of 1,3-dichloro-2-butene for one hour. The solid product was extracted with three 3-ml. portions of boiling ether, filtered and evaporated to dryness. The resulting yellowish solid was triturated with 5 ml. of 5% sodium carbonate solution and filtered with suction. More sodium carbonate solution followed by distilled water was used to wash the derivative.

Recrystallization of the benzoates from an ethanol–water solution produced nearly white crystals, melting at 75–76° for the low boiling dichloride, and 58–59° for the high boiling isomer. Further purification by this procedure produced no change in the melting points.

**Basic Hydrolysis of the 1,3-Dichloro-2-butenes.**—One hundred and twenty-five grams of the dichloride (1.0 mole) was treated with 106 g. of sodium carbonate (1.0 mole) in 2500 g. of water (4% sodium carbonate) in a 3-l. three-necked flask equipped with a stirrer. After three hours at 80° the two phases became homogeneous. The chloro-alcohol was distilled off as an azeotrope (98.1° for the low boiling isomer and 98.8° for the high boiling isomer). The aqueous layer in the distillate was further concentrated by distilling through a 3-ft column packed with glass helices; an additional quantity of the chloro-alcohol separated when the solution was saturated with sodium chloride. Yield of the crude 3-chloro-2-buten-1-ol was 75%.

**Catalytic Hydrolysis of the 1,3-Dichloro-2-butenes.**—The hydrolysis procedure used was similar to that for the basic hydrolysis except that the hydrolyzing solution contained 1.5% hydrochloric acid and enough copper (I) oxide to have 0.1 mole of cuprous chloride for each mole of allylic chloride and hydrogen chloride. The reaction was completed in less than a third of the time required for the basic hydrolysis, but the yield of the 3-chloro-2-buten-1-ol was not as high, because of a side reaction producing methylvinyl ketone.[9]

The isomeric chloro-alcohols were obtained by distillation through a 40-cm. column at 20 mm. pressure. As in the case of the corresponding dichloride, the high boiling isomer was readily converted to the low boiling, stable isomer by heat. Atmospheric boiling points were obtained on a semi-micro scale. The physical data obtained for these compounds are given in Table I.

**3,5-Dinitrobenzoate of the 3-Chloro-2-buten-1-ols.**—One ml. of each isomer of the chloro-alcohol was heated for ten minutes near its boiling point in a small test-tube with 0.5 g. of 3,5-dinitrobenzoyl chloride. The products were recrystallized from hot ethanol–water solution and identified by their melting points. The 3,5-dinitrobenzoxy derivative of the low-boiling 3-chloro-2-buten-1-ol melted at the same point as the 3,5-dinitrobenzoxy derivative of

the low boiling 1,3-dichloro-2-butene (75–6°). A mixture of the two dinitrobenzoxy derivatives also melted at 75–6°. The high boiling 3-chloro-2-buten-1-ol apparently gave a mixture of both isomers of 1-(3,5-dinitrobenzoxy)-3-chloro-2-butene.

**Regeneration of the 1,3-Dichloro-2-butenes from the 3-Chloro-2-buten-1-ols.**—Hydrogen chloride was passed for fifteen hours at room temperature into a 20-ml. sample of the chloro-alcohol contained in a small flask fitted with a reflux condenser. Heat developed at first, and there was an aqueous layer toward the end of the reaction. The product was washed twice with 25-ml. portions of water and dried over calcium chloride. Analysis by distillation at 20 mm. showed that while the corresponding dichloride was obtained from the low boiling chloro-alcohol, the high boiling isomer gave both isomeric 1,3-dichloro-2-butenes.

## Summary

The two geometrical isomers of 1,3-dichloro-2-butene have been prepared and the index of refraction, density, boiling point and the melting point of the 3,5-dinitrobenzoxy derivative of each isomer have been obtained.

The higher boiling isomer was converted into the lower boiling isomer at its boiling point, but it was stable at room temperature.

The index of refraction, density, freezing point, and boiling point of each isomer of 3-chloro-2-buten-1-ol have also been determined.

The low boiling 3-chloro-2-buten-1-ol gave the same 3,5-dinitrobenzoxy derivative as the low boiling dichloride but the high boiling chloro-alcohol gave a mixture of the two isomeric benzoates.

The high boiling 3-chloro-2-buten-1-ol is converted to the low boiling isomer by heat, and when treated with hydrogen chloride, a mixture of the isomeric 1,3-dichloro-2-butenes is formed.

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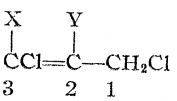
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

# Allylic Chlorides. VII. Relative Reactivities of the 1,3-Dichloro-2-butenes

BY LEWIS F. HATCH AND STUART G. BALLIN

Current work on allylic chlorides has shown that geometrical isomerism plays an important part in determining the reactivity of the allylic chlorine with potassium iodide in acetone,[1] sodium ethoxide in ethanol,[2] and in the cuprous chloride catalyzed hydrolysis reaction.[3] These studies have been made using dichlorides with the basic structure



where X and Y are either both hydrogens, or where X is hydrogen and Y is a methyl group.

The recent availability of the two isomers of 1,3-dichloro-2-butene[4] has made possible an extension of this investigation to include a compound where X is a methyl group and Y is hydrogen. A compound of this type should be especially useful in evaluating the influence of steric hindrance of groups on the number 3 carbon for an $S_N2$ type reaction involving the number 1 carbon. A study of the influence of the relative position of the vinyl chlorine has been made by Tishchenko[5] for hydrolysis using calcium carbonate and water. He made no effort to separate the two isomers of 1,3-dichloro-2-butene.

## Experimental

**1,3-Dichloro-2-butenes.**—The isomeric 1,3-dichloro-2-butenes were prepared by the addition of hydrogen chloride to chloroprene.[4] They had the following physical properties: low boiling (alpha) isomer: b. p. (20 mm.) 33.3°; $n^{25}D$ 1.4695; $d^{25}_4$ 1.1528; high boiling (beta) isomer: b. p. (20 mm.) 34.0°; $n^{25}D$ 1.4711; $d^{25}_4$ 1.1542.

**Catalytic Hydrolysis with Cuprous Chloride in Hydrochloric Acid.**—The procedure previously reported[3] was modified to permit the use of the more stable cuprous oxide (Baker C. P. Analyzed, 98.8%) instead of cuprous chloride. One-fourth gram (0.0017 mole) of cuprous oxide was placed in a 200-ml. 3-necked flask fitted with a stirrer, condenser, and combination thermometer-well and carbon dioxide delivery tube. One hundred milliliters of 1.5% hydrochloric acid (0.041 mole) was added to the reaction flask and the cuprous oxide dissolved in about fifteen minutes at 75–85°. Carbon dioxide was slowly passed over the surface of the solution from the time the hydrochloric acid was added to the flask until the run was completed.

A five gram sample of the 1,3-dichloro-2-butene was weighed to the nearest milligram into 4 gelatin capsules (size 000). These capsules were added to the flask by removing the condenser, and dissolved within ten seconds under vigorous stirring. The reaction was carried out at a temperature of 40 ± 0.5°. At the end of the desired time the reaction mixture was cooled to 20° in about three minutes and a 1-ml. sample of the aqueous layer was pipetted into 50 ml. of distilled water containing 2 ml. of 10% sodium hydrogen carbonate solution. The extent of reaction was determined from the increase in chloride ion in a manner similar to that previously reported.[3]

Data for the hydrolysis of both isomers are given in Table I and Fig. 1. Both isomers gave chloride ion concentrations indicating that both chlorine atoms were hydrolyzable under the conditions of the reaction. The lower boiling isomer (alpha) gave the following data in addition to those in Table I: 6.25 hours, 122.0%; 9.00 hours, 131.5%.

The reaction mixtures apparently contained in addition to 3-chloro-2-buten-1-ol, a relatively large amount of methyl vinyl ketone. Tishchenko has reported[5] the formation of about 2% methyl vinyl ketone when 1,3-dichloro-2-butene was hydrolyzed with calcium carbonate.

**Attempted Catalytic Hydrolysis of 3-Chloro-2-buten-1-ol.**—Attempts were made to hydrolyze the vinyl chlorine of the lower boiling isomer of 3-chloro-2-buten-1-ol using the same conditions as used for the dichloride. There was no appreciable hydrolysis in half an hour at 40°, 60°, 80° or in 4.5 hours at 60°.

(1) Hatch, Gordon and Russ, THIS JOURNAL, **70**, 1093 (1948).
(2) Hatch and Alexander, *ibid.*, **71**, 1037 (1949).
(3) Hatch and Roberts, *ibid.*, **68**, 1196 (1946).
(4) Hatch and Ballin, *ibid.*, **71**, 1039 (1949).
(5) Tishchenko, *J. Gen. Chem.* (*USSR*), **7**, 658 (1937).

TABLE I

RELATIVE REACTIVITIES OF THE 1,3-DICHLORO-2-BUTENES

| | | | | | | |
|---|---|---|---|---|---|---|
| **Hydrolysis with Cuprous Chloride at 40°** | | | | | | |
| Low boiling | Time, hr. | 0.50 | 1.00 | 2.00 | 3.50 | 4.50 |
| | % reacted | 17.3 | 32.8 | 57 3 | 89.5 | 101.5 |
| High boiling | Time, hr. | 0.50 | 1.00 | 2.00 | 4.00 | 8.00 |
| | % reacted | 25.9 | 42.7 | 69.3 | 106.5 | 141.2 |
| **Reaction with Potassium Iodide in Acetone at 20°** | | | | | | |
| Low boiling | Time, min. | 15 | 30 | 45 | 54 | 80 |
| | % reacted | 44.6 | 62.7 | 77.9 | 83.6 | 94.7 |
| | $k$ | 5.40 | 4.63 | 4.85 | 4.90 | 5.57 |
| | Av. $k$ | | | 5.07 | | |
| | Relative reactivity[a] | | | 23.3 | | |
| High boiling | Time, min. | 12 | 24 | 36 | 54 | 72 |
| | % reacted | 40.4 | 64.5 | 79.2 | 88.4 | 94.6 |
| | $k$ | 5.88 | 6.09 | 6.32 | 5.91 | 6.13 |
| | Av. $k$ | | | 6.07 | | |
| | Relative reactivity[a] | | | 27.8 | | |
| **Reaction with Sodium Ethoxide in Ethanol in 50°** | | | | | | |
| Low boiling | Time, hr. | 3.00 | 4.00 | 5.00 | 6.00 | 7.00 |
| | % reacted | 42.5 | 48.9 | 54.5 | 58.7 | 61.1 |
| | $k$ | 5.62 | 5.89 | 5.64 | 5.74 | 5.49 |
| | Av. $k$ | | | 5.68 | | |
| | Relative reactivity[b] | | | 4.77 | | |
| High boiling | Time, hr. | 3.00 | 4.00 | 5.00 | 6.00 | 7.00 |
| | % reacted | 46.5 | 56.3 | 61.1 | 64.3 | 66.5 |
| | $k$ | 6.80 | 7.75 | 7.68 | 7.31 | 7.12 |
| | Av. $k$ | | | 7.33 | | |
| | Relative reactivity[b] | | | 6.16 | | |

[a] Allyl chloride as 1.00 with $k$ = 0.218. [b] Allyl chloride as 1.00 with $k$ = 1.19 (Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 119 (1941)).

**Reaction with Potassium Iodide in Acetone.**—The same procedure was used as previously described.[1] Reaction rates and other data are given in Table I.

**Reaction with Sodium Ethoxide in Ethanol.**—These rates were also determined using a previously described procedure.[2] The concentration of the 1,3-dichloro-2-butenes was 0.1000 molar and the sodium ethoxide solution in ethanol was 0.0905 molar. The rate constants and other data are also given in Table I.

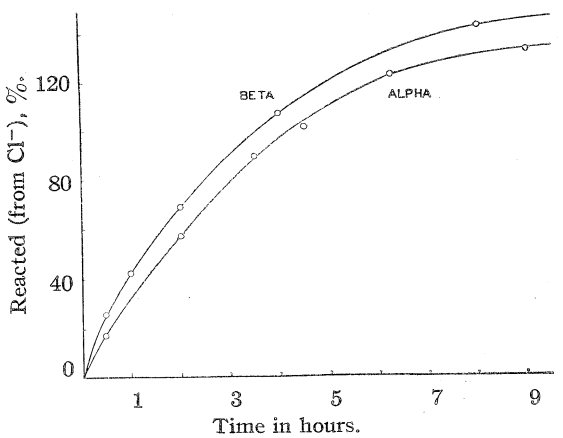



Fig. 1.—Catalytic hydrolysis of 1,3-dichloro-2-butene with cuprous chloride in hydrochloric acid.

## Discussion

Previous work on the influence of geometrical isomerism on the reactivity of allylic chlorides has been with isomers of the types Cab–Cad and Cab–Cdc. The *cis* configuration for the latter type has been assigned to the isomer with the vinyl chlorine and the chloromethyl group on the same side of the molecule. The same convention is used with 1,3-dichloro-2-butene.

Neither of the isomers of either 1,3-dichloropropene or 1,3-dichloro-2-methyl-1-propene undergoes interconversion to the more stable form at its boiling point. With 1,3-dichloro-2-butene, however, the higher boiling isomer is readily converted at its boiling point to the lower boiling isomer.[4] Usually the *cis* form of geometrical isomers is the labile form and the *trans* form the stable one. The higher boiling (beta) isomer of 1,3-dichloro-2-butene is therefore tentatively assigned the *cis* configuration and the lower boiling (alpha) isomer the *trans* configuration.

It has previously been proposed from chemical evidence that the higher boiling isomers of both 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene have the *cis* configuration. Chemical evidence of the type obtained in these studies, however, may be amenable to several interpretations. Andrews and Kepner[6] have interpreted some of these results in such a way as to indicate that the higher boiling isomers have the *trans* configuration.

**Catalytic Hydrolysis.**—From the nature of the reaction and the errors inherent in following its course it has not been considered desirable to calculate a rate constant for the cuprous chloride catalyzed hydrolysis of 1,3-dichloro-2-butene. Figure 1 gives a graphic indication of the differences in rate of reaction between the two isomers.

As with 1,3-dichloropropene[3,7] the high boiling isomer of 1,3-dichloro-2-butene is the more reactive, but the difference in reactivity between the two isomers is not as great as it is between the isomers of 1,3-dichloropropene. This would indicate that a methyl group on the number 3 carbon of the *cis* isomer offers some interference to this reaction, although the over-all effect of a methyl group on this carbon is one of activation.

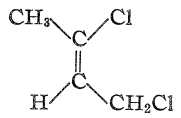
The fact that both chlorines of 1,3-dichloro-2-butene are hydrolyzable by cuprous chloride in hydrochloric acid while the vinyl chlorine in 3-chloro-2-buten-1-ol is not hydrolyzed under the same conditions is being studied further. Because both chlorines are removed from the dichloride, it was not possible to compare the rate of reaction of this compound with 1,3-dichloropropene to evaluate the effect of replacing a hydrogen on the number 3 carbon with a methyl group.

**Potassium Iodide.**—An interpretation of the results of the $S_N2$ reaction of potassium iodide with 1,3-dichloro-2-butene is based on the assumption that the reaction involves a nucleophilic attack on the carbon atom holding the allylic chlorine. A reaction of this type would be inhibited by the group in the *cis* position on the number 3 carbon with the size of the group governing the degree of inhibition. With 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene the two substit-

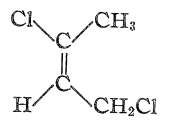
(6) Andrews and Kepner, THIS JOURNAL, **69**, 2230 (1947).

(7) Data for the 1,3-dichloro-2-methyl-1-propenes will be given in a forthcoming paper.

uents are chlorine and hydrogen with a consequent wide difference in the relative reactivity of the geometrical isomers. When the two substituents are chlorine and a methyl group as with 1,3-dichloro-2-butene the difference in reactivity is only slight with the *cis* form being the most reactive.




*cis*, more reactive




*trans*, less reactive

The larger methyl group would be expected to cause the *trans* isomer to be less reactive.

A methyl group increases the reactivity of the allylic chlorine for this reaction when it is not in the *cis* position, where its activating effect is counteracted by its steric hindrance. This activation of the allylic chlorine by a methyl group on the number 3 carbon has been noted by Tamele, *et al.*,[8] and in these laboratories with 1-chloro-3-methyl-2-butene.[9]

**Sodium Ethoxide.**—The two isomers of 1,3-dichloro-2-butene show a relatively small difference in reactivity with the higher boiling isomer being the more reactive. This is similar to the results obtained with 1,3-dichloropropene and 1,3-dichloro-2-methyl-1-propene[2] and provides further evidence that this reaction is of a type different from that with potassium iodide and is only slightly affected by geometrical isomerism. As with the reaction with potassium iodide, substituting a methyl group for a hydrogen on the number 3 carbon increases the reactivity of the allylic chlorine. This observation has also been made by Tamele, *et al.*[8]

(8) Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

(9) Unpublished work of Louis S. Gerhardt.

## Summary

The relative reactivity of the geometrical isomers of 1,3-dichloro-2-butene has been determined for their reaction with potassium iodide, sodium ethoxide, and the cuprous chloride catalyzed hydrolysis reaction.

The high boiling (beta) isomer was the most reactive with each reagent.

The high boiling (beta) isomer is converted at its boiling point into the low boiling (alpha) isomer.

For these reasons the low boiling (stable) isomer of 1,3-dichloro-2-butene has tentatively been assigned the *trans* structure.

A methyl group on the number 3 carbon increases the reactivity of the allylic chlorine of 1,3-dichloro-2-butene.

AUSTIN, TEXAS RECEIVED APRIL 20, 1948

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[CONTRIBUTION FROM PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

# Preparation and Properties of Certain Alkyl Azamalonates[1]

BY CHESTER E. SLIMOWICZ AND ED. F. DEGERING

Although urethan, or ethyl carbamate, and many of its derivatives have been investigated as physiologically active agents,[2,3] no record has been found of a similar study of the unsubstituted alkyl azamalonates. The preparation of a few of these compounds has been reported, namely, ethyl methyl,[6] dimethyl,[7] diethyl,[4] and the ethyl phenyl[5] azamalonates.

Recently, Tompkins and Degering[10] have described a series of N-substituted diethyl azamalonates. In connection with this work, it was deemed desirable to prepare a series of N-unsubstituted azamalonates of the general formula ROOCNHCOOEt. These compounds were prepared by a modification of the procedure employed by Kraft.[8] The reaction may be represented by the equations

$$H_2NCOOEt + Na \longrightarrow H(Na)NCOOEt + {}^1/_2H_2, \text{ then}$$
$$H(Na)NCOOEt + ClCOOR \longrightarrow ROOCNHCOOEt + NaCl$$

It was found, however, that besides the expected mixed alkyl ethyl ester there were obtained the symmetrical diethyl and dialkyl di-esters. It is significant to note that the yield of the dialkyl di-ester, in general, was higher than that for the expected mixed ester. This result may be interpreted by assuming that a redistribution reaction occurred.

The compounds were either white crystalline solids having fairly low melting points, or colorless liquids having high boiling points. In all cases the di-esters were solids and the mixed esters were liquids. All of the compounds were generally soluble in the common organic solvents and insoluble in water. Their identification was based

(1) Abstracted from a thesis presented by Chester E. Slimowicz to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Master of Science, Feb., 1947.

(2) Dixon, "Manual of Pharmacology," Arnold, London, 1908, p. 68.

(3) Hirshfelder and Bieter, *Physiol. Rev.*, **12**, 190 (1932).

(4) Diels, *Ber.*, **36**, 736 (1903); see also refs. 6, 8, 9a, 9b, 9c.

(5) Diels and Jacoby, *ibid.*, **41**, 2397 (1908).

(6) Diels and Nawiasky, *ibid.*, **37**, 3672 (1904).

(7) Franchimont and Klobbie, *Rec. trav. chim.*, **8**, 294 (1889).

(8) Kraft, *Ber.*, **23**, 2786 (1890).

(9) (a) Wurtz and Henninger, *Chem. Zentr.*, **56**, 564 (1885); (b) *Bull. soc. chim.*, **44**, 30 (1885); (c) *Compt. rend.*, **100**, 1419 (1885).

(10) Tompkins with Degering, THIS JOURNAL, **69**, 2616 (1947).

TABLE I

ALKYL AZAMALONATES, $RO_2C{\cdot}NH{\cdot}CO_2R'$

| Compound | M. p., °C.[a] | B. p. °C. | Mm.[b] | $n^{27}D$ | Molecular formula | Nitrogen, % Calcd. | Found | Fungicidal properties[c] % Inhibition[d] *A. Niger*,[e] *M* 0.01 | 0.001 | *Trichoderma T-1*,[f] *M* 0.01 | 0.001 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diethyl | 49–50 | | | | $C_6H_{11}O_4N$ | 8.70 | 8.71 8.50 | 66 | 18 | 50 | 35 |
| Butyl ethyl | | 104–106 | 4 | 1.4407 | $C_8H_{15}O_4N$ | 7.41 | 7.24 7.44 | 87 | 53 | 100 | 65 |
| Dibutyl | 42–43 | | | | $C_{10}H_{11}O_4N$ | 6.45 | 6.34 8.28 | 100 | Y | 100 | Y |
| Allyl ethyl | | 112–115 | 3 | 1.4544 | $C_7H_{11}O_4N$ | 8.10 | 8.43 8.11 | 60 | 29 | 49 | 13 |
| Diallyl | 43–45 | | | | $C_8H_{11}O_4N$ | 7.57 | 7 66 7.78 | 65 | 22 | 45 | +1 |
| Amyl ethyl | | 102–106 | 1 | 1.4395 | $C_9H_{17}O_4N$ | 6.90 | 6.99 6.87 | 100 | 60 | 100 | 71 |
| Diamyl | 61–62 | | | | $C_{12}H_{23}O_4N$ | 5.71 | 5.80 5.71 | 76 | 66 | 67 | 83 |
| Ethyl hexyl | | 111–116 | 2 | 1.4468 | $C_{10}H_{14}O_4N$ | 6.45 | 6.25 6.72 | 87 | 80 | 83 | 65 |
| Dihexyl | 39–40 | | | | $C_{14}H_{27}O_4N$ | 5.13 | 4.92 5.01 | 88 | 82 | 79 | 79 |
| Ditetradecyl | 77–78 | | | | $C_{30}H_{59}O_4N$ | 2.82 | 2.96 3.02 | X | 3 | X | +88 |

[ab] Melting and boiling points are uncorrected. [c] Results are averages of triplicates. One hundred per cent. inhibition on all standard G-4. 2,2'-Methylene bis-(4-chlorophenol) control plates at 0.01 or 0.001 *M*. No tests performed with *Chaetomium globosum* since medium is not yet satisfactory. No tests performed with *Penicillium citrinum* since this organism is to be used only with mercury containing compounds. [d] % Inhibition = 100 − (Radial growth in mm. per hr. of test compound plate/radial growth in mm. per hr. of untreated control plate × 100). An interesting fungicide is considered to be one which would show 100% inhibition at concentrations of 0.001 *M* or lower. [e] *A. Niger* is TC 215-4247, Steinberg. [f] *Trichoderma T-1* is A. T. C. C. 9645. Y = not tested at this concentration. X = sample insufficient to test at this concentration. + Figures indicate that test compound plate growth exceeded that of normal untreated control.

on the characterization of the saponification products of each and on nitrogen determinations.

The compounds prepared, together with the evaluation of their fungicidal activity and their physical properties are summarized in Table I.

## Experimental[11]

The alkyl chloroformates used in this investigation were prepared by a method developed in this Laboratory by Engelman and Degering[12] in which yields of 85 to 95% were obtained.[13] Other investigators have reported yields approximately half these values.[14] The reactions were carried out in an efficiently ventilated hood.

The following examples may be considered as typical.

**Butyl Chloroformate.**—One mole (74 g.) of butyl alcohol was added dropwise (or in small amounts, if the alcohol is a solid), with stirring, to a half-molar excess (85 g.) of liquid phosgene contained in a large $1^1/_2'' \times 12''$ test-tube immersed in a salt–ice, or Dry Ice–trichloroethylene bath. (The latter was found a little more convenient to handle.) The reaction temperature during the addition of the alcohol was maintained at 0°, or slightly lower, otherwise the formation of the carbonate is favored. When all of the alcohol had been added, the bath temperature was allowed to rise very slowly to room temperature. (During this period the stopcock of the dropping funnel, which was protected by a drying tube filled with calcium chloride, was left open to permit the escape of excess phosgene. In case the phosgene boiled off too rapidly, it was necessary to cool the bath.) Then the reaction mixture was stirred ten to fifteen hours. The stirrer and dropping funnel arrangement was replaced by a stopper containing an inlet tube extending to the bottom of the reaction vessel and an outlet tube. The inlet tube was connected to a source of air and the reaction mixture aerated to expel the excess phosgene. As a precautionary measure the outlet tube was extended well into the hood vent by means of a rubber tubing connection.

After all of the phosgene had been expelled, the butyl chloroformate was purified[15] by distillation at reduced pressure. The fraction, b. p. 35–36° (13 mm.), weighed 117 g. (85% of the theoretical yield).

**Butyl Ethyl and Dibutyl Azamalonates.**—One mole (89 g.) of urethan was dissolved in 1.2 l. of xylene (purified grade) contained in a 3-l., three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and water-cooled reflux condenser protected by a drying tube filled with anhydrous calcium chloride. One gram atom (23 g.) of metallic sodium was added and the mixture stirred and heated cautiously until all of the sodium had reacted. When the mixture had cooled to approximately 60°, one mole (136 g.) of butyl chloroformate was added dropwise. An exothermic reaction accompanied the addition of the chloroformate. The mixture was stirred at room temperature for approximately thirty hours, after which time it was filtered through a fritted glass filter. Three to five grams of filter-cel was stirred in with the mixture prior to filtration in order to facilitate the separation of the finely precipitated sodium chloride.

A red-brown colored oil was obtained from the filtrate after the solvent had been distilled at reduced pressure. On distillation, 116 g. of colorless liquid, b. p. 138–150° (13 mm.), was collected. This distillate was fractionated to give 20 g. of solid, b. p. 90–104° (3–4 mm.); 52 g. of liquid, b. p. 104–115° (3–4 mm.); and 42 g. of a solid pot residue.

The 20 g. fraction was recrystallized twice from petroleum ether (60–70°) to yield 14 g. of fine white needles, m. p. 48–50°. A mixture of this product with an authentic specimen of diethyl azamalonate, m. p. 49–50°, did not depress the melting point.

The 52 g. fraction was rectified in a 24-in. Podbielniak type column and yielded 25 g. of colorless liquid, b. p. 104–106° (4 mm.). Five grams of this product was refluxed for thirty hours with 40 ml. of 40% aqueous sodium hydroxide. The distillate from the alkaline solution was saturated with anhydrous potassium carbonate. The resulting alcoholic phase was pipetted into a 10-ml. Vigreux type distilling flask and fractionated to give one fraction distilling up to 85°, and the other, 85–115°. The lower boiling fraction gave positive iodoform and ceric nitrate tests; the higher boiling one gave a negative iodoform test and a positive ceric nitrate test. Each of these fractions was treated with 0.5 g. of 3,5-dinitrobenzoyl chloride to yield an ester, m. p.'s 90–91° and 62–63°, respectively, for the lower and higher boiling fractions. The

(11) All melting and boiling points are uncorrected.

(12) Engelman, Doctoral thesis, Purdue University, Feb., 1948.

(13) A thorough search of the literature by the junior author of this paper, however, disclosed that Thiele used a similar procedure in the synthesis of benzyl chloroformate, but failed to report the yield; Thiele and Dent, *Ann.*, **302**, 257 (1898).

(14) Hamilton and Sly, THIS JOURNAL, **47**, 437 (1925).

(15) Tetradecyl chloroformate was not distillable.

reported melting point for the ethyl ester is 93°; for butyl 64°.[16]

*Anal.* Calcd. for $C_8H_{15}O_4N$: N, 7.41. Found: N, 7.24, 7.44.

The 42-g. pot residue was recrystallized three times from ether–petroleum ether mixture to yield 38 g. of fine white needles, m. p. 42–43°. Four grams of this solid was saponified in the manner previously described. The saponification distillate gave a positive ceric nitrate test and a negative iodoform test. Treatment of the alcoholic phase of the distillate with 3,5-dinitrobenzoyl chloride resulted in an ester, m. p. 63–64°. The reported melting point for butyl 3,5-dinitrobenzoate is 64°.[16]

*Anal.* Calcd. for $C_{10}H_{19}O_4N$: N, 6.45. Found: N, 6.34, 6.28.

(16) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 185.

**Acknowledgment.**—The authors wish to express their appreciation to the Hooker Electrochemical Company for the generous supply of allyl chloroformate.

## Summary

The synthesis of a number of new alkyl azamalonate has been described and a redistribution reaction has been postulated for the formation of the symmetrical di-esters. These compounds are to be tested for their pharmacological activity.

Fungicidal data are presented.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED, HUNGARY]

# A Synthesis of Adrenaline-like Compounds

BY GÁBOR FODOR AND ÖDÖN KOVÁCS

According to a recent review[1] on the subject, the best method of obtaining aryl methylaminoethanols, *e. g.*, synephrine, is the condensation of ω-chloro-*p*-benzoyloxyacetophenone with methylbenzylamine, followed by hydrolysis and subsequent hydrogenation.[2] Another useful method[3] consists of the condensation of hydroxy derivatives of benzaldehyde bisulfite with a salt of nitromethane, followed by the reductive condensation of the nitro ethanol with formaldehyde[3] to the corresponding aryl aminoethanol.

An excellent synthesis of ephedrine is described by Manske and Johnson[4] from phenyl methyl methyl diketone with methylamine. In this process the authors applied, for the first time, ketonic aldehydes and diketones as starting materials[5]; no similar reactions have been reported previously in the literature.

However, the use of methoxy and hydroxy derivatives, even in the case of diketones, offered some difficulties. It was thought, therefore, to be of interest to work out a synthesis of hydroxy aryl ethanolamines, starting from hydroxy arylglyoxals, similar to that of phenyl-methylaminopropanol.[4]

4-Hydroxyphenylglyoxal[6] (II) has been obtained from phenol through 4-hydroxyphenyltrichloromethyl-carbinol.[7] We have synthesized it in another manner: first, 4-hydroxyacetophenone (I) was prepared according to Meerwein.[8] This was then oxidized with selenium dioxide, without protecting the phenolic group, to 4-hydroxyphenylglyoxal; this latter was isolated as a crystalline hydrate and further identified by its well defined quinoxaline derivative (V). Several attempts were made for the condensation of this ketonic aldehyde with methylamine, with subsequent or simultaneous reduction of the azomethine formed (III). However, when this amorphous compound or an equimolecular mixture of the glyoxal and of methylamine was reduced catalytically, a sudden initial reaction occurred, but the hydrogen consumption stopped with an absorption of only 0.5 to 0.8 mole of hydrogen against the calculated 2 moles. The expected 1-(4-hydroxyphenyl)-2-methylamine ethanol (IV) could not be obtained from the reaction mixture. We supposed that our failure to obtain the desired compound was due to the fact that the 4-hydroxyphenylglyoxal reacted with methylamine in much the same manner as phenylglyoxal, which gives heterocyclic condensation products with hydroxylamine,[9] ammonia[10] and methylamine.[11] In order to prevent these undesired reactions, we carried out experiments in which the azomethine was reduced instantaneously after its formation: the alcoholic solution of 4-hydroxy-phenylglyoxal was added under vigorous mechanical stirring drop by drop to a suspension of palladium on charcoal in an alcoholic solution of methylamine in a hydrogen atmosphere. Two moles of hydrogen were consumed for each mole of 4-hydroxy phenylglyoxal hydrate and a colorless solution resulted giving 1-(4′-hydroxyphenyl)-2-methylaminoethanol with good yield and high degree of purity. It seems, there-

(1) Priestley and Moness, *J. Org. Chem.*, **5**, 355 (1940).

(2) Stolz and Hallensleben, *Chem. Zentr.*, **102**, II, 1056 (1931), German Patent 526,087.

(3) Kamlet, *ibid.*, **110**, II, 3451 (1939).

(4) Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

(5) Manske, *ibid.*, **51**, 1907 (1929).

(6) Boehringer, *Chem. Zentr.*, **101**, II, 2442 (1930), German Patent 496,646.

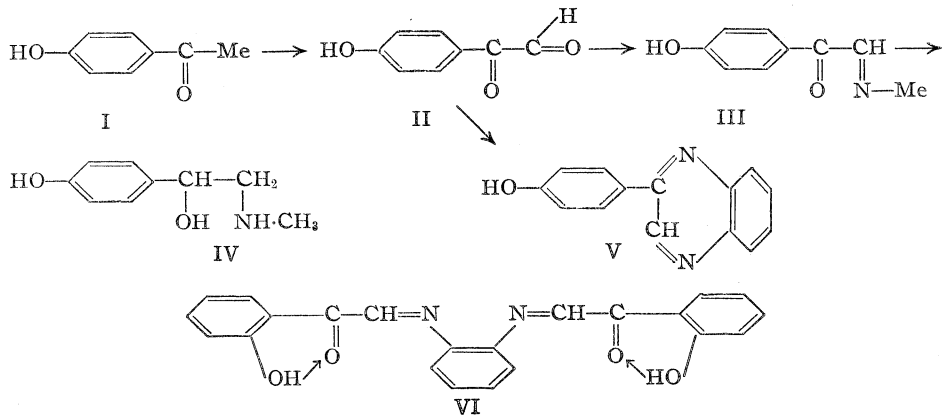
(7) Pauly and Schanz, *Ber.*, **56**, 981 (1923); *cf.* Austrian Patent 141,159.

(8) Meerwein, *Ber.*, **66**, 411 (1933).

(9) Angelico and Cusmano, *Gazz. chim. ital.*, **66**, 791 (1936).

(10) Müller and Pechmann, *Ber.*, **22**, 2559 (1889); *cf.* Pinner, *ibid.*, **35**, 1134 (1902).

(11) Gastaldi, *Gazz. chim. ital.*, **51**, 233 (1921).




fore, that the methylamine did not react with the ketonic group of the arylglyoxal (II).

Phenylglyoxal reacts with aminoguanidine in alkaline medium similarly as an aldehyde, whereas in acid medium a selective condensation of the ketonic group occurs.[12]

2-Hydroxyacetophenone[13] (Type I) was converted in a similar manner into the 2-hydroxy phenylglyoxal (Type II), characterized by its crystalline condensation product (VI) with *o*-phenylenediamine. Two moles of this *o*-hydroxy ketonic aldehyde reacted only with their aldehyde groups with one mole of diamine, as the ketonic group could be chelated by the *o*-standing hydroxy group, a hydrogen bridge being formed. Hydrogenation of 2-hydroxyphenylglyoxal by the method described above led to *o*-synephrine[14] (Type IV). 3-Hydroxyphenylglyoxal was obtained in the same way from 3-hydroxyacetophenone[15] and converted into the crystalline quinoxaline derivative.

4-Methoxyacetophenone[16] gave on oxidation with selenium dioxide the crystalline 4-methoxyphenylglyoxal hydrate (Type II). On reducing the latter together with methylamine, the expected amino alcohol could not be obtained; however, 1-(4′-methoxyphenyl)-ethanediol-1,2 was isolated with a good yield. Phenylglyoxal was converted similarly into 1-phenyl-ethanediol-1,2. In these cases the hydrogenation reaction of the ketonic aldehydes has a greater velocity than their condensation reaction with methylamine.

In order to employ the method for the synthesis of adrenaline derivatives, *e. g.*, N-isopropyl-nor-adrenaline,[17] it was necessary to prepare 3,4-dihydroxyphenylglyoxal as an intermediate. This was obtained by the oxidation of 3,4-diacetoxyacetophenone[18] to the corresponding 3,4-diacetoxyphenylglyoxal and subsequent hydrolysis with boiling water. It could not be obtained by the direct oxidation of 3,4-dihydroxyacetophenone with selenium dioxide as the *o*-hydroxy groups are oxidized prior to the methyl group.

When 3,4-dihydroxy phenylglyoxal was reduced catalytically together with isopropylamine, N-isopropylamino-nor-adrenaline[17] was obtained, as sulfate. We synthesized the same compound also from 3,4-dibenzyloxy phenylglyoxal, prepared from 3,4-dibenzyloxyacetophenone[19] with selenium dioxide, by reductive condensation with isopropylamine with a simultaneous hydrogenolysis of the benzyl ether linkage.

It is surprising that under our experimental conditions reductive condensation occurs smoothly only in the presence of free phenolic hydroxyl.

This 3-step synthesis of synephrine is far simpler than those discussed by Priestley and Moness,[1] or by Kamlet.[3] The new synthesis of N-isopropyl-nor-adrenaline, from catechol, via diacetoxyacetophenone and dihydroxyphenylglyoxal is also useful, as only these two intermediates must be isolated. The method is consequently of general value for the preparation of hydroxyaryl ethanolamines.[20]

## Experimental

**Phenylglyoxal hydrate**[21] was converted in a concentrated aqueous solution into 2-phenylquinoxaline,[22] m. p. 78°.

**4-Hydroxyphenylglyoxal Hydrate.**—Twenty-two and two-tenths grams (0.2 mole) of selenium dioxide was dissolved in 120 ml. of dioxane and 4 ml. of water at 60°, then 27.2 g. (0.2 mole) of 4-hydroxyacetophenone[8] was added and the reaction mixture boiled for four hours in a steam-bath. The separated selenium was filtered off, the yellow solution was evaporated in vacuum at 40°. The residue was treated with 150 ml. of water on the steam-bath for three hours under stirring, the resulting solution decolorized with charcoal, filtered and concentrated to a small volume. The yellowish colored hydrate crystallized. Yield was 31.4 g. (87%). Recrystallized from the fourth amount of water, 27 g. of greenish white prisms was obtained, m. p. 111°.[6] Oxidation in alcoholic solution gave a similar

(12) Ekeley, Carlson and Ronzio, *Rec. trav. chim.*, **59**, 496 (1940).
(13) Friedländer and Neudörfer, *Ber.*, **30**, 1080 (1897).
(14) Legerlotz, German Patent 522,790.
(15) Rupe and Majewski, *Ber.*, **33**, 3407 (1900).
(16) Kästner, "Neuere Methoden d. präparativen organischen Chemie," Verlag Chemie, 1941, p. 413.
(17) Boehringer, Schwitzer Patent 214,499.
(18) Voswinckel, *Ber.*, **42**, 4653 (1911).
(19) Dützmann and Krauss. *Chem. Zentr.*, **96**, II, 612 (1925).
(20) Servita, Ltd., Fodor and Kovács, Hungarian Patent Appl. no. S-20,468.
(21) Organic Syntheses, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 509.
(22) Fischer and Schindler, *Ber.*, **39**, 2243 (1906).

(85%) yield; whereas in aqueous solution only 42% 4-hydroxyphenylglyoxal could be obtained.

**2-(4'-Hydroxyphenyl)-quinoxaline** was recrystallized from methanol as white plates, m. p. 204°.

*Anal.* Calcd. for $C_{14}H_{10}ON_2$: C, 75.66; H, 4.54. Found: C, 75.85; H, 4.68.

**4-Methoxyphenylglyoxal Hydrate.**—A mixture of 50 ml. of dioxane, 2 ml. of water, 11.1 g. (0.1 mole) of selenium dioxide and 15 g. (0.1 mole) of 4-methoxyacetophenone[16] was refluxed for forty-eight hours. After removal of selenium and of the solvent, the oily residue was treated with 500 ml. of water at 100° for four hours with stirring, the solution was clarified with charcoal, the hydrate crystallized on cooling. A second crop of crystals was obtained by concentrating the solution: yield was 15 g. (82%), m. p. 84°.

**2-(4'-Methoxyphenyl)-quinoxaline.**—Long colorless needles, from ethanol, m. p. 102°.

*Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 75.76; H, 5.12. Found: C, 75.99; H, 4.88.

**3-Hydroxyphenylglyoxal.**—A mixture of 10 g. of selenium dioxide (0.09 mole), 60 ml. of dioxane, 2 ml. of water and 13.6 g. (0.1 mole) of 3-hydroxyacetophenone[15] was refluxed for twenty hours, then worked up as described above. The hydrate, 14.3 g., could not be crystallized. It was identified by its crystalline quinoxaline derivative.

**2-(3'-Hydroxyphenyl)-quinoxaline.**—Yellow needles from ethanol, m. p. 169°.

*Anal.* Calcd. for $C_{14}H_{10}ON_2$: C, 75.66; H, 4.54. Found, C, 75.64; H, 4.65.

**2-Hydroxyphenylglyoxal.**—Thirteen and six-tenths grams (0.1 mole) of 2-hydroxyacetophenone[13] was oxidized in the same manner as described before. The oily glyoxal derivative, 12.1 g., could not be crystallized for identification; it was condensed with *o*-phenylenediamine.

**1,2-*bis*-(2'-Hydroxyphenyl-glyoxalylidene)-phenylenediamine.**—One and forty-three hundredths grams of the oily product was dissolved in 5 ml. of water, a hot solution of 1 g. *o*-phenylenediamine was added and the separated yellowish crystals filtered off. Recrystallization from ethanol produced delicate needles, 1.72 g., m. p. 295°.

*Anal.* Calcd. for $C_{22}H_{16}O_4N_2$: C, 70.79; H, 4.33; N, 7.54. Found: C, 70.69; H, 4.19; N, 7.20.

**3,4-Dibenzyloxyphenylglyoxal.**—From 10 g. (0.09 mole) of selenium dioxide in 150 ml. of ethanol (96%) and 33.2 g. (0.1 mole) of 3,4-dibenzyloxyacetophenone[19] 28.3 g. of recrystallized dibenzyloxyphenylglyoxal was obtained, m. p. 98–100°, white needles from ethanol.

**2-(3',4'-Dibenzyloxyphenyl)-quinoxaline.**—2-(3',4'-Dibenzyoxyphenyl)-quinoxaline was prepared in methanolic solution, since the glyoxal is insoluble in water; wadding-like needles from methanol, m. p. 118°.

*Anal.* Calcd. for $C_{28}H_{22}O_2N_2$: C, 80.36; H, 5.29. Found: C, 80.07; H, 5.30.

**3,4-Dihydroxyphenylglyoxal.**—A mixture of 11.1 g. (0.1 mole) of selenium dioxide and 26 g. (0.11 mole) of 3,4-diacetoxyacetophenone,[18] 65 ml. of dioxane and 2 ml. of water was refluxed for thirty hours. Selenium and the solvent were removed in the usual manner and the brownish oily residue hydrolyzed by treatment with 120 ml. of water and heating in a nitrogen atmosphere for six to ten hours in a steam-bath. The endpoint of the reaction is indicated by the formation in a sample taken from the solution of a crystalline precipitate with *o*-phenylenediamine. The decolorized solution yielded in the usual manner 18.1 g. of a solid foam.

**2-(3',4'-Dihydroxyphenyl)-quinoxaline,** yellow colored needles from diluted ethanol (50%), m. p. 254–256°.

*Anal.* Calcd. for $C_{14}H_{10}O_2N_2$: C, 70.58; H, 4.23. Found: C, 70.41; H, 4.42.

***dl*-1-(4'-Hydroxyphenyl)-2-methylaminoethanol.**—All reductions were carried out in a three-necked, round-bottomed flask, equipped with a ground glass mechanical stirrer (1000 to 1200 r. p. m.), a dropping funnel and a gas introducing tube.

One and six-tenths grams of Pd-charcoal (containing 12% PdO) in 100 ml. of ethanol was saturated with hydrogen, then 1.12 g. (0.03 mole or 20% excess) of methylamine in 60 ml. of ethanol was introduced. A solution of 5.31 g. (0.03 mole) 4-hydroxyphenylglyoxal hydrate in 80 ml. of alcohol was added slowly through the dropping funnel (10–12 drops per minute), followed by 40 ml. of alcohol. The mixture absorbed 1420 normal ml. of hydrogen in 110 minutes (calcd. 1344 ml. for 2 moles). The pale yellow colored solution was filtered from the catalyst and both the solvent and the excess methylamine were removed under reduced pressure at 50°. When the solution had been concentrated to one third of its volume, the product began to crystallize. The residue was cooled, filtered and washed with 5 ml. of ice-cold ethanol; yield was 4.05 g. (81%) of synephrine, m. p. 180°; after recrystallization from alcohol, the m. p. rose to 184°.[2]

*Anal.* Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84. Found: C, 64.61; H, 7.69. Similar yields were obtained by using an Adams catalyst, or a Raney-nickel catalyst instead of palladium–charcoal.

**1-(2'-Hydroxyphenyl)-2-methylaminoethanol.**—Five and a half grams of the crude 2-hydroxyphenylglyoxal was condensed in the same manner as above with 1.39 g. of methylamine in the presence of 1.2 g. of the catalyst in 280 ml. of ethanol; 1080 ml. of hydrogen (calcd. for 2 moles 1344 ml.) was absorbed in 230 minutes. Evaporation in a vacuum furnished a crop (2.8 g.) of white crystals of the amino alcohol; recrystallized from ethanol (87%), m. p. 211°.

*Anal.* Calcd. for $C_9H_{13}O_2N \cdot H_2O$: C, 58.35; H, 6.42; N, 7.56. Found: C, 58.17; H, 6.11; N, 7.31.

**1-(3',4'-Dihydroxyphenyl)-2-isopropylaminoethanol (N-Isopropylnoradrenaline). A. From 3,4-Dihydroxyphenylglyoxal Hydrate.**—To a suspension of 1.6 g. of Pd-charcoal in 160 ml. of ethanol containing 1.92 g. (0.033 mole) of isopropylamine, 5 g. (0.03 mole) of the amorphous 3,4-dihydroxyphenylglyoxal in 120 ml. of ethanol was added drop by drop (5–8 drops per minute) at 50° in a hydrogen atmosphere under mechanical stirring. During 370 minutes 980 ml. (standard) of hydrogen was taken up (calcd. 1090 ml.). The solution was neutralized with 2 *N* sulfuric acid (calcd. for isopropylamine) and evaporated to a small volume. The sulfate of N-isopropyl-nor-adrenaline crystallized in white prisms, yield 3.75 g. (47%), m. p. 180°. It may be recrystallized from alcohol (90%). This compound was assayed by Prof. B. Issekutz, Jr., on guinea pigs for bronchospasmolytic activity and found as effective as aleudrine.[17]

*Anal.* Calcd. for $C_{11}H_{17}O_3N \cdot 0.5H_2SO_4$: N, 5.3. Found: N, 5.1.

**B. From 3,4-Dibenzyloxyphenylglyoxal.**—Ten grams (0.03 mole) of 3,4-dibenzyloxyphenylglyoxal, 2 g. (0.034 mole) of isopropylamine in 280 ml. of alcohol in the presence of 1.6 g. Pd-charcoal absorbed at 50° 2580 N ml. of hydrogen (calcd. for 4 moles 2690 N ml.) in 330 minutes. Yield was 4.9 g. (61%) of the same amino alcohol sulfate.

**1-Phenylethanediol-1,2.**—A solution of 4.56 g. (0.03 mole) of phenylglyoxal hydrate was added in ninety minutes to a suspension of 0.8 g. of Pd-charcoal in 160 ml. of ethanol, containing 1.4 g. (0.045 mole) of methylamine by the above-described method. During 120 minutes 1370 N ml. of hydrogen was absorbed (calcd. for 2 moles 1344 ml.). The solution was evaporated, the residue recrystallized from 10 ml. of benzene, furnishing 2.95 g. (71%) of white needles, m. p. 67°.[23] It does not contain nitrogen.

*Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.51; H, 7.22. Found: C, 69.49; H, 7.21.

**1-(4'-Methoxyphenyl)-ethanediol-1,2.**—Starting with 5.46 g. of 4-methoxyphenylglyoxal hydrate, hydrogenation occurs under the same conditions as described for phenylglyoxal. The addition of the glyoxal required 110 minutes, the uptake of hydrogen stopped after 190 minutes and was 1350 N ml. (instead of 1344 ml. calcd.).

(23) Zincke, *Ann.*, **216**, 293 (1883).

Recrystallization produced 4.45 g. (68%) of 4-methoxyphenylethanediol, m. p. 82°. It is free of nitrogen.

*Anal.* Calcd. for $C_9H_{12}O_3$: C, 64.32; H, 7.17. Found: C, 64.50; H, 7.17.

**Acknowledgment.**—The authors are indebted to Mrs. Bruckner-Hatz and to Miss Kovács Oskolás for the microanalyses and to Prof. B. Issekutz, Jr., for the pharmacological assay of some compounds.

## Summary

A new synthesis of hydroxyaryl N-alkylamino ethanols is described. Hydroxyaryl methyl ketones, respectively, their esters or ethers were oxidized by means of selenium dioxide with very good yields to the corresponding aryl glyoxals. Some hydroxyaryl, respectively, benzyloxyaryl glyoxals were reduced together with methyl amine, respectively, isopropylamine to the adrenalinelike aryl ethanolamines. Synephrine and N-isopropyl-nor-adrenaline were prepared with good yields. Phenylglyoxal and 4-methoxy phenylglyoxal gave under the same conditions only the corresponding glycols as in these cases condensation before reduction of the glyoxals did not take place.

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# Alkaloids of *Dichroa febrifuga*. I. Isolation and Degradative Studies[1]

BY J. B. KOEPFLI, J. F. MEAD[2] AND JOHN A. BROCKMAN, JR.

A part of the war-born government sponsored research on malaria[3] was directed to a search for new antimalarials from plant sources. In papers by Liu[4] there is incidental mention of an antimalarial drug indigenous to Yunnan, and samples of this drug (SN 6355),[5] supplied by Liu, when tested in this country were found to be quite active against avian malaria. The samples were labeled "Chunine Leaf Powder" and further identified only as "from Saxifragaceae." The significance of the Saxifragaceae as a source of new antimalarials was further indicated when the Chinese drug Ch'ang Shan (SN 10767), reputed to be the roots of the Saxifrage, *Dichroa febrifuga*, Lour., also proved active in avian malaria. The availability of an adequate supply of Ch'ang Shan plant material led to this investigation the results of which have been briefly communicated by us.[6]

In 1943 when we began our work, the available information on Ch'ang Shan was meager and often contradictory.[7] Furthermore, we were particularly concerned as to the botanical identity of our plant material since the Ch'ang Shan supplied us had been obtained from Chinese herb stores either in this country or abroad. Comparison of some of our root material with herbarium specimens and information[8,9] later available indicate that the type of Ch'ang Shan used in this investigation is derived from the roots of *D. febrifuga*. Supporting evidence of a chemical nature was obtained when we were able to isolate from *D. febrifuga* (SN 6521), botanically identified at the time of collection in India, the same alkaloids isolated from our supply of Ch'ang Shan.

Since *D. febrifuga* has long been used in the treatment of "intermittent fevers" in southeastern Asia it is surprising that except for one reference to a possible glucoside, "dichroin(?),"[10] no chemical examination of the plant has been reported until lately. References to investigations which have appeared recently will be cited below.

## Isolation and Characterization[11]

**Isolation from Ethanol Extracts.**—From crude basic fractions of *D. febrifuga* we have isolated two alkaloids for which we have proposed[6] the names febrifugine (DR 15381)[12] and isofebrifugine (SN 14821). Reports that this plant does not contain alkaloids[13,14] are probably explained by the fact that the alkaloidal content of the root material is small, 0.05 to 0.1%, and by the fact that Meyer's reagent which is commonly used as a test for alkaloids is remarkably insensitive for these bases.

(1) This work was done in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology, and in part by grants from the United States Public Health Service and the Research Corporation, New York.

(2) Present address: University of California at Los Angeles.

(3) "A Survey of Antimalarial Drugs, 1941–1945," ed. by F. Y. Wiselogle, J. W. Edwards, Ann Arbor, Michigan, 1946.

(4) S. K. Liu, Y. Chang, T. Ch'un and S. Tan, *Chinese Medical Jour.*, **59**, 575–577 (1941); and S. K. Liu, *National Medical Jour. of China*, **27**, 327 (1941).

(5) The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs, ref. 3.

(6) J. B. Koepfli, J. F. Mead and J. A. Brockman, Jr., THIS JOURNAL, **69**, 1837 (1947).

(7) K. Kimura, *China Journal*, **23**, 109 (1935).

(8) C. S. Jang, *Chinese Medical Jour.*, April–June, 1944.

(9) C. Crevost and A. Petelot, "Catalogue des Produits de l'Indochine," Vol. V, Part 1, Produits Medicinaux, p. 164 (1928); and K. Heyne, "De Nuttige Planten van Nederlandsch Indië," 2nd ed., Vol. I, p. 687; Buitenzorg (1927).

(10) C. Hartwich, Neue Arzneidrog, 1897, p. 125; C. Wehmer, "Die Pflanzenstoffe," Vol. I, 2nd ed., G. Fisher, Jena, 1929, p. 428.

(11) All melting points are corrected.

(12) The designation "DR" identifies a drug in the Antimalarial Drug Repository of the National Institute of Health, Bethesda, Maryland.

(13) I. M. Tonkin and T. S. Work, *Nature*, **156**, 630 (1945).

(14) D. Hooper, *Nature*, **157**, 106 (1946).

**Crude Basic Fractions.**—The ground root material was extracted exhaustively with hot 96% ethanol, and the extract evaporated to a thick paste. The paste was extracted with 0.1 *N* hydrochloric acid, the acid solution was extracted with chloroform, and the chloroform was discarded. The aqueous phase was then made basic with sodium carbonate and extracted with chloroform. Evaporation of the chloroform at room temperature left a crude basic residue, A.

The alkaline aqueous phase was next extracted with butanol, the butanol was extracted with *N* hydrochloric acid, and the acid solution was made basic and extracted with chloroform. Evaporation of the chloroform gave a crude basic residue, B.

**Isofebrifugine.**—A sample of the crude basic fraction, A, was triturated and washed with acetone until no more color was extracted. The light buff-colored solid remaining melted at 125 to 127°. This was crystallized from methanol or from chloroform–ethanol mixture by slow evaporation at room temperature. If prolonged heating is avoided, it will crystallize from hot methanol in colorless chunky prisms, m.p. 129–130°, $[\alpha]^{25}D$ +131° (*c* 0.35, chloroform). At room temperature it is approximately 0.5% soluble in water, 3 to 4% in methanol, 7% in chloroform, very soluble in methanol–chloroform mixtures, almost insoluble in acetone, and very insoluble in ether, benzene and petroleum ether. It is easily extracted from basic solution by chloroform (distribution coefficient, $K = 10$) and by butanol ($K = 6$).

*Anal.* Isofebrifugine. Calcd. for $C_{16}H_{19}O_3N_3$: C, 63.8; H, 6.4; N, 14.0. Found: C, 63.3, 63.5; H, 6.4, 6.0; N, 14.0, 14.1.

A comparison of the antimalarial activity of isofebrifugine with that of its mother liquors indicated that the latter still contained most of the activity. The properties of the compound responsible for this activity necessitated an extensive chromatographic study which ultimately led to the isolation of febrifugine and to the establishment of its homogeneity.

Several adsorbents were tried and found to be unsatisfactory, but new alumina gave a single, reproducible zone which yielded pure, crystalline febrifugine. When this chromatographic zone was divided into three equal parts and each section was eluted and worked up separately, three crops of crystalline material with identical properties were obtained. Such behavior is strongly indicative of a pure substance.

Some samples of reclaimed alumina, as well as samples of calcium carbonate, gave the curious "double zone" effect described by Schroeder[15] for silicic acid.

**Febrifugine.**—Pure febrifugine was isolated from the crude basic fraction, B, by chromatographing the material from chloroform solution on to ALORCO, Grade F, minus 80 mesh alumina, reground to pass 200 mesh, and mixed with one-half part of Celite. As a developer 2% methanol in chloroform was used. The columns were post-washed with chloroform so that the developer would not interfere with the streak. The zone of febrifugine was located by streaking the column with an aqueous solution containing 0.1% potassium permanganate and 1% sodium hydroxide. The zone was evidenced by an immediate green streak which soon bleached. Elution of the febrifugine was accomplished with methanol.

Under the proper conditions, isofebrifugine appears in the filtrate of the chromatogram and can be recovered and purified as indicated above.

To obtain pure febrifugine from the eluate it was evaporated to dryness at room temperature under vacuum. The residue was taken up in dilute hydrochloric acid, extraneous oil (extracted from the alumina) was removed by extracting with ligroin and chloroform, the solution was made basic and extracted with butanol, and the butanol extract was evaporated to dryness at room temperature under vacuum. The febrifugine left as a residue crystallized from ethanol in colorless needles, m.p. 139–140°, $[\alpha]^{25}D$ + 6° (*c* 0.5, chloroform) and + 28° (*c* 0.5, ethanol).

At room temperature febrifugine is approximately 1 to 3% soluble in water, ethanol, acetone and chloroform, very soluble in methanol–chloroform mixtures and in water–ethanol mixtures, and very insoluble in ether, benzene and petroleum ether. From basic solution it is easily extracted by butanol ($K = 31$) and by 1:4 butanol–chloroform mixture ($K = 11$) but not very well by chloroform ($K = 0.7$).

*Anal.* Febrifugine. Calcd. for $C_{16}H_{19}O_3N_3$: C, 63.8; H, 6.4; N, 14.0. Found: C, 63.5, 63.5; H, 6.1; 6.3; N, 13.9, 14.0.

Febrifugine dihydrochloride was prepared by adding a 10% excess of 12 *N* hydrochloric acid to febrifugine dissolved in sufficient absolute ethanol so that the final solvent was 90 to 95% ethanol. It was recrystallized from 90% ethanol, m.p. 220–222° (dec.).

*Anal.* Febrifugine dihydrochloride. Calcd. for $C_{16}H_{21}O_3N_3Cl_2$: C, 51.3; H, 5.7; N, 11.2; Cl, 18.9. Found: C, 51.2, 51.3; H, 5.6, 5.8; N, 11.2, 11.2; Cl (Carius) 18.6, (ionic) 18.9.

**Dimorphism of Febrifugine.**—A crude base melting at *ca.* 150° was occasionally encountered during our early isolation studies, and at one time was thought to be a third alkaloid, isomeric with febrifugine and isofebrifugine. Subsequently the base has been obtained from water by the addition of the theoretical amount of 2.5 *N* sodium hydroxide to a saturated solution of febrifugine dihydrochloride and from spontaneous crystallization of melted isofebrifugine. The highest melting point obtained for this base is 154–156°, $[\alpha]^{25}D$ + 28° (*c* 0.5, ethanol).

A comparison with febrifugine revealed that both bases, in addition to having the same optical rotation, give the same zone when chromatographed on alumina under standard conditions and give the same dihydrochloride. Furthermore, a chloroform solution of febrifugine at room temperature, seeded with a crystal of the high melting base, deposits crystals of that base on slow evaporation, and conversely a chloroform solution of the high melting base gives febrifugine when appropriately seeded. This would appear to be conclusive evidence that the base of m.p. 154–156° is not an isomer of febrifugine but merely a higher melting modification and that febrifugine is dimorphic.

**Interconversion of Isofebrifugine and Febrifugine.**—In the early stages of this investigation attempts to characterize these alkaloids were greatly complicated by apparent anomalies in physical behavior. These difficulties were resolved when febrifugine was found to be dimorphic (see above) and when the bases were found to be readily interconvertible.

A 51-mg. sample of isofebrifugine was refluxed for one-half hr. in 10 ml. of absolute ethanol. The solution was

(15) W. A. Schroeder, "Annals N. Y. Acad. Sci.," Vol. XLIX, Art. 2, p. 211 (1948).

evaporated to a small volume and seeded with febrifugine to give a yield of 13.3 mg. of febrifugine, m.p. 138–139°. The mother liquors after further refluxing with alcohol for two hours, yielded an additional 12.5 mg. of febrifugine, and, on addition of hydrochloric acid, 7.7 mg. of febrifugine dihydrochloride. Isofebrifugine (74 mg.) was heated for a few minutes at 135° until crystallization took place (in some cases seeding was necessary). The solid was washed with acetone and dried to give 53 mg. of the higher melting form (154–156°) of febrifugine.

A 52-mg. sample of febrifugine was refluxed in 25 ml. of chloroform for three hours. The solution was chromatographed on alumina. The yield of crude isofebrifugine was 22.3 mg., which on recrystallization gave 16.0 mg. of pure isofebrifugine, m.p. 129–130°.

**Isolation from Acid Extracts.**—With a few centigrams of the pure alkaloids available it was possible to determine some of their properties and devise a far more satisfactory extraction and isolation procedure.

**Isolation of Febrifugine and Isofebrifugine by Adsorption on Fuller's Earth.**—The plant material was ground to 8 to 10 mesh and extracted with portions of 0.1 *N* hydrochloric acid until it was essentially free of alkaloids as indicated by a test of the extract with Dragendorff's reagent. The concentration of alkaloids in the combined extracts was then at least 75 μg./ml. Dragendorff's reagent is a sensitive test for the alkaloids, three drops of the reagent giving an immediate cloudiness with 1 ml. of 0.1 *N* hydrochloric acid containing 12 μg. of alkaloids, a barely perceptible cloudiness in one-half to one minute with 6 μg., and a clear solution with 3 μg. The test is not critically dependent on the acid concentration, but the sensitivity is somewhat less, and the precipitate forms more slowly at higher concentrations of acid.

The combined extracts were stirred for a few hours with fuller's earth and sufficient 12 *N* hydrochloric acid to keep the mixture acidic to congo red. A crude adsorption isotherm indicated that 150 g. of fuller's earth under these conditions is sufficient to adsorb more than 99% of 1 g. of the alkaloids. An amount of Celite equal to one-third the weight of fuller's earth was added, and the mixture was filtered through a pad of Celite weighing about one-sixth the weight of fuller's earth.

The filter cake was mixed with enough sodium carbonate solution (6 g. per 100 ml.) to make a thin paste, three volumes of butanol were added, and the mixture was vigorously agitated for about two hours. The butanol layer was separated and a second and third extraction made.

The combined wet butanol extracts were diluted with one-half volume of ligroin (60–70°) and extracted with dilute hydrochloric acid. The acid extracts were made basic with sodium carbonate and extracted with 1:4 butanol–chloroform mixture, and the extraction into acid and back into butanol–chloroform mixture from basic solution was repeated. The butanol–chloroform solution was then dried with sodium sulfate and evaporated almost to dryness at reduced pressure and room temperature. A light-colored solid separated, and it was mixed with a little ether and filtered off. Evaporation of the filtrate gave a second crop.

The crude alkaloids were taken up in sufficient hot absolute ethanol so that after a 10% excess of 12 *N* hydrochloric acid was added to convert the material to dihydrochlorides the final solvent was 90 to 95% ethanol. The mixture was seeded with febrifugine dihydrochloride and allowed to crystallize overnight in the cold. The febrifugine dihydrochloride obtained can be recrystallized by dissolving it in a minimum of hot 1:1 water–ethanol mixture, and adding sufficient absolute ethanol to make the final concentration of ethanol 90%.

The mother liquors from the febrifugine dihydrochloride were taken almost to dryness at room temperature, the residue taken up in a small amount of water, sufficient sodium carbonate added to make the solution basic, and the mixture extracted with chloroform. Evaporation of the chloroform at room temperature gave crude isofebrifugine which was purified by recrystallization from hot methanol.

Mother liquors from the above crystallizations are best worked up for additional material by chromatographing them from chloroform on alumina as previously described.

**Results with *D. febrifuga*.**—The fuller's earth adsorption method has given higher and more consistent yields of the alkaloids than could be obtained from ethanol extracts. The results of applying the method to the various plant materials available to us indicated that the root material of Chinese origin had a crude base content of 0.08–0.1% and that 55% of this consisted of febrifugine and isofebrifugine. The ratio of febrifugine to isofebrifugine varied from 6:1 to 1:1 which is not surprising in view of their interconvertibility. The root material from India had a crude base content of 0.05% of which 63% was febrifugine and only 2% isofebrifugine. Although botanically identified leaf material from China was not available to us, that from India had a crude base content of only 0.01–0.02% of which 50% was febrifugine (the presence or absence of isofebrifugine was not confirmed).

**Results with "Chunine Leaf Powder."**—Liu[4] in mentioning the leaves of a plant called by him "Chunine tree" stated that the antimalarial activity was due to an alkaloid "chunine," but he gave no experimental evidence whatsoever for the presence of alkaloids.

Since our interest in antimalarials of Chinese origin was first occasioned by Liu's report, we made numerous unsuccessful attempts to learn something of the nature of his "chunine leaf powder" from the small supply available. In this connection the effectiveness of the fuller's earth adsorption method was demonstrated in that we have now been able to isolate from a 25-g. sample of Liu's material (SN 6355), 8 mg. of febrifugine, identified by melting point, dihydrochloride, and absorption spectrum. This supplies experimental evidence for the presence of an alkaloid in Liu's material and suggests that the material was derived in whole or in part from *D. febrifuga* or a related plant.

**Pharmacology.**[16]—Isofebrifugine when given intravenously three times a day to ducks infected with *P. lophurae* was found to have a *Q* of 1 (tests G-5 and I-2), whereas it was found to be inactive at the maximum tolerated dose in test D-1 when given intravenously two times a day.

Febrifugine has a *Q* of 100 when tested against *P. lophurae* in ducks (tests G-5 and I-2) and a *Q* of 64 against *P. gallinaceum* in chicks (test A-1). When tested against the trophozoites of *P. cynomolgi* in the monkey it is at least 100 times as active as quinine.[17]

Studies of the acute oral toxicity of febrifugine[17]

(16) Description of the avian tests, A-1, D-1, G-5 and I-1, together with a definition of *Q*, the quinine equivalent, will be found in ref. 3.

(17) Private communication from Dr. L. H. Schmidt, Christ Hospital, Cincinnati, Ohio.

indicate that the $LD_{50}$ for the white mouse is *ca.* 2.5 to 3.0 mg. per kg. This is somewhat more than 100 times that of quinine but the toxic symptoms are quite different. Febrifugine is slower in its action, giving rise to symptoms some two to four hours after administration. These symptoms include effects on respiration, urinary incontinence, sweating and a corrosive effect on the gastric mucosa.

Experiments on subacute toxicity were carried out with rhesus monkeys.[17] An animal receiving 0.3 mg. per kg. daily (administered in three doses, one every eight hours) survived sixteen days of treatment with no untoward reactions. An animal receiving 0.75 mg. per kg. daily succumbed on the ninth day of treatment, and marked hyperemia of the gastric mucosa (but no frank ulceration) was the only finding of note on autopsy. Febrifugine did not affect the formed elements of peripheral blood or bone marrow and did not produce methemoglobinemia or cyanosis.

Preliminary results[18] of a clinical trial of febrifugine indicate that while the drug reduces the parasite count when given in four oral doses totaling 2.5 mg. per day it is at the same time such a powerful emetic as to probably preclude its clinical use in malaria.[19]

## Structural Studies[11]

A potentiometric titration of isofebrifugine indicated two basic groups of $pK_{B_1}$ 5.7 and $pK_{B_2}$ 12. A comparative value of $pK_{B_1}$ 6.3 for febrifugine was calculated from distribution coefficient values around *p*H 7.

Zeisel determinations for methoxyl groups were negative for both alkaloids. The Herzig and Meyer determination for N-methyl gave varying results of *ca.* 1% with either alkaloid whereas the theoretical value for one such group is 5%.

Both alkaloids reduce Tollens reagent at room temperature, but a number of color tests for aldehydes or methyl ketones (Schiff reagent, sodium nitroprusside, *o*-dianisidine in glacial acetic, and sodium bisulfite) were negative.

Acetylation and benzoylation of the alkaloids gave oily products which could not be crystallized.

TABLE I

MELTING POINTS

| Compound | Febrifugine | Isofebrifugine |
|---|---|---|
| Free base | 139–140° | 129–130° |
| | 154–156° | |
| Dihydrochloride | 220–222° (dec.) | Hygroscopic |
| Dibenzenesulfonyl | 148.0–148.5° | 182.5–183.5° |
| Semicarbazone | 187–188° (dec.) | ..... |
| Oxime | 224–225° (dec.) | ..... |
| N-Nitroso | 171.5–172.5° | 185–186.5° |
| Dihydro | 192–193° | 156.5–157.5° |

(18) Private communication from Dr. G. Robert Coatney, National Institute of Health, Bethesda, Maryland.

(19) For recent reports of the clinical use of extracts of Ch'ang Shan in the treatment of malaria see ref. 8 and C. F. Tsu, *J. Trop. Med. and Hyg.*, **50**, 75 (1947).

Several crystalline derivatives of the alkaloids have been prepared and analyzed, and their melting points and those of the free bases may be compared in Table I.

**Benzenesulfonyl Derivatives.**—The alkaloids were treated overnight with excess benzenesulfonyl chloride in pyridine. Addition of water and dilute acid caused the derivatives to precipitate. The derivative of isofebrifugine was recrystallized from chloroform–ethanol mixture and from aqueous ethanol, and that of febrifugine from aqueous ethanol. Both derivatives were insoluble in dilute sodium hydroxide and dilute hydrochloric acid.

*Anal.* Calcd. for $C_{28}H_{27}O_7S_2N_3$: C, 57.9; H, 4.7; N, 7.2. Found for isofebrifugine: C, 57.9; H, 4.6; N, 7.3. Found for febrifugine: C, 57.8; H, 5.0; N, 7.3.

**Febrifugine Semicarbazone and Oxime.**—Febrifugine dihydrochloride was treated overnight with sodium acetate and either semicarbazide hydrochloride or hydroxylamine hydrochloride in aqueous solution. The derivative separated when the solutions were made just basic with sodium hydroxide. The semicarbazone was recrystallized from ethyl acetate or absolute ethanol and the oxime from aqueous ethanol.

*Anal.* for semicarbazone: Calcd. for $C_{17}H_{23}O_3N_6$: C, 56.9; H, 6.4; N, 23.4. Found: C, 57.1; H, 6.5; N, 23.1.

*Anal.* for oxime: Calcd. for $C_{16}H_{20}O_3N_4$: C, 60.8; H, 6.3; N, 17.7. Found: C, 60.9; H, 6.2; N, 17.5.

Under similar conditions isofebrifugine did not give an oxime or semicarbazone.

**Nitroso Derivatives.**—The alkaloids were treated in dilute hydrochloric acid with excess sodium nitrite for one-half hour at 0°. The nitroso compounds separated when the solutions were made basic. N-Nitrosofebrifugine was recrystallized from ethanol and N-nitrosoisofebrifugine from ethanol and from butanone.

*Anal.* Calcd. for $C_{16}H_{18}O_4N_4$: C, 58.2; H, 5.5; N, 17.0. Found for febrifugine: C, 58.4; H, 5.7; N, 17.1. Found for isofebrifugine: C, 58.1; H, 5.7; N, 17.2.

**Absorption Spectra.**—The absorption spectra of febrifugine and isofebrifugine are almost identical. In Fig. 1 the ultraviolet absorption spectra for febrifugine, 2-methyl-4-quinazolone, and 3-allyl-4-quinazolone in ethanol are shown. The striking similarity of the spectrum of febrifugine and that of the 3-substituted-4-quinazolone is evident. The maxima of the spectra of febrifugine (and isofebrifugine) and 3-allyl-4-quinazolone show a bathochromic shift in acidic solution, but not in basic solution. The maxima of the spectrum of the 3-unsubstituted-4-quinazolone show a bathochromic shift in both acidic and basic solution. Molal extinctions calculated for the extremes of these various spectra, assuming a molecular weight of 301 for the alkaloids, likewise show a remarkable agreement, the difference in corresponding values being in general less than 10%.

Absorption spectra were taken in absolute ethanol which had been redistilled from all-glass apparatus. The spectra were taken at concentrations which gave extinctions between 0.3 and 0.9 as read with a Beckman quartz spectrophotometer, model DU.

2-Methyl-4-quinazolone was synthesized by the method of Niementowski,[20] m.p., 238–241°, and 3-allyl-4-quinazolone was synthesized by the method of Hanford, *et al.*,[21] m.p. 65–66°.

(20) J. Niementowski, *J. prakt. Chem.*, **51**, 564 (1895).

(21) W. E. Hanford, P. Liang and R. Adams, THIS JOURNAL, **56**, 2782 (1934).

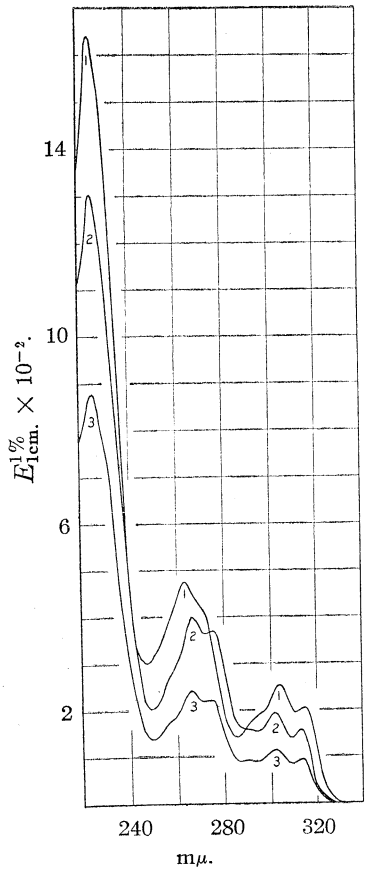



Fig. 1.—Absorption spectra in absolute ethanol: (1), 2-methyl-4-quinazolone; (2), 3-allyl-4-quinazolone; and (3), febrifugine.

**Reduction.**—In ethanol in the presence of platinum at room temperature and pressure both alkaloids take up one mole of hydrogen. Crystalline dihydro derivatives can be isolated, but in yields which suggest that each reduction leads to the formation of more than one product. In glacial acetic acid, febrifugine takes up one mole and isofebrifugine two or more moles of hydrogen, but in neither case could crystalline products be isolated.

Absorption spectra of the dihydro-alkaloids are very nearly the same as those of the original alkaloids. Dihydrofebrifugine does not form an oxime nor a semicarbazone. Neither of the dihydro-alkaloids reduces Tollens reagent, and both give negative results in N-methyl determinations.

**Dihydrofebrifugine.**—A 409-mg. sample of febrifugine was hydrogenated at room temperature and one atmosphere pressure in 50 ml. of absolute ethanol in the presence of 50 mg. of Adams catalyst. In one hour the volume of hydrogen taken up became constant and corresponded to one mole of hydrogen per mole of febrifugine. The catalyst was filtered off, the solution evaporated to dryness at reduced pressure and room temperature, and the crystalline residue recrystallized from hot ethanol to yield a first crop of 263 mg. (64%) of colorless crystals melting at 187–192° and a second crop of 34 mg. melting at 163–184°. The mother liquors taken to dryness gave 107 mg. of oil. The dihydrofebrifugine was recrystallized from ethanol to constant melting point, 192–193°.

*Anal.* Calcd. for $C_{16}H_{21}O_3N_3$: C, 63.3; H, 7.0; N, 13.9. Found: C, 63.3; H, 7.0; N, 14.1.

**Dihydroisofebrifugine.**—The same method was used as given for dihydrofebrifugine. A 400-mg. sample of isofebrifugine took up the theoretical amount of hydrogen in three hours. The residue on evaporation of the solvent was an oil which was crystallized from acetone to give a first crop amounting to 182 mg. (45%), m.p. 151–154°. A second crop from acetone–benzene amounted to 97 mg., m.p. 86–124°. The mother liquors, evaporated to dryness, left 127 mg. of oil. The dihydroisofebrifugine was recrystallized from acetone to constant melting point, 156.5–157.5°.

*Anal.* Calcd. for $C_{16}H_{21}O_3N_3$: C, 63.3; H, 7.0; N, 13.9. Found: C, 63.4; H, 6.9; N, 13.8.

**Oxidation.**—The alkaloids are relatively stable toward acid permanganate, but both are oxidized rapidly by alkaline permanganate to give good yields of 4-quinazolone. Either alkaloid is oxidized rapidly by periodate in neutral or slightly alkaline solution to give the same crystalline product. Although this periodate oxidation product has not been fully characterized and will be dealt with in a later paper, the analyses suggest that it is formed from either alkaloid by the loss of two hydrogens.

**Alkaline Permanganate Oxidation.**—An aqueous solution of 160 mg. of febrifugine dihydrochloride made alkaline with potassium hydroxide was treated dropwise with a saturated solution of potassium permanganate until the rapid decolorization had ceased. After centrifugation, the supernatant was neutralized with hydrochloric acid and evaporated to dryness. The residue was extracted with absolute ethanol, and the soluble portion recrystallized from ethanol and acetone to give 40 mg. of 4-quinazolone, m.p. 212–213°, identified by absorption spectra and mixed m.p. with a sample prepared by the method of Niementowski.[20]

*Anal.* Calcd. for $C_8H_6ON_2$: C, 65.7; H, 4.1; N, 19.2. Found: C, 65.3; H, 4.1; N, 19.0.

Oxidation of isofebrifugine under similar conditions gave the same result.

**Periodate Oxidation.**—A 270-mg. sample of isofebrifugine was dissolved in 30 ml. of water, and 150 ml. of 0.026 *N* disodium paraperiodate was added. After one hour, the solution was saturated with carbon dioxide and extracted with 150 ml. of chloroform in five equal portions. The chloroform solution was dried over anhydrous sodium sulfate and evaporated at reduced pressure. There was obtained 103 mg. of crude solid which, after several crystallizations from ethanol, gave 72 mg. of colorless clusters of needles, m.p. 165–166° (dec.).

*Anal.* Calcd. for $C_{16}H_{17}O_3N_3$: C, 64.2; H, 5.7; N, 14.0. Found: C, 64.4; H, 6.0; N, 13.7.

Febrifugine oxidized under the same conditions gave the same product.

**Hydrolysis.**—Both alkaloids are very stable toward acid hydrolysis. It was possible to isolate unchanged febrifugine from a solution of the alkaloid in 70% sulfuric acid after heating at 100° for one hour.

Both alkaloids are very susceptible to alkaline hydrolysis and at room temperature overnight in 2.5 *N* sodium hydroxide either is hydrolyzed to give a good yield of anthranilic acid, a low yield of ammonia, and formic acid. Oils and resins of unknown constitution also result on

alkaline hydrolysis, and these when heated give a positive pine splinter test.

Dihydrofebrifugine also is easily hydrolyzed under alkaline conditions, and such a hydrolysis, does not result in the formation of oils and resins, nor of ammonia, although anthranilic acid and formic acid are formed. It has been possible to isolate from such a hydrolyzate a benzenesulfonyl derivative with the tentative formula $C_8H_{13}ON_2(C_6H_5SO_2)_3$.

**Alkaline Hydrolysis of the Alkaloids.**—Several hydrolyses were carried out by allowing *ca.* 100-mg. samples of the alkaloids to stand one to two days at room temperature in 2.0 ml. of 2.5 *N* sodium hydroxide. In two experiments a closed system was used, nitrogen was passed through the solutions, and the effluent gas was passed through a known amount of standard hydrochloric acid. Back-titration indicated the formation of 0.044 milliequivalent of volatile base from 0.30 millimole of isofebrifugine and 0.015 milliequivalent from 0.27 millimole of febrifugine. That the volatile base was ammonia was confirmed by evaporating the titration solutions and preparing the characteristic octahedra of ammonium chloroplatinate.[22]

The alkaline hydrolyzates were next brought to *p*H 8–9 by adding hydrochloric acid, and the mixtures extracted with 1:4 butanol–chloroform. These extracts on drying and evaporating to dryness yielded about 20% of the original weight of alkaloid as a dark brown oil, soluble in dilute hydrochloric acid and precipitated from the acid solution by base. Attempts to prepare the acetyl derivative, the picrate and the chloroplatinate led to amorphous, colored precipitates. When this material was heated with 20% aqueous sodium hydroxide, a blob of resin collected rapidly. When this resin was heated in a dry test-tube, the vapors above it gave a pine splinter test for pyrrole.

The hydrolyzate was next acidified with hydrochloric acid to *p*H 3–4, and the mixture was extracted with chloroform. This chloroform extract when taken to dryness gave a light crystalline solid amounting to *ca.* 40% of the original weight of the alkaloid. It was sublimed, recrystallized from aqueous alcohol and proved to be anthranilic acid (m.p. 145–146° with no depression in mixed melting point with an authentic sample).

The aqueous phase from these extractions was next taken to dryness in a vacuum desiccator over sodium hydroxide. This residue if warmed with 20% aqueous sodium hydroxide gave very rapidly a blob of resin which gave a pine splinter test for pyrrole when heated with zinc dust. Attempts to prepare an acetyl derivative, a picrate, a chloroplatinate, an oxime and a phenacyl ester from this residue were unsuccessful.

A little of the original hydrolyzate when treated with magnesium in hydrochloric acid, and then warmed with chromotropic acid in 72% sulfuric acid gave a violet color, indicating the presence of formic acid.[23]

**Alkaline Hydrolysis of Dihydrofebrifugine.**—When 311 mg. of dihydrofebrifugine was allowed to stand with 4.0 ml. of 2.5 *N* sodium hydroxide for two days it slowly went into solution. The solution was then acidified with hydrochloric acid to *p*H 3–4, and extracted with chloroform to remove anthranilic acid (a previous experiment had shown that under these conditions a 75% yield of anthranilic acid was isolated). The solution was then evaporated on a steam-cone with a stream of air until the volume was *ca.* 5 ml. One-half gram of sodium hydroxide and 1 ml. of benzenesulfonyl chloride were added and the mixture shaken vigorously, with cooling. The solid which separated was crystallized from acetonitrile to give 98 mg. of colorless crystals which were recrystallized to constant melting point, 211–213°.

*Anal.* Calcd. for $C_{26}H_{28}O_7S_3N_2$: C, 54.2; H, 4.9; S, 16.7; N, 4.9. Found: C, 54.3; H, 5.1; S, 16.7; N, 5.1.

## Discussion of Results

With the exception of the alkaloids of the Cinchona type occurring in certain species of the Rubiaceae, those isolated from plants used in some of the native remedies for malaria have generally proven to be without plasmocidal activity. The alkaloids isolated from *D. febrifuga* are therefore of particular interest not only because they are the first to be found in a plant of the Saxifragaceae but also because one of them has high plasmocidal activity.

In avian tests the antimalarial activity of various samples of *D. febrifuga* leaf material has consistently been about twice that of the roots. However, we have always found five to ten times more febrifugine in root than in leaf material. The amount of febrifugine actually isolated was sufficient to account for *ca.* 25% of the activity of the roots but only 2% of the activity of the leaf material. These discrepancies, even though the bioassay cannot be relied on to better than a factor of two, are still so great as to suggest the presence, at least in leaf material, of some active principle other than febrifugine and isofebrifugine. This possibility is being investigated.

With respect to the relative quantities of febrifugine and isofebrifugine which may be present in *D. febrifuga*, we can only point out that we have consistently isolated from various samples of both root and leaf material more febrifugine than isofebrifugine, and in view of the interconvertibility of the alkaloids it is quite possible that there is little or no isofebrifugine in the intact plant.

Our analytical data for the free bases and their derivatives indicate that the empirical formula for febrifugine and isofebrifugine is $C_{16}H_{19}O_3N_3$. The formation of 4-quinazolone on oxidation, the formation of anthranilic and formic acids on hydrolysis, the ease of hydrolysis (atypical of 3-unsubstituted-4-quinazolones), and the striking agreement in absorption spectra leave little doubt that the aromatic portion of the molecules is a 3-substituted-4-quinazolone. The isolation of a $C_8$-fragment containing two nitrogen atoms from the hydrolyzate of dihydrofebrifugine not only confirms this conclusion but suggests that the 4-quinazolone nucleus is substituted only at the 3-position.

The quinazolone nucleus accounts for the function of two of the nitrogen atoms and one of the oxygen atoms in the alkaloids. There is reasonably good evidence that the third nitrogen atom forms a secondary aliphatic amine, for both alkaloids have basic groups, $pK_B$ *ca.* 6, both form non-basic, non-acidic dibenzenesulfonyl derivatives, and both form N-nitroso derivatives.

The function of the remaining two oxygen atoms is less clearly indicated. The formation of an oxime and a semicarbazone indicate the presence

(22) Chamot and Mason, "Handbook of Chemical Microscopy," John Wiley and Sons, Inc., New York, N. Y., 1931, Vol. II, pp. 75–76.

(23) F. Feigl, "Spot Tests," Elsevier Press, New York, N. Y., 3rd. ed., p. 397.

of a keto-group at least in febrifugine. The formation of dibenzenesulfonyl derivatives may indicate the presence of an alcoholic hydroxyl group. One benzenesulfonyl group is presumably attached to the secondary amine nitrogen, and the other to one of two atoms, either an oxygen which was originally a hydroxyl group or to the 1-nitrogen of the quinazolone ring. This latter possibility is indicated by the fact that the dibenzenesulfonyl derivatives are insoluble in dilute hydrochloric acid, although the 1-nitrogen of normal 4-quinazolones is sufficiently basic to render them soluble in dilute acid. The involvement of the 1-nitrogen atom in the formation of such a derivative is known in the case of rutacarpine, which forms a monoacetyl and a monobenzoyl derivative.[24]

Alkaloids containing a quinazolone ring system are comparatively rare, the only two previously known being rutacarpine and evodiamine. Furthermore, if as we believe the 4-quinazolone nucleus is attached only through its nitrogen at the 3-position to the other basic portion of the molecule, it will constitute a novel structural feature in alkaloidal chemistry. Lastly, febrifugine and isofebrifugine represent the first instance known to us in which two optically active isomeric alkaloids are so readily interconvertible.

It is evident from published reports that, quite independently of ourselves, investigators both here and abroad have been engaged on the chemistry of *D. febrifuga*. Thus Chou, *et al.*,[25] report the isolation of *three isomeric* alkaloids, $\alpha$-, $\beta$- and $\gamma$-dichroines. Despite some disagreement in melting points it is evident that the $\alpha$-dichroine of the Chinese investigators corresponds to our isofebrifugine, but contrary to their interpretation we believe their own physical data clearly indicate that their $\beta$- and $\gamma$-dichroines are not two different isomeric alkaloids but correspond to the two crystalline modifications of our febrifugine. Investigators[26] in this country have, without assigning names or mentioning the dimorphism of the higher melting alkaloid, reported results in substantial agreement with ours.

It would appear that some confusion has been occasioned by the way in which investigations of *D. febrifuga* in China have been reported.[25,27,28,29,30] We selected names derived from the plant species to avoid possible confusion with the "dichroin" of Hartwich[10] or the names "Dichroine A" and "Dichroine B" used by Jang, *et al.*,[27] for two incorrectly characterized alkaloids.[29,30] To avoid causing further confusion in the literature we prefer to adhere to the names febrifugine and isofebrifugine since they were the first to be proposed in a publication[6] which gives an adequate characterization of two isomeric alkaloids obtained from *D. febrifuga*.

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## Summary

Two interconvertible, isomeric, crystalline, optically active alkaloids, febrifugine and isofebrifugine, have been isolated from the roots and leaves of *Dichroa febrifuga*. Febrifugine is a powerful antimalarial, having about 100 times the activity of quinine against bird malaria.

An empirical formula, $C_{16}H_{19}O_3N_3$ is proposed, and evidence is given which indicates that structurally these alkaloids are 4-quinazolones substituted only on the 3-nitrogen.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 1-Cyano-1,3-butadienes: *cis, trans*-Isomers of 1-Cyano-1,3-butadiene[1]

BY H. R. SNYDER, JOHN M. STEWART[2a] AND ROBERT L. MYERS[2b]

In a study of the possible use of certain cyanodienes as replacements for styrene in butadiene–styrene copolymers, 1-cyano-1,3-butadiene has been prepared in quantity sufficient to permit the separation of the *cis*- and *trans*-forms. This substance has been studied previously,[3–15] but apparently only as a mixture of geometric isomers. In the present work the mixture was prepared by the pyrolysis[4–8] of the benzoate or acetate of crotonaldehyde cyanohydrin; the synthesis *via* the benzoate proved the more convenient. 1-Cyano-2-methyl-1,3-butadiene was prepared similarly from tiglic aldehyde.

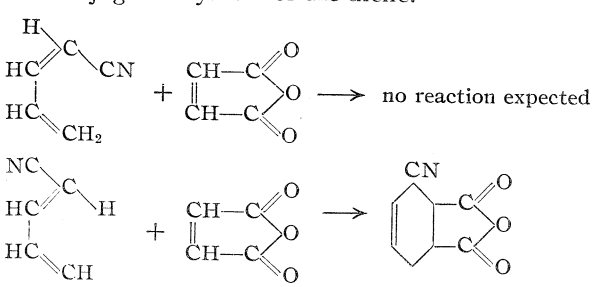
$$CH_3CH{=}CHCHO \xrightarrow[C_6H_5COCl]{NaCN} CH_3CH{=}CHCHOCOC_6H_5 \xrightarrow{(575°)} CH_2{=}CHCH{=}CHCN + C_6H_5CO_2H$$

(CN)

The first indications that the 1-cyano-1,3-butadiene so prepared was a mixture were found in the slight variations in boiling point and index of refraction of the products of various runs and in the concomitant variations of reaction rates observed with samples of the different lots in copolymerizations with butadiene. Separation of the isomers was achieved by fractionation of the mixture through a twenty-five plate, helix-packed column. Two different fractions (I, b.p. 49.5° (31.5 mm.), $n^{20}D$ 1.4852; II, b.p. 57.3° (31.5 mm.), $n^{20}D$ 1.4960) were obtained. In the polymerization studies it was observed that the higher-boiling fraction underwent copolymerization with butadiene at a faster rate than the lower-boiling fraction. Of the two dried rubber-like polymers made in these copolymerizations only the one from the higher-boiling fraction had the strong odor previously associated with all the butadiene copolymers made from the mixture of cyanodienes.

The formation of a by-product of sufficient volatility to possess an odor, in the copolymerization of the higher-boiling isomer, suggested that a Diels–Alder reaction with butadiene might have occurred. In tests with liquid butadiene at 50°, in the absence of polymerization catalysts, only the higher-boiling 1-cyano-1,3-butadiene underwent reaction; the product was a liquid of a very strong, unpleasant odor (somewhat similar to that of isonitriles). The higher-boiling 1-cyano-1,3-butadiene also gave an adduct with maleic anhydride, whereas the lower-boiling isomer failed to react.

The observation of the greater reactivity of the higher-boiling 1-cyano-1,3-butadiene with maleic anhydride permits the tentative assignment of the *trans*-configuration to this isomer. This assignment is made on the basis of the analogy with the closely related piperylenes[16]; only the *trans*-piperylene undergoes Diels–Alder reactions with maleic anhydride, acrylonitrile or with a second molecule of the diene (dimerization).[17] The failure of the *cis*-isomer to react with maleic anhydride is ascribed to the fact that the shape of the molecule is such as to prevent close approach of the dienophile to the ends of the conjugated system of the diene.




## Experimental

**Crotonaldehyde Cyanohydrin Benzoate.**—To a well-stirred mixture of 420 g. (6 moles) of freshly distilled crotonaldehyde and 1200 ml. of benzene, maintained at −10°, was slowly added 843 g. (6 moles) of benzoyl chloride. Then 392 g. (8 moles) of reagent grade sodium cyanide in 2 l. of distilled water was added dropwise while the reaction mixture was kept at the same temperature. After the cyanide had been added the mixture was stirred for two

(1) This investigation was sponsored by the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the government synthetic rubber program.

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hours at −10° and then was allowed to warm to room temperature. The organic layer was separated, washed with two 200-ml. portions of 5% sodium carbonate solution, and dried over anhydrous magnesium sulfate. After distillation of the benzene, the residue was fractionated through a 12-inch, helix-packed, jacketed column. The fraction boiling at 125° (1 mm.), $n^{20}D$ 1.5220, was collected. The yield was 1085 g. or 89%.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.75; H, 5.58.

**Crotonaldehyde cyanohydrin acetate** was prepared by the same method with the substitution of acetic anhydride for the benzoyl chloride. From 271 g. (3.88 moles) of crotonaldehyde, 395 g. (3.88 moles) of acetic anhydride, and 275 g. (5.6 moles) of sodium cyanide there was obtained 371 g. (70%) of the crotonaldehyde cyanohydrin acetate, b.p. 78.5° (4 mm.), $n^{20}D$ 1.4340.

*Anal.* Calcd. for $C_7H_9O_2N$: C, 60.42; H, 6.52. Found: C, 60.34; H, 6.57.

**1-Cyano-1,3-butadiene.**—Pyrolysis of either the benzoate or acetate of crotonaldehyde cyanohydrin produced 1-cyano-1,3-butadiene. Pyrolysis of the benzoate was found to be more satisfactory because the separation of the cyanodiene from benzoic acid was much more convenient than separation from acetic acid. The esters were pyrolyzed by passage through a vertical, 18-mm. Pyrex tube packed for a distance of about 30 cm. with 4-mm. glass beads and heated to 575 ± 10° by means of a combustion furnace. The temperature was indicated by a thermocouple inserted in the tube. The material was introduced at a rate of one drop per second. A cooled distilling flask connected to the pyrolysis tube by a ground-glass joint served as the receiver for the pyrolysate. The yield of cyanodiene could be increased by the addition of an efficient polymerization inhibitor (such as picric acid) to the ester and the receiving flask. It was necessary to heat the tube (conveniently with an infrared lamp) between the furnace and the receiver to prevent the benzoic acid produced from solidifying. The 1-cyano-1,3-butadiene was separated from the benzoic acid by a flash distillation at reduced pressure. Redistillation through a 12-inch, helix-packed column yielded 1-cyano-1,3-butadiene; b.p. 49.5–53° (31 mm.), $n^{20}D$ 1.4852–1.4895. Coffman[2] reported b.p. 49–53° (30 mm.), $n^{20}D$ 1.4880, $d^{20}_4$ 0.8644.

The yield of redistilled material from the pyrolysis of the benzoate was 70%; from the acetate 55% (based on the recovery of 34% of the unchanged ester). A sample was redistilled for analysis.

*Anal.* Calcd. for $C_5H_5N$: C, 75.92; H, 6.37. Found: C, 75.90; H, 6.48.

1-Cyano-1,3-butadiene was separated into its geometric isomers by fractionation of the mixture through a twenty-five plate, helix-packed column at a reflux ratio of about 15:1. The two fractions (I, b.p. 49.5° (31.5 mm.), $n^{20}D$ 1.4852; II, b.p. 57.3° (31.5 mm.), $n^{20}D$ 1.4960) had nearly identical microanalyses.

*Anal.* Calcd. for $C_5H_5N$: C, 75.92; H, 6.37. Found (fraction I): C, 75.90; H, 6.48; (fraction II): C, 75.97; H, 6.50.

**Maleic Anhydride Adduct of 1-Cyano-1,3-butadiene.**—In two 2-oz., screw-cap bottles were placed 6.2 g. of maleic anhydride and 25 ml. of dry benzene. In the first bottle (A) was placed 5.0 g. of 1-cyano-1,3-butadiene (fraction I, $n^{20}D$ 1.4852). In the second (B) was placed 5.0 g. of 1-cyano-1,3-butadiene (fraction II, $n^{20}D$ 1.4960). A few crystals of picric acid were added to each bottle to prevent polymerization. The bottles were capped and placed in a 50° water-bath and rotated for forty-eight hours. The vessels were removed from the bath and cooled, and about 10 ml. of low-boiling petroleum ether was added to each. From bottle A only unchanged maleic anhydride, m.p. 58–59°, was isolated. From bottle B there was obtained a yellow oil, which was induced to crystallize by rubbing it against the side of the container. After six recrystallizations from dry benzene, the material had a constant melting point of 110–111°.

*Anal.* Calcd. for $C_9H_7O_3N$: C, 61.01; H, 3.98. Found: C, 60.86; H, 3.77.

These reactions were repeated several times and in each instance an adduct was obtained only from the higher-boiling fraction, $n^{20}D$ 1.4960.

**Diels–Alder Adduct of 1-Cyano-1,3-butadiene with 1,3-Butadiene.**—Five-gram samples of 1-cyano-1,3-butadiene, fraction I, $n^{20}D$ 1.4852, and fraction II, $n^{20}D$ 1.4960, an excess of 1,3-butadiene, and a few crystals of picric acid were placed in 2-oz., screw-cap bottles. The bottles were capped and placed in the 50° water-bath and rotated for forty-eight hours. The bottles were removed, and the unchanged 1,3-butadiene was allowed to evaporate. Distillation of the residual liquid from experiments with fraction I resulted only in the recovery of 1-cyano-1,3-butadiene. From experiments with fraction II, along with some unchanged cyanobutadiene, there was obtained a liquid boiling at 94° (8 mm.), $n^{20}D$ 1.4940, $d^{20}_4$ 0.9471. This liquid had the foul odor previously associated with the copolymers of butadiene and 1-cyano-1,3-butadiene (mixture of isomers). A sample of this material was redistilled for analysis.

*Anal.* Calcd. for $C_9H_{11}N$: C, 81.15; H, 8.33. Found: C, 81.05; H, 8.24.

Attempts to effect dehydrogenation of this compound with sulfur or with palladium-on-carbon at high temperature failed. When 13.3 g. (0.1 mole) of the adduct was reduced over Raney nickel catalyst there was obtained 10.2 g. of an amine, b.p. 96° (22 mm.), $n^{20}D$ 1.4653, $d^{20}_4$ 0.8461.

*Anal.* Calcd. for $C_9H_{19}N$: C, 76.51; H, 13.55; N, 9.92. Found: C, 76.45; H, 13.38; N, 10.08.

A picrate of this material was prepared, and after three recrystallizations from 95% ethanol it melted at 189–190° (dec.).

In an attempt to identify the adduct, *o*-cyanostyrene was reduced over nickel but it was not possible to prepare a crystalline picrate of the reduction product.

**1-Cyano-2-methyl-1,3-butadiene.**—The benzoate of tiglic aldehyde cyanohydrin was prepared by the same method used for the benzoate of crotonaldehyde cyanohydrin. From 63 g. (0.75 mole) of tiglic aldehyde (2-methylcrotonaldehyde), 106 g. (0.75 mole) of benzoyl chloride, and 45 g. (0.92 mole) of sodium cyanide there was obtained 120 g. (75%) of tiglic aldehyde cyanohydrin benzoate, b.p. 134° (2 mm.), $n^{20}D$ 1.5200.

*Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.49; H, 6.23.

Pyrolysis of tiglic aldehyde cyanohydrin benzoate in a manner exactly analogous to that employed for the pyrolysis of crotonaldehyde cyanohydrin benzoate yielded 1-cyano-2-methyl-1,3-butadiene. From 120 g. of the benzoate there was obtained 29 g. (56%) of 1-cyano-2-methyl-1,3-butadiene, b.p. 65° (28 mm.), $n^{20}D$ 1.4986.

*Anal.* Calcd. for $C_6H_7N$: C, 77.38; H, 7.58. Found: C, 77.37; H, 7.68.

## Summary

The *cis*- and *trans*-isomers of 1-cyano-1,3-butadiene have been separated. The higher-boiling isomer undergoes Diels–Alder reactions with maleic anhydride and 1,3-butadiene. This isomer is considered to have the *trans*-structure, on the basis of the reaction with maleic anhydride. 1-Cyano-2-methyl-1,3-butadiene has been prepared, but no stereochemical study of the product has been made.

URBANA, ILLINOIS RECEIVED MAY 19, 1948

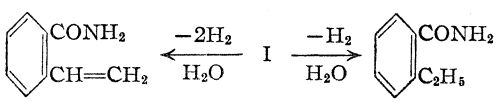
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 1-Cyano-1,3-butadienes. II. Carbon Structure of the Adduct Formed by the Diels–Alder Condensation of 1-Cyano-1,3-butadiene with 1,3-Butadiene

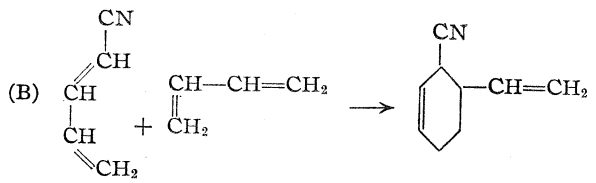
BY H. R. SNYDER AND GEORGE I. POOS

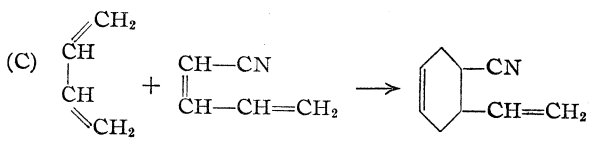
In an attempt to identify the amine obtained by the complete hydrogenation[1] of the adduct from 1-cyano-1,3-butadiene and butadiene, 2-ethylhexahydrobenzylamine was prepared by the catalytic hydrogenation of 2-ethylbenzonitrile. Reduction of the 2-ethylbenzonitrile at high pressure over Raney nickel catalyst produced 2-ethylbenzylamine, which resisted further hydrogenation under these conditions. However, in the presence of platinum catalyst 2-ethylbenzylamine was hydrogenated (2–3 atmospheres, 65°) to 2-ethylhexahydrobenzylamine. The phenylthiourea derivatives of 2-ethylhexahydrobenzylamine and the hydrogenated adduct had the same composition but were found to have different melting points. The difference may be attributed to *cis–trans* isomerism of the amine. The lower melting derivative was obtained from the reduction of 2-ethylbenzylamine and is presumably *cis*, inasmuch as low pressure catalytic hydrogenation of the benzene ring usually produces the *cis* isomer.[2] Attempts to isomerize the phenylthiourea derivatives of the amines thermally either had no effect or resulted in decomposition of the compounds.

Proof of the carbon structure of the adduct was obtained by aromatizing the substance and hydrolyzing the nitriles so obtained to 2-ethylbenzamide in one instance and to 2-vinylbenzamide in another (equation A). The aromatizations were carried out by bromination of the adduct with N-bromosuccinimide followed by dehydrobromination with a high-boiling tertiary amine. When an equivalent amount of the brominating agent was used in the first step, basic hydrolysis of the aromatic nitrile yielded 2-ethylbenzamide, identified by mixed melting point. When two equivalents of N-bromosuccinimide were employed, hydrolysis of the aromatic nitrile in the presence of hydrogen peroxide produced 2-vinylbenzamide. The identity of the latter amide was established by mixed melting point and analysis.

(A) 


1-Cyano-1,3-butadiene and 1,3-butadiene might condense in two ways to give a 2-cyano-1-vinylcyclohexene (equations B and C) and therefore it is not possible to assign the position of the cyclohexene double bond on the basis of the carbon structure. Furthermore, preliminary analyses of the infrared absorption spectrum of the adduct indicate that the substance possesses a conjugated olefinic bond. Apparently the initial condensation product is unstable and changes to a conjugated isomer during or before the distillation of the reaction mixture. The product of equation B would be expected to change readily to a conjugated isomer, and this equation may represent the course of the condensation.

(B) 


(C) 


## Experimental[2a]

**2-Ethylhexahydrobenzylamine.**—2-Ethylaniline was converted by means of the Sandmeyer reaction into 2-ethylbenzonitrile (60%); b.p. 103° (19 mm.) lit.,[3] 212° (atm. pressure); $n^{20}D$ 1.5232. In an attempt to hydrogenate 2-ethylbenzonitrile completely over Raney nickel catalyst at temperatures from 130 to 175° and pressures from 500 to 2800 p.s.i., only 31% of the theoretical amount of hydrogen could be added. The main product was 2-ethylbenzylamine, which rapidly forms the carbonate upon exposure to the atmosphere. The picrate after recrystallization from 95% ethanol melted at 215° with decomposition.

*Anal.* Calcd. for $C_{15}H_{16}O_7N_4$: C, 49.45; H, 4.43. Found: C, 49.52; H, 4.62.

In addition to the primary amine, there was obtained a small amount of the corresponding secondary amine. The hydrochloride of the secondary amine was recrystallized from high-boiling petroleum ether–absolute ethanol and after drying *in vacuo* over phosphorus pentoxide the hygroscopic salt melted at 158.5–159°.

*Anal.* Calcd. for $C_{18}H_{24}NCl$: C, 74.59; H, 8.35. Found: C, 74.59; H, 8.19.

To a solution of 10.0 g. of 2-ethylbenzylamine in 100 ml. of 75% ethanol in a low pressure hydrogenation bottle was added 1.1 g. of platinic oxide and 2 drops of concentrated hydrochloric acid. The bottle was heated to 65° and shaken in a Parr machine under 2–3 atmospheres of hydrogen. When 53% of the theoretical amount of hydrogen had been added, the reduction had stopped and it was necessary to filter the solution and add fresh catalyst. After a total of forty-seven hours, 87% of the theoretical amount of hydrogen had been added. The reaction mixture was then filtered, the low boiling material was removed by distillation and the residue was distilled through a small column. There was obtained 7.2 g. of an amine that could not be separated in a sufficient state of purity for analysis.

(1) Snyder, Stewart and Myers, THIS JOURNAL, **71**, 1055 (1949).

(2) Linstead, *et al.*, *ibid.*, **64**, 1985–2026 (1942).

(2a) All melting points are uncorrected.

(3) Giebe, *Ber.*, **29**, 2535 (1896).

From this amine and phenyl isothiocyanate there was obtained phenyl-2-ethylhexahydrobenzylthiourea as a heavy oil which hardened after standing for three days. When recrystallized twice from 50% ethanol and once from high-boiling petroleum ether it melted at 88°.

*Anal.* Calcd. for $C_{16}H_{24}N_2S$: C, 69.52; H, 8.75. Found: C, 69.52; H, 8.93.

**Phenylthiourea of the Reduced Adduct.**—From phenyl isothiocyanate and the amine obtained by the reduction of I[4] there was obtained an oil which was induced to crystallize by cooling its alcoholic solution to −80°. After being recrystallized twice from 50% ethanol and once from high-boiling petroleum ether the product melted at 146–148°.

*Anal.* Calcd. for $C_{16}H_{24}N_2S$: C, 69.52; H, 8.75. Found: C, 69.57; H, 8.98.

**Aromatization of I. A. Bromination with One Equivalent of Brominating Agent and Dehydrobromination.**—To a solution of 5.0 g. (0.038 mole) of I[4] in 50 ml. of ethylene dichloride was added 6.8 g. (0.038 mole) of purified N-bromosuccinimide, and the mixture was heated to boiling with stirring. After refluxing for one and one-half hours, the solution gave a negative test for active bromine with acidified potassium iodide solution. The mixture was cooled, the precipitated succinimide was removed by filtration and the ethylene dichloride was distilled. The bromide was separated from a small amount of succinimide by extraction of the residue with cold absolute ethanol. The alcohol was then removed by distillation. To the dark residual oil was added 12 g. of quinoline and the mixture was distilled (oil-bath temp. 170–180°) slowly under reduced pressure through a small column. The distillate boiling from 110–114° (16 mm.) was shaken with dilute hydrochloric acid to remove any quinoline and the nitrile was extracted with ether and redistilled.

Attempted hydrolysis of this mixture with 75% sulfuric acid yielded only tar. However, when 0.40 g. of the material was refluxed for forty-seven hours with 0.5 g. of potassium hydroxide in 6.5 ml. of 60% ethanol, in addition to unhydrolyzed nitrile, there was isolated a small quantity of a white crystalline material. After recrystallization from water and chloroform it melted at 151–152° and showed no depression in melting point when mixed with a sample of 2-ethylbenzamide.[3] There was not enough of this material for analysis.

**B. Bromination with Two Equivalents of Brominating Agent and Dehydrobromination.**—To a solution of 5.0 g. (0.038 mole) of I[4] in 85 ml. of benzene was added 13.7 g. (0.076 mole) of purified N-bromosuccinimide and the solution was heated to boiling with stirring. After refluxing for two hours a positive test for active bromine was still obtained. The reaction mixture was cooled to 0° and the precipitated succinimide was removed by filtration. Distillation of the benzene was accompanied by the evolution of hydrogen bromide. To the residual oil was added 16.8 g. of lepidine and the mixture was distilled slowly under reduced pressure through a small column. The distillate boiling at 80–88° (3 mm.) was collected, shaken with dilute hydrochloric acid, recollected in ether, and redistilled to yield a colorless oil that darkened rapidly.

A portion of this nitrile was hydrolyzed in alcoholic sodium hydroxide solution in the presence of 30% hydrogen peroxide.[5] The alcohol was removed by distillation and the cold aqueous residue was extracted with chloroform. Concentration of the extract yielded 2-vinylbenzamide, which after recrystallization from chloroform melted at 151.5–152°.

*Anal.* Calcd. for $C_9H_9ON$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.15; H, 6.16; N, 9.71.

This amide showed no depression in melting point when mixed with 2-vinylbenzamide prepared by hydrolysis of 2-cyanostyrene.

**2-Vinylbenzamide.**—Hydrolysis of 0.50 g. of 2-cyanostyrene[6] in the presence of 30% hydrogen peroxide by the same procedure as described above yielded 0.22 g. of crude 2-vinylbenzamide which melted at 143–147°. Recrystallization from chloroform raised the melting point to 151.5–152°.

*Anal.* Calcd. for $C_9H_9ON$: C, 73.45; H, 6.16. Found: C, 73.54; H, 6.36.

## Summary

The Diels–Alder adduct of 1-cyano-1,3-butadiene with 1,3-butadiene is shown to be a 2-cyano-1-vinylcyclohexene. Proof of the carbon structure is accomplished by bromination of the adduct, dehydrobromination and hydrolysis to 2-ethylbenzamide and 2-vinylbenzamide.

(4) Sample furnished by Dr. R. L. Myers.

(5) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 586.

(6) Sample furnished by Dr. C. S. Marvel; see Marvel and Hein, THIS JOURNAL, **70**, 1895 (1948).

URBANA, ILLINOIS RECEIVED JULY 29, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Amine Replacement Reactions of α-Dimethylaminomethyl-β-methoxynaphthalene

BY H. R. SNYDER AND JAMES H. BREWSTER[1]

α-Dimethylaminomethyl-β-naphthol, a typical phenolic Mannich base, possesses a labile amino group which can easily be replaced by an activated aromatic nucleus,[2] by a cyano[3] group or by another amine residue.[4] A methylene quinone has been suggested as an intermediate in the amine exchange reaction[4]; such an intermediate could also participate in the other amine replacement reactions of phenolic Mannich bases. It has been suggested previously that a vinyl ketone is formed in the first step of amine replacement reactions of ketonic Mannich bases[5] and their quaternary salts.[6]

In a test of the hypothesis that amine elimination is the first step in amine replacement reactions of Mannich bases, it was desired to prepare α - dimethylaminomethyl - β - methoxynaphthalene (V) and its methiodide (VI) and to subject these compounds to the conditions of amine exchange and amine replacement reactions.

β-methoxynaphthalene failed to undergo the

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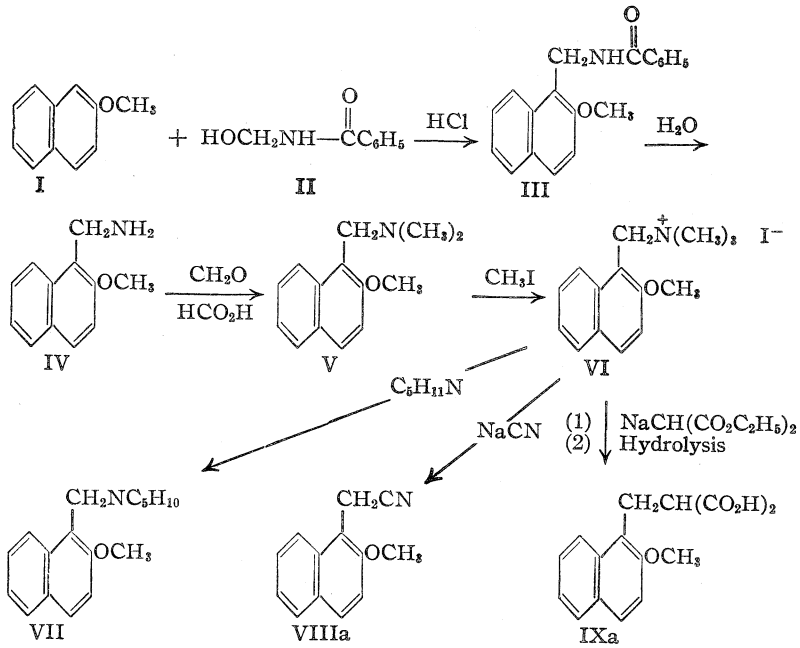
(2) Auwers and Dombrowsky, *Ann.*, **344**, 280 (1906).

(3) Salzer, U. S. Department of Commerce, U. S. Publication Board, P. B. Report, No. 706 (1946).

(4) Snyder and Brewster, THIS JOURNAL, **70**, 4230 (1948).

(5) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

(6) du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).




Mannich reaction,[7] differing in this respect from 1-methylindole.[8] Mannich bases of β-naphthol could not be etherified with either methyl iodide or dimethyl sulfate, apparently because quaternary salt formation occurred more readily. The method shown in the diagram was finally adopted for the preparation of V. In this synthesis α-aminomethyl-β-methoxynaphthalene (IV) was prepared by hydrolysis of the amide (III) with hot 20% sodium hydroxide solution; the stability of the primary amine (IV) to the alkaline solution is in marked contrast to the lability of naphthol Mannich bases in the presence of alkali.[2] The tertiary amine (V) also was stable to alkali; it could be distilled, and it yielded an isolable methiodide. In all these respects it differs from α-dimethylaminomethyl-β-naphthol. It failed to react with piperidine, piperidine acetate, sodium cyanide in aqueous ethanol or malonic ester in the presence of powdered sodium hydroxide. The low reactivity of the substance (V) indicates that the lability of the amino group in a phenolic Mannich base is great only when amine elimination is possible.

The quaternary salt (VI) reacted with piperidine by amine exchange, and with sodium cyanide and sodiomalonic ester by amine replacement. The activity of the salt (VI) in these reactions is similar to that of quaternary salts of benzylamine,[9,10,11,12] and less than that of 1-methylgramine methiodide.[8]

## Experimental[13,14]

**α-Benzamidomethyl-β-methoxynaphthalene (III)** was prepared by modifications of the method described[15] for the analogous α-chloroacetyl derivative. A mixture of 100 ml. of methanol, 31.6 g. of β-methoxynaphthalene[16] and 30.2 g. of N-methylolbenzamide[17] was stirred at 35–40° while a rapid stream of hydrogen chloride gas was introduced until a clear solution formed. Introduction of the gas was discontinued, and after six hours at room temperature the mixture was poured into ice and water. The thoroughly washed solid was dried, boiled for three hours with 300 ml. of methanol, recovered by filtration of the cooled suspension, washed repeatedly with water, and dried over calcium chloride to give 56 g. (97%) of III of m.p. 152–153°; recrystallization from eight parts of ethanol raised the m.p. to 153.5–154° (lit.[18] 155°). Since the substance apparently has not been prepared previously by this method, a sample was analyzed.

*Anal.* Calcd. for $C_{19}H_{17}O_2N$: C, 78.35; H, 5.84; N, 4.82. Found: C, 78.26; H, 5.80; N, 4.75.

**α-Aminomethyl-β-methoxynaphthalene (IV).**—A mixture of 50 g. of III with a solution of 45 g. of sodium hydroxide in 50 ml. of water and 250 ml. of ethanol was refluxed twenty-four hours. The clear hot solution was poured into 1 l. of water; the solid was collected, washed, suspended in 1 l. of water and dissolved by the addition of about 25 ml. of 37% hydrochloric acid. The amine (IV) was recovered by the addition of alkali to the filtered, cooled solution. After washing and drying, the nearly pure IV (31.1 g., 96%) melted at 68–69° (lit. 41–42°[18]; *ca.* 100°[15]); it could be recrystallized from 75% ethanol or distilled at 141–142° (1 mm.).

*Anal.* Calcd. for $C_{12}H_{13}NO$: C, 77.01; H, 6.94. Found: C, 76.90; H, 7.10.

Saturated alcoholic picric acid solution was added to a warm alcoholic solution of the amine. The bright yellow *picrate* precipitated as micro-needles. After it had been recrystallized from 95% ethanol it melted at 197–198°. Dey and Rajagopalan[18] reported this picrate as melting at 215° and having a nitrogen content of 14.12 per cent., which they compared to the value of 14.00% based on the formula $C_{18}H_{16}N_4O_7$; however, the formula of the monopicrate is $C_{18}H_{16}N_4O_8$ and the theoretical nitrogen content thus becomes 13.46%. The analysis of our sample was satisfactory.

*Anal.* Calcd. for $C_{18}H_{16}N_4O_8$: C, 51.95; H, 3.85; N, 13.46. Found: C, 52.08; H, 4.02; N, 13.27.

**α-Dimethylaminomethyl-β-methoxynaphthalene (V)** was prepared from IV, 40% formalin and formic acid by modification of a standard procedure[19] for the Clarke–Eschweiler reaction; the tertiary amine V, b.p. 146–150° (2 mm.), $n^{20}D$ 1.6002, was obtained in 60% yield.

*Anal.* Calcd. for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.01; H, 7.86; N, 6.57.

(7) Blicke, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 303.
(8) Snyder and Eliel, THIS JOURNAL, **70**, 1703 (1948).
(9) Snyder and Speck, *ibid.*, **61**, 668, 2895 (1939).
(10) von Braun, Kühn and Goll, *Ber.*, **59**, 2330 (1926).
(11) von Meyer, *Abhandlung d. mathem.-phys. Klasse d. sächs. Gesellschaft d. Wissenschaften*, **31**, 179 (1908); [*Chem. Zentr.*, **80**, II, 1800 (1909)].
(12) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).
(13) All melting points corrected.
(14) Microanalyses by Misses Theta Spoor and Emily Davis and Mr. Howard Clark.
(15) Einhorn and Spröngerts, *Ann.*, **361**, 163 (1908).
(16) Davis, *J. Chem. Soc.*, **77**, 37 (1900).
(17) Einhorn, Bischkopff and Szelinski, *Ann.*, **343**, 223 (1905).
(18) Dey and Rajagopalan, *Arch. Pharm.*, **277**, 359 (1939).
(19) Icke and Wisegarver, in "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 89.

**The picrate** was prepared as above. It crystallized from alcohol in large bright yellow plates, m.p. 164–165°.

*Anal.* Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.02; H, 4.62; N, 12.55.

**The methiodide VI,** prepared (95% yield) in ether from a 40% excess of methyl iodide, melted at 158–159°.

*Anal.* Calcd. for $C_{15}H_{20}NOI$: C, 50.43; H, 5.64; N, 3.92; I, 35.53. Found: C, 50.14; H, 5.79; N, 3.73; I, 35.70.

**α-Piperidinylmethyl-β-methoxynaphthalene (VII).**—When a mixture of 1.78 g. of the methodide (VI) and 8.5 g. of piperidine was heated under reflux a gaseous amine was evolved rapidly. After about three hours the mixture was added to aqueous alkali, and the ether-soluble portion was collected and freed of piperidine by evaporation, finally under diminished pressure. The acid-soluble portion of the residue was recovered and recrystallized from aqueous ethanol to give 0.60 g. (47%) of VII, m.p. 65–66°.

*Anal.* Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.41, 80.34; H, 8.58, 8.61; N, 5.45.

**2-Methoxy-1-naphthaleneacetonitrile (VIIIa).**—When aqueous solutions of the methiodide (VI) and excess sodium cyanide were refluxed for as long as a week, no amine replacement reaction occurred. The method of von Meyer[11] was finally employed. To a solution of 3.57 g. of α-dimethylaminomethyl-β-methoxynaphthalene methiodide (VI) in 10 ml. of water in a 50-ml. distilling flask was added 2.5 g. of sodium cyanide. The mixture was warmed until the cyanide had dissolved; a heavy oil separated. Water was slowly distilled from the solution at water-pump pressure until the solid residue was nearly dry. The bulb of the distilling flask was placed in a Wood's metal-bath which was heated (about 140°) until the material began to froth vigorously. The bath temperature was slowly raised to 250°. When evolution of trimethylamine had ceased, the mixture was distilled. The waxy product, b.p. 154° (0.5 mm.), was recovered from the side-arm of the flask by extraction with a small amount of hot acetone and crystallized from 50% aqueous acetone to yield 0.86 g. (43.5%) of light yellow crystals of 2-methoxy-1-naphthaleneacetonitrile (VIIIa) which melted at 111.5–112.5° (lit.[20] 111°). Alkaline hydrolysis of a portion of the nitrile gave **2-methoxy-1-naphthaleneacetic acid (VIIIb),** m.p. 208–209° (lit. 208°,[21] 210–211°).[22]

**(β-Methoxy-α-naphthylmethyl)-malonic Acid (IXa).**—Freshly cut sodium (0.25 g.) was converted to sodium sand under xylene. The xylene was decanted and replaced by absolute diethyl carbitol[23] (25 ml.). Diethyl malonate (4.0 g.) was added, and the solution was stirred with cooling until all of the sodium had reacted. α-Dimethylaminomethyl-β-methoxynaphthalene methiodide (VI) (3.57 g.) was added and the mixture was heated with stirring at 120–130° for seventy-two hours and finally at 150–160° for one hour. Trimethylamine was evolved during the entire heating period. The cooled mixture was treated with 40 ml. of 10% hydrochloric acid and extracted with benzene. The benzene solution was extracted with 10% sodium hydroxide, then with 37% hydrochloric acid (to remove diethyl carbitol) and finally with water. The dried benzene solution was concentrated and the thick oily residue was treated with a hot solution of 5 g. of sodium hydroxide in 5 ml. of water and 2 ml. of ethanol. A thick white paste formed when the mixture was stirred. After one-half hour the saponification mixture was warmed for a few minutes on a steam cone. The substituted malonic acid, recovered by dilution with water and acidification, was recrystallized from 10% ethanol. The white micro-crystals of (β-methoxy-α-naphthylmethyl)-malonic acid (IXa) weighed 1.73 g. (61%) and melted at 158–159° (dec.).

*Anal.* Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.15; neutral equivalent, 137. Found: C, 65.90; H, 5.39; neutral equivalent, 138.4.

**2-(β-Methoxy-α-naphthyl)-propionic Acid (IXb).**—The malonic acid (IXa) (0.4 g.) was heated under reflux for one hour with pyridine (4. g.).[24] The solution was cooled and 10% hydrochloric acid (40 ml.) was added. The white precipitate was collected and crystallized from a 10% ethanol. The propionic acid (IXb) formed white needles melting at 131–132° (lit.[25] 128°).

*Anal.* Calcd. for $C_{14}H_{14}O_3$: neut. equiv., 230. Found: neut. equiv., 230.2.

## Summary

α-Dimethylaminomethyl-β-methoxynaphthalene (V) was prepared by benzamidomethylation of β-naphthyl methyl ether, followed by hydrolysis of the amide so formed and methylation of the primary amine. The dimethylamino group of V could not be replaced by reaction with piperidine, sodium cyanide or ethyl malonate; the compound was stable to alkali. The phenolic hydrogen atom appears to participate in the amine exchange and replacement reactions of phenolic Mannich bases.

The methiodide of V reacted by amine replacement with piperidine, sodium cyanide and sodio malonic ester. The reactivity of this quaternary salt resembles that of quaternary salts of benzylamine.

URBANA, ILLINOIS RECEIVED JULY 26, 1948

(20) Cook, Downer and Hornung, *J. Chem. Soc.*, 502 (1941).

(21) Mayer, Schafer and Rosenbach, *Arch. Pharm.*, **267**, 571 (1929).

(22) Mauthner, *J. prakt. Chem.*, [2] **95**, 55 (1917).

(23) Commercial diethyl carbitol was distilled, b. p. 92–93° (30 mm.), the distillate was heated for eight hours with 1% of its weight of sodium, and finally distilled from the sodium that remained. The distillate was almost inert to sodium and after it was redistilled over sodium it failed to react even with molten sodium. The yield of absolute diethyl carbitol was about 70–80%.

(24) Grigsby, Hind, Chanley and Westheimer, THIS JOURNAL, **64**, 2606 (1942).

(25) Barger and Starling, *J. Chem. Soc.*, **99**, 2033 (1911).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Reactions of β-Dimethylaminopivalophenone and its Methiodide

BY H. R. SNYDER AND JAMES H. BREWSTER[1]

Ketonic Mannich bases and their quaternary salts alkylate active methylene compounds[2,3] by a process of amine replacement and react with secondary amines by amine exchange.[4] Amine replacement also occurs in the reaction of sodium cyanide with the hydrochlorides of ketonic Mannich bases.[5]

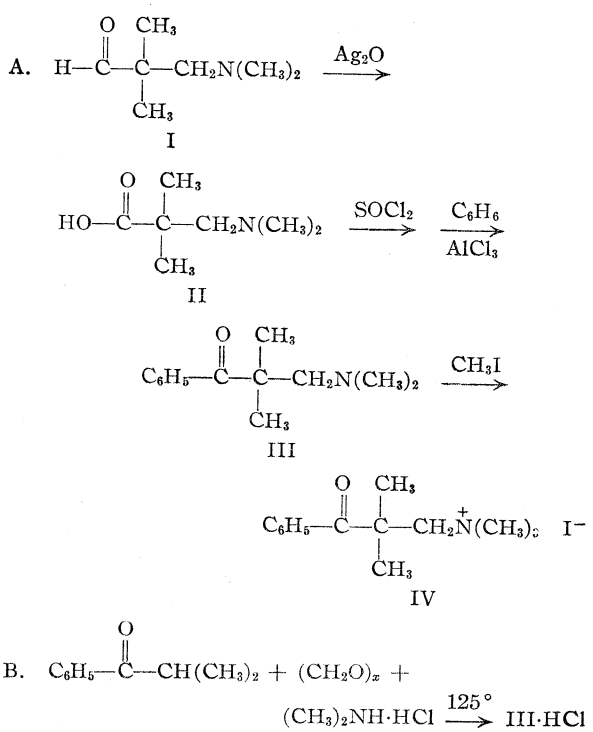
The ease with which vinyl ketones can be prepared from β-aminoketones[6,7] has suggested that amine elimination is the first step in amine replacement[2,3] and exchange[4] reactions. Nisbet has presented evidence that amine elimination precedes ring closure in the formation of pyrazolines from the phenylhydrazones of ketonic Mannich bases.[8]

In connection with studies of the reactions of Mannich bases which cannot suffer amine elimination,[9,10] β-dimethylaminopivalophenone (III) and its methiodide (IV) were prepared and subjected to the conditions of amine replacement and exchange reactions. These compounds (III and IV) would be expected to be extremely unreactive in such processes; not only is amine elimination impossible, but also $S_N2$ amine displacements[11] are prevented by the steric hindrance offered by the α-methyl groups,[12] and $S_N1$ amine replacements[11] are hindered because no resonance-stabilized "carbonium ion" (or its solvated equivalent)[13] can be formed as an intermediate.

Although isobutyraldehyde readily undergoes the Mannich reaction to form β-dimethylaminopivaldehyde (I),[14] isobutyrophenone (V) is not attacked under the conditions generally employed for this process.[15] The ketonic Mannich base (III) could, however, be prepared in low yield by the reaction of isobutyrophenone with dimethylamine hydrochloride and an excess of molten paraformaldehyde (eqn. B). The β-aminoketone so formed was identical with that prepared from β-dimethylaminopivalic acid (II) by the method of Dalmer, Diehl and Pieper[16] (eqn. A).

The β-aminoketone (III) failed to react with alcoholic alkali, morpholine or malonic ester. Although III apparently formed a phenylhydrazone, this derivative could not be crystallized, nor could it be cyclized to a pyrazoline, in contrast to the phenylhydrazone of the dimethylamino Mannich base of acetophenone.[17] When heated with aqueous-alcoholic sodium cyanide, III formed isobutyrophenone in 67% yield. A similar reverse Mannich reaction occurred readily when a dilute hydrochloric acid solution of III was distilled. A possible mechanism for this reaction is indicated in equation C.

The methiodide (IV) formed no appreciable amounts of neutral or acidic products when heated with aqueous sodium cyanide or sodiomalonic ester in diethyl carbitol. When an aqueous solution of IV and sodium cyanide was distilled to dryness, III was formed by demethylation of the quaternary salt. Hot aqueous alkali slowly converted IV to benzoic acid, trimethylamine and, perhaps, isobutylene, possibly by the mechanism shown in equation D.



(1) Present address: Department of Chemistry, University of Chicago, Chicago, Illinois.

(2) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

(3) du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

(4) Snyder and Brewster, THIS JOURNAL, **70**, 4230 (1948).

(5) Knott, *J. Chem. Soc.*, 1190 (1947).

(6) Blicke, in "Organic Reactions," Vol. I, John Wiley and Sons Inc., New York, N. Y., 1942, p. 303.

(7) Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(8) Nisbet, *J. Chem. Soc.*, 126 (1945).

(9) Snyder and Eliel, THIS JOURNAL, **70**, 1703, 1857 (1948).

(10) Snyder and Brewster, *ibid.*, **71**, 1058 (1949).

(11) Hughes, Ingold and Patel, *J. Chem. Soc.*, 526 (1933).

(12) Dostrovsky, Hughes and Ingold, *ibid.*, 173 (1946).

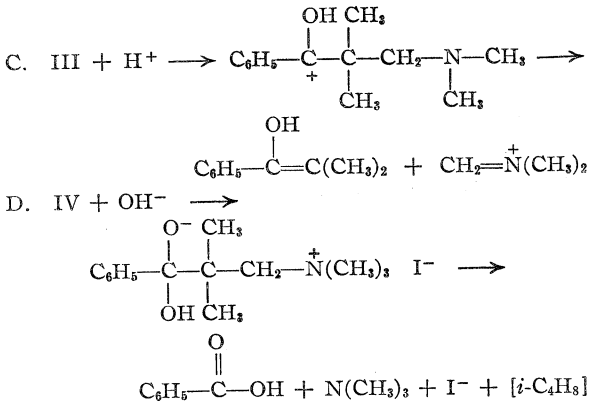
(13) Swain, THIS JOURNAL, **70**, 1119 (1948).

(14) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).

(15) Winstein, Jacobs, Seymour and Linden, *J. Org. Chem.*, **11**, 215 (1946).

(16) Dalmer, Diehl and Pieper, German Patent 606,349; *Frdl.*, **21**, 622 (1937); German Patent 629,054; *Frdl.*, **23**, 584 (1940).

(17) Jacob and Madinaveitia, *J. Chem. Soc.*, 1929 (1937).



## Experimental[18,19]

**β-Dimethylaminopivalophenone (III). 1. By the Friedel–Crafts Reaction.**—β-Dimethylaminopivaldehyde[14] (I, 14.8 g.) was added dropwise to a stirred suspension of thoroughly washed silver oxide (prepared from 39.2 g. of silver nitrate) in 150 ml. of water. The oxidation was completed by heating the mixture on the steam-bath for two hours. The crude amino acid (II), obtained by evaporation (at 25 mm.) of the filtered aqueous solution, was dissolved in a mixture of 200 ml. of acetone and 5 ml. of water, and the filtered hot solution was placed in the ice-chest. After twelve hours pure II was collected as glistening white needles melting at 98–99° (lit.[16] 100°); yield, 12.2 g. (74%). The amino acid was converted to the ketone (III) as previously described[16]; the ketone (III) was obtained as a nearly odorless, water-white liquid, b.p. 103–105° (2.5 mm.), $n^{20}D$ 1.5128; the yield of III from II was 32%.

**2. By the Mannich Reaction of Isobutyrophenone.**—In a 300-ml. Kjeldahl flask fitted with an air-cooled condenser a mixture of 7.4 g. of isobutyrophenone, 8.2 g. of dimethylamine hydrochloride and 7.5 g. of paraformaldehyde was heated for two hours at 140–150° (oil-bath temperature). The cooled mixture was diluted with 150 ml. of water, filtered and washed with ether. The aqueous layer was made alkaline and extracted with ether. Distillation of the residue from evaporation of the dried ether extracts gave 2.03 g. (19%) of III, b.p. 83–84° (1 mm.), $n^{20}D$ 1.5130.

*Anal.* Calcd. for $C_{13}H_{19}ON$: C, 76.05; H, 9.34; N, 6.82. Found: C, 76.03; H, 9.48; N, 6.88.

The hydrochloride[16] melted at 143–144°, alone or mixed with the hydrochloride prepared from the product of the first synthesis.

**The methiodide** (IV) formed when III was allowed to stand with a fivefold excess of methyl iodide for twelve hours or longer; it separated as a dark oil which crystallized when the mixture was diluted with ether. The salt could be recrystallized by the slow addition of dry ether to an absolute ethanol solution. It melted at 122–122.5°; samples prepared from the two lots of II were identical.

*Anal.* Calcd. for $C_{14}H_{22}ONI$: C, 48.42; H, 6.39. Found: C, 48.64; H, 6.49.

**Attempted Amine Exchange Reaction with β-Dimethylaminopivalophenone.**—β - Dimethylaminopivalophenone (III) (0.41 g.) and morpholine (4.35 g.) were refluxed for forty-eight hours under nitrogen. The solution was cooled and 20 ml. of water was added. The cloudy mixture was extracted with three 5-ml. portions of ether. The combined ether extract was distilled, finally under vacuum (water pump), to remove the morpholine that had been extracted along with the aminoketone. A large excess of methyl iodide was added to the residue; the methiodide of β-dimethylaminopivalophenone (IV), m.p. 122–123°, identical with that previously prepared, was obtained; yield, 0.45 g. (65%).

**Attempted Alkylation of Malonic Ester with β-Dimethylaminopivalophenone.**—To a solution of β-dimethylaminopivalophenone (III) (0.41 g.) and malonic ester (1.00 g.) in 5 ml. of xylene was added a small amount of powdered sodium hydroxide. The mixture was refluxed under nitrogen for forty-eight hours. No amine evolution was observed. The solution was cooled and extracted with three 5-ml. portions of 10% hydrochloric acid. The combined acid extract was made strongly alkaline and the oil which separated was taken up in ether; the ether was evaporated and the residue was treated with an excess of methyl iodide. The methiodide of the Mannich base was obtained; yield, 0.43 g. (62%), m.p. 122–123°.

**Reverse Mannich Reaction of Isobutyrophenone Mannich Base.**—β-Dimethylaminopivalophenone (2.05 g.) and sodium cyanide (1.00 g.) were heated together in 30 ml. of 50% ethanol for four days. A volatile amine was evolved. Water (70 ml.) was added to the cooled solution, which was then extracted with 20-ml. portions of ether. The combined ether extract was distilled, finally under reduced pressure. Isobutyrophenone, (1 g., 67.5%) b.p. 56° (1 mm.), $n^{20}D$ 1.5189 (lit.[20] $n^{20}D$ 1.5190), was the sole product obtained. The 2,4-dinitrophenylhydrazone melted at 162–162.5°.[20]

A similar reverse Mannich reaction occurred when the Mannich base was heated in acid medium.

β-Dimethylaminopivalophenone (1.00 g.) was dissolved in a mixture of 2 ml. of 37% hydrochloric acid and 10 ml. of water. The solution was slowly distilled almost to dryness from an oil-bath maintained at 130–140°. When no further distillation occurred more water was added and the distillation was resumed. This process was continued until only a clear distillate was obtained; there was a small amount of tarry residue.

The acidic, cloudy distillate (20 ml.) was extracted with ether. The ether was evaporated, and the residue, dissolved in 95% ethanol, was treated with 1 g. of 2,4-dinitrophenylhydrazine. The solution was brought to boiling, and, after it had been cooled slightly, 37% hydrochloric acid (1.3 ml.) was added. The acid solution was heated under reflux for one hour; the crude 2,4-dinitrophenylhydrazone of isobutyrophenone, m.p. 153–155°, 1.34 g. (81.8%), crystallized from the solution when it was chilled in ice. The reddish crystals were digested with ethanol to give 1.02 g. (62.3% from the Mannich base) of the pure derivative, m.p. 162.5–163°.[20]

β-Dimethylaminopivalophenone (1.0 g.) was heated with a solution of sodium hydroxide (2 g.) in 75% ethanol (20 ml.) for two days. No appreciable evolution of basic gases occurred. The flask was cooled and water (30 ml.) was added. The oil which separated was collected in ether and extracted with 10% hydrochloric acid. The ether solution left no residue on evaporation. The acid solution was made strongly basic and 0.75 g. (75%) of the unchanged Mannich base, b.p. 90° (1 mm.), $n^{20}D$ 1.5125 was recovered.

**Reaction of the Methiodide of β-Dimethylaminopivalophenone with Sodium Cyanide.**—A solution of the methiodide of β-dimethylaminopivalophenone (IV) (1.74 g.) and sodium cyanide (0.50 g.) in water (5 ml.) was distilled to dryness at atmospheric pressure in a flask with a low-set wide side-arm. The bulb of the flask was set in a Wood's metal-bath, and, while the pressure inside the flask was maintained at about 35 mm., the bath temperature was raised slowly to 180°. A liquid formed in the bulb of the flask but did not distil. After half an hour the mixture was allowed to cool somewhat and was distilled at 1.5 mm. pressure yielding a fraction of b.p. 100–120° (1.5 mm.).

The solid residue in the distillation flask was extracted with ether, and this ethereal solution was used in an extraction of the first (aqueous) distillate and was then added to the volatile material from the final distillation. The ether solution was extracted with 10% sodium hydroxide

(18) Microanalyses by Misses Theta Spoor and Betty Snyder.

(19) All melting points corrected.

(20) Evans, *J. Chem. Soc.*, 788 (1936).

solution and then with 10% hydrochloric acid. The neutral and base-soluble fractions contained only traces of material. The acid-soluble fraction was recovered and treated with methyl iodide to give 0.87 g. (50%) of the methiodide of β-dimethylaminopivalophenone; m. p. 122–123°. No melting point depression occurred on admixture of authentic IV to this salt.

**Reaction of Methiodide of β-Dimethylaminopivalophenone with Sodium Hydroxide.**—The methiodide (IV) (1.04 g.) was heated under reflux with 8 ml. of 5% sodium hydroxide for forty-eight hours. A basic gas was evolved rapidly during the first few hours. The cooled solution was filtered, the filtrate acidified, and the precipitated benzoic acid was collected in benzene; m.p. (and mixed m.p.) 122–122.5°, after recrystallization from water; yield 0.21 g. (57%).

## Summary

β-Dimethylaminopivalophenone has been prepared by the Mannich reaction of isobutyrophenone. This β-aminoketone cannot suffer amine elimination, is sterically hindered to amine displacement, and cannot form a resonance-stabilized "carbonium ion." It failed to undergo amine exchange and replacement reactions; it was stable to strong base, but it readily underwent the reverse Mannich reaction in weakly basic or acidic medium.

The methiodide of this Mannich base reacted with sodium cyanide by demethylation rather than by amine replacement. Hot aqueous alkali caused cleavage of the methiodide to benzoic acid.

URBANA, ILLINOIS RECEIVED JULY 29, 1948

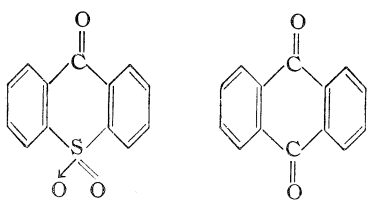
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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA AND SWARTHMORE COLLEGE]

# The Thiaxanthone Dioxide–Thiaxanthenol Dioxide–Thiaxanthene Dioxide Oxidation–Reduction System: A Sulfone Series Analog of the Anthraquinone–Anthrahydroquinone–Anthrone System[1]

BY EDWARD A. FEHNEL[2]

Several investigators have called attention to the peculiar color reactions of thiaxanthone-5-dioxide and substituted thiaxanthone-5-dioxides in the presence of zinc dust and alkali,[3] but no detailed study of these reactions has previously been reported and the nature of the chromogen has remained a subject for speculation.[3] Our interest in the physico-chemical properties of the sulfone function[4] led us to investigate the color reactions of thiaxanthone-5-dioxide in some detail, and we are now able to report the isolation and characterization of the substance responsible for color formation and to suggest a mechanism for the reactions involved.[5]



I II

On treatment with zinc dust or sodium hydrosulfite and alkali, alcoholic solutions of thiaxanthone-5-dioxide (I) give an intense blue color, which is discharged on shaking with air. The striking similarity of this behavior to that shown by anthraquinone[6] (II) under the same conditions immediately suggests that the color is to be attributed to the formation of a sulfone anion analogous to the deeply colored, readily oxidizable anthrahydroquinone anion formed in the familiar vatting reaction.[7] Our data on the oxidation–reduction reactions in the thiaxanthone dioxide series are in accord with this interpretation. The demonstration of a close parallelism in the reactions of the thiaxanthone dioxide and anthraquinone series of compounds is of particular interest in view of the fact that the formulation of a sulfone oxidation–reduction system analogous to the anthraquinone–anthrahydroquinone system requires

(1) Presented at the Meeting-in-Miniature of the Philadelphia Section of the American Chemical Society, January 20, 1949.

(2) American Chemical Society Postdoctoral Fellow at the University of Pennsylvania, 1946–1948. Present address: Department of Chemistry, Swarthmore College, Swarthmore, Pa.

(3) (a) Graebe and Schulthess, *Ann.*, **263**, 1 (1891); (b) Ullmann and Lehner, *Ber.*, **38**, 729 (1905); (c) Ullmann and Glenck, *ibid.*, **49**, 2487 (1916); (d) Amstutz, Fehnel and Hunsberger, THIS JOURNAL, **70**, 133 (1948).

(4) Fehnel and Carmack, *ibid.*, **71**, 231 (1949).

(5) NOTE ADDED IN PROOF.—While the present paper was in press, Heymann [*ibid.*, **71**, 260 (1949)] reported a closely related study of the thiaxanthone dioxide–thiaxanthenol dioxide oxidation–reduction system, in which essentially the same conclusions were reached with regard to the reaction mechanism.

(6) For a detailed discussion of the chemistry of anthraquinone and its reduction products, see Houben and Fischer, "Das Anthracen und die Anthrachinone," Georg Thieme, Leipzig, 1929, esp. pp. 143–172 and 197–206. An excellent concise summary of the more important oxidation-reduction reactions has been given by Fieser and Fieser, "Organic Chemistry," D. C. Heath, Boston, 1944, pp. 798–802.

(7) NOTE ADDED IN PROOF.—Strictly speaking, it is not entirely accurate to attribute the color to the simple ion, since the colored species is undoubtedly the semiquinone ion-radical which results from the loss of one electron by the doubly-charged anion (*cf.* Heymann, ref. in footnote 5). This idea is, of course, implicit in the present discussion of the thiaxanthone-enol dioxide oxidation–reduction system, since it follows from the analogy with the anthraquinone–anthrahydroquinone system, in which the blood-red color of the "anthrahydroquinone anion" is almost certainly due to the presence of the corresponding semiquinone ion-radical (see, however, Dufraisse and Priou, *Bull. soc. chim.*, [5] **6**, 1649 (1939), who postulate a biradical anion).

the assumption of an expanded valence shell for sulfur.[4]

The reactions in the thiaxanthone dioxide system are best described by reference to Fig. 1.

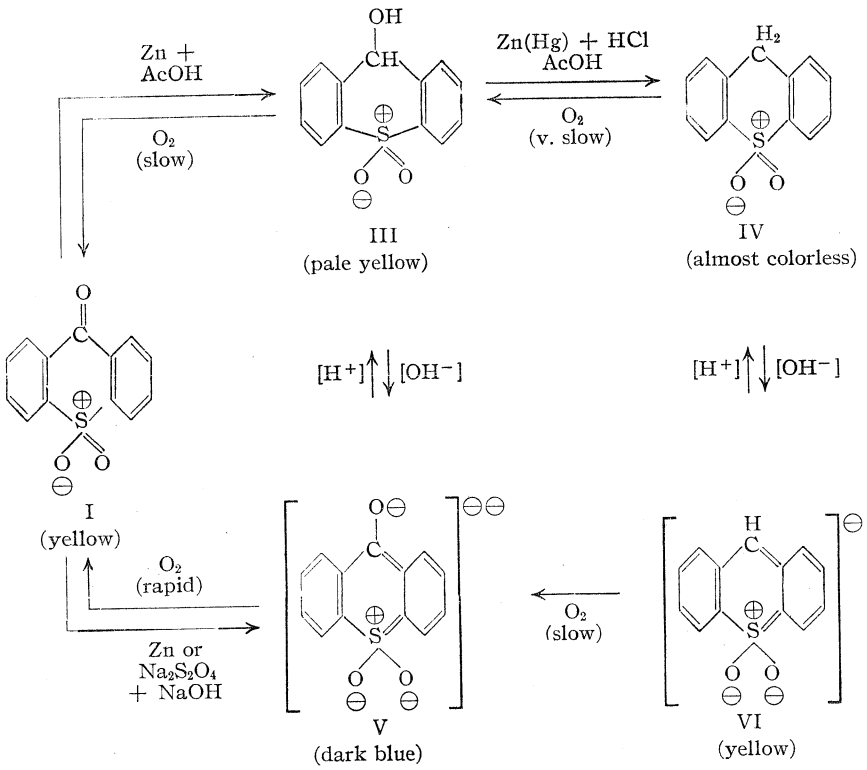
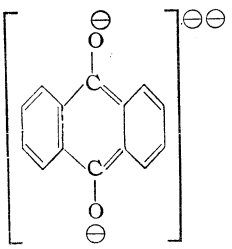



Fig. 1.

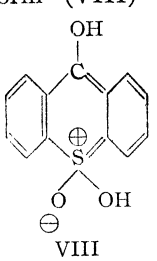
Reduction of thiaxanthone-5-dioxide (I) with zinc dust in dilute acetic acid affords a pale yellow crystalline compound, $C_{13}H_{10}O_3S$, which readily forms a monoacetyl derivative on treatment with acetic anhydride in the presence of sulfuric acid. This compound, which is undoubtedly thiaxanthenol-5-dioxide (III), dissolves in aqueous or alcoholic alkali with the production of a deep blue color. On shaking with air, the color is rapidly discharged and thiaxanthone-5-dioxide (I) precipitates from the solution. Neutral alcoholic solutions of thiaxanthenol-5-dioxide (III) also undergo oxidation on prolonged exposure to air, but the rate of reaction, as evidenced by the slow precipitation of the slightly soluble thiaxanthone-5-dioxide (I) is much lower under these conditions than in the presence of alkali. A slow autoxidation of crystalline thiaxanthenol-5-dioxide (III) is indicated by the gradual development of a deep yellow color when the solid is allowed to stand in contact with air for several weeks; no such change is observed with samples stored under nitrogen.

The crystalline product obtained on acidification of the deep blue solution from the alkaline sodium hydrosulfite reduction of thiaxanthone-5-dioxide (I) was shown, by the method of mixed melting points, to be identical with the thiaxanthenol-5-dioxide (III) obtained from the acid reduction. An oxidation–reduction cycle analogous to the anthraquinone–anthrahydroquinone system is thus established. The ground-state structure (V) assigned to the resonating anion responsible for the intense blue color is the sulfone series counterpart of the ground-state structure of the anthrahydroquinone anion (VII).[7] While structure



VII (blood-red)

V very probably represents the most stable electronic configuration for the sulfone anion, the addition of protons to the system is represented in Fig. 1 as resulting in the formation of the sulfone analog, not of anthrahydroquinone, but of its tautomer, oxanthrone. It seems likely, however, that the compound characterized as thiaxanthenol-5-dioxide (III) is at all times in equilibrium with a small but significant amount of the tautomeric form (VIII) corresponding to



VIII

anthrahydroquinone. This assumption seems necessary to account for the autoxidation of the compound in the crystalline state and in neutral solutions,[8] and it is strongly supported by the observation that thiaxanthenol-5-dioxide exhibits a blue fluorescence, since in the anthraquinone series the phenomenon of fluorescence is regarded as evidence for the presence of an *o*-quinonoid structure.[9]

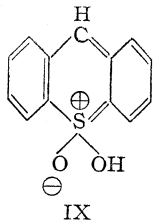
(8) Thus, in the anthraquinone series, the ketonic forms of the reduction products (oxanthrone, anthrone) are resistant to air oxidation, while the enolic forms (anthrahydroquinone, anthranol) are very sensitive to oxidation by air (see ref. 6).

(9) Houben and Fischer, ref. 6, pp. 13–14.

With a reducing agent of sufficiently high potential, such as amalgamated zinc in the presence of hydrochloric acid, it is possible to complete the reduction of thiaxanthenol-5-dioxide (III) and thus to obtain thiaxanthene-5-dioxide (IV).[10,11] The identity of the nearly colorless crystalline product (m. p. 171–172°) obtained in this way was established by its failure to depress the melting point of authentic thiaxanthene-5-dioxide (m. p. 170–171°) prepared by the oxidation of thiaxanthene. Attempts to prepare the same compound (IV) by alkaline reduction of thiaxanthenol-5-dioxide have thus far been unsuccessful, possibly because the anion V undergoes ring cleavage at the sulfonyl group on prolonged treatment with hot alkali.

Although thiaxanthene-5-dioxide (IV) is much less sensitive to oxidation than thiaxanthenol-5-dioxide (III), its ability to undergo gradual oxidation in the presence of air, particularly in alkaline solutions, was demonstrated by treating solutions of the pure compound, after prolonged exposure to air, with zinc dust or sodium hydrosulfite and alkali. The appearance of a deep blue color indicated the presence of thiaxanthone-5-dioxide (I) in the solutions exposed to air; control solutions which were kept under nitrogen gave no color reaction.[12] As was anticipated, the thiaxanthenol-5-dioxide (III) (or, in alkaline solutions, its anion V) which was presumably formed as an intermediate in the oxidation could not be detected in these solutions, since the much greater susceptibility of these molecules to oxidation prevents their accumulating in the mixture.

Like anthrone, of which it is the sulfonyl analog, thiaxanthene-5-dioxide (IV) appears to be the more stable member of a tautomeric pair of isomers. The existence of an equilibrium system involving at least traces of the enolic form (IX) is indicated both by the tendency of alcohol solu-



IX

tions of thiaxanthene-5-dioxide to undergo autoxidation and by the blue fluorescence which this compound exhibits on exposure to ultraviolet light.

**Acknowledgment.**—The author wishes to express his appreciation to Dr. Marvin Carmack for many helpful suggestions and valuable discussions during the course of this work.

## Experimental[13]

**Preparation of Compounds.—Thiaxanthone,** prepared according to the directions of Graebe and Schulthess,[3a] was oxidized to **thiaxanthone-5-dioxide** by treatment with excess 30% hydrogen peroxide in acetic acid.[3d] The crude product (48% over-all yield based on anthranilic acid) was recrystallized from ethanol (Norit) to give yellow needles, m. p. 185.5–186° (reported[3a] m. p. 185°). **Thiaxanthene,** which has previously been prepared by reduction of thiaxanthone with hydrogen iodide and red phosphorus,[3a,14] was conveniently obtained in the present investigation by the Huang-Minlon modification[15] of the Wolff–Kishner reduction; from 1.80 g. of thiaxanthone there was thus obtained 1.15 g. (69%) of pale yellow microcrystalline powder, which afforded colorless needles melting at 127–127.5° (reported[3a] m. p., 128°) after recrystallization from ethanol (Norit). Oxidation of this product with excess hydrogen peroxide in acetic acid[12] yielded 97% of the theoretical amount of **thiaxanthene-5-dioxide** as almost colorless needles, which melted at 170–171° (reported[14] m. p., 170°) after recrystallization from ethanol (Norit).

**Reduction of Thiaxanthone-5-dioxide (I) to Thiaxanthenol-5-dioxide (III): (a) With Zinc Dust and Acetic Acid.**—A mixture of 12.2 g. (0.050 mole) of thiaxanthone-5-dioxide, 10 g. of zinc dust (activated by washing with dilute hydrochloric acid), and 150 ml. of 80% acetic acid was refluxed under nitrogen for thirty minutes, after which it was cooled, filtered, and diluted with 800 ml. of water. The resultant yellow precipitate was collected, washed with water and dried *in vacuo* over calcium chloride; yield, 8.6 g. (70%) of yellow powder, m. p. 165–168°. Recrystallization of this material from chloroform afforded pale yellow crystals, m. p. 184–185°, which exhibited a blue fluorescence on exposure to ultraviolet light; mixed m. p. with thiaxanthone-5-dioxide, *ca.* 146–152°. On treatment with aqueous or alcoholic sodium hydroxide, this product gave a dark blue solution from which the color was discharged on shaking with air.

*Anal.* Calcd. for $C_{13}H_{10}O_3S$: C, 63.39; H, 4.09. Found: C, 63.10; H, 4.11.

When a suspension of 0.50 g. of the above product in 2 ml. of acetic anhydride was treated with 1 drop of concentrated sulfuric acid and allowed to stand for fifteen minutes, a semicrystalline paste was obtained from which 0.58 g. of the acetyl derivative was separated by diluting the mixture with water and filtering off the insoluble product. Recrystallization from ethanol gave almost colorless crystals, m. p. 155.5–156°, which dissolved slowly in aqueous or alcoholic sodium hydroxide with the production of a deep blue color.

(10) The compound prepared by Amstutz and Neumoyer [THIS JOURNAL, **69**, 1925 (1947)] by brief treatment of 2,8-diaminothiaxanthone-5-dioxide with zinc dust in dilute acetic acid and designated 2,8-diaminothiaxanthene-5-dioxide monohydrate was in all probability *2,8-diaminothiaxanthenol-5-dioxide* (*Anal.* Calcd. for $C_{13}H_{12}N_2O_4S$: S, 11.60. Found: S, 11.57, 11.73). This possibility has been called to Dr. Amstutz' attention and is now being checked in the light of the results described in the present paper.

(11) NOTE ADDED IN PROOF.—The reference in Heymann's paper (see "Preparative Part" of ref. in footnote 4) to the previously reported zinc dust–acetic acid reduction of substituted thiaxanthone-5-dioxides to thiaxanthene-5-dioxides apparently refers to the above paper by Amstutz and Neumoyer (footnote 10), not to that by Amstutz, Fehnel and Hunsberger (footnote 3d) as erroneously indicated.

(12) The recent report (ref. 3d) that certain substituted thiaxanthene-5-dioxides give colored solutions on treatment with aqueous-alcoholic alkali is almost certainly in error. The color reactions observed with these compounds must in all probability be ascribed to the presence of traces of the corresponding thiaxanthenol-5-dioxides, formed either during the preparation of the compounds by hydrogen peroxide oxidation of the thiaxanthenes or by subsequent autoxidation of the pure thiaxanthene-5-dioxides. The problem of completely freeing samples of thiaxanthene-5-dioxide from thiaxanthenol-5-dioxide was overcome in the present investigation only by repeated, rapidly conducted recrystallizations, until the product no longer gave a blue color with aqueous-alcoholic alkali.

(13) Microanalyses were performed by Mrs. Sarah M. Woods. All melting points are corrected.

(14) Hilditch and Smiles, *J. Chem. Soc.*, **99**, 145 (1911).

(15) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

*Anal.* Calcd. for $C_{15}H_{12}O_4S$: C, 62.49; H, 4.20. Found: C, 62.27; H, 4.17.

(b) **With Sodium Hydrosulfite and Alkali.**—A solution of 1.0 g. of sodium hydrosulfite and 1.0 g. of sodium hydroxide in 10 ml. of water was added to a suspension of 0.60 g. of thiaxanthone-5-dioxide in 10 ml. of ethanol, and the mixture was warmed to *ca.* 50° under a nitrogen atmosphere for ten minutes. The resultant dark blue solution was cooled to room temperature, acidified with hydrochloric acid, and diluted with 100 ml. of water. The yellow precipitate was collected, washed with water, and dried *in vacuo* over calcium chloride; yield, 0.40 g. (66%) of yellow powder, m. p. 167–171°. Recrystallization of this material from chloroform afforded pale yellow crystals which melted at 181–183° and showed no depression in melting point when mixed with the acid-reduction product described above.

**Reduction of Thiaxanthone-5-dioxide (I) to Thiaxanthene-5-dioxide (IV).**—A mixture of 1.22 g. (0.0050 mole) of thiaxanthone-5-dioxide, 3 g. of amalgamated zinc dust, 15 ml. of acetic acid, and 3 ml. of hydrochloric acid was refluxed under nitrogen for three hours. Another 1 ml. of hydrochloric acid was added during the refluxing, and at the end of the three-hour period the unreacted zinc was filtered off and the filtrate as diluted with 100 ml. of water. The precipitate was collected, washed with water, and dried; yield, 1.08 g. (94%) of pale yellow microcrystalline powder, m. p. 150–155°, which gave a blue color on treatment with aqueous-alcoholic sodium hydroxide. After repeated recrystallization from ethanol, the pure product was obtained as almost colorless crystals, m. p. 171–172°, which gave *no color* on treatment with aqueous-alcoholic sodium hydroxide and which failed to depress the melting point of authentic thiaxanthene-5-dioxide prepared by the oxidation of thiaxanthene. This product exhibited a blue fluorescence on exposure to ultraviolet light.

**Reduction of Thiaxanthenol-5-dioxide (III) to Thiaxanthene-5-dioxide (IV).**—When an acetic acid solution of 1.23 g. (0.0050 mole) of thiaxanthenol-5-dioxide was treated with amalgamated zinc and hydrochloric acid in the same manner as in the preceding example, 0.85 g. (74%) of pale yellow powder, m. p. 139–144°, was obtained, which crystallized from ethanol in the form of almost colorless needles melting at 169–171°. No depression of the melting point was observed when this material was mixed with authentic thiaxanthene-5-dioxide.

**Air Oxidation of Thiaxanthenol-5-dioxide (III).**—A suspension of 0.62 g. of thiaxanthenol-5-dioxide in 10 ml. of ethanol was treated with 10 ml. of 10% aqueous sodium hydroxide, and air was blown into the mixture through a sintered glass gas-dispersion tube until the blue color was completely discharged (five to ten minutes). The resultant yellow suspension was diluted with water and filtered, thus affording 0.55 g. (90%) of yellow microcrystalline powder, m. p. 185–186°, which gave a blue color with aqueous-alcoholic alkali only after the addition of zinc dust or sodium hydrosulfite. This product failed to depress the melting point of thiaxanthone-5-dioxide prepared by the oxidation of thiaxanthone.

When a saturated solution of thiaxanthenol-5-dioxide in 95% ethanol was shaken with air for ten days in a mechanical shaker, a small amount of yellow insoluble material was precipitated which melted at 182–185° and showed no melting point depression when mixed with authentic thiaxanthone-5-dioxide.

**Air Oxidation of Thiaxanthene-5-dioxide (IV).**—A suspension of 0.20 g. of freshly purified thiaxanthene-5-dioxide in 10 ml. of 10% aqueous sodium hydroxide was refluxed for ten minutes while a stream of air was bubbled through the boiling mixture. Although the thiaxanthene-5-dioxide used in this experiment gave no color with alkali and sodium hydrosulfite, the yellow solid filtered out of the above suspension gave the characteristic blue color test for thiaxanthone-5-dioxide on treatment with these reagents.

When neutral, saturated solutions of pure thiaxanthene-5-dioxide in 95% ethanol were similarly aerated and refluxed for periods of several hours, addition of aqueous sodium hydroxide and sodium hydrosulfite resulted in the formation of a dark blue color. If the refluxing was carried out under nitrogen and no air was bubbled through the solution, no color test could be obtained even after four hours.

## Summary

The color reactions of thiaxanthone-5-dioxide in the presence of alkaline reducing agents have been studied and shown to be similar to the familiar vatting reactions of anthraquinone. The intermediate reduction product responsible for the characteristic color reactions has been isolated and identified as thiaxanthenol-5-dioxide, which dissolves in alkali with the formation of a highly colored, readily oxidizable anion analogous to the anthrahydroquinone anion. On the basis of the assumption that sulfur is capable of expanding its valence shell, the thiaxanthone dioxide–thiaxanthenol dioxide–thiaxanthene dioxide oxidation–reduction system is formulated as the sulfone series counterpart of the anthraquinone–anthrahydroquinone–anthrone system.

SWARTHMORE, PA. RECEIVED SEPTEMBER 8, 1948

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# Reactions of Vanillin and its Derived Compounds. VII.[1] Some New Esters of Vanillic Acid and Related Acids[2,3]

BY IRWIN A. PEARL AND DONALD L. BEYER

Several esters of vanillic acid were recently shown[4,5] to have high toxicity toward representative microörganisms and to be of value as food preservatives. These results led to the synthesis of the new esters of vanillic acid, orthovanillic acid, and 5-chlorovanillic acid described in Table I.

The new esters of vanillic acid reported herein comprise esters of polyhydric alcohols, their chlorohydrins, and their ethers. Most of these were prepared by the various methods described earlier.[4] The chlorohydrin esters were prepared by reaction of the chlorohydrin with vanillic

(1) For paper VI of this series, see THIS JOURNAL, **70**, 2008 (1948).

(2) Presented before The Division of Organic Chemistry at the 113th meeting of The American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) Pearl and McCoy, THIS JOURNAL, **69**, 3071 (1947).

(5) Pearl and McCoy, *Food Industries*, **17**, 1458 (1945).

TABLE I

ESTERS OF VANILLIC, ORTHOVANILLIC AND 5-CHLOROVANILLIC ACIDS

| Ester | Yield, % | B. p.[a] °C. | Mm. | $n^t$D | $t$, °C. | M. p.,[b] °C. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Inhibiting concn.,[c] % *Aero. aero.* | *Bac. myc.* | *Asper. niger* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Vanillic acid**[d] | | | | | | | | | | | | | | |
| $MeOCH_2CH_2$[e] | 61 | 160 | 4 | | | 39[f] | $C_{11}H_{14}O_5$ | 58.40 | 58.13 | 6.24 | 6.29 | >0.21 | >0.21 | >0.21 |
| $EtOCH_2CH_2$[g] | 50 | 142 | 3 | 1.5345 | 21.8 | | $C_{12}H_{16}O_5$ | 59.99 | 59.38 | 6.71 | 6.58 | > .21 | > .21 | .21 |
| $BuOCH_2CH_2$ | 38 | 176 | 4 | 1.5099 | 21.8 | | $C_{14}H_{20}O_5$ | 62.67 | 62.10 | 7.51 | 7.95 | .09 | .03 | .09 |
| $Et_2CHCH_2OCH_2CH_2$[h] | 73 | 200 | 3 | 1.5161 | 24 | | $C_{16}H_{24}O_5$ | 64.84 | 64.65 | 8.16 | 8.27 | > .21 | .003 | > .21 |
| $PhOCH_2CH_2$[h] | 81 | | | | | 113 | $C_{16}H_{16}O_5$ | 66.66 | 66.65 | 5.60 | 5.67 | > .21 | > .21 | > .21 |
| $MeOCH_2CH_2OCH_2CH_2$[h] | 40 | 216–219 | 3 | 1.5398 | 23 | | $C_{13}H_{18}O_6$ | 57.77 | 56.65 | 6.71 | 6.43 | | | |
| $EtOCH_2CH_2OCH_2CH_2$[h] | 61 | 209 | 3 | 1.5305 | 23 | | $C_{14}H_{20}O_6$ | 59.14 | 58.34 | 7.09 | 7.12 | | | |
| $CH_2ClCH_2$ | 74[i] | 161 | 3 | | | 58–59 | $C_{10}H_{11}O_4Cl$ | 52.07 | 52.20 | 4.81 | 4.78 | > .21 | > .21 | .21 |
| $MeCHClCH_2$[j] | 57 | 162 | 2 | | | 49 | $C_{11}H_{13}O_4Cl$ | 54.00 | 54.06 | 5.35 | 5.44 | .09 | .03 | .09 |
| $CH_2ClCH_2CH_2$[k] | 52 | 192–204 | 4 | | | 67–68 | $C_{11}H_{13}O_4Cl$ | 54.00 | 54.27 | 5.35 | 5.48 | .09 | .09 | .09 |
| $CH_2ClCHClCH_2$ | 63[l] | 195 | 3 | | | 42–43[f] | $C_{11}H_{12}O_4Cl_2$ | 47.33 | 47.54 | 4.33 | 4.34 | .03 | .015 | .21 |
| $(CH_2Cl)_2CH$ | 49 | 190 | 0.2 | 1.5513 | 24 | | $C_{11}H_{12}O_4Cl_2$ | 47.33 | 46.94 | 4.33 | 4.45 | .09 | .009 | .21 |
| $CCl_3CMe_2$[m] | 10 | | | | | 138–139 | $C_{12}H_{13}O_4Cl_3$ | 44.00 | 44.87 | 4.00 | 4.00 | > .21 | .009 | > .21 |
| $CH_2OHCH_2$[n] | 52[o] | 198 | 2 | | | 85–86[p] | $C_{10}H_{12}O_5$ | 56.60 | 56.67 | 5.70 | 5.82 | > .21 | > .21 | > .21 |
| $C_2H_4$-bis[q] | 33[r] | | | | | 144[s] | $C_{18}H_{18}O_8$ | 59.67 | 59.64 | 5.01 | 5.01 | > .21 | > .21 | > .21 |
| $MeCHOHCH_2$[n] | 42 | 175 | 1 | | | | $C_{11}H_{14}O_5$ | 58.40 | 58.09 | 6.24 | 6.24 | > .21 | > .21 | > .21 |
| **Orthovanillic acid**[t] | | | | | | | | | | | | | | |
| Me[u] | 87 | | | | | 64–65[f] | | | | | | .09 | .09 | .09 |
| Et[u] | 75 | 121 | 3 | 1.5342 | 20 | | | | | | | .21 | .15 | .09 |
| Pr | 91 | | | | | 52[s] | $C_{11}H_{14}O_4$ | 62.84 | 62.85 | 6.71 | 6.76 | .15[v] | .15 | .009 |
| iso-Bu | 52 | 139 | 3.5 | | | 52–53 | $C_{12}H_{16}O_4$ | 64.27 | 64.41 | 7.19 | 7.25 | .21 | .03 | > .21 |
| Bu | 80 | 131 | 1.5 | | | 39–40 | $C_{12}H_{16}O_4$ | 64.27 | 64.01 | 7.19 | 7.18 | > .21 | .009 | > .21 |
| iso-Am | 85 | 147 | 2 | 1.5160 | 22 | | $C_{13}H_{18}O_4$ | 65.53 | 65.32 | 7.61 | 7.64 | > .21 | .009 | > .21 |
| Am | 94 | | | | | 55–56 | $C_{13}H_{18}O_4$ | 65.53 | 65.39 | 7.61 | 7.62 | .21[v] | .09 | > .21 |
| $Et_2CHCH_2$ | 83 | 144 | 2 | 1.5174 | 22 | | $C_{14}H_{20}O_4$ | 66.64 | 66.40 | 7.99 | 7.99 | > .21 | .003 | > .21 |
| $EtOCH_2CH_2$ | 60 | 157–163 | 4 | | | 31[f] | $C_{12}H_{16}O_5$ | 59.99 | 60.14 | 6.71 | 6.75 | .15[v] | .09 | .09 |
| $PhOCH_2CH_2$[h] | 86 | | | | | 93 | $C_{16}H_{16}O_5$ | 66.66 | 66.65 | 5.60 | 5.74 | > .21 | .21 | > .21 |
| Ph[w] | 35 | | | | | 66[s] | $C_{14}H_{12}O_4$ | 68.84 | 68.62 | 4.95 | 4.97 | .21[v] | .009 | > .21 |
| **5-Chlorovanillic acid**[t] | | | | | | | | | | | | | | |
| Me | 95 | | | | | 136–137 | $C_9H_9O_4Cl$ | 49.90 | 49.90 | 4.19 | 4.19 | > .21[v] | .15 | .15 |
| Et | 91.5 | | | | | 119–120 | $C_{10}H_{11}O_4Cl$ | 52.07 | 52.05 | 4.81 | 4.84 | > .21[v] | .15 | > .21 |
| Pr | 92 | | | | | 117–118 | $C_{11}H_{13}O_4Cl$ | 54.00 | 54.09 | 5.35 | 5.36 | > .21[v] | > .21 | > .21 |
| Bu | 84 | | | | | 109–110 | $C_{12}H_{15}O_4Cl$ | 55.71 | 55.76 | 5.84 | 5.89 | > .21[v] | > .21 | > .21 |

[a] All melting points and boiling points are uncorrected. [b] All compounds were recrystallized from petroleum ether (b. p. 65–110°) except where indicated. [c] Inhibiting concentrations were determined in accordance with the method described earlier.[4] Abbreviations used: *Aero. aero.* = *Aerobacter aerogenes; Bac. myc.* = *Bacillus mycoides; Asper. niger* = *Aspergillus niger*. [d] See Pearl, THIS JOURNAL, **68**, 429, 1110, 2180 (1946). [e] Prepared by the reaction of vanillic acid with 2-methoxyethanol in the presence of sulfuric acid. All esters were prepared by this general method unless otherwise indicated. [f] Recrystallized from petroleum ether (b. p. 30–60°). [g] Monohydrate from petroleum ether (b. p. 30–60°), m. p. 47–48°. *Anal.* Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.02. Found: C, 55.81; H, 7.02. [h] Prepared by reaction of acid with corresponding alcohol in presence of hydrogen chloride. [i] 59% by hydrogen chloride method from ethylene glycol. [j] Hydrogen chloride method from propylene glycol. [k] Hydrogen chloride method from trimethylene glycol. [l] 60% by hydrogen chloride method from glycerol. [m] Prepared by refluxing trichloro-*t*-butyl alcohol with vanillic acid in toluene under a water separatory head. Wolffenstein, German Patent 267,980 (Dec. 6, 1913), reported a m. p. of 130° for a compound prepared by heating trichloro-*t*-butyl alcohol with vanillic acid in the presence of zinc chloride. Wolffenstein's results could not be repeated. [n] Prepared by the reaction of potassium vanillate with the corresponding chlorohydrin. [o] 25% yield by refluxing vanillic acid with excess ethylene glycol without a condensing agent; 30% by reaction of carbethoxyvanilloyl chloride with ethylene glycol (see Pearl and McCoy).[4] [p] Recrystallized from chloroform. [q] Prepared by reaction of carbethoxyvanilloyl chloride with ethylene glycol through the intermediate, ethylene glycol biscarbethoxy vanillate, m. p. 139°. *Anal.* Calcd. for $C_{24}H_{26}O_{12}$: C, 56.91; H, 5.18. Found: C, 56.37; H, 5.24. [r] 20% yield by refluxing vanillic acid with excess ethylene glycol without a condensing agent (together with 2-hydroxyethyl vanillate). [s] Recrystallized from dilute ethanol. [t] See Pearl, *J. Org. Chem.*, **12**, 85 (1947). [u] This is a previously reported compound. [v] Dissolved in ethanol for all microbiological analyses. [w] Prepared by reaction of orthovanillic acid with phenol in the presence of phosphorus oxychloride. Method patterned after preparation of phenyl salicylate by Seifert, *J. prakt. Chem.*, [2] **31**, 472 (1885).

acid and by reaction of the parent glycols with vanillic acid in the presence of anhydrous hydrogen chloride. The structure of the dichloropropyl vanillate resulting from the reaction of glycerol with vanillic acid and anhydrous hydrogen chloride was established by its identity with 2,3-dichloropropyl vanillate prepared unequivocally from vanillic acid and glycerol 1,2-dichlorohydrin. Glycol esters were prepared by the carbethoxy route, reaction of the chlorohydrin with potassium vanillate, and by refluxing glycol with vanillic acid without a condensing agent. Esters of 5-chlorovanillic and orthovanillic acids were prepared by similar methods.

The inhibiting concentrations of these esters were determined for the three representative aerobic microörganisms—namely, non-sporeforming (*Aerobacter aerogenes*) and sporeforming (*Bacillus mycoides*) bacteria and molds (*Aspergillus niger*). Most of the vanillates were found to inhibit *Bacillus mycoides* and *Aspergillus niger* in low concentrations. The chlorohydrin esters,

in addition, possessed remarkable toxicity toward *Aerobacter aerogenes*. This property was also characteristic of 2-butoxyethyl vanillate, but was not exhibited by trichloro-*t*-butyl vanillate. The esters of orthovanillic acid appear to be less specific in their toxicity. Of the 5-chlorovanillic acid esters, only the methyl and ethyl esters exhibited any toxicity whatsoever. Toxicity data are given in Table I.

**Acknowledgment.**—The authors are indebted to John F. McCoy and to Virginia West Martin, respectively, for the microbiological and chemical analyses reported in this paper.

## Summary

A large number of new esters of vanillic acid and the closely related acids, orthovanillic and 5-chlorovanillic, were prepared. The inhibiting concentrations of these esters were determined for representative microörganisms.

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[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

# Infrared and Ultraviolet Spectroscopic Studies on Ketones[1]

BY R. S. RASMUSSEN, D. D. TUNNICLIFF AND R. ROBERT BRATTAIN

The infrared, Raman, and ultraviolet spectra of aldehydes and ketones have been the subjects of numerous studies in the literature.[2] Some further investigations, which were made in connection with the OSRD program on penicillin structure, are reported here. These studies were made in order to gain a better insight into the influence of structure on the spectra of carbonylic compounds.

The infrared spectra, from 2 $\mu$ to 15 $\mu$, of the compounds studied are shown in tabular form in Table I; the ultraviolet spectra, from 2200 to 3500 Å., are given in Figure 1. All spectra are of pure liquids or solutions. The sources of samples and further spectroscopic experimental details are given at the end of this paper. Discussion of the infrared spectra is limited to the 3 $\mu$ region (NH, OH, and CH stretching vibrations) and 6 $\mu$ region (double-bond stretching vibrations). These were the regions actually used on the penicillin structure work and are the ones having an obvious correlation with structure. Thompson and Torkington, however, have noted several interesting regularities at longer wave lengths,[2] and such regularities are also present in Raman spectra.[2]

## Infrared Work

**Unconjugated Ketones.**—Previous published infrared and Raman work[2] together with unpublished work from this laboratory, indicates that unconjugated ketones exhibit their C=O absorption very near 5.83 $\mu$ (1715 cm.$^{-1}$). The only compound of this type discussed here in detail, diacetone alcohol, was examined to determine the effect of simple hydrogen bonding on the band position. Badger and Bauer[3] have given evidence, based on studies of the third harmonic of the OH stretching fundamental, that intramolecular hydrogen bonding is present in this compound. The band at 5.84 $\mu$ (1712 cm.$^{-1}$) indicates that the effect of hydrogen bonding on the C=O band is small, in contrast to the large effects noted by many investigators on the OH band position (*e. g.*, the shifts of 0.1–0.2 $\mu$ noted by Gordy[4] between $CH_3OD$ in benzene and in ketones and other proton acceptor solvents). An auxiliary experiment was carried out by examining a 10% (vol.) solution of methyl ethyl ketone in methanol. Under these conditions, where a large amount of hydrogen bonding of the type $CH_3OH \cdots O{=}CR_2$ is to be expected, the observed C=O band position was 5.86 $\mu$ (1706 cm.$^{-1}$), again indicating only a small effect.

The strong OH band is present in the diacetone alcohol spectrum at 2.87 $\mu$ (3484 cm.$^{-1}$), the usual position for hydrogen-bonded alcoholic OH groups.

**Conjugated Ketones.**—Two examples of ketone C=O conjugated to C=C, namely, isophorone and acetophenone, were examined. The strong bands at 5.98 $\mu$ and 5.93 $\mu$, respectively, (1672 and 1686 cm.$^{-1}$) are to be attributed to the C=O vibration. These positions are in the range found by others from Raman[5] and infrared[6] work for this band type (roughly 1670–1690 cm.$^{-1}$). The factors influencing the exact amount of this conjugation shift are not yet understood, due to lack of data on a sufficient number of compounds. It is clear, however, that conjugation with C=C effects a shift of the order of 30 cm.$^{-1}$.

Other features of interest in the spectrum of isophorone are: (1) The weak band at 5.83 $\mu$ (1715 cm.$^{-1}$) which is probably caused by an unconjugated ketonic impurity (1 or 2% impurity would be sufficient to give a band of this intensity);

(1) The major part of this work was done under contract between the Office of Scientific Research and Development, and the Shell Development Company (Contract OEM-cmr-445).

(2) *Infrared:* H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945); R. B. Barnes, R. C. Gore, U. Liddel and V. Z. Williams, "Infrared Spectroscopy," Reinhold, New York, 1944; R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, THIS JOURNAL, **70**, 2024 (1948). *Raman:* See J. H. Hibben, "The Raman Effect and its Chemical Applications," A. C. S. Monograph, Reinhold Publishing Corp., New York, N. Y., 1939. *Ultraviolet:* See H. Sponer and E. Teller, *Rev. Mod. Phys.*, **13**, 75 (1941).

(3) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

(4) W. Gordy, *J. Chem. Phys.*, **7**, 93 (1939).

(5) *E. g.*, K. W. F. Kohlrausch and A. Pongratz, *Z. physik. Chem.*, **B27**, 176 (1934).

(6) *E. g.*, Thompson and Torkington, ref. 2.

TABLE I

INFRARED SPECTRA OF KETONES

1. Diacetone alcohol (4-methyl-4-hydroxy-2-pentanone), 0.02 mm. pure liquid.
2. Acetophenone, 0.15 mm. 10% soln. in $CCl_4$.
3. Isophorone (3,5,5-trimethyl-2-cyclohexen-1-one), 0.02 mm. pure liquid.
4. Biacetyl, 0.15 mm. 5% soln. in $CCl_4$.
5. Benzil (bibenzoyl), 0.15 mm. 5% soln. in $CHCl_3$.
6. Dibenzoylmethane, 0.15 mm. 10% soln. in $CCl_4$.
7. Acetylacetone, 0.15 mm. 10% soln. in $CCl_4$.
8. Acetylacetone acetate (4-acetoxy-3-penten-2-one), 0.15 mm. 5% soln. in $CHCl_3$.
9. 5,5-Dimethyl-1,3-cyclohexanedione, 0.15 mm. 3% soln. in $CHCl_3$. (Wave lengths in $\mu$; intensity in units of 10% absorption; S = solvent interference.) Bands due to ketone C=O stretching vibrations are underlined.

| 1 | 2 | 3 | 3 | 5 | 6 | 6 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| 2.87(9) | 3.285(3) | 3.36(7) | 10.08(1) | 3.2–3.4 S | 3.22(3) | 12.0–14.0 S | 3.2–3.4 S | 3.2–3.4 S |
| 3.33(8) | 5.12(1) | 3.41(4) | 10.52(1) | 5.07(1) | 3.72(1) | 14.09(5) | 5.68(7) | ~3.8(2) |
| 5.84(9) | 5.28(1) | 5.83(2) | 10.92(1) | 5.22(1) | 5.08(1) | 14.53(8) | 5.90(5) | 5.80(1) |
| 6.80(3) | 5.53(1) | 5.98(10) | 11.085(7) | 5.50(1) | 5.23(1) | 7 | 6.01(1) | 5.875(7) |
| ~7.0(5) | 5.93(8) | 6.10(4) | 11.36(1) | 5.95(8) | 5.50(1) | 3.32(5) | 6.125(7) | 6.23(8) |
| 7.34(10) | 6.25(3) | 6.81(3) | 11.625(5) | 6.245(4) | 5.64(1) | ~3.7(3) | 7.00(5) | 6.83(2) |
| 7.47(2) | 6.315(2) | 6.955(5) | 12.18(7) | 6.31(4) | 6.1–6.5(10) | 5.85(5) | 7.29(8) | 7.30(1) |
| 7.62(2) | 6.915(2) | 7.02(3) | 12.51(1) | 6.895(3) | 6.75(10) | 6.1–6.3(10) | 7.64(1) | 7.45(3) |
| 7.92(3) | 7.00(1) | 7.24(6) | 4 | 7.545(3) | 7.64(4) | 7.02(10) | ~7.9(3) | 7.57(3) |
| 8.20(6) | 7.36(7) | 7.305(6) | 2.92(2) | 7.77(1) | 7.79(3) | 7.34(10) | 7.9–8.4 S | 7.76(4) |
| 8.44(7) | 7.69(3) | 7.59(2) | 3.335(2) | 7.9–8.4 S | 8.155(7) | 8.01(10) | 8.48(8) | ~8.0(4) |
| 8.71(5) | 7.925(8) | 7.705(4) | 5.69(1) | 8.485(5) | 8.435(5) | 8.53(5) | 8.665(4) | 7.9–8.4 S |
| 8.83(1) | 8.04(2) | 7.81(5) | 5.82(8) | 8.60(1) | 8.60(1) | 9.97(5) | 8.83(8) | 8.59(3) |
| 9.76(3) | 8.485(3) | 7.92(1) | 5.95(1) | 9.10(1) | 9.035(3) | 10.38(8) | 9.77(7) | 8.73(5) |
| 10.00(3) | 8.62(1) | 8.025(6) | 6.90(1) | 9.31(1) | 9.36(6) | 10.60(8) | 10.29(1) | 8.89(1) |
| 10.485(5) | 9.08(1) | 8.41(2) | 7.05(5) | 9.745(2) | 9.72(5) | 10.915(9) | 10.54(4) | 9.20(1) |
| 10.91(5) | 9.275(3) | 8.69(3) | 7.24(2) | 9.995(1) | 9.98(2) | >12.0 S | 10.80(4) | ~9.85(2) |
| 12.275(3) | 9.77(5) | 8.89(2) | 7.38(6) | 11.44(5) | 10.24(3) | | 11.36(4) | 11.24(1) |
| 12.93(2) | 10.48(6) | 9.67(1) | 7.61(1) | >12.0 S | 10.765(2) | | >12.0 S | >12.0 S |
| 13.185(2) | 10.85(2) | 9.78(3) | >8.0 run | | | | | |
| | >12.0 S | 9.94(1) | discontinued | | | | | |

(2) The moderately intense band at 6.10 $\mu$ (1639 cm.$^{-1}$) assignable as the C=C band shifted by conjugation. Other unpublished studies on this type of conjugated ketone reveal that the shifted C=C band falls in the range 6.07 $\mu$ to 6.17 $\mu$ (1647 to 1621 cm.$^{-1}$); published Raman data indicate the same thing.[5] Hence the shift from the unconjugated C=C position (*circa* 1660 cm.$^{-1}$) is of the order of 30 cm.$^{-1}$, about the same amount as the C=O shift noted above. In simple conjugated dienes, the shift is about the same in magnitude[7] so that it may be deduced that the amount of conjugation in the C=C—C=O system is about the same as in the C=C—C=C system.

The spectrum of acetophenone shows, in addition to the C=O band, the following features:

1. The three weak bands near 5.10 $\mu$, 5.30 $\mu$ and 5.60 $\mu$ (1961 cm.$^{-1}$, 1887 cm.$^{-1}$ and 1786 cm.$^{-1}$) observed in compounds containing the phenyl ring.[8] From their wave-length region and weakness, these must be assigned to overtones of the ring fundamentals.

2. The two bands of weak-to-moderate intensity at 6.25 $\mu$ and 6.315 $\mu$ (1600 cm.$^{-1}$ and 1584 cm.$^{-1}$) which, from work on other benzoyl-containing compounds (to be described in later papers

(7) Actually, infrared and Raman spectra of conjugated dienes show the two C=C frequencies split considerably apart: R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120 (1947); K. Bradacs and L. Kahovec, *Z. physik. Chem.*, **B48**, 63 (1940). The splitting in this case is due to mechanical interaction, and as a measure of the shift due to electronic resonance alone the average of these values has been used.

(8) *E. g.*, see Barnes, *et al.*, ref. 2, Table 4, p. 24.

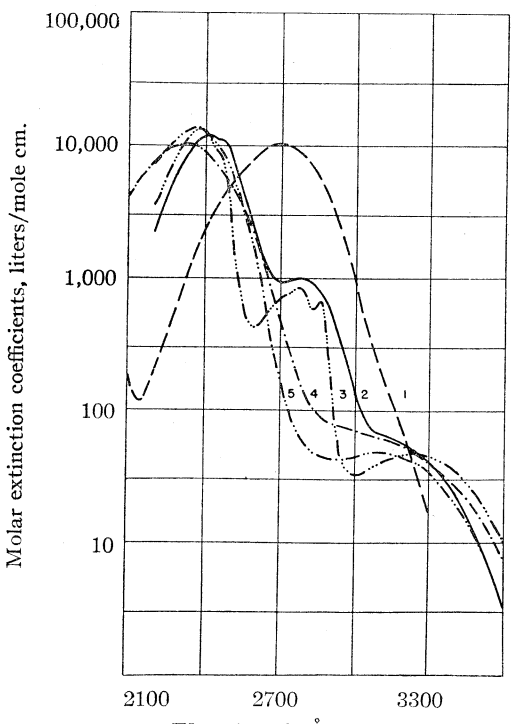



Fig. 1.—Ultraviolet absorption of conjugated ketones: 1, acetylacetone, in isoöctane; 2, acetophenone, in methanol; 3, hexadecanophenone, in isoöctane; 4, acetylacetone acetate (4-acetoxy-3-penten-2-one), in methanol; 5, isophorone, in methanol.

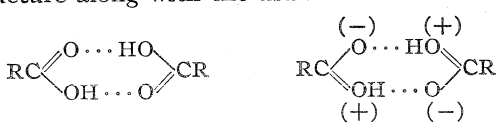
of this series), are universally found for the benzoyl group. The phenyl group itself, not conjugated to other groups, gives a single weak-to-moderate band near 6.25 $\mu$ (1600 cm.$^{-1}$).[8] Since one of the degenerate fundamental ring stretching frequencies of benzene lies at this position,[9] it is conceivable that in the unconjugated phenyl derivatives the analogous two ring frequencies are still very close even though the degeneracy is removed; but on conjugation with the C=O group, and the resulting change in character of the ring bonds, the two frequencies are split apart enough to exhibit themselves as the two bands at 6.25 $\mu$ and 6.31 $\mu$ (1600 cm.$^{-1}$ and 1584 cm.$^{-1}$) referred to above.

Spectra of two compounds in which one carbonyl is conjugated with another—biacetyl and benzil—are given in Table I. In each case only a single strong band attributable to C=O was found, at 5.82 $\mu$ and 5.95 $\mu$ (1718 cm.$^{-1}$ and 1681 cm.$^{-1}$), respectively. Since these positions are the ones expected for unconjugated and phenyl-conjugated C=O, respectively, it would seem that little or no conjugation between the adjacent C=O groups is present. Spectroscopic work on glyoxal[10] and electron diffraction work on biacetyl[11] indicate (not strongly) that the *trans* forms of these are the stable ones; benzil, by analogy and also because of repulsion of the phenyl groups, would be expected to be *trans*. Hence only one of the two C=O bands should be infrared active. Raman studies give 1725 cm.$^{-1}$ (5.80 $\mu$) and 1683 cm.$^{-1}$ (5.94 $\mu$) as the frequencies of the Raman-active vibration for biacetyl and benzil, respectively.[12] The small splitting between the infrared and Raman active frequencies is indicative of little mechanical interaction, and hence presumably indicates a weak central C–C bond and a low degree of conjugation. This result substantiates the conclusion made above from the C=O band position.

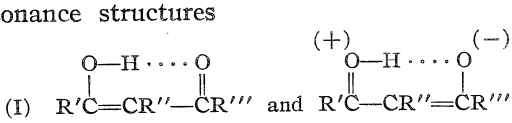
**$\beta$-Diketones.**—The Raman spectra of this class of compounds have been studied most intensively by Kohlrausch and collaborators,[13] who showed that the Raman spectrum of enolizable $\beta$-diketones is consistent with the usually formulated structure, R′C(OH)=CR″=CO—R‴, in some cases admixed with the keto form. Some further conclusions can be drawn from the infrared spectra. Spectra of acetylacetone and dibenzoylmethane are given in Table I. Both of these enolize almost completely as shown by chemical[14] and Raman spectral[13] methods.

Features of note in the 3 $\mu$ region are the lack of absorption near 3.0 $\mu$ (3333 cm.$^{-1}$) where simple hydrogen-bonded OH absorption occurs, and the weak band near 3.7 $\mu$ (2703 cm.$^{-1}$), an unusual absorption position. The latter absorption is very broad (not indicated in Table I), being in this respect reminiscent of the similar very broad OH band of fatty acid dimers[15]; the fatty acid dimer band is also shifted considerably beyond the normal hydrogen-bonded OH position (~3.0 $\mu$) to about 3.4 $\mu$ (2941 cm.$^{-1}$), where it becomes superposed on the narrower CH stretching bands near 3.4 $\mu$.

Pauling[16] has accounted for the greater strength of hydrogen bonds in fatty acid dimers on the basis of a large contribution of an ionic resonance structure along with the usual covalent structure



The ionic contribution is presumably increased in the dimer over its value in the monomer because of stabilization arising from the favorable position of the electropositive proton with respect to the negative carbonyl oxygen. The greater shift of the OH band in fatty acid dimers as compared with, for example, hydrogen-bonded alcohols, follows from this explanation as arising from the additional loosening of the OH bond due to the charges. It is clear that a similar explanation can be applied to the enolized $\beta$-diketones, since these can have contributions from the resonance structures



(I) R′C=CR″—CR‴ and R′C—CR″=CR‴

the latter being stabilized by the hydrogen bond. On this basis, the 3.7 $\mu$ (2703 cm.$^{-1}$) band may be accounted for as the OH vibration, extremely shifted and broadened in an analogous way to the fatty acid dimer band.

Enolized acetylacetone and dibenzoylmethane exhibit unusual absorption phenomena in the 6 $\mu$ region also. The former has a moderate band at 5.85 $\mu$ (1709 cm.$^{-1}$) which from its position is attributable to the keto form. No band is observed in the usual conjugated ketone region (5.90–5.98 $\mu$) (1695–1672 cm.$^{-1}$) for either compound. Each, however, exhibits a tremendously strong band in the 6.1–6.5 $\mu$ (1639–1538 cm.$^{-1}$) region, which from the breadth of the region of total absorption is estimated to be stronger by a factor of 100 or more than usual ketone C=O bands. Since C=C bands are usually not very intense in the infrared, these bands must be assigned as due to C=O. Both their extreme shifts from the usual ketone C=O positions and

(9) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules" D. Van Nostrand Co., New York, N. Y., 1945, p. 362.

(10) H. W. Thompson, *Trans. Faraday Soc.*, **36**, 988 (1940).

(11) J. E. LuValle and V. Schomaker, THIS JOURNAL, **61**, 3520 (1939).

(12) K. W. F. Kohlrausch and A. Pongratz, *Ber.*, **67B**, 976 (1934).

(13) *E. g.*, K. W. F. Kohlrausch and A. Pongratz, *ibid.*, **B67**, 1465 (1934).

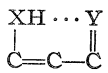
(14) *E. g.*, see J. B. Conant and A. F. Thompson, Jr., THIS JOURNAL, **54**, 4039 (1932).

(15) R. Hofstadter, *et al.*, *J. Chem. Phys.*, **6**, 531, 534, 540 (1938); M. M. Davies and G. B. B. M. Sutherland, *ibid.*, **6**, 755 (1939).

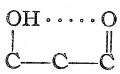
(16) L. Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell Press, Ithaca, N. Y., 1940, p. 306.

their extreme intensities may be explained reasonably in terms of the resonance structures written above. The enhanced participation of the ionic structure leads to a greater decrease in double-bond character of the C=O bond than would be the case with simple conjugation, thus resulting in the long wave-length shift; and the increased charge on the carbonylic oxygen results in the high intensity. If this interpretation is correct, the lack of an observed C=C band must be accounted for by its being hidden by the very strong C=O band, or by its being shifted out of the double-bond region because of loss of double-bond character.

It is clear that a conjugated system of the type

(II) 

where XH and Y can participate as a hydrogen bond donor-acceptor system, is necessary for this type of extreme shift. Examples other than enolized $\beta$-diketones which have also been found to exhibit this behavior will be described in ensuing papers. Since the structure II is a particular type of a chelate system, the name "conjugated chelate" system is suggested for it, to differentiate it from the type of structure represented by, say, diacetone alcohol, which is also a

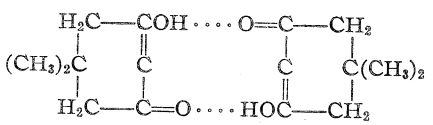


chelate system but only by virtue of the ordinary sort of hydrogen bonding.

Resonance structures of the type I can be written for compounds in which the C=C is part of an aromatic ring. Thus Gordy[17] found the C=O bands of *o*-hydroxyacetophenone and salicylaldehyde, among other compounds, to be shifted to the 6.1–6.2 $\mu$ (1639–1613 cm.$^{-1}$) region, and he demonstrated that the hydroxyl group was necessary for the shift. On the basis of the above discussion, this shift is not to be attributed to simple hydrogen bonding, but to the existence of the conjugated chelate system. Also the early findings by Wulf, Liddel, and coworkers[18] that strongly intramolecularly hydrogen-bonded substances showed no absorption in the 7000 cm.$^{-1}$ region (second harmonic region of the usual 3.0 $\mu$ OH absorption) are attributable to the fact that all such compounds examined were of the conjugated chelate type, and hence the OH absorption was shifted completely out of the region examined. The second harmonic of this absorption should fall near 5000 cm.$^{-1}$.

The difference between ordinary conjugated systems and conjugated chelate systems is strikingly illustrated by the spectrum of acetylacetone acetate (spectrum 8, Table I). Acetylation of the OH group of enolized acetylacetone effectively removes the possibility of resonance indicated by formulae I, and reduces the system to the simple conjugated C=C—C=O type. The bands at 5.90 $\mu$ (1695 cm.$^{-1}$) and 6.125 $\mu$ (1633 cm.$^{-1}$) are attributable to conjugated C=O and C=C, respectively, being close to the regions noted above for such groups and being of the usual intensity for such bands. The somewhat enhanced intensity of the C=C band over its usually lower value may be ascribed to the oxygen substituent. The band at 5.68 $\mu$ (1761 cm.$^{-1}$) is at the position expected for the ester C=O of the vinyl ester grouping.[19]

The final spectrum of Table I, of 5,5-dimethyl-1,3-cyclohexanedione, illustrates a case in which the same resonance conditions as for acetylacetone can be realized in a different way. The moderately strong band at 5.875 $\mu$ (1702 cm.$^{-1}$) indicates that a good proportion of the molecules are in the keto form. However, the bands at 3.8 $\mu$ (2632 cm.$^{-1}$) and 6.23 $\mu$ (1605 cm.$^{-1}$) are indicative of the conjugated chelate type of enolization. Since the ring makes it impossible sterically for the OH of the enolized form to approach closely enough to the carbonylic oxygen of the same molecule to interact with it in the manner indicated by structures I, the necessary stabilization of the ionic structure must be accomplished through dimerization of the sort



**Ultraviolet Work.**—The conclusion drawn above as to the essential difference between a simple conjugated system (C=C—C=O) and the conjugated chelate system is well verified by ultraviolet spectra. Thus, spectra of the three simple conjugated ketones shown in Fig. 1 (isophorone, acetophenone, and hexadecanophenone) exhibit the characteristic strong band near 2350 Å. (molar extinction coefficient ~10,000) and the weak band or shoulder near 3200 Å. (molar extinction coefficient ~40) noted by many investigators[2] for the conjugated system and discussed theoretically by McMurry.[20] The two benzoyl-containing compounds show also the band or shoulder near 2800 Å. associated with the phenyl ring.

Acetylacetone gives a spectrum markedly different from the above cases, exhibiting a very strong band with a maximum at 2700 Å., and molar extinction coefficient ~10,000 (Fig. 1). This is at roughly the same position as the band of simple unconjugated ketones, but the latter band is much weaker (molar extinction coefficient ~20). Acetylation to acetylacetone acetate effects the same result here as it did in the infrared, converting the absorption from that of the con-

(17) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

(18) U. Liddel, O. R. Wulf, *et al.*, THIS JOURNAL, **55**, 3574 (1933); **57**, 1464 (1935); **58**, 548, 1991, 2287 (1936).

(19) Barnes, *et al.*, ref. 2, spectrum 166, p. 72.

(20) H. L. McMurry, *J. Chem. Phys.*, **9**, 241 (1941).

jugated chelate type to that of a simple conjugated ketone (Fig. 1), with maxima at 2300 and 3250 Å. (molar extinction coefficients ~13,000 and ~60, respectively).

## Experimental

**Infrared Spectra.**—These were obtained by means of the recording rock-salt prism spectrograph of this laboratory, described elsewhere.[21] Each spectrum given in Table I was the result of a single run. Wave-length values as read directly from the record were corrected for temperature effects or mechanical shifts by observing the deviation of the $CO_2$ 4.235 $\mu$ band, or of one of the known solvent bands, from its true position and correcting all wave lengths according to a standard correction curve. This curve was constructed from several calibration runs on $CO_2$, $NH_3$, and $C_2H_4$ vapors. The reproducibility for sharp bands is within $\pm 0.02$ $\mu$. Intensities were estimated visually on a scale of 0 to 10. Solutions were made up (not highly accurately) on a weight-to-volume basis.

**Ultraviolet Spectra.**—The ultraviolet spectra were obtained from point-by-point readings on a Beckman quartz photoelectric spectrophotometer (Model DU). Solutions were made up accurately in the solvents noted in Fig. 1, using spectroscopically pure solvents. Molar extinction coefficients quoted are in units of liters/mole cm.

**Sources of Samples.**—The sources and purification procedures for the samples used were as follows:

Diacetone alcohol was obtained from a laboratory distillation of commercial material, the fraction boiling at 167.6–168.2° being used.

Isophorone was obtained from a careful laboratory distillation of commercial material, the resulting pure fractions being used also for determination of other physical constants.

Eastman White Label acetophenone and benzil were used without further purification.

The sample of biacetyl used was from an earlier laboratory preparation, and was not further purified.

Commercial acetylacetone was fractionated and the cut boiling at 139.0–139.1° used.

A dibenzoylmethane sample already on hand was used for this material (m. p. 77.5–78.0°, lit. 78°).

The sample of 5,5-dimethyl-1,3-cyclohexanedione had been prepared earlier in these Laboratories by the procedure of "Organic Synthesis," Collective Volume 2. The sample melted at 148.5–149.0° (lit., 148–150°).

Acetylacetone acetate was prepared by the method of Spence and Degering.[22] A cut of b. p. 95.1–95.6° (20 mm.), $n^{20}D$ 1.4529, was used.

Hexadecanophenone was prepared from hexadecanonitrile plus phenyl Grignard reagent, and was purified by distillation at 1.5 mm. and crystallization from ether-alcohol mixture.

**Acknowledgments.**—We wish to thank Drs. D. S. Melstrom and C. W. Smith of these laboratories for furnishing the samples, and P. S. Zucco, Mrs. Z. Alcorn, Mrs. E. Dugle and Miss R. Hatch for operation of the spectrometers and measurement of the records.

## Summary

1. Infrared absorption maxima in the 2–15 $\mu$ region are tabulated for diacetone alcohol, isophorone, acetopheonone, biacetyl, benzil, acetylacetone, dibenzoylmethane, 5,5-dimethyl-1,3-cyclohexanedione, and acetylacetone acetate. Ultraviolet spectra from 2100 to 3600 Å. are given for isophorone, acetophenone, hexadecanophenone, acetylacetone, and acetylacetone acetate.

2. Simple hydrogen bonding to the ketone C=O group has practically no effect on the C=O vibrational frequency, the infrared band appearing very near 5.83 $\mu$ (1715 cm.$^{-1}$) as in simple ketones.

3. Conjugation of C=C to the ketone C=O group gives rise to typical conjugation shifts in the infrared, the C=O band going to the region 5.90–6.00 $\mu$ (1695–1667 cm.$^{-1}$) and the C=C to 6.07–6.17 $\mu$ (1647–1621 cm.$^{-1}$) and also gives rise to the typical strong ultraviolet band near 2350 Å. (molar extinction coefficient ~10,000) and weak band near 3200 Å. (molar extinction coefficient ~40).

4. Simultaneous conjugation and chelation ("conjugated chelation") as in enolized $\beta$-diketones leads to an extreme shift of the C=O infrared band (to ~6.2 $\mu$), (1613 cm.$^{-1}$) to a great enhancement of its intensity, and to the appearance of a broad weak band near 3.7 $\mu$ (2703 cm.$^{-1}$) attributable to an extremely perturbed OH vibration. The ultraviolet spectrum of one example of this class of compound exhibits a strong band at 2700 Å. (molar extinction coefficient ~10,000).

5. Conjugation of two ketonic C=O groups to each other has little or no effect on their observed infrared band positions.

EMERYVILLE, CALIFORNIA RECEIVED AUGUST 23, 1948

(21) R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120 (1947).

(22) J. A. Spence with E. F. Degering, THIS JOURNAL, **66**, 1624 (1944).

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

# Infrared Spectra of Some Carboxylic Acid Derivatives[1]

BY ROBERT S. RASMUSSEN AND R. ROBERT BRATTAIN

In continuation of the discussion of spectroscopic studies initiated in the preceding paper, and done in connection with penicillin structure, this paper reports the infrared spectra of a series of esters, lactones, chlorides and salts of carboxylic acids.

Experimental details are the same as those given previously,[2] the reproducibility in wave length being better than $\pm 0.03$ $\mu$. The spectra are presented in tabular form in Tables I to IV. As with the previous paper of this series, discussion will be limited to the 3 $\mu$ (NH, OH and CH) and 6 $\mu$ (double-bond) regions. Thompson and Torkington,[3a] in a much more detailed study of a series of saturated esters, have described many other regularities at longer wave lengths. Recent papers containing some information on carboxylic acid derivatives have been published by Thompson[3b] and Jones, *et al.*[3c]

**Esters.**—The spectra of a series of esters, studied principally for information on the effects of induction and conjugation on the ester C=O band, are shown in Table I.

Normal aliphatic esters exhibit the C=O band very near 5.75 $\mu$ (1739 cm.$^{-1}$), from the work of Thompson and Torkington and others. The spectra of methyl pivalate, ethyl diphenylacetate, and methyl sarcosinate (Table I; 1, 2, 3) have bands so near this position that it is clear that inductive effects due to $\alpha$-alkyl, $\alpha$-aryl or $\alpha$-amino substituents exert no appreciable effect on the C=O force constant. Ethyl cyanoacetate, on the other hand, shows its band at a somewhat shorter wave length (5.71 $\mu$), (1751 cm.$^{-1}$), presumably due to the inductive effect of the C≡N group (Table I; 4). In addition to the C=O bands, the above compounds have the additional expected bands due to phenyl (6.24 and 6.68 $\mu$), (1603 cm.$^{-1}$ and 1497 cm.$^{-1}$), NH (2.985 $\mu$) (3350 cm.$^{-1}$) and C≡N (4.43 $\mu$), (2257 cm.$^{1}$).

The effect of conjugation of C=O with C=C is illustrated by methyl methacrylate (Table I; 5). The ester C=O band appears at 5.82 $\mu$ (1718 cm.$^{-1}$) and the C=C band at 6.11 $\mu$ (1637 cm.$^{-1}$) the shift of each to longer wave length being due to the conjugation. Conjugation of the C=O with the phenyl group, as in methyl benzoate (Table I; 7), seems to give a somewhat smaller shift (to 5.80 $\mu$) (1724 cm.$^{-1}$) although Thompson and Torkington[3] found that ethyl benzoate gave the band at 1716 cm.$^{-1}$ (5.83 $\mu$) within the limits of measurability of their published spectrum. Ethyl *o*-, *m*- and *p*-nitrobenzoates (Table I; 8, 9, 10) exhibit a marked lessening of the conjugation shift, the C=O bands occurring near 5.77 $\mu$ (1733 cm.$^{-1}$). Evidently the competition of the nitro group for electrons from the ring, through both resonance and induction, accounts for this effect. A similar phenomenon is observed for ethyl $\beta,\beta$-diethoxyacrylate (Table V; 6), where the band appears at 5.76 $\mu$ (1736 cm.$^{-1}$). In this case the decrease of conjugation must be attributed to the inductive attraction of the ethoxy groups for electrons, which opposes the ionic resonance structure (+)C—C=C—O(−).

Other bands in the 3 and 6 $\mu$ regions of the spectra of these conjugated esters are explicable as follows. Weak bands at 2.70 to 2.90 $\mu$ (3704 cm.$^{-1}$ to 3448 cm.$^{-1}$) are due to traces of water or hydroxylic impurities. The strong band of ethyl $\beta,\beta$-diethoxyacrylate at 6.20 $\mu$ (1613 cm.$^{-1}$) is attributable to the C=C vibration; the long wave-length shift from the usual C=C position near 6.0 $\mu$ (1667 cm.$^{-1}$) need not be attributed to conjugation (see above), but may presumably be due simply to the alkoxy substituents. Weak bands from 4.5 to 5.6 $\mu$ (2222 to 1786 cm.$^{-1}$) in spectra of the phenyl-containing compounds are overtones of the ring vibrations. Methyl benzoate exhibits the 6.25 and 6.69 $\mu$ (1600 and 1495 cm.$^{-1}$) bands which are common to all mono-substituted phenyl compounds, as well as the band at 6.29 $\mu$ (1590 cm.$^{-1}$) given by benzoyl compounds.[2] The nitro compounds have the very strong band near 6.50 $\mu$ (1538 cm.$^{-1}$) ascribable, from work on aliphatic nitro compounds, to the $NO_2$ group, and also show bands near 6.18 $\mu$ (1618 cm.$^{-1}$) and 6.75 $\mu$ (1481 cm.$^{-1}$) which are presumably the analogs of the 6.25 $\mu$ (1600 cm.$^{-1}$) and 6.69 $\mu$ (1495 cm.$^{-1}$) bands of simple phenyl compounds. Other weak bands in the 6 $\mu$ region do not occur with any regularity in similar compounds, and hence are attributable to impurities.

A further effect noted in ester spectra is to be found in the vinyl ester type of compound. Barnes, *et al.*,[4] give a spectrum of vinyl acetate in which the C=O band appears near 5.65 $\mu$ (1770 cm.$^{-1}$). This short wave-length shift is also exhibited by phenyl acetate and *o*-nitrophenyl acetate (Table V; 12, 13), the C=O bands being 5.70 and 5.60 $\mu$ (1754 and 1786 cm.$^{-1}$), respectively. The other bands observed are attributable to the phenyl or nitrophenyl groups, or to impurities.

(1) Most of this work was done under contract between the Office of Scientific Research and Development and the Shell Development Company (Contract OEM-cmr-445).

(2) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949).

(3a) H. W. Thompson and P. Torkington *J. Chem. Soc.*, 640 (1945).

(3b) H. W. Thompson, *ibid.*, 328 (1948).

(3c) R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, THIS JOURNAL, **70**, 2024 (1948).

(4) R. B. Barnes, R. C. Gore, U. Liddel and V. Z. Williams, "Infrared Spectroscopy," Reinhold Publ. Corp., New York, N. Y., 1944.

The unusual compound 1,1-diacetoxypropane, $CH_3CH_2CH(OOCCH_3)_2$ (Table I; 11), also exhibits its ester C=O band at shorter wave length (5.68 $\mu$) (1761 cm.$^{-1}$) than normal. This indicates that there may be some inductive effect on the ester C=O band position due to negative $\alpha$-substituents on the alcohol part of the molecule, the substituent in this case being another acetoxy group. A similar effect has been noted with $\alpha$-cyano substituents (acetates of cyanohydrins).

In Table II are shown spectra of several esters which illustrate the effect of conjugated chelation.[2] Ethyl $\alpha,\alpha$-dimethylacetoacetate (Table II; 1) which has no possibility of enolizing to give a

TABLE I

INFRARED SPECTRA OF ESTERS, ILLUSTRATING INDUCTION AND CONJUGATION EFFECTS

1. Methyl pivalate (methyl trimethylacetate), 0.15 mm. 5% soln. in $CCl_4$.
2. Ethyl diphenylacetate, 0.15 mm. 5% soln. in $CHCl_3$.
3. Ethyl cyanoacetate, 0.15 mm. 5% soln. in $CCl_4$.
4. Phenyl acetate, 0.02 mm. pure liquid.
5. Ethyl $\beta,\beta$-diethoxyacrylate, 0.02 mm. pure liquid.
6. Methyl sarcosinate (N-methylglycine methyl ester), 0.02 mm. pure liquid.
7. Methyl methacrylate, 0.02 mm. pure liquid.
8. 1,1-Diacetoxypropane, 0.03 mm. pure liquid.
9. Methyl benzoate, 0.02 mm. pure liquid.
10. Ethyl *o*-nitrobenzoate, 0.02 mm. pure liquid.
11. Ethyl *m*-nitrobenzoate, 0.15 mm. 10% soln. in $CCl_4$.
12. Ethyl *p*-nitrobenzoate, 0.15 mm. 10% soln. in $CCl_4$.
13. *o*-Nitrophenyl acetate, 0.15 mm. 10% soln. in $CCl_4$.

(Wave lengths in $\mu$; intensity in units of 10% absorptions; S = solvent interference.)
Bands due to ester C=O stretching vibrations are underlined.

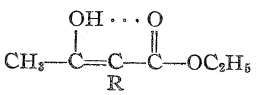
| 1 | 2 | 3 | 4 | 4 | 5 |
|---|---|---|---|---|---|
| 3.35(6) | 3.2–3.4 S | 3.345(4) | 2.90(2) | 7.76(2) | 2.90(1) |
| 5.76(8) | 5.785(8) | 4.43(1) | 3.28(4) | 8.1–8.5(10) | 3.34(8) |
| 6.755(4) | 6.24(2) | 5.71(9) | 3.42(1) | 8.60(9) | 5.76(10) |
| 6.85(3) | 6.68(3) | 6.81(3) | 4.78(1) | 9.34(5) | 5.97(1) |
| 6.97(3) | 6.89(2) | 6.915(2) | 5.00(1) | 9.57(4) | 6.20(9) |
| 7.165(2) | 7.295(3) | 7.15(4) | 5.14(2) | 9.795(4) | 6.48(1) |
| 7.31(3) | 7.45(2) | 7.30(5) | 5.54(1) | 9.895(7) | 6.86(10) |
| 7.77(7) | 7.65(2) | 7.52(7) | ~5.70(9) | 10.38(1) | ~7.15(10) |
| 8.37(5) | 7.86(1) | 7.71(1) | 6.09(1) | 10.795(8) | 7.5–9.7(10) |
| 8.64(9) | 7.9–8.4 S | 7.95(9) | 6.285(7) | 11.205(6) | 10.45(3) |
| 9.65(2) | 8.64(6) | 8.40(9) | 6.50(2) | 12.06(1) | 10.65(4) |
| 10.13(4) | 8.69(1) | 8.98(1) | 6.725(8) | 12.255(7) | 11.51(4) |
| 10.64(1) | 9.11(1) | 9.085(2) | 6.885(2) | 12.63(1) | 11.81(3) |
| 11.585(4) | 9.25(1) | 9.71(7) | 7.00(4) | 13.33(8) | Not |
| >12.0 S | 9.725(6) | 10.69(3) | 7.30(8) | 14.42(7) | contd. |
| | 10.46(1) | 11.745(3) | 7.59(1) | | further |
| | >12.0 S | >12.0 S | | | |

| 6 | 7 | 8 | 9 | 9 |
|---|---|---|---|---|
| 2.985(3) | 3.37(5) | 2.30(1) | 2.76(1) | 8.20(1) |
| 3.37(7) | 5.04(1) | 2.50(1) | 2.91(1) | 8.37(5) |
| 3.54(2) | 5.82(10) | 2.885(2) | 3.25(2) | 8.48(5) |
| 5.74(8) | 6.11(7) | 3.35(8) | 3.29(4) | 8.61(2) |
| 6.75(1) | 6.91(7) | 3.62(1) | 3.35(3) | ~ 9.00(10) |
| 6.88(6) | 6.96(7) | 4.71(1) | 3.48(1) | 9.305(8) |
| 6.95(8) | 7.13(2) | 5.68(10) | 4.77(1) | 9.725(9) |
| 7.06(2) | 7.265(3) | ~6.50(1) | 5.18(2) | 9.965(1) |
| 7.30(5) | 7.555(8) | 6.84(6) | 5.59(1) | 10.32(8) |
| 7.81(2) | 7.685(8) | 6.96(6) | 5.80(9) | 10.645(4) |
| 8.25(10) | 8.34(10) | 7.28(9) | 5.94(3) | 11.755(1) |
| 8.51(9) | 8.59(10) | 7.9–8.3(10) | 6.06(1) | 12.125(6) |
| 8.86(6) | 9.84(5) | 8.55(3) | 6.245(2) | 12.325(3) |
| 9.94(7) | 10.02(1) | 8.98(10) | 6.29(2) | 13.135(1) |
| 10.33(5) | 10.155(2) | 9.27(9) | 6.69(2) | ~14.0(10) |
| 10.68(2) | 10.61(9) | 9.6–10.0(10) | 6.92(8) | 14.52(5) |
| 11.23(2) | 10.74(2) | 10.33(10) | 7.59(5) | 14.79(4) |
| 11.36(2) | 12.03(3) | 10.80(8) | ~7.80(10) | |
| 11.92(1) | 12.265(8) | 11.02(8) | | |
| ~13.1(10) | | 11.36(2) | | |
| ~14.4(5) | | 12.82(4) | | |

TABLE I (*Continued*)

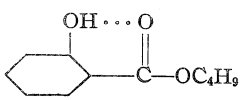
| 10 | 11 | 12 | 13 |
|---|---|---|---|
| 2.77(1) | 3.205(1) | 3.295(4) | 3.21(1) |
| 3.24(2) | 3.315(4) | 5.12(1) | 3.39(2) |
| 3.34(5) | 5.77(8) | 5.51(1) | 5.48(1) |
| 5.78(9) | 6.16(4) | 5.76(8) | 5.60(8) |
| 6.19(5) | 6.48(8) | 6.02(1) | 5.77(1) |
| 6.32(2) | 6.75(5) | 6.185(5) | 6.195(6) |
| 6.50(10) | 6.915(4) | 6.485(8) | 6.25(2) |
| 6.76(5) | 7.17(3) | 6.74(3) | 6.495(8) |
| 6.91(4) | 7.29(3) | 6.80(3) | 6.73(4) |
| ~7.37(10) | 7.385(6) | 6.89(3) | 6.86(1) |
| ~7.82(10) | 7.585(3) | 7.06(4) | 6.965(2) |
| 8.51(5) | 7.73(7) | 7.16(2) | 7.28(4) |
| 8.84(9) | 7.90(8) | 7.29(1) | 7.38(7) |
| 9.09(1) | 8.49(3) | 7.385(9) | 7.51(1) |
| 9.295(8) | 8.80(8) | 7.56(3) | 8.40(10) |
| 9.625(5) | 8.96(1) | 7.82(10) | 8.575(4) |
| 9.87(7) | 9.095(3) | 8.00(2) | 8.705(2) |
| 10.38(2) | 9.305(6) | 8.19(2) | 9.145(7) |
| 11.28(1) | 9.81(7) | 8.50(4) | 9.58(4) |
| 11.51(3) | 10.62(1) | ~9.0(9) | 9.895(7) |
| 11.64(3) | 10.80(4) | 9.20(1) | 10.17(2) |
| 11.805(5) | 10.96(3) | 9.81(7) | 10.455(4) |
| 12.64(7) | 11.55(5) | 11.42(7) | 11.00(8) |
| 12.84(5) | 11.92(4) | 11.87(8) | 11.44(5) |
| 13.58(8) | 12.0–14.0 S | 12.0–14.0 S | 11.75(6) |
| 14.28(5) | 13.86(9) | 13.85(9) | 12.0–14.0 S |
| | | | 14.275(8) |
| | | | 14.83(4) |

conjugated chelate ring, shows only a single band in the double-bond region, at 5.79 $\mu$ (1727 cm.$^{-1}$). Examined in more dilute solution, this band is found to have a strong component at 5.82 $\mu$ (1718 cm.$^{-1}$), and a weaker one, appearing as a shoulder, at 5.74 $\mu$ (1742 cm.$^{-1}$). These are clearly to be ascribed to the ketone and ester groups, respectively. Ethyl $\alpha$-methylacetoacetate and ethyl acetoacetate (Table II; 2, 3) each exhibit an additional band near 6.06 $\mu$ (1650 cm.$^{-1}$), ascribable to the C=O of the conjugated chelate ring:



That the enolization is only partial is seen from the persistence of a strong 5.78 $\mu$ (1730 cm.$^{-1}$) band. This result is essentially identical with that from Raman work.[5] However, as with acetylacetone,[2] the 6.06 $\mu$ (1650 cm.$^{-1}$) band is more reasonably ascribed to the C=O rather than the C=C vibration in contradistinction to the assignment given by Kohlrausch and Pongratz. The 3.7 $\mu$ (2703 cm.$^{-1}$) band expected from the OH of the enol was not observed, very probably because the concentration of enol was not high enough to bring it out. Diethyl $\alpha,\beta$-diacetylsuccinate (Table II; 4) exhibits only the unmodified ester and ketone bands, with no evidence of enolization or chelation.

As an example of an aromatic conjugated chelate system, *n*-butyl salicylate was examined (Table II; 5). Bands are found at 3.14 $\mu$ (3185 cm.$^{-1}$) and 5.97 $\mu$ (1675 cm.$^{-1}$) attributable, respectively, to OH and to ester C=O in the conjugated chelate system:



Both bands are shifted considerably beyond their "normal" positions (hydrogen-bonded OH, 3.0 $\mu$ (3333 cm.$^{-1}$); conjugated ester, 5.82 $\mu$ (1718 cm.$^{-1}$)), but are not shifted as much as in enolized chelate $\beta$-diketones or $\beta$-ketoesters (OH = *circa* 3.7 $\mu$ (2703 cm.$^{-1}$) C=O, 6.05 $\mu$ (1653 cm.$^{-1}$) or more). Hence the chelation is apparently not quite so strong as with this latter class, probably due to the only partial double-bond character of the CC bonds of the ring. That conjugated chelation nevertheless has influenced the spectrum markedly is attested to by an examination of acetylated *n*-butyl salicylate (Table II; 6). The OH band disappears, and the salicylate C=O band returns to the usual conjugated ester position, appearing at 5.805 $\mu$ (1723 cm.$^{-1}$). The acetate C=O band, arising from the vinyl ester type of system, appears at a shorter wave length (5.65 $\mu$) (1770 cm.$^{-1}$) than normal unconjugated esters, as discussed above.

(5) *E. g.*, K. W. F. Kohlrausch and A. Pongratz, *Z. physik. Chem.*, B27, 176 (1934).

TABLE II

INFRARED SPECTRA OF ESTERS, ILLUSTRATING CHELATION EFFECTS

1. Ethyl $\alpha,\alpha$-dimethylacetoacetate, 0.15 mm. 10% soln. in $CCl_4$.
2. Ethyl $\alpha$-methylacetoacetate, 0.15 mm. 10% soln. in $CCl_4$.
3. Ethyl acetoacetate, 0.15 mm. 10% soln. in $CCl_4$.
4. Diethyl $\alpha,\beta$-diacetylsuccinate, 0.15 mm. 5% soln. in $CCl_4$.
5. $n$-Butyl salicylate, 0.15 mm. 10% soln. in $CCl_4$.
6. $n$-Butyl acetylsalicylate, 0.15 mm. 5% soln. in $CCl_4$.
7. Methyl N-methylanthranilate, 0.15 mm. 10% soln. in $CCl_4$.
8. Methyl N,N-dimethylanthranilate, 0.15 mm. 10% soln. in $CCl_4$.
9. Methyl N-methyl-N-acetylanthranilate, 0.15 mm. 10% soln. in $CCl_4$.

(Wave lengths in $\mu$; intensity in units of 10% absorption; S = solvent interference.) Bands due to ester C=O stretching vibration are underlined.

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 3.33(6) | 3.345(5) | 3.34(5) | 3.37(3) |
| 5.79(10) | 5.79(10) | 5.78(10) | 5.775(5) |
| 6.82(8) | 6.05(2) | 6.07(9) | 5.83(4) |
| 6.92(2) | 6.875(6) | 6.80(2) | 6.83(2) |
| 7.205(4) | 7.04(2) | 6.915(3) | 6.94(1) |
| 7.365(6) | 7.355(5) | 7.05(4) | 7.045(2) |
| 7.69(2) | 7.57(4) | 7.20(1) | 7.20(1) |
| 7.89(9) | 7.91(2) | 7.32(5) | 7.38(6) |
| 8.08(1) | 8.045(6) | 7.62(6) | 7.81(8) |
| 8.47(2) | 8.34(7) | 8.09(10) | 8.00(8) |
| 8.64(7) | 8.66(6) | 8.42(4) | 8.535(8) |
| 8.94(8) | 9.08(3) | 8.68(9) | 8.76(3) |
| 9.09(1) | 9.275(4) | 8.97(1) | 8.965(1) |
| 9.30(1) | 9.51(3) | 9.095(4) | 9.115(2) |
| 9.725(5) | 9.74(4) | 9.58(8) | 9.635(3) |
| 10.315(2) | 11.09(2) | 9.87(3) | 9.80(3) |
| 11.62(2) | 11.62(4) | 10.68(4) | 10.74(1) |
| >12.0 S | >12.0 S | >12.0 S | 11.50(2) |
| | | | >12.0 S |

| 5 | 5 | 7 | 8 | 9 |
|---|---|---|---|---|
| 3.14(5) | 10.54(2) | 2.975(6) | 3.345(5) | 3.35(5) |
| 3.39(6) | 11.03(1) | 3.39(6) | 3.43(2) | 5.775(6) |
| 5.21(1) | 11.34(2) | 4.89(1) | 3.51(1) | 6.05(8) |
| 5.53(1) | 11.57(3) | 5.215(1) | 5.21(1) | 6.23(5) |
| 5.97(9) | 11.70(1) | 5.935(9) | 5.79(6) | 6.32(1) |
| 6.195(4) | >12.0 S | 6.22(3) | 6.22(5) | 6.55(2) |
| 6.30(3) | | 6.31(6) | 6.36(3) | 6.695(5) |
| 6.65(1) | 6 | 6.585(6) | 6.645(6) | 6.885(5) |
| 6.75(3) | 3.38(5) | 6.78(2) | 6.87(3) | 6.96(3) |
| 6.83(3) | 5.65(6) | 6.85(2) | 6.95(5) | 7.04(1) |
| 7.10(2) | 5.805(6) | 6.965(8) | 7.375(5) | 7.24(7) |
| 7.165(4) | 6.22(3) | 7.27(1) | 7.71(5) | 7.395(2) |
| 7.53(5) | 6.33(1) | 7.545(8) | 7.98(9) | 7.73(9) |
| 7.68(6) | 6.74(2) | ~8.0(10) | 8.255(9) | 7.96(9) |
| 7.995(6) | 6.89(4) | 8.395(4) | 8.38(1) | 8.375(3) |
| 8.11(1) | 6.98(1) | 8.52(5) | 8.575(5) | 8.65(1) |
| 8.275(7) | 7.31(6) | 8.595(3) | 8.835(8) | 8.73(1) |
| 8.445(3) | 7.74(5) | 8.855(8) | 9.25(8) | 8.86(4) |
| 8.625(5) | 7.95(8) | 9.16(8) | 9.485(4) | 9.07(4) |
| 8.78(5) | 8.37(9) | 9.375(6) | 10.31(3) | 9.305(7) |
| 9.155(8) | 8.62(3) | 9.60(3) | 10.505(6) | 9.595(4) |
| 9.43(2) | 8.815(4) | 11.52(1) | >12.0 S | 10.32(4) |
| 9.68(4) | 8.90(1) | 11.83(1) | | 10.81(2) |
| 10.07(2) | 9.23(7) | 11.98(3) | | >12.0 S |
| 10.365(2) | 9.59(3) | 12.0-14.0 S | | |
| 10.48(1) | 9.92(5) | 14.20(7) | | |
| | 10.47(1) | | | |
| | 10.93(6) | | | |
| | 11.44(1) | | | |
| | >12.0 S | | | |

The final group of esters examined were derivatives of methyl anthranilate, and are of interest in ascertaining whether the NH group can participate in conjugated chelation in the same fashion as does OH.

Methyl N-methylanthranilate (Table II; 7) exhibits a C=O band at 5.935 $\mu$ (1685 cm.$^{-1}$) indicating some chelation effect of almost the same magnitude as with the salicylates. The NH band at 2.975 $\mu$ (3361 cm.$^{-1}$), however, appears not to be shifted from its usual position in simple hydrogen-bonding. Removal of the chelating hydrogen, as in methyl N,N-dimethylanthranilate or in methyl N-methyl-N-acetylanthranilate (Table II; 8, 9) results in disappearance of the NH band and in return of the ester C=O band to ~5.78 $\mu$ (1730 cm.$^{-1}$), near the usual position for conjugated esters. Actually, the shift due to conjugation with the phenyl ring is smaller than for other similar compounds (*e. g.*, *n*-butyl acetylsalicylate above), but the reason for this is not clear. The N-acetyl compound also shows the 6.05 $\mu$ (1653 cm.$^{-1}$) band due to amide C=O.

All the salicylic and anthranilic derivatives discussed above (Table II; 5, 6, 7, 8, 9) exhibit in the main the bands expected from the phenyl ring. These are: (1) the bands near 6.20 $\mu$ (1613 cm.$^{-1}$) and 6.6 to 6.7 $\mu$ (1515 to 1493 cm.$^{-1}$) found regularly with simple phenyl compounds, and (2) that near 6.30 $\mu$ (1587 cm.$^{-1}$) found also in benzoyl compounds. The 6.20 $\mu$ (1613 cm.$^{-1}$) bands, which are weak for phenyl rings with carbon substituents, are enhanced in intensity for O- or N-substituted rings, as noted from unpublished work of this Laboratory on phenols and anilines; this effect is to be seen also in the above described salicylate and anthranilate spectra. Two anomalies in the above explanation are: (1) the enhanced intensity of the 6.31 $\mu$ (1585 cm.$^{-1}$) band in methyl N-methylanthranilate as compared with the other compounds, and (2) the unexplained band at 6.55 $\mu$ (1527 cm.$^{-1}$) in the spectrum of methyl N-methyl-N-acetylanthranilate. Both of these may be due to impurities.

**Lactones.**—Spectra of some lactones are given in Table III.

As an exemplar of the simple saturated 5-membered lactones, $\gamma$-valerolactone was studied (Table III; 1). The sample was evidently considerably impure, as attested to by unexplainable bands at 5.76 and 6.12 $\mu$ (1736 and 1634 cm.$^{-1}$) (2.80 $\mu$ (3571 cm.$^{-1}$) is due to adventitious water). However, the strong 5.65 $\mu$ (1770 cm.$^{-1}$) band is certainly ascribable to the lactone C=O stretching vibration. The reason for this shift from the open chain ester position must be sought in ring strain, but the exact mechanism is unclear. Taufen and Murray[6] give the Raman spectrum of $\beta$-butyrolactone, from which it is apparent that the C=O band of this compound would appear near 5.50 $\mu$ (1818 cm.$^{-1}$), even further shifted from the open-chain position. On the other hand, $\delta$-valerolactone

(6) H. J. Taufen and M. J. Murray, THIS JOURNAL, **67**, 754 (1945).

TABLE III

INFRARED SPECTRA OF LACTONES

1. γ-Valerolactone, 0.02 mm. pure liquid.
2. β,γ-Angelica lactone (4-hydroxy-3-pentenoic acid γ-lactone), 0.02 mm. pure liquid.
3. Acetate of lactone form of levulinic acid (γ-acetoxy-γ-valerolactone), 0.15 mm. 10% soln. in $CHCl_3$.
4. α-Acetyl-γ-butyrolactone, 0.02 mm. pure liquid.
5. δ-Valerolactone, 0.02 mm. pure liquid.
6. Coumarin (o-hydroxycinnamic acid δ-lactone), 0.15 mm. 10% soln. in $CHCl_3$.

(Wave lengths in μ; intensity in units of 10% absorption; S = solvent interference). Bands due to the lactone C=O stretching vibrations are underlined.

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| 2.80(1) | 2.59(1) | 2.365(1) | 2.865(1) | 2.89(3) | 3.2–3.4 S |
| 3.35(6) | 2.79(1) | 3.2–3.4 S | 2.925(1) | 3.38(9) | ~5.80(10) |
| 5.65(9) | 3.19(1) | 5.565(5) | 3.33(3) | 5.75(10) | 5.96(2) |
| 5.76(3) | 3.375(3) | 5.715(5) | 3.40(3) | 6.77(3) | 6.15(4) |
| 6.12(1) | 4.51(1) | 7.195(3) | 5.64(6) | 6.84(4) | 6.19(6) |
| 6.85(5) | 4.905(1) | 7.27(3) | 5.82(6) | 6.92(3) | 6.37(5) |
| 7.025(5) | 5.56(10) | Not contd. | 6.04(3) | 7.13(6) | 6.77(2) |
| 7.20(6) | 5.945(5) | further | 6.74(2) | 7.45(5) | 6.88(5) |
| 7.42(6) | 6.92(3) | | 6.875(3) | 7.83(4) | 7.13(5) |
| 7.67(3) | 6.96(2) | | 7.025(4) | ~8.04(10) | 7.505(1) |
| 7.80(2) | 7.15(1) | | 7.28(6) | ~8.62(10) | 7.825(3) |
| 8.17(5) | 7.20(5) | | 7.35(6) | 9.28(3) | 7.925(3) |
| 8.35(3) | 7.36(1) | | 7.51(2) | 9.48(9) | 7.9–8.4 S |
| 8.52(9) | 7.745(4) | | 7.75(3) | 10.16(3) | 8.45(8) |
| 8.90(5) | 7.875(7) | | 8.07(2) | 10.75(6) | 8.90(6) |
| 9.02(2) | 8.10(1) | | 8.205(6) | 11.39(2) | 9.03(7) |
| 9.11(3) | 8.46(7) | | 8.66(10) | 12.09(3) | 9.70(1) |
| 9.44(8) | 8.99(10) | | 9.01(1) | 12.50(2) | 10.14(1) |
| 9.60(2) | 9.61(2) | | 9.185(3) | 13.36(3) | 10.57(2) |
| 10.00(5) | 9.88(4) | | 9.765(7) | | 10.71(8) |
| 10.39(2) | 10.30(7) | | 9.98(5) | | 11.185(7) |
| 10.60(8) | 10.71(8) | | 10.25(1) | | 11.53(3) |
| 11.14(7) | 11.955(6) | | 10.64(4) | | 12.025(8) |
| 12.09(2) | 13.41(7) | | 11.54(1) | | >12.0 S |
| 12.42(4) | 14.305(4) | | 12.72(4) | | |
| 13.45(1) | | | 14.305(4) | | |

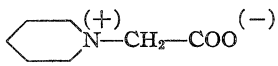
exhibits its band at 5.75 μ (1739 cm.$^{-1}$), the same position as open-chain esters (Table III; 5). Hence the strain is sufficiently reduced in the six-membered ring to exert no effect spectroscopically. Similar shifts from the open-chain position are to be observed in five- and four-membered cycloketone and lactam rings.

The remaining lactones discussed here demonstrate further effects on the lactone C=O band position which are identical with effects described above for the open-chain esters. Thus β,γ-angelica lactone (Table III; 2) is essentially a vinyl ester type of compound. The shift of its C=O band to 5.56 μ (1799 cm.$^{-1}$), a short wave-length shift from the saturated 5-ring lactone position (5.65 μ), (1770 cm.$^{-1}$), parallels the shift of open-chain vinyl esters from the saturated open-chain ester position (see preceding section). The C=C band appears at 5.945 μ (1682 cm.$^{-1}$). Similarly, γ-acetoxy-γ-valerolactone (Table III; 3) exhibits its lactone C=O band at 5.565 μ (1797 cm.$^{-1}$) and its acetate group C=O band at 5.715 μ (1750 cm.$^{-1}$), the short wave-length shifts here paralleling the ones observed for 1,1-diacetoxypropane (see preceding section of this paper).

The β-ketoester type of lactone is represented by α-acetyl-γ-butyrolactone (Table III; 4). The non-enolized form is evidenced by a normal 5-ring lactone band at 5.64 μ (1773 cm.$^{-1}$) and a normal ketone band at 5.82 μ (1718 cm.$^{-1}$), whereas the rather weak band at 6.04 μ (1656 cm.$^{-1}$) indicates a small amount of enolization to a conjugated chelate system (see discussion of acetoacetic esters in preceding section).

A more complex lactone is illustrated by coumarin (Table III; 6). The multiple conjugation here makes it useless to attempt a specific assignment of the double-bond bands until such systems are further studied.

Salts.—Two examples of spectra of salts of carboxylic acids are given in Table IV. Sodium acetate possesses as its only absorption in the 6 μ region a band at 6.33 μ (1580 cm.$^{-1}$). This must be attributed to one of the vibrations of the $COO^-$ group. Work of other laboratories in the penicillin project on spectra of salts indicated considerable variability in the infrared band position, but it generally falls in the range 6.20 to 6.35 μ (1613 to 1575 cm.$^{-1}$). An example of an extreme shift in position is found in pyridine betaine (Table III; 2),



The band attributable to $COO^-$ occurs at 6.055 $\mu$ (1652 cm.$^{-1}$), indicating a powerful inductive or electrostatic effect of the positive nitrogen on the $COO^-$ group.

TABLE IV

INFRARED SPECTRA OF SALTS AND ACID CHLORIDES OF CARBOXYLIC ACIDS

1. Sodium acetate, 0.02 mm. 5% soln. in $CH_3OH$.
2. Pyridine betaine, 0.02 mm. 20% soln. in $CH_3OH$.
3. Acetyl chloride, 0.15 mm. 10% soln. in $CCl_4$.
4. Phenylacetyl chloride, 0.15 mm. 10% soln. in $CCl_4$.
5. Benzoyl chloride, 0.15 mm. 5% soln. in $CCl_4$.

(Wave lengths in $\mu$; intensity in units of 10% absorption; S = solvent interference.) Bands due to the C=O stretching vibration are underlined.

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| 6.33(6) | 6.055(7) | 2.75(1) | 3.265(3) | 3.245(1) |
| (studied | 6.75(4) | 3.27(2) | 3.40(1) | 5.64(6) |
| from | 7.27(6) | 3.35(2) | 5.13(1) | 5.76(5) |
| 5-7$\mu$ | 7.67(3) | 4.86(1) | 5.23(1) | 6.255(2) |
| only) | 8.19(1) | 5.23(3) | 5.56(9) | 6.305(2) |
| | 8.40(2) | ~5.50(10) | 5.84(1) | ~6.70(2) |
| | (studied | 5.71(5) | 6.05(1) | 6.895(4) |
| | from | 7.01(7) | 6.28(2) | 7.05(1) |
| | 5-9$\mu$ | 7.325(7) | 6.675(4) | 7.21(1) |
| | only) | 7.725(4) | 6.875(4) | 7.44(1) |
| | | ~9.07(10) | 7.02(1) | 7.60(2) |
| | | 9.78(3) | 7.125(3) | 7.67(1) |
| | | 10.46(9) | 7.635(1) | 8.305(9) |
| | | >12.0 S | 8.43(5) | 8.50(6) |
| | | | 8.62(1) | 9.075(1) |
| | | | 9.03(1) | 9.27(1) |
| | | | 9.275(3) | 9.73(1) |
| | | | 9.71(3) | 9.975(2) |
| | | | 9.885(7) | 10.68(1) |
| | | | 10.015(6) | 11.41(10) |
| | | | 10.44(10) | 12.0-14.0 S |
| | | | 12.0-14.0 S | 14.56(8) |
| | | | 14.09(8) | 14.83(8) |
| | | | 14.30(5) | |

**Acid Chlorides.**—Spectra of three acid chlorides are given in Table IV. Both acetyl chloride and phenylacetyl chloride exhibit the C=O band near 5.55 $\mu$ (1802 cm.$^{-1}$). The moderately intense band of the former at 5.71 $\mu$ (1751 cm.$^{-1}$) is ascribable to a hydrolytic impurity of acetic acid, and the same explanation may be applicable for some of the weak bands of phenylacetyl chloride. The spectrum of benzoyl chloride is anomalous in that two bands appear in the double-bond region (5.64, 5.76 $\mu$) (1773, 1736 cm.$^{-1}$), aside from the bands of the phenyl ring (6.255, 6.305, 6.70 $\mu$) (1599, 1586, 1493 cm.$^{-1}$). It is improbable that one of these results from hydrolysis, since benzoic acid C=O bands are found near 5.9 $\mu$ (1695 cm.$^{-1}$), and since repeat experiments in which precautions were taken against hydrolysis yielded the same spectrum. Two possible causes of this doubling are partial association into dimers, and inter-action with a low thermally-excited vibration. Aside from this anomaly, the expected long wave-length shift due to conjugation is present, as is evident by a comparison with acetyl and phenylacetyl chlorides.

## Experimental

The sources and purities of samples used were as follows (synthetic work carried out by Drs. C. W. Smith and D. S. Melstrom):

**Methyl pivalate** was prepared by treatment of pivalic acid with diazomethane. The product was washed with bicarbonate, dried over sodium sulfate, and fractionated through a micro still. The heart cut, b. p. 100° (lit. 100 to 102°), $n^{20}D$ 1.3892, was used.

**Ethyl diphenylacetate** was prepared from diphenylketene and absolute ethanol. The product was recrystallized from absolute ethanol, m. p. 56.5 to 57° (lit., 57 to 59°).

**Methyl Sarcosinate.**—Methylaminoacetonitrile was prepared from methylamine hydrochloride, formaldehyde and potassium cyanide, according to the method of Lilly.[7] It was converted to methyl sarcosinate hydrochloride with hydrochloric acid in methanol. The ester was liberated from the hydrochloride, and fractionated twice. The final product used had the constants: b. p. (20 mm.) 43.0–43.5°, $n^{20}D$ 1.4154. *Anal.*: C, 46.76, 46.48; H, 8.83, 8.85. (Calcd.: C, 46.59; H, 8.80.)

**Ethyl Cyanoacetate.**—Eastman Kodak Co. White Label was used without further purification.

**Methyl methacrylate** was taken from a careful distillation of technical material.

**Ethyl $\beta,\beta$-diethoxyacrylate** was prepared from ethyl cyanoacetate with ethanol and hydrochloric acid by the method of Reitter and Weindel.[8] The product was distilled from a Claisen flask and a fraction b. p. 80 to 86° (1 mm.) was used for the spectroscopic work (lit. b. p. 127.8 to 128.2° (12 mm.)).

**Methyl benzoate,** the three ethyl nitrobenzoates, and phenyl acetate were Eastman Kodak Co. White Label products used without further purification. The *o*-nitrophenyl acetate sample was Eastman Yellow Label, with a stated m. p. of 37 to 39°, and was not further purified.

**1,1-Diacetoxy-2-propene** was prepared from acrolein and acetic anhydride by the method of Wohl and Maag.[9] The product was hydrogenated over nickel (15 p. s. i.) to give the diacetoxypropane, and had the constants: b. p. 62° (5 mm.), $n^{20}D$ 1.4070.

**The ethyl acetoacetate** used was a commercial sample, b. p. (10 mm.) 78 to 79°.

**Ethyl $\alpha$-methylacetoacetate** was prepared by alkylation of acetoacetic ester with methyl iodide according to the method of Folkers and Adkins.[10] The final product had a b. p. (23 mm.) of 81 to 84°. *Anal.*: C, 58.2, 58.45; H, 8.43, 8.43. (Calcd.: C, 58.32, H, 8.39.)

**Ethyl $\alpha,\alpha$-dimethylacetoacetate** was prepared by further methylation of the above monomethylated compound. Unreacted monomethylated ester was removed from the product by extraction of a benzene solution with 25% aqueous potassium hydroxide according to the method of Pedersen.[11]

**Diethyl $\alpha,\beta$-diacetylsuccinate** was prepared from sodium acetoacetic ester and iodine according to the procedure of Knorr and Haber[12]; m. p. 85 to 88° (lit. 85–88°).

**The *n*-butyl salicylate** sample used was Eastman White Label without further purification; b. p. (20 mm.) 145 to 146°. Its acetyl derivative was obtained by treatment with acetic anhydride in pyridine; b. p. (0.9–1 mm.) 128 to 130°; sp. gr. 20/4 1.101, 1.102; $n^{20}D$ 1.4989.

**Methyl N-methylanthranilate** was prepared from Eastman White Label N-methylanthranilic acid. The N,N-dimethyl compound was obtained from this and methyl iodide according to the method of Kahn.[13] The N-

(7) Lilly, L-XIII-10; Reports of the Penicillin Structure and Synthesis Project.

(8) H. Reitter and A. Weindel, *Ber.*, **40**, 3358 (1907).

(9) A. Wohl and R. Maag, *Ber.*, **43**, 3293 (1910).

(10) K. Folkers and H. Adkins, THIS JOURNAL, **53**, 1416 (1931).

(11) K. J. Pedersen, *ibid.*, **58**, 240 (1936).

(12) L. Knorr and F. Haber, *Ber.*, **27**, 1155 (1894).

(13) R. Willstätter and W. Kahn, *ibid.*, **37**, 401 (1904).

methyl-N-acetyl compound was prepared from methyl N-methylanthranilate by treatment with acetic anhydride in pyridine, and removal of unreacted material under reduced pressure and by hydrochloric acid extraction. The product was an oil which failed to crystallize at the time the infrared spectrum was taken, but which crystallized later.

**γ-Valerolactone** was produced by catalytic reduction of β,γ-angelica lactone (see below) in absolute ethanol with Raney nickel at 25° and 40 p. s. i. (max.) hydrogen. The product was twice fractionated; b. p. (20 mm.) 93.5. *Anal.*: C, 58.99, 58.74; H, 8.40, 8.29. (Calcd.: C, 59.98; H, 8.06).

**β,γ-Angelica lactone** was prepared by destructive distillation of levulinic acid (lactone form) acetate (see below), following the method of Thiele, Tischbein, and Lossow.[14] The product was washed with bicarbonate solution and twice distilled; b. p. (12 mm.) 56.2–57.0°. *Anal.*: C, 60.87, 60.76; H, 6.19, 6.14. (Calcd.: C, 61.21; H, 6.17.)

**The acetate of the lactone form of levulinic acid** was prepared from freshly distilled levulinic acid, acetic anhydride and a trace of acetyl chloride, after the method of Thiele, *et al.*[14] The product was recrystallized twice from ethanol and once from dilute aqueous ethanol: m. p. 74.5 to 75°. *Anal.*: C, 52.94, 53.01; H, 6.45, 6.43. (Calcd.: C, 53.16; H, 6.37.)

**α-Acetyl-γ-butyrolactone** was prepared from sodium acetoacetic ester and ethylene oxide in absolute ethanol according to the method of Knunyantz, Chelintzev, and Osetrova[15]: b. p. (20 mm.) 135 to 136°; $n^{20}D$ 1.4600. *Anal.*: C, 56.19, 56.17; H, 6.39, 6.43. (Calcd.: C, 56.24; H, 6.29.)

**δ-Valerolactone** was made by hydrogen peroxide oxidation of δ-hydroxyvaleraldehyde in acetic acid. The product had b. p. 80° (4 mm.); $n^{20}D$ 1.4532. *Anal.*: C, 58.90, 58.89; H, 8.12, 8.13. (Calcd.: C, 59.98; H, 8.05.)

The coumarin used was Eastman White Label with no further purification.

Sodium acetate and acetyl chloride were taken from Baker's C. P. quality materials.

**Pyridine betaine hydrochloride** and the free betaine were prepared from pyridine and chloroacetic acid by the procedure of Edsall and Wyman.[16] A portion of the free pyridine betaine product was dried for 6.6 hours in a vacuum desiccator over phosphorus pentoxide. *Anal.*: N, 9.8, 9.9. (Calcd.: 10.22.)

Phenylacetyl chloride and benzoyl chloride were Eastman White Label samples.

(14) J. Thiele, R. Tischbein and E. Lossow, *Ann.*, **319**, 180 (1901).

(15) J. L. Knunyantz, G. V. Chelintzev and E. D. Osetrova, *C. r. acad. sci. U. S. S. R. (N. S.)*, **1**, 312 (1934); *C. A.*, **28**, 4382 (1934).

(16) J. T. Edsall and J. Wyman, Jr., THIS JOURNAL, **57**, 1964 (1935).

**Acknowledgments.**—We wish to thank Drs. C. W. Smith and D. S. Melstrom of these laboratories for preparation and purification of many of the samples. The assistance of Mr. P. S. Zucco, Mrs. J. K. Alcorn and Mrs. E. Dugle in operation of the spectrograph and measurement of the curves is acknowledged.

## Summary

1. Infrared absorption maxima in the 2-to-15 μ region are tabulated for a group of carboxylic acid esters, lactones, salts, and acid chlorides.

2. Unconjugated esters exhibit their C=O bands near 5.75 μ (1739 cm.$^{-1}$), although sufficiently electronegative α-substituents may shift the position down as far as 5.70 μ (1754 cm.$^{-1}$).

3. Conjugation of the ester C=O to C=C or phenyl shifts the C=O band position to *circa* 5.81 μ (1721 cm.$^{-1}$). The amount of this shift may be markedly modified by induction or resonance effects due to substituents on the conjugated system.

4. Vinyl ester or phenyl ester compounds exhibit the ester C=O band shifted to *circa* 5.65 μ (1770 cm.$^{-1}$).

5. Enolized β-ketoesters, and salicylic esters, show the enhanced shift in C=O position expected from conjugated chelate systems. The C=O bands appear near 6.0 μ (1667 cm.$^{-1}$) in these cases. An anthranilic ester showed a similar conjugated chelation effect, but the C=O shift was only to 5.935 μ (1685 cm.$^{-1}$).

6. Saturated five-membered lactone rings give a C=O band near 5.65 μ (1770 cm.$^{-1}$). This may be modified by conjugation, vinyl ester and chelation effects as described for open-chain esters. A saturated six-membered lactone gives a band at 5.75 μ (1739 cm.$^{-1}$), *i.e.*, unshifted from the open-chain ester position.

7. Salts of carboxylic acids yield a band near 6.3 μ (1587 cm.$^{-1}$).

8. Unconjugated acid chlorides exhibit the C=O band near 5.55 μ (1802 cm.$^{-1}$).

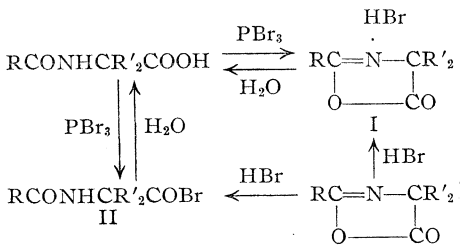
EMERYVILLE, CALIFORNIA RECEIVED AUGUST 23, 1948

[CONTRIBUTION FROM THE SHELL DEVELOPMENT COMPANY]

# Spectroscopic Evidence Concerning the Structure of 2-Phenyl-4,4-dimethyl-5(4)-oxazolone Hydrobromide

BY CURTIS W. SMITH AND ROBERT S. RASMUSSEN

The reactions of phosphorus tribromide, phosphorus trichloride, or thionyl chloride with α-acylamino acids give products which have been considered as oxazolone hydrohalides (I) or as α-acylamino acid halides (II). Treatment of an oxazolone with hydrogen chloride or hydrogen bromide gives similar products.




Fischer,[1] Mohr,[2] and Neher, Wettstein and Miescher[3] assigned the α-acylamino acid halide structure (II) to products of this type.

Evidence presented in two chapters[4,5] of the Monograph on Penicillin might be interpreted to favor the oxazolone hydrohalide structure. However, it was pointed out by Cornforth[5] that it was not possible to distinguish between the two structures, I and II, with the evidence at present available. He further suggested that the two structures may be in equilibrium.

In an attempt to gain further knowledge as to the structure of these reaction products the infrared absorption of the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been obtained in these laboratories.

α-Benzamidoisobutyric acid in dry chloroform was treated with an equimolar quantity of phosphorus tribromide and the infrared absorption of the solution was examined shortly thereafter. This same procedure was carried out using as the solvent, dioxane, which had been freshly distilled over sodium. The spectra of the two solutions (see Table I, spectra 2 and 3) were consistent with each other and showed a broad general absorption around the 4 μ (2500 cm.$^{-1}$) region, a rather sharp band near 5.28 μ (1894 cm.$^{-1}$) and a strong, sharp band near 6.10 μ (1639 cm.$^{-1}$), with only a trace of absorption in the 5.78 μ (1730 cm.$^{-1}$) region. The lack of a 6.6 μ (1515 cm.$^{-1}$) band was evident in the chloroform solution but was especially striking in the dioxane solution.

In an experiment in which more concentrated solutions were used, phosphorus tribromide was added in equimolar quantity to a solution of α-benzamidoisobutyric acid in dry dioxane. The precipitate which separated was collected on a funnel and washed twice quickly with small quantities of dioxane with minimum exposure to air. A five per cent. solution of this material in chloroform was prepared immediately and its infrared absorption spectrum obtained within an hour. The spectrum (Table I, spectrum 4) still showed the strong bands at 5.28 μ (1894 cm.$^{-1}$) and 6.10 μ (1639 cm.$^{-1}$) observed in the preceding experiments but now showed in addition a band of about equal intensity at 5.75 μ (1739 cm.$^{-1}$) attributable to the expected hydrolysis product, α-benzamidoisobutyric acid (Table I, spectrum 1).

## Spectral Interpretations

On the basis of these infrared absorption spectra the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been assigned the formula 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide (II) instead of α-benzamidoisobutyryl bromide (I) for the following reasons:

(1) An extensive study of the infrared absorption of monosubstituted amides[6] has shown that this grouping almost without exception gives rise to two bands at about 6.0 and 6.6 μ (1667 and 1515 cm.$^{-1}$). With α-benzamidoisobutyric acid the bands due to the amide linkage are at 6.01 and 6.56 μ (1664 and 1524 cm.$^{-1}$). Two bands near these same positions would be expected from the amide grouping in the α-benzamidoisobutyryl bromide structure. The absence of the band in the 6.6 μ (1515 cm.$^{-1}$) region from the spectra under consideration furnishes strong evidence against the α-benzamidoisobutyryl bromide formula.

(2) The infrared absorption spectra of acetyl chloride, acetyl bromide and α-toluyl chloride[7] show strong bands respectively as follows: 5.52, 5.52 and 5.54 μ (1812, 1812 and 1805 cm.$^{-1}$). The acid bromide grouping of α-benzamidoisobutyryl bromide might be expected to give rise to a band in this region (5.5–5.65 μ) (1818–1770 cm.$^{-1}$). The absence of such a band in the

(1) Fischer, *Ber.*, **38**, 612 (1905).

(2) Mohr, *Ber.*, **42**, 252 (1909); *J. prakt. Chem.*, [2] **81**, 49, 322, 473 (1910).

(3) Neher, Wettstein and Miescher, *Helv. Chim. Acta*, **29**, 1815 (1946).

(4) Hunter, Hinman and Carter, "Methyl Benzylpseudopenicillinate" in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(5) Cornforth, "Oxazoles and Oxazolones," *ibid.*

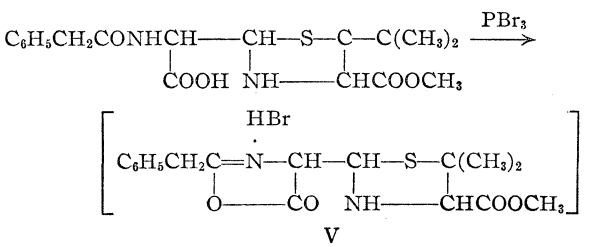
(6) Thompson, Brattain, Randall and Rasmussen, "Infrared Spectroscopic Studies on the Structure of Penicillin" in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949.

(7) O. S. R. D., Penicillin Program, Randall and Fowler, R2, Chart VII (U. S. Office of Publication Board, PB L80195).

spectra observed for the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide is evidence against the acid bromide structure. The band near 5.30 μ (1887 cm.$^{-1}$) observed with this reaction product is definitely outside the range found in known acid halides.

(3) Triamylamine hydrochloride and an N-alkyldialkylketimine hydrochloride[8] showed a broad general absorption in the 4 μ (2500 cm.$^{-1}$) region attributable to the $^{+}$NH grouping. The 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide (I) would be expected to show this absorption. α-Benzamidoisobutyryl bromide (II) would not be expected to show this absorption. Thus the presence of the 4μ (2500 cm.$^{-1}$) band in the spectra observed might be considered evidence favoring the oxazolone hydrobromide formula. However, absorption due to dissolved hydrogen bromide[9] would appear at the 4 μ (2500 cm.$^{-1}$) position and have a similar appearance. Since some hydrogen bromide could have been present in each case where a 4 μ band appeared, evidence for an $^{+}$NH group is not without question.

During a study of the reaction of β-methyl benzylpenicilloate with phosphorus tribromide, collaborators from the University of Michigan and the Upjohn Company[4] determined the infrared absorption of a solution of the penicilloate and phosphorus tribromide in carefully dried dioxane immediately after combination and then again at short intervals. The oxazolone hydrobromide shown in the accompanying equation was considered as a more or less transitory (V) intermediate in the reaction.



V

In the spectrum obtained immediately after combination, and to a decreasing degree in later spectra, bands at 5.60 and 5.98 μ (1786 and 1672 cm.$^{-1}$) not present in the β-methyl benzylpenicilloate or phosphorus tribromide were noted. Since these bands were at 5.60 μ (1786 cm.$^{-1}$) and 5.98 μ (1672 cm.$^{-1}$) instead of at 5.28 μ (1899 cm.$^{-1}$) and 6.10 μ (1639 cm.$^{-1}$) as observed with the 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide, it is difficult to see how the bands at 5.60 and 5.98 μ (1768 and 1672 cm.$^{-1}$) could be assigned to an oxazolone hydrobromide and, consequently, the infrared evidence may be considered as contraindicating the formation of a transitory oxazolone hydrobromide.

(8) O. S. R. D., Penicillin Program, Shell Development Co., Sh 7, Figure 44 (U. S. Office of Publication Board, PB L80258).

(9) Plyler and Williams, *Phys. Rev.*, **49**, 215 (1936).

## Experimental

**2-Phenyl-4,4-dimethyl-5(4)-oxazolone Hydrobromide.**—**A. In Chloroform.**—A solution of 0.30 g. of α-benzamidoisobutyric acid,[10] m. p. 201.4–202.4°, in 15 ml. of chloroform was treated with 0.40 g. of phosphorus tribromide. After the solution had stood for thirty minutes its infrared absorption was determined (Table I (2)).

**B. In Dioxane.**—To 0.4 g. of α-benzamidoisobutyric acid in 35 ml. of dioxane was added 1.30 g. of phosphorus tribromide. The solution was allowed to stand for ten minutes before determining its infrared absorption (Table I (3)).

**C. Isolated.**—To a solution of 1.03 g. of α-benzamidoisobutyric acid in 25 ml. of dioxane, freshly distilled over sodium, was added 0.37 ml. of phosphorus tribromide. After the solution had stood for about three minutes, crystals began separating. The solution was allowed to stand at room temperature for ten minutes and was then cooled in an ice-bath. The precipitate was collected on a filter and washed twice with dry dioxane with a minimum of contact with air. The infrared absorption of a solution (5%) of this material in chloroform was obtained without delay (Table I (4)). Most of the crystalline material was dried over phosphorus pentoxide at 56° (0.05 mm.) for two and one-half hours. Another sample was placed immediately on a melting block under a cover glass and melted at 153–158° with decomposition.

The bromide content of the dried product was determined shortly by Volhard titration.

*Anal.* Calcd. for $C_{11}H_{12}NO_2Br$: Br, 29.58. Found: Br, 29.0, 28.8.

Two factors may be responsible for the low bromine content: (1) loss of hydrogen bromide; (2) absorption of water.

TABLE I

INFRARED ABSORPTION SPECTRA

1. α-Benzamidoisobutyric acid, 0.15 mm. < 1% soln. in $CHCl_3$.
2. Same + $PBr_3$ (equimolar), 0.15 mm. 2% soln. in $CHCl_3$.
3. Same + $PBr_3$ (equimolar), 0.15 mm. 2% soln. in dioxane.
4. Ppt. from dioxane soln. of α-benzamidoisobutyric acid + $PBr_3$ redissolved in $CHCl_3$, 0.15 mm. 5% soln.

(Wave lengths in μ; intensity (figures in parentheses) in units of 10% absorption; S = solvent interference; concentrations of solutions are on a wt./vol. basis.)

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| 5.78(1) | 3.2–3.4 S | 3.2–3.7 S | 3.2–3.4 S |
| 6.01(1) | ~4(7) | 5.38(4) | 4(6) |
| ~6.56(1) | 5.28(3) | ~5.68(3) | 5.27(4) |
| No other | 6.10(6) | 6.07(8) | 5.75(8) |
| bands ob- | 6.24(1) | | |
| served be- | 6.31(1) | 6.25(2) | 6.10(10) |
| cause of | 6.86(2) | | 6.22(2) |
| diluteness | 7.24(3) | 6.32(1) | 6.31(1) |
| of solution | 7.37(2) | | |
| | 7.44(2) | >6.7 S | 6.58(6) |
| | 7.56(1) | | |
| | 7.67(1) | | 7.20(1) |
| | 8.1–8.4 S | | |
| | 8.97(5) | | 7.33(5) |
| | 9.26(3) | | |
| | 9.93(7) | | 7.43(2) |
| | 10.39(4) | | |
| | 11.74(4) | | Discontinued |
| | >12 S | | |

(10) Mohr and Geis, *Ber.*, **41**, 798 (1908).

## Summary

On the basis of its infrared absorption spectrum the reaction product of α-benzamidoisobutyric acid with phosphorus tribromide has been assigned the structure, 2-phenyl-4,4-dimethyl-5(4)-oxazolone hydrobromide rather than α-benzamidoisobutyryl bromide. This is the first reported instance of an infrared absorption spectrum of a compound of this type.

Since the infrared absorption observed in the reaction of β-methyl benzylpenicilloate with phosphorus tribromide is at distinct variance with that of the above oxazolone hydrobromide, it would appear that this later reaction does not involve an oxazolone hydrobromide.


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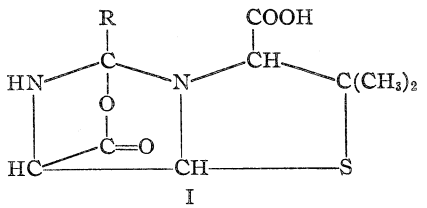
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# Assignment of Amide Structures to the Supposed 2,3-Dihydro-2-benzimidazolols and their Acylation Products[1]

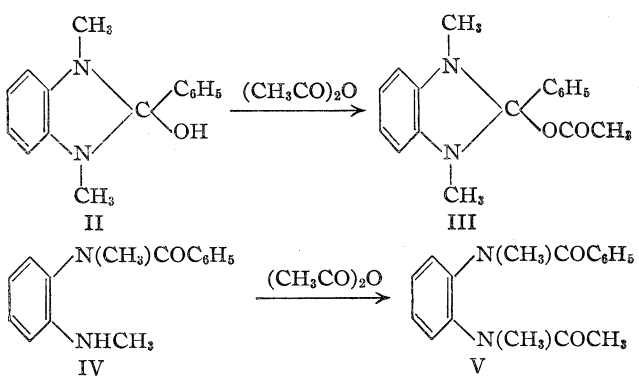
BY CURTIS W. SMITH, ROBERT S. RASMUSSEN AND SEAVER A. BALLARD

One of the structures proposed for penicillin which had received much consideration before acceptance of the fused thiazolidine-β-lactam formula is shown as formula I.



I

As a part of the general program of examining the infrared absorption spectra of model compounds as nearly like the most plausible structures for penicillin as possible, the infrared absorption was obtained of a compound previously presumed from chemical evidence to be 1,3-dimethyl-2-phenyl-2,3-dihydro-2-benzimidazolol acetate[2] (III). However, when the infrared absorption spectrum of this compound was obtained in these laboratories, it was indicated that instead of the ester grouping shown in formula III there existed amide linkages which would be more consistent with the isomeric formula V, namely, N-acetyl-N′-benzoyl-N,N′-dimethyl-*o*-phenylenediamine. The compound previously thought to have structure III and now indicated as having structure V had been first prepared in the laboratories of Eli Lilly and Company,[2] by acetylation of a compound thought to be 1,3-dimethyl-2-phenyl-2,3-dihydro-2-benzimidazolol (II). The infrared absorption of this parent compound II or IV gave strong indication of the presence of an amide group and was thus in agreement with structure IV and contrary to structure II.



II III

IV V

The first example of a compound thought to be of type II was prepared by Niementowski[3] in 1887. Subsequently Fischer and Romer[4] gave a serious and lengthy consideration to the structures of these compounds. The literature now contains a large number of compounds assigned the benzimidazolol structure.

The following discussion is divided into four sections. First is a critique of the literature designed to show the fallacy of some of the steps which led the earlier workers to favor the benzimidazolol formula (II) instead of the amide formula (IV). Second is the presentation of evidence definitely establishing for the first time the diamide structure of a compound N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XV), similar to V. Thus the benzimidazolol ester formula (III) has been eliminated as a possibility for this type of compound. Third is the presentation of new evidence strongly favoring the amide structure (IV) rather than the benzimidazolol structure (II) for a compound, N-acetyl-N,N′-dimethyl-4-methyl-1,2-phenylenediamine (XIII). Fourth is a short section on the stability of benzimidazolium hydroxides.

## I. Critique of the Literature on the Structure of 2-Benzimidazolols

The arguments for the benzimidazolol, structure

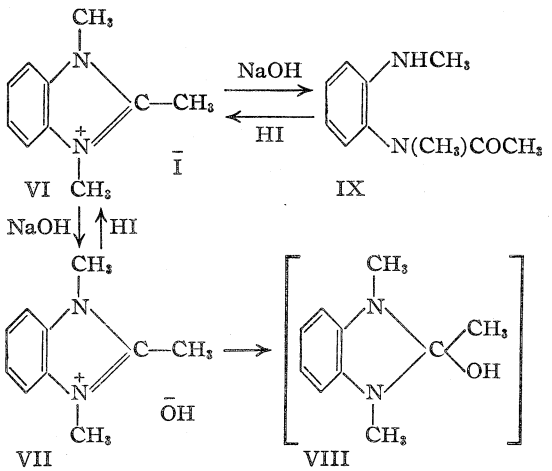
(1) The work discussed in this paper was carried out at Shell Development Company, during a study of the structure of penicillin, under contract with the Office of Scientific Research and Development (O. S. R. D.). *Cf. Science*, **105**, 653 (1947).

(2) O. S. R. D., Penicillin Program, Eli Lilly and Company, L6, 6; 11, 14 (U. S. Office of Publication Board, PB/L80033 and 80037).

(3) Niementowski, *Ber.*, **20**, 1886 (1887).

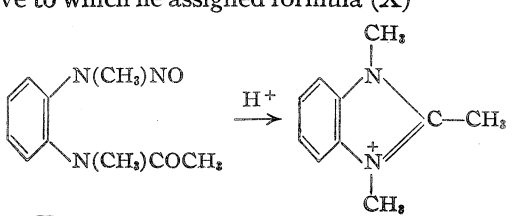
(4) Fischer and Romer, *J. prakt. Chem.*, [2] **73**, 419 (1906).

VIII, seem to have been developed[3,4] in the literature on the following assumptions. The compound had been synthesized from the benzimidazolium iodide by reaction with caustic and could be reverted to the benzimidazolium salt on treatment in the cold with acid. Therefore, it seemed logical to assume that the cyclic structure would be retained. Furthermore, it was thought that inasmuch as the product was not strongly basic and was volatile with steam, it was not the corresponding quaternary hydroxide (VII) but rather had been converted to the benzimidazolol form (VIII).




When the open amide form (IX) was eventually considered, it seemed less likely to the original investigators that it would be converted to the quaternary salt (VI) on treatment with acid. And yet in the same paper[4] it was assumed that the amide form (IX) could not be separated in pure condition because it was so readily converted to the benzimidazolol (VIII). It is readily apparent that these two assumptions are irreconcilable, for if both the conversion of the amide (IX) to the benzimidazolol (VIII) and the conversion of the benzimidazolol (VIII) to the quaternary salt (VI) are fast and readily carried out then the over-all reaction (IX to VI) must be rapid and simple.

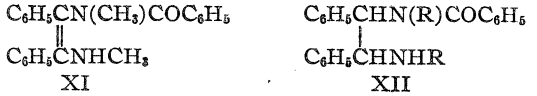
Several observations reported in the literature furnish corroborative evidence for the conversion of the amide form (IX) to the benzimidazolium salt (VI). Fischer[4] found that treatment of N-acetyl-N,N′-dimethyl-*o*-phenylenediamine (IX), thought to be 1,2,3-trimethyl-2,3-dihydro-2-benzimidazolol (VIII), with cold nitrous acid involving minimal contact with acid gave a nitroso derivative to which he assigned formula (X)




X VI

This compound was hydrolyzed readily with acid to give the benzimidazolium salt (VI). If Fischer's structure for the nitroso derivative is correct, as it appears to be, then it is obvious that conversion of the amide structure to the quaternary salt is a simple and feasible reaction.

If we accept the open amide structure postulated for the derivatives of lophin[4] (XI) and amarin[5] (XII) corresponding to structure (IX) then the ready conversion of the amide form (IX) to the corresponding benzimidazolium salt in acid has a ready parallel, for this type of transformation is known to occur with these compounds.

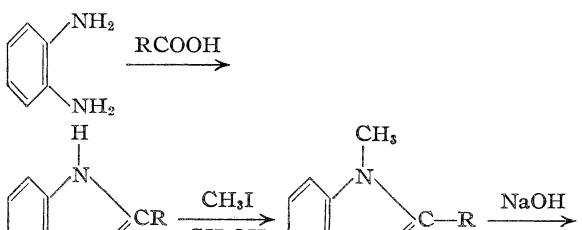



It is of interest to note that when hydrolysis products of lophonium salts were first obtained, they were assigned the carbinol structure,[6] (related to structure (VIII)), but when diacyl derivatives were prepared both these and the monoacyl derivatives (XI and XII) were assigned the amide structure.

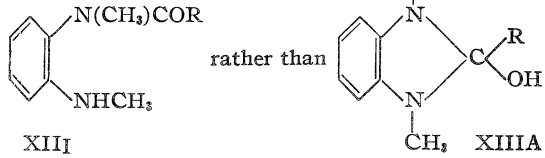
It is also of interest to note that the amide structure has been assigned[7] N-benzoyl-N,N′-diphenyl-*o*-phenylenediamine, and that the diacetyl derivative of N,N′-diphenyl-*o*-phenylenediamine has been assigned[8] the diamide structure. However, no proof of structure was given in either instance.

## II. Proof of Structure for N-Acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine

In order to establish the diamide structure of N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XV) and consequently to eliminate the benzimidazolol ester structure the following series of reactions was carried out.



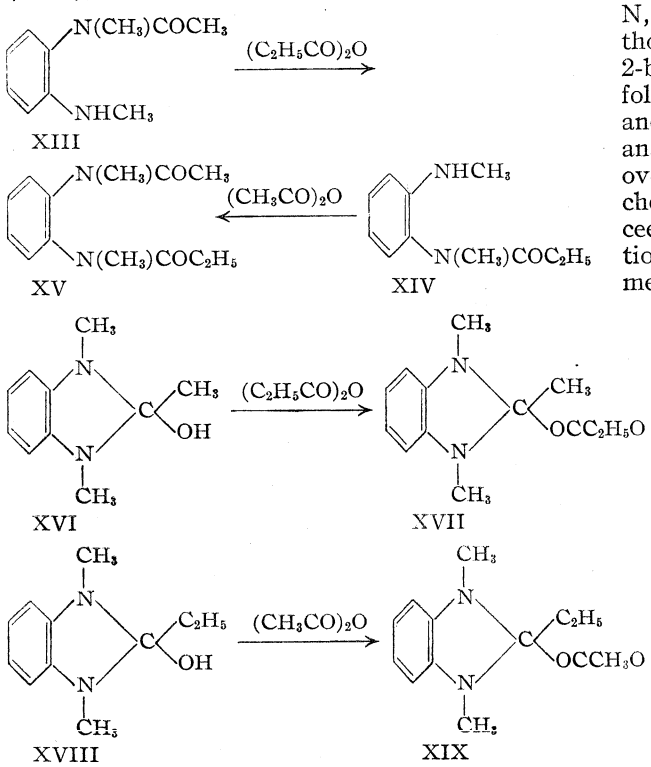

R = $CH_3$ and $C_2H_5$




(5) Japp and Moir, *J. Chem. Soc.*, **77**, 619 (1900).
(6) Japp and Davidson, *ibid.*, **67**, 33 (1895).
(7) Chapman and Perott, *ibid.*, 1775 (1932).
(8) Clemo, Perkin and Robinson, *ibid.*, **125**, 1751 (1924).

The reactions follow closely those outlined by workers at Eli Lilly and Company.[2] Starting with *o*-phenylenediamine and acetic acid 2-methylbenzimidazole was readily obtained by the method of Phillips.[9] Treatment of this material with methyl iodide gave the corresponding 1,2,3-trimethylbenzimidazolium iodide which was hydrolyzed with strong sodium hydroxide to give N-acetyl-N,N′-dimethyl-*o*-phenylenediamine (XIII). Starting with *o*-phenylenediamine and propionic acid the same series of reactions was carried out and there was obtained 2-ethylbenzimidazole, 1,3-dimethyl-2-ethylbenzimidazolium iodide and finally N-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XIV)

It can readily be seen that treatment of N-acetyl-N,N′-dimethyl-*o*-phenylenediamine (XIII) with propionic anhydride or of N-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XIV) with acetic anhydride should give the same compound, N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XV). However, if, as it had been previously thought, the products had the benzimidazolol structures, (XVI) and (XVIII), then the products of acylation, compounds (XVII) and (XIX), should be different.




These acylations were carried out by treatment with the respective acid anhydrides in pyridine at room temperature according to the method first used by Eli Lilly and Company.[2]

The two products had the same melting point, gave no depression of melting point in a mixture and gave identical infrared absorption spectra. From these results the structure of this compound has been considered established as N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (XV) and not as the benzimidazolol ester (XVII or XIX). With this structure established, it would seem logical that the product prior to acylation should have the amide structure (XIII) and not the benzimidazolol structure (XVI).

However, in consideration of the possibility that the conditions for the acylation of the supposed benzimidazolol might result in the opening of the ring and formation of the diamide, it is to be pointed out that the conditions for the acylation were quite mild, *i. e.*, acid anhydride in pyridine at room temperature followed by recrystallization from benzene–petroleum ether. These conditions were at least as mild as those by which the monoacetylated product is formed, *i. e.*, hot strong alkali on the benzimidazolium salt or acid anhydride on the N,N′-dialkyl-*o*-phenylenediamine.

## III. Structural Evidence for N-Acetyl-N,N′-dimethyl-4-methyl-1,2-phenylenediamine

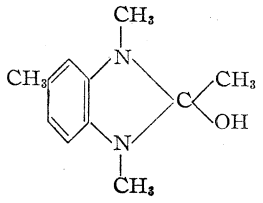
Niementowski[3] who first prepared N-acetyl-N,N′-dimethyl-4-methyl-1,2-phenylenediamine thought it to be 1,2,3,5-tetramethyl-2,3-dihydro-2-benzimidazolol. He purified it by distillation followed by recrystallization from aqueous ethanol and observed that in spite of the fact that the analysis was satisfactory the compound melted over a range, 115–135°. Fischer and Romer[4] checked these results and extending the study succeeded in separating this material into two fractions: One on recrystallization from ligroin melted at 148–150°; the other on recrystallization from aqueous ethanol or slow sublimation melted at 166–167°. However, they believed these to be two crystalline modifications of the benzimidazolol (XX).

If it could be proved that these two isomers isolated by Fischer and Romer[4] were really structural isomers as shown by (XXA) and (XXB) then the amide nature of the product would be established.

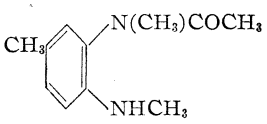
To gain additional information concerning these isomers, an attempt was made to repeat the work of Fischer and Romer.[4] The results were in agreement in that the first product gave a satisfactory analysis in spite of the fact that it melted at 115–125° and that a good yield of isomer which melted at 166–167° was obtained upon recrystallization from methanol.

Propionylation of the purified isomer which melted at 166–166.5° gave after evaporation of the excess liquid reagents a highly crystalline residue. One recrystallization from petroleum ether gave an 83% yield of the propionyl derivative which melted at 94.5–95.5°. It would appear that a uniform product had been obtained. Similar

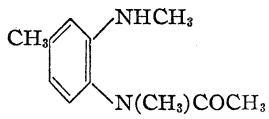
(9) Phillips, *J. Chem. Soc.*, 2393 (1928).



XX



XXA



XXB

propionylation of the mixture of isomers which melted at 115–125° gave after removal of the liquid reagents a sirupy residue which could be converted to soft crystals only with difficulty. Recrystallization of this material gave a 63% yield of a propionyl derivative which melted at 75.3–78.3°. A mixture of this material and that from the preceding experiment (m. p. 94.5–95.5°) melted over a seven-degree range, 76–83°. The difference in the behavior of these two fractions on propionylation is taken as an indication that the fraction melting at 115–125° is a mixture of structural isomers (XXA and XXB) of the amide form.

## IV. Stability of Benzimidazolium Hydroxides

During the course of this work it has been found that benzimidazolium hydroxides are quite stable in the absence of excess soluble base. 1,3-Dimethyl-2-ethylbenzimidazolium hydroxide, prepared from the corresponding iodide by treatment with silver oxide, was not destroyed on standing in aqueous solution for a week followed by heating at 90° for two hours. This stability was demonstrated by the fact that the solution remained strongly alkaline, the ultraviolet absorption spectrum remained constant and the hydrolysis product, N,N′-dimethyl-N-propionyl-*o*-phenylenediamine, which is sparingly soluble in water, was not precipitated.

Tinkler[10] observed that an aqueous solution of the supposed 1,3-dimethyl-2,3-dihydro-2-benzimidazolol became strongly basic on standing and that its ultraviolet absorption spectrum changed from that of the "benzimidazolol" to that of benzimidazolium salt. No such change was observed by the present authors with the N-propionyl-N,N′-dimethyl-*o*-phenylenediamine in alcohol or aqueous solution. These solutions remained completely neutral and gave a constant ultraviolet absorption spectrum even after standing for one week. In the light of present knowledge, no explanation of Tinkler's observations presents itself.

**Acknowledgment.**—The assistance of Mr. Douglas G. Norton and Mr. Lloyd J. Mitchell in carrying out certain preparations is gratefully acknowledged.

(10) Tinkler, *J. Chem. Soc.*, **101**, 1245 (1912).

## Experimental

### A. N-Acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine

**2-Ethylbenzimidazole.**—This material was prepared from *o*-phenylenediamine with propionic acid according to the method of Phillips.[9] The 2-ethylbenzimidazole melted at 172–173° after recrystallization from 50% ethanol.

*Anal.* Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.67, 66.88; H, 7.77, 7.80.

**1,3-Dimethyl-2-ethylbenzimidazolium Iodide.**—A mixture of 40 g. of crude 2-ethylbenzimidazole, 80 g. of methyl iodide and 44 ml. of methanol was heated in sealed tubes at 150° for ten hours. The product was dissolved in 200 ml. of hot methanol and then 200 ml. of ether was added. Cooling the solution caused the separation of 50.2 g. (60% yield) of material which melted at 168–170°. A recrystallization of 40.2 g. of this material from 250 ml. of absolute alcohol involving treatment with charcoal gave 21 g. of crystals which melted at 170.5–172°. Addition of ether to the filtrate caused the separation of 11 g. of product which melted at 172.5–173°. Additional recrystallizations gave 1,3-dimethyl-2-ethylbenzimidazolium iodide which melted at 173–173.5°.

*Anal.* Calcd. for $C_{11}H_{15}N_2I$: I, 42.00. Found: I, 42.1, 41.7.

**N-Propionyl-N,N′-dimethyl-*o*-phenylenediamine.**—1,3-Dimethyl-2-ethylbenzimidazolium iodide, 23 g., was hydrolyzed with 46 g. of potassium hydroxide and 230 ml. of water at reflux for ninety minutes. The cooled solution was extracted with three 50-ml. portions of benzene. The extract was dried, concentrated to about 35 ml., and diluted with 60 ml. of petroleum ether. Cooling the solution caused the separation of 7 g. (48% yield) of crystals which melted at 160–162°. Recrystallization from a mixture of 50 ml. of benzene and 50 ml. of petroleum ether involving treatment with charcoal and then from 20 ml. of carbon tetrachloride gave 4.8 g. of N-propionyl-N,N′-dimethyl-*o*-phenylenediamine which melted at 161–162.2°.

*Anal.* Calcd. for $C_{11}H_{15}N_2O$: C, 69.08; H, 7.91. Found: C, 68.56, 68.61; H, 8.32, 8.34.

**N-Acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (By Acetylation).**—A solution of 1.23 g. (0.0066 mole) of crude N-propionyl-N,N′-dimethyl-*o*-phenylenediamine, m. p. 158–160°, in 13.5 g. of pyridine and 5.4 g. (0.053 mole) of acetic anhydride was allowed to stand at room temperature for seventy-two hours. Removal of liquid reagents under reduced pressure left a crystalline mass which melted at 120.5–121.5°. One recrystallization from a mixture of benzene and petroleum ether treated with charcoal gave 0.93 g. (62% yield) of N′-acetyl-N-propionyl-N,N′-dimethyl-*o*-phenylenediamine which melted at 121–121.5°. A mixture of this material with that subsequently obtained upon propionylation of N,N′-dimethyl-N-acetyl-*o*-phenylenediamine melted at 121–121.5°.

**N-Acetyl-N,N′-dimethyl-*o*-phenylenediamine.**—This material, m. p. 163–164°, was prepared according to the procedure outlined by workers at Eli Lilly and Company,[2] which is very similar to that just described for N,N′-dimethyl-N-propionyl-*o*-phenylenediamine. A mixture with a sample furnished by them melted at 163–164°.

**N-Acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine (By Propionylation).**—A solution of 1 g. (0.0056 mole) of N-acetyl-N,N′-dimethyl-*o*-phenylenediamine, 14.6 g. of pyridine and 5.85 g. (0.045 mole) of propionic anhydride was allowed to stand at room temperature for seventy-two hours. The solution was concentrated under reduced pressure (3 mm.) to a crystalline mass which melted at 121–121.5°. One recrystallization from a mixture of benzene and petroleum ether gave 1.06 g. of N-acetyl-N′-propionyl-N,N′-dimethyl-*o*-phenylenediamine which melted at 121–121.5°. Additional recrystallizations did not alter the melting point.

*Anal.* Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.67, 66.88; H, 7.77, 7.80.

### B. N-Acetyl-N,N'-dimethyl-4-methyl-1,2-phenylenediamine

**Hydrolysis of 1,2,3,5-Tetramethylbenzimidazolium Iodide.**—This procedure follows that of Fischer.[6] A mixture of 55 g. of 1,2,3,5-tetramethylbenzimidazolium iodide, 70 g. of potassium hydroxide and 210 g. of water was heated on a steam-cone for one hour. The mixture was cooled and the white solid which separated was collected on a filter. After drying in air overnight this material weighed 45 g. and melted from 115–135°. One recrystallization from ethanol and water gave 40 g. of crystalline material which melted at 115–125°. In agreement with the results of Niementowski[3] and Fischer and Romer[4] this material was found to give a satisfactory analysis in spite of the wide range of its melting point. These results have been interpreted as favoring the presence of isomers, *i. e.*, N-acetyl-N,N'-dimethyl-4-methyl-1,2-phenylenediamine and the N'-acetyl isomer, rather than impurity.

*Anal.* Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39. Found: C, 68.9, 68.9; H, 8.3, 8.4.

In consideration of the possibility that the fraction melting at 115–125° contained some impurity other than a mixture of amide forms, there exist three experimental observations indicating that such is not the case: (1) satisfactory elementary analysis by three independent investigators; (2) infrared absorption spectrum of the fraction melting at 115–125° shows no evidence of impurity; (3) elementary analysis of the propionylation product, reported subsequently, was in close agreement with the theoretical values even though the product melted over a three-degree range.

This material was dissolved in 225 ml. of 95% ethanol and 25 ml. of water was added. Cooling the solution caused the separation of 7.5 g. of crystals which were collected from solution A by filtration and melted at 165–165.6°. After three additional crystallizations from ethanol, the N-acetyl-N,N'-dimethyl-4-methyl-1,2-phenylenediamine melted sharply at 166–166.5°.

*Anal.* Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.7, 68.6; H, 8.1, 8.3; N, 14.0, 14.2.

Recrystallization of this material from petroleum ether did not change the melting point.

Evaporation of the solvent from solution A to a low volume followed by cooling gave 23 g. of crystalline material which melted at 163.5–167°. The solvent was removed from the residue to leave 9 g. of material which was taken up in petroleum ether. Successive cooling, concentration and cooling gave the following fractions: 1.6 g., m. p. 148–152°; 1.7 g., m. p. 120–125°; 2.0 g., m. p. 124–130°; 3.0 g., m. p. 100–110°. The first fraction was recrystallized from petroleum ether and gave 1.1 g., m. p. 160.0–162.8°. The second and third fractions were crystallized several times from petroleum ether with some elevation of melting point. Finally a sample which melted at 137.5–138° was analyzed.

*Anal.* Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39. Found: C, 68.7; H, 8.2.

**Propionylation of Hydrolysis Products of 1,2,3,5-Tetramethylbenzimidazolium Iodide.**—One gram of the isomer, m. p. 166–166.5°, from the above experiment was placed in a glass-stoppered flask with 15 g. of pyridine and 6 g. of propionic anhydride and allowed to stand at room temperature for four days. The liquid materials were removed under reduced pressure. The crystalline residue was taken up in 60 ml. of boiling petroleum ether. After the hot solution had been treated with a little "Norite" it was cooled in ice. The white crystalline material which separated weighed 1 g. (83% yield) and melted at 94.5–95.5°. Another recrystallization from petroleum ether gave 0.75 g. of material, which melted at 95.5–96.3°.

*Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12. Found: C, 67.9, 67.9; H, 7.9, 8.2.

One gram of the mixture of isomers, m. p. 115–125°, from the previous hydrolysis experiment was placed in a glass-stoppered flask with 15 g. of pyridine and 6 g. of propionic anhydride and allowed to stand at room temperature for four days. Liquids were removed by stripping the product under reduced pressure. The sirupy residue was taken up in 60 ml. of boiling petroleum ether. The hot solution was treated with a little "Norite" and filtered. Cooling the filtrate in ice caused the separation of 0.8 g. (67% yield) of white crystalline material which melted at 75.3–78.3°. Recrystallization from petroleum ether gave 0.5 g. of product which melted at 75.5–78.3°.

*Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12. Found: C, 67.7, 67.6; H, 8.1, 8.2.

A mixture of this material and that from the preceding experiment which melted at 94.5–95.5°, melted at about 76–83°.

### C. 1,3-Dimethyl-2-ethylbenzimidazolium Hydroxide

A solution of 1,3-dimethyl-2-ethylbenzimidazolium iodide, 0.5 g. (0.00167 mole) in 60 ml. of water, was treated with silver oxide. (A solution of 0.425 g. (0.0025 mole) of silver nitrate in 2.1 ml. of water was treated with 0.112 g. (0.0028 mole) of sodium hydroxide in 1 ml. of water. The silver oxide was collected on a filter and washed well with water.) The silver iodide and slight excess of silver oxide were removed by filtration. The filtrate was strongly alkaline and gave a negative test for iodide ion. The ultraviolet absorption spectra of the solution shortly after preparation, and again after standing at room temperature for one week followed by additional heating at 90° for two hours were identical. The solution was still strongly alkaline after this heating had been completed. The fact that no material separated from this solution on cooling indicated that only a very small amount, if any, of N-propionyl-N,N'-dimethyl-*o*-phenylenediamine could have been formed since this material is insoluble in water.

### Interpretation of Infrared Spectra

**I. N-Acetyl-N'-propionyl-N,N'-dimethyl-*o*-phenylenediamine.**—The spectrum of this material as a 5% (wt./vol.) solution in chloroform showed one strong band at 6.04 $\mu$ (1656 cm.$^{-1}$) attributable to the amide carbonyl and a weaker band at 6.25 $\mu$ (1600 cm.$^{-1}$) attributable to the phenyl ring but with increased intensity due to the fact that the phenyl ring is attached to an amine nitrogen atom. If this compound were an ester of a benzimidazolol as this type of compound had been previously thought to be, it would be expected to show a strong band in the double bond region near 5.75 $\mu$ (1739 cm.$^{-1}$) and no band near 6.0 $\mu$ (1667 cm.$^{-1}$).

**II. N-Acetyl-N'-benzoyl-N,N'-dimethyl-*o*-phenylenediamine.**—The spectrum of this material (10% (wt./vol.) solution in chloroform) was very similar to that of the previous compound, I, but exhibited the additional weak band near 6.30 $\mu$ (1587 cm.$^{-1}$) arising from the benzoyl group.

**III. N-Acetyl-N,N'-dimethyl-*o*-phenylenediamine.**—The spectrum of this material (5% (wt./vol.) solution in chloroform) showed a weak band near 3.0 $\mu$ (3333 cm.$^{-1}$) attributable to —NH and a strong band at 6.07 $\mu$ (1647 cm.$^{-1}$) attributable to amide carbonyl. Weaker bands at 6.22 $\mu$ and 6.59 $\mu$ (1608 cm.$^{-1}$ and 1517 cm.$^{-1}$) are ascribable to the phenyl ring. This compound had been previously thought to be 1,2,3-trimethyl-2,3-dihydro-2-benzimidazolol. The absorption to be expected from such a compound would be a strong band near 3.0 $\mu$ (3333 cm.$^{-1}$) and only weak to moderate absorption in the double-bond region (5.5–6.4 $\mu$) (1818–1562 cm.$^{-1}$) due to the ring system, as indicated by studies on simpler benzimidazole derivatives.

**IV. N-Benzoyl-N,N'-dimethyl-*o*-phenylenediamine.**—The spectrum of a 3% (wt./vol.) solution of this material in carbon tetrachloride was very similar to that of the previous compound III, except that again a 6.32 $\mu$ (1582 cm.$^{-1}$) band was present, due to the benzoyl group.

The spectra reported in Table I were obtained with a 0.15 mm. cell width. The wave lengths are in "$\mu$." The intensities (figures in parentheses) are expressed in units of 10% absorption. The letter "S" represents solvent absorption.

TABLE I

| I | II | III | IV |
|---|---|---|---|
| 2.90(1) | ~2.90(1) | 2.93(3) | 2.95(2) |
| 3.2–3.4 S | 3.2–3.4 S | 3.2–3.4 S | 3.38(1) |
| 6.04(9) | 6.06(10) | 6.07(10) | 6.08(6) |
| 6.25(3) | 6.24(3) | 6.21(4) | 6.20(3) |
| 6.67(5) | 6.31(2) | 6.58(8) | 6.32(2) |
| 6.85(3) | 6.66(8) | 7.02(6) | 6.56(5) |
| 7.24(7) | ~7.0(8) | 7.22(8) | 6.78(1) |
| 7.38(3) | 7.25(9) | 7.38(4) | 6.90(1) |
| 7.65(1) | 7.38(4) | 7.57(5) | 7.02(2) |
| 7.75(1) | 7.63(5) | 7.71(6) | 7.25(4) |
| 8.0–8.4 S | 7.9(2) | 8.0–8.4 S | 7.37(3) |
| 8.76(4) | 8.0–8.4 S | 8.54(4) | 7.56(3) |
| 9.02(1) | 8.45(1) | 8.75(8) | 7.67(2) |
| 9.27(4) | 8.77(3) | 9.01(1) | 7.98(4) |
| 9.57(2) | 8.88(2) | 9.26(3) | 8.54(3) |
| 9.98(2) | 9.08(2) | 9.43(2) | 8.97(2) |
| 10.20(3) | 9.26(4) | 9.63(4) | 9.12(2) |
| >11.5 S | 9.56(1) | 10.23(2) | 9.35(1) |
| | 9.74(2) | >11.5 S | 9.59(1) |
| | 9.91(2) | | 9.70(1) |
| | 10.17(3) | | 9.93(2) |
| | >11.5 S | | 10.81(1) |
| | | | 11.40(1) |
| | | | >12 S |


## Summary

Spectroscopic and chemical data are presented which furnish strong evidence that the hydrolysis product of a 1,3-dialkylbenzimidazolium salt has an amide structure, N-acyl-N,N′-dialkyl-*o*-phenylenediamine instead of a 1,2,3-trialkyl-2,3-dihydro-2-benzimidazolol structure as previously supposed.

The product derived by subsequent acylation has been established as a diamide, N,N′-diacyl-N,N′-dialkyl-*o*-phenylenediamine rather than the previously supposed 1,2,3-trialkyl-2,3-dihydro-2-benzimidazolol ester.

In view of this disagreement, a critique of prior literature has been presented.

Finally it has been shown that the benzimidazolium hydroxides are stable in aqueous or alcohol solution in the absence of excess soluble base.


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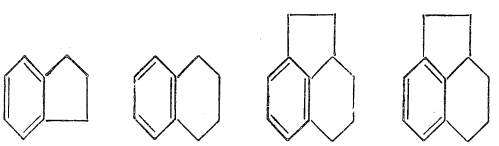
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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Tetrahydroacenaphthene and the Mills–Nixon Effect

BY WILLIAM S. JOHNSON AND HOWARD J. GLENN[1]

The original postulate of Mills and Nixon[2]—that the double bonds of the hydrindene and tetralin molecules are stabilized in the forms I and II due to steric effects exerted on the benzenoid nucleus by the fused alicyclic rings—although not literally acceptable in view of current concepts, nevertheless leads to the suggestion that molecules containing these ring structures might be expected to exhibit behavior attributable to steric inhibition of resonance in which the forms I and II contribute more than the alternate (Kekulé) canonical forms to the electronic state of the molecule. Since all attempts thus far to detect any marked degree of such resonance inhibition have failed, it occurred to us that such an effect might be more recognizable with a molecule such as tetrahydroacenaphthene (IIIa or b) in which the tetralin molecule is superimposed on the hydrindene structure in such a way that the postulated straining effect of the exocyclic rings is reinforced.[3] Thus if this strain were sufficient to render the structure IIIb enough higher in energy than IIIa, it might be expected that tetrahydroacenaphthene and its derivatives would behave chemically more like IIIa than a hybrid of IIIa and IIIb. With a view to studying this hypothesis, we have prepared tetrahydroacenaphthene and certain derivatives, and have made preliminary observation of some of their properties.



I II IIIa IIIb

Tetrahydroacenaphthene was readily secured in 95% yield by hydrogenation of acenaphthene over Raney nickel catalyst. The difficulty in stopping the reduction at the tetrahydro stage, which has been the experience of previous workers,[4] was eliminated by limiting the amount of hydrogen available in the bomb to the calculated quantity. The reduction was thus simply carried out by shaking until all of the hydrogen was absorbed.[5] The in-

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(2) Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

(3) This hypothesis involves the assumption—justified only on the basis of examination of crude molecular models—that the mutual fusion of the five-six-membered alicyclic rings of tetrahydroacenaphthene does not in some way counteract the steric influence which these rings independently exert upon the benzenoid nucleus.

(4) (a) v. Braun and Kirschbaum, *Ber.*, **55**, 1680 (1922); (b) Goswami, *Compt. rend.*, **179**, 1269 (1924); (c) Orlow and Belopolski, *Ber.*, **62**, 1226 (1929); (d) Ipatiev, *Ber.*, **42**, 2092 (1909).

(5) We are indebted to Dr. Homer Adkins for suggesting this procedure.

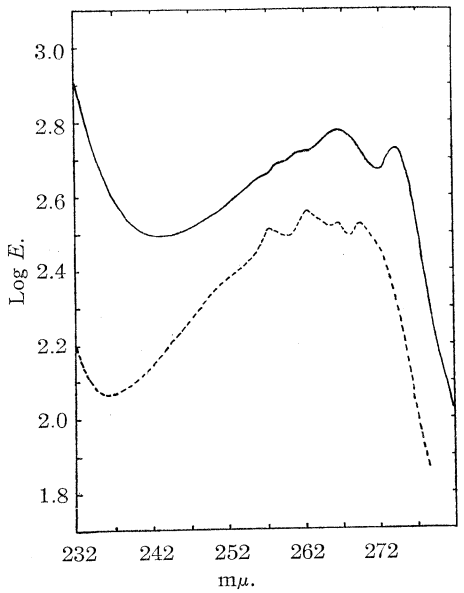
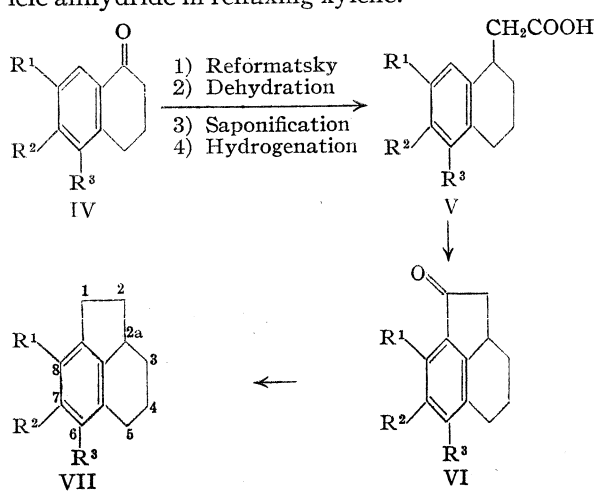



Fig. 1.—Solid line: 2a,3,4,5-tetrahydroacenaphthene; dotted line: 1,2,3-trimethylbenzene.[7]

dex of refraction ($n^{25}$D 1.5573) of the product was in fair agreement with that of material prepared by synthesis from 1-tetralone according to the scheme represented in the flow sheet (formulas IV → VII, $R^1 = R^2 = R^3 = H$), but did not agree with that ($n$D 1.5777) reported for a substance, supposedly tetrahydroacenaphthene prepared by sodium and alcohol reduction of acenaphthene.[6] The $M$D found for our material was 50.54, while the calculated value is 49.63. The chemical behavior of the hydrocarbon is like that of simple polyalkylbenzenes,[4a] and the ultraviolet absorption spectrum (Fig. 1) resembles that reported[7] for 1,2,3-trimethylbenzene, the former exhibiting a slight bathochromic shift and increase of log $E$. Tetrahydroacenaphthene did not react with maleic anhydride in refluxing xylene.




(6) Fleischer and Siefert, *Ann.*, **422**, 272 (1921).

(7) The curve shown in Fig. 1 was constructed from data given by Conrad-Billroth, *Z. physik. Chem.*, **B29**, 170 (1935).

Although the hypothesis of "bond fixation" as tested by coupling experiments with hydroxy derivatives of hydrindene and tetralin has been largely abandoned,[8,9] it is suggested[8,9] that there may be a "qualitative" effect in hydrindene from the fact that in strongly alkaline solutions the 5-hydroxy-6-methyl derivative undergoes coupling with diazonium salts somewhat less effectively than 2,4-dimethylphenol or other 5-hydroxyhydrindene derivatives having the 6-position available. If this difference in reactivity is due to steric inhibition of resonance, it might be expected, granting certain assumptions,[3] that similar and possibly more pronounced behavior would be observed with the appropriately substituted hydroxytetrahydroacenaphthene. Accordingly VII ($R^1$ = OH, $R^2 = R^3$ = H) and VII ($R^1$ = H, $R^2$ = OH, $R^3 = CH_3$) might be expected to undergo coupling less effectively than VII ($R^2$ = OH, $R^1 = R^3$ = H) or than β-naphthol. These tricyclic phenols were, therefore, synthesized from the corresponding 1-tetralones, IV, by the scheme outlined in the accompanying flow sheet and the coupling behavior studied. In those cases where $R^2 = OCH_3$ the cyclization step V → VI was effected by the inverse Friedel–Crafts method.[10] The phenol, m. p. 98–99°, obtained by v. Braun and Kirschbaum[4a] by alkaline fusion of the sulfonic acid from direct sulfonation of tetrahydroacenaphthene and presumed to be the 7-hydroxy derivative, was shown to be a mixture.

The coupling experiments were carried out with *p*-nitrobenzenediazonium chloride at controlled alkalinity by approximately the same method employed by Lothrop.[8] The results which are summarized in Table I indicate that all of the hydroxytetrahydroacenaphthenes have comparably highly reactive coupling centers. They appear to be somewhat more effective couplers than β-naphthol at *p*H 11–13 and somewhat less in 0.4 *N* sodium hydroxide solution. It is striking that under the latter conditions where the test for relative reactivity was expected to be most critical by analogy to the behavior in the hydrindene series,[8]

TABLE I

COUPLING EXPERIMENTS WITH *p*-NITROBENZENEDIAZONIUM CHLORIDE

| Compound | % Yield of crude product at *p*H 8–10 | at *p*H 11–13 | in 0.4 *N* NaOH | in 1.0 *N* NaOH |
|---|---|---|---|---|
| β-Naphthol | 100 | 61 | 17 | 0 |
| VII ($R^1$ = OH, $R^2 = R^3$ = H) | 98 | 94 | 0 | 0 |
| VII ($R^2$ = OH, $R^1 = R^3$ = H) | 95 | 100 | 0 | 0 |
| VII ($R^1$ = H, $R^2$ = OH, $R^3 = CH_3$) | 87 | 100 | 7.4 | 0 |
| VII ($R^1 = R^2$ = H) | 0 | ... | .. | .. |

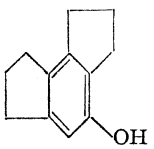
(8) Lothrop, THIS JOURNAL, **62**, 132 (1940).

(9) Fieser, Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1943, pp. 138–139.

(10) Johnson and Glenn, THIS JOURNAL, **71**, 1092 (1949).

the 6-methyl-7-hydroxy compound, VII ($R^1$ = H, $R^2$ = OH, $R^3$ = $CH_3$)—in which the position that would be expected to be most active is blocked by the methyl group—is *more* effective in coupling than the compound VII ($R^2$ = OH, $R^1$ = $R^3$ = H), lacking the 6-methyl substituent.

It may be concluded that experiments thus far have failed to reveal any marked steric inhibition of resonance in the tetrahydroacenaphthene system. It is hoped to investigate the coupling of the phenol VIII which would be of particular interest, because the benzene nucleus is under the influence of two five-membered rings acting independently, thus eliminating certain assumptions required in the present study.[3]




VIII

## Experimental[11]

**2a,3,4,5-Tetrahydroacenaphthene, VII** ($R^1$ = $R^2$ = $R^3$ = H).—In a steel bomb (total void 270 ml.) was placed 30.8 g. (0.20 mole) of acenaphthene,[12] m. p. 94–94.5°, and enough ethanol to bring the total volume of suspension to 115 ml. at 23°. One-fourth teaspoon of Raney nickel catalyst[13] was added and hydrogen introduced to a pressure of 1010 p. s. i. (0.40 mole at 23°). The temperature was raised slowly as the bomb was shaken. At 100° the hydrogenation became rapid and slightly exothermic raising the temperature to 115°, and after fifteen minutes the hydrogenation appeared to be complete. The shaking was continued at 110° for an additional thirty minutes, and then the mixture was worked up in the usual way. The product was distilled through a 20-cm. modified Widmer column giving 29.84 g. (95% yield) of colorless hydrocarbon, b. p. 113.5–114° (10 mm.), $n^{25}D$ 1.5573. A sample of crude hydrogenation product was distilled through a 44-cm. Fenske column packed with glass helices and the refractive index was practically constant throughout, $n^{25}D$ 1.5570–1.5578; $d^{25}_4$ 1.0082; $M_D$ (found) 50.54, $M_D$ (calcd.) 49.63.

*Anal.* Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.25; H, 8.79.

The absorption spectrum (Fig. 1) was determined in ethanol on a Beckman ultraviolet spectrophotometer: λ max. 266 mμ (log $E$ 2.77), 274 (2.72).

**Sulfonation of 2a,3,4,5-tetrahydroacenaphthene** at 0° according to the method described by von Braun and Kirschbaum[4a] did not proceed satisfactorily, so the following modification was adopted.

A mixture of 16.80 g. of the hydrocarbon and 26.0 g. of 97% sulfuric acid was shaken vigorously for one hour with occasional cooling to maintain the temperature at about 23°. The dark red viscous solution was allowed to stand at room temperature overnight, then poured into 100 ml. of water. The solution was treated with Norit, washed once with ether to remove some unchanged hydrocarbon, neutralized with sodium carbonate and treated (at 65°) with about 50 ml. of saturated sodium chloride solution. On cooling 20.10 g. of crude sodium tetrahydroacenaphthenesulfonate crystallized. It was recrystallized from water before being employed in the alkaline fusion.

**Alkaline Fusion of Sodium Tetrahydroacenaphthenesulfonate.**—The procedure of von Braun and Kirschbaum,[4a] reported to give 10–15% yields, could not be repeated successfully. The following modification gave yields of phenol as high as 20%.

A mixture of 3.00 g. of dried sulfonate, 6.0 g. of potassium hydroxide and 4.0 g. of sodium hydroxide was placed in a steel bomb. The system was flushed with nitrogen, the bomb sealed, and heated with shaking for one and one-quarter hours as the temperature was raised to 335°. After an additional hour at this temperature, the bomb was cooled and the product worked up in the usual manner. The phenolic material after clarification with Norit was obtained as colorless crystals, m. p. 89.5–93.5° with previous softening; yield 0.40 g. Evaporative distillation at 110–120° (0.1 mm.) gave material (94% recovery) melting at 94.5–95.5°. A second evaporative distillation raised the m. p. to 96–97.2° with softening at 95°.

*Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.09. Found: C, 82.55; H, 7.97.

Recrystallization of this phenol from ethyl acetate–petroleum ether (60–68°) did not improve the melting point (*cf.* the behavior of 8-hydroxy-2a,3,4,5-tetrahydroacenaphthene described below). A mixture with 7-hydroxy-2a,3,4,5-tetrahydroacenaphthene, m. p. 96.8–97.6°, prepared as described below, melted at 76–94° with softening at 71°. A mixture with the 8-hydroxy compound, m. p. 99.6–102.6°, melted at 92.5–98.5° with softening at 89°.

The crude aryloxyacetic acid derivative prepared from 0.103 g. of the phenol, 0.40 ml. of 33% sodium hydroxide, 0.30 ml. of a 50% solution of chloroacetic acid in water and 1.5 ml. of water according to the usual procedure[14] amounted to 0.068 g. (50% yield) and melted with dec. at 183–184° and softening at 179°. Successive recrystallizations from ethyl acetate–petroleum ether (60–68°) gave material with the m. ps. 190.5–192°, 194.5–198.5°, 196–197.5°, the last crystallizate amounting to 7 mg.

*Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.48; H, 6.74.

On admixture with the aryloxyacetic acid derivative of 8-hydroxy-2a,3,4,5-tetrahydroacenaphthene, m. p. 202–203°, the m. p. was 197–200°.

### Synthesis of Tetrahydroacenaphthene Derivatives from Tetralones

The general scheme of synthesis is outlined in the flow sheet in the discussion part. For the Reformatsky reaction the procedure described by Bachmann, Cole and Wilds[15] with slight modifications proved most successful. The zinc was prepared from pure zinc foil which was cleaned with sandpaper, then cut into one-eighth inch squares and activated as described.[15] The proportion of solvent was decreased considerably, and mechanical stirring (mercury-sealed Hershberg wire stirrer) was employed throughout the heating period. No attempt was made to purify the hydroxy ester which was isolated in the crude form by evaporation of the ether–benzene solution and then dehydrated by refluxing for thirty minutes with 88–90% formic acid (about 2 ml. per gram of starting ketone). The acid was evaporated on the steam-bath in a current of air, and the brown oily residue saponified by refluxing for three and one-half hours with dilute methanolic potassium hydroxide (about 2–2.5 ml. each of methanol and 20% potassium hydroxide per gram of starting ketone). The methanol was removed on the steam-bath in a current of air, and the mixture diluted with two volumes of water. After cooling, the alkaline solution was washed with ether to remove unsaponified material, and after clarification with Norit, was acidified slowly in the cold with vigorous stirring. The unsaturated acid was thus obtained as a pale tan to colorless solid, melting over a wide range. This product was pure enough for low pressure hydrogenation in ethyl acetate solution over 5% palladium on charcoal,[16] which afforded the tetrahydronaphthylacetic acid V

(11) Unless otherwise specified all melting points are corrected.

(12) Reilly Tar and Chemical Corp. commercial grade, once recrystallized from alcohol.

(13) Mozingo, *Org. Syn.*, **21**, 14 (1941).

(14) McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1946, p. 247.

(15) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

(16) Catalyst B, Mozingo, *Org. Syn.*, **26**, 77 (1946).

in good yield. The remaining steps of the synthesis are described below in connection with the individual cases.

**2a,3,4,5-Tetrahydroacenaphthene, VII** ($R^1 = R^2 = R^3 = H$).—When the procedure of Schroeter[17] was employed for the Reformatsky reaction and the product hydrogenated either directly or after dehydration with phosphorus pentoxide, a very impure acid was produced which was shown to consist of a mixture of the desired 1,2,3,4-tetrahydronaphthyl-1-acetic acid (about 43%) and 1-naphthylacetic acid (about 47%) evidently produced by disproportionation. The latter substance remained unchanged when the mixture was treated with hydrogen fluoride and was identified by conversion to the amide.

The disproportionation was not observed with the procedure described above. Thus from 15.0 g. of 1-tetralone, 30.0 g. of zinc,[18] 16 ml. of methyl bromoacetate, and 200 ml. of 1 to 1 ether–benzene there was obtained after dehydration and saponification, 14.2 g. (73% yield) of mixture of unsaturated acids, m. p. 86–96°. Hydrogenation of 13.0 g. of this material in 75 ml. of ethyl acetate at 2–3 atmospheres over a total of 5 g. of 5% palladium on charcoal,[16] afforded 12.1 g. (92% yield) of crude 1,2,3,4-tetrahydronaphthyl-1-acetic acid, V ($R^1 = R^2 = R^3 = H$) which was obtained as a viscous oil (reported m. p. 35–36°[19]). Cyclization of 11.0 g. with hydrogen fluoride[20] (six hours at room temperature) gave 7.40 g. (74% yield) of almost colorless crystalline 2a,3,4,5-tetrahydro-1-acenaphthenone, VI ($R^1 = R^2 = R^3 = H$), m. p. 100–101.5° (reported,[21] 102°). A solution of 7.00 g. of the ketone in 75 ml. of acetic acid containing 0.5 ml. of 60% perchloric acid[22] was hydrogenated over 2.0 g. of 5% palladium on charcoal catalyst,[16] at 2–3 atmospheres. In this case the hydrogenation did not go to completion and it was necessary to remove the catalyst, treat the partially reduced material with Raney nickel, and then to continue the reduction with fresh palladium catalyst. The mixture was filtered, made alkaline with excess potassium hydroxide solution and the hydrocarbon extracted. Distillation through a 20-cm. modified Widmer column gave 1.83 g. of colorless material, b. p. 125–126° (17 mm.), $n^{25}D$ 1.5566. The remainder of the product was retained as hold-up in the distillation apparatus.

**8-Hydroxy-2a,3,4,5-tetrahydroacenaphthene, VI** ($R^1 = OH$, $R^2 = R^3 = H$).—From 34.7 g. of 7-methoxy-1-tetralone,[10] m. p. 61–62°, 60 g. of zinc,[18] 28 ml. of methyl bromoacetate, and 400 ml. of 1 to 1 ether–benzene, there was obtained after dehydration and saponification, 41.8 g. (97% yield) of mixture of unsaturated acids, m. p. 122.5–138.5°. Hydrogenation of 10.9 g. of material, which was recrystallized once from alcohol, in 50 ml. of ethyl acetate at 2–3 atmospheres over 1.0 g. of 5% palladium on charcoal[16] was complete in about twenty minutes and afforded after trituration of the crude product with petroleum ether (40–60°) 10.02 g. of crystalline 7-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic acid, V ($R^1 = OCH_3$, $R^2 = R^3 = H$), m. p. 88.5–89.5° (reported,[23] 88–89°). An additional 0.36 g. of crude material, m. p. 77–85° was obtained from the petroleum ether solution.

A 10.00-g. sample of the above acid, m. p. 88.5–89.5°, was cyclized with hydrogen fluoride[20] (twenty hours at room temperature) to give 8.85 g. (96% yield) of crystalline **8-methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone, VI** ($R^1 = OCH_3$, $R^2 = R^3 = H$), m. p. 98–99.5°. This material seemed to be somewhat unstable showing a tendency to turn yellow during recrystallization. It was obtained as plates or needles from benzene–petroleum ether (60–68°), and after three recrystallizations melted at 95.8–98° with slight previous softening.

*Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.30; H, 6.80.

A 10.10-g. sample of the above ketone was reduced by the Clemmensen method,[24] and 5.00 g. of the resulting 9.12 g. (97% yield) of oil,[25] was demethylated by refluxing with 50 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid for four and one-half hours in an atmosphere of nitrogen. Since insoluble oil still remained after this treatment 50 ml. of acetic acid was added and refluxing continued for eight and one-half hours. The mixture was concentrated to about one-third its volume, diluted with water, and extracted with ether. The ether solution was washed with 5% sodium bicarbonate, and the phenol was then extracted with 5% potassium hydroxide followed by Claisen alkali.[26] The alkaline extracts were combined and acidified liberating 3.11 g. of tan crystalline phenol, m. p. 96–98.5°. An additional 0.50 g. of material of the same m. p. was obtained from the filtrate by extraction, thus making the total yield 78%. Evaporative distillation at 145–150° (0.1 mm.) gave in 88% recovery colorless crystals, m. p. 102–103° with slight previous softening. This material proved to be quite sensitive and on boiling in 60–68° petroleum ether the solution became turbid as a small amount of insoluble material gradually precipitated. After two recrystallizations from this solvent (each time turbidity necessitated filtration), the product melted at 101.5–102.5° to a cloudy liquid which did not clear up completely until about 180°. The high-melting contaminant could be removed by evaporative distillation. After a second evaporative distillation the product was obtained as pale yellow needles, m. p. 99.5–102.5°. The lower m. p. than that observed with the crude sample may have been due to polymorphism.

*Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.09. Found: C, 82.52; H, 8.00.

The **aryloxyacetic acid derivative** was prepared from 0.121 g. of 8-hydroxy-2a,3,4,5-tetrahydroacenaphthene, 0.40 ml. of 33% sodium hydroxide, 0.30 ml. of 50% chloroacetic acid in water, and 0.5 ml. of water according to the usual procedure.[14] The crude derivative amounted to 0.068 g. (42% yield), m. p. 202–203° with darkening and softening at 200°. Recrystallization from ethyl acetate gave colorless needles, m. p. 202–203° (turning red).

*Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 6.61.

**7-Hydroxy-2a,3,4,5-tetrahydroacenaphthene, VII** ($R^2 = OH$, $R^1 = R^3 = H$).—From 10.0 g. of 6-methoxy-1-tetralone,[27] m. p. 76–77.5°, 20 g. of zinc,[18] (10 ml.) of methyl bromoacetate, and 150 ml. of 1 to 1 ether–benzene, there was obtained after dehydration and saponification 9.50 g. (77% yield) of mixture of unsaturated acids, melting at about 64°, resolidifying at about 90° and remelting at 100–111°. Hydrogenation of 8.30 g. of this product in 75 ml. of ethyl acetate at 2–3 atmospheres over a total of 3 g. of 5% palladium on charcoal,[16] was complete after about three hours, and afforded 8.00 g. (95% yield) of crude 6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic acid, V ($R^2 = OCH_3$, $R^1 = R^3 = H$), m. p. 76–80°. Recrystallization from benzene–petroleum ether (60–68°) raised the m. p. to 79–81.5°. In other runs material of better quality, m. p. 81–83.5°, was obtained although in lower (83%) yield. Recrystallization gave an 88% recovery of material m. p. 82.5–84° (reported, 84°[28] and

(17) Schroeter, *Ber.*, **58B**, 713 (1925).

(18) This represents the total amount of zinc which was added in six portions (see ref. 15). The unchanged zinc was recovered and used again, after reactivation. This material was found to be more reactive than the fresh metal.

(19) von Braun, Gruber and Kirschbaum, *Ber.*, **55B**, 3664 (1922).

(20) See the procedure in "Organic Reactions," Vol. II, 1944, p. 158.

(21) von Braun and Reutter, *Ber.*, **59B**, 1922 (1926).

(22) Kindler and Dachi-yin-Kwok, *Ann.*, **554**, 9 (1943); Rosenmund and Karg, *Ber.*, **75**, 1850 (1942); Baker and Jenkins, THIS JOURNAL, **68**, 2102 (1946).

(23) Plimmer, Hill and Short, *J. Chem. Soc.*, 694 (1938).

(24) Martin in Adams, "Organic Reactions," Vol. I, 1942, p. 163.

(25) This product did not give a test with 2,4-dinitrophenylhydrazine reagent.

(26) Claisen, *Ann.*, **418**, 96 (1919); 35 g. of potassium hydroxide in 25 g. of water diluted to 100 ml. with methanol.

(27) Prepared by the procedure of Stork, THIS JOURNAL, **69**, 576 (1947).

(28) Schwenk and Papa, *ibid.*, **67**, 1432 (1945).

87°[29]). The cyclization of this acid to 7-methoxy-2a,3,4,-5-tetrahydro-1-acenaphthenone, VI ($R^2$ = $OCH_3$, $R^1$ = $R^3$ = H) is described elsewhere.[10] A 1.015 g. sample of the ketone was reduced by the Clemmensen method[24] and 0.711 g. of the resulting 0.732 g. (77% yield) of oil,[25] was demethylated by refluxing with 10 ml. of 48% hydrobromic acid and 15 ml. of acetic acid for four hours in an atmosphere of nitrogen. The product was worked up essentially as described above for the 8-methoxy isomer except that the crude phenol being oily was separated by extraction. The total yield of crude semi-solid material was 0.620 g. (94%). Evaporative distillation at 100–110° (0.1 mm.) gave in about 65% recovery colorless crystalline phenol, m. p. 89–95°. The pure material was obtained by crystallization from petroleum ether (60–68°) followed by evaporative distillation. It was obtained as colorless needles, m. p. 96–97.6°.

*Anal.* Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.09. Found: C, 82.68; H, 7.96.

**6-Methyl-7-hydroxy-2a,3,4,5-tetrahydroacenaphthene, VII** ($R^1$ = H, $R^2$ = OH, $R^3$ = $CH_3$).—5-Methyl-6-methoxytetralone-1, IV ($R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = $CH_3$), was prepared according to the method of Martin and Robinson.[30] By slight modifications in the oxidation step it was possible to improve the yield of ketone as follows. A solution of 11.4 g. of chromic oxide in 70 ml. of acetic acid and 10 ml. of water was added slowly over a period of one and one-half hours to a stirred solution of 11.4 g. of 5-methyl-6-methoxytetralin, m. p. 49–50°, in 115 ml. of acetic acid, the internal temperature being maintained at 10–15°. After the addition was complete the mixture was stirred for one and one-half hours in the cold (ice-bath) and two hours at room temperature. After eighteen hours at room temperature (without stirring) 25 ml. of methanol was added, the mixture stirred for thirty minutes and then concentrated under reduced pressure. The gummy residue was treated with 200 ml. of water and extracted with ether. The ether solution was washed with 5% sodium carbonate solution, saturated salt solution, clarified with Norit, and dried over anhydrous potassium carbonate. Evaporation of the ether gave 10.28 g. (83% yield) of yellow ketone, m. p. 106.5–109.5°. Martin and Robinson[30] report an average yield of 70% of light yellow ketone, m. p. 103–105°. Our material after two recrystallizations from methanol melted at 109.5–111° (reported m. p.,[30] 112–113°).

From 4.23 g. of the above ketone, 10 g. of zinc,[18] 8 ml. of methyl bromoacetate and 80 ml. of 1 to 1 ether–benzene there was obtained after dehydration and saponification 3.84 g. (74% yield) of mixture of unsaturated acids, m. p. 146–154° (dec.). Hydrogenation of 3.00 g. of this product in 25 ml. of ethyl acetate at atmospheric pressure over a total of 1.5 g. of 5% palladium on charcoal,[16] was complete after about fifteen hours, and afforded 2.77 g. (91% yield) of **5-methyl-6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic acid, V**, $R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = $CH_3$, m. p. 154–156°. Recrystallization from ethyl acetate–petroleum ether (60–68°) gave a total of 2.38 g. of colorless blades, m. p. 158.5–159°. Further recrystallizations raised the m. p. to 159.2–159.8°.

*Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H. 7.47.

The cyclization of the above acid to 6-methyl-7-methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone, VI ($R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = $CH_3$), is described elsewhere.[10] A 0.173-g. sample of this ketone, m. p. 123–125.5°, in 15 ml. of acetic acid containing 0.2 ml. of 60% perchloric acid[22] was hydrogenated at atmospheric pressure over 0.150 g. of 30% palladium on charcoal.[31] The uptake of hydrogen ceased after one and three-quarters hours, the calculated amount being absorbed. The mixture was filtered, diluted with water, neutralized with solid sodium bicarbonate and extracted with ether. The ether solution was washed with water, then with saturated salt solution and dried over anhydrous potassium carbonate. Evaporation of the ether left 0.162 g. of a colorless oil which crystallized on drying, m. p. 35–40.5°. Two recrystallizations from petroleum ether (40–60°) solution cooled in a Dry Ice–acetone bath gave colorless plates of **6-methyl-7-methoxy-2a,3,4,5-tetrahydroacenaphthene, VII** ($R^1$ = H, $R^2$ = $OCH_3$, $R^3$ = $CH_3$), m. p. 42–44°.

*Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.94; H, 8.74.

In another experiment it was noted that the perchloric acid was unnecessary for complete hydrogenolysis, but the rate of reaction was decreased, nine hours being required to reduce 0.458 g. of ketone. The yield was 0.430 g., m. p. 39.5–42.5°. A 0.430-g. sample of this material was demethylated by refluxing with 5 ml. of 48% hydrobromic acid and 10 ml. of acetic acid for ten hours in an atmosphere of nitrogen. The product was worked up essentially as described above for the 8-methoxy homolog to give 0.344 g. (86% yield) of crude tan crystalline phenol, m. p. 103–107.5°. Evaporative distillation at 130–140° (0.5 mm.) gave a 95% recovery of colorless needles, m. p. 106.5–108°. Recrystallization from ethyl acetate–petroleum ether (60–68°) gave colorless prisms, m. p. 109–110.4°.

*Anal.* Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.98; H, 8.35.

### Coupling Experiments

Five grams of *p*-nitroaniline hydrochloride, prepared by treating the amine in dioxane solution with anhydrous hydrogen chloride, was diazotized by the procedure of Hantzsch and Jochem[32] with the following modifications. *n*-Butyl nitrite was used instead of amyl nitrite. Attempts to use the dried diazonium salt for preparing a standard solution did not appear promising since water-insoluble material was produced. A satisfactory procedure consisted in separating the diazonium salt by filtration, washing well with anhydrous ether to remove acetic acid and dissolving the ether-moist product in water at 0°. The solution was diluted to 250 ml. and standardized by titration of an aliquot with alkali using phenolphthalein as an indicator. The solution then was shown to contain 0.106 millimole of *p*-nitrobenzenediazonium chloride per ml. of solution.

The coupling procedure was as follows: The phenol (0.201–0.202 millimole) was dissolved in 10 ml. of buffered (or alkaline) solution and 5 ml. of purified[33] dioxane, and the solution cooled to 0° in an ice-bath. To this was added 3.00 ml. of the standardized diazonium salt solution (also at 0°) and the mixture was kept at 0° for twenty minutes. The mixture was then warmed on the steam-bath for twenty minutes and the dark red precipitate separated by filtration, washed with water, digested for five to ten minutes with warm 5% potassium carbonate solution (steam-bath), separated by filtration, washed with the carbonate solution and finally with water. The dyes were dried to constant weight in a vacuum desiccator and the melting points determined on a micro hot stage.

The melting point of the crude coupling products from β-naphthol varied from 251–254° to 253–255° (reported m. p.,[34] 250–251°).

The crude coupling product obtained from 8-hydroxy-2a,3,4,5-tetrahydroacenaphthene at *p*H 8–10 had the m. p. 211–216° and at *p*H 11–13, 213–217°. A sample purified by recrystallization from dioxane was obtained as red-brown needles, m. p. 219.5–220.5°.

*Anal.* Calcd. for $C_{18}H_{17}O_3N_3$: C, 66.86; H, 5.30. Found: C, 66.91; H, 5.04.

The crude coupling product obtained from 7-hydroxy-2a,3,4,5-tetrahydroacenaphthene at *p*H 8–10 had the m. p. 168–172° and at *p*H 11–13, m. p. 172–175°. A

(29) Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

(30) Martin and Robinson, *ibid.*, 491 (1943).

(31) Linstead and Thomas, *ibid.*, 1127 (1940).

(32) Hantzsch and Jochem, *Ber.*, **34**, 3337 (1901).

(33) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 2nd ed., 1941, p. 368.

(34) Charrier and Ferreri, *Gazz. chim. ital.*, **44**, 165 (1914).

sample purified by recrystallization from dioxane–petroleum ether (b. p. 60–68°), was obtained as red-brown needles, m. p. 181.5–183°.

*Anal.* Calcd. for $C_{18}H_{17}O_3N_3$: C, 66.86; H, 5.30. Found: C, 66.73; H, 5.10.

The crude coupling product from 6-methyl-7-hydroxy-2a,3,4,5-tetrahydroacenaphthene obtained at *p*H 8–10 had the m. p. 202–210°; at *p*H 11–13, m. p. 192–197°; in 0.4 *N* sodium hydroxide, m. p. 200–206°. A sample purified by recrystallization from dioxane was obtained as red-brown needles, m. p. 207–209°.

*Anal.* Calcd. for $C_{19}H_{19}O_3N_3$: C, 67.64; H, 5.68. Found: C, 67.68; H, 5.35.

## Summary

2a,3,4,5-Tetrahydroacenaphthene has been prepared both by selective hydrogenation of acenaphthene and by synthesis from 1-tetralone. The properties of the hydrocarbon resemble those of simple polyalkylbenzenes.

7-Hydroxy-, 8-hydroxy-, and 6-methyl-7-hydroxy-2a,3,4,5-tetrahydroacenaphthene were prepared by synthesis from the appropriately substituted tetralones, and their coupling behavior with *p*-nitrobenzenediazonium chloride was observed at various concentrations of alkali. All of the phenols were comparably effective couplers, and it may be concluded that experiments thus far have failed to reveal any marked steric inhibition of resonance in the tetrahydroacenaphthene ring system.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# Intramolecular Acylation. II.[1] The Inverse Friedel–Crafts Method

BY WILLIAM S. JOHNSON AND HOWARD J. GLENN[2]

Of the numerous methods available for effecting ring closure of β-arylpropionic or γ-arylbutyric acid derivatives to cyclic ketones, the intramolecular Friedel–Crafts reaction of the acid chloride with aluminum chloride promises to be particularly useful for acids like β-*p*-methoxyphenylpropionic acid, which are resistant to cyclization due to unfavorable reactivity of the aromatic nucleus.[1] Excellent yields have not been generally realized by this method, probably because a large proportion of the cylizations reported in the literature have been conducted under unfavorable conditions. In the present work we are describing a cyclization technique which combines the best features suggested by previous experience.[3] This procedure, which has been tested with nine acids of varying susceptibility to cyclization, apparently differs from others previously reported only in minor respects, some of which nevertheless, have proved to be critical factors and merit emphasis. (1) It has been found important to use acids of good quality, since small amounts of impurities may result in a very impure product. (2) For preparation of the acid chloride, phosphorus pentachloride instead of thionyl chloride was employed because of occasional complications which have been reported to attend the use of the latter.[4] The phosphorus oxychloride produced was always carefully removed, because its presence has been shown to interfere with the cyclization giving lower yields.[5,1] (3) The Friedel–Crafts step was carried out in the inverse manner, *i.e.*, the acid chloride (in benzene solution) was added to a stirred suspension of aluminum chloride in benzene. This technique has the advantage over the conventional method of (*a*) facilitating temperature control through regulation of the rate of addition of the acid chloride and (*b*) maintaining a high concentration of catalyst, a condition that has been shown in *inter*molecular acylation to minimize self-condensation of the resulting ketone,[6] which is a side-reaction that also competes with certain *intra*molecular acylations.[7] The yields for fifteen cases that were found in the literature in which the inverse Friedel–Crafts cyclization was employed apparently without particular regard to other critical factors, were nevertheless generally well above average,[3] thus suggesting a real advantage in this method. (4) Since heating has been shown to have undesirable effects,[7] the temperature of the reaction mixture was never permitted to rise above 25° during the cyclization step. Even with acids that are unusually resistant to cyclization, this treatment afforded excellent yields of ketones. Thus with β-*p*-methoxyphenylpropionic acid, I ($R^1$ = $OCH_3$, $R^2$ = H), which is notoriously resistant to cyclization,[1,8] 6-methoxy-1-hydrindone, II ($R^1$ = $OCH_3$, $R^2$ = H), of fair purity was obtained in practically quantitative yield on a 3-g. scale.

The ring closure of α,γ-diphenylbutyric acid, III ($R^1$ = H, $R^2$ = $C_6H_5$), afforded an interesting test since Newman[9] had studied this cyclization

(1) See Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945), for the first communication of this series.

(2) Wisconsin Alumni Research Foundation research assistant, 1946–1947; du Pont predoctorate fellow 1947–1948. Present address: Abbott Laboratories, North Chicago, Illinois.

(3) Johnson in Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1944, Chapter 4.

(4) See ref. 3, p. 137.

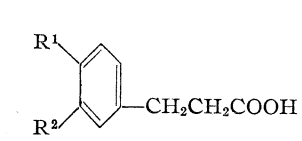
(5) Newman, THIS JOURNAL, **62**, 870 (1940).

(6) Calloway and Green, *ibid.*, **59**, 809 (1937).

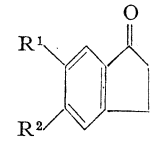
(7) See ref. 3, p. 130.

(8) Heinzelmann, Kolloff and Hunter, THIS JOURNAL, **70**, 1386 (1948).

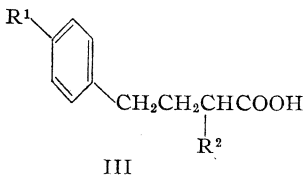
(9) See Procedure III, ref. 3, p. 145.



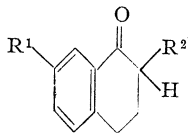

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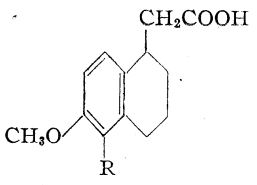

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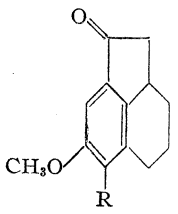

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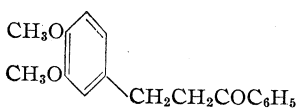

VI

carefully and developed conditions requiring a rather critical heat treatment whereby yields as high as 94% could be realized. When the procedure described in the present work was applied, practically quantitative yields of the ketone, IV ($R^1$ = H, $R^2$ = $C_6H_5$), were produced without heating.

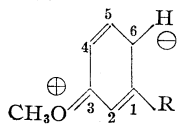
β-Phenylpropionyl chloride was cyclized to 1-hydrindone, II ($R^1$ = $R^2$ = H) in nearly quantitative yield, γ-phenylbutyric acid, III ($R^1$ = $R^2$ = H), to tetralone-1, IV ($R^1$ = $R^2$ = H), in 90% yield on a 50-g. scale,[10] γ-*p*-methoxyphenylbutyric acid, III ($R^1$ = $OCH_3$, $R^2$ = H), to 7-methoxytetralone, IV ($R^1$ = $OCH_3$, $R^2$ = H), in practically quantitative yield on a 20-g. scale, and β-*m*-methoxyphenylpropionic acid, I ($R^1$ = H, $R^2$ = $OCH_3$), to a mixture of 5- and 7-methoxy-1-hydrindone (predominantly the former) in 89% yield. The cyclization of 6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic acid, V (R = H), to VI (R = H) proceeded in only 77% yield, although the 5-methyl homolog V (R = $CH_3$) was cyclized to VI (R = $CH_3$) in quantitative yield. Both of these cases involve five-membered ring closure meta to a methoxyl group.

### Deactivation by Coördination with Catalyst

Application of the cyclization procedure to β-3,4-dimethoxyphenylpropionic acid, I ($R^1$ = $R^2$ = $OCH_3$), gave most unexpected results. Instead of 5,6-dimethoxy-1-hydrindone, II ($R^1$ = $R^2$ = $OCH_3$), we isolated as the preponderant product (70% yield) a crystalline ketone melting after purification at 68–68.5° and having an analysis compatible with the formula $C_{17}H_{18}O_3$. That this was 3,4-dimethoxybenzylacetophenone, VII, arising from intermolecular acylation of the solvent follows from the agreement of its properties with those reported for VII obtained by hydrogenation of 3,4-dimethoxybenzalacetophenone.[11] These observations were all the more surprising in view of the fact that under the same conditions the *p*-methoxy acid I ($R^1$ = $OCH_3$, $R^2$ = H) is cyclized in quantitative yield. It would be expected, however that the latter would be considerably less susceptible to cyclization than the acid I ($R^1$ = $R^2$ = $OCH_3$) which has the additional 3-methoxy group to activate the 6-position into which the ring closes, thus cancelling the de-activating influence of the 4-methoxy group. That I ($R^1$ = $R^2$ = $OCH_3$) does indeed have a greater intrinsic susceptibility to cyclization than I ($R^1$ = $OCH_3$, $R^2$ = H) is suggested by its behavior toward hydrogen fluoride which promoted ring closure to II ($R^1$ = $R^2$ = $OCH_3$) in 88% yield. The acid I ($R^1$ = $OCH_3$, $R^2$ = H) in contrast is cyclized in only 3% yield under the same conditions.[1]




VII




VIII

According to current theories the activating influence of the 3-methoxy group may be rationalized by its participation in the resonance of the benzene nucleus, thus enhancing the contribution of the polarized form VIII (or the corresponding *ortho* quinoid modification) to the electronic state of the molecule. The resultant high electron density at the 6-position favors reaction with the electrophilic carbon of the carbonyl group at the end of the side-chain R thus effecting cyclization. Coördination of the 3-methoxy group with an acid would inhibit the contribution of VIII and, if powerful enough, would tend to render the 6-position sufficiently less nucleophilic (by induction as in the de-activation of the benzene nucleus by the quaternary ammonium ion) than the carbon atom of the solvent benzene, so that reaction could occur more rapidly with the latter. This hypothetical situation was not actually realized with β-*m*-methoxyphenylpropionic acid, I ($R^1$ = H, $R^2$ = $OCH_3$), which underwent only intramolecular acylation (see above), but with the acid I ($R^1$ = $R^2$ = $OCH_3$) the second methoxy group in the 4-position exerts on the 6-position an additional de-activating influence of the type observed with β-*p*-methoxyphenylpropionic acid. The combined effects appear to render the nucleus so unreactive that the competing intermolecular reaction takes precedence. According to this postulate an acid somewhat weaker than aluminum chloride, should favor intramolecular reaction because the inhibition of resonance by coördination would be decreased. The reaction was therefore carried out with stannic instead of aluminum chloride, and indeed a 54% yield of cyclic ketone

(10) This represents an improvement over the procedure of Martin and Fieser, *Org. Syn.*, Coll. Vol. II, 569 (1943), which gives varying yields of 74–91% and involves a laborious steam distillation.

(11) Pfeiffer, Kalckbrenner, Kunze and Levin, *J. prakt. Chem.*, **119**, 109 (1928).

was obtained, none of the product VII of intermolecular acylation being found.

## Experimental[12]

**General Cyclization Procedure.**—To phosphorus pentachloride (in the ratio of 1.1 mole per mole of acid) in a flame-dried distilling flask (protected by a calcium chloride tube) was added 3.00 g. of pure, dried organic acid. In larger runs the acid was added in portions.[13] If the reaction did not start immediately the mixture was warmed gently or a few ml. of benzene added. After copious evolution of hydrogen chloride ceased (usually about fifteen minutes), 15 ml. of dried (over sodium) benzene was added and the flask was fitted with a stopper bearing a small addition funnel and a tube drawn out to a fine capillary extending to the bottom of the flask. The volatile phosphorus compounds were then co-distilled with the benzene at 60–70° (oil-bath temperature) under reduced pressure (water pump), dry air or nitrogen being admitted through the capillary tube. When the volatile materials were largely removed, another 15 ml. of benzene was added from the dropping funnel and the distillation continued. This process was repeated twice again each time with the addition of 15-ml. portions of benzene. The residual acid chloride was then cooled, dissolved in 20 ml. of dry, thiophene-free benzene and transferred with the aid of an additional 15 ml. of solvent through a plug of glass wool into a dropping funnel which was attached to a flame-dried flask bearing a Hershberg mercury-sealed wire stirrer, thermometer and calcium chloride tube. Aluminum chloride[14] (in the ratio of 1.2–1.4 mole per mole of acid) was introduced into the flask with 40 ml. of dry thiophene-free benzene and the suspension stirred with cooling (ice-bath) as the solution of acid chloride was added slowly at such a rate that the temperature of the reaction mixture never rose above 10°. The addition ordinarily required about fifteen minutes during which a highly colored complex formed. The funnel was finally rinsed with an additional 25 ml. of benzene and the stirring continued for two to five hours while the temperature was allowed to rise slowly to 22–24° (not higher).

The mixture was chilled, about 50 ml. of ether introduced to prevent emulsion formation, and then 100 ml. of cold 1:1 hydrochloric acid added with stirring at such a rate that the temperature remained below 15°. The organic layer was separated, washed successively with three portions of 1:1 hydrochloric acid, followed by saturated sodium bicarbonate,[15] 5% potassium hydroxide,[15] water and finally saturated salt solution. Appropriate washing of the aqueous layers in turn with a fresh portion of ether was necessary for effecting clean separations. The combined organic solutions were shaken with a small amount of Norit, dried over anhydrous potassium carbonate, filtered, evaporated and dried to constant weight *in vacuo*.

Any uncyclized acid was recovered by acidification of the bicarbonate solutions, and phenolic material (resulting from demethylation of methoxy derivatives) by acidification of the potassium hydroxide wash solutions.

### Cyclization Experiments

**β-*p*-Methoxyphenylpropionic Acid, I** ($R^1 = OCH_3$, $R^2 = H$).—A 3-g. sample of the pure acid,[1] m. p. 103.5–104° was treated by the above procedure with 3.64 g. of phosphorus pentachloride. Cyclization was effected with 3.10 g. of aluminum chloride for five hours. The crude tan ketone, II ($R^1 = OCH_3$, $R^2 = H$), amounted to 2.73 g. (quantitative yield), m. p. 103–106°. Distillation in a two-bulb flask at 0.1 mm. was attended by some mechanical hold-up giving 2.20 g. of colorless product, m. p. 108–108.5°. In another experiment with 2.50 g. of acid in which the molecular ratio of catalyst was dropped to 1.25 instead of 1.4, 2.10 g. (93% yield) of product melting at 105–106.2° was obtained. Evaporative distillation under reduced pressure gave a 95% recovery of colorless ketone, m. p. 108–108.5°. Cyclization of a specimen of the acid having approximately the same m. p. as the sample above, but having been submitted to one less recrystallization, gave a quantitative yield of crude ketone which, however, melted at 50–106°. Only 43% of this material could be obtained relatively pure, m. p. 103–105°.

**β-Phenylpropionic Acid, I** ($R^1 = R^2 = H$).—Since the acid chloride, b. p. 118–120° (17 mm.), was available, a 3.08-g. sample was treated with 3.04 g. of aluminum chloride for five hours. The yield of almost colorless hydrindone was 2.40 g. (99%), m. p. 39–39.6° with softening at 38.5°. Evaporative distillation at 0.3 mm. gave a 94% recovery of colorless ketone, m. p. 39.8–40.2° (reported,[16] 40–41°). Using the inverse Friedel-Crafts cyclization, Thiele and Wanscheidt,[17] obtained 1-hydrindone in 95% yield. They used petroleum ether as the solvent and warmed the reaction mixture until the complex dissolved.

**β-*m*-Methoxyphenylpropionic Acid, I** ($R^1 = H$, $R^2 = OCH_3$).—The acid was prepared by methylation of β-*m*-hydroxyphenylpropionic acid[18] with dimethyl sulfate followed by crystallization from ether–petroleum ether (40–60°) and recrystallization from dilute methanol; m. p. 44–46.5° (reported,[19] 45°). A 1.50-g. sample was treated with 1.90 g. of phosphorus pentachloride and cyclization was effected with 1.55 g. of aluminum chloride for three and one-half hours at 7–17°. The pale yellow product amounted to 1.20 g. (89% yield), m. p. 63–103°, evidently consisting of a crystalline mixture of 5- and 7-methoxy-1-hydrindone as shown by analysis of material sublimed at 75–90° (0.05 mm.) which melted at 63–100°.

*Anal.* Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.01; H, 6.06.

On crystallization of the sublimate from dilute methanol three-fourths of the product separated as fairly pure 5-methoxy-1-hydrindone, m. p. 108–110.5°, with previous softening, indicating that this isomer was formed in preponderance. The m. p. after recrystallization was 109–110.5°, and was not depressed on admixture with an authentic specimen of the ketone.[18]

The only previous report of cyclization of this acid is by Ingold and Piggott[19] who used aluminum chloride in petroleum ether on the acid chloride. The conditions involved heating on the steam-bath which effected some demethylation. No yields were reported, but the presence of both possible isomers was demonstrated.

**γ-Phenylbutyric Acid, III** ($R^1 = R^2 = H$).—A 50-g. sample of the acid, m. p. 47–49.5°, was converted to the acid chloride with 70 g. of phosphorus pentachloride, five 25-ml. portions of benzene being used for removal of the phosphorus oxychloride. The acid chloride was then dissolved in 100 ml. of benzene and added to 56 g. of aluminum chloride suspended in 150 ml. of solvent. After the addition which required forty-five minutes, 50 ml. of benzene was used for rinsing the funnel. The mixture was stirred for fifteen minutes in the cold and four hours at 22–24°, and then the addition complex was decomposed with 100 ml. of ether and 250 ml. of 1:1 hydrochloric acid. The 1-tetralone, b. p. 165–170° (46–49 mm.) amounted to 40.0–40.4 g. (90–91% yield). Starting acid amounting to 2.4 g., m. p. 45–47.5°, was recovered from the bicarbonate washings.

**α,γ-Diphenylbutyric Acid, III** ($R^1 = H$, $R^2 = C_6H_5$).—A 3.00-g. sample of the acid[20] (m. p. 72.7–73.5° after

(12) All melting points are corrected.

(13) See footnote 116b of ref. 3.

(14) Aluminum chloride supplied by either Merck and Co. (yellow powdered material) or J. T. Baker Chemical Co. (reagent grade) was used with equal success.

(15) Washing was continued with successive portions until no turbidity was produced on acidification.

(16) Kipping, *J. Chem. Soc.*, 480 (1894).

(17) Thiele and Wanscheidt, *Ann.*, **376**, 269 (1910).

(18) Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 218 (1944).

(19) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923).

(20) Prepared from α-phenyl-β-benzoylpropionitrile, *Org. Syn.*, Coll. Vol. II, 498 (1943), according to the procedure of Newman THIS JOURNAL, **60**, 2947 (1938).

three recrystallizations from 60–68° petroleum ether) was treated with 2.74 g. of phosphorus pentachloride, and cyclization was effected with 2.32 g. of aluminum chloride for five hours. The yield of crude product was 2.71–2.78 g. (98–100%) with a melting point varying from 75–76 to 73–75°. The acidic material recovered from the alkaline washings was negligible. Recrystallization of the 2.78-g. product from petroleum ether (60–68°) gave 2.38 g. melting at 76–77° and 0.24 g. melting at 74–76°, making the total yield of recrystallized material 94%. The reported m. p. is 76.2–77°.[20]

When a sample of the acid of approximately the same m. p., but having been recrystallized only twice was cyclized, the yield of crude product was good (97%) but the quality inferior (m. p. 69–73°). Recrystallization gave only 81% yield of ketone melting at 73–76°.

**γ-*p*-Methoxyphenylbutyric Acid, III** ($R^1 = OCH_3$, $R^2 = H$).—A 20.0-g. sample of the acid (m. p. 60.5–62° after recrystallization from petroleum ether (60–68°) containing a small proportion of benzene) was converted to the acid chloride with 24.0 g. of phosphorus pentachloride, four 15-ml. portions of benzene being used for removal of the phosphorus oxychloride. The acid chloride was then dissolved in 50 ml. of benzene and added to 19.3 g. of aluminum chloride suspended in 50 ml. of benzene. After the addition, which required twenty minutes, 25 ml. of benzene was used for rinsing making the total volume 125 ml. The mixture was stirred for fifteen minutes in the cold, then four hours at 22–24°. The yield of crude pale yellow crystalline ketone was 17.90 g. (99%), m. p. about 59–61°. Recrystallization from ether–petroleum ether (60–68°) gave in the first crop 14.33 g. of light tan prisms, m. p. 61–62° (reported,[21] 62–63°). From the bicarbonate wash 0.17 g. of acid was recovered, m. p. 54–57°. The potassium hydroxide washings yielded 0.08 g. of oil having a phenolic odor. This acid has been cyclized in 88% yield by the action of stannic chloride on the acid chloride.[22]

**6-Methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic Acid, V** (R = H).—A 3.00-g. sample of the acid, m. p. 83–84°,[23] was treated with 3.12 g. of phosphorus pentachloride, and cyclization was effected with 2.66 g. of aluminum chloride for four hours. The yield of crude 7-methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone, VI (R = H), m. p. 78.5–82.5°, was 2.12 g. (77%). Only 0.10 g. of acidic product was recovered from the bicarbonate washings. Evaporative distillation at 130–140° (0.2 mm.) gave a 71% recovery of colorless material m. p. 88–89.5°. An additional 10% of less pure material, m. p. 84.5–88°, was recovered by continuing the distillation. An analytical sample was prepared from the first fraction by three recrystallizations from petroleum ether (60–68°) followed by evaporative distillation. The colorless needles melted at 89.6–90.8°.

*Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.34; H, 6.86.

**5-Methyl-6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic Acid, V** (R = $CH_3$).—A 1.00-g. sample of this acid, m. p. 159–159.5°,[23] was treated with 1.00 g. of phosphorus pentachloride, and cyclization was effected with 0.81 g. of aluminum chloride suspended in 20 ml. of benzene. The addition of the acid chloride in 15 ml. of solvent required fifteen minutes, 15 ml. of benzene being used for rinsing. The mixture was then stirred for an additional fifteen minutes in the cold, and for two and one-half hours at 22–24°. The yield of crude 6-methyl-7-methoxy-2a,3,4,-5-tetrahydro-1-acenaphthenone, VI (R = $CH_3$), m. p. 121–125.5°, was 0.925 g. (100%). A single crystallization of 0.920 g. from ethyl acetate–petroleum ether (60–68°) gave in the first crop 0.717 g., m. p. 123–125.5° and in the second 0.034 g., m. p. 122–124°. Recrystallization gave colorless blades, m. p. 124.4–126.4°.

*Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.97; H, 7.16.

**β-3,4-Dimethoxyphenylpropionic Acid, I** ($R^1 = R_2 = OCH_3$).—3,4-Dimethoxycinnamic acid was prepared by the condensation of veratraldehyde (83 g.) with malonic acid (93 g.) in pyridine (115 ml.) with 1 ml. of piperidine according to the procedure for the preparation of *p*-methoxycinnamic acid.[1] The crude product was dissolved in 5% sodium carbonate, filtered, washed with ether, and acidified. The yield of 3,4-dimethoxycinnamic acid was 100 g. (96%), m. p. 183.4–184.2° with softening at 180° (reported,[24] 180°). Hydrogenation of once recrystallized (from benzene-petroleum ether) material in glacial acetic acid over platinum oxide catalyst gave a 94% yield of crude I ($R^1 = R^2 = OCH_3$), m. p. 95–97°, softening at 92°. Material for the cyclizations was twice recrystallized from benzene to give colorless crystals, m. p. 97.5–98.5° (reported,[25] 97°).

(*a*) *Cyclization with Hydrogen Fluoride.*—A 3.00-g. sample of the acid was treated with hydrogen fluoride overnight at room temperature by the procedure described for β-*p*-methoxyphenylpropionic acid.[1] The cyclization apparently proceeded in only one direction giving 2.42 g. (88% yield) of 5,6-dimethoxy-1-hydrindone, II ($R^1 = R^2 = OCH_3$), m. p. 118.8–119.5° (reported, 115,[25] and 116–117[26]). Recrystallization did not raise the melting point. When the reaction time was reduced to three hours the yield dropped to 73%.

The **semicarbazone** crystallized from alcohol in the form of pale yellow needles, m. p. 234–235° dec. (introduced at 200°).

*Anal.* Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.07. Found: C, 57.83; H, 6.52.

(*b*) *Cyclization with Phosphorus Pentoxide.*—Perkin and Robinson[25] obtained an 82% yield of the ketone by cyclization with phosphorus pentoxide. In our hands this procedure gave an 86% yield of quite impure material, m. p. 111–116° from which only a 51% yield of pure II ($R^1 = R^2 = OCH_3$), m. p. 118.4–119.4°, could be isolated by crystallization. The remaining material melted quite low, 93–108°, and may have contained some of the isomeric 6,7-dimethoxy-1-hydrindone.

(*c*) *Cyclization with Stannic Chloride.*—A 0.63-g. sample of the acid was cyclized with 0.700 g. of phosphorus pentachloride and 2.23 g. of stannic chloride according to the procedure of Wilds.[27] A total of 25 ml. of benzene was used, and the reaction mixture was allowed to stand for fifteen hours at room temperature. The total neutral product amounted to 0.311 g. (54% yield) of fairly pure 5,6-dimethoxy-1-hydrindone, m. p. 113.5–117°. Evaporative distillation at 130–135° (0.1 mm.) raised the m. p. to 116–117.5° which was not depressed on admixture with the specimen prepared by hydrogen fluoride cyclization (see above, part *a*).

(*d*) *Attempted Cyclization by the Inverse Aluminum Chloride Method.*—A 3.00-g. sample of the acid, m. p. 96.6–97.8°, was treated (according to the cyclization procedure described at the beginning of the experimental section) with 3.14 g. of phosphorus pentachloride, and then 5.75 g. of aluminum chloride for three hours. The neutral product amounted to 2.72 g., m. p. 59.6–65°. Crystallization of 1.00 g. from petroleum ether gave a total 0.90 g. of colorless plates melting between 63 and 67.8°, the first crop, 0.74 g., melting at 67.4–67.8°. A sample recrystallized four times melted at 67.8–68.4° which is in agreement with the m. p. (67.5–68.5°) reported for 3,4-dimethoxybenzylacetophenone (VII).[11]

*Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.52; H, 6.65.

The oxime crystallized from benzene–petroleum ether (60–68°) in the form of almost colorless prisms, m. p. 109–109.8° (reported,[11] 109°).

The **semicarbazone** was unusually low-melting and sol-

(21) Campbell and Todd, THIS JOURNAL, **64**, 928 (1942).

(22) Thomas and Nathan, *ibid.*, **70**, 331 (1948).

(23) Preparation described by Johnson and Glenn, *ibid.*, **71**, 1087 (1949).

(24) Perkin and Schiess, *J. Chem. Soc.*, **85**, 159 (1904).

(25) Perkin and Robinson, *J. Chem. Soc.*, **91** 1073 (1907).

(26) Konek and Szamak, *Ber.*, **55B**, 102 (1922).

(27) Ref. 3, p. 136.

uble in ether. Crystallization from ethyl acetate gave pale yellow needles, m. p. 124.4–125° dec.

*Anal.* Calcd. for $C_{18}H_{21}O_3N_3$: C, 66.04; H, 6.47. Found: C, 65.63; H, 6.63.

In order to test for the presence of 5,6-dimethoxy-1-hydrindone in the acylation experiment, a sample of the crude product was converted to the semicarbazone. The derivative was formed in 96% yield, and although the m. p. (115–120°) indicated some impurity the product was completely soluble in ether indicating the absence of the ether-insoluble semicarbazone of the dimethoxyhydrindone.

In order to discover if 3,4-dimethoxybenzylacetophenone is convertible to 5,6-dimethoxy-1-hydrindone, 1.00 g. of the former was treated with 1.53 g. of aluminum chloride in benzene for twelve hours at room temperature. The mixture was worked up in the usual way yielding 0.53 g. (53% recovery) of neutral material which was fairly pure starting ketone, m. p. 66–67.5°. The remainder of the material was phenolic and appeared in the potassium hydroxide washings. Methylation with dimethyl sulfate gave 0.46 g. (46%) of tan ketone, m. p. 67–68.5° undepressed on admixture with 3,4-dimethoxybenzylacetophenone.


## Summary

The behavior of nine acids of varying susceptibility to ring closure has been studied in connection with a cyclization procedure involving an inverse Friedel–Crafts technique in which a solution of the acid chloride in benzene is added to a suspension of aluminum chloride in benzene. The yields of cyclic ketones were generally excellent, except in the case of 3,4-dimethoxyphenylpropionic acid which was shown to effect intermolecular acylation of the solvent giving 3,4-dimethoxybenzylacetophenone. This unusual behavior may be attributed to an inhibition of resonance by coördination of the catalyst with the methoxyl groups. The weaker coördinating agent, stannic chloride, effects intramolecular acylation giving the cyclic ketone.


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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# The Synthesis of DL-Threonine.* I. From α-Bromo-β-methoxy-*n*-butyric Acid and Derivatives

BY KARL PFISTER, 3RD., E. E. HOWE, C. A. ROBINSON,[1a] A. C. SHABICA,[1b] E. W. PIETRUSZA[1c] AND MAX TISHLER

Of all the known essential α-amino acids DL-threonine is the most difficult to isolate and to synthesize. The increasing demand for mixtures of the essential amino acids prompted us to evaluate the existing syntheses for DL-threonine with the view of developing a low cost process.

The best-known synthesis of DL-threonine consists in the conversion of crotonic acid into α-bromo-β-methoxy-*n*-butyric acid followed by amination and cleavage of the methoxy group. This sequence of reactions however is complicated by the formation of a mixture of two diastereoisomeric bromo acids, one of which leads to O-methyl-DL-threonine and the other to O-methyl-DL-allothreonine. Of the various reported methods for the preparation of α-bromo-β-methoxy-*n*-butyric acids and their simple derivatives all but one lead to mixtures too poor in the DL-threonine precursor to be useful in the synthesis of this amino acid.

Previous studies of the synthesis of DL-threonine have been handicapped by the facts that no simple separation from DL-allothreonine was known, and no method of analysis of mixtures of the diastereoisomeric amino acids had been developed. The recent description of a microbial assay for L-threonine[2] has greatly simplified the problem. With the aid of this analysis it has become possible to make direct comparisons of the various reported syntheses of DL-threonine and DL-allothreonine and to test the effect of experimental variables and modifications on the relative amounts of the two substances formed in each synthesis. The present paper reports the results of such studies, together with a new practical synthesis of DL-threonine developed in the course of the work.

Until recently the best recorded synthesis of DL-threonine was that of Carter and West.[3] In this method, crotonic acid is treated with mercuric acetate in methanol, and the addition product is brominated. The mixture of bromo acids is aminated, and the reaction products are separated by formylation and isolation of N-formyl-O-methyl-DL-threonine. The latter is converted into pure DL-threonine by boiling hydrobromic acid. The over-all yield of DL-threonine from crotonic acid is about 20%. The yield of DL-threonine from the bromo acid mixture is 30–33% of theory as determined by microbial assay.

Attempts to alter the ratio of diastereoisomeric bromo acids formed by the bromination of α-acetoxymercuri-β-methoxy-*n*-butyric acid were

* This nomenclature is in accord with the rules approved by the American Chemical Society Committee on Nomenclature, Spelling and Pronunciation, as reported by Vickery, *J. Biol. Chem.*, **169**, 237 (1947) and Crane, *Chem. Eng. News*, **25**, 1363 (1947). Throughout this paper the small capital letter prefix will be used in the amino acid sense rather than in the carbohydrate sense. For the sake of brevity however, we have deleted the subscripts which refer to serine, the fundamental substance to which amino acids that bear structural resemblance to the carbohydrates can be formally related.

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(2) Stokes, Gunness, Dwyer and Caswell, *J. Biol. Chem.*, **160**, 35 (1945); Gunness, Dwyer and Stokes, *ibid.*, **163**, 159 (1946).

(3) (a) Carter and West, *Org. Syn.*, **20**, 101 (1940); *cf.* (b) Abderhalden and Heyns, *Ber.*, **67**, 530 (1934).

unsuccessful. Bromination in sunlight[3a] or in darkness, variation of the temperature or the reaction time did not significantly affect the ratio of isomers.

It is interesting that the same ratio of bromo acids is obtained when ethyl crotonate is methoxymercurated and the addition product is brominated as when the procedure of Abderhalden and Heyns[3b] is used. This fact was established by hydrolysis of the mixture of bromo esters to the free acids, amination of this mixture, cleaving the methoxy group and estimating microbially the L-threonine content of the mixture of isomers isolated from the cleavage.

Carter and Ney[4] also prepared a mixture of the bromo acids by treatment of ethyl α,β-dibromo-n-butyrate with two moles of sodium methoxide followed by saponification of the bromo esters. According to the authors, the mixed bromo acids on amination form predominantly DL-allothreonine. Microbial assay of the amination mixture (after cleavage of the methoxy group) indicated that DL-threonine is produced from the bromo acid mixture in 20–23% yield. The same results are obtained when ethyl α-bromocrotonate is substituted for ethyl α,β-dibromo-n-butyrate in the above sequence of reactions.

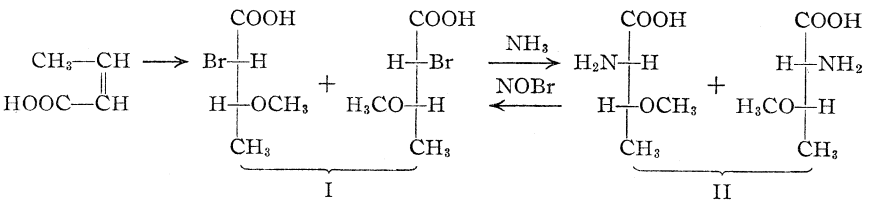
It was of interest to treat ethyl α-bromoisocrotonate with sodium methoxide since the unidirectional addition of methanol should produce a mixture of bromo acids richer in the precursor of DL-threonine.[5] The isolated mixture of amino acids, however, actually contained the same low proportion of DL-threonine as was found when ethyl α-bromocrotonate was the starting material. Both reactions presumably proceed through a common enolate ion.

The addition of the elements of methyl hypobromite to crotonic acid has been shown by West, Krummel and Carter[6] to yield essentially a pure bromo acid, which can be converted into DL-allothreonine. Microbial assays of the mixture resulting from amination of the crude bromo acid and subsequent cleavage indicated a maximum yield of 6–8% DL-threonine.

Since the addition of the elements of methyl hypobromite appears to be predominantly unidirectional, it was of interest to apply the same procedure to isocrotonic acid.[7]

Isocrotonic acid was converted in 80% yield into a crude α-bromo-β-methoxy-n-butyric acid, which on amination and hydrolysis formed DL-threonine in 52–55% yield as determined by microbial assay.[8] DL-Threonine was obtained in a 36% overall yield by isolation of O-methyl-DL-threonine as the N-formyl derivative followed by acid cleavage of the latter. From the mother liquors of the formylation step, a small amount of allothreonine was isolated.

Although the pure bromo acid (m. p. 62–63°) convertible into DL-allothreonine has been prepared,[3b,6] the preparation of the pure α-bromo-β-methoxy-n-butyric acid (I) corresponding to DL-threonine has not been reported. We prepared this compound by treatment of O-methyl-DL-threonine (II) with nitrosyl bromide. This bromo acid is lower melting (m. p. 48–50°) than its diastereoisomer and was converted into DL-threonine in 75% yield (microbial assay) or into pure N-formyl-O-methyl-DL-threonine in 61% yield. DL-Allothreonine could not be detected in the mother liquors. The pure high-melting bromo acid is also prepared by treatment of O-methyl-DL-allothreonine with nitrosyl bromide and on amination forms DL-threonine in only 2% yield (microbial assay). On the basis of these data, the bromo acid obtained from isocrotonic acid consists of about 70% low-melting acid. The presence of the higher melting acid may be due to the ease of isomerization of isocrotonic acid into crotonic acid.[9]




A summary of the amount of DL-threonine formed from the various bromo acid mixtures is presented in Table I. The recorded yields were ascertained by microbial assays of solutions of the different reaction mixtures processed by a standardized procedure described in the Experimental Section.

TABLE I

| Bromo acid mixture | Yield DL-threonine, % |
|---|---|
| West, Krummel and Carter[6] | |
| Crude, undistilled product (77.4% yield) | 6–8 |
| Recrystallized product (m. p. 59–61°) | 2–3 |
| Carter and Ney[4] | 20–23 |
| Carter and West[3a] | 30–33 |
| From isocrotonic acid | 52–55 |
| Pure low-melting bromo acid | 75 |

In connection with the reaction between O-methyl-DL-threonine, II, and nitrosyl bromide and

(4) Carter and Ney, THIS JOURNAL, **64**, 1223 (1942).

(5) The authors are indebted to Dr. H. R. Snyder for this suggestion.

(6) West, Krummel and Carter, *J. Biol. Chem.*, **122**, 605 (1938).

(7) This synthesis was first suggested by Carter, *ibid.*, **112**, 769 (1936), but apparently was pursued no further.

(8) The bromo acid prepared by Carter and West's procedure[3a] on amination and cleavage gave DL-threonine in 30–33% yield as established by microbiological assays.

(9) A similar situation exists with the addition of the elements of methyl hypobromite to cinnamic and allocinnamic acids.[6] The former gave exclusively one isomer, whereas the latter gave predominantly a second isomer plus small amounts of the first.

TABLE II

DERIVATIVES OF α-BROMO-β-METHOXY-*n*-BUTYRIC ACID

| Derivative | Yield, %[a] | M. p., °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|
| High-melting acid | | | | | | |
| $-NH_2$[b] | 69 | 106–107 | 30.03 | 30.48 | 5.14 | 5.18 |
| $-N(CH_3)_2$ | 80 | B. p. 101–104 (6–7 mm.)[c] | 37.51 | 37.74 | 6.30 | 6.32 |
| $-NHC_6H_5$ | 79 | 106–107 | 48.54 | 48.24 | 5.18 | 5.19 |
| $-NC_5H_{10}$ | 68 | 41–43 | 45.46 | 45.68 | 6.87 | 7.13 |
| Low-melting acid | | | | | | |
| $-NHC_6H_5$ | 62 | 87–88 | 48.59 | 48.81 | 5.18 | 5.36 |
| $-NC_5H_{10}$ | 79 | B. p. 115 (2–3 mm.)[d] | 45.46 | 45.22 | 6.87 | 6.64 |

[a] After recrystallization or distillation. [b] *Anal.* Calcd.: N, 7.15. Found: N, 7.34. [c] $n^{20}D$ 1.4915. [d] $n^{20}D$ 1.5091.

amination of the resulting low-melting bromo acid, I, evidently a Walden inversion occurs in neither step or in both steps of the cycle. If it is assumed that the carboxyl group does not participate through β-lactone formation,[10] and that the addition of the elements of methyl hypobromite to crotonic and isocrotonic acids occurs in a *trans* fashion; then the bromo acids have the same configuration as the derived amino acids. On this basis, the amination of our bromo acid takes place with retention of configuration. The O-methyl ethers of threonine and allothreonine are similar to valine and isoleucine, which have been shown to undergo no change in configuration when subjected to the action of nitrosyl bromide followed by amination of the bromo acids.[11] Other α-amino acids thus far examined undergo a change of configuration during the cycle of bromination and amination.[12]

A possible means of bringing about inversion during the amination step and thus utilizing the readily available high-melting bromo acid for the preparation of DL-threonine was suggested by the work of Fischer and Scheibler.[11a] These authors found that although the amination of dextrorotatory α-bromoisovaleric acid produced D-valine, conversion of this bromo acid into α-bromoisovalerylglycine followed by amination and hydrolysis of the amide linkage gave L-valine. Similarly Abderhalden and Zeisset[11b] obtained L-isoleucine by amination of (+)-β-bromo-β-methylvaleric acid but L-alloisoleucine on amination and hydrolysis of the glycine derivative of the same bromo acid.

A series of amide derivatives of the two diastereomeric forms of α-bromo-β-methoxy-*n*-butyric acid were prepared and aminated. The various amides studied are listed in Table II. As indicated in Table III, the amides behave toward amination differently from the free bromo acids. DL-Threonine was formed in significant yield from each of the amides of the higher melting bromo acid. The piperidide of this acid was studied most thoroughly; since it is readily isolated in a pure state and is converted into pure DL-threonine by amination, followed by cleavage of the methoxy group and hydrolysis of the amide linkage. The yields in the amination and in the subsequent steps are good, and the method constitutes a practical synthesis of DL-threonine.

The formation of DL-threonine from the amides of the high melting bromo acid indicates that amination occurred with inversion, and that with the piperidide the inversion was complete or nearly so. Inversion also occurs when the amides of the low melting bromo acid are aminated although the degree of inversion has not been ascertained. The anilide and piperidide of the low melting bromo acid on amination gave DL-threonine in 44.8 and 33.8% yield, respectively (micro-

TABLE III

AMINATION OF DERIVATIVES OF α-BROMO-β-METHOXY-*n*-BUTYRIC ACID

| Derivative | % Yield DL-threonine[a] | % Yield isolated threonine-allo-threonine[b] | Microbial assay of product % DL-threonine | Over-all yield DL-threonine |
|---|---|---|---|---|
| High-melting acid | | | | |
| –OH | 6–8[c] | .. | ... | .. |
| $-NH_2$[d] | 46 | 47.2 | 72 | 34 |
| $-N(CH_3)_2$ | 50.5 | 21.1 | 92 | 19.4 |
| $-NHC_6H_5$ | 55 | 55.2 | 72 | 39.8 |
| $-NC_5H_{10}$[e] | 63.7 | 58.2 | 100 | 58.2 |
| Low-melting acid | | | | |
| –OH | 74–76 | .. | | |
| $-NHC_6H_5$ | 44.8 | .. | | |
| $-NC_5H_{10}$ | 33.6 | 20.2 | 84 | 17 |
| Carter-Ney acid | | | | |
| –OH | 24.6 | .. | ... | .. |
| $-OC_2H_5$ | 45.1 | .. | ... | .. |

[a] These figures were obtained by microbial assay of aliquots of the solutions obtained after hydrolysis of the amination products. [b] These yields are for analytically pure DL-threonine-DL-allothreonine mixtures. [c] Same result obtained whether aminated with methanol–liquid ammonia or aqueous ammonia. [d] After eight hours of hydrolysis the % yield of DL-threonine was only 42.5%. [e] Aminated twenty-four hours at 75° instead of 100° as were all other aminations.

(10) Tarbell and Bartlett, THIS JOURNAL, **59**, 407 (1937).

(11) (a) Fischer and Scheibler, *Ber.*, **41**, 889 (1908); (b) Abderhalden and Zeisset, *Z. physiol. Chem.*, **200**, 179 (1931).

(12) See also Fischer and Warburg, *Ann.*, **340**, 168 (1905); Fischer and Schoeller, *ibid.*, **357**, 1 (1907); Fischer, *ibid.*, **381**, 123 (1911); Fischer, *Ber.*, **39**, 2893, 2929 (1906); Fischer and Carl, *ibid.*, **39**, 3996 (1906); Abderhalden and Chang, *Z. physiol. Chem.*, **77**, 471 (1912); Senter, Drew and Martin, *J. Chem. Soc.*, **113**, 151 (1918).

bial assay), whereas the parent acid forms DL-threonine in 75% yield.

The difference in behavior of the bromo amides from the bromo acids in the ammonia replacement reaction indicates that the carboxyl ion plays a role that is suppressed when ionization is blocked. The "neighboring group" effect[13] is probably involved.

It is interesting to note that the bromo acids corresponding to threonine, valine and isoleucine have a substituent on the β-carbon atoms. This fact may be responsible for the difference in amination behavior of these α-bromo acids as compared to others. Before the nature of the stereochemical transformation can be definitely described, a kinetic study will be required to determine the reaction order.

## Experimental

**Amination of Bromo Acid Mixtures.**—For purposes of comparison, the various bromo acid mixtures were prepared as described in the literature. Amination, hydrolysis and microbial assay as described below gave the values reported in Table I.

Five grams of bromo acid mixture in 55 cc. of concd. ammonium hydroxide was heated at 100° for two hours. This solution was concentrated to dryness under reduced pressure, and the residue was redissolved in water and again concentrated. The residue was hydrolyzed by refluxing for two hours with 17.5 cc. of 40% hydrobromic acid. A solution for microbial assay was prepared by concentrating to dryness, dissolving in water and again concentrating to remove excess acid, adjusting *p*H to neutral, filtering and diluting.

**α-Bromoisocrotonic Acid.**—The method of Michael and Schulthess[14] was employed for preparing α-bromoisocrotonic acid, m. p. 92–93°, in 54% yield from crotonic acid. α-Bromoisocrotonic acid is reported to melt at 92° and α-bromocrotonic acid at 106.5°.

**Ethyl α-Bromoisocrotonate.**—α-Bromoisocrotonic acid was esterified according to the method of Auwers and Harres[15] with ethanol in the presence of sulfuric acid. Twice distilled product boiling at 72–73.5° (12 mm.) was obtained in 57% yield. A sample of the ester on hydrolysis gave pure α-bromoisocrotonic acid, which indicated that no isomerization had occurred.

**Ethyl α-Bromo-β-methoxybutyrate.**—To a vigorously agitated solution of 110 cc. of methanol containing 1.4 g. (0.03 mole) of sodium methoxide, 43 g. (0.223 mole) of ethyl α-bromoisocrotonate was slowly added while the temperature was held below 25°. The reaction mixture was agitated for an additional two hours and then poured into 250 cc. of ice water containing 5-cc. of concentrated hydrochloric acid. The ester layer was separated, and the aqueous phase was extracted with three 60-cc. portions of ether. The combined ester layer and ether extracts were washed once with a saturated solution of calcium chloride and dried with sodium sulfate. The ether was removed by evaporation, and the ester was distilled at reduced pressure. A product boiling at 85–87° (18 mm.) was obtained in 79% yield (39.3 g.).

This ester after saponification, amination, and cleavage with hydrobromic acid gave in 31% yield a mixture of DL-threonine and DL-allothreonine in an 18:82 ratio (microbial assay).

**Isocrotonic Acid.**—This material was prepared according to the procedure of Michael and Schulthess[14] by action of phosphorus pentachloride on acetoacetic ester to produce β-chlorocrotonic (18–20% yield) and β-chloroisocrotonic (29–30% yield) acid, which are separable by steam distillation. Reduction of the latter with sodium amalgam gave isocrotonic acid in 50% yield after purification as the sodium salt and distillation. Isocrotonic acid was also prepared by conversion of β-chlorocrotonic acid into tetrolic acid[16] (20–30% yield) followed by hydrogenation with palladium on Norit (75% yield).[17] All isocrotonic acid used was carefully separated from crotonic acid via the sodium salts and then distilled, b.p. 70–71° (16–17 mm.), m. p. 12–15°.

**α-Bromo-β-methoxy-n-butyric Acid from Isocrotonic Acid.**—A run was made exactly as described by West, Krummel and Carter,[6] but isocrotonic was substituted for crotonic acid. The yield of crude α-bromo-β-methoxy-*n*-butyric acid obtained as an oil by concentrating the ether solution to constant weight was 79.8% of theory. When crotonic acid was used, the crude product resulted in nearly identical yield (77.4%).

**Pure Low-melting α-Bromo-β-methoxy-n-butyric Acid from O-Methyl-DL-threonine.**—Pure N-formyl-O-methyl-DL-threonine[3a] (100 g., 0.621 mole) was refluxed for three hours with 1 l. of 1 *N* hydrobromic acid. The resulting solution of O-methyl-DL-threonine was concentrated under reduced pressure, and the gummy residue was dissolved in 200 cc. of water and again concentrated to dryness. The residue was dissolved in 1240 cc. of 2.5 *N* sulfuric acid containing 250 g. of potassium bromide. The solution was cooled to 0° and stirred while 65.5 g. of sodium nitrite was added in small portions over a period of one and one-half hours. The solution was stirred for an hour at 0°, then heated to 25° and stirred another hour. Ether extraction followed by washing with water, drying over sodium sulfate and concentrating gave α-bromo-β-methoxy-*n*-butyric acid (113.9 g., 93.7%). Fractional distillation yielded chiefly material (101 g.) that distilled at 126–128° (6 mm.) and on cooling gave a solid of m. p. 48–50°.

*Anal.* Calcd. for $C_5H_9O_3Br$: C, 30.48; H, 4.61. Found: C, 30.25; H, 4.65.

**N-Formyl-O-methyl-DL-threonine.**—The bromo acid (45.0 g., 0.228 mole) from isocrotonic acid and 495 cc. of concentrated aqueous ammonia were heated at 100° in an autoclave for two hours. Exactly 10% of the resulting solution was concentrated to dryness; the residue was dissolved in water and again concentrated to dryness. This residue was refluxed for two hours with 15.5 cc. of 40% hydrobromic acid and the resulting solution concentrated to dryness as described above. The residue was again taken up in water and the solution diluted to 100 cc. for microbial assay. Found: 14.1 mg. of DL-threonine/cc. or a total of 14.1 g. or 51.8%. The remaining 90% of the amination mixture was concentrated to dryness, diluted with 30 cc. of water and again concentrated to dryness. A solution of the solid white residue in 101 cc. of 88% formic acid at 45° was treated dropwise with 33.8 cc. of acetic anhydride. The addition took fifteen minutes, and the temperature rose to 60°. After fifteen minutes at 60°, concentration gave a residue, which was dissolved in 40 cc. of water and again concentrated to dryness. The residue was dissolved in 35 cc. of hot water and cooled to 0° for several hours. Filtration gave crude N-formyl-O-methyl-DL-threonine of m. p. 164–168° in 51.8% yield. Recrystallization of this material from water gave N-formyl-O-methyl-DL-threonine of m. p. 176–177.5° in two crops totaling 40.8% yield from the bromo acid.

The combined mother liquors were concentrated, and the residue dissolved in 84 cc. of 40% hydrobromic acid was refluxed for two hours. The mixture was concentrated to dryness, and the dried residue was extracted with 200 cc. of ethyl alcohol. The alcoholic solution was made alkaline with concentrated ammonia, and a small precipitate of inorganic material was filtered. On standing overnight at 0°, the filtrate deposited crystalline material (8.1 g.), which was recrystallized from 10 cc. of hot water and 23 cc. of alcohol. This product (3.4 g.) was again

(13) Defined and studied by S. Winstein and his students. The more recent papers are Winstein and Seymour, THIS JOURNAL, **68**, 119 (1946); Winstein and Grunwald, *ibid.*, **68**, 536 (1946).

(14) Michael and Schulthess, *J. prakt. Chem.*, [2] **46**, 236 (1892).

(15) Auwers and Harres, *Z. physik. Chem.*, **A143**, 1 (1929).

(16) Deprez, *Bull. soc. chim.*, [3] **11**, 392 (1894).

(17) Paul and Schiedewitz, *Ber.*, **63**, 766 (1930).

recrystallized from water–alcohol to give a mixture of DL-threonine and DL-allothreonine melting at 213–214° (2.4 g., 9.8% yield).

*Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62. Found: C, 40.19; H, 7.59.

Since bioassay showed this material was 60% DL-threonine, the isolated yield of DL-allothreonine was 3.9%.

When the pure low melting (m. p. 48–50°) α-bromo-β-methoxy-*n*-butyric acid was subjected to the above amination steps, the yield of DL-threonine (microbial assay) was 75%. Application of the formylation step gave N-formyl-O-methyl-DL-threonine melting at 176–178° (no recrystallization) in 60.3% yield. When the mother liquors of the formylation step were hydrolyzed with hydrobromic acid, more pure DL-threonine was isolated (9% yield). No DL-allothreonine could be detected.

**Amides of α-Bromo-β-methoxy-*n*-butyric Acid.**—These derivatives were prepared essentially by the procedure described below for the piperidide of the high-melting bromo acid. Analyses and some physical properties of these derivatives are listed in Table II. The high melting acid employed in this work was the crude acid obtained by the procedure of West, Krummel and Carter,[6] whereas the low-melting acid was prepared from O-methyl-DL-threonine by the nitrosyl bromide reaction (b. p. 126–128° (6 mm.). The solid amides were recrystallized from benzene or Skelly-solve D.

**α-Bromo-β-methoxy-*n*-butyric Acid Piperidide.**—A mixture of 29.6 g. (0.15 mole) of high melting α-bromo-β-methoxy-*n*-butyric acid, 150 cc. benzene and 2 drops of pyridine was treated with 13.5 cc. of thionyl chloride and then refluxed for one and one-half hours. The mixture was concentrated under reduced pressure until 50 cc. of benzene was removed. After addition of 100 cc. of benzene, the solution was cooled to 5° and added dropwise at 4–5° over a period of one and one-fourth hours to an ice-cooled solution of 32.5 cc. (0.33 mole) of piperidine in 100 cc. of benzene. After removal of the ice-bath the mixture was stirred one-half hour before the piperidine hydrochloride was filtered.

The benzene solution was extracted with three 50-cc. portions of water and then concentrated under reduced pressure to constant weight, 36.1 g. (91.2%). The yellow oil crystallized on standing at 5° but became sticky at room temperature. The crude product was recrystallized from 20 cc. of Skelly-solve D, refrigerated overnight and filtered on a pre-cooled Buchner funnel. After being washed with a small amount of ice-cold Skelly-solve and dried, the product weighed 26.8 g. (67.7%), m. p. 41–43°. This piperidide is soluble in all the common solvents except water.

**Amination of the Bromo Amides.**—The amination of the bromo amides was carried out by the procedure described below for the piperidide of the high-melting bromo acid except that the reaction temperature was 100°. In every case, Volhard titration of the completed reaction mixture showed that over 98% of the organic bromine had been converted into bromide ion. A hydrolysis time of fifteen hours was found to give DL-threonine in maximum yields.

**DL-Threonine.**—A solution of 13.2 g. (0.05 mole) of the piperidide of the high-melting bromo acid in 60 cc. of methanol and 30 cc. of liquid ammonia was heated at 75° for twenty-four hours in a glass-lined bomb.

The solution was concentrated under reduced pressure and the residue refluxed with 40 cc. of 40% hydrobromic acid for fifteen hours. After the reaction mixture was concentrated to dryness water was added and again removed. This operation was repeated after which the residue was dissolved in 40 cc. of water and made alkaline with concentrated ammonium hydroxide solution. Piperidine was removed by extraction with ether and a sample of the aqueous solution taken for bioassay. Found: 63.7% of theoretical yield of DL-threonine.

The remaining solution was made acid to congo red with concentrated hydrochloric acid and concentrated to dryness. The residue was extracted with three 25-cc. portions of boiling isopropyl alcohol. After cooling a little more inorganic material precipitated in the isopropyl alcohol extract and was removed by filtration. Aniline (7.8 cc.) was added to the warm isopropyl alcohol solution, and the resulting slurry was stirred overnight at room temperature. The white product was filtered, washed with isopropyl alcohol and ether, and dried at 65°; yield, 3.8 g. (74.8%). The crude product was recrystallized by the addition of 45 cc. of isopropyl alcohol to a vigorously agitated solution in 19 cc. of hot water. After being chilled overnight DL-threonine was obtained (2.96 g., 58.2% from the piperidide).

*Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.03; H, 7.70; N, 11.96.

Microbial assay indicated this material was 100% pure, while solubility analysis showed a purity of over 97%.

**Acknowledgment.**—We are indebted to Mr. R. N. Boos for the microanalytical data and to Dr. J. L. Stokes for the microbial assays.

## Summary

1. An evaluation of the previously described α-bromo-β-methoxy-*n*-butyric acid mixtures for the preparation of DL-threonine has been made.

2. DL-Threonine has been prepared from isocrotonic acid in substantially higher yields than from crotonic acid through the corresponding α-bromo-β-methoxy-*n*-butyric acids.

3. Evidence indicating that a Walden inversion does not occur during the amination of α-bromo-β-methoxy-*n*-butyric acid is presented. Amination of the amides of the bromo acid takes place with inversion.

4. A practical synthesis of DL-threonine from the piperidide of the readily available, high-melting α-bromo-β-methoxy-*n*-butyric acid is described.

RAHWAY, NEW JERSEY RECEIVED NOVEMBER 27, 1948

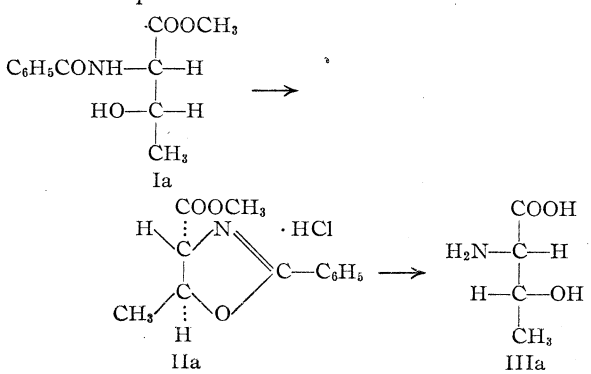
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# The Synthesis of DL-Threonine. II. Interconversion of DL-Threonine and DL-Allothreonine[1]

BY KARL PFISTER, 3RD., C. A. ROBINSON,[2a] A. C. SHABICA[2b] AND MAX TISHLER

In connection with a search for more practical syntheses of DL-threonine, useful methods of converting the more readily available DL-allothreonine into its epimer were sought. A method of effecting the inversion was discovered and announced in a preliminary communication.[3] While that paper was in press a report[4a] in the recent British literature on the same subject reached this country, and was followed later by a second article.[4b] We wish to elaborate at this time our previous communication on the method for the interconversion of DL-allothreonine and DL-threonine, which is also the basis of a higher yielding synthesis of the latter.

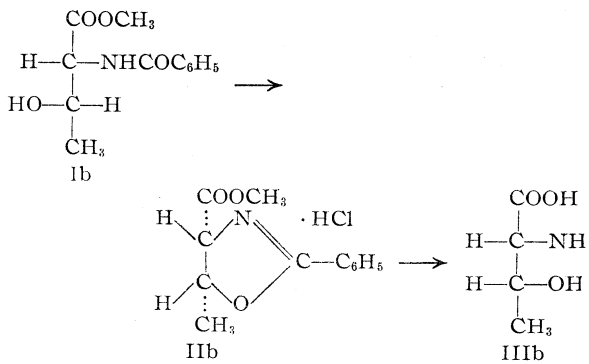
The reaction of $\alpha$-acylamido-$\beta$-hydroxy compounds with dehydrating agents such as thionyl chloride and phosphorus chlorides to give oxazolines is of general application.[5] Accordingly, 2-phenyl-5-methyl-4-carbomethoxyoxazoline hydrochloride,[6] IIa, was prepared in quantitative yield by treatment of the methyl ester of N-benzoyl-DL-allothreonine, Ia, with thionyl chloride. The oxazoline, IIa, on treatment with dilute mineral acids gave DL-threonine, IIIa, in 96.7% yield as determined by microbial assay and in 70% yield as isolated pure material.



Ia IIa IIIa

The hydrolysis of the oxazoline, IIa, can be carried out stepwise. When a water solution is refluxed one hour, the methyl ester of O-benzoyl-DL-threonine hydrochloride is obtained in excellent yield. The latter is converted into DL-threonine by acid hydrolysis and is rearranged to N-benzoyl-DL-threonine by treatment with alkali.

The inversion described can be utilized to convert DL-threonine into DL-allothreonine. By the same series of reactions, DL-threonine was converted via N-benzoyl-DL-threonine methyl ester, Ib, and the isomeric 2-phenyl-5-methyl-4-carbomethoxyoxazoline hydrochloride, IIb, into DL-allothreonine, IIIb. The yield of isolated product from the oxazoline, IIb, was 81%.



Ib IIb IIIb

We overlooked the important observation made by Elliot[4b] that the oxazoline made from threonine, IIb, can be converted into the more stable isomeric oxazoline, IIa, by treatment with alkali. We did note that both isomers were sensitive to alkali; since on heating with 2.5 *N* sodium hydroxide for four hours, the yield of DL-threonine in each case was about 27% as determined by microbial assay. In agreement with Elliot, we also observed that when the ethyl ester of DL-allothreonine hydrochloride was treated with benzylimido ethyl ether and the resulting oxazoline subjected to acid hydrolysis, no threonine was formed.

Masking of the carboxyl group during oxazoline formation is necessary, since otherwise azlactonization occurs. Thus, after treatment of N-benzoyl-DL-allothreonine with thionyl chloride, only the azlactone, 2-phenyl-4-ethylidene-5-oxazolone, could be isolated. Hydrolysis of the reaction mixture from such treatment followed by microbial assay showed DL-threonine in less than 1.7% of the theoretical yield, indicating that oxazoline formation was entirely suppressed.

The formation of an oxazoline hydrochloride from N-acyl derivatives of DL-serine and some chemical properties of this oxazoline have been

(1) For the preceding paper of the series, see Pfister, Howe, Robinson, Shabica, Pietrusza and Tishler, THIS JOURNAL, **71**, 1096 (1949).

(2) Present address: (a) Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts; (b) Ciba Pharmaceutical Products, Inc., Summit, N. J.

(3) Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **70**, 2297 (1948), (D-threonine in line 11 paragraph 3 of this communication is a typographical error which should read DL-threonine). Additional data are recorded by Pfister and Tishler, U. S. Patent 2,446,196; *C. A.*, **42**, 811 (1948).

(4) (a) Attenburrow, Elliot and Penny, *J. Chem. Soc.*, 310 (1948); (b) Elliot, *Nature*, **162**, 657 (1948).

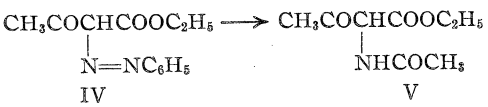
(5) Bergmann and Brand, *Ber.*, **56**, 1280 (1923).

(6) All configurational formulations in this paper are in accord with Fischer's conventions. To effect economy of space only one enantiomorph is given although it should be understood that the second enantiomorph is included when the text refers to the DL-form. The stereochemical formulations for the oxazolines (IIa, IIb and VII) are those suggested by the English workers.[4]

described by Bergmann.[7] Since serine contains only one asymmetric carbon atom, the full significance of this series of reactions was not realized. Nagai and Kanao,[8] however, did convert *dl*-N-benzoyl-norephedrine through the oxazoline into the diastereomeric *dl*-N-benzoyl-norisoephedrine. The latter report and the additional data we shall present in a later publication indicate the method is a general one for the interconversion of diastereoisomers containing an amino and a hydroxyl group on adjacent asymmetric carbon atoms.

The successful utilization of the oxazoline inversion reaction for a practical, total synthesis of DL-threonine requires an easy method for the preparation of esters of N-acyl derivatives of allothreonine. Acetoacetic ester proved to be an excellent starting point for this synthesis.

Ethyl α-acetamidoacetoacetate, V, was obtained in 88% yield from acetoacetic ester by the preparation and reductive acetylation of ethyl α-phenylazoacetoacetate, IV.



IV V

The preparation of this acetamido compound by the reductive acetylation of ethyl α-oximinoacetoacetate has been reported recently.[9] The present method is preferred, since the use of the unstable oximino compound is avoided, and a better over-all yield is obtained.[10]

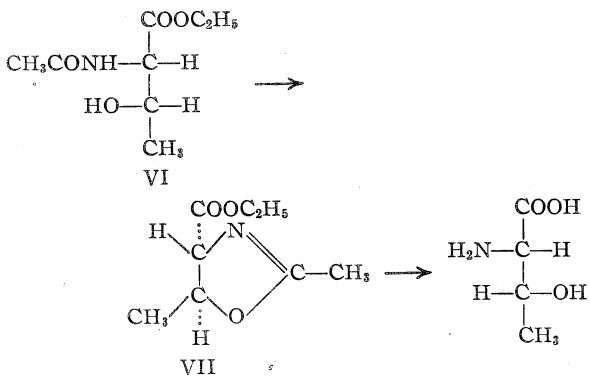
The behavior of ethyl α-acetamidoacetoacetate toward catalytic hydrogenation was studied, since Adkins and Reeve[11] reported that a mixture of DL-threonine and DL-allothreonine was obtained on catalytic hydrogenation and subsequent hydrolysis of ethyl α-oximinoacetoacetate. A variety of hydrogenation procedures were tried and appraised by hydrolysis of the reaction mixture and determination of the DL-threonine content microbiologically. The results, listed in Table I, are similar to those reported by Albertson and co-workers[9] and establish the fact that the ethyl ester of N-acetyl-DL-allothreonine is formed predominantly.

TABLE I

| Catalyst | Solvent | DL-Threonine, % yield |
|---|---|---|
| Platinum oxide | Water | 15–20 |
| Platinum oxide | Glacial acetic acid | 19 |
| Platinum oxide | Alcohol | 26 |
| Raney nickel[a] | Water | 30 |
| Raney nickel | Water | 34 |

[a] This run was made at high pressure; all others at 15–40 p.s.i.

By the use of platinum oxide in aqueous solution, ethyl α-acetamidoacetoacetate was readily hydrogenated at room temperature and low pressure to give in theoretical yield a colorless oil having an 80–85% content of N-acetyl-DL-allothreonine ethyl ester. An identical product was also obtainable by catalytic reductive acetylation of ethyl α-phenylazoacetoacetate, removal of acetanilide and further hydrogenation. Repeated crystallization gave pure N-acetyl-DL-allothreonine ethyl ester (VI). Hydrolysis of this material and microbial assay of the solution showed DL-threonine in only a 0.7% yield. When the purified N-acetyl-DL-allothreonine ester was treated with thionyl chloride, the oxazoline VII was obtained. Acid hydrolysis of VII produced DL-threonine in 94.6% yield as established by microbial assay.



VI VII

When the entire hydrogenation product was treated with thionyl chloride and the oxazoline-containing reaction solution was hydrolyzed, crude DL-threonine of 83.2% purity (bioassay) was isolated in 88.7% yield. Simple crystallization in this case failed to yield DL-threonine free from contaminating DL-allothreonine produced by inversion of the N-acetyl-DL-threonine ethyl ester in the hydrogenation product. In order to avoid wasteful recrystallization of the hydrogenation product, it was necessary to devise a separation of the diastereoisomeric amino acids. Although a number of procedures are available for separating various derivatives of DL-threonine and DL-allothreonine,[12] none have been reported for the unsubstituted amino acids. We have found that the sodium salt of DL-threonine is far less soluble in ethanol than that of DL-allothreonine and is, in fact, well-suited to separation of these isomers. By this method the crude DL-threonine obtained without purification of the hydrogenation product was converted into pure DL-threonine sodium salt in 83.5% yield. Reconversion into DL-threonine in 91% yield followed by a recrystallization (96.8% recovery)

(7) Bergmann and Miekeley, *Z. physiol. Chem.*, **140**, 128 (1924); Bergmann, Miekeley, Weinmann and Kann, *ibid.*, **143**, 108 (1925).

(8) Nagai and Kanao, *Ann.*, **470**, 160, 175 (1929).

(9) Albertson, Tullar, King, Fishburn and Archer, THIS JOURNAL, **70**, 1151 (1948); Wiley and Borum, *ibid.*, **70**, 1666 (1948).

(10) An attractive procedure for preparing ethyl α-benzamidoacetoacetate from hippuric acid and acetic anhydride is described by Attenburrow, Elliot and Penny.[4a]

(11) Adkins and Reeve, THIS JOURNAL, **60**, 1328 (1938).

(12) West and Carter, *J. Biol. Chem.*, **119**, 109 (1937); Carter and Risser, *ibid.*, **139**, 255 (1941).

gave pure DL-threonine in 57% over-all yield from acetoacetic ester.

The oxazoline, VII, was found to be similar in chemical reactivity to the phenylated oxazoline, IIa. Its hydrochloride was converted into O-acetyl-DL-threonine ethyl ester hydrochloride on exposure to moist air. On treatment with alkali, the latter was transformed into N-acetyl-DL-threonine. Other reactions are described in the experimental section.

A study of the inversion mechanism using optically active compounds is under way. Our data support the views of the English investigators[4] that inversion occurs during ring closure involving the $\beta$-carbon atom. The oxazoline, convertible into DL-threonine by hydrolysis, has the same *trans* configuration as threonine, whereas the isomeric oxazoline has the *cis* configuration.

## Experimental

### I. Conversion of DL-Allothreonine into DL-Threonine

**N-Benzoyl-DL-allothreonine Methyl Ester, I.**—N-Benzoyl-DL-allothreonine[13] was treated with an ether solution containing an excess of diazomethane. After evaporation of solvent and reagent, the crystalline ester, m. p. 109–110°, remained. A sample crystallized from benzene in rosettes of needles, m. p. 110–111°.

*Anal.* Calcd. for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.37. Found: C, 60.86; H, 5.99.

**2-Phenyl-5-methyl-4-carbomethoxyoxazoline Hydrochloride, IIa.**—The crude methyl ester from above (2.37 g.) was added in portions to 6.0 cc. of ice-cold thionyl chloride. A little heat was evolved, and the solution was allowed to stand at room temperature for two hours. The solution was poured into 150 cc. of absolute ether; the precipitated gum crystallized when scratched. The yield after filtering, washing with ether and drying was 2.55 g. (quantitative); m. p. 117–118° with HCl evolution.

Solution in cold dry chloroform (5 cc./g.) and precipitation with absolute ether (15 cc./g.) gave material that melted at 118–119° on rapid heating from 110°.

*Anal.* Calcd. for $C_{12}H_{13}O_3N\cdot HCl$: C, 56.36; H, 5.52. Found: C, 56.50; H, 5.71.

**DL-Threonine.**—Two grams of crude oxazoline IIa in 20 cc. of 10% hydrochloric acid was refluxed three hours. After the solution was cooled in ice for one-half hour the benzoic acid was removed by filtration (73.4% yield, m. p. 120–121°), and the filtrate was concentrated to dryness on an aspirator. The residue was again dissolved in water and concentrated, and the residue was taken up in water for microbial assay. The assay showed the presence of DL-threonine in 96.7% yield (0.90 g.).

Two-thirds of the bioassay solution was concentrated to dryness as described above, taken up in alcohol and again concentrated. The residue was dissolved in 15 cc. of warm anhydrous alcohol and the solution made alkaline to litmus with ammonium hydroxide. The crystalline product (0.75 g.) was dissolved in 4 cc. of water, and the solution was diluted with 9.3 cc. of alcohol. After four hours at 5°, the crystalline DL-threonine was filtered, washed with alcohol and ether, and dried. The product weighed 0.435 g. (70.1% yield) and melted at 229–230°.

*Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.35; H, 7.70; N, 11.46.

Bioassay showed this material was 100% DL-threonine.

**O-Benzoyl-DL-threonine Methyl Ester Hydrochloride.**—Crude oxazoline hydrochloride IIa (1.28 g.) was refluxed for one hour in 10 cc. of water. The solution was concentrated under reduced pressure and the residue dissolved in chloroform was again concentrated to ensure the absence of water. A solution of the residue in 10 cc. of chloroform was treated with Norit, filtered and diluted with 20 cc. of absolute ether. The nicely crystalline precipitate weighed 1.2 g. (87.5%) and melted at 151–153°. Reprecipitation of a sample as above gave a product sintering at 145° and melting at 155–156° with gas evolution.

*Anal.* Calcd. for $C_{12}H_{15}O_4N\cdot HCl$: C, 52.66; H, 5.89; N, 5.12. Found: C, 52.60; H, 6.06; N, 5.37.

A solution of 0.25 g. in 3 cc. of 10% hydrochloric acid was boiled three hours, concentrated to dryness, and the residue was dissolved in water for microbial assay. Found: 0.105 g. of DL-threonine (88.3% yield).

N-Benzoyl-DL-threonine was obtained in 69% yield from the methyl ester of O-benzoyl-DL-threonine hydrochloride by storing a solution of the latter (0.5 g.) in 4.75 cc. of normal sodium hydroxide for fifteen hours. The resulting mixture was made acid to congo paper with hydrochloric acid and refrigerated for four hours. The product was obtained as needles, m. p. 145–146°; wt. 0.28 g., and was identified as N-benzoyl-DL-threonine by a mixed m. p. determination with an authentic sample.

**Benzoyl-$\alpha$-aminocrotonic Azlactone.**—A mixture of 2.33 g. of N-benzoyl-DL-allothreonine and 6 cc. of thionyl chloride was held at room temperature for two hours. The mixture was diluted with 50 cc. of ether, and the crystalline solid (0.35 g., m. p. 85–86°) was collected. After recrystallization from dilute alcohol, the product melted at 89–92° and did not depress the m. p. of an authentic sample of the "Azlactone I" described by Carter, Handler and Melville.[14]

A similar run was worked up by subjecting the completed reaction mixture to hydrolysis with 10% hydrochloric acid, separation of benzoic acid and microbial assay. The yield of DL-threonine was less than 1.7%.

### II. Conversion of DL-Threonine into DL-Allothreonine

**N-Benzoyl-DL-threonine Methyl Ester.**—A sample of N-benzoyl-DL-threonine treated with ethereal diazomethane and concentrated to dryness gave a viscous oil, which slowly crystallized, m. p. 82–84°. Recrystallization of a sample from benzene–ether did not change the melting point.

*Anal.* Calcd. for $C_{12}H_{14}O_4N$: C, 60.76; H, 6.37. Found: C, 60.97; H, 6.50.

The product is very sparingly soluble in ether or hot ligroin (b. p. 80–115°), but dissolves readily in benzene, alcohols or hot water.

**2-Phenyl-5-methyl-4-carbomethoxyoxazoline Hydrochloride, IIb.**—Treatment of N-benzoyl-DL-threonine methyl ester exactly as described for the N-benzoyl-DL-allothreonine ester gave material of m. p. 130–131° (2.45 g., 96%). A sample purified by precipitation from chloroform with ether melted at 131–132° (capillary inserted at 120°).

*Anal.* Calcd. for $C_{12}H_{13}O_3N\cdot HCl$: C, 56.36; H, 5.52. Found: C, 56.58; H, 4.91.

A mixture of IIb with pure oxazoline IIa (m. p. 118–119°) melted lower than the latter alone.

The oxazoline was converted into pure DL-allothreonine in 80.6% yield in the same way as the oxazoline IIa was transformed into DL-threonine. Microbial assays of a solution of the hydrolyzed oxazoline indicated less than 0.8% yield of DL-threonine.

### III. Synthesis of DL-Threonine from Acetoacetic Ester

**Ethyl $\alpha$-Phenylazoacetoacetate, IV.**—This intermediate was prepared in 92.7% yield from acetoacetic ester essentially by the method of Bülow and Neber.[15]

**Ethyl $\alpha$-Acetamidoacetoacetate, V.**—A mixture of glacial acetic acid (513 cc.) and acetic anhydride (257 cc.

(13) West and Carter, *J. Biol. Chem.*, **119**, 109 (1937).

(14) Carter, Handler and Melville, *ibid.*, **129**, 359 (1939).

(15) Bülow and Neber, *Ber.*, **45**, 3732 (1912).

was cooled to 10°, and 390 g. of zinc dust was added to the vigorously stirred solution. While the temperature was kept at 10–15°, a solution of 217.4 g. (0.927 mole) of ethyl α-phenylazoacetoacetate in 232 cc. of glacial acetic acid was added over one and one-half to two hours. The mixture was then allowed to warm to 25–30°, and stirring was continued for three hours. The slurry was filtered and the cake of zinc dust and zinc acetate washed well with glacial acetic acid. Concentration of the filtrate and washings under reduced pressure gave a residue to which was added 500 cc. of water at 55°. After being stirred for five minutes the mixture was cooled to 10°, and the remaining acetic acid was neutralized with solid sodium bicarbonate. The mixture was held at 0° for one-half hour, and the acetanilide (113.5 g., 91% yield) was collected.

The filtrate was extracted with four 250-cc. portions of chloroform, and the combined extracts were concentrated to dryness under reduced pressure. The viscous residue weighed 164.2 g. (94.6% yield) and solidified on standing; m. p. 39–42°.

A sample recrystallized from toluene melted at 47.5–48.5°.

*Anal.* Calcd. for $C_8H_{13}O_4N$: C, 51.34; H, 6.95. Found: C, 51.56; H, 7.08.

**Ethyl α-Acetamido-β-hydroxybutyrate, VI. (a) From Ethyl α-Acetamidoacetoacetate.**—A solution of 65.5 g. (0.35 mole) of ethyl α-acetamidoacetoacetate in 525 cc. of water was made barely alkaline by adding 5 cc. of 1 *N* sodium hydroxide and hydrogenated at 25° and 30–40 p. s. i. in the presence of 0.65 g. of platinum oxide catalyst. The theoretical amount of hydrogen was absorbed in four hours, and a ferric chloride test at this point was negative. After separation of the catalyst the filtrate was concentrated to dryness on the water aspirator and the residue dissolved in benzene and reconcentrated to constant weight. The thick, colorless oil (33.2 g.) is readily soluble in water, chloroform and alcohol, somewhat less soluble in benzene and ethyl acetate, and sparingly soluble in ether, toluene and carbon tetrachloride.

A considerable number of such reductions were made, and aliquots were hydrolyzed with hydrochloric acid and assayed microbiologically for DL-threonine. The assays fixed the DL-threonine yield as 15 to 20%, corresponding to a 15–20% content of N-acetyl-DL-threonine ethyl ester in the hydrogenation product.

The hydrogenation of ethyl α-acetamidoacetoacetate under other conditions was studied. As indicated in Table I, the yield of N-acetyl-DL-threonine ethyl ester does vary with the catalyst, solvent and temperature. Raney nickel at low pressure favors the formation of threonine. The yield of DL-threonine was established by microbial assays.

**(b) From Ethyl α-Phenylazoacetoacetate.**—A solution of ethyl α-phenylazoacetoacetate (36.5 g.) in 156 cc. of glacial acetic acid was treated with 0.5 g. of Darco and filtered. After the addition of 36.8 cc. of acetic anhydride and 4.0 g. of 5% palladium on Darco the solution was hydrogenated at room temperature and 25–40 p. s. i. Two moles of hydrogen were absorbed in six hours. The solution was filtered and concentrated to dryness. Two additions of water followed by concentration to dryness (reduced pressure) removed most of the acetic acid. The reddish oil was treated with 117 cc. of water, stirred at 0° for one-half hour, and the crystalline acetanilide was collected; wt. 19.3 g. (92% yield).

The filtrate was neutralized with sodium hydroxide, treated with charcoal and hydrogenated at room temperature and 25–40 p. s. i. in the presence of 0.3 g. of platinum oxide. The hydrogenation was slow, and only after fifteen hours was the ferric chloride test negative. Filtration and concentration of the reduced mixture gave the same type of product as above with acetanilide as a contaminant. Microbial assay of a hydrolyzed aliquot established a 15.8% yield of N-acetyl-DL-threonine ethyl ester.

**DL-Threonine. (a) From Partially Purified N-Acetyl-DL-allothreonine Ethyl Ester.**—The residue obtained from the reduction of 32.8 g. of ethyl α-acetamidoacetoacetate carried out and worked up in the manner described above was dissolved in 25 cc. of hot ethyl acetate and allowed to crystallize at 5° for sixteen hours. The product was filtered, washed with 5 cc. of cold ethyl acetate and dried; wt. 17.5 g. (52.8% recovery), m. p. 68–74°. (According to the microbial assay procedure, the product contained 3.6% of the DL-threonine precursor.) Repeated recrystallizations from ethyl acetate gave pure ester as large rectangular prisms melting at 76–77°.

*Anal.* Calcd. for $C_8H_{15}O_4N$: C, 50.78; H, 7.99. Found: C, 50.54; H, 8.04.

A solution of 16.0 g. of the partially purified ester (m. p. 68–74°) in 17.3 cc. of benzene was cooled to 10° and stirred; thionyl chloride (14 cc.) was added dropwise while the temperature was kept at 13–15°. After the addition (three-fourths hour) the temperature was raised to 30° and held there for an hour. The solution was cooled to below 10° while 43 cc. of cold water was added slowly. The layers were separated and the benzene layer extracted twice with 12-cc. portions of water. The combined aqueous extracts were washed with 5 cc. of benzene and refluxed for two and one-half hours. After treatment with charcoal, an aliquot was subjected to the microbial assay procedure. The assay yield of DL-threonine was 88.5%.

The remainder of the reaction mixture was concentrated to dryness under reduced pressure. The colorless residue was dissolved in 62 cc. of hot isopropyl alcohol, and 15 cc. of aniline was added to the solution. The mixture was agitated at room temperature for fourteen hours and filtered. The product (8.65 g., 89.4% yield) was found to be 98.6% DL-threonine by microbial assay. Recrystallization of 6.1 g. from 30.5 cc. of water and 71 cc. of absolute ethanol gave pure product; 5.5 g., 90.2% recovery, 37.6% yield from ethyl acetoacetate, m. p. 229–230°, bioassay 100%.

*Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62. Found: C, 40.46; H, 7.64.

When the pure ester (m. p. 76–77°) was subjected to the cyclization reaction, the yield of DL-threonine was 94.6% as established by the microbial assay.

**(b) From Crude Ethyl α-Acetamido-β-hydroxybutyrate.**—Ethyl α-acetamidoacetoacetate (29.1 g.) was hydrogenated as described above, and the residual oil in 32 cc. of benzene was treated with 25.9 cc. of thionyl chloride. The reaction mixture was worked up and hydrolyzed in the manner just described. The solid residue of threonine and allothreonine hydrochloride was dissolved in 116 cc. of hot isopropyl alcohol and precipitated by the addition of 28.2 cc. of aniline. The crystalline product weighed 16.4 g. (88.7% yield) and contained 83.2% DL-threonine (microbial assay).

For elimination of DL-allothreonine, 15.6 g. (0.131 mole) of this product was added to a hot solution of sodium ethoxide prepared from 3.02 g. (0.131 mole) of sodium and 60.4 cc. of anhydrous alcohol. The mixture was refluxed for five minutes to ensure complete solution. Shortly thereafter the crystalline sodium salt of DL-threonine separated. After storage for sixteen hours at room temperature the salt was collected, washed with 15 cc. of alcohol and dried at 50–55°; wt. 15.43 g.; 83.5% yield. Fifteen grams (0.106 mole) of sodium salt was added to 18.5 cc. (0.222 mole) of ice-cold concentrated hydrochloric acid, and while the solution was stirred 120 cc. of isopropyl alcohol was added. The mixture was heated to 60° to ensure completion of reaction and then refrigerated for twelve hours. The sodium chloride was filtered, and the filtrate was treated with 20.4 cc. of aniline and held at 5° for sixteen hours. The product (11.5 g., 91% yield) was recrystallized by solution in 28.8 cc. of hot water and dilution with 86 cc. warm ethanol. After refrigeration for twelve hours, the pure DL-threonine was collected; wt. 11.14 g.; 96.8% recovery; yield from ethyl acetoacetate, 57.2%.

*Anal.* Calcd. for $C_4H_9O_3N$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.42; H, 7.32; N, 11.82.

**This material was 100% pure by microbial assay and 99.6% pure by solubility analysis.**

**Hydrolysis of N-Acetyl-DL-allothreonine Ethyl Ester.**—For complete identification of this compound, hydrolysis to N-acetyl-DL-allothreonine was carried out. A mixture of 1.69 g. of the ester (m. p. 76–77°) and 10 cc. of normal sodium hydroxide was held at room temperature for one hour. The mixture was acidified with hydrochloric acid to *p*H 3.5, and the solution was extracted with *n*-butyl alcohol. The extract was washed with a little water and concentrated to dryness. A solution of the residue in 10 cc. of absolute alcohol was filtered and concentrated to a pale yellow oil, which was extracted three times with 25 cc. portions of boiling ethyl acetate. The combined extracts on cooling deposited the product as small dense prisms. The combined yield of the first and second crops was 65.2%; m. p. 133–135°. Recrystallization from ethanol and ether gave pure N-acetyl-DL-allothreonine melting at 134–135°.

*Anal.* Calcd. for $C_6H_{11}O_4N$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.81; H, 7.04; N, 8.77.

**2,5-Dimethyl-4-carbethoxyoxazoline Hydrochloride, VII.**—The crude hydrogenation product (33.2 g.) from ethyl α-acetamidoacetoacetate was dissolved in 40 cc. of benzene and treated with 25.4 cc. of thionyl chloride at 10–15°. After being stirred an additional hour without cooling, the solution was poured into 965 cc. of anhydrous ether, and the mixture was refrigerated for sixteen hours. The crystalline product was collected, washed with ether and dried *in vacuo* over concentrated sulfuric acid; wt. 31.0 g.; m. p. 95–98°. An analytically pure sample was prepared by precipitation of a solution of 5.0 g. in 15.5 cc. of dry chloroform with 90 cc. of dry ether; m. p. 105–106°.

*Anal.* Calcd. for $C_8H_{13}O_3N\cdot HCl$: C, 46.27; H, 8.79; N, 6.75; N.E., 207.7. Found: C, 46.11; H, 6.87; N, 6.97; N. E., 202.2.

Very careful drying of all solvents used in this reaction is absolutely essential to obtain pure oxazoline, since this compound hydrolyzes rapidly. The pure oxazoline hydrochloride gave DL-threonine on hydrolysis in 92% yield (bioassay).

**O-Acetyl-DL-threonine Ethyl Ester Hydrochloride.**—A sample of 2,5-dimethyl-4-carbethoxyoxazoline hydrochloride (m. p. 102–103°) exposed to the air for twenty-four hours had a melting point of 128–130°. After drying at 56° and 5 mm. for one hour the weight loss was only 1.8% (calculated for one mole of water is 8.08%), and the melting point was 130–131°.

*Anal.* Calcd. for $C_8H_{15}O_4N\cdot HCl$: C, 42.57; H, 7.15; N. E., 225.7. Found: C, 42.33; H, 7.45; N. E., 225.3.

Hydrolysis of a sample with 10% hydrochloric acid gave DL-threonine in 91% yield (bioassay).

**N-Acetyl-DL-threonine.**—A solution of O-acetyl-DL-threonine ethyl ester hydrochloride (2.25 g.) in 26 cc. of 1 *N* sodium hydroxide was kept at room temperature overnight. After filtration to remove a trace of insoluble material, the solution was made acid to congo paper with 17 cc. of 1 *N* hydrochloric acid, and extracted with five 25-cc. portions of *n*-butyl alcohol. The extract was concentrated to dryness and the residue taken up in benzene and reconcentrated. A solution of this residue in 20 cc. of alcohol was filtered from a little inorganic material and concentrated to give a colorless oil (1.55 g., 96.3% yield), which crystallized on standing in the refrigerator; m. p. 126–128°. Two recrystallizations from ethyl acetate gave clusters of prisms melting at 129–130°.

*Anal.* Calcd. for $C_6H_{11}O_4N$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.73; H, 6.65; N, 8.65.

A mixture of this material and N-acetyl-DL-allothreonine (m. p. 134–135°) melted at 105–113°. Hydrolysis of this compound with hydrochloric acid gave a 96% yield of DL-threonine (microbial assay).

**N-Acetyl-DL-threonine Ethyl Ester.**—Oxazoline hydrochloride, VII (3.11 g.) was added to a solution of 1.4 g. of sodium bicarbonate in 20 cc. of water. After storage for fourteen hours at room temperature, the solution was extracted with eight 10-cc. portions of chloroform. The extract was washed with water, dried over anhyd. magnesium sulfate, and concentrated to an oil, which crystallized on refrigeration, wt. 1.75 g., m. p. 84–85°. Recrystallization from isopropyl alcohol gave flat prisms of the same melting point.

*Anal.* Calcd. for $C_8H_{15}O_4N$: C, 50.78; H, 7.99. Found: C, 50.98; H, 7.93.

The same ester was prepared in almost quantitative yield from N-acetyl-DL-threonine by treatment with ethereal diazoethane. When mixed with a sample of the above ester, the melting point remained unchanged.

**N-Acetyl-DL-threonine methyl ester** was also prepared from N-acetyl-DL-threonine and ethereal diazomethane. When recrystallized from benzene, it is obtained as lustrous needles, m. p. 105–106°.

*Anal.* Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48. Found: C, 48.18; H, 7.40.

**Acknowledgment.**—We are happy to acknowledge the technical assistance of Mrs. E. V. Crabtree, and to express our thanks to Dr. J. L. Stokes and Mr. R. N. Boos and their associates for the microbial assays and microanalytical data, respectively. In addition we are grateful to Dr. Nelson Trenner for infrared absorption spectra, which facilitated rapid identification of the reaction products derived from 2,5-dimethyl-4-carbethoxyoxazoline hydrochloride.

## Summary

1. The interconversion of DL-threonine and DL-allothreonine in high yields has been described. The interconversion is based upon the inversion of the configuration about one of the asymmetric carbon atoms

2. By utilization of this inversion, the synthesis of DL-threonine from acetoacetic ester can be accomplished in an over-all yield of 57%.

3. A practical method for the separation of DL-threonine from DL-allothreonine has been developed. This method depends upon the difference in solubility of the sodium salts in ethanol.

4. A number of new derivatives of DL-threonine and DL-allothreonine have been prepared and reported.

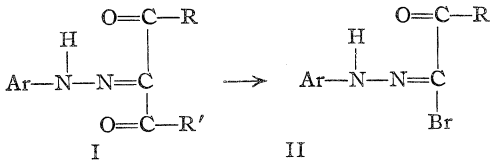
RAHWAY, NEW JERSEY RECEIVED NOVEMBER 27, 1948

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

# A Mechanism for the Cleavage of Certain Phenylhydrazones by Bromine

BY DEXTER B. SHARP[1]

F. D. Chattaway and co-workers[2] published a number of papers describing the products obtained from the action of halogens on certain phenylhydrazones, represented by formula I. Bromine reacted almost quantitatively with

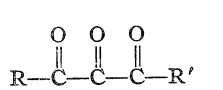


I II

Ar = $C_6H_5$- or substd. $C_6H_5$-
R = $C_2H_5O$-, $CH_3$-
R′ = $C_6H_5$-, $CH_3$-, $C_2H_5O_2C$-

compounds of type I in cold acetic acid–sodium acetate solution to give halides of type II, a cleavage of a carbon–carbon bond having occurred during the reaction. The papers cited above reported no mechanism studies. This paper presents the results of experiments designed to elucidate the mechanism of this cleavage reaction.

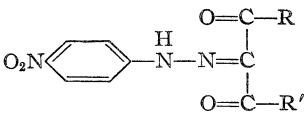
Two of the three parent compounds of this series, *i.e.*, vicinal tricarbonyl compounds, were found to be unaffected by bromine under the conditions favoring cleavage of the hydrazones of type I. Ethyl 3-phenyl-2,3-dioxopropanoate



| Cpd. | R | R′ |
|---|---|---|
| III | $C_2H_5O$- | $C_6H_5$- |
| IV | $C_2H_5O$- | $CH_3$- |
| V | $C_6H_5$- | $C_6H_5$- |

(III) and 1,3-diphenylpropane-1,2,3-trione (V) were prepared and added to a solution of bromine and sodium acetate in glacial acetic acid. After one to three days at room temperature, the reaction mixtures were diluted with water and the starting compounds were recovered as hydrates in good yields. Ethyl 2,3-dioxobutanoate (IV) decolorized bromine over a four-hour period and no hydrate was isolated. This result may be attributed to a bromine attack upon the terminal methyl group rather than a $C_2$–$C_3$ cleavage.

The stability of III and V toward bromine indicates that the hydrazone group at carbon number two is necessary for the cleavage reaction and it was found that the 2-*p*-nitrophenylhydrazone derivatives of compounds III, IV and V (VI, VII, VIII) were cleaved in excellent yields by bromine in acetic acid–sodium acetate solutions maintained at or below room temperature.

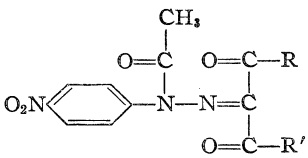


| Cpd. | R | R′ |
|---|---|---|
| VI | $C_2H_5O$- | $C_6H_5$- |
| VII | $C_2H_5O$- | $CH_3$- |
| VIII | $C_6H_5$- | $C_6H_5$- |

In all cases the bromine was decolorized as rapidly as it was added. Compounds VI and VII both gave the same bromo compound, ethyl α-bromoglyoxylate α-*p*-nitrophenylhydrazone (IX), the bromine having replaced a benzoyl and an acetyl group, respectively. Compound VIII gave ω-bromophenylglyoxal *p*-nitrophenylhydrazone (X), a benzoyl group having been replaced by a bromine atom. The cleavage of VII was reported by Chattaway,[2c] and earlier by Bowack and Lapworth.[3] The cleavage of VI and VIII is in line with the observations of Chattaway.

Bromine in glacial acetic acid containing no sodium acetate was found to have no action on compounds VI, VII or VIII. These compounds were recovered in very good yield. The influence of substances of higher basic strength than sodium acetate was not investigated due to the sensitivity of the halogen compounds (II) toward more basic agents.

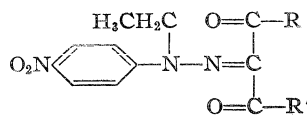
The hydrazone groups in VI, VII and VIII were modified by direct N-acetylation with acetic anhydride. The N-acetyl compounds,



| Cpd. | R | R′ |
|---|---|---|
| XI | $C_2H_5O$- | $C_6H_5$- |
| XII | $C_2H_5O$- | $CH_3$- |
| XIII | $C_6H_5$- | $C_6H_5$- |

ethyl 3-phenyl-2,3-dioxopropanoate-2-(acetyl-*p*-nitrophenylhydrazone) (XI), ethyl 2,3-dioxobutanoate-2-(acetyl-*p*-nitrophenylhydrazone) (XII), and 1,3-diphenylpropane-1,2,3-trione-2-(acetyl-*p*-nitrophenylhydrazone) (XIII) were unaffected by bromine under conditions favoring cleavage of type I compounds.

N-Ethyl-*p*-nitrophenylhydrazones analogous to VI and VIII were prepared by the reaction of α-ethyl-α-*p*-nitrophenylhydrazine (XIV) with III



| Cpd. | R | R′ |
|---|---|---|
| XV | $C_2H_5O$- | $C_6H_5$- |
| XVI | $C_6H_5$- | $C_6H_5$- |

and V. Ethyl 3-phenyl-2,3-dioxopropanoate-2-(ethyl-*p*-nitrophenylhydrazone) (XV) and 1,3-diphenylpropane-1,2,3-trione-2-(ethyl-*p*-nitrophenylhydrazone) (XVI) were unaffected by bromine under conditions favoring cleavage of

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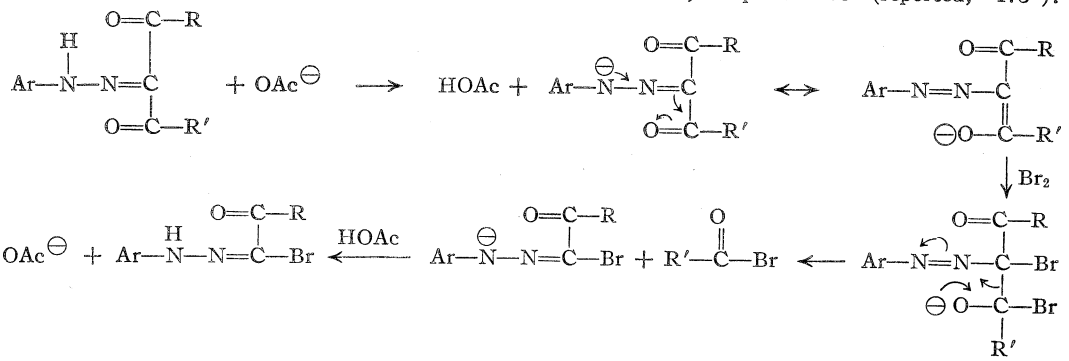
(2) (a) Chattaway and Lye, *Proc. Roy. Soc.* (*London*), **A135**, 282 (1932); (b) **A137**, 489 (1932); (c) Chattaway and Ashworth, *J. Chem. Soc.*, 475 (1933); (d) Chattaway and Lye, *ibid.*, 480 (1933); (e) Chattaway and Ashworth, *ibid.*, 1143 (1933); (f) 1624 (1933); (g) 930 (1934); (h) 1985 (1934).

(3) Bowack and Lapworth, *J. Chem. Soc.*, **87**, 1854 (1905).

type I compounds. Compounds III and V with *p*-nitrophenylhydrazine gave substances identical with VI and VIII, respectively, whose structures as 2-*p*-nitrophenylhydrazones are fixed through their synthesis by the Japp–Klingemann reaction. By analogy, it is inferred that the central carbonyl groups in III and V were attacked by the disubstituted hydrazine molecule. Since IV with *p*-nitrophenylhydrazine gave a derivative which was not identical with VII from the coupling reaction, the corresponding ethyl-*p*-nitrophenylhydrazone was not prepared. Attempts to ethylate VI, VII and VIII directly were unsuccessful.

Summarizing the results above, the following facts are clear. (1) Rapid cleavage of compounds of type I by bromine occurred almost quantitatively under mild conditions in glacial acetic acid containing sodium acetate. (2) No cleavage occurred in the absence of sodium acetate. (3) Replacement of the hydrogen on the nitrogen of the hydrazone link by an acetyl or ethyl group prevented cleavage, thus demonstrating the requirement that this hydrogen is necessary for cleavage to occur.

From a consideration of these facts, the following base-catalyzed mechanism is proposed for the reaction.



## Experimental[4]

**Vicinal Tricarbonyl Compounds. Ethyl 3-Phenyl-2,3-dioxopropanoate (III).**—Ethyl benzoylacetate (96 g.) was converted to III by adapting the method described by Bigelow and Hanslick[5] for the preparation of 1,3-diphenylpropane-1,2,3-trione. The product (47 g., 45%) was a yellow oil; b. p. (2 mm.) 117–123° (reported,[6] 150–153° at 13 mm.), $d^{27}_4$ 1.179 (reported,[6] $d^{20}_4$ 1.188), $n^{20}D$ 1.5191.

**Ethyl 2,3-Dioxobutanoate (IV).**—Ethyl acetoacetate (130 g.) was converted to IV by the method of Denis.[7] The nitrogen oxides were generated by the action of sirupy phosphoric acid on excess sodium nitrite. The product (7.3 g., 5%) was a yellow oil; b. p. (14 mm.) 68.5–72° (reported,[7] 76–82° at 18–22 mm.), $d^{26}_4$ 1.151 (reported,[8] $d^{20}_4$ 1.125), $n^{20}D$ 1.4240 (reported,[8] $n^{15.8}D$ 1.42210).

**1,3-Diphenylpropane-1,2,3-trione (V).**—A sample of V hydrate, m. p. 89–91° (reported,[5] 90–92°), was dehydrated by distillation at reduced pressure to give V, a yellow-orange solid; m. p. 69–71° (reported,[5] 68–70°).

**Bromine Action on III, IV and V.**—Mole portions of III, IV and V, respectively, were added to appropriate volumes of glacial acetic acid containing an excess of anhydrous sodium acetate and a mole portion of bromine. The mixtures were maintained at room temperature for varying periods. Excess bromine was removed at reduced pressure, water was added, and the respective hydrates precipitated.

A sample of III (4.0 g.) gave III hydrate (3.6 g., 80%); m. p. and mixed m. p. 55–59° with authentic III hydrate.

Compound IV decolorized bromine over a four hour period, possibly due to an attack on the highly activated methyl group rather than $C_2$-$C_3$ cleavage. No IV hydrate was obtained from this reaction.

A portion of V (15.8 g.) gave V hydrate (15.2 g., 90%); m. p. and mixed m. p. 82–90° with authentic V hydrate.

**2-*p*-Nitrophenylhydrazone Derivatives of III, IV and V. A. Coupling Reaction.**—*p*-Nitrobenzenediazonium chloride coupled with the appropriate β-dicarbonyl compounds in sodium acetate buffered solutions to give the desired derivatives, following the method of Chattaway and Ashworth.[2c] Ethyl benzoylacetate (19 g.) gave ethyl 3-phenyl-2,3-dioxopropanoate 2-*p*-nitrophenylhydrazone (VI). The product (21 g., 61%) crystallized as yellow platelets from dilute ethanol; m. p. 112.5–114° (reported,[9] 114°).

Ethyl acetoacetate (65 g.) gave ethyl 2,3-dioxobutanoate 2-*p*-nitrophenylhydrazone (VIII). The product (120 g., 86%) crystallized as yellow needles from dilute ethanol; m. p. 126–127° (reported,[2c] 126–127°).

Dibenzoylmethane (22.5 g.) gave 1,3-diphenylpropane-1,2,3-trione 2-*p*-nitrophenylhydrazone (VIII). The product (24.5 g., 66%) separated as yellow needles from dilute acetone; m. p. 172–173° (reported,[10] 173°).

**B. Direct Action.**—Compounds VI and VIII were obtained by the direct action of *p*-nitrophenylhydrazine on III and V, respectively. Mole portions of the hydrazine and tricarbonyl compound were added to ethanol containing several drops of acetic acid. Filtration and dilution of the filtrate with water caused the product to crystallize.

By this method, III (1.0 g.) gave compound VI (1.6 g., 94%); m. p. and mixed m. p. 112–114° with VI prepared by the coupling reaction.

Similarly, V hydrate (3.33 g.) gave VIII (4.40 g., 86%); m. p. and mixed m. p. 170–171° with authentic VIII prepared by the coupling reaction.

Compound IV gave a red substance, m. p. 175–176°, quite different from the desired compound (VII); m. p. 126–127°.[2c]

**Bromine Action on VI, VII and VIII. A. With Sodium Acetate.**—A mole portion of VI, VII and VIII, respectively, was added to glacial acetic acid containing an excess of sodium acetate. The reaction mixture was stirred at room temperature or less while a mole portion of bromine in acetic acid was added. In each case a rapid decoloration of bromine was noted. The solid products were obtained by filtration after the reaction mixtures were diluted with water.

(4) Each m. p. and b. p. was corrected for stem exposure.

(5) Bigelow and Hanslick, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 244.

(6) Wahl, *Compt. rend.*, **144**, 212 (1907).

(7) Denis, *Am. Chem. J.*, **38**, 587 (1907).

(8) von Auwers, *Ber.*, **51**, 1120 (1918).

(9) Bülow and Hailer, *ibid.*, **35**, 926 (1902).

(10) Dimroth, *ibid.*, **40**, 2409 (1907).

Compound VI (5.0 g.) gave ethyl α-bromoglyoxylate-α-*p*-nitrophenylhydrazone (IX). The product (4.3 g., 93%) crystallized as granular yellow crystals from benzene; m. p. 199–201° (reported,[2e] 202–203°).

*Anal.* Calcd. for $C_{10}H_{10}BrN_3O_4$: C, 37.99; H, 3.19. Found: C, 38.19; H, 3.60.

Compound VII (25.0 g.) gave IX (26.5 g., 94%); m. p. and mixed m. p. 199–201° with IX from the preceding reaction.

Compound VIII (5.0 g.) gave ω-bromophenylglyoxal *p*-nitrophenylhydrazone (X). The product (4.5 g., 96%) separated as yellow needles from ethyl acetate; m. p. 245–247° (reported,[2f] 247°).

**B. Without Sodium Acetate.**—The reactions in (A) were repeated without the sodium acetate: From VI (5.0 g.) there was recovered VI (4.7 g., 94%); m. p. 112–114°. From VII (5.0 g.) there was recovered VII (4.6 g., 92%); m. p. 125–127°. From VIII (5.0 g.) there was recovered VIII (4.7 g., 94%); m. p. 171–172°.

**N-Acetyl Derivatives of VI, VII and VIII.**—Following a method described by Bülow and Hailer,[9] compounds VI, VII and VIII were acetylated by treatment with acetic anhydride containing several drops of concentrated sulfuric acid. The excess acetic anhydride was hydrolyzed by pouring the reaction mixture onto ice and the solid product was collected and recrystallized repeatedly from dilute acetone and dilute acetic acid.

Compound VI (5.0 g.) gave ethyl 3-phenyl-2,3-dioxopropanoate 2-(acetyl-*p*-nitrophenylhydrazone) (XI). The product (1.0 g., 18%) crystallized as white needles from dilute acetone; m. p. 141–142°.

*Anal.* Calcd. for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47. Found: C, 59.90; H, 4.40.

Compound VII (28 g.) gave ethyl 2,3-dioxobutanoate-2-(acetyl-*p*-nitrophenylhydrazone) (XII). The product (2.5 g., 8%) crystallized as white needles from dilute acetone; m. p. 135–136°.

*Anal.* Calcd. for $C_{14}H_{15}N_3O_6$: C, 52.34; H, 4.71. Found: C, 52.37; H, 4.92.

Compound VIII (3.0 g.) gave 1,3-diphenylpropane-1,2,3-trione-2-(acetyl-*p*-nitrophenylhydrazone) (XIII). The product (1.1 g., 33%) separated as yellow needles from dilute acetic acid; m. p. 202–202.5°.

*Anal.* Calcd. for $C_{23}H_{17}N_3O_5$: C, 66.50; H, 4.13. Found: C, 66.39; H, 4.03.

**Bromine Action on Compounds XI, XII and XIII.**—Mole portions of XI, XII and XIII, respectively, were added to appropriate volumes of acetic acid containing mole portions of bromine and excess sodium acetate. After one day at room temperature the reaction mixtures were diluted with water and the solids were removed by filtration. From XI (0.452 g.) there was recovered XI (0.343 g., 76%); m. p. and mixed m. p. 138–140° with authentic XI. From XII (1.0 g.) there was recovered XII (1.0 g., 100%); m. p. and mixed m. p. 133–135° with authentic XII. From XIII (0.859 g.) there was recovered XIII (0.837 g., 97%); m. p. and mixed m. p. 201–202° with authentic XIII.

**N-Ethyl Derivatives of VI and VIII.**—Compound XIV, α-ethyl-α-*p*-nitrophenylhydrazine, was prepared in poor yield by the method of Ciusa and Rastelli.[11] Benzaldehyde *p*-nitrophenylhydrazone (50 g.) gave XIV (6.2 g., 16%), a yellow crystalline solid from ligroin; m. p. 68.5–69.5° (reported,[11] 74°).

*Anal.* Calcd. for $C_8H_{11}N_3O_2$: C, 53.02; H, 6.12. Found: C, 52.73; H, 6.07.

Mole portions of III and V, respectively, were added to ethanol–acetic acid (3:1 by volume) containing mole portions of XIV. The reaction mixtures, after one hour on the steam-bath and one day at room temperature, were diluted with water and the solid products were removed by filtration.

Compound III (1.60 g.) with XIV (1.36 g.) gave ethyl 3-phenyl-2,3-dioxopropanoate-2-(ethyl-*p*-nitrophenylhydrazone) (XV), (2.05 g., 74%). The product crystallized as yellow needles from dilute acetone; m. p. 128–129°.

*Anal.* Calcd. for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.19. Found: C, 61.96; H, 5.40.

V hydrate (0.66 g.) with XIV (0.45 g.) gave 1,3-diphenylpropane-1,2,3-trione 2-(ethyl-*p*-nitrophenylhydrazone) (XVI). The product (0.35 g., 33%) crystallized as yellow needles from dilute acetone; m. p. 166–167°.

*Anal.* Calcd. for $C_{23}H_{19}N_3O_4$: C, 68.81; H, 4.77. Found: C, 69.08; H, 5.05.

In view of the anomalous behavior of IV with *p*-nitrophenylhydrazine the corresponding N-ethyl derivative was not prepared.

**Bromine Action on XV and XVI.**—Mole portions of XV and XVI, respectively, were added to appropriate volumes of glacial acetic acid containing mole portions of bromine and excess sodium acetate. The reaction mixtures, after one day at room temperature, were diluted with water and the solids were removed by filtration. From XV (1.60 g.) there was recovered XV (1.0 g., 62%); m. p. and mixed m. p. 126–128° with authentic XV. From XVI (0.50 g.) there was recovered XVI (0.46 g., 92%); m. p. and mixed m. p. 164–166° with authentic XVI.

**Acknowledgments.**—The author wishes to express his appreciation to Dr. C. F. Koelsch for his extremely helpful guidance and deep interest throughout this problem. The carbon–hydrogen microanalyses were carried out by Messrs. R. Amidon and J. Buckley, and Dr. S. Sundet.

## Summary

A study of the carbon–carbon cleavage by bromine of 2-*p*-nitrophenylhydrazones of 1,2,3-trioxo compounds revealed that the reaction is base-catalyzed and applies only to mono-substituted phenylhydrazones of the type mentioned.

A mechanism is proposed to account for these facts.

MINNEAPOLIS, MINNESOTA RECEIVED MAY 24, 1948

(11) Ciusa and Rastelli, *Gazz. chim. ital.*, **54**, 72 (1924).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

# Introduction of Alkylamino and Dialkylamino Groups into the Quinoline Nucleus

BY NYDIA G. LUTHY,[1] F. W. BERGSTROM[2] AND HARRY S. MOSHER

It has been shown that quinine is detoxified in the body by oxidation to the 2-hydroxy derivative which has much less therapeutic activity.[3] Since antimalarials containing a quinoline nucleus may suffer a similar fate, the problem of introducing groups into the 2-position in order to block this mode of detoxification was undertaken. It was hoped that amino and substituted alkylamino groups would overcome such objections, and so a study was made on the ease of substitution of such groups in the 2-position of quinoline and of finding the optimum conditions for such introduction.

The direct introduction of the amino group by the use of alkali amides in liquid ammonia, tertiary amines, or inert solvents has become a well established reaction.[4] It has been shown also, that alkylamino groups can be introduced by the use of the fused sodium–potassium amide eutectic in the presence of an excess of a primary amine.[5] It has now been shown that in some cases 2-aminoquinoline may also be produced in this reaction. In this Laboratory 2-methylaminoquinoline has been produced by the reaction of quinoline with lithium methylamide in ether solution and nitrogen atmosphere. However, the methods for the direct introduction of 2-dialkylamino groups have not been so well established. Roser[6] and Cohen, *et al.*,[7] alkylated the methiodide of 2-aminoquinoline stepwise to obtain 2-dimethylaminoquinoline. Quinoline 2-sulfonic acid (prepared from 2-chloroquinoline and sodium sulfite solution) when heated with an aqueous solution of a dialkylamine will yield compounds of the type of 2-dialkylaminoquinoline.[8] Fourneau, *et al.*,[9] combined 2-chloroquinoline itself with a benzene solution of diethylamine in a heated sealed tube to obtain 2-diethylaminoquinoline hydrochloride. Buchman and Hamilton[10] found that both halogen atoms in 2,4-dichloroquinoline were quite reactive and gave good yields of 2,4-di-(N-morpholino)-quinoline. Magidson and Rubtsov[11] and certain patent literature[12] make reference to the successful reaction of 2-chloroquinoline and 2-chloroquinoline derivatives with various basically substituted amines such as 1-diethylamino-4-aminopentane. In addition certain aromatic amino derivatives have been made by the reaction of 2-chloroquinoline with substituted anilines.[13]

We have not been able as yet to accomplish the direct introduction of dialkylamino groups into the quinoline nucleus using alkali dialkylamides. Even in a sealed two-legged tube, potassium dimethylamide in methylamine gave no reaction with quinoline, while only unreacted starting material could be obtained when quinoline was treated with lithium dimethylamide in anhydrous ether, benzene, or toluene. Therefore, it seemed advisable to investigate the general nature of the reaction of 2-chloroquinoline with dialkylamines and to study the properties of the compounds produced. The results are summarized in Tables I and II.

## Experimental

Accordingly a series of compounds ranging from 2-dimethylamino- to diamylaminoquinoline was prepared by treating 2-chloroquinoline with the corresponding amine either in a sealed tube or, if the boiling point of the amine was sufficiently high, by refluxing. Hydrolysis of the hydrochlorides so formed was effected by 20% sodium carbonate solution, and after the free base was separated by benzene extraction, it was purified by vacuum distillation.

In this series with the exception of the first compound, all were pale-yellow, stable oils boiling from 140–170° at 2 mm. forming only monomethiodides and hydrochlorides. As the alkyl group became larger, higher temperatures were needed to bring about the reaction of 2-chloroquinoline with the dialkylamine. The salts of the resulting compounds were crystallized with greater difficulty and their melting points tended to become lower.

In a similar manner 2-methylamino-, 2-propylamino- and 2-piperidinoquinoline were also prepared. By treating 4-chloroquinoline with methylamine in a sealed tube heated at 100° for five hours, a 96% yield of 4-methylaminoquinoline was obtained.

The monoalkylaminoquinolines were white crystalline solids which formed only mono-salts. Mono-salt formation may be explained by postulating an amidine type resonance (Fig. 1) in which the positive charge prevents the approach of another molecule of methyl iodide. That




Fig. 1.

(1) Material herein presented based on the M.S. Thesis of Nydia Goetz, Stanford University, August, 1945, and on the Ph.D. Thesis of Nydia Goetz-Luthy, Stanford University, August, 1948.

(2) Deceased March 29, 1946.

(3) Kelsey, Geiling, Oldham and Dearborn, *J. Pharmacol. and Exp. Therap.*, **80**, 391 (1944).

(4) Leffler, "The Amination of Heterocyclic Bases by Alkali Amides" in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942.

(5) Bergstrom, Sturz and Tracy, *J. Org. Chem.*, **11**, 239 (1946).

(6) Roser, *Ann.*, **282**, 384 (1894).

(7) Cohen, Cooper and Marshall, *Proc. Roy. Soc. (London)*, **108**, 130 (1931).

(8) German Patent 615,184 (I. G. Farbenindustrie) (1935).

(9) Fourneau, Tréfouel and Benoit, *Ann. Inst. Pasteur*, **44**, 719 (1930).

(10) Buchman and Hamilton, THIS JOURNAL, **64**, 1357 (1942).

(11) Magidson and Rubtsov, *J. Gen. Chem. (U. S. S. R.)*, **7**, 1896 (1937); *Chem. Abst.*, **32**, 564 (1938).

(12) Zerweck and Kunze, U. S. Patent 2,086,691 (July 13, 1937); German Patent 615,184 (June 28, 1935); British Patent 437,137 (Oct. 28, 1935).

(13) Narang and Ray, *J. Chem. Soc.*, 976 (1931).

TABLE I

REACTION OF 2-CHLOROQUINOLINE WITH ALKYL AND DIALKYLAMINES

| Amine | Yield, % | Product[a] M. p. or b. p., °C. | Mm. | Picrate[b] M. p., °C. | Formula | Analyses,[c] % Calculated Carbon | Calculated Hydrogen | Found Carbon | | Found Hydrogen | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimethyl-[d] | 90 | 70.5–71[l] | | 215–217 | $C_{11}H_{12}N_2$ | 76.69 | 7.02 | 76.68 | 76.75 | 7.00 | 7.07 |
| Diethyl-[e] | 30 | 154–155 | 4 | 184–185 | $C_{14}H_{19}N_2I$ | 49.1 | 5.6 | 49.34 | 49.21 | 5.73 | 5.71 |
| Di-*n*-propyl-[f] | 60 | 140–145 | 2 | 188–190.5 | $C_{16}H_{23}N_2I$ | 51.9 | 6.26 | 51.52 | 51.8 | 6.29 | 6.31 |
| Di-*n*-butyl-[g] | 60 | 155–157 | 2 | 176–178 | $C_{18}H_{27}N_2I$ | 54.28 | 6.83 | 54.27 | 54.09 | 6.73 | 6.65 |
| Di-*n*-amyl-[h] | 57 | 165–167 | 2 | 180–185 | $C_{20}H_{31}N_2I$ | 56.33 | 7.33 | 55.87 | 55.8 | 7.28 | 7.2 |
| Monomethyl-[i] | 98 | 71–71.5 | | 228–230 | | | | | | | |
| Mono-*n*-propyl-[j] | 60 | 78–78.5 | | | | | | | | | |
| | | 140–145 | 3 | 196–196.5 | $C_{12}H_{14}N_2$ | 77.38 | 7.58 | 77.03 | 76.92 | 7.50 | 7.46 |
| Piperidine[k] | 98 | 49–50 | | 173–176 | $C_{14}H_{16}N_2$ | 79.21 | 7.6 | 79.36 | | 7.62 | |

[a] Where no pressure is given, the value is for the m. p. [b] Recrystallization generally from ethyl alcohol or methyl isobutyl ketone. [c] Analyses on the methiodide derivative or free base by Huffman Microanalytical Laboratories, Denver, Colorado. [d] Sealed tube heated six hours at 90°. *Anal.* Calcd.: N, 16.22. Found: N, 16.31. [e] Sealed tube heated eighteen hours at 120°. [f] Reaction in ground glass apparatus refluxed at 111° for two hours. [g] Reaction in ground glass apparatus refluxed at 160° for four hours. [h] Refluxed at 205° for four hours. [i] Sealed tube heated for six hours at 100°. See Bergstrom, *Chem. Rev.*, **35** 177 (1944). [j] Sealed tube heated for seven hours at 130°. The reaction with isopropylamine was poor; approximately 10% yield of 2-isopropylaminoquinoline was obtained identified only by its gold salt. [k] Sealed tube heated at 100° for one hour; base recrystallized from aqueous alcohol after vacuum distillation at 130–135°, 0.4–0.45 mm. [l] See reference 8.

TABLE II

DERIVATIVES OF 2-ALKYLAMINO- AND 2-DIALKYLAMINOQUINOLINES

| Quinoline derivatives | Monomethiodide[a] M. p., °C. | % Iodine[b] Calcd. | Found | | Monohydrochloride[c] M. p., °C. | Neutral equiv.[d] Calcd. | Found | | Platinum salt[e] M. p., °C. | % Platinum Calcd. | Found | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-Dimethylamino- | 197–197.5 | 40.41 | 40.43 | 40.12 | 232–234 | 208.6 | 210.6 | | | | | |
| 2-Diethylamino- | 195–195.5 | 37.1 | 36.71 | 36.78 | 169–170.5[i] | 236.6 | 235.4 | 235.9 | | | | |
| 2-Di-*n*-propylamino- | 160.5–161 | 34.78 | 33.87 | 34.32 | 145–146 | 264.8 | 265.3 | 266.1 | | | | |
| 2-Di-*n*-butylamino- | 151.5–152 | 31.87 | 31.87 | 31.95 | (Oil) | | | | | | | |
| 2-Di-*n*-amylamino- | 136–137.5 | | | | | | | | 192–194 | 19.59 | 19.23 | 19.62 |
| 2-Monomethylamino-[g] | 195–196[h] | | | | | | | | 199–200[f] | 39.56 | 39.54 | 39.45 |
| 2-Monopropylamino- | 249–250 | 38.67 | 38.46 | 38.86 | | | | | 198–198.5 | 24.45 | 24.82 | 24.88 |
| 2-Piperidino- | | | | | | | | | 198.5–199.5 | | | |

[a] Monomethiodides were all formed by treating the 2-alkylamino- or di-alkylaminoquinoline with excess methyl iodide in a sealed tube at 100°. [b] Quantitative determination of percentage iodine made according to method of Willard and Furman, "Elementary Quantitative Analyses," 3rd ed., Van Nostrand Co., New York, N. Y., 1940, p. 320. [c] Hydrochlorides generally recrystallized from isopropyl alcohol or methyl isobutyl ketone, followed by drying over phosphorus pentoxide in a vacuum desiccator. [d] The neutral equivalent determined by dissolving sample in neutralized alcohol and titrating with standardized sodium hydroxide using phenolphthalein as indicator. [e] Calculated as $PtCl_6 \cdot 2$ Base. [f] Gold salt, per cent. gold calculated on the basis of $C_{10}H_{10}N_2 \cdot HAuCl_4$. [g] The positional isomer 4-methylaminoquinoline was prepared by treating 4-chloroquinoline with methylamine in a sealed tube heated at 100° for five hours. The purified compound melted at 227–227.5°, 96% yield. The compound sublimes readily; the picrate recrystallized from alcohol gives m. p. 249–250°. *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 76.04; H, 6.15. The methiodide recrystallized from methyl isobutyl ketone, m. p. 310°. [h] Roser, ref. 6, reports a hydrate melting at 160°. [i] Fourneau, *et al.*, ref. 9, reported the m. p. as 165–170° after decomposition at about 155°.

it is the ring nitrogen which forms the quaternary salt is indicted by the fact that both 2-aminoquinoline methiodide and 2-dimethylaminoquinoline methiodide are converted to 1-methyl-2-quinolone by boiling in aqueous alkaline solution.[7]

## Summary

1. A series of 2-dialkylaminoquinolines and 2-alkylaminoquinolines has been prepared by heating 2-chloroquinoline with the corresponding anhydrous amine in a sealed tube. 4-Methylaminoquinoline was obtained from 4-chloroquinoline in a similar manner.

2. Only monomethiodides and monohydrochlorides could be formed from these quinoline bases. The platinum, gold, and picrate derivatives are described for a number of compounds of this series.

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# NOTES

## 3,4-Dimethylaniline from Fenchone Using the Schmidt Reaction

By Frederic R. Benson, Lawrence W. Hartzel and Walter L. Savell

One of the newer methods for the preparation of 3,4-dimethylaniline which is convenient for laboratory use is that developed by Zaugg.[1] His procedure involves conversion of fenchone to 3,4-dimethylacetophenone, isolation as the oxime, Beckmann rearrangement and subsequent hydrolysis.

In order to reduce the time required for this synthesis, investigation of an alternative method has been made. The modification developed in this laboratory consists of subjecting the crude 3,4-dimethylacetophenone obtained from fenchone to the Schmidt reaction, followed by hydrolysis of the crude 3,4-dimethylacetanilide. The present procedure eliminates the need for isolation of dimethylacetophenone as the oxime and the time consuming Beckman rearrangement. In the method described below the benzene solution of crude dimethylacetophenone, obtained according to Zaugg, is treated directly with hydrazoic acid in benzene to form crude dimethylacetanilide. Hydrolysis and distillation affords a fairly pure product which can be recrystallized to form 3,4-dimethylaniline of good purity. The over-all yield from fenchone of completely purified material is 21%.

A by-product of the Schmidt reaction was obtained in small amounts from one run. This is probably 1-(3′,4′-dimethylphenyl-5-methyltetrazole, although it is possible that it may be the isomer, 1 methyl-5-(3′,4′-dimethylphenyl)-tetrazole.

### Experimental

A solution of 126 g. of crude 3,4-dimethylacetophenone in 585 ml. of dry benzene was prepared from 200 g. of commercial fenchone as described by Zaugg.[1]

To a 100-ml. portion of this solution (containing 21.4 g. of 3,4-dimethylacetophenone), mixed with 30 ml. of concentrated sulfuric acid was added with stirring 191 ml. of a 4.1% hydrazoic acid solution in benzene. The temperature was maintained at 38–41° during the addition, which took approximately fifty minutes. After all the solution had been added, the mixture was allowed to stir for five minutes longer, then cooled and poured into a separatory funnel. The sulfuric acid layer was poured into 400 ml. of water and made alkaline with ammonium hydroxide (120 ml.). The yellow oil which separated solidified on cooling. The precipitate was filtered off, washed once with water and refluxed for two hours with 75 ml. of concentrated hydrochloric acid. The solution was poured into 250 ml. of water, extracted with ether, and made alkaline with 6 *N* sodium hydroxide. The alkaline solution was extracted with ether, the ether solution dried over potassium hydroxide and distilled to yield 7.0 g. of crude 3,4-dimethylaniline, b. p. 138–143° (55 mm.), m. p. 47°. On recrystallization from light petroleum ether 5.7 g. of pure 3,4-dimethylaniline was obtained (21% yield from fenchone), m. p. 50–51°. Purity by titration with perchloric acid in glacial acetic acid, 99.1%.

In another experiment conducted as described above, except that the temperature of the Schmidt reaction was maintained at 10–15°, the ether extract of the acid hydrolysis product was allowed to evaporate. The dark, gummy crystals obtained were dissolved in boiling water and treated with charcoal. On filtration and cooling, white crystals separated. A second recrystallization from water afforded 100 mg. of white glistening crystals melting at 111–111.5°.

*Anal.* Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.95; H, 6.25; N (Dumas), 29.95.

The authors are indebted to Dr. Paul D. Sternglanz for the analytical data presented in this note.

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(1) Zaugg, This Journal, **67**, 1861 (1945).

## Synthesis of 1-Aminofluorene

By E. Bergmann and Milton Orchin[1]

In view of the widespread current interest in the unusual carcinogenic properties of 2-aminofluorene,[2] we wish to report at this time the preparation of the isomeric 1-aminofluorene. The synthesis consisted essentially of the oxidation of fluoranthene to fluorenone-1-carboxylic acid, reduction of the latter to fluorene-1-carboxylic acid and replacement of the carboxyl group by an amino group.

### Experimental[3]

**Fluorenone-1-carboxylic Acid.** I.—Fluoranthene was purchased from the Reilly Tar and Chemical Company. It had a melting point of 107.0–109.4°. Careful chromatography on alumina–celite and determination of the ultraviolet absorption spectra of the fractions showed the presence of a small quantity of pyrene and the probable presence of phenanthrene as impurities. Sulfuric acid extraction of a tetrachloroethane solution of the fluoranthene,[4] resulted in a spectrographically pure fluoranthene, m. p. 110.4–111.2°. On a large scale, the purification was more conveniently achieved by heating fluoranthene at 200° with sodium for half an hour. The fluoranthene was distilled, b. p. 180–90° (4–5 mm.) and the distillate crystallized from ethanol whereby colorless material, m. p. 110.4–111.4°, was obtained. This fluoranthene (95 g.) was oxidized with chromic acid in acetic acid according to the directions of Fieser and Seligman.[5] The procedure for the isolation of the product was simplified as follows:

(1) We wish to thank the John Simon Guggenheim Foundation for a fellowship grant to M. O. which made this work possible. Present address, U. S. Bureau of Mines, Pittsburgh, Pa.

(2) Wilson, De Eds and Cox, *Cancer Research*, **1**, 595 (1941); Bielschowsky, *Brit. med. Bull.*, **4**, 382 (1947); Pinck, *Ann. New York Acad. Sci.*, **50**, 1 (1948).

(3) All melting points corrected.

(4) Compare the purification of chrysene: Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2nd edition, Reinhold Publishing Corp., New York, N. Y., 1937, p. 19.

(5) Fieser and Seligman, This Journal, **57**, 2174 (1935).

After the acid was precipitated by dilution with ice and water, the product was filtered and washed twice with hot water. The product was digested in warm, dilute hydrochloric acid, filtered and washed well with hot water. The insoluble material was digested in 500 cc. of water containing 45 g. of sodium carbonate. The hot solution was treated with norite and filtered. The filtrate was acidified with cold, concentrated hydrochloric acid and the precipitate filtered and dried overnight at 80°. Crystallization from acetic acid gave 55.5 g. of the desired acid, brownish-red needles, m. p. 193.4–195.4°. A sample recrystallized from acetic acid had a melting point of 196.8–197.6°. The alkali insoluble material was treated with aqueous sodium bisulfite,[6] the mixture filtered and the filtrate acidified with concentrated sulfuric acid. The precipitated material was filtered and twice recrystallized from ethanol giving red brown crystals of fluoranthenequinone, m. p. 193.0–193.8°.[7]

**Ethyl Fluorenone-1-carboxylate.**—The keto acid, I, was esterified with ethanol and hydrogen chloride in the usual way. The ester was isolated as gold-yellow crystals after two crystallizations from ethanol, m. p. 84.8–85.4°; reported melting point, 75–76°[8] and 84–86°.[9] On a third recrystallization from ethanol, the crystals had a melting point of 76.0–76.5°. After melting, the melt was cooled and the solid remelted whereupon softening took place at 76° and sharp liquefaction occurred at 84.0–84.8°. Both the high and low melting forms gave identical ultraviolet absorption spectra.

**Methyl Fluorenone-1-carboxylate.**—This compound was prepared from I with methanol and hydrogen chloride and was crystallized from methanol as yellow needles, m. p. 86.6–87.4°; reported[9] melting point, 86–89°.

**Fluorenone-1-carboxamide.**—The keto acid, I, was converted *via* the chloride to the amide which was crystallized from acetic acid and separated as yellow-orange crystals, m. p. 235.8–237.0°; reported melting point, 229–230°,[8] and 226.5–227°.[10]

**1-Aminofluorenone.**—The Hofmann reaction on the amide gave the aminofluorenone. The amine was recrystallized first from ethanol and then from petroleum ether and was thus obtained as orange plates, m. p. 119.0–120.0°; reported melting point, 110°[8] and 118–118.5°.[10]

**Fluorene-1-carboxylic Acid, II.**—The keto acid, I, was reduced by the Huang–Minlon modification[11] of the Wolff–Kishner reduction. A mixture of 16.6 g. of I, 10 g. of sodium hydroxide, 10 cc. of 85% hydrazine hydrate and 130 cc. of trimethylene glycol was refluxed for three hours. The temperature of the boiling contents was about 150°. The condenser was removed and the boiling continued in the open (hood) until the temperature in the flask was about 205°. At this point refluxing was resumed and continued for two and one-half hours. The mixture was cooled and poured into ice and hydrochloric acid. The precipitate was filtered and dried overnight. Crystallization from acetic acid gave 13.0 g., m. p. 246–249° as a first crop and 1.0 g., m. p. 243–246° (90% yield) as a second crop. The reduction of the keto acid has been done previously[5] with sodium amalgam but in much poorer yield and we are indebted to Dr. Fieser for suggesting the application of the above procedure to improve his yield.

**Methyl Fluorene-1-carboxylate, III.**—A suspension of 5.16 g. of II in 100 cc. absolute methanol was saturated with hydrogen chloride and the ester isolated in the usual way. Crystallization of the ester from methanol gave 4.94 g. of colorless crystals, m. p. 86.6–87.4°. *Anal.* Calcd. for $C_{15}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 80.4; H, 5.2.

**Ethyl fluorene-1-carboxylate** was prepared from ethanol and II as above. Crystallization from ethanol gave colorless crystals, m. p. 53.6–54.8°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.9; H, 5.8.

**Fluorene-1-carboxamide** was prepared from II *via* the acid chloride. Crystallization from acetic acid gave colorless crystals, m. p. 251.0–253.0°. *Anal.* Calcd. for $C_{14}H_{11}ON$: C, 80.4; H, 5.3. Found: C, 79.8; H, 5.1.

**Hydrazide of Fluorene-1-carboxylic Acid, IV.**—A solution of 5.0 g. of the methyl ester, III, 20 cc. of absolute ethanol and 5 cc. of 85% hydrazine hydrate was refluxed for twenty-four hours. A white solid appeared during the refluxing. The mixture was cooled and filtered and washed with ethanol to give 3.84 g. of white fluffy needles, m. p. 216.6–218°. *Anal.* Calcd. for $C_{14}H_{12}N_2O$: N, 13.2. Found: N, 13.0.

**1-Fluorenylurethan, V.**—A solution of 1.06 g. of IV in 20 cc. of glacial acetic acid was treated with 0.5 cc. of concentrated hydrochloric acid. The suspension was cooled to 0° and 0.8 g. of sodium nitrite in 5 cc. of water added. The suspension was stirred in the cold for one hour then at room temperature for one hour. The mixture was diluted with water and filtered. The precipitate was washed with water and dried in a vacuum desiccator. The solid weighed 1.00 g.; it melted at 85° with gas evolution and was very soluble in organic solvents. *Anal.* Calcd. for $C_{14}H_9N_3O$; N, 17.9. Found: N, 18.6. A solution of 0.85 of the crude azide in 25 cc. of absolute ethanol was warmed to about 70°. Rapid gas evolution occurred. The solution was then refluxed for two hours. The solution was filtered from a small amount of insoluble material and the filtrate concentrated. The urethan (0.62 g.) was obtained from ethanol as colorless plates, m. p. 132.0–132.6°. *Anal.* Calcd. for $C_{16}H_{15}NO_2$: N, 5.6. Found: N, 5.8.

**1-Aminofluorene.**—A mixture of 0.5 g. of the urethan, V, 10 cc. of acetic acid and 15 cc. of concentrated hydrochloric acid was heated in a sealed tube at 140° for four hours. After cooling, the tube was opened, the contents diluted with water and filtered. The insoluble material (m. p. > 270°) was placed in a separatory funnel with 10% potassium hydroxide solution and ether. After shaking for several minutes, the solid disappeared. The ether layer was separated and evaporated to dryness and the residue crystallized from dilute ethanol to give 0.31 g. of tan crystals, m. p. 117–119°; recrystallized from benzene–petroleum ether, m. p. 124.0–124.6°. *Anal.* Calcd. for $C_{13}H_{11}N$: N, 7.7. Found: N, 8.0. The trinitrofluorenone complex[12] separated from benzene as beautiful, almost black needles, m. p. 211.0–211.8°. *Anal.* Calcd. for $C_{26}H_{16}N_4O_7$: N, 11.3. Found: N, 11.3.

(6) The procedure described in *Org. Syntheses*, **24**, 1 (1944), for the isolation of acenaphthenequinone was used.

(7) Fittig and Liepmann, *Ann.*, **200**, 5 (1879).

(8) Goldschmeidt, *Monatsh.*, **23**, 894 (1902).

(9) Goldschmeidt and Lipschitz, *ibid.*, **25**, 1175 (1904). In this article the authors state that the melting point of 75–76° reported for the ethyl ester in their earlier work (ref. 8) was a misprint. However, in view of our isolation of a low melting form, it is quite possible that their early observation was genuine. The melting point of our low melting form did not change even after standing more than a year.

(10) Huntress, Pfister and Pfister, THIS JOURNAL, **64**, 2846 (1942).

(11) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(12) Orchin and Woolfolk, *ibid.*, **68**, 1727 (1946); Orchin, Reggel and Woolfolk, *ibid.*, **69**, 1225 (1947).

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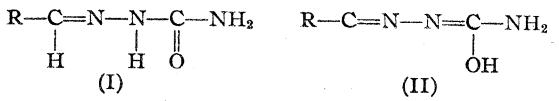
## On the Structure of Aromatic Aldehyde Semicarbazones[1]

BY GIUSEPPE CILENTO

By chemical evidence, structure (I) has been attributed to the semicarbazones. The enolic structure (II), although it might explain the abnormal ultraviolet absorption maximum of these compounds, has been ruled out, since essentially

(1) This investigation was supported by a grant from the Fundação Virginia Matarazzo, São Paulo, Brazil.

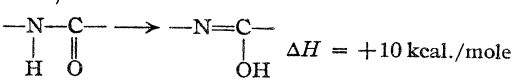
the same light absorption is shown by the corresponding N-methyl semicarbazones, where enolization cannot occur.[2] Additional information has been obtained by investigating the ultraviolet absorption spectra of aqueous solutions of benzaldehyde and *p*-nitrobenzaldehyde semicarbazones at different hydrogen ion concentrations.



(I) (II)

The spectrum of benzaldehyde semicarbazone remains almost the same in the range from *p*H 2.6 to 11.0, showing $\lambda_{max.} = 278$ m$\mu$, (Fig. 1). We conclude that the same kind of molecule must be present in these solutions.

That there is one kind only, and that kind must have the carbonyl structure, can be supported by energetic considerations, as the enol formation would be accompanied by an increase of ten kilocalories/mole.[3]



This cannot be overbalanced by the extra resonance energy.

At *p*H 1.0 the spectrum of benzaldehyde semicarbazone is modified, showing a new band at shorter wave length ($\lambda_{max.} = 249$ m$\mu$). The intensity of the new band increases and that of the original band decreases with time, but after four hours we noticed no further change (Fig. 1).

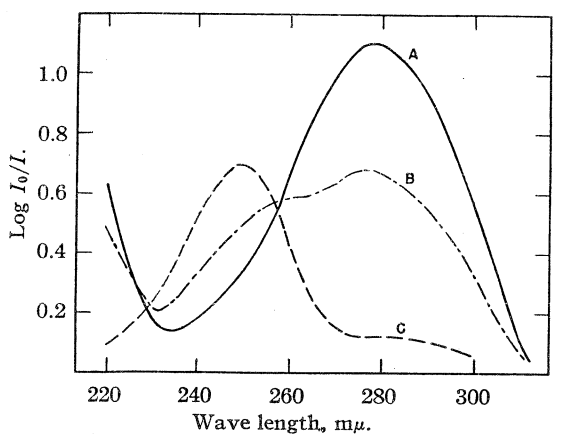



Fig. 1.—Ultraviolet absorption spectrum of benzaldehyde semicarbazone in aqueous solution: A, *p*H 11.0, *p*H 6.0 and *p*H 2.6; B, *p*H 1.0; C, *p*H 1.0 after four hours.

It is very probable that this alteration results from chemical, rather than physico-chemical changes. However, the possibility of hydrolysis can be ruled out on account of the value 0.0015 at 25° for the constant of limiting hydrolysis in acid solution.[4]

(2) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

(3) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 289.

(4) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 2881 (1932).

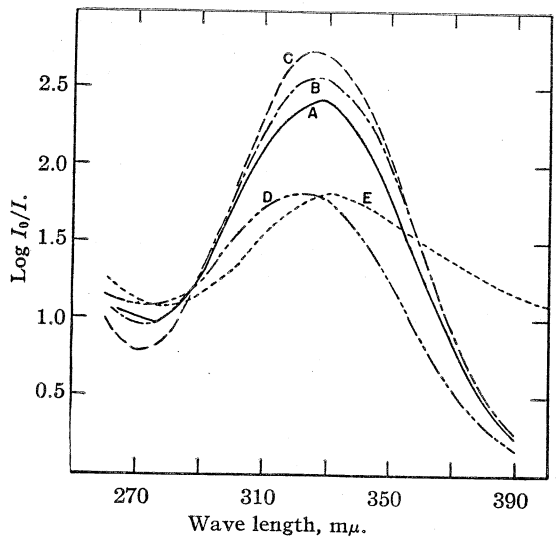
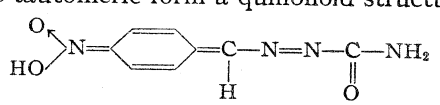



Fig. 2.—Ultraviolet absorption spectrum of *p*-nitrobenzaldehyde semicarbazone in aqueous solution: A, *p*H 1.3; B, *p*H 2.5; C, *p*H 5.7; D, *p*H 9.5; E, *p*H 11.3.

The effect of *p*H on the ultraviolet absorption spectrum of *p*-nitrobenzaldehyde semicarbazone is illustrated in Fig. 2. An isobestic point occurs at about 287 m$\mu$. The wave length of the absorption maximum remains at about 325 m$\mu$ but at *p*H 11.3 a shift of 5 m$\mu$ toward the red is observed. The isobestic point indicates a change in the molecular structure with a change in *p*H. We suggest for the tautomeric form a quinonoid structure



Such a structure can explain also the solubility in alkaline solution of this, and other aromatic nitro-aldehyde semicarbazones (such as *o*-nitrobenzaldehyde and 5-nitro-2-furfuraldehyde), and the insolubility of *m*-nitrobenzaldehyde semicarbazone.

The spectrum in 1 *N* hydrochloric acid solution shows a new band at 267 m$\mu$, the band at 287 m$\mu$ being reduced to an inflection.

On standing in alcoholic solution, the absorption spectrum of *p*-nitrobenzaldehyde semicarbazone showed a drop in intensity and a shift toward the shorter wave length (331 m$\mu$ → 320 m$\mu$), probably due to a *cis–trans* rearrangement. The Fisher–Hirschfelder–Taylor models suggest that the *cis* isomer cannot assume a planar configuration, due to steric hindrance between the secondary nitrogen atom and the ortho hydrogens.

On crystallization from water, *p*-nitrobenzaldehyde semicarbazone may separate in a white or a yellow form, depending upon conditions. These forms have been studied in a polarizing microscope. The yellow form is needle-like, with an extinction angle of 44°; the white form appeared in rectangular crystals, which showed practically no extinction when the microscope stage was turned

360°, the nicols being crossed. The crystals were bi-axial, section perpendicular to an optical axis; the isogyra was practically straight at rotation of the section. The angle between the optical axis must be nearly 90°; optically +.

### Experimental

The aldehydes and the semicarbazones have been prepared by the usual methods. The latter were recrystallized from water and dried in a vacuum desiccator over calcium chloride. A solution of approximately 100 mg. per liter of benzaldehyde semicarbazone was prepared and solutions at different *p*H values were obtained by adding 2 cc. of the above solution in a 25 cc. volumetric flask and filling up with distilled water and acid (HCl, 1 *N*) or base (NaOH, 1 *N*).[5] A similar procedure was used with the *p*-nitro derivative.

Spectral measurements were carried out in a Beckman D. U. Quartz Spectrophotometer, using 1 cm. silica cells.

(5) The *p*H's were checked with a potentiometer.

DEPARTMENT OF HISTOPHYSIOLOGY
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## Melting Point of Magnetite–Silica Mixtures in Air

BY L. S. DARKEN

In commenting on my recent paper, "Melting Points of Iron Oxides in Contact with Silica,"[1] one of the referees questioned the value (1442°) reported there for the melting point of magnetite–silica mixtures in air. Such question arises naturally from several statements in the literature. For example, Bowen and Schairer[2] found "no more than a little liquid" formed by heating mixtures of iron oxide and silica to temperatures approaching 1500°, even in a vacuum furnace. Cook[3] observed fusion of magnetite–silica mixtures only near and above 1600°.

An attempt was made to resolve this apparent discrepancy by determining the approximate melting point by a more common method, namely, to prepare an intimate mixture of magnetite and silica by a preliminary fusion and then to determine the melting point of the mixture. Equal weights of magnetite and quartz were mixed by grinding in a mortar to pass a 400-mesh sieve. The mixture was placed in a small (1 ml.) platinum crucible and heated in an air atmosphere in a tubular "Globar" furnace. Starting at 1540° it was held at each of successively higher temperatures for fifteen minutes, being removed and examined in between. This procedure was continued until 1680° (near the limiting temperature of furnace) was reached, at which temperature the charge had sintered only slightly and was easily broken by gentle tapping or probing with a needle.

The failure to obtain a premelt by the above method was somewhat surprising: In order to avoid a large excess of silica another method was tried. A 2-cm. length of clear vitreous silica rod was placed vertically in the crucible and surrounded with magnetite (the same used by Darken and Gurry[4]). This charge was then heated in air to slightly above the melting point of magnetite (1597°) and held there one hour. The molten oxide was thus undoubtedly saturated, or nearly saturated, with silica. The charge was cooled and removed from the crucible; the silica rod and adjacent portions of the melt were discarded.

Having thus obtained a fused intimate mixture of magnetite and silica the melting point was determined as follows: The finely crystalline massive oxide was broken into small pieces about 3 mm. across. One of these pieces was placed in a platinum wire helix[5] and held about ten minutes at a predetermined temperature in an air atmosphere in the furnace. If extensive melting occurred the molten oxide ran down the helix and adhered to the lowest convolution. If no melting occurred the sharp corners and edges of the broken piece were still visible after cooling. From a series of such tests it was found that melting did occur at 1455 ± 5° but did not occur 20° lower. No attempt was made to establish closer limits.

Thus the difficulty in melting the mechanical mixture confirms the reports of Bowen and Schairer and of Cook, whereas the determination of the melting point by remelting confirms roughly the results of my previous investigation which placed the melting point at 1442°.

(1) L. S. Darken, THIS JOURNAL, **70**, 2046 (1948).
(2) Bowen and Schairer, *Am. J. Sci.*, **24**, 177 (1932).
(3) W. J. Cook, *J. Am. Ceram. Soc.*, **22**, 322 (1938).
(4) Darken and Gurry, THIS JOURNAL, **68**, 798 (1947).
(5) The platinum helix was previously loaded with the oxide and held near 1500° for several hours so that the surface would absorb sufficient iron to be in substantial equilibrium with the melt. This precaution was taken lest the platinum absorb sufficient iron from the test specimen to seriously lower the iron–oxygen ratio to a value below that corresponding to the gas equilibrium.

RESEARCH LABORATORY
UNITED STATES STEEL CORPORATION
KEARNY, NEW JERSEY RECEIVED JANUARY 3, 1949

## Standard Potential of the Mercury–Mercury(I) Phosphate Electrode

BY THOMAS DE VRIES AND DONALD COHEN

A study was made of the mercury–mercury (I) phosphate electrode in phosphoric acid solutions of various concentrations with cells of the type: $H_2$, $H_3PO_4$ (*m*), $Hg_2HPO_4$ (s), Hg. There is very little information in the literature about mercurous phosphate. Gerhardt[1] in 1849 and Haack[2] in 1891 had prepared mercurous orthophosphate by adding a solution of mercurous nitrate to an excess of sodium phosphate solution. They obtained a white or yellow precipitate. Latimer and Hildebrand[3] give the formula of the orthophosphate as $Hg_6(PO_4)_2$.

### Experimental

**Mercurous Phosphate.**—Mercury(I) nitrate was dissolved in water acidified with nitric acid. This solution was slowly added at room temperature to a solution of primary sodium phosphate, $NaH_2PO_4$, present in excess. A fine white precipitate first formed and gradually changed to a pale yellow or even a deep yellow color. The temperature at which the precipitation was carried out had no effect on the color. Analysis indicated the yellow compound to be the tertiary phosphate, $Hg_3PO_4$.

*Anal.* Calcd. for $Hg_3PO_4$: Hg, 85.21. Found: Hg, 85.41, 85.50.

(1) Gerhardt, *Jahresber.*, 288 (1849).
(2) Haack, *Ann.*, **262**, 192 (1891).
(3) Latimer and Hildebrand, "Reference Book of Inorganic Chemistry," The Macmillan Co., New York, N. Y., 1940.

When mercury(I) nitrate was added to a dilute solution of orthophosphoric acid, a pure white crystalline precipitate was obtained which did not change color. The precipitate was filtered, washed with water and dried in a desiccator over anhydrous calcium chloride.

*Anal.* Calcd. for $Hg_2HPO_4$: Hg, 80.71. Found: Hg, 79.2, 80.8.

The various concentrations of phosphoric acid were made by diluting a stock solution which had been prepared from 85% acid and standardized by titration against standard sodium hydroxide using thymolphthalein as indicator.

The platinized platinum electrodes were prepared with the usual care. Several were used and they checked with each other to within 0.3 millivolt. The hydrogen was bubbled through a solution of chromous chloride acidified with acetic acid[4] to remove oxygen, then through a solution of phosphoric acid of the same concentration as that used in the cell. The cell was H-shaped with a sintered glass diaphragm in the horizontal arm. Potentials were measured with a Rubicon, type B, potentiometer at 25 ± 0.05°.

The cells made with the yellow tertiary mercurous phosphate did not give constant or reproducible potentials. In all cases the potential would decrease with time and approach a minimum value. In some cases the yellow phosphate had changed to a white color in the 0.2 *M* phosphoric acid after several days. Typical potentials were 0.7364, 0.7392 and 0.7492 decreasing to 0.7245, 0.7228 and 0.7313 after seven days.

The cells made with the white secondary mercurous phosphate gave fairly constant and reproducible results and equilibrium values were established within one day. For the cell $H_2$ ($a$ = 1), $H_3PO_4(m)$, $Hg_2HPO_4$(s), Hg, the cell reaction is $H_2 + Hg_2HPO_4 = H^+ + H_2PO_4^- + Hg$, and if the secondary and tertiary ionizations are assumed to be negligible, the potential at 25° is given by the equation $E = E^0 - 0.02957 \log a_{H^+}a_{H_2PO_4^-}$. For $a_{H^+}a_{H_2PO_4^-} = K_1 a_{H_3PO_4}$, the value of $K_1 = 7.516 \times 10^{-3}$ was used as reported by Nims.[5] The activities of the undissociated phosphoric acid were taken from the results of Mason and Blum.[6] The calculated molal standard potential of the cell is given in the last column of Table I. The $E^0$ for the most dilute solution does not agree with the other values. Excluding that value, the average is 0.639 ± 0.002 volt.

An independent calculation for the $E^0$ of the cell can be made by using the Debye–Hückel limiting law for the mean ion activity coefficient of phosphoric acid and by using the degree of dissociation, $\alpha$, tabulated by Mason and Blum,[6] to calculate the concentration, $m_1$, of the hydrogen and the dihydrogen phosphate ion. The previous equation becomes $E^{0\prime} = E + 0.05914 \log \alpha m = E^0 + 0.0301\sqrt{\alpha m}$, using $\log \gamma_\pm = -0.5085\sqrt{\mu}$ and $\mu = m_1 = \alpha m$. The results of such a calculation are given in Table II. The average value of 0.638 ± 0.002 for the $E^0$ of the cell agrees better than one should expect. The molal potential for the electrode Hg, $Hg_2HPO_4$, $H_2PO_4^-$ is −0.639 ± 0.002 volt at 25°.

(4) Stone and Skavinski, *Ind. Eng. Chem., Anal. Ed.*, **17**, 495 (1945).

(5) Nims, THIS JOURNAL, **56**, 1110 (1934).

(6) Mason and Blum, *ibid.*, **69**, 1246 (1947).

TABLE I

POTENTIAL OF CELLS AND CALCULATION OF STANDARD POTENTIAL, $E^0$, OF THE CELL

| $m$ | $E$ | | $a_{H_3PO_4}$ | $E^0_{298.1}$ |
|---|---|---|---|---|
| 0.001026 | 0.7998 | 0.7995 | 0.0001050 | 0.6191 |
| .01026 | .7730 | .7750 | .004204 | .6409 |
| .02052 | .7601 | .7600 | .01223 | .6406 |
| .05130 | .7433 | .7453 | .03440 | .6382 |
| .1032 | .7341 | .7336 | .08057 | .6388 |
| .2071 | .7215 | .7221 | .1776 | .6368 |

TABLE II

STANDARD POTENTIAL CALCULATED FROM DEGREE OF IONIZATION DATA

| $m$ | $\alpha$ | $E$ | $E^{0\prime}$ | $E^0$ |
|---|---|---|---|---|
| 0.01026 | 0.599 | 0.7740 | 0.6432 | 0.6400 |
| .02052 | .492 | .7600 | .6421 | .6378 |
| .05130 | .366 | .7443 | .6423 | .6365 |
| .1032 | .290 | .7339 | .6438 | .6365 |

CHEMISTRY DEPARTMENT
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RECEIVED JULY 26, 1948

## The Ziegler Bromination of Ethyl Tetrolate

BY J. ENGLISH, JR., AND J. DELAFIELD GREGORY[1]

In a recent review article Djerassi[2] commented on the lack of data on the reactions of N-bromosuccinimide with acetylenic compounds. This prompts us to record our observations on the bromination of ethyl tetrolate by this method.

Tetrolic acid was synthesized by the action of carbon dioxide on propynylmagnesium bromide and converted to its ethyl ester in the usual manner.[3] Pure samples of the ester were then dissolved in carbon tetrachloride and treated with N-bromosuccinimide at reflux temperatures, with addition of benzoyl peroxide, under ultraviolet light, without either, and finally in a sealed vessel at 150°. In all cases most of the ester was recovered unchanged. The only product that could be isolated in pure form was ethyl $\alpha,\beta$-dibromocrotonate, resulting apparently from the addition of two atoms of bromine at the triple bond.

A somewhat analogous addition reaction accompanying the Ziegler bromination of cyclobutene and methylene cyclobutane has been reported by Buchman and Howton.[4] In the present instance, although no hydrogen bromide was noted, the rather extensive decomposition observed might well have produced some of this substance and hence made bromine available to the reaction mixture as pointed out by these authors.

(1) Present address: Rockefeller Institute for Medical Research, N. Y.

(2) C. Djerassi, *Chem. Rev.*, **43**, 296 (1948); see also A. Wohl and K. Jachinowski, *Ber.*, **54**, 476 (1921).

(3) Stolz, communication cited in Beilstein, II, p. 480.

(4) E. R. Buchman and D. R. Howton, THIS JOURNAL, **70**, 2517, 3510 (1948).

### Experimental

A suspension of 19.5 g. of N-bromosuccinimide in 30 cc. of carbon tetrachloride was mixed with 12.0 g. of ethyl tetrolate and 0.5 g. of freshly recrystallized dibenzoyl peroxide. After fifty minutes at reflux temperature the pale yellow solution was decanted from 15 g. of dark tarry material, the solvent evaporated and the residue distilled. In addition to 6.6 g. (55%) of ethyl tetrolate there was obtained 3.5 g. (12%) of a fraction boiling at 68–75° at 2 mm. This product was combined with those from other experiments and carefully fractionated to yield pure ethyl $\alpha,\beta$-dibromocrotonate b. p. 58.5–60° at 0.8 mm., $n^{20}D$ 1.5175, $d^{20}_4$ 1.744.

*Anal.* Calcd. for $C_6H_8O_2Br_2$: C, 26.50; H, 2.96; Br, 58.77. Found: C, 26.60; H, 3.05; Br, 58.62.

For further identification a sample was saponified by refluxing with 10% aqueous potassium hydroxide. From the highly colored product there was isolated by extraction with ligroin pure $\alpha,\beta$-dibromocrotonic acid, m. p. 118.5–119.5°. Michael reported the melting point of this substance as 120°.[5]

(5) A. Michael, *Ber.*, **34**, 4221 (1901).

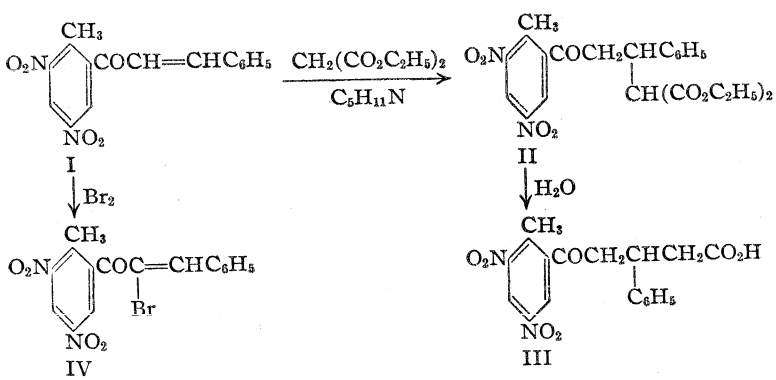
STERLING CHEMISTRY LAB.
YALE UNIVERSITY
NEW HAVEN, CONN. RECEIVED NOVEMBER 17, 1948

## The Condensation of 2′-Methyl-3′,5′-dinitrochalcone with Ethyl Malonate

BY REYNOLD C. FUSON AND GEORGE MUNN

2′-Methyl-3′,5′-dinitrochalcone (I) was prepared in the hope that it might undergo an intramolecular Michael condensation to yield the corresponding substituted $\alpha$-tetralone. However, under the conditions ordinarily employed for Michael condensations no ring closure occurred. That this chalcone is capable of undergoing reactions of the Michael type was demonstrated by condensing it intermolecularly with ethyl malonate.

The product (II) which was obtained when the chalcone was allowed to react with ethyl malonate was hydrolyzed and the resulting acid decarboxylated to form 2-phenyl-3-(2-methyl-3,5-dinitrobenzoyl)-butyric acid (III).




The 2′-methyl-3′,5′-dinitrochalcone yielded a monobromo derivative when it was allowed to react with bromine in acetic acid solution. Oxidation of the bromochalcone with permanganate produced 3,5-dinitro-*o*-toluic acid, showing that the bromine was not attached to the methyl group. It thus seems probable that the addition of bromine to the double bond is followed by the loss of hydrogen bromide, forming 2′-methyl-3′,5′-dinitro-$\alpha$-bromochalcone (IV).

### Experimental

**2-Methyl-3,5-dinitroacetophenone.**—2-Methyl-3,5-dinitrobenzoyl chloride was prepared by heating a mixture of 45 g. of 3,5-dinitro-*o*-toluic acid,[1] 35 ml. of purified thionyl chloride, and 200 ml. of dry benzene under reflux until the acid completely dissolved. The solvents were then removed by distillation under diminished pressure, and the residue was dissolved in 250 ml. of dry ether. This ether solution was used without further purification.

An ether solution of the ethoxymagnesium salt[2] of malonic ester was made in the following manner: Five milliliters of absolute ethanol, 0.5 ml. of carbon tetrachloride, and 5.25 g. of magnesium turnings were placed in a flask and allowed to react for a few minutes. Seventy-five milliliters of anhydrous ether was then added and to this mixture a solution of 35.2 g. of ethyl malonate, 20 ml. of absolute ethanol and 25 ml. of dry ether was added at a rate such that mild refluxing was maintained.

When the magnesium had dissolved, the solution of 2-methyl-3,5-dinitrobenzoyl chloride was added with stirring over a period of thirty minutes. The contents of the flask were then heated under reflux for an additional thirty minutes and then acidified with dilute sulfuric acid. The ether layer and an ether extract of the water layer were combined and the solvent was removed by distillation. The residual liquid was heated under reflux for four hours in a mixture of 60 ml. of acetic acid, 7.5 ml. of concentrated sulfuric acid and 40 ml. of water. The mixture was cooled, diluted with water and extracted with ether. The ether was washed with sodium bicarbonate solution, dried over calcium chloride, and the solvent was removed by distillation. The residue was distilled under diminished pressure at 150–152° (2 mm.). The yield was 27 g. (60%). When recrystallized from methanol, the 2-methyl-3,5-dinitroacetophenone melted at 72–73°.

*Anal.* Calcd. for $C_9H_8N_2O_5$: C, 48.24; H, 3.60; N, 12.50. Found: C, 48.47; H, 3.79; N, 12.40.

**2′-Methyl-3′,5′-dinitrochalcone (I).**—Dry hydrogen chloride was bubbled slowly over a period of two days into a solution of 22.6 g. of 2-methyl-3,5-dinitroacetophenone and 12 ml. of benzaldehyde in 150 ml. of glacial acetic acid. During this time a crystalline precipitate appeared. The mixture was then heated under reflux for two hours and poured on ice. The white precipitate which formed was collected on a filter and recrystallized from ethanol. Twenty-one grams of 2′-methyl-3′,5′-dinitrochalcone was obtained; m. p. 128–129°; 67%.

*Anal.* Calcd. for $C_{16}H_{12}N_2O_5$: C, 61.53; H, 3.88; Found: C, 61.65; H, 3.90.

**Condensation of 2′-Methyl-3′,5′-dinitrochalcone with Ethyl Malonate.**—A mixture of 3.1 g. of 2′-methyl-3′,5′-dinitrochalcone, 2 ml. of ethyl malonate, 100 ml. of absolute ethanol, and 5 drops of piperidine was heated under reflux for twenty-four hours. It was then diluted with water, acidified and extracted with ether. The ether layer was dried over calcium chloride, and the solvent was removed by distillation. The residue was recrystallized several times from methanol with the use of charcoal; 1.8 g. of white crystals (II) was obtained; m. p. 96–97°.

*Anal.* Calcd. for $C_{23}H_{24}N_2O_9$: C, 58.47; H, 5.12; N, 5.93. Found: C, 58.78; H, 5.16; N, 6.09.

(1) McGookin, Swift and Tittensor, *J. Soc. Chem. Ind.* (*Trans.*), **59**, 92 (1940).

(2) Walker and Hauser, THIS JOURNAL, **68**, 1386 (1946).

**2-Phenyl-3-(2-methyl-3,5-dinitrobenzoyl)-butyric Acid.**—One gram of the malonic ester adduct was heated under reflux for four hours in a mixture of 10 ml. of glacial acetic acid, 7 ml. of water, and 1.5 ml. of concentrated sulfuric acid. The reaction mixture was then poured into 100 ml. of cold water; the acid precipitated as a brown gum. When this substance was recrystallized from methanol with the use of charcoal, it yielded 2-phenyl-3-(2-methyl-3,5-dinitrobenzoyl)-butyric acid (III) as white crystals melting at 137–138°.

*Anal.* Calcd. for $C_{18}H_{16}N_2O_7$: C, 58.06; H, 4.33; N, 7.53. Found: C, 58.32; H, 4.42; N, 7.78.

**2′-Methyl-3′,5′-dinitro-α-bromochalcone.**—A solution of 3.1 g. of 2′-methyl-3′,5′-dinitrochalcone and 5 ml. of bromine in 100 ml. of glacial acetic acid was allowed to stand at room temperature for twenty-four hours. At the end of this time the reaction mixture was poured into ice water and the excess bromine was destroyed by the addition of sodium sulfite solution. The white precipitate which formed was collected on a filter and recrystallized from ethanol. The bromochalcone (IV) formed white crystals which melted at 137°; yield 3 g.

*Anal.* Calcd. for $C_{16}H_{11}BrN_2O_5$: C, 49.12; H, 2.83. Found: C, 49.44; H, 2.79.

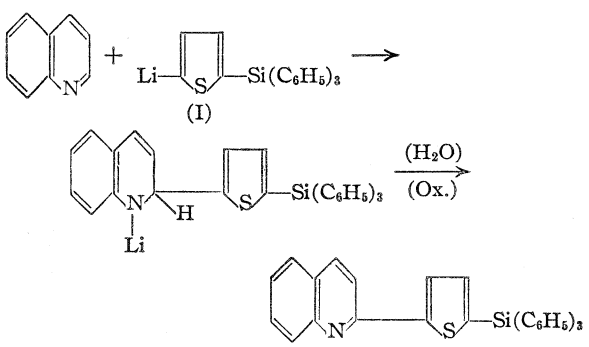
When the bromochalcone was oxidized with potassium permanganate in aqueous acetone, 3,5-dinitro-*o*-toluic acid was formed.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS RECEIVED NOVEMBER 10, 1948

## Some Anil Additions Involving Organosilicon Compounds

BY HENRY GILMAN AND MARY ALYS PLUNKETT[1]

In connection with studies on pharmacological action and chemical constitution, it seemed of interest to make a molecule containing both silicon and the quinoline nucleus. Consequently, compounds were prepared in which a lithiosilane was added to the anil linkage of a quinoline compound, as in the reaction




Triphenyl-[2-(5-lithio)-thienyl]-silane (I) reacted with quinoline, 6-methoxyquinoline and 4,7-dichloroquinoline. It is very probable that the substance isolated in each case was the 2-substituted quinoline, and not the 1,2-dihydro compound initially formed by hydrolysis of the N–Li intermediate from the addition of I across the azomethine linkage. Isolation through the picrates often leads to the oxidation of 1,2-dihydroquinolines by the picric acid.[2] The 1,2-dihydro compounds show an instability toward purification by crystallization, and cannot usually be obtained with a definite melting point range, as were the compounds described in this communication.

The preparation of I and a typical anil addition reaction are given in the experimental.

The authors are grateful to William Meikle for assistance, and particularly to Parke, Davis and Company for arranging for pharmacological testing, the results of which will be reported elsewhere.

### Experimental

**Triphenyl-[2-(5-lithio)-thienyl]-silane (I).**—To a solution of 5.5 g. (0.016 mole) of triphenyl-2-thienylsilane[3] under nitrogen in a mixture of equal parts of benzene and anhydrous ether was added 0.016 mole of *n*-butyllithium[4] in ether; the reaction mixture was refluxed for five hours. The solution gave a negative color test II.[5] It was used on the basis of an 80% yield, but the RLi compound was not, of course, isolated.

**Triphenyl-[5-(2′-quinolyl)-2-thienyl]-silane.**—To approximately 0.012 mole of I under nitrogen was added 1.5 g. (0.012 mole) of freshly distilled quinoline (previously dried over potassium hydroxide). A very slow reflux set in as the addition was made and the reaction mixture changed from red to dark yellow. After refluxing for one hour, the mixture was hydrolyzed and worked up to give 5 g. of crude solid, which was dissolved in dioxane and treated with a hot alcoholic solution of picric acid. The red picrate which precipitated was decomposed by boiling with a 5% solution of sodium hydroxide. After recrystallization from dilute dioxane, 40% of product melting at 168–170° was obtained.

*Anal.* Calcd. for $C_{31}H_{23}NSSi$: N, 2.98; S, 6.82. Found: N, 2.86; S, 6.61.

Addition of I to 4,7-dichloroquinoline gave triphenyl-[5-(4′,7′-dichloro-2′-quinolyl)-2-thienyl]-silane, m. p. 200–203°.

*Anal.* Calcd. for $C_{31}H_{21}NCl_2SSi$: S, 5.95; Cl, 13.03. Found: S, 6.26; Cl, 13.30.

Addition of I to 6-methoxyquinoline gave triphenyl-[5-(6′-methoxy-2′-quinolyl)-2-thienyl]-silane, m. p. 227–228°.

*Anal.* Calcd. for $C_{32}H_{25}ONSSi$: N, 2.80. Found: N, 3.14.

(1) Present address: Vassar College, Poughkeepsie, N. Y.

(2) Gilman, Towle and Spatz, THIS JOURNAL, **68**, 2017 (1946); Gilman and Benkeser, *ibid.*, **69**, 123 (1947).

(3) R. A. Benkeser, unpublished studies, Iowa State College.

(4) The titer of the *n*-butylilithium solution was determined by the procedure of Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).

(5) Gilman and Swiss, *ibid.*, **62**, 1847 (1940).

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA RECEIVED OCTOBER 29, 1948

## The Reaction of *o*-Hydroxy and *o*-Chlorobenzaldehyde with Ethanolamine[1]

BY LOUIS H. GOODSON AND HOPE CHRISTOPHER

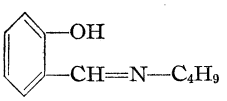
In studying the reaction of ethanolamine with salicylaldehyde and with *o*-chlorobenzaldehyde, M. Meltsner, E. Waldman and Chester B. Kremers[2] report that in these two cases addition com-

(1) This investigation was supported in part by a research grant from the National Cancer Institute of the National Institute of Health, U. S. Public Health Service.

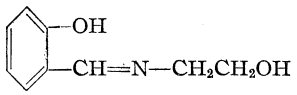
(2) M. Meltsner, E. Waldman and Chester B. Kremers, THIS JOURNAL, **62**, 3494 (1940).

pounds are formed without the elimination of water. They suggest that the failure of these two aldehydes to yield oxazolidines is due to chelation. We have found that water is eliminated in both of these reactions and that salicylaldehyde gives a Schiff base and that *o*-chlorobenzaldehyde yields an oxazolidine derivative.

In our initial experiments, salicylaldehyde was dissolved in an excess of benzene and treated with ethanolamine whereupon a mildly exothermic reaction took place and a water layer separated. Azeotropic distillation of the mixture effected the separation of one mole of water from one mole of each of the reactants. It was thought that perhaps the elimination of water in our experiment was due to the use of conditions differing from those used by Meltsner and co-workers.[2] Accordingly, we followed their procedure as carefully as possible but noted a layer of water in the receiver on removal of the butyl alcohol from the reaction mixture by slow distillation. The analyses and refractive indices of the products obtained from salicylaldehyde and ethanolamine show that the products are the same whether the reaction is carried out in benzene or in butyl alcohol. The intense yellow color of the material, even in thin layers, suggests that the Schiff base structure is the probable one. This structure is further supported by the ultraviolet absorption spectra (Fig. 1) of this and related compounds. Curve A is the absorption spectrum for N-*n*-butyl-2-hydroxybenzalamine (I) which was prepared by the reaction of salicylaldehyde and *n*-butylamine. Its absorption spectrum confirms the fact that it is a Schiff base possessing a double bond conjugated with a benzene ring. Curve B represents the absorption spectrum of the reaction product obtained from salicylaldehyde and ethanolamine. The similarity of these two curves indicates that this product is then the N-(2-hydroxyethyl)-2-hydroxybenzalamine (II), which is a Schiff base containing a double bond conjugated with the benzene ring.



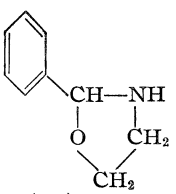

(I)



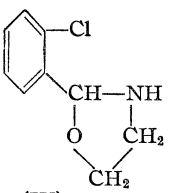

(II)

The structure, 2-(2-hydroxyphenyl)-oxazolidine, is eliminated because it would be expected to have an absorption spectrum resembling curves C and D (Fig. 1).

Similarly the reaction of *o*-chlorobenzaldehyde with ethanolamine in benzene yielded the theoretical quantity of water necessary for the formation of the Schiff base or the oxazolidine. However, this colorless product is thought to be the 2-(2-chlorophenyl)-oxazolidine (IV) in spite of Meltsner's report that his analysis agreed with a chelation compound formed without the elimination of water. Curve D (Fig. 1) gives the ultraviolet absorption spectrum of 2-phenyloxazolidine[3] (III)




(III)




(IV)

whose assigned structure was based on an analogy with known oxazoles and on its method of preparation. Because the oxazolidine ring system is relatively unstable, compounds bearing this structure react in the same manner as the open chain Schiff bases. For example, treatment of 2-phenyloxazolidine with dilute acid readily gives benzaldehyde and ethanolamine hydrochloride. Further, treatment of 2-(4-methoxyphenyl)-oxazolidine[2] with benzylmagnesium chloride gives a product similar to that obtained with Grignard reagents on various Schiff bases.[4] For these and other reasons it is difficult in most cases to distinguish between the Schiff base and the oxazolidine structures by their chemical reactivities. Curve C gives the ultraviolet absorption spectrum of 2-(2-chlorophenyl)-oxazolidine, (IV). Comparison of this curve with Curve D indicates the absence of the Schiff base structure and also a similarity with the known oxazolidine spectrum.

The molecular refractivities of four compounds discussed in this paper have been reported. In each case there appears to be an exaltation ranging from 2.57 to 3.35 units. Other Schiff bases and oxazolidines to be reported later in connection with other work, show exaltations of similar magnitudes. An attempt to differentiate between

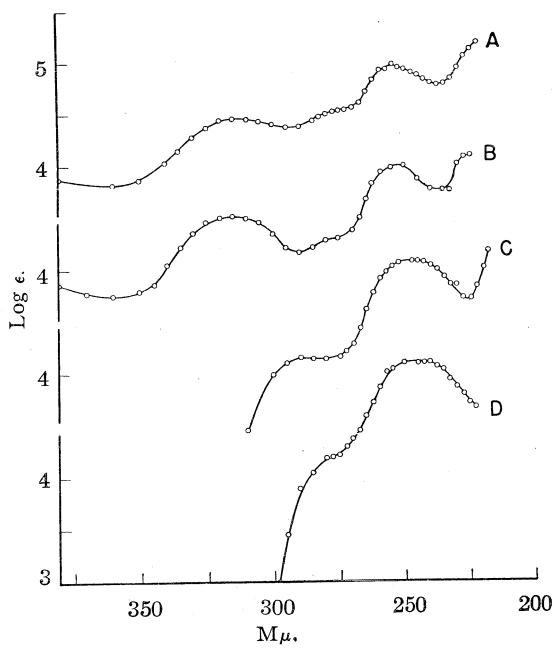



Fig. 1.

(3) Knorr and Matthes, *Ber.*, **34**, 3487 (1901).

(4) R. B. Moffett and W. M. Hoehn, THIS JOURNAL, **69**, 1792 (1947); K. N. Campbell, C. H. Helbing and Sr. M. Patricia, O.S.F., and B. K. Campbell, *ibid.*, **70**, 3868 (1948).

oxazolidine and Schiff base structures on the basis of their molecular refractivities was unsuccessful.

### Experimental[5]

**N-Butyl-*o*-hydroxybenzalamine (I).**—Azeotropic distillation of a mixture of 91.6 g. of salicylaldehyde, 54.7 g. of butylamine and an excess of benzene for two hours gave the theoretical quantity of water in the distillate. The benzene was removed under reduced pressure and the residue was distilled. The fraction, b. p. 84° at 0.1 mm., was yellow and weighed 127 g., $n^{25}D$ 1.5442; $d^{25}_4$ 0.9919; $MR_D$ (calcd.) 53.76; $MR_D$ (obsd.) 56.43.

*Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.55; H, 8.51; N, 7.91. Found: C, 74.70; H, 8.48; N, 7.92.

**N-(2-Hydroxyethyl)-2-hydroxybenzalamine (II).**—Method (a): A mixture of 61 g. of salicylaldehyde, 30.5 g. of ethanolamine and 200 ml. of benzene was refluxed using a water-trap (9 ml. of water was collected in two hours). The residue was distilled and the fraction b. p. 110–120° at 0.2 mm. was yellow and weighed 74 g.; $n^{25}D$ 1.6052; $d^{25}_4$ 1.1608; $MR_D$ (calcd.) 46.04; $MR_D$ (obsd.) 49.02.

*Anal.* Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.48.

Method (b): To a solution of 30.5 g. of salicylaldehyde in 68 ml. of reagent grade *n*-butanol was added 15.2 g. of ethanolamine. An exothermic reaction caused the temperature to rise from 28 to 63°. The clear deep-yellow solution was boiled for four hours and then distilled. During the early part of the distillation a water layer was visible under the butanol. The fraction b. p. 110–115° at 0.2 mm. weighed 36 g.; $n^{25}D$ 1.6050; $d^{25}_4$ 1.1608.

*Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.31; H, 6.80; N, 8.46.

**2-Phenyloxazolidine (III).**—This compound, prepared by the method of Knorr and Matthes,[3] was colorless, b. p. 86–88° at 0.1 mm.; $n^{25}D$ 1.5729; $d^{25}_4$ 1.0707; $MR_D$ (calcd.) 43.36; $MR_D$ (obsd.) 45.93.

**2-*o*-Chlorophenyloxazolidine (IV).**—A mixture of 70.3 g. of *o*-chlorobenzaldehyde, 30.5 g. of ethanolamine and 200 ml. of benzene (exothermic on mixing) was refluxed for two hours using a water-trap (9 ml. of water collected). The material was distilled and the fraction b. p. 102–104° at 0.2 mm., weighed 82 g. After redistillation it was a colorless oil weighing 78 g.; $n^{25}D$ 1.5793; $d^{25}_4$ 1.2073; $MR_D$ (calcd.) 47.22; $MR_D$ (obsd.) 50.57.

*Anal.* Calcd. for $C_9H_{10}ClNO$: C, 58.86; H, 5.49; N, 7.63. Found: C, 58.82; H, 5.46; N, 7.66.

**Ultraviolet Absorption Spectra.**—The data given in Fig. 1 were obtained using a Beckman quartz spectrophotometer with the hydrogen discharge lamp and quartz cells with a light path of 1 cm. A solution of 2.45 mg. of compound (I) in 100 ml. of absolute alcohol showed maxima at 255 mμ, $\epsilon$ = 95,500 and 315 mμ, $\epsilon$ = 30,000 (Curve A). A solution of 2.28 mg. of compound (II) in 100 ml. of absolute alcohol showed maxima at 252.5 mμ, $\epsilon$ = 100,000 and at 315 mμ, $\epsilon$ = 34,100 (Curve B). A solution of 2.53 mg. of compound (III) in 100 ml. of abs. alcohol showed maxima at 247.5 mμ, $\epsilon$ = 127,400 and 290 mμ, $\epsilon$ = 14,480 (Curve C). A solution of 2.28 mg. of compound (IV) in 100 ml. of abs. alcohol showed a maximum at 245 mμ, $\epsilon$ = 127,600 (Curve D).

(5) Nitrogen analyses done by semi-micro Kjeldahl procedure. Carbon and hydrogen analyses by Micro-Tech Laboratories of Skokie, Ill.

MIDWEST RESEARCH INSTITUTE
KANSAS CITY, MISSOURI RECEIVED AUGUST 9, 1948

## Preparation of Anhydrous Methyl Vinyl Ketone and Methyl Isopropenyl Ketone

BY HUGH J. HAGEMEYER, JR.

The preparation of methyl isopropenyl ketone by the aldol condensation of methyl ethyl ketone with formaldehyde and an evaluation of the method was reported by Landau and Irany.[1] In both the liquid phase aldol condensation and in the catalytic vapor phase condensation of formalin with methyl ketone[2,3] considerable difficulty is encountered in drying the unsaturated ketone and in removing traces of formaldehyde.

An alternate method of preparing methyl vinyl ketone and methyl isopropenyl ketone has now been evolved using the Mannich Reaction.[4,5,6,7] The Mannich base is prepared by treating a ketone with a secondary amine hydrochloride and formalin or paraformaldehyde. With acetone, diethylamine hydrochloride and formalin the reaction can be represented by the equation

$$CH_3COCH_3 + CH_2O + (C_2H_5)_2NH\cdot HCl \longrightarrow CH_3COCH_2CH_2N(C_2H_5)_2\cdot HCl + H_2O$$

The tertiary base is separated from the reaction mixture by treating the reaction product with 50% caustic. After drying and distillation it is suspended in an inert medium such as Dowtherm and an equivalent of anhydrous hydrogen chloride is added. The tertiary amine salt is then deaminated by heating to temperatures of 145–160°

$$CH_3COCH_2CH_2N(C_2H_5)_2\cdot HCl \longrightarrow CH_3COCH{=}CH_2 + (C_2H_5)_2NH\cdot HCl$$

The secondary amine hydrochloride can be recovered from the inert medium by filtration or extraction with water and reused in a subsequent batch. In practice it is preferred to add the tertiary amine hydrochloride gradually to the deaminating flask and the unsaturated ketone is distilled off continuously.

It is significant that with methyl ethyl ketone only methyl isopropenyl ketone was formed and there was no evidence for the formation of ethyl vinyl ketone. This indicates the mono-tertiary amine formed to be exclusively α-methyl-β-dimethylaminoethyl methyl ketone.

$$CH_3COCH_2CH_3 + CH_2O + (CH_3)_2NH\cdot HCl \longrightarrow CH_3COCH(CH_3)CH_2N(CH_3)_2HCl + H_2O$$

The methyl isopropenyl ketone prepared by deamination of this tertiary amine hydrochloride had the same constants as those reported for pure methyl isopropenyl ketone by Brant.[8]

### Experimental

**General Procedure.**—A mixture of ketone, dialkylamine hydrochloride and formaldehyde is refluxed for eight to twelve hours. A large excess of ketone is preferred in order to minimize the formation of di-tertiary amine products. In some instances the addition of a small amount of ethanol or isopropyl alcohol is advantageous in order to give a homogeneous mixture. At the end of the reaction excess ketone is removed by distillation. An excess

(1) Landau and Irany, *J. Org. Chem.*, **12**, 422 (1946).
(2) Brant, U. S. Patent 2,245,567.
(3) McMahon, Roper, Utermohlen, Hasek, Harris and Brandt, THIS JOURNAL, **70**, 2971 (1948).
(4) Defeu, McQuillan and Robinson, *J. Chem. Soc.*, 3089 (1931).
(5) Mannich, *Arch. Pharm.*, **255**, 261 (1917).
(6) Mannich and Salzmann, *Ber.*, **72**, 506 (1949).
(7) Mannich and Haf, *Arch. Pharm.*, **265**, 589 (1927).
(8) Brant, THIS JOURNAL, **64**, 2224 (1942).

of 50% alkali hydroxide is added slowly with cooling and the tertiary amine layer is separated, dried and distilled. It is desirable to concentrate the water solution in order to complete the separation of the tertiary amine.

By varying the conditions and the mole ratios of the reactants yields of 80–90% of the mono-tertiary amine can be realized. The tertiary amine is diluted with a suitable inert solvent and treated with an equivalent of anhydrous hydrogen chloride. The amine hydrochloride is suspended in Dowtherm and is deaminated by heating to 145–165°. Care should be exercised in the deaminating reaction so that no decomposition of the secondary amine hydrochloride takes place.

**Methyl Vinyl Ketone.**—Acetone (700 g., 12 moles) and diethylamine hydrochloride (6 moles) in 30% aqueous solution are mixed together. To this are added paraformaldehyde (240 g., 8 moles) and 150 cc. of isopropyl alcohol. The mixture is refluxed for six hours and then concentrated at reduced pressure from a water-bath. Five hundred grams of a 50% alkali hydroxide solution was added gradually with cooling. The tertiary amine layer is separated off and dried by distillation. The anhydrous amine distils at 74–75° at 15 mm. and titrates the theoretical equivalent weight of 143. The yield is 690 g. or 80.5%.

One hundred and forty-three grams (1 mole) of the tertiary amine is suspended in Dowtherm (1000 cc.) and anhydrous hydrogen chloride (35 g.) is added to form the amine hydrochloride. The suspension is added gradually to 500 cc. of Dowtherm in a 3-liter flask heated to 150° and equipped with a sweep stirrer and a short Vigreux column (45 cm.). Pure anhydrous methyl vinyl ketone distils off at 81° (734 mm.). The deamination is quantitative and the diethylamine hydrochloride is separated from the Dowtherm by washing with water.

**Methyl Isopropenyl Ketone.**—Methyl ethyl ketone (12 moles), dimethylamine hydrochloride (6 moles) and paraformaldehyde (8 moles) together with 300 cc. of isopropyl alcohol are mixed and refluxed for eight hours. The solution is concentrated, treated with excess 50% alkali hydroxide and the α-methyl-β-dimethylaminomethyl ethyl ketone is separated off and distils at 58° and 15 mm. Yield is 695 g. or 89%.

One mole (165 g.) of the tertiary amine hydrochloride is suspended in Dowtherm and deaminated at 160°. A 92% yield of anhydrous methyl isopropenyl ketone distilling at 96–97° at 734 mm. is obtained.

CHEMICAL DEVELOPMENT LABORATORIES
TENNESSEE EASTMAN CORP.
KINGSPORT, TENNESSEE RECEIVED OCTOBER 9, 1948

## Surface Tension of Chloroform

BY M. CONSILIA HANNAN AND M. CLARE MARKHAM

Recently R. Fanelli[1] has discussed the values of surface tension of chloroform determined by many investigators using various methods. Since no values were determined by the pendant-drop method, it was interesting to use apparatus already constructed in this Laboratory in connection with other work, to determine values of surface tension of chloroform.

This apparatus was similar to that of Hauser and his associates[2] and the techniques and method of calculation used, have been developed by Hauser. The chloroform was prepared from C. P. analyzed grade by washing with water, drying over calcium chloride and fractionally distilling. The portion boiling at 61° was used.

(1) R. Fanelli, THIS JOURNAL, **70**, 1792 (1948).

(2) J. M. Andreas, E. A. Hauser and W. B. Tucker, *J. Phys. Chem.*, **42**, 1001 (1938).

The surface tension values obtained at 25.00° were: 26.6, 26.6, 26.5, 26.5, 26.4, 26.5; average 26.5 dynes per cm.

Fanelli reports average values of 26.53 dynes per cm. obtained at 25.0° by the maximum bubble pressure, Sugden's double capillary method, using dried nitrogen; and average 26.46 dynes per cm. using nitrogen saturated with chloroform. The values obtained as noted above by the pendant-drop method check very closely those of Fanelli.

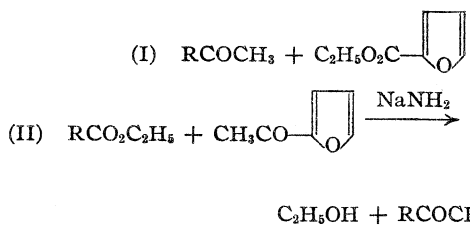
SAINT JOSEPH COLLEGE
WEST HARTFORD, CONN. RECEIVED NOVEMBER 22, 1948

## The Synthesis of Certain β-Diketones Containing a Furan Nucleus[1]

BY SAMUEL R. HARRIS[2] AND ROBERT LEVINE

The synthesis of a number of β-diketones by the acylation of 2-acetylthiophene with a series of esters has been reported in a recent communication from this Laboratory.[1] In the present investigation, several β-diketones containing a furan ring have been prepared. Two of these compounds have been prepared previously by other investigators.[3,4] Thus, acetyl-2-furoylmethane was prepared by acylating acetone with ethyl furoate using sodium ethoxide as the condensing agent[3] and benzoyl-2-furoylmethane has been synthesized by acylating acetophenone with ethyl furoate in the presence of sodium ethoxide[3] or metallic sodium.[4]

In the present work, two methods were used to prepare the β-diketones. The following equations, in which R represents an alkyl, aryl, or 2-thienyl group, indicate the reactions which take place.



The method of acylation used consists of allowing an ethereal suspension of two equivalents of sodium amide to react with two equivalents of the methyl ketone. The sodio derivative of the ketone thus formed is then acylated with an equivalent of the appropriate ester and the reaction mixture stirred and refluxed for two hours. This procedure is essentially that reported previously from this[1] and other laboratories.[5]

(1) Paper III in the series, Condensation Effected by the Alkali Amides. For Paper II, see THIS JOURNAL, **70**, 3360 (1948).

(2) Present address: Department of Chemistry, Howard University, Washington, D. C.

(3) Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2665 (1934).

(4) Semmler and Ascher, *Ber.*, **42**, 2355 (1909).

(5) Levine, Conroy, Adams and Hauser, THIS JOURNAL, **67**, 1510 (1945).

TABLE I

ACYL-2-FUROYLMETHANES

| Ketone | Ethyl ester | Product | Yield, % | B. p. °C. | B. p. Mm. | Copper salt, m. p. °C. |
|---|---|---|---|---|---|---|
| Acetone | 2-Furoate | Acetyl-2-furoyl-methane[a] | 43.3 | 107–110 | 10 | 219–222 |
| 2-Acetylfuran | Acetate | | 3.9 | | | |
| Methyl isobutyl | 2-Furoate | Isovaleryl-2-furoyl-methane[b] | 73.4 | 119–121 | 4 | 93–97 |
| 2-Acetylfuran | Isovalerate | | 3.6 | | | |
| Methyl *n*-amyl | 2-Furoate | Caproyl-2-furoyl-methane[c] | 79.1 | 143–146 | 7 | 97–101 |
| 2-Acetylfuran | Caproate | | 1.9 | | | |
| Acetophenone | 2-Furoate | Benzoyl-2-furoyl-methane[a] | 86.7 | 165–169 | 3 | 245–248 |
| 2-Acetylfuran | Benzoate | | 5.4 | 68–68.5 (m. p.) | | |
| 2-Acetylthiophene | 2-Furoate | 2-Furoyl-2-thenoyl-methane[d] | 74.5 | 192–195 | 6 | 272–274 |
| | | | | 54.5–55.5 (m. p.) | | |

[a] See ref. 3. [b] *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.11; H, 7.32. [c] *Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75. Found: C, 69.12; H, 7.75. [d] *Anal.* Calcd. for $C_{11}H_8O_3S$: S, 14.56. Found: S, 14.81.

The results of the present study are found in Table I. It may be seen that when the same $\beta$-diketone is prepared according to Schemes I and II above, the yield using ethyl 2-furoate as the acylating ester is invariably much higher than when an aliphatic or aromatic ester is used to acylate 2-acetylfuran. This large discrepancy in yield might have been difficult to explain if there had not been a visible side reaction occurring. It was observed that as soon as the first few drops of the 2-acetylfuran, which was being added from an addition funnel, came in contact with the ethereal suspension of sodium amide in the reaction flask, the residual 2-acetylfuran in the funnel became cloudy and as the addition was continued a fluid solid material formed in the funnel. It was felt that this solid was formed by the interaction of the ketone with ammonia. Ammonia is present in the reaction mixture either because some remains in solution when the sodium amide is suspended in ether or because of the following reaction which is the first step in the acylation of ketones with esters.

$$RCOCH_3 + NaNH_2 \longrightarrow RCOCH_2Na + NH_3$$

A sample of freshly distilled 2-acetylfuran was dissolved in absolute ether and the solution was then saturated with gaseous ammonia. An exothermic reaction took place and a brown solid material precipitated out of solution. This solid was water-soluble and unreactive toward 2,4-dinitrophenylhydrazine reagent, indicating that the carbonyl group was no longer free. An analysis of this solid (calcd. N, 11.02. Found: N, 11.11) suggested a molecular formula, $C_6H_9O_2N$ for the compound. It is probably a ketone ammonia and should therefore not be acylated by esters.

A detailed investigation of the reactions of 2-acetylfuran with ammonia and amines is now in progress in this Laboratory.

### Experimental

**Synthesis of Acyl-2-furoylmethanes.**—The apparatus used in these reactions consisted of a 1000-ml. three-necked round-bottomed flask having ground-glass joints and equipped with a mercury-sealed stirrer, an addition funnel, and a condenser (protected from atmospheric moisture by a drying tube filled with Drierite). Four-tenths of a mole of sodium (9.2 g.) is converted to sodium amide and suspended in absolute ether as described previously.[6] To the rapidly stirred suspension of sodium amide in ether, 0.4 mole of the appropriate ketone dissolved in 50 ml. of absolute ether is added, followed after fifteen minutes by 0.2 mole of the acylating ester. The reaction mixture is refluxed for two hours on a water-bath and then worked up as described earlier.[1,6] The yields of the compounds prepared are found in Table I.

(6) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944).

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RECEIVED OCTOBER 27, 1948

## Maleimide as a Dienophile

BY STEWART C. HARVEY[1]

Although maleic anhydride, maleic acid, and maleic esters have been used extensively as dienophiles in the Diels–Alder diene synthesis, the dienophilic character of maleimide has remained uninvestigated. In order to test its activity, maleimide was dissolved in ether with cyclopentadiene-1,3; the quantitative separation of a crystalline adduct, subsequently shown to be 3,6-endomethylene-1,2,3,6-tetrahydro-*o*-phthalimide, gave clear evidence of dienophilic activity. The structure of the adduct was confirmed by alkaline hydrolysis to give the known 3,6-endomethylene-1,2,3,6-tetrahydro-*o*-phthalic acid, which was identified by a mixed melting point procedure employing the same compound prepared in another manner.[2]

### Experimental

**3,6-Endomethylene-1,2,3,6-tetrahydro-*o*-phthalimide.**—A mixture consisting of 1.1 g. (1.4 ml.) of cyclopentadiene-1,3 and 1.6 g. of maleimide in 40 ml. of anhydrous ether was allowed to stand at room temperature. Evidence of a reaction was the appearance of a faint yellow color a few minutes after the reagents were brought together. The following morning 2.5 g. of gleaming white needles had separated from the solution. Recrystallization from alcohol–ether (1:2) gave a product melting at 187°. It was found to be very soluble in acetone, hot

(1) Present address: University of Texas School of Dentistry, Houston 4, Texas.

(2) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).

ethanol, 5% sodium hydroxide; slightly soluble in water, cold ethanol, cold acetic acid, diluted hydrochloric acid; insoluble ether. The adduct decomposed at temperatures above the melting point to give the original reagents; the addition was also somewhat reversible in cold sodium hydroxide solutions.

*Anal.* Calcd. for $C_9H_9O_2N$: N, 8.58. Found: N, 8.51.

**3,6-Endomethylene-1,2,3,6-tetrahydro-*o*-phthalic Acid.**—Two-tenths gram of 3,6-endomethylene-1,2,3,6-tetrahydro-*o*-phthalimide were placed on a steam-bath with 5 ml. of 10% potassium hydroxide and heated for three hours, at the end of which time no ammonia was detectable in the vapors above the flask. Concentrated hydrochloric acid was added in excess, and the mixture was then evaporated to dryness. The residue was then triturated in 20 ml. of ether to remove the maleic acid formed by the alkali-catalyzed reversal of the addition. The remaining organic constituents were taken up in 10 ml. of boiling acetone, and petroleum ether was added to the solution until it became cloudy, whereupon the mixture was left at 0° to crystallize. After one recrystallization from alcohol–ether (1:2) the melting point was observed to be 177°, which was not lowered by 3,6-endomethylene-1,2,3,6-tetrahydro-*o*-phthalic acid from another source.

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## N,N-Dimethyl-N′-(2-pyridyl)-N′-(2-furfuryl)-ethylenediamine

BY L. P. KYRIDES AND M. F. ZIENTY

In a recent publication Vaughan and Anderson[1] described the preparation of N,N-dimethyl-N′-(2-pyridyl)-N′-(2-furfuryl)-ethylenediamine (I) originally synthesized by Viaud.[2]

These authors reported that (I) is very unstable at temperatures even as low as −80° and that they were unable to prepare its mineral acid salts.[3]

Prior to the disclosure of Vaughan, *et al.*, the monohydrochloride of (I) had been prepared in this Laboratory for pharmacological evaluation. Since our findings do not support the observations reported, we are prompted to record our results.

Furfuryl alcohol was converted to the chloride in 75% yield by a modification of a synthesis described by Kirner,[4] with thionyl chloride in ether solution in the presence of pyridine at −15–20°. Distilled furfuryl chloride[5] was then treated with the lithium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine in benzene solution at room temperature. After removal of the solvent and unreacted N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine the desired product distilled as a yellow oil, stable at room temperature.

The monohydrochloride was prepared as well as the dihydrogen citrate salt.

The synthesis of (I) is described in detail.

### Experimental[6]

**N,N-Dimethyl-N′-(2-pyridyl)-N′-(furfuryl)-ethylenediamine.**—To a suspension of 8.3 g. (0.36 mole) of lithium amide in 500 cc. of dry benzene was added 59.4 g. (0.36 mole) of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine,[7,8] and the mixture refluxed for three hours with stirring. The reaction was cooled to 25° and maintained at this temperature while a solution of 42 g. (0.36 mole) of furfuryl chloride in 200 cc. of dry benzene was added dropwise during one hour, then refluxed for one hour. On cooling, the solid material was removed by suction filtration and the solvent distilled under reduced pressure. After a forerun of 17.7 g. (28.7% recovery) of the starting ethylenediamine (b. p. 100–105° (0.4 mm.)), 45.9 g. (52%) of the desired tertiary amine was collected as a light yellow oil, b. p. 117.5–118° (0.2 mm.). The dihydrogen citrate was prepared in 88% yield by treating a methanol solution of 4.9 g. (0.026 mole) anhydrous citric acid with a methanol solution of 10 g. (0.04 mole) of (I) and precipitation with dry ether. Recrystallization of this salt from methanol–ether gave colorless crystals, m. p. 95–97°.[1a]

The monohydrochloride was prepared by treating an ethyl acetate solution of 36.2 g. (0.14 mole) (I) with 5 g. (0.14 mole) dry hydrochloric acid in methanol. On cooling, 37.8 g. (92%) of monohydrochloride was obtained. Recrystallization from ethyl acetate yielded colorless needles, m. p. 117–119°.

*Anal.* Calcd. for $C_{14}H_{19}N_3O\cdot HCl$: Cl, 12.61. Found: Cl, 12.80.

(1) Vaughan and Anderson, THIS JOURNAL, **70**, 2607 (1948), reported m. p. 95–97°.

(2) Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947).

(3) In a personal communication, Dr. Anderson, after receiving the manuscript of this article, has written us as follows: "We today converted a sample of our stable citrate to the base and then to the hydrochloride in solution. In contrast to our previous experience, the solution remained colorless. Our only explanation is that an impurity in the original base caused its instability to temperature and mineral acids, and in the process of preparing the citrate this impurity was removed. We found also that the 5-bromofurfuryl analog hydrochloride appears to be stable when made from the citrate," and authorizes us to publish this statement as a footnote.

(4) Kirner, THIS JOURNAL, **50**, 1958 (1928).

(5) Gilman and Vernon, *ibid.*, **46**, 2576 (1924), reported furfuryl chloride as extremely unstable.

(6) All melting points are corrected.

(7) Whitmore, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(8) Huttrer, Djerassi, Beears, Mayer and Scholz, *ibid.*, **68**, 1999 (1946).

RESEARCH LABORATORIES OF
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## The Influence of Crystal Face in the Catalytic Deposition of Cobalt on a Single Crystal of Copper[1]

BY HENRY LEIDHEISER, JR., AND RICHARD MEELHEIM

It has previously been shown in two different cases[2,3] that the rate of gaseous, catalytic reactions on the surface of a metal differs with the crystal face exposed at the surface. It has also been shown by Beeck, Smith and Wheeler[4] that the rate of the reaction of hydrogen and ethylene on a nickel film with a (110) orientation parallel to the surface is greater than that on an unoriented film. Results reported herein show that the rate of another type of catalytic reaction, the

(1) This work was supported by a grant from the Research Corporation.

(2) Reaction of hydrogen and oxygen on copper: Leidheiser and Gwathmey, THIS JOURNAL, **70**, 1200 (1948).

(3) Decomposition of carbon monoxide on nickel: Leidheiser and Gwathmey, *ibid.*, **70**, 1206 (1948).

(4) Beeck, Smith and Wheeler, *Proc. Roy. Soc.* (*London*), **A177**, 62 (1940).

chemical deposition from solution of one metal on a crystal of another, differs with the face exposed at the surface. An explanation for the results is proposed on the basis of interatomic distances.

In the study of catalytic reactions with the aid of large single crystals, there are two general methods by which the rates of reaction on the different faces may be determined. When the products of the reaction are continually removed from the catalyst surface, it is necessary to expose only one face at a time. The rate of formation of the product is then determined by analysis of the exit gases or liquids. A second method consists of using a monocrystalline sphere[5] containing all crystal faces, and choosing a reaction which leaves a deposit on the surface, from which conclusions may be drawn concerning the comparative activity of the various faces. Both methods have their advantages and disadvantages but the latter method possesses the unique advantage of exposing all crystal faces simultaneously.

Monocrystalline spheres of copper, $^5/_8$ in. in diameter with a shaft $^3/_{16}$ in. in diameter, were mechanically and electrolytically polished by the method previously described.[6] They were immersed in potassium formate solutions of a cobalt salt at 180–250° and cobalt was catalytically[7] deposited on the surface. From the known reaction of other metallic salts in potassium formate solution,[8] the reaction was considered to be: $CoCl_2 + HCOOK \rightarrow Co + CO_2 + HCl + KCl$. The greatly different catalytic activities of the various faces were indicated by a pattern on the surface. The same pattern was observed over a large concentration range with cobalt chloride, cobalt carbonate, and cobalt sulfate solutions. The relative catalytic activities of the faces of copper in order of decreasing activity were as follows: (210), (310), (321), and (320); (311) and (211); (100); (331) and (221); (110); and (111). Faces whose indices were all different, such as (210), (310), etc., were far more active than any of the others. At 240° with a concentration of cobalt chloride hexahydrate of 1 g. per 100 g. of potassium formate, a cobalt deposit was observed on the (210) face in less than 30 seconds whereas the (111) face remained free of a visible deposit of cobalt for ten minutes.

There were two separate steps which took place in this catalytic reaction. First cobalt deposited catalytically on certain faces of the copper sphere. Then cobalt deposited catalytically on the cobalt deposits. From the pattern formed it was concluded that the rates of both of these reactions differed with the crystal face exposed at the surface.

Evidence was obtained in these experiments which suggests that the formate molecule was largely responsible for the relative rates of catalytic reaction on the different faces of a copper crystal in potassium formate solution. This evidence is summarized in the following statements. (1) The reaction pattern was independent of the anion of the metallic salt present in the solution. (2) An entirely different pattern was obtained when cobalt was chemically deposited on copper from a hypophosphite solution by the method of Brenner and Riddell.[9] (3) A third and different pattern was obtained when cobalt was electrodeposited on a copper crystal from several aqueous baths. Attempts were made to electrodeposit cobalt from formic acid solutions and from aqueous solutions containing formate, but secondary electrochemical reactions predominated. The essential process in all of these experiments was the reduction of cobalt ions in solution to cobalt at the surface of a monocrystalline sphere of copper. However, in each case the chemical environments were different. (4) Nickel salts in potassium formate yielded exactly the same pattern as cobalt salts. It should be pointed out that the chemical properties and interatomic spacings of nickel are similar to those of cobalt.

Additional indirect evidence for the influence of potassium formate on the reaction pattern is found in the comparative spacings of the formate radical and the copper–copper distance. At room temperature the spacing between oxygen atoms in the formate molecule is 2.24 Å.[10] and the distance of closest approach of copper atoms is 2.55 Å. The next shortest copper–copper spacing is 3.60 Å. No data are available for the formate molecule at the temperatures used in this study, but it would be expected that the qualitative relationship of these two important spacings would still hold. When the results are examined, it is observed that only those faces which do not have a 2.55 Å. copper–copper spacing parallel to the surface—thus faces with indices (*xyz*)—are the most active ones in the catalytic deposition of cobalt. In addition faces with the greatest number of 2.55 Å. spacings parallel to the surface are the least active. Thus it is proposed that the formate molecule or ion is adsorbed most strongly on the 2.55 Å. copper–copper spacing and partially blocks the surface for reaction. The activity of all faces containing

(5) In the case of the face-centered cubic metal copper, each face occurs on the sphere a minimum of six times. Thus when the various crystal faces react differently, a pattern, due to the repetition of results in each octant on the surface, occurs during reaction and the faces may be identified from the symmetry of this pattern.

(6) Gwathmey and Benton, *J. Phys. Chem.*, **44**, 35 (1940).

(7) The copper crystal is considered to be a catalyst in this study because it accelerated the rate of the reaction. It is appreciated that there might be objections to considering this reaction as a catalytic process according to the accepted definition in that the copper surface was visibly altered as the cobalt deposited. In the opinion of the authors, the same factors which make a substance a catalyst in the conventional sense were operative in the reaction described here.

(8) Gurevich and Pokrovskiĭ, *Ukrainskii Khem. Zhurnal*, **2**, 414 (1926): *Chem. Abst.*, **22**, 1714 (1928).

(9) Brenner and Riddell, *J. Research Natl. Bur. Standards*, **39**, 385 (1947).

(10) L. Pauling, "Nature of the Chemical Bond," second edition, Cornell University Press, Ithaca, New York, 1945, p. 203.

the 2.55 Å. spacing would not be equal because of the unequal effectiveness of the blocking by interaction of or competition for sites by neighboring formate molecules. As regards the second of the catalytic reactions, the deposition of cobalt on cobalt, it is known[11] that thin deposits of cobalt on copper continue the orientation, structure, and approximate lattice constants of copper. Thus the interpretation of results on the basis of the spacing of the copper crystal would apply equally well to the catalytic deposition of cobalt on the cobalt surface.

We wish to express our appreciation to Dr. Allan T. Gwathmey for his encouragement and constructive criticism.

(11) Cochrane, *Proc. Phys. Soc.* (*London*), **48**, 723 (1936).

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## Synthesis and Antifungal Action of 2-Methylmercapto-1,4-naphthoquinone[1,2]

BY JOHN E. LITTLE, THOMAS J. SPROSTON AND MURRAY W. FOOTE

Many methoxyquinones are known to possess marked antibiotic activity. Among these are fumigatin, spinulosin and javanicin. Many others have been tested and found to be remarkably inhibitory to various types of organisms.[3,4,5]

Since naturally occurring 2-methoxy-1,4-naphthoquinone was found to be highly fungistatic against several plant pathogenic fungi,[6] the synthesis of the sulfur analog of this compound was carried out and its fungistatic activity measured.

A simple synthesis in good yield was developed which was based upon mercaptan addition to 1,4-naphthoquinone. The work of Fieser and Turner,[7] involving the addition of mercaptans to 2-methyl-1,4-naphthoquinone, served as a pattern for the synthesis of this new compound.

We have found that the yield can be increased markedly by the well-timed addition of ferric chloride to the reaction mixture. This material probably causes the oxidation step to proceed farther toward completion.[7] It was found that the addition of the ferric chloride increased the yield of crude product (m. p. 183°) from 27 to 56%. When the salt was added at the beginning of the reaction, no product could be obtained. The final pure crystalline product separated from alcohol as yellow needles melting at 186.5–187° (cor.).

The spectrophotometric absorption curve of this compound was obtained. The wave length and intensities of the principal maxima are as follows: 256 mμ ($\epsilon$ = 19,700), 298 mμ ($\epsilon$ = 7,700) and 407 mμ ($\epsilon$ = 3,310). The characteristic naphthoquinone maximum at 330 is evident only as a slight inflection.

The substitution of a sulfur atom for oxygen in the 2-methoxy-1,4-naphthoquinone molecule results in a marked increase in antifungal activity. The L.D.$_{50}$ value for this compound as measured against the spores of *Monolinia fructicola*[8] was found to be 1.00 part per million (0.00100 mg. per ml.) as compared to 3.65 parts per million (0.00365 mg. per ml.) for 2-methoxy-1,4-naphthoquinone[6]; an increase in potency of approximately 3.5 fold.[9]

The solubility of 2-methylmercapto-1,4-naphthoquinone determined spectrophotometrically was found to be 7.0 mg. per liter at 26°. The insoluble nature of this material would be of benefit if it were to be used as a plant fungicide.

### Experimental

**Preparation of 2-Methylmercapto-1,4-naphthoquinone.**—16.5 g. of nearly pure naphthoquinone was dissolved in 1000 ml. of absolute alcohol by warming to 40°. The solution was cooled to room temperature and a small quantity of a dark impurity removed by filtration. The solution was then cooled in ice to 15° and 10 g. of ice-cold methyl mercaptan added suddenly while the flask was swirled.

After standing for thirty minutes at room temperature a yellow crystalline precipitate appeared; 15 ml. of 70% $FeCl_3 \cdot 6H_2O$ was now added and a further crystallization observed. After standing for fifteen minutes 22 ml. more of the ferric chloride solution was added and the quantity of precipitate again increased. Further addition of ferric chloride had no effect. The suspension was now cooled to 7°, filtered and dried with petroleum ether on the funnel; 11.9 g. of yellow crystalline material was obtained, m. p. 183°. The yield was 56% of the theoretical. One recrystallization of this material from hot alcohol after treatment with norite and filtration gave 9.16 g., m. p. 186.5–187°. The over-all yield was 45%.

*Anal.* Calcd. for $C_{11}H_8O_2S$: C, 64.69; H, 3.95; S, 15.70. Found: C, 64.88; H, 4.06; S, 15.93.

**Determination of Solubility.**—Fifteen milligrams of the finely ground 2-methylmercapto-1,4-naphthoquinone (m. p. 186.5–187°) was stirred in 5 l. of distilled water for thirty-six hours at room temperature. At the end of this time, all of the material had dissolved. The optical density of this solution at the 256 mμ maximum was found to be 0.309. Comparison of this density to that obtained with a saturated solution showed the solubility to be 7.0 mg. per liter.

(1) Printed by permission of Vermont Agricultural Experiment Station; Journal Series No. 1.

(2) We are grateful to the Herman Frasch Foundation for a grant in support of this work.

(3) Geiger, *Arch. Biochem.*, **11**, 23 (1946).

(4) Colwell and McCall, *Science*, **101**, 592 (1945).

(5) Oxford, *Chem. and Ind.*, **161**, 189 (1942).

(6) Little, Sproston and Foote, *J. Biol. Chem.*, **174**, 335 (1948).

(7) Fieser and Turner, THIS JOURNAL, **69**, 2335 (1947).

(8) Committee on Standardization of Fungicidal Tests, *Phytopathology*, **33**, 627 (1943); **37**, 354 (1947).

(9) A more detailed discussion of the fungistatic action of this and other naphthoquinones is in preparation for publication in the near future.

RECEIVED AUGUST 14, 1948

## Configurations of Radicals Derived from *cis*- and *trans*-Isomers

BY FRANK R. MAYO AND KENNETH E. WILZBACH

To obtain evidence concerning the recent proposal of Kistiakowsky,[1] that radicals have a non-

(1) Kistiakowsky, *The Indicator*, **28**, No. 3, 6 (1947), Nichols Medal Address, March 7, 1947.

planar configuration, some copolymerization experiments with *cis*- and *trans*-dichloroethylenes have been carried out. If a monomer added to each isomer in the same way, *i. e.*, predominantly *cis* or *trans*, and if the configuration of the resulting radical was maintained until addition to another monomer occurred, stereoisomeric dichlorides would be produced. In view of the conclusions of Young and Dillon[2] that the stereoisomeric 2,3-dibromobutanes react with potassium iodide at widely different rates, it seemed probable that the steroisomeric dichloroethylene copolymers would also show a difference in rate of reaction with potassium iodide. Since no difference was found, and if it is assumed that addition to both isomers is predominantly *cis* or predominantly *trans*, then the results show that the R–CHCl–ĊHCl radicals involved have either a planar configuration or else a pyramidal configuration which inverts or racemizes faster than the radicals add to vinyl acetate. Racemization, indeed, might be anticipated from the racemization of optically active hydrocarbons during chlorination with sulfuryl chloride.[3]

Copolymers of vinyl acetate with *cis*- and *trans*-1,2-dichloroethylene, containing about four vinyl acetate units per dichloroethylene unit, were prepared[4] at 15% conversion at 60° and the rates of reaction of these copolymers with potassium iodide were followed at 100°.

TABLE I

RATE OF IODINE LIBERATION FROM COPOLYMERS OF *cis*- AND *trans*-DICHLOROETHYLENE WITH VINYL ACETATE AT 100°

| $t$, hours | $I_2$ formed, milliequiv in 20 ml. | $k_2 \times 10^3$[a] |
|---|---|---|
| *cis* (18.13% Cl), $[KI]_0 = 0.2503$, $[C_2H_4Cl_2]_0 = 0.0342$ | | |
| 24 | 0.0310 | 3.83 |
| 48 | .0425 | 2.64 |
| 72 | .0530 | 2.20 |
| 96 | .0689 | 2.17 |
| *trans* (19.09% Cl), $[KI]_0 = 0.2503$, $[C_2H_4Cl_2] = 0.0379$ | | |
| 24 | 0.0320 | 3.56 |
| 48 | .0493 | 2.77 |
| 72 | .0594 | 2.24 |
| 96 | .0719 | 2.10 |

[a] $k_2 = \frac{2.303}{t(a-2b)} \log \frac{a-2b\theta}{a(1-\theta)}$ where $a = [KI]_0$, $b = [C_2H_4Cl_2]_0$, and $\theta$ is the fraction of dichloroethylene units which have reacted. $k_2$ is defined by: $d[I_w]/dt = k_2[KI]\cdot[C_2H_4Cl_3]$.

The results in Table I show that, although the reactions do not follow the simple second order kinetics found[2] for the dibromobutanes, there is no significant difference in the rates of iodine liberation from the two copolymers.

(2) Dillon, Young and Lucas, THIS JOURNAL, **52**, 1953 (1930).

(3) Brown, Kharasch and Chao, *ibid.*, **62**, 3435 (1940).

(4) Lewis and Mayo, *ibid.*, **70**, 1533 (1948), present data from which the feeds required for preparation of these polymers can be calculated.

### Experimental

The polymers were prepared in evacuated tubes from carefully fractionated monomers and were isolated by the frozen benzene technique.[5] Methanol was distilled from potassium hydroxide before use. Tubes of 30-ml. capacity containing 5 milliequivalents of potassium iodide and sufficient polymer to provide about 1.5 milliequivalents of available iodine in 20 ml. of 96% methanol were sealed in vacuum and heated at 100° from one to four days. The contents of the tubes were then poured into 75 ml. of water containing 2 g. of potassium iodide and a known slight excess of sodium thiosulfate to prevent occlusion of iodine by the polymers as they precipitated in the aqueous solution. The solutions were then titrated to the starch end-point with 0.05 *N* iodine solution. A weighed amount of iodine added to one of two otherwise identical tubes required the calculated additional thiosulfate, showing that the titration was valid and a correction factor was unnecessary.

(5) Lewis and Mayo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 134 (1945).

GENERAL LABORATORIES
U. S. RUBBER CO.
PASSAIC, N. J.

RECEIVED NOVEMBER 2, 1948

## Synthesis of 2- and 6-Fluoronicotinamides[1]

BY JOHN T. MINOR,[2] G. F. HAWKINS,[3] CALVIN A. VANDERWERF[2] AND ARTHUR ROE[4]

The current hypothesis which attributes the antimetabolite activity of such compounds as sulfanilamide and pyridine-3-sulfonic acid to the structural similarity but functional dissimilarity of these compounds to essential metabolites, suggests that a study of the physiological activity of various fluorine substituted vitamins should be of considerable interest.

Of the non-metallic elements, other than hydrogen, which commonly form single covalent bonds, fluorine is the one which most closely approximates hydrogen in atomic size and weight. The question of whether the substitution of a fluorine for a hydrogen atom in the molecules of various vitamins will lead to derivatives which possess vitamin or anti-vitamin activity is, therefore, a significant one. Of interest in this connection, is the observation of Mitchell and Niemann[5] that 3-fluorotyrosine and 3-fluorophenylalanine act as growth inhibitors for *Neurospora crassa* 8815–3a.

As part of a broad study, we have completed the synthesis of two compounds of this type, 2- and 6-fluoronicotinamides. The critical steps in these syntheses, the replacement of the amino-group by the fluorine atom in the commercially available compounds 2-amino-3-methylpyridine and 2-amino-5-methylpyridine, proceeded only in low yields when the amines were diazotized in anhydrous hydrogen fluoride and the resulting diazonium fluorides decomposed, and also when the conventional Schiemann reaction was employed. The modification of the Schiemann reaction de-

(1) The authors are indebted to the Office of Naval Research and to Eli Lilly and Company for support of this and related projects.

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(5) Mitchell and Niemann, THIS JOURNAL, **69**, 1232 (1947).

veloped by two of the present authors,[6] however, gave good results. Antimetabolite tests showed no inhibition of growth of *E. coli, Staph. aureus,* or *Strep. varidans in vitro* by 1:2000 dilution of either 2- or 6-fluoronicotinic acid. These tests were carried out by the Lilly Research Laboratories. Testing of the fluoronicotinamides is in progress.

### Experimental

**2-Fluoro-3-methylpyridine.**—To a solution of 80 g. (0.74 mole) of redistilled 2-amino-3-methylpyridine[7] in 310 g. of 40% fluoboric acid contained in an ice-cooled 1500 ml. beaker, 51 g. (0.74 mole) of sodium nitrite was gradually added in small portions with mechanical stirring. When the addition was complete, the solution was stirred for an additional thirty minutes at ice-bath temperature, and was then warmed to 45° to ensure complete decomposition. The solution was neutralized with sodium carbonate and steam-distilled. The yellow oil which separated from the distillate was removed and the remaining water layer extracted with ether. The oil and ether extracts were combined, dried over anhydrous sodium sulfate, and the ether removed. Distillation of the residue gave 39.5 g. (48%) of 2-fluoro-3-methylpyridine, b. p. 150.5–151.0° at 757 mm.

*Anal.* Calcd. for $C_6H_6NF$: C, 64.9; H, 5.4; N, 12.6. Found: C, 64.7; H, 5.6; N, 12.5.

**2-Fluoronicotinic Acid.**—A mixture of 38 g. (0.33 mole) of 2-fluoro-3-methylpyridine, 126 g. (0.80 mole) of potassium permanganate, and 1.5 l. of water contained in a 3-liter three-necked flask, fitted with condenser and sealed stirrer, was refluxed gently for four hours. The mixture was first steam-distilled to remove unreacted 2-fluoro-3-methylpyridine (8.0 g.) and then filtered hot. The resulting solution was evaporated to approximately 700 ml., cooled in an ice-bath, and acidified with concentrated hydrochloric acid. The precipitate which formed was filtered, dried, and recrystallized from water to yield 23.0 g. (49% based on starting methyl compound or 63% based on amount reacted) of 2-fluoronicotinic acid, m. p. 164–165°,[8] with decomposition.

*Anal.* Calcd. for $C_6H_4O_2NF$: C, 51.1; H, 2.9; N, 9.9; F, 13.5. Found: C, 51.2; H, 3.1; N, 9.9; F, 13.7.

**2-Fluoronicotinamide.**—A solution of 28.2 g. (0.20 mole) of 2-fluoronicotinic acid in 250 ml. of thionyl chloride was refluxed for forty-five hours. The excess thionyl chloride was then removed under reduced pressure, and the residue of 2-fluoronicotinyl chloride, b. p. 84.0–85.0° at 4 mm., was dissolved at once in 115 ml. of dry benzene. Dry ammonia was bubbled through the solution for thirty minutes and the solids formed were removed by filtration. These were extracted with dry acetone, the solvent was taken off, and the remaining yellow crystals were recrystallized from water. The yield of pure 2-fluoronicotinamide, m. p. 120.9–122.0° was 67.5%.

*Anal.* Calcd. for $C_6H_5ON_2F$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.4; H, 3.5; N, 19.8.

Approximately the same yield was obtained when the acid chloride was prepared by reaction of the acid with phosphorus pentachloride in phosphorus oxychloride solvent.

**2-Fluoro-5-methylpyridine.**—This compound was prepared according to the directions given for 2-fluoro-3-methylpyridine, except that 2-amino-5-methylpyridine was the starting material. A 46% yield of pure product, b. p. 155–156° at 752 mm., was obtained.

*Anal.* Calcd. for $C_6H_6NF$: C, 65.0; H, 5.4; N, 12.6. Found: C, 64.7; H, 5.5; N, 12.8.

**6-Fluoronicotinic Acid.**—This product was obtained in 60% yield, based on starting 2-fluoro-5-methylpyridine (71% based on that reacted), according to the method described for the preparation of the 2-fluoro-isomer. It was purified by sublimation and melted at 146–147° with decomposition.

*Anal.* Calcd. for $C_6H_4O_2NF$: C, 51.1; H, 2.9; N, 9.9; F, 13.5. Found: C, 51.0; H, 3.1; N, 9.8; F, 13.8.

**6-Fluoronicotinamide.**—Prepared in 65% yield from 6-fluoronicotinic acid by the method described for the 2-fluoro-isomer, this compound melted at 166.2–167.0°, after recrystallization from water.

*Anal.* Calcd. for $C_6H_5ON_2F$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.4; H, 3.8; N, 19.7.

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(6) Roe and Hawkins, THIS JOURNAL, **69**, 2443 (1947).

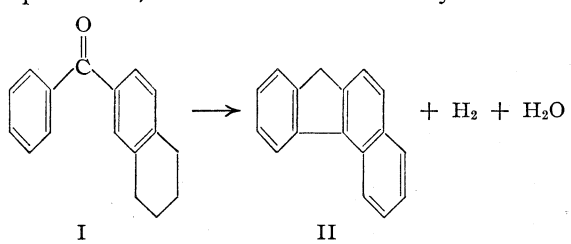
(7) Obtained from the Reilly Tar and Chemical Corporation.

(8) Melting points are corrected.

## Aromatic Cyclodehydrogenation. VIII. Experiments with 2-Benzoyl-5,6,7,8-tetrahydronaphthalene[1]

BY MILTON ORCHIN,[2] E. O. WOOLFOLK[2] AND LESLIE REGGEL[2]

A possible convenient two-step synthesis of 3,4-benzfluorene, II, consists of its formation by direct cyclization of 2-benzoyl-5,6,7,8-tetrahydronaphthalene, I. The latter is readily available,




I II

since acylating agents substitute exclusively at the 6-position of 1,2,3,4-tetrahydronaphthalene. In the respect that the conversion would involve a cyclization of a diaryl ketone, accompanied by loss of water, the reaction bears a superficial resemblance to the Elbs reaction. Although no suitable catalyst has been found for the Elbs reaction,[3] it seemed reasonable to expect, in the present instance, that a chromia-on-alumina catalyst would combine dehydration and cyclization activity. It has been found that vapor-phase treatment of I over such a catalyst at 450-470° gave, as a major product, 2-benzylnaphthalene. Only a little of the expected 3,4-benzfluorene was formed, accompanied by a small quantity of 2,3-benzfluorene. Both benzfluorenes were probably formed *via* 2-benzylnaphthalene, the former by cyclization into the 1-position and the latter by closure at the 3-position.

Liquid-phase treatment of 2-benzoyl-5,6,7,8-

(1) Article not copyrighted.

(2) Organic Chemist, Bureau of Mines, Office of Synthetic Liquid Fuels, Research and Development Branch, Pittsburgh, Pa.

(3) For a review of this reaction see Fieser in "Organic Reactions," John Wiley & Sons, N. Y., Vol. I, p. 129.

tetrahydronaphthalene, I, in the presence of a palladium-on-charcoal catalyst also gave principally 2-benzylnaphthalene. An analogous internal dehydrogenation–hydrogenation has been reported with 2-acetyl-5,6,7,8-tetrahydronaphthalene.[4] Treatment of I with sulfur in the liquid phase gave 2-benzoylnaphthalene, in agreement with the work reported by Barbot.[5] In general, it appears that sulfur dehydrogenation of a hydroaromatic compound containing oxygen seldom results in elimination of oxygen. With palladium-on-charcoal, however, the hydrogen liberated from one part of a molecule during dehydrogenation is frequently used in the hydrogenation or hydrogenolysis of another susceptible portion of the molecule and may in suitable cases even be transferred intermolecularly.[6] It is of interest to note that, even in the vapor-phase reaction mentioned above, such an intramolecular dehydrogenation–hydrogenation occurred.

### Experimental[7]

**2-Benzoyl-5,6,7,8-tetrahydronaphthalene, I.**—This compound was prepared from benzoyl chloride and tetrahydronaphthalene according to the directions of Scharwin,[8] except that nitrobenzene was used as the solvent instead of carbon disulfide. Purification by crystallization from methanol gave pure I, m. p. 40.4–41.2°, which has previously been reported[8] as an oil.

**Sulfur Dehydrogenation of I.**—A mixture of 10 g. of I and 2.7 g. of sulfur was heated at 200–270° for seventy minutes. The crude product was distilled, and the distillate (7.8 g.) was chromatographed on alumina–celite whereby 5.8 g. of phenyl 2-naphthyl ketone was isolated. Crystallization from ethanol gave colorless crystals, m. p. 81.4–81.8°. A stable picrate could not be prepared.[9]

**Palladium Dehydrogenation of I.**—A mixture of 10 g. of I and 0.09 g. of 30% palladium-on-charcoal[10] was heated gradually from 220 to 320° over a period of ninety-five minutes. Vacuum distillation of the product gave 8.2 g. of oil. Chromatography of the crude product on alumina gave as a first, less strongly adsorbed fraction, 6.1 g. (66%) of 2-benzylnaphthalene, which after crystallization from ethanol was obtained as thick, colorless prisms, m. p. 54.3–55.3°. The picrate had a melting point of 94.2–95.0°.[11] The more strongly adsorbed fractions from the chromatogram gave 1.6 g. (16%) of phenyl 2-naphthyl ketone.

**Chromia-on-Alumina Dehydrogenation of I.**—During three and one-half hours, 15 g. of I was passed over 92 g. of the chromia-on-alumina catalyst[10] at 450–470°, using the apparatus previously described.[10] The product, a mixture of green oil and water, weighed 12.03 g. It was dissolved in benzene, the water distilled off, and an aliquot containing 4.83 g. chromatographed on alumina–supercel. The percolate fractions gave 0.12 g. of naphthalene, identified by melting point and mixed melting point. The column was extruded and divided into three sections. The bottom portion (non-fluorescent, least strongly adsorbed) gave 3.28 g. of 2-benzylnaphthalene, identified by melting point and mixed melting point of the hydrocarbon and its picrate. The intermediate purple-fluorescent band gave 0.07 g. of material, identified as 3,4-benzfluorene by its ultraviolet absorption spectrum.[12] The uppermost, green-fluorescent band gave 0.02 g. of material, identified as 2,3-benzfluorene by its ultraviolet absorption spectrum.[12] It is of interest to note that the separation of 3,4- and 2,3-benzfluorene was easily achieved by chromatography, whereas the separation of 1,2- and 2,3-benzfluorene is extremely difficult.[13]

(4) Newman and Zahm, THIS JOURNAL, **65**, 1097 (1943).
(5) Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930).
(6) Orchin, THIS JOURNAL, **66**, 535 (1944).
(7) All melting points corrected.
(8) Scharwin, *Ber.*, **35**, 2511 (1902).
(9) Rousset, *Bull. soc. chim.*, [3] **15**, 71 (1896), reported the melting point of the ketone as 82° and stated that a picrate was formed which had a melting point of 112–113°.
(10) Orchin, Reggel, Friedel and Woolfolk, Bureau of Mines T. P. 708. This preparation is essentially the catalyst-*d* of Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).
(11) These properties are in agreement with those listed in Heilbron, "Dictionary of Organic Compounds," Vol. 3, p. 432 (1943).
(12) We wish to thank Dr. R. A. Friedel and Mrs. Lois Harnack for the spectra determinations. The comparison spectrum for 3,4-benzfluorene was obtained from the work of Mayneord and Roe, *Proc. Roy. Soc.* (*London*), **A158**, 634 (1937); that for 2,3-benzfluorene was obtained from a sample in our possession.[13]
(13) Orchin and Reggel, THIS JOURNAL, **70**, 1245 (1948). A forthcoming paper will discuss the ultraviolet spectra and fine structure of the three benzfluorenes.

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## 1,2-Diphenylcyclohexane

BY STANLEY M. PARMERTER[1]

Although several preparations of 1,2-diphenylcyclohexane have been reported[2,3,4,5] subsequent investigations[6,7] have shown that the product was actually the 1,4-isomer.

The synthesis of 1,2-diphenylcyclohexane has now been accomplished by an unequivocal method. The reaction between phenylmagnesium bromide and 2-phenylcyclohexanone produced a carbinol which was dehydrated to a diphenylcyclohexene. Hydrogenation of the diphenylcyclohexene with palladium–on–charcoal catalyst yielded 1,2-diphenylcyclohexane, which the author presumes to be the *cis*-form.

### Experimental

**Diphenylcyclohexene.**—A solution of 62 g. (0.36 mole) of 2-phenylcyclohexanone[8] in 300 cc. of absolute ether was added in ninety minutes to a stirred, refluxing solution of phenylmagnesium bromide, prepared from 63 g. (0.40 mole) of bromobenzene and 9.7 g. (0.40 g. atom) of magnesium turnings in 250 cc. of absolute ether. After an additional two hours of stirring and refluxing, the mixture was left overnight at room temperature. The mixture was then decomposed with ammonium chloride solution and the product was extracted in two 300-cc. portions of ether. The dried ether solution upon evaporation left the crude carbinol which was dehydrated by stirring with an equal volume of 85% phosphoric acid for four hours on the steam-bath. The acid mixture was diluted with water and the product taken up in benzene. Distillation of the benzene solution gave a fraction of 64 g. boiling at 170–188° (10 mm.). Upon recrystallization from methanol there was obtained 44.5 g. (53%) of colorless needles, m. p. 50–52°. An analytical sample melted at 51–52°.

(1) Present address: Eastman Kodak Co., Rochester, N. Y.
(2) Kursanoff, *Ann.*, **318**, 309 (1901).
(3) Gustavson, *Compt. rend.*, **146**, 640 (1908).
(4) Bodroux, *Ann. chim.*, [10] **11**, 511 (1929).
(5) Wertyporoch and Sagel, *Ber.*, **66**, 1306 (1933).
(6) Nenitzescu and Curcaneanu, *ibid.*, **70**, 346 (1937).
(7) Corson and Ipatieff, THIS JOURNAL, **60**, 747 (1938).
(8) Price and Karabinos, *ibid.*, **62**, 1159 (1940).

*Anal.* Calcd. for $C_{18}H_{18}$: C, 92.28; H, 7.72. Found: C, 92.22, 92.10; H, 7.78, 7.71.

**1,2-Diphenylcyclohexane.**—A solution of 11.7 g. of the diphenylcyclohexene in 200 cc. of ethanol was shaken with hydrogen at two to three atmospheres pressure in the presence of 1 g. of 10% palladium–on–charcoal until absorption of hydrogen ceased. At this point approximately 1 mole equivalent of hydrogen had been absorbed. The catalyst was removed by filtration and the solution concentrated to 75 cc. on the steam-bath. Chilling produced 8.3 g. of colorless needles, m. p. 45–46°. Further concentration of the mother liquor gave an additional 2.1 g. of product, m. p. 42–46°. This represents a yield of 88%. An analytical sample, recrystallized three times from methanol, melted at 46–47°.

*Anal.* Calcd. for $C_{18}H_{20}$: C, 91.50; H, 8.50. Found: C, 91.50, 91.48; H, 8.50, 8.56.

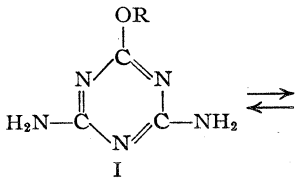
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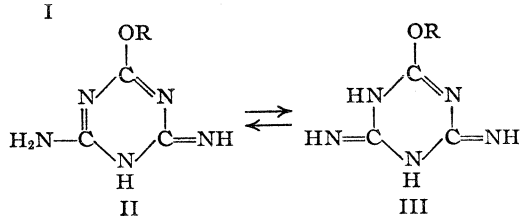
## Alkoxy-*s*-triazines. II

BY WILLIAM M. PEARLMAN AND C. K. BANKS

In the first paper of this series[1] a group of 2-alkoxy-4,6-diamino-*s*-triazines having antihistaminic activity was reported. Most of these compounds contained no alkyl substituents on nitrogen. Since the tautomeric possibilities of the triazine nucleus (I–III) are limited by the number and arrangement of alkyl substituents on nitrogen, it was considered of interest to prepare a series of ethers in which one to four of the hydrogens on the two amine groups were replaced by alkyl groups. These compounds were prepared by the reaction of the chosen sodium alkoxide with an appropriate 2-chloro-4,6-di-(amino or substituted amino)-*s*-triazine. The necessary chlorodiaminotriazines have been reported pre-



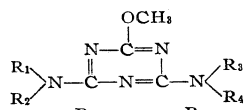
I



II III

TABLE I

METHYL ETHERS



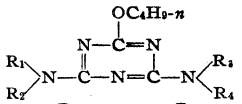
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | M. p., °C. | Yield, % | Recrystallization solvent | Analyses,[a] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | A. H.[b] Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | 229–230 | 81 | Ref. 1 | | | | | 50 |
| Methyl | H | H | H | 155–156 | 66 | Benzene | 38.70 | 38.97 | 5.85 | 5.81 | 50 |
| Ethyl | H | H | H | 168–170 | 24 | Water | 42.59 | 42.59 | 6.55 | 6.31 | 25 |
| *n*-Propyl | H | H | H | 148–150 | 81 | Water | 45.89 | 46.20 | 7.15 | 7.03 | 12 |
| *n*-Butyl | H | H | H | 125–127 | 89 | Methanol–water | 48.71 | 49.13 | 7.67 | 7.64 | >50 |
| *n*-Amyl | H | H | H | [c] | 86 | Benzene–isoöctane | 51.38 | 51.19 | 8.13 | 8.23 | 12 |
| *n*-Hexyl | H | H | H | 104–106 | 92 | Isoöctane | 53.31 | 53.03 | 8.50 | 8.73 | 12 |
| Allyl | H | H | H | 148–150 | 89 | Water | 46.40 | 46.66 | 6.12 | 6.07 | 12 |
| Methallyl | H | H | H | 129–131 | 88 | Methanol–water | 49.22 | 49.30 | 6.71 | 6.66 | >50 |
| Cyclohexyl | H | H | H | 170–172 | 99 | Benzene | 53.79 | 53.62 | 7.67 | 7.47 | 12 |
| Methyl | Methyl | H | H | 169–171 | 81 | Water | 42.59 | 42.62 | 6.55 | 6.31 | 25 |
| Ethyl | Ethyl | H | H | 113–115 | 73 | Methanol–water | 48.71 | 48.58 | 7.67 | 7.42 | 12 |
| Allyl | Allyl | H | H | 87–89 | 83 | Methanol–water | 54.31 | 54.12 | 6.83 | 6.59 | >50 |
| Methallyl | Methallyl | H | H | 101–103 | 90 | Methanol–water | 57.80 | 57.84 | 7.68 | 7.65 | 50 |
| $HOCH_2CH_2$ | Ethyl | H | H | 162–164 | 87 | Methanol–water | 45.06 | 45.02 | 7.09 | 7.04 | >50 |
| $HOCH_2CH_2$ | Phenyl | H | H | 224–226 | 91 | Methylcellosolve–$H_2O$ | 55.12 | 55.47 | 5.78 | 5.74 | 50 |
| —$C_5H_{10}$—[d] | | H | H | 137–139 | 95 | Chloroform | 51.66 | 51.59 | 7.23 | 7.42 | 6 |
| —$C_2H_4OC_2H_4$—[e] | | H | H | 182–184 | 80 | Methanol–water | 45.49 | 45.65 | 6.20 | 6.07 | 50 |
| Methyl | H | Methyl | H | 184–186 | 76 | Methanol–water | 42.59 | [h] | 6.55 | [h] | 6 |
| Ethyl | H | Ethyl | H | 81–83 | 46 | Ethanol–water | 48.71 | 48.69 | 7.63 | 7.64 | 6 |
| Allyl | H | Allyl | H | 84–86 | 88 | Methanol–water | 54.28 | 54.28 | 6.83 | 6.92 | 25 |
| Methallyl | H | Methallyl | H | 112–114 | 93 | Methanol–water | 57.80 | 57.76 | 7.68 | 7.34 | 12 |
| Methyl | Methyl | Methyl | H[f] | 187–188 | 80 | Methanol | 45.89 | 45.64 | 7.15 | 7.00 | 25 |
| Ethyl | Ethyl | Ethyl | H | 107–109 | 99 | Isoöctane | 53.31 | 53.30 | 8.50 | 8.24 | 12 |
| Methyl | Methyl | Methyl | Methyl | 90–92 | 73 | Methanol–water | 48.71 | 48.75 | 7.66 | 7.48 | 25 |
| Ethyl | Ethyl | Ethyl | Ethyl | 146–149/1.5[g] | 65 | | 56.89 | 57.22 | 9.15 | 9.09 | 50 |
| Allyl | Allyl | Allyl | Allyl | 150–153/1[g] | 93 | | 63.76 | 64.07 | 7.69 | 7.88 | >50 |
| Methallyl | Methallyl | Methallyl | Methallyl | 151–154/1.5[g] | 71 | | 67.19 | 66.83 | 8.74 | 8.44 | >50 |
| —$C_5H_{10}$—[d] | | —$C_5H_{10}$—[d] | | 89–91 | 94 | Isoöctane | 60.62 | 60.60 | 8.36 | 7.93 | >50 |
| —$C_2H_4OC_2H_4$—[e] | | —$C_2H_4OC_2H_4$—[e] | | 153–155 | 78 | Methanol–water | 51.23 | 51.38 | 6.81 | 6.86 | 12 |

[a] Analyses by Mr. A. W. Spang and Miss Patricia Keller. [b] Determined by Dr. Graham Chen and Mr. C. R. Ensor. Dose of compound in mg./kg. intraperitoneally allowing survival of 50% of histamine-shocked guinea pigs, see Ref. 1 for details. The comparable dose for Aminophylline is 50 and for Benadryl is 1.5. [c] Sinters 98–104°, plastic 104–108°, glass 108–122°. [d] Piperidino. [e] Morpholino. [f] Prepared by Mr. John Controulis. [g] Boiling point, not crystallized at −40°. [h] Concordant results not obtained on repeated assays. This may be due to solvation.

(1) Controulis and Banks, THIS JOURNAL, **67**, 1946 (1945).

TABLE II

BUTYL ETHERS



| $R_1$ | $R_2$ | $R_3$ | $R_4$ | M. p., °C. | Yield, % | Recrystallization solvent | Analyses,[a] % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | A. H.[b] Value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | 174–175 | | Ref. 1 | | | | | 25 |
| Methyl | H | H | H | 173–175 | 88 | Chloroform | 48.71 | 48.76 | 7.67 | 7.81 | 6 |
| Ethyl | H | H | H | 116–118 | 86 | Chloroform | 51.16 | 50.91 | 8.11 | 7.99 | 12 |
| *n*-Propyl | H | H | H | 116–118 | 85 | Isoöctane | 53.31 | 53.54 | 8.50 | 8.48 | 25 |
| *n*-Butyl | H | H | H | 103–104 | 72 | Isoöctane | 55.20 | 55.36 | 8.85 | 8.63 | .. |
| *n*-Amyl | H | H | H | 107–109 | 81 | Isoöctane | 56.89 | [h] | 9.15 | 9.17 | 12 |
| *n*-Hexyl | H | H | H | 119–121 | 99 | Ethanol–water | 58.41 | 58.76 | 9.43 | 9.52 | 12 |
| Allyl | H | H | H | 87–89 | 75 | Dioxane–water | 53.79 | 53.57 | 7.68 | 7.57 | 12 |
| Methallyl | H | H | H | 106–108 | 79 | Isoöctane | 55.67 | 55.77 | 8.07 | 8.13 | >50 |
| Cyclohexyl | H | H | H | 141–143 | 96 | Carbon tetrachloride | 55.84 | [h] | 8.74 | [h] | >50 |
| Methyl | Methyl | H | H | 103–104 | 88 | Ethanol–water | 51.16 | 50.98 | 8.11 | 7.97 | 12 |
| Ethyl | Ethyl | H | H | 73–75 | 51 | Isoöctane | 55.20 | 54.77 | 8.85 | 8.77 | 50 |
| Allyl | Allyl | H | H | 172–175/1[g] | 65 | | 59.29 | 59.64 | 8.04 | 7.93 | >50 |
| Methallyl | Methallyl | H | H | 60–62 | 87 | Isoöctane | 61.82 | 61.56 | 8.65 | 8.66 | >50 |
| $HOCH_2CH_2$ | Ethyl | H | H | 123–125 | 64 | Ethanol–water | 51.74 | 51.47 | 8.29 | 8.24 | >25 |
| $HOCH_2CH_2$ | Phenyl | H | H | 157–159 | 61 | Ethyl cellosolve–$H_2O$ | 59.38 | 59.44 | 6.98 | 7.18 | >50 |
| —$C_5H_{10}$—[d] | | H | H | 115–117 | 87 | Ethanol–water | 57.34 | 57.70 | 8.42 | 8.28 | >50 |
| —$C_2H_4OC_2H_4$—[e] | | H | H | 108–110 | 43 | Ethanol–water | 52.16 | 52.37 | 7.56 | 7.41 | 12 |
| Methyl | H | Methyl | H | 103–104 | 60 | Propanol–water | 51.16 | 51.36 | 8.11 | 8.09 | 12 |
| Ethyl | H | Ethyl | H | 50–52 | 85 | Ethanol–water | 55.20 | 55.58 | 8.85 | 9.05 | 25 |
| Allyl | H | Allyl | H | 185–190/1[g] | 51 | | 59.29 | 59.35 | 8.04 | 8.00 | 25 |
| Methallyl | H | Methallyl | H | 58–60 | 70 | Methanol–water | 61.82 | 61.72 | 8.65 | 8.55 | .. |
| Methyl | Methyl | Methyl | H[f] | 129–131 | 87 | Benzene | 53.31 | 53.52 | 8.50 | 8.58 | >25 |
| Ethyl | Ethyl | Ethyl | H | 80–82 | 96 | Ethanol–water | 58.40 | 58.19 | 9.43 | 9.49 | >50 |
| Methyl | Methyl | Methyl | Methyl | 155–157/4[g] | 69 | | 55.20 | 55.51 | 8.85 | 8.79 | >25 |
| Ethyl | Ethyl | Ethyl | Ethyl | 164–165/4[g] | 84 | | 60.98 | 60.97 | 9.89 | 9.64 | >25 |
| Allyl | Allyl | Allyl | Allyl | 157–160/1[g] | 93 | | 66.41 | 66.92 | 8.51 | 8.53 | >50 |
| Methallyl | Methallyl | Methallyl | Methallyl | 164–167/1[g] | 82 | | 69.14 | 69.31 | 9.34 | 9.28 | >25 |
| —$C_5H_{10}$—[d] | | —$C_5H_{10}$—[d] | | 182–185/2[g] | 71 | | 63.91 | 63.98 | 9.15 | 9.09 | >50 |
| —$C_2H_4OC_2H_4$—[e] | | —$C_2H_4OC_2H_4$—[e] | | 117–119 | 66 | Isoöctane | 55.71 | 55.90 | 7.79 | 7.90 | >25 |

Footnotes the same as for Table I.

viously.[2] In order to limit the variables concerned, the methyl and *n*-butyl ethers of each triazine residue were prepared by the method reported previously.[1] The methyl ethers are reported in Table I and the butyl ethers in Table II.

During the preparation of the necessary chlorotriazines it was noted that the degree of substitution markedly influenced the physical properties of the resulting compounds. Thus, compounds having the structure of 2-chloro-4,6-diamino-*s*-triazine wherein one, any two, or three of the amino hydrogens were replaced by methyl groups were all high melting solids while the corresponding tetramethyl compound was very low melting. Similarly, the mono-, di- and triethyl, -allyl and -methylallyl derivatives were solids while the tetrasubstituted compounds were oils which failed to solidify at −40°. A similar relationship was expected with the ethers. While the tetraalkyldiamino ethers were all liquids except for one low melting solid, the melting points of the mono-, di- and tri-substituted ethers did not follow regular progression noted for the chloro compounds.

The compounds were tested for antihistamine activity in guinea pigs using the histamine–aerosol technique of E. R. Loew.[3] In the previous series of unsubstituted aminotriazine ethers, a regular variation in activity dependent on the length of the alkoxy chain was observed. No orderly variation in activity was noted with variation in the alkyl chain on nitrogen or with multiple substitution on the amine groups.

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(2) Pearlman and Banks, THIS JOURNAL, **70**, 3726 (1948).

(3) Loew, *et al.*, *J. Pharmacol.*, **83**, 120 (1945).

## The Resolution of Chloroquine, SN 7618[1]

BY BYRON RIEGEL AND L. T. SHERWOOD, JR.

Since 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline (chloroquine) proved to be one of the most effective suppressive drugs for malaria developed during the war, its resolution was undertaken in the hope that the toxicity or activity of one of the forms might be favorably different. The salts of *l*-malic, *d*-camphorsulfonic, *l*-menthoxyacetic, *d*-tartaric and *dl*-mandelic were all unsuitable as resolving agents but an adaptation of the work of Chelintsev and Osetrova[2] on the resolution of atabrine with *d*-bromocamphorsulfonic acid proved fairly satisfactory.

(1) This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University.

(2) G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1978 (1940).

The salts obtained by the addition of two moles of *d*-bromocamphorsulfonic acid to one of chloroquine were low melting, hygroscopic, finely divided, and somewhat unstable crystals. This made handling difficult and some mechanical loss unavoidable. The quality of the *d*-bromocamphorsulfonic acid was also of great importance and the poor results of some runs was supposed due to slight decomposition during preparation of the free acid. The enantimorphs of the drug are much more soluble than the racemic mixture.

Neither of the optically active forms submitted to the Survey Office showed any significant differences[3] in antimalarial activity in birds and for toxicity in dogs from the racemate.

### Experimental

**Starting Materials.**—Chloroquine diphosphate was kindly furnished by Dr. R. C. Elderfield of Columbia University. The free base was liberated from an aqueous solution of the salt with ammonia and was recrystallized from benzene and hexane. We are indebted to Dr. H. R. Snyder of the University of Illinois for the ammonium salt of *d*-bromocamphorsulfonic acid. The free acid was liberated from the salt by the method of Pope and Peachey.[4]

A solution was made of 21 g. of chloroquine and 45 g. of *d*-bromocamphorsulfonic acid in 300 ml. of hot absolute ethanol. The solution was filtered to remove any insoluble material and then allowed to crystallize in a cold room. The crystals were separated rapidly by filtration and recrystallized from about 150 ml. of absolute ethanol to a constant rotation of $[\alpha]^{27}D + 62°$ (0.200 g. was made up to 10 ml. with water). The base was obtained by dissolving the salt in water, adding an excess of ammonia, and extracting with benzene. The benzene solution was filtered and mixed with an equal volume of petroleum ether (b.p. 80–100°). The solution was concentrated until crystallization took place upon standing in the cold room. The crystals (9.7 g.) melted at 84–86°; $[\alpha]^{25}D + 12.3°$ (0.200 g. was made up to 10 ml. with 95% ethanol).

The *l*-form of the drug was liberated by evaporating the mother-liquor from the crystalline salt almost to dryness, dissolving in water, and treating as above. The concentration of the benzene and petroleum ether solution was adjusted so as to precipitate about one gram of solid in the cold. This material, almost inactive, was discarded and the solution was concentrated further. On cooling, 4.3 g., m.p. 84–87°, of the *l*-form separated; $[\alpha]^{27}D -13.2°$ (0.200 g. made up to 10 ml. with 95% ethanol).

(3) F. Y. Wiselogle, "A Survey of Antimalarial Drugs," J. W. Edwards, Ann Arbor, Michigan, 1946, p. 388.

(4) W. J. Pope and S. J. Peachey, *J. Chem. Soc.*, **73**, 893 (1898).

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS RECEIVED OCTOBER 29, 1948

## An Improved Laboratory Preparation of Copper–Chromium Oxide Catalyst

BY THOMAS W. RIENER[1]

During the course of an investigation[2] of copper chromium oxides as a catalyst for hydrogenation of fatty esters to alcohols, a very satisfactory laboratory procedure for the decomposition of the copper ammonium chromate was developed. A catalyst of high activity and long life was obtained by this improved technique.

The method described here is similar to that previously reported[3] except that the decomposition of the copper ammonium chromate is carried out under carefully controlled conditions. If excessive temperatures are reached during the decomposition of the copper ammonium chromate, the activity of the catalyst is seriously affected.

A batch of copper ammonium chromate was prepared in the usual manner[3] and divided into several portions. A portion (I) was placed in a muffle furnace at 320° and in a short time the temperature inside the mixture reached 635°. Another portion (II) was fired as described below at 400°. A third portion (III) was similarly fired at 350°.

The catalysts obtained in each experiment were used in the hydrogenation of the lauryl ester of coconut oil fatty acids. The reductions were carried out in a 480-cc. Parr Instrument shaking bomb using 2 g. catalyst and 80 g. ester and run for two hours at 275°/3000 lb. $H_2$: (I) gave 30.5% hydrogenation; (II) gave 88.3% hydrogenation; (III) gave 92.1% hydrogenation.

### Experimental

A solution of 260 g. of copper nitrate ($Cu(NO_3)_2 \cdot 3H_2O$) in 900 cc. of tap water at 80° was added while stirring to a solution of 178 g. of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) and 225 cc. of 28% ammonium hydroxide made up to 900 cc. at 25°. The precipitate was collected on a Buchner funnel and washed by slurrying in water three times. The copper ammonium chromate was dried at 75–80° overnight.

The copper ammonium chromate was powdered and added in small portions to a one-liter three-neck flask equipped with a stainless steel stirrer of the crescent type which scraped close to the bottom of the flask. The flask was partially immersed in a Woods metal-bath heated at 350°. The time of addition was fifteen minutes. The mixture was heated and stirred at 350° for fifteen minutes after all of the complex had been added. It was then passed through a 200-mesh screen with the aid of a camel's hair brush.

(3) Connor, Folkers and Adkins, THIS JOURNAL, **54**, 1138 (1932).

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## The Effect of Heat and Sodium Sand upon Sodium Polybutadiene[1]

BY ROBERT M. ROSS

The percentage of external double bonds in sodium-polymerized polybutadiene has been shown to be dependent upon the temperature of polymerization.[2,3] Polybutadiene, polymerized with sodium at 30°, contains 65–75% external

(1) Present address: Industrial Rayon Corporation, Cleveland, Ohio.

(2) Work done at Rohm & Haas Company.

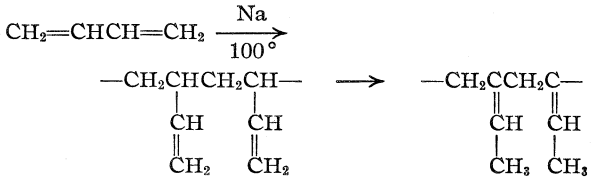
(1) The work described in this manuscript was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program. The author is deeply indebted to Dr. C. S. Marvel for initiating this investigation, as well as for his advice during the course of the work.

(2) Ziegler, Grimm and Willer, *Ann.*, **542**, 90 (1939).

(3) Kolthoff, Lee and Mairs, *J. Polymer Sci.*, **2**, 220 (1947).

double bonds, whereas the polymer formed at 110° possesses about 15% external double bonds. In direct contrast to the product obtained from the sodium-catalyzed polymerization of butadiene, the terminal double bond percentage of polybutadiene, formed by emulsion methods, has been found to be independent of the polymerization temperature.[3]

Ziegler, Grimm and Willer[2] have explained these facts on the basis that at higher temperatures an increased amount of 1,4-addition occurs in the sodium-catalyzed polymerization. Another possible explanation is that the relative amount of 1,2- or 1,4-addition remains constant, but that an allylic rearrangement occurs in the presence of sodium so as to transform terminal methylene groups into ethylidene groups



Accordingly it was the objective of this work to learn if preformed polybutadiene, prepared by sodium-catalysis methods, showed a decrease in the percentage of terminal double bonds when it was treated with sodium and heated. When sodium-polymerized polybutadiene was heated to 110° for five hours in the presence of sodium sand, analysis by perbenzoic acid titration[4] of the product obtained indicated that no appreciable double bond shifts from external-to-internal positions had occurred. Similar results were obtained when butadiene was polymerized in the presence of sodium sand at 30° and then heated to 100° for five hours.

It may be concluded, therefore, that an allylic shift, catalyzed by sodium, is not responsible for the difference in the products obtained from the sodium-catalyzed polymerization of butadiene and polybutadiene prepared by emulsion methods. Furthermore, since the terminal double bond percentage in polybutadiene formed by emulsion methods is independent of polymerization temperature, the two polymerization methods must proceed by different mechanisms.[5]

## Experimental

**Attempted Isomerization of Sodium Polybutadiene with Sodium Sand.**—In a 500-ml., three-necked, round-bottomed flask were placed 3 g. of sodium-polymerized polybutadiene,[6] which had been reprecipitated by ethanol from benzene solution, and 250 ml. of redistilled toluene (b. p. 110–111°). The flask was equipped with a glass-sleeved Hershberg stirrer and reflux condenser. Solution was complete after about fifteen hours. At the end of this time, 0.3 g. of freshly cut sodium metal was added to the toluene solution. The contents of the flask were heated to the reflux temperature, and at this point vigorous stirring was commenced. The sodium was dispersed to a fine sand. The reaction mixture was then maintained at the reflux temperature with continuous stirring for five hours. At the end of this time, the mixture was allowed to cool to about 30°. A small amount of tarry material formed during the heating period. The excess sodium was destroyed by the addition of 100 ml. of absolute ethanol and stirring was stopped.

The insoluble macrogel and tarry material which had formed during the course of the experiment were removed by filtration through a wire screen. The filtrate was added in a fine stream to a rapidly stirred solution of 2 g. of phenyl β-naphthylamine in 1 liter of ethanol. The precipitated polymer was washed with 200 ml. of 0.2% phenyl β-naphthylamine in ethanol and finally dried at 80° for one hour under a reduced pressure of less than 1 mm. The dried polymer weighed 2.3 g. and was stored away from light and in a desiccator under reduced pressure. The polymer thus obtained and the reprecipitated polymer employed as starting material were analyzed for external double bonds by perbenzoic acid titration.[4] The results of the analyses expressed as % external double bonds are as follows: reprecipitated sodium-polymerized polybutadiene, 71.2%; reprecipitated sodium-polymerized polybutadiene, heated with sodium sand for five hours, 66.8%.

**Polymerization of Butadiene and the Subsequent Application of Heat to the Sodium Polybutadiene Formed.**—The sodium sand-catalyzed polymerization of butadiene was carried out according to the directions of Marvel, Bailey and Inskeep.[7] In conducting this experiment, two simultaneous and analogous polymerizations were carried out at 30° for twenty-one hours using about 0.4% by weight of sodium sand in terms of the weight of butadiene. At the end of this time, the polymerization bottles were removed from the constant temperature bath and chilled to 0°. One polymerization bottle was opened, flushed out with nitrogen, recapped, and finally heated on a water-bath for five hours at 100°. At the end of this time, the bottle and contents were cooled to room temperature and opened. The excess sodium was destroyed by the addition of 100 ml. of a 10% ethanol in benzene solution which contained 0.2 g. of phenyl β-naphthylamine. To this mixture was added 300 ml. of benzene, and the resulting suspension was allowed to stand with occasional stirring for about twenty-four hours. At the end of this time, solution was virtually complete, and the insoluble gel present was removed by filtration through a wire screen. The filtrate was added in a fine stream to 1 liter of a rapidly stirred solution of 0.2% phenyl β-naphthylamine in methanol. The precipitated polymer was washed with 200 ml. of 0.2% phenyl β-naphthylamine in methanol and finally dried at 80° for five hours under a reduced pressure of less than 1 mm.

The polymer contained in the second polymerization bottle was used as the control sample. After the twenty-one hour polymerization period at 30°, which was followed by cooling of the reaction mixture at 0°, the bottle was opened. The excess sodium was destroyed with a 10% solution of ethanol in benzene. The polymer was purified and isolated in exactly the fashion described in the previous paragraph for the heated polymer.

The products obtained above were analyzed by perbenzoic acid titration[4] for external double bonds. The analytical values obtained are expressed as per cent external double bonds as follows: control polymer, polymerized for twenty-one hours at 30°, 66.1%; polymer, heated to 100° for five hours after polymerization period of twenty-one hours at 30°, 65.8%.

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(4) Kolthoff and Lee, *J. Polymer Sci.*, **2**, 206 (1947).

(5) NOTE ADDED IN PROOF: See Robertson and Marion, *Can. J. Research*, **26B**, 657 (1948).

(6) The sample of sodium-polymerized polybutadiene used had been prepared by Dr. Bailey at the University of Illinois Laboratories in connection with the Government Synthetic Rubber Program.

(7) Marvel, Bailey and Inskeep, *J. Polymer Sci.*, **1**, 275 (1946).

## Matching Factors of Beckman Spectrophotometer Cells

BY H. SHEFFER AND H. J. HADOW

This note describes some sources of error which are of importance if the highest accuracy is demanded of the Beckman Quartz Spectrophotometer. One of these instruments (Model DU) is being used here to measure the turbidities of solutions of polystyrene in methyl ethyl ketone as standards for calibrating a light-scattering apparatus.[1] At a wave length of 546 mμ, the transmissions of such solutions in 5-cm. silica cells are in the range 93–97% of that of the solvent. These correspond to turbidities of 0.014 to 0.006 cm.$^{-1}$.

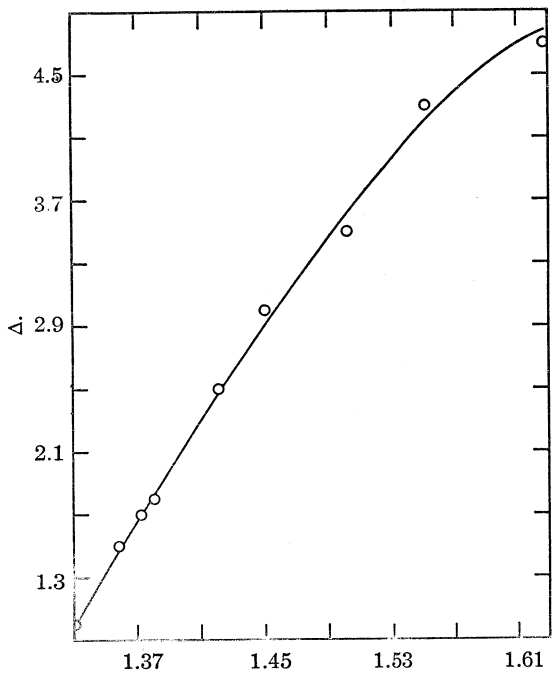



Fig. 1.—Δ plotted against refractive index of solvent.

Since there is a considerable range of wave lengths over which both the red-sensitive (RS) and the ultraviolet sensitive (UVS) phototubes may be used, it was decided to use one to check the other. With solvent in each, the 5-cm. cells were matched at 546 mμ using the RS-phototube, the correction being about 0.1%. The turbidity of a solution was then determined at this wave length using both the RS and UVS-tubes. Applying the matching correction of 0.1%, the transmissions measured by the two phototubes differed from one another by about 1%. This represents the very large discrepancy of 10–30% in turbidity. In addition there was no indication at this stage as to which tube gave the more nearly correct result. It was finally found that a separate matching factor must be determined using the UVS-tube and that, provided the appropriate factor was applied, results with the two phototubes agreed to within 0.1% in terms of transmission.

Since the matching factor is a measure of the *relative* intensity of light transmitted through the two cells filled with the same solvent, it was very surprising to find that its magnitude depended on the photo-tube used. The effects of slit width and of stray light were first eliminated as possible explanations for this behavior. The transmission of colored glass matched against air was found to be independent of the phototube used. However, the difference in the two matching factors rose to 3–4% using 10-cm. cells, indicating that the effect was more important with the longer cells.

When the wave length was increased over the range 400–600 mμ, it was found that the matching factors (10-cm. cells), using the RS-tube, varied in a random way between 0 and 0.5%, while the corresponding factors, using the UVS-tube rose gradually from about 1 to 3%. This led to the thought that differences in refractive index might be responsible for the large variations found with the UVS-phototube. In order to investigate this point the following solvents (in ascending order of refractive index) were used: water, acetone, ethyl acetate, ethyl methyl ketone, dioxane, cyclohexanone, benzene, *o*-dichlorobenzene and quinoline. With a transmission setting of 100% for benzene in one of the 10-cm. cells, readings were taken for each of the solvents in the other cell of the pair. This procedure was carried out using both phototubes at a wave length of 600 mμ and the results, expressed as RS-phototube reading minus UVS-phototube reading for each solvent (Δ), are shown plotted against refractive index in Fig. 1. From this it is apparent that the difference in matching factors increases markedly with increasing refractive index under these conditions. Values of Δ which varied similarly with refractive index were obtained at other wave lengths and also on a second Beckman Spectrophotometer.

In these instruments the light beam is not parallel but diverges slightly. Thus, even if the cells are lined up perfectly parallel to one another and perpendicular to the beam front, the spot of light striking the phototube will vary in area depending on the length of the cell and on the refractive index of the medium in it. If the cells are off by small angles, which is the case in practice, the position of the light spot will change slightly as well as its area. It appears, therefore, that a change in position of the light beam falling on the face of the phototube makes quite a difference in the response of the UVS-tube while that of the RS-tube is relatively unaffected. This point was tested by changing the angle of one of the cells by small amounts relative to the horizontal axis. With benzene in both 10-cm. cells, one cell was used as the standard while the position of the other was altered. Two successive changes of a little over one degree altered the difference in the matching factors for the two phototubes from +2.4 to 0 and from 0 to

(1) Doty, Affens and Zimm, *Trans. Faraday Soc.*, **42B**, 66 (1946).

−2.2. The effect of refractive index on the position and size of the light spot was measured directly by photographing the spot near the face of the phototube. A 30% decrease in area of the spot was observed when a 10-cm. cell filled with water was introduced into the beam. Further successive decreases in area of the order of 5% were observed when the water (R.I. = 1.33) was replaced first by dioxane (1.42) and then by benzene (1.50) and small changes in the positions of the spots were also noticed.

Although for the 5 and 10 cm. cells the differences in matching factors may be large and quite variable with refractive index, good agreement can be obtained using both phototubes as long as the matching factors at a given wave length are obtained separately for each phototube and each liquid used. In this way discontinuities in absorption curves, which are sometimes obtained at the point where the tubes are interchanged, can be eliminated. The source of error discussed is particularly important when solutions varying widely in refractive index are matched against one solvent.

The effect was also determined for 1-cm. cells which are used by the majority of investigators. The difference in the matching factors for several of these cells changed by 0.1–0.3% (in terms of transmission) when benzene in the cells was replaced by water. These amounts become appreciable in terms of optical density only when very low absorptions are being measured.

For work of the highest accuracy, matching factors should be rechecked with any change of operating conditions whatsoever. Due to the zonal variations in spectral sensitivity of phototubes, differences in matching factors may be expected whenever the effective area of the phototube illuminated is altered in any way. In addition to the effect of refractive index, such changes may be brought about by slight localized variations in transmission of the absorption cells due to striae, scratches, etc., and when cells are shifted in orientation with respect to the phototubes.

The authors wish to acknowledge the assistance of Mr. J. C. Hyde.

DEFENCE RESEARCH CHEMICAL LABORATORIES
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## Phenoxyacetaldehyde

BY ROBERT J. SPEER AND HENRY R. MAHLER

Hatch and Nesbitt[1] have reported the synthesis of phenoxyacetaldehyde in 45% yield by the lead tetraacetate oxidation of glycerol α-phenyl ether. In connection with the radiochemical program of this Laboratory, the aldehyde in question has been prepared as an intermediate for certain labeled amino acids. It has been found that a modification of the above preparative technique results in an improved yield.

(1) L. F. Hatch and S. S. Nesbitt, THIS JOURNAL, **67**, 39 (1945).

In order to avoid even a temporary excess of oxidant, the order of addition of reagents has been reversed. That is, a slurry of lead tetraacetate (1.0 mole) in benzene was added slowly to a stirred benzene solution of glycerol α-phenyl ether[2] (1.0 mole). This addition was accomplished during *ca.* two hours while the reaction mixture was stirred vigorously at a temperature of 20–25°. After isolation as previously described,[1] the product was fractionated through a 24-in. Widmer column, b. p. 82–83°(4–5 mm.). The aldehyde thus obtained represented a yield of 60% of theory; $n^{20}D$ 1.5360, $d^{20}_4$ 1.1308 (*cf.* Huntress and Mulliken[3] $n^{21}D$ 1.5380, $d^{21}_4$ 1.1310). Molecular refraction, 37.54 (found), 37.20 (calcd.).

The value of this simple modification has been confirmed by one of us[4] in the case of other sensitive aldehydes.

(2) Supplied through courtesy of the Miner Laboratories, Chicago, Ill.

(3) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds—Order I," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 66.

(4) Henry R. Mahler, Thesis, University of California, 1948.

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## Ascaridole in Oil of Chenopodium. III.[1] The Characterization of Ascaridole

BY H. HARRY SZMANT AND ALFRED HALPERN

In connection with the investigation of the chemistry of ascaridole in progress in our Laboratories[1,2] it was desirable to reexamine the physical properties of ascaridole in view of the discrepancies noted in the literature.[3] The physical properties of ascaridole are of particular importance since no solid derivative of ascaridole is known.

Oil of chenopodium[4] was fractionated using an all-glass system equipped with a Vigreux column. The physical properties and yields of the various fractions are summarized in Table I.

The fractions obtained from the preliminary distillation above, were analyzed for ascaridole content according to the method of Cocking and Hymas[5] and the results are included in Table I. A portion of fraction "C," which analyzed iodometrically for pure ascaridole, was subjected to a careful fractionation in a two-foot glass-helices-packed column. The physical properties of the fractions obtained during this refractionation are reported in Table II.

(1) For paper II in this series see Halpern, *J. Am. Pharm. Assocn.*, **37**, 465 (1948).

(2) Halpern, *ibid.*, **37**, 161–165 (1948).

(3) Henry and Paget, *J. Chem. Soc.*, **119**, 1714 (1921); Paget, *ibid.*, 829–833 (1938); Paget, *Analyst*, **51**, 180–186 (1930); Khavin, *Ukrain. Gosudarst. Inst. Eksptl. Farm.* (*Kharkov*), *Konsul'tatsionnye Materialy* **1939**, No. 6, 165, *cf. C. A.*, **36**, 2997 (1942); Janot and Chaigneau, *Compt. rend.*, **214**, 746–747 (1942); Thoms and Dobke, *Arch. Pharm.*, **268**, 128–137 (1930).

(4) Oil of chenopodium meeting all of the N. F. VIII requirements was obtained from Magnus, Mabee and Reynard, Inc., New York.

(5) Cocking and Hymas, *Analyst*, **55**, 183 (1930).

TABLE I

FRACTIONATION OF OIL OF CHENOPODIUM[a]

| Fraction | B. p.° at 0.5–1 mm. | Weight, g. | $n^{25}D$ | $d^{25}_{25}$ | Apparent ascaridole content, %[b] |
|---|---|---|---|---|---|
| A | 34–36 | 25.0 | 1.4755 | 0.8733 | 22.1 |
| B | 57–58 | 5.1 | 1.4740 | 0.9513 | 87.6 |
| C | 58.5–60 | 61.5 | 1.4720 | 1.0012 | 102.7[c] |
| D | 61–63 | 5.0 | 1.4715 | 1.0216 | 79.0 |
| E | 64–68 | 5.4 | 1.4715 | 1.0467 | 63.8 |

[a] The original oil of chenopodium had the following constants: $d^{25}_{25}$ 0.9782, $n^{25}D$ 1.4740; weight of oil sample fractionated 110 g., containing 68% ascaridole. [b] Based on the assumption that ascaridole is the only reactant of oil of chenopodium in the determination. [c] Freezing point 3.5°.

TABLE II

THE FRACTIONATION OF ASCARIDOLE

| Fraction | B. p., °C., 1 mm. | Weight, g. | $n^{25}D$ | $d^{25}_{25}$ | F. p., °C. |
|---|---|---|---|---|---|
| 1 | 32–65 | 2.0 | 1.4732 | .... | .. |
| 2 | 64–70 | 1.0 | 1.4720 | .... | .. |
| 3 | 74–75[a] | 8.2 | 1.4722 | 1.0047 | 5 |
| 4 | 74[a] | 8.3 | 1.4724 | 1.0051 | 5 |
| 5 | 75[a] | 16.3 | 1.4718 | 1.0061 | 5[b] |
| 6 | 76–77 | 7.9 | 1.4720 | .... | .. |
| Residue | ... | .. | .... | .... | .. |

[a] B. p. at 1.5 mm. [b] $M_D$ calcd. 46.80; found 46.79. The peroxide linkage assumed to be equivalent to two ether values.

Fraction "5" was analyzed[6] and was found to contain 71.00% carbon, and 9.45% hydrogen in agreement with the calculated analysis of ascaridole (calcd. for $C_{10}H_{16}O_2$: C, 71.38; H, 9.58). The ultraviolet absorption spectrum in absolute methanol determined by means of the Beckman quartz spectrophotometer, and the infrared absorption spectrum,[7] of fraction "5" are reproduced in Figs. 1 and 2, respectively.

It is of interest to note that the ultraviolet absorption spectrum indicates the presence of only one major absorbing group, namely, that of the simple carbon–carbon double bond. This is of significance since the oil of chenopodium contains an appreciable quantity of compounds possessing conjugated double bond systems.

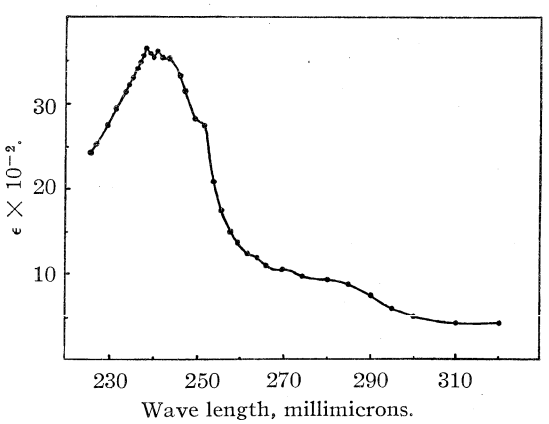



Fig. 1.—The ultraviolet absorption spectrum of ascaridole.

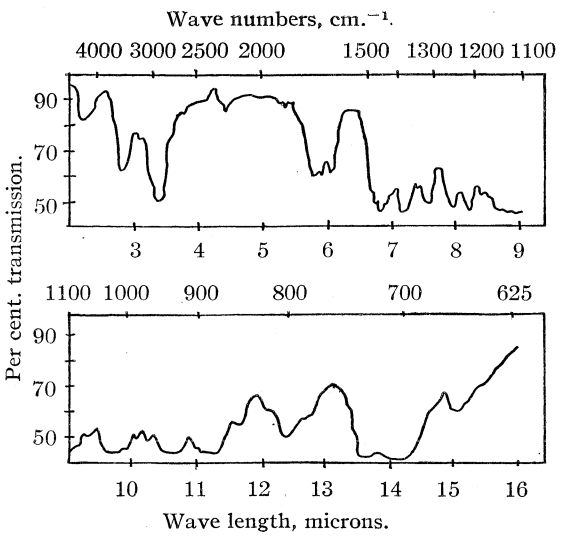



Fig. 2.—The infrared absorption spectrum of ascaridole.

In view of the correct analysis, the relative simplicity of the ultraviolet absorption spectrum, and the higher freezing point of our product, we believe to have obtained ascaridole of a higher purity than has hitherto been reported. The physical properties of ascaridole were found to be as follows: b. p. 75° (1.5 mm.); $n^{25}D$ 1.4718; $d^{25}_{25}$ 1.0061; f. p. 5°.

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SCHOOL OF PHARMACY
DUQUESNE UNIVERSITY
PITTSBURGH 19, PA.

RECEIVED SEPTEMBER 8, 1948

(6) Microanalyses by Samuel P. Sadtler & Son, Philadelphia, Pa.

(7) We gratefully acknowledge the coöperation of Dr. Philip Sadtler of Samuel P. Sadtler & Son, Philadelphia, Pa., in determining the absorption spectrum.

## The Preparation of 3,4-bis-(3′-Methyl-4′-hydroxy-5′-allylphenyl)-2,4-hexadiene

BY PHILIP WEISS[1] AND JOSEPH B. NIEDERL

Subsequent to studies in tetra alkyl substituted analogs of dienestrol and hexestrol,[2] an investigation was undertaken to study the estrogenic effects produced by the introduction of an allyl group in the 5′-position of the synthetic estrogen 3,4-bis-(3′-methyl-4′-hydroxyphenyl)-2,4-hexadiene.[3]

The synthesis of 3,4-bis-(3′-methyl-4′-hydroxy-5′-allylphenyl)-2,4-hexadiene was accomplished in the following manner. The diallyl ether of 3,4-bis-(3′-methyl-4′-hydroxyphenyl)-2,4-hexadiene was prepared by refluxing the substituted dienestrol with allyl bromide in the presence of anhydrous potassium carbonate, using dry acetone as the solvent. The Claisen rearrangement[4] was effected by refluxing with diethylaniline thus

(1) Present address: Wallace and Tiernan Products Inc., Belleville 9, New Jersey.

(2) J. B. Niederl and P. Weiss, THIS JOURNAL, **70**, 2894 (1948).

(3) V. Niederl and co-workers, *ibid.*, **70**, 508 (1948).

(4) E. Kaiser and J. J. Svarz, *ibid.*, **68**, 636 (1946).

yielding the desired 3,4-bis-(3′-methyl-4′-hydroxy-5′-allylphenyl)-2,4-hexadiene, as a red gum. This tetraalkyl substituted analog of dienestrol was characterized by the preparation of the corresponding diacetate and dipropionate.

The estrogenic assays on these compounds were carried out by administering orally the test sample to ovariectomized female rats. Vaginal smears were examined and only full cornification was regarded as a positive oestrus response. The results of preliminary measurements of gross estrogenic activity indicate that at the 100 microgram dose level; the 3,4-bis-(3′-methyl-4′-propionoxy-5′-allylphenyl)-2,4-hexadiene shows a 20% oestrus response; the 3,4-bis-(3′-methyl-4′-acetoxy-5′-allylphenyl)-2,4-hexadiene gives a 25% response, and the 3,4-bis-(3′-methyl-4′-hydroxy-5′-allylphenyl)-2,4-hexadiene shows a 35% oestrus response. Control rats injected with 0.65 microgram of U.S.P. Reference Estrone produced a 40% oestrus response.

**Acknowledgment.**—The authors desire to express their appreciation to Dr. C. T. Van Meter of Reed and Carnrick, Jersey City, N. J., for the estrogenic assays.

### Experimental[5]

**3,4-bis(3′-Methyl-4′-allyloxyphenyl)-2,4-hexadiene.**—A mixture of 15 g. (0.05 mole) of 3,4-bis-(3′-methyl-4′-hydroxyphenyl)-2,4-hexadiene,[3] 15 g. (0.11 mole) of allyl bromide, 15 g. (0.1 mole) of anhydrous potassium carbonate, and 200 ml. of dry acetone were refluxed for six hours, and then set aside at room temperature for twenty-four hours. Water was added to the reaction mixture, it was extracted with ether, and the ether layer was extracted with ice cold 10% aqueous sodium hydroxide solution to remove any unreacted dihydroxy compound. The excess alkali was removed by washing with water, the neutral ether solution was dried over anhydrous potassium carbonate, filtered, and the solvent removed by distillation. Crystallization and re-crystallization from dilute ethanol yielded 11.2 g. (59%) of a white crystalline solid; m. p. 67.5–68°.

*Anal.* Calcd. for $C_{26}H_{30}O_2$: C, 83.42; H, 8.02. Found: C, 83.57; H, 8.31.

**3,4-bis-(3′-Methyl-4′-hydroxy-5′-allylphenyl)-2,4-hexadiene.**—The procedure used by Kaiser and Svarz[4] for the preparation of 3,4-bis-(3′-allyl-4′-hydroxyphenyl)-hexene-3 was employed. A solution of 6.8 g. of 3,4-bis-(3′-methyl-4′-allyloxyphenyl)-2,4-hexadiene in 40 ml. of diethylaniline was refluxed for five hours in a nitrogen atmosphere. The desired product was isolated as a red gum (2.2 g. or 32%) which could not be crystallized, but gave proper analytical results.

*Anal.* Calcd. for $C_{26}H_{30}O_2$: C, 83.42; H, 8.02. Found: C, 83.20; H, 8.26.

The diacetate, prepared in 68% yield by refluxing in acetic anhydride for four hours, formed white crystals from dilute ethanol, m. p. 125–126°.

*Anal.* Calcd. for $C_{30}H_{34}O_4$: C, 78.60; H, 7.42. Found: C, 78.31; H, 7.29.

The dipropionate was prepared in 61% yield in a similar manner, m. p. 114–115°.

*Anal.* Calcd. for $C_{32}H_{38}O_4$: C, 79.01; H, 7.81. Found: C, 78.83; H, 7.71.

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(5) All melting points given are uncorrected.

## Closed-Circuit Seals in Glassblowing

BY ROGER K. TAYLOR

In fabricating glass apparatus in which one part is multiply connected to the rest, the customary procedure is to make the seals after the first by using a thin rod to pull together or bridge over the edges of the open-ended immobilized tubes that are to be joined. Difficulties occasionally arise, especially when the seal is not readily accessible from all directions, in manipulating the rod and obtaining a completely tight seal.

The writer for some years has on occasion used an alternative method which avoids these troubles. Although it is difficult to believe that the same idea has not occurred to others, neither the method nor a description of it has been seen elsewhere; and it is in the hope that the scheme may be of some general assistance that the following exposition is offered.

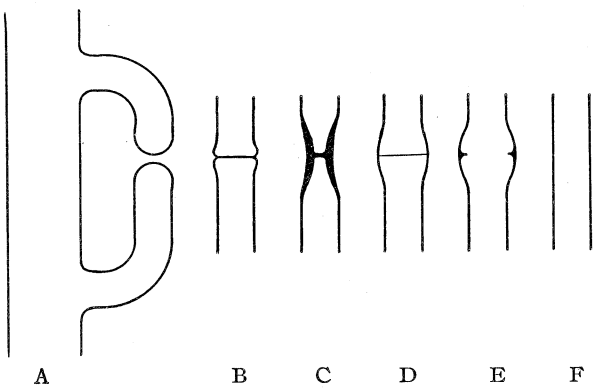



Fig. 1.—Closed-circuit seals in glassblowing.

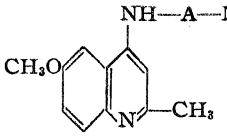
The innovation consists in closing the ends of the tubes where the joint is to be made (a). Then, when both ends are hot, blowing brings together the bulbs formed, producing a septum (b). When the enlarged portion is permitted to shrink (c), a portion of the glass of the septum is picked up by the wall; alternate blowing and shrinking (d, c) ultimately reduces the thickness of the septum to the point that it breaks (e), after which the joint is readily smoothed out (f). Glass can of course be added or removed with a thin rod as necessary, if the wall thickness at the seal does not match that of the rest of the tubing.

An advantage is that the annoyance of air leakage is avoided in the blowing, during making the seal; and this is particularly important when several connections have to be made between immobilized parts. It is also unnecessary to fit the parts so precisely, to give the small clearances required for easy working when the tubes are open. Furthermore there is no chance of leaving pinholes in the seals. The chief disadvantage is that prolonged working of the glass may lead to devitrification.

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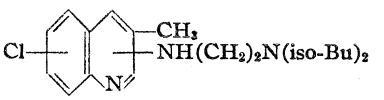
TABLE I

6-METHOXYQUINALDINES




| SN[a] | -A- | R | R' | Yield, % | Formula | M. p., °C. | Analyses, %[b] Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|---|
| .. | $-(CH_2)_3-$ | H | Iso-Pr | 34 | $C_{17}H_{25}ON_3 \cdot 2HCl \cdot 2H_2O$[c] | 150–153 | 56.65 | 7.56 | 56.54 | 7.55 |
| | | | | | | | | | 56.62 | 7.59 |
| 5204 | $-(CH_2)_3-$ | H | Iso-Bu | 32 | $C_{18}H_{27}ON_3 \cdot 2HCl \cdot H_2O$[d] | 283–284 | 57.75 | 7.81 | 57.83 | 7.75 |
| .. | $-(CH_2)_3-$[e] | Iso-Bu | Iso-Bu | 43.5 | $C_{22}H_{35}ON_3$ | 159–160 | 73.90 | 9.87 | 73.85 | 9.72 |
| 6556 | $-p-C_6H_4-$ | Me | Me | 45 | $C_{19}H_{21}ON_3 \cdot 2HCl$ | 276–277 | 60.00 | 6.10 | 59.90 | 6.08 |
| 6557 | $-HC(CH_2CH_2)_2CH-$ | Me | Me | 31 | $C_{19}H_{27}ON_3 \cdot 2HCl$ | 295–297 | 59.05 | 7.57 | 59.70 | 7.67 |
| 6560 | $-HC(CH_2CH_2)_2CH-$ | Et | Et | 32 | $C_{21}H_{31}ON_3 \cdot 2HCl$ | 270–272 | 60.85 | 8.03 | 60.74 | 8.03 |

3-METHYLQUINOLINES




| | Diamine position | Cl position | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 9215 | 2 | 7 | 38 | $C_{20}H_{30}N_3Cl \cdot 2HCl \cdot H_2O$[e] | 203–206 | 57.10 | 7.67 | 57.16 | 7.62 |
| 6562 | 4 | 7 | 53 | $C_{20}H_{30}N_3Cl \cdot 2HCl$ | 213–215 | 57.10 | 7.67 | 57.16 | 7.64 |
| 9216 | 4 | 5 | 29.5 | $C_{20}H_{30}N_3Cl \cdot 2HCl$[f] | 215–217 | 57.10 | 7.67 | 57.03 | 7.64 |

[a] The reference number of compounds listed in "A Survey of Antimalarial Drugs," ed. by Wiselogle, J. W. Edwards, Ann Arbor, Mich., 1946. [b] Analyses on the anhydrous material, in the case of the hydrates. [c] *Anal.* calcd. for dihydrate: $Cl^-$, 17.89. Found: $Cl^-$, 17.85. [d] Moisture loss at 125°: 4.82%; calcd. for monohydrate: 4.59%. Free base, 66.5% yield, b. p. (0.5 mm.) 200–215°. [e] Moisture loss at 125°: 4.07%; calcd. for monohydrate: 4.28%. [f] Free base had m. p. 129–131°.

## Some Quinaldine and 3-Methylquinoline Derivatives

BY KEITH W. WHEELER, CHARLES H. TILFORD, M. G. VAN CAMPEN, JR., AND ROBERT S. SHELTON

Termination of our work on antimalarials left unfinished a proposed series of 4-substituted-6-methoxyquinaldines and a similar group of 3-methylquinoline derivatives. Since further work in this direction is not anticipated, it seems desirable to record the preparation and properties of those compounds we did obtain and which have not been previously described in the literature. None of these compounds was appreciably active against the malaria parasite, the activities ranging from $Q<0.03$ for SN9215 to $Q<1.0$ for SN5204, although serveral of them showed moderate activity against *T. equiperdum* in mice.[1]

The intermediates 4-chloro-6-methoxyquinaldine,[2] 4,5-dichloro-3-methylquinoline,[3] 4,7-dichloro-3-methylquinoline[3] and 2,7-dichloro-3-methylquinoline[4] were prepared by standard procedures. The required diamines were obtained from the catalytic hydrogenation of the β-(di)-alkylaminopropionitrile, or the commercially available *p*-aminodiethyl (or methyl) anilines, and from the phthalimide synthesis.

**Procedure.**—A mixture of 0.1 mole of the chloroquinoline and 0.2 mole of the diamine was heated for eight to fifteen hours at 175–200° or for twenty-four to thirty-six hours at 145–150°. Water and ether were added to the mixture, the layers were separated, and the ether layer was washed with 10% hydrochloric acid. The aqueous layer and acidic extracts were combined and made strongly basic. The liberated oil was taken up in ether, dried, and distilled under reduced pressure in some cases, while in other cases only the more volatile material was distilled, leaving the crude free base as a residue. The hydrochloride salts were prepared in the usual manner and recrystallized from mixtures of ethanol and butanone or from aqueous ethanol.

The yields, properties, and analyses of the new compounds prepared are recorded in Table I. The yields reported here do not take into account the quinoline bases recovered in some instances.

**Acknowledgment.**—We wish to express our appreciation to Mr. Wm. J. Corbett for technical assistance.

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CINCINNATI 15, OHIO RECEIVED NOVEMBER 22, 1948

(1) We are indebted to Dr. Lloyd D. Seager, Woman's Medical College of Pennsylvania, for these tests.

(2) Conrad and Limpach, *Ber.*, **21**, 1650 (1888).

(3) Steck, Hallock and Holland, THIS JOURNAL, **68**, 380–383 (1946).

(4) This compound, m. p. 125–127°, was obtained along with the known 4,7-dichloro isomer from the action of phosphoryl chloride on 7-chloro-3-methylquinoline N-oxide. Although no analytical data are available, it is assumed to be the 2,7-isomer.

## Optically Active 2-Methylbutyl 3,5-Dinitrobenzoate

BY JONATHAN W. WHITE, JR., AND W. P. RATCHFORD

A lack of agreement in the literature concerning the melting point of optically active 2-

methylbutyl 3,5-dinitrobenzoate was encountered during a study of the volatile constituents of apple juice. The melting point of 2-methylbutyl 3,5-dinitrobenzoate is reported as 62°,[1] 70°[2] (both presumably from *d,l* alcohol), and 83–84°[3] (from alcohol of $[\alpha]$ +5.21°). The last value is the only one for a preparation obtained from an active alcohol of a given specific rotation. The stereoisomer available from fusel oil is *d*-2-methylbutanol, $[\alpha]^{20}D$ −5.90.[4] No data were found on the optical activity of the derivative.

An alcohol was obtained from apple juice which gave a dinitrobenzoate with a melting point of 81.5° (all melting points given here are uncorrected); its analysis was that of an amyl derivative. Mixed melting points with all inactive and racemic amyl derivatives were depressed below the melting point of either component except that with *dl*-2-methylbutyl dinitrobenzoate (m. p. 66.5°). The compound was optically active, $[\alpha]^{25}D$ +4.4°.

To determine which isomer had been obtained from apples, refined fusel oil was fractionally distilled. A fraction with $[\alpha]^{25}D$ −5.67° was obtained, equivalent to a purity of 96%. From this was prepared a 3,5-dinitrobenzoate, which melted at 83–84° and had $[\alpha]^{25}D$ +4.9°. This identified the alcohol from apples as *d*-2-methylbutanol, *i. e.*, the same as present in fusel oil.

### Experimental

**Dinitrobenzoate from Apple Fraction.**—A distillate fraction (the full procedure appears elsewhere,[5] 0.98 g. b. p. (150 mm.) 90–100°, $n^{20}D$ 1.4104, yielded a chromatographically[6] homogeneous 3,5-dinitrobenzoate on treatment with dinitrobenzoyl chloride in the presence of pyridine. It had a m. p. of 81.5–82.5°, analyzed as an amyl derivative, and failed to depress the m. p. of only the *dl*-2-methylbutyl derivative (m. p. 66.5°), in which case the melting range was 67–79°. It was then found to have $[\alpha]^{25}D$ +4.4° (4.8% in acetone). *Anal.* Calcd. for $C_{12}H_{14}O_6N_2$: C, 51.10, H, 4.96, N, 9.93. Found: C, 51.09; H, 5.04; N, 9.99.[7]

**Distillation of *d*-2-Methylbutanol from Fusel Oil.**—One gallon (3.78 l.) of "isoamyl alcohol"[8] was fractionated at atmospheric pressure in a Podbielniak column operated with intermittent take-off; it yielded 200 ml. of crude *d*-2-methylbutanol, b. p. 128–129°, estimated to be 53% pure. When redistilled, this fraction yielded 65 ml. of the alcohol, 93% pure. This material, redistilled in turn, yielded a fraction, b. p. 128.5°, $n^{20}D$ 1.4105, $[\alpha]^{25}D$ −5.67°, which is 96.1% of the accepted value.[4] The 3,5-dinitrobenzoate of this fraction melted at 83–84°, and had $[\alpha]^{25}D$ +4.9° (6.4% in acetone). *Anal.* Calcd. for $C_{12}H_{14}O_6N_2$: C, 51.10; H, 4.96. Found: C, 51.00; H, 5.00. A mixed melting point with the product from apple juice was 82–84°; therefore the alcohol from apples was -*d* 2-methylbutanol.

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RECEIVED AUGUST 27, 1948

(1) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1948, p. 226.

(2) Reichstein, *Helv. Chim. Acta*, **9**, 799 (1926).

(3) Gordon, *J. Am. Pharm. Assoc.*, **16**, 419 (1927).

(4) W. Markwald and A. McKenzie, *Ber.*, **34**, 485 (1901).

(5) White, THIS JOURNAL, in press.

(6) Chromatography was on silicic acid-rhodamine 6G by the method of White and Dryden, *Anal. Chem.*, **20**, 853 (1948).

(7) The authors are indebted to C. L. Ogg for the microanalyses.

(8) This alcohol, $[\alpha]^{25}D$ −1.06°, was kindly donated by Publicker Industries, Inc.

(9) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration.

## 2,2-Disubstituted-thiazolidine-4-carboxylic Acids

BY RICHARD H. WILEY AND J. F. JEFFRIES

The present report describes the application of the method of Woodward and Schroeder,[1] first used to prepare thiazolidine carboxylic acids from cysteine and acetone, to cysteine and three other ketones to form the corresponding substituted thiazolidine carboxylic acids.

**2-Methyl-2-ethylthiazolidine-4-carboxylic acid.**—One gram of cysteine[2] was refluxed with 200 ml. of methyl ethyl ketone, b. p. 79–80°, in a 300-ml. flask attached by ground glass connection to a reflux condenser. After three hours the cysteine had nearly all dissolved. The solution was filtered, evaporated to 15 ml., and cooled to deposit crystals which were recrystallized from methyl ethyl ketone; yie d, 1.0 g., 70% of the theoretical amount, m. p. 131°. No reaction took place when rubber stoppered equipment was used.

*Anal.* Calcd. for $C_7H_{13}NO_2S$: C, 48.00; H, 7.42; N, 7.98; S, 18.28. Found: C, 47.75; H, 7.19; N, 8.02; S, 18.38.

**2-Methyl-2-isopropylthiazolidine-4-carboxylic acid** was prepared from methyl isopropyl ketone as in the preceding example; yield, 0.69 g. from 1 g. of cysteine, 44% of the theoretical amount, m. p. 154° recrystallized from methyl isopropyl ketone.

*Anal.* Calcd. for $C_8H_{15}NO_2S$: C, 50.8; H, 7.92; N, 7.40; S, 16.90. Found: C, 50.9; H, 7.94; N, 7.51; S, 17.20.

**2,2-Tetramethylenethiazolidine-4-carboxylic acid** was prepared from cysteine and cyclopentanone; yield 0.86 g. from 1 g. of cysteine, 56% of the theoretical amount, m. p. 138°, recrystallized from cyclopentanone.

*Anal.* Calcd. for $C_8H_{13}NO_2S$: C, 51.2; H, 6.94; N, 7.48; S, 17.10. Found: C, 50.8; H, 6.92; N, 7.34; S, 16.90.

(1) Woodward and Schroeder, THIS JOURNAL, **59**, 1690 (1937).

(2) Toennies and Bennett, *J. Biol. Chem.*, **121**, 323 (1937).

CONTRIBUTION FROM THE
VENABLE CHEMICAL LABORATORY
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, N. C. RECEIVED NOVEMBER 6, 1948

# NEW COMPOUNDS

### Esters of Mono-, Di- and Tri-chloro-acetic Acids[1]

The new esters of mono-, di-, and tri-chloro-acetic acids, listed in Table I, have been synthesized by refluxing the alcohol with a slight molar excess of the acid in the presence of benzene. A Dean–Stark moisture trap was included in the apparatus to collect the water produced during the reaction. Refluxing was continued until the theo-

(1) Work done at the American Home Products Corp. Development Laboratory, New York, N. Y.

retical amount of water was collected. The reaction mixture was then cooled, washed with dilute bicarbonate solution and dried over anhydrous sodium sulfate. The product was isolated by vacuum distillation. Yields were in the neighborhood of 80–90%.

TABLE I

| Esters of | B. p. °C. | B. p. mm. | Chlorine, % Calcd. | Chlorine, % Found |
|---|---|---|---|---|
| Monochloroacetic acid | | | | |
| 2-Phenylcyclohexyl | 141–143 | 1.5 | 14.05 | 14.38 |
| Butyl cellosolve | 85–87 | 1.5 | 18.25 | 18.10 |
| Dichloroacetic acid | | | | |
| 2-Phenylcyclohexyl | 149–151 | 1.5 | 24.70 | 24.42 |
| Cyclohexyl | 80–82 | 1.5 | 33.60 | 33.76 |
| Butyl cellosolve | 90–93 | 1.5 | 31.00 | 31.25 |
| Trichloroacetic acid | | | | |
| 2-Phenylcyclohexyl | 157–159 | 1.5 | 32.50 | 32.70 |
| Cyclohexyl | 85–88 | 2 | 43.00 | 43.30 |

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A. HIEMENZ[2]
OSCAR GAWRON

RECEIVED NOVEMBER 5, 1948

(2) Deceased.

### 1-Benzyl-3-phenyl-2-thiohydantoin

**Ethyl N-Benzylglycinate.**—Ethyl chloroacetate was condensed with benzylamine according to the directions of Mason and Winder.[1] The yield of ethyl N-benzylglycinate on the second distillation, 128–131° at 6 mm., was 55%. The picrate derivative was prepared by mixing ethereal solutions of the two substances and scratching to induce crystallization. These yellow plates, washed with ether, melted 166–168° (micro-block).[2] A benzoyl derivative was also attempted but it could not be prepared by either the Schotten–Baumann method or by boiling with benzoyl chloride in benzene solution. This unexpected behavior prompted the attempt to form a thiourea derivative.

**1-Benzyl-3-phenyl-2-thiohydantoin.**—Approximately equal amounts of ethyl N-benzylglycinate and phenyl isothiocyanate were mixed in alcoholic solution and boiled for a minute or two. The product which separated on cooling was recrystallized from alcohol to give a good yield of long flat needles, m. p. 188.5–189.5° (micro-block). Instead of the expected thiourea the product indicated by analysis was the 2-thiohydantoin which resulted from cyclization of the thiourea by splitting out of ethanol. This type of cyclization is not unusual, though it generally requires higher temperatures[3] or acid catalysis.[4] *Anal.* Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.05; H, 5.12; N, 9.93.

NUTRITION RESEARCH LABORATORIES
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BY ARTHUR J. TOMISEK[5]

RECEIVED NOVEMBER 9, 1948

(1) Mason and Winder, *J. Chem. Soc.*, 188 (1894).

(2) Slight decomposition—as evidenced by the evolution of a distillate—was noticeable as low as 150°. This might bear some relationship to the 154° m. p. reported by Mason and Winder.[1]

(3) Wheeler and Brautlecht, *Am. Chem. J.*, **45**, 446 (1911).

(4) Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., N. Y., 1946, p. 459.

(5) Present address: Department of Chemistry, University of Wisconsin, Madison, Wis.

# COMMUNICATIONS TO THE EDITOR

## STUDIES OF FIBRINOGEN AND FIBRIN WITH THE ELECTRON MICROSCOPE

*Sir:*

Electron micrographs of metal-shadowed bovine Fraction I and human fibrinogen have been obtained showing that these materials consist largely of filamentous elements which are nodous in outline, somewhat like a string of beads, about 40 Å in diameter. Since the filaments tend to intermingle, it is difficult to measure all lengths with certainty, but such filaments as can be discerned vary in length from 300 to 1100 Å., with an average of about 600 Å. From flow-birefringence data it has been concluded that the fibrinogen particle can be represented by a prolate ellipsoid with a major axis of 700 Å. and an axial ratio of 18:1.[1] The widths observed are not appreciably different from the calculated minor axis. Numerous filaments occur with lengths close to the 700 Å. predicted, but the correlation is unsatisfactory in that flow-birefringence data indicate a constancy in length, while the electron microscope observations show a distribution of lengths. The discrepancy might be due to differences in samples or to difficulties inherent in the electron microscope methods.

An axial periodicity of about 250 Å. has been reported in bovine fibrin[2] after staining with phosphotungstic acid. The macroperiod is superficially similar to that in collagen[3] and certain other protein fibrils. In the present investigation, electron micrographs were obtained with improved resolution, showing that in bovine and human fibrin, the macroperiod consists of narrow stain-receptive bands midway between denser and wider stain-receptive bands whose average distance center-to-center along the fibril axis is about 230 Å. The spacing is constant to about 3% in individual fibrils, but varies by as much as 20% between separate fibrils. The fibrils appear to consist of particles having diameters in the range 30 to 50 Å. Metal-shadowing shows that the stain-receptive bands represent higher portions, indicating that the intervening regions have shrunk during drying. It is concluded that the periodic structure represents regular fluctuations in protein concentration in the originally hydrated system.

(1) J. T. Edsall, J. F. Foster and H. Scheinberg, THIS JOURNAL, **69**, 2731 (1947).

(2) C. V. Z. Hawn and K. R. Porter, *J. Exp. Med.*, **86**, 285 (1947).

(3) C. E. Hall, M. A. Jakus and F. O. Schmitt, THIS JOURNAL, **64**, 1234 (1942).

The micrographs indicate that fibrin is produced through a predominantly lateral association of fibrinogen filaments. The characteristic striation does not appear under all circumstances, for example, in fibrils with widths below about 200 Å., or in tapered ends with widths less than this. Unstriated fibrils show a randomly particulate structure, while in the striated portions the particles are more concentrated in the stained bands. The micrographs of fibrinogen do not show any degree of regularity either in length or internal structure comparable to the regularity in fibrin. It appears that the periodicity in fibrin is not a manifestation of rigid dimensional units in fibrinogen, but is, rather, a characteristic developed subsequent to initial aggregation The anomalous variations in protein concentration indicate that some of the constituents have experienced local axial shifts to preferred positions.

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RECEIVED FEBRUARY 12, 1949

## FERMENTATION OF GLUCOSE-1-C$^{14}$

*Sir:*

We have synthesized *d*-glucose-1-C$^{14}$ from *d*(−)-arabinose by the Fischer–Kiliani method.[1] The mixed glucono- and mannonolactones were reduced catalytically,[2] carrier glucose added, and the radioglucose isolated and recrystallized to constant specific activity (about 6000 counts per gram minute). The glucose (in 0.2-g. samples) was then fermented anaerobically by Fleischmann's baker's yeast in phosphate buffers in the absence of a source of combined nitrogen; the fermentation yields (based on the carbon dioxide obtained) were 75–90%. The Embden–Meyerhof fermentation mechanism[3] predicts that all the radiocarbon will appear in the methyl group of the alcohol so obtained; this prediction has been substantially confirmed.

The carbon dioxide obtained directly in the fermentation was counted as $BaCO_3$. The alcohol was degraded to acetone by the method outlined below; the latter was counted as its 2,4-dinitrophenylhydrazone.

$$C^{14}H_3CH_2OH \xrightarrow[H_2SO_4]{K_2Cr_2O_7} C^{14}H_3CO_2H \xrightarrow{Ba(OH)_2} (C^{14}H_3CO_2)Ba(O_2CCH_3) \xrightarrow[\text{Vacuum}]{530^\circ} C^{14}H_3COCH_3 + BaCO_3$$

In a set of control experiments on the pyrolysis using methyl-labelled acetic acid,[4] we found 0.1–0.3% of the activity in the barium carbonate produced. Further in these control experiments, the specific activity of the acetone 2,4-dinitrophenylhydrazone was only 77% of that anticipated from the specific activity of the barium acetate, even after making the usual corrections[5] for self-absorption, etc. The specific activities of all samples of acetone 2,4-dinitrophenylhydrazone were therefore corrected by the factor 1/0.77. The final results, together with the counting errors (95% confidence level), are given below:

| pH | Other conditions | Per cent. of radioactivity (based on glucose fermented) found in $CO_2$ | $CH_3$ | $CH_2OH$ |
|---|---|---|---|---|
| 6.2 | Live yeast | 6.5 ± 2.4 | 92 ± 4.0 | 4.8 ± 2.4 |
| 5.7 | Live yeast | 1.0 ± 1.8 | 76 ± 4.0 | 7.6 ± 2.8 |
| 5.7 | Dried yeast powder | 3.7 ± 1.8 | 92 ± 7.8 | 0.2 ± 0.4 |

We are currently investigating the causes of the slight radioactivity in the carbon dioxide obtained directly in the fermentation and in the barium carbonate from the pyrolysis.

(1) Kiliani *Ber.*, **19**, 3033 (1886).
(2) Glattfeld and Schimpf, THIS JOURNAL, **57**, 2204 (1935).
(3) Meyerhof, *Biochem. Symposia*, **V**, 141 (1941).
(4) The methyl labelled acetic acid was kindly supplied to us by Professor Konrad Bloch.
(5) Yankwich and Weigl, *Science*, **107**, 651 (1948); Libby, *Ind. Eng. Chem., Anal. Ed.*, **19**, 2 (1947).

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RECEIVED FEBRUARY 3, 1949

## A NEW SYNTHESIS OF 2-PHENAZINOL, THROUGH THE DI-N-OXIDE

*Sir:*

The chlorine atom of 2-chlorophenazine can be labilized toward aqueous-alcoholic sodium or potassium hydroxide by converting the base to 2-chlorophenazine-5,10-dioxide (red-orange needles, m. p. 190–191° (dec.)[1] *Anal.*[2] Calcd. for $C_{12}H_7ClN_2O_2$: C, 58.4; H, 2.87. Found: C, 58.5; H, 3.06. This conversion is readily effected, using the method employed by Clemo and McIlwain[3] for other phenazines. Refluxing the chlorophenazine dioxide for about twelve hours with aqueous-alcoholic potassium or sodium hydroxide gives a deep purple solution of the alkali salt, from which hydrochloric acid precipitates the free 2-phenazinol-5,10-dioxide (orange-red, begins to darken at 236°). *Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.2; H, 3.54. Found: C, 63.1; H, 3.87. Reduction of this by sodium hyposulfite (sodium "hydrosulfite") in alkaline solution at room temperature gives a red solution of the sodium salt of 2-phenazinol, from which the free phenol[4] is precipitated by acid. (Clemo and McIlwain[3] found sodium hyposulfite effective in reducing 1-phenazinol-5,10-dioxide.) The 2-phenazinol may be purified by vacuum sublimation and chromatographic adsorp-

(1) All melting points are corrected.
(2) Analyses by Mr. W. C. Alford, Mrs. M. M. Ledyard and Mrs. E. G. Peake.
(3) Clemo and McIlwain, *J. Chem. Soc.*, **483** (1938).
(4) Kehrmann and Cherpillod, *Helv. Chim. Acta*, **7**, 975 (1924). As these authors indicate, in saying that the 2-phenazinol melts at "about" 253–254° with decomposition, this compound does not appear to have a sharp melting point.

tion on alumina. *Anal.* Calcd. for $C_{12}H_8N_2O$: C, 73.4; H, 4.11. Found: C, 73.8; H, 4.25.

The 2-chlorophenazine was made by the method of Waterman and Vivian,[5] starting from 4-chloro-2-nitrodiphenylamine.

The antitubercular activity of the phenazine dioxides[6] makes both of the new dioxides reported above of interest, especially the alkali-soluble hydroxy compound; and by this synthesis the 2-phenazinol itself is rendered more easily accessible.

(5) Waterman and Vivian, *J. Org. Chem.*, March, 1949; U. S. Patent 2,292,808 (Aug. 11, 1942).

(6) Ihland, *Nature*, **161**, 1010 (June 26, 1948). Antitubercular activity of certain other phenazines: Barry, Belton, Conalty and Twomey, *ibid.*, **162**, 622 (Oct. 16, 1948).

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RECEIVED FEBRUARY 18, 1949

## PREPARATION OF HIGH-PURITY HYDROGEN DEUTERIDE FROM LITHIUM ALUMINUM HYDRIDE

*Sir:*

Hydrogen deuteride of very high purity has been prepared previously by the fractional distillation of a mixture of $H_2$, $D_2$, and HD at liquid hydrogen temperatures.[1] We have now found that very pure HD can be prepared more simply by the action of certain metallic hydrides on heavy water. Thus, sodium hydride with heavy water gives 87% HD with $H_2$ and $D_2$ as impurities. Lithium aluminum hydride with heavy water gives 93% HD in some cases and in others 97%, with 2.5% $H_2$ + 0.5% $D_2$.[2] Determinations were made on a consolidated mass spectrometer for which instrumental condition were: magnet current of 0.15 ampere and voltages of 3800 for mass 1 ($H^+$), 1900 for mass 2 ($H_2^+$ and $D^+$), 1267 for mass 3 ($HD^+$), and 950 for mass 4 ($D_2^+$).

It was suspected that the heat evolved in the reaction promoted the formation of $D_2$ and $H_2$. Accordingly the preparation with lithium aluminum hydride was carried out in a bath at 0°, with the resulting formation of 99% pure HD. The exact nature of the temperature dependence is not known, but the variation in composition of the gas product may be due to a shifting of the $H_2 + D_2 \rightleftarrows HD$ equilibrium, as well as to the presence of impurities in the lithium aluminum hydride.

Our preferred procedure for this preparation, therefore, was as follows:

Pure $D_2O$ (99.8%) contained in a hypodermic syringe was injected through a neoprene serum stopper, into a stirred ice-cold slurry of lithium aluminum hydride in *n*-butyl ether contained in the reaction flask of a modified Zerewitinoff apparatus.[3] After the vigorous reaction subsided, the evolved gas was collected in an evacuated sample bottle.

This very simple preparation of HD from lithium aluminum hydride and knowledge of its fragmentation pattern should improve the mass spectrometric analyses of $H_2$, $D_2$ and HD mixtures, especially those low in $H_2$.

We wish to acknowledge the helpful assistance of A. G. Sharkey, Jr.

(1) Scott and Brickwedde, *Phys. Rev.*, **48**, 483 (1935).

(2) Beutler, Brauer and Junger, *Naturwissenschaften*, **24**, 347 (1936) reported the preparation of a mixture rich in HD by the action of lithium hydride on heavy water.

(3) Orchin and Wender, *Anal. Chem.*, in press.

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RECEIVED NOVEMBER 22, 1948

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JOURNAL OF THE
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VOLUME 71 APRIL 23, 1949 NUMBER 4

# Report of Committee on Atomic Weights

BY G. E. F. LUNDELL, *Chairman*

The following pieces of work have been reported since the material was gathered for the Report which was published in *Chemical and Engineering News*, **26,** 1619 (1948), and reprinted in the *Journal of the American Chemical Society*, **70,** 3531 (1948).

**Cerium and Lanthanum.**—Inghram, Hayden and Hess[1] determined the isotopic constitution of cerium and of lanthanum by means of a mass spectrometer.

The abundances of the cerium isotopes of masses 136, 138, 140 and 142 were shown to be 0.193 ± 0.005, 0.250 ± 0.005, 88.48 ± 0.10, and 11.07 ± 0.01%, respectively. Calculation of the chemical atomic weight of cerium from these abundances, assuming a packing fraction of $-3.0 \times 10^{-4}$, and the factor 1.000275 in converting from physical to chemical atomic weights, gives 140.10, a value which is in agreement with the chemically determined International value of 140.13.

The abundances of the lanthanum isotopes of masses 138 and 139 were found to be 0.089 ± 0.001 and 99.911 ± 0.001%, respectively. Calculation of the chemical atomic weight from these abundances, using Dempster's value[2] of $-3.2 \times 10^{-4}$ for the packing fraction and the conversion factor 1.000275, gives 138.92, a value which is in complete agreement with the chemically determined International value of 138.92.

**Neodymium and Praseodymium.**—Inghram, Hess and Hayden[3] determined the isotopic constitution of neodymium and of praseodymium by means of a mass spectrometer.

The abundances of the neodymium isotopes of masses 142, 143, 144, 145, 146, 148 and 150 were found to be 27.13 ± 0.2, 12.20 ± 0.1, 23.87 ± 0.2, 8.30 ± 0.05, 17.18 ± 0.2, 5.72 ± 0.06 and 5.60 ± 0.06%, respectively. Assuming a packing fraction of $-2.7 \times 10^{-4}$, and with the conversion factor 1.000275, the chemical atomic weight is 144.25, which is in good agreement with the International chemical value of 144.27.

Assuming a packing fraction of $-3.0 \times 10^{-4}$ for praseodymium with its single isotope at mass 141, and with the conversion factor 1.000275, the chemical atomic weight is 140.92, which is in complete agreement with the International value of 140.92.

**Samarium.**—Inghram, Hess and Hayden[4] determined the isotopic composition of samarium.

The abundances of the samarium isotopes of masses 144, 147, 148, 149, 150, 152 and 154 were found to be 3.16 ± 0.10, 15.07 ± 0.15, 11.27 ± 0.11, 13.84 ± 0.14, 7.47 ± 0.07, 26.63 ± 0.26 and 22.53 ± 0.22%, respectively. Calculation of the chemical atomic weight from these abundances, assuming a packing fraction for samarium of $-2.4 \times 10^{-4}$, and with the conversion factor 1.000275, gives a value of 150.35. The International value is 150.43.

**Cadmium and Zinc.**—Leland and Nier[5] determined the relative abundances of the isotopes of cadmium and of zinc. The abundances of the cadmium isotopes of masses 106, 108, 110, 111, 112, 113, 114 and 116 were found to be 1.215, 0.875, 12.39, 12.75, 24.07, 12.26, 28.86 and 7.58% respectively. By using a packing fraction of $-6.0 \times 10^{-4}$ and the conversion factor 1.000275, the calculated value of the chemical atomic weight is 112.42, which agrees very well with the International chemical value of 112.41.

(1) Mark G. Inghram, Richard J. Hayden and David C. Hess, Jr., *Phys. Rev.*, **72,** 967-970 (1947).

(2) A. J. Dempster, *ibid.*, **33,** 869 (1938).

(3) Mark G. Inghram, David C. Hess, Jr., and Richard J. Hayden, *ibid.*, **74,** 98-99 (1948).

(4) Mark G. Inghram, David C. Hess, Jr., and Richard J. Hayden, *ibid.*, **73,** 180 (1948).

(5) Wallace T. Leland and Alfred O. Nier, *ibid.*, **73,** 1206-1207 (1948).

The relative abundances of the isotopes of zinc of masses 64, 66, 67, 68 and 70 were found to be 48.89, 27.81, 4.07, 18.61 and 0.620%, respectively. With a packing fraction of $-7.0 \times 10^{-4}$ and the conversion factor 1.000275, the computed chemical atomic weight is 65.40, whereas the International chemical value is 65.38.

WASHINGTON, D. C. RECEIVED FEBRUARY 11, 1949

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, STATE COLLEGE OF WASHINGTON, AND DIVISION OF INDUSTRIAL RESEARCH, WASHINGTON STATE INSTITUTE OF TECHNOLOGY]

# The System Aluminum Sulfate–Sulfuric Acid–Water at 60°

BY JACK L. HENRY[1] AND G. BROOKS KING

This report is part of a study of the more extensive system aluminum oxide–sulfur trioxide–water at 60° which is being investigated in connection with the development of an alumina-from-clay extraction process. The temperature 60° has been found most advantageous for the process as determined with laboratory scale and pilot plant extraction towers.[2] Although the leach operations are carried on within the basic region, it was felt desirable to conduct a study of the system in its entirety. In connection with the acid system presented in this paper, no complete ternary systems have been reported. F. Wirth[3] has studied the solubility of aluminum sulfate in sulfuric acid solutions of concentrations up to 75% at 25° and has reported but one solid phase, the 18 hydrate. At the same temperature Motida[4] has found the 16 hydrate in addition to the 18 hydrate, but presented no data for sulfuric acid concentrations above 48%. Kremann and Hüttinger[5] in their work on the solubility of freshly precipitated aluminum hydroxide in aluminum sulfate solutions report that the 16 hydrate exists as the solid phase in the less basic region at 20, 40 and 60°. This would seem to be in agreement with the views of P. M. Delacharlonny,[6] who favors the 16 hydrate. Horan and Skarulis,[7] however, failed to prepare the 18 hydrate and suggest the possibility of $Al_2(SO_4)_3 \cdot 17H_2O$ at the temperature 0°. Following this work, N. O. Smith,[8] by repeating at 25° the parts of three ternary systems which involve hydrated aluminum sulfate as the solid phase, showed further evidence in favor of the 17 hydrate. The following hydrates of aluminum sulfate have been found reported in the literature: 2, 3, 6, 9, 10, 12, 14, 16, 17, 18, 22, 24 and 27. That they are all true chemical individuals, however, seems questionable. The present paper treats the system over sulfuric acid concentrations up to 96.08% and shows the presence of the four solid phases at 60°: $Al_2(SO_4)_3 \cdot 16H_2O$, $Al_2(SO_4)_3 \cdot 9H_2O$, $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 12H_2O$ and $Al_2(SO_4)_3$.

(1) Submitted in partial fulfillment of the requirements for the Ph.D. degree, the State College of Washington.

(2) *Ind. Eng. Chem.*, **38**, 1181 (1946).

(3) F. Wirth, *Z. anorg. Chem.*, **79**, 360 (1912).

(4) Motida, *Science Repts. Tohôku Imp. Univ.*, First Ser., **26**, 611–617 (1938).

(5) R. Kremann and K. Hüttinger, *Jahrbuch d. k. k. geol. Reichsanstalt. Wien*, **58**, 637 (1908).

(6) P. M. Delacharlonny, *Compt. rend.*, **96**, 844 (1883).

(7) Horan and Skarulis, THIS JOURNAL, **61**, 2689 (1939).

(8) N. O. Smith, *ibid.*, **64**, 41 (1942).

## Experimental

**Materials and Apparatus.**—Mallinckrodt analytical reagent aluminum sulfate and sulfuric acid were employed throughout the system. Aluminum sulfate was recrystallized from a solution of specific gravity about 1.33 as suggested by Horan and Skarulis.[7] Extensive solubility studies on the system at 60° showed, however, that any deviations caused by impurities present in the unrecrystallized reagent could not be detected by the analytical methods used. Because of the high percentage of waste involved in recrystallization and the large amount of aluminum sulfate used, the unrecrystallized salt was employed in more than half the studies.

An electrically controlled thermostat which held the temperature at 60 ± 0.1° was employed. Evaporation loss from the bath was limited by a fabricated sheet aluminum cover. Glass-stoppered Pyrex tubes of about 40-ml. capacity which held the solutions under investigation were fitted with cotton-filled caps and secured to a wheel which rotated continually beneath the water surface of the bath. Such tumbling action provided efficient agitation during the time required for the solutions to reach equilibrium.

**Methods of Analysis.**—Aluminum sulfate was determined gravimetrically as $Al_2O_3$ by ignition at 1150°. Sulfuric acid was titrated directly in the presence of aluminum sulfate with standard sodium hydroxide solution. The aluminum which was combined in a complex by use of an excess of sodium oxalate[9] did not interfere with the titration. In regions of low sulfuric acid concentration the titrations were carried out electrometrically, whereas phenol red indicator was used at higher concentrations. The volumetric method for sulfuric acid gave satisfactory checks against the gravimetric barium sulfate procedure and proved to be much more rapid.

**Solubility Determinations.**—Various mixtures of aluminum sulfate, sulfuric acid and water were weighed out approximately and placed in the described tubes. The mixtures were brought to equilibrium from the supersaturated condition in most cases. Tubes were removed from the wheel at intervals and samples taken for analysis to determine the progress in attainment of equilibrium. Time for establishment of equilibrium conditions increased with increasing sulfuric acid concentration. Equilibrium was attained in the less acidic regions within forty-eight hours, but in no case did the time exceed six days. At lower sulfuric acid concentrations the crystals, although quite small, separated quickly and completely. Above 50% sulfuric acid the equilibrium mixture proved difficult to handle in that the resulting viscous slurries failed to separate well into liquid and solid phases. A constant temperature centrifuge was designed and built in which the samples could be centrifuged at 60 ± 0.1°. This incor-

(9) M. F. Adams (not yet published), presented at American Chemical Society regional meeting, Seattle, Washington, 1945.

porated an air-bath electrically controlled by a bimetallic spiral thermoregulator and a space heater. Successful separations were achieved by this means up to concentrations of sulfuric acid in excess of 85%. Above this concentration the density of the mother liquor so closely approached that of the minute crystals that centrifuging for a permissible length of time failed to bring about complete separation. The few points treated in this region were separated by gravitational settling over a period of from one to two weeks.

The method of "wet residues"[10] was used in nearly all cases except in the establishment of isothermally invariant points. In these, accurately synthesized complexes were employed. It was found that glass-stoppered tubes properly sealed with DeKhotinsky cement were highly satisfactory for the work with complexes.

## Results

The compositions of the solutions and residues are given in Table I and shown graphically in Fig. 1. Tie-lines are constructed to intersect at the probable solid phase.

TABLE I

THE SYSTEM $Al_2(SO_4)_3$–$H_2SO_4$–$H_2O$ AT 60°

| Solution, wt. % $Al_2(SO_4)_3$ | Solution, wt. % $H_2SO_4$ | Residue, wt. % $Al_2(SO_4)_3$ | Residue, wt. % $H_2SO_4$ | Solid phase | Error in % $Al_2(SO_4)_3$ by algebraic extrapolation |
|---|---|---|---|---|---|
| 31.83 | 0.00 | ... | ... | | |
| 29.31 | 2.37 | 46.24 | 0.94 | M | −3.11 |
| 27.87 | 4.55 | 44.68 | 1.74 | M | −0.83 |
| 26.15 | 7.09 | 43.00 | 3.05 | M | −1.47 |
| 23.82 | 11.03 | 37.89 | 6.14 | M | −1.30 |
| 21.88 | 14.25 | 37.14 | 7.80 | M | −1.34 |
| 19.29 | 19.57 | 38.51 | 8.90 | M | −0.28 |
| 16.44 | 25.93 | 36.46 | 12.29 | M | −0.24 |
| 14.59 | 32.52 | 37.52 | 13.83 | M | −0.23 |
| 14.51 | 35.29 | 36.96 | 17.14 | M + N | |
| 14.79 | 35.00 | 21.50 | 29.50[a] | M + N | |
| 14.70 | 35.27 | 18.00 | 32.50[a] | M + N | |
| 10.41 | 39.61 | 19.00 | 34.00[a] | N | −3.21 |
| 7.67 | 43.95 | 34.59 | 24.81 | N | −1.63 |
| 5.99 | 48.11 | 28.51 | 30.55 | N | +0.18 |
| 5.04 | 50.95 | 32.02 | 28.56 | N | +1.39 |
| 4.43 | 55.09 | 19.87 | 41.70 | N | −0.12 |
| 4.09 | 56.86 | 9.92 | 51.75[a] | N | −1.12 |
| 3.82 | 59.02 | 23.04 | 41.29 | N + O | |
| 3.69 | 58.84 | 13.77 | 51.07 | N + O | |
| 4.25 | 60.82 | 17.48 | 48.50[b] | N | −1.72 |
| 0.92 | 65.61 | 12.08 | 56.44 | O | +1.36 |
| .63 | 69.94 | 8.95 | 62.36 | O | +0.61 |
| .63 | 72.82 | 7.89 | 65.77 | O | +0.05 |
| .99 | 76.18 | 9.43 | 67.27 | O | −0.33 |
| 1.74 | 78.49 | 8.00 | 73.00[a] | O + P | |
| 1.81 | 78.45 | 8.00 | 73.50[a] | O + P | |
| 1.72 | 77.97 | 8.00 | 72.50[a] | O + P | |
| 0.17 | 82.57 | 7.00 | 77.00[a] | P | −1.42 |
| .17 | 86.84 | 10.67 | 77.54 | P | +0.85 |
| .09 | 90.89 | 6.25 | 85.25 | P | +0.64 |
| Trace | 96.08 | 4.32 | 91.78 | P | +3.47 |

[a] Complex made up against analytical balance. [b] Metastable. M = $Al_2(SO_4)_3 \cdot 16H_2O$, N = $Al_2(SO_4)_3 \cdot 9H_2O$, O = $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 12H_2O$, P = $Al_2(SO_4)_3$.

Data were plotted and graphical extrapolations made on an accurately drawn triangular diagram

(10) Schreinemakers, *Z. physik. Chem.*, **11**, 75 (1893).

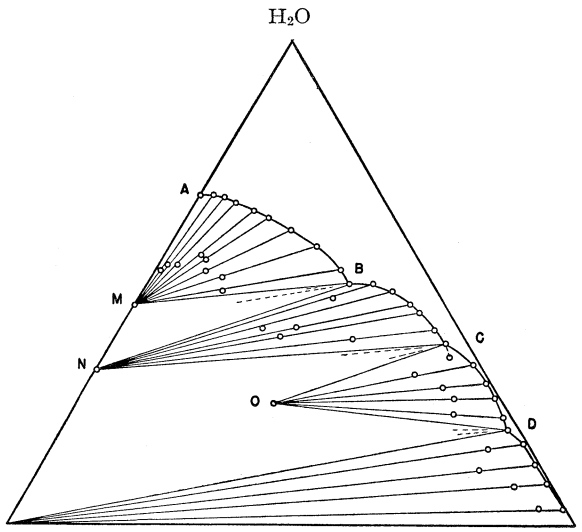



Fig. 1.—System $Al_2(SO_4)_3$–$H_2SO_4$–$H_2O$ at 60°: M = $Al_2(SO_4)_3 \cdot 16H_2O$, N = $Al_2(SO_4)_3 \cdot 9H_2O$, O = $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 12H_2O$, P = $Al_2(SO_4)_3$.

with edge dimensions of 50 cm. To check the accuracy of the solid phases determined by such graphical means, algebraic extrapolations[11] were carried out for each of the four solids. By algebraic extrapolation of data on curve AB the points nearest the edge of the triangle would seem to favor the 15 hydrate of aluminum sulfate, whereas those data nearer point B show the 16 hydrate to be the probable solid phase. Extrapolations of data nearest point A appear more erratic, however. This might be expected since the tie-lines are so nearly parallel to the edge of the diagram. Such uncertainty in this region would suggest that more weight be placed on those data nearer point B on the curve. Algebraic extrapolations from the four points nearest B show an average error in per cent. $Al_2(SO_4)_3$ of −0.53 from the 16 hydrate and +1.09 from the 15 hydrate. The 18 hydrate reported by Motida[4] to exist over the range of sulfuric acid concentration up to 7.24% at 25° was not observed at this higher isotherm although the possibility of a transition near A was given careful consideration. Extension of the work into the basic region, not yet published, throws little light on the possibility of an 18 hydrate because the curve breaks soon after passing the $Al_2(SO_4)_3$–$H_2O$ axis.

Since our value of 31.8% for the solubility of pure aluminum sulfate at 60° differs so greatly from the value 37.2% reported by Poggiale[12] it was felt that the binary system $Al_2(SO_4)_3$–$H_2O$ should be re-investigated at least in part. Whereas the solubilities near 25 and 30° lie close to the values obtained by Poggiale, a large negative deviation is observed at higher temperatures. The

(11) Hill and Ricci, THIS JOURNAL, **53**, 4305 (1931).

(12) Poggiale, *Ann. Chim. Phys.*, [3] **8**, 467 (1843).

results reported by Poggiale are shown by the broken line in Fig. 2. Much work has been done on solubility studies of aluminum sulfate at 25 and 30°, but relatively little above these temperatures. The fact that Poggiale's binary study agrees with recent investigators in this more common range may explain why re-investigation of the system at elevated temperatures has not been conducted. Data for the binary study are given in Table II and shown graphically in Fig. 2. Equilibrium was established from both undersaturation and supersaturation in each case. No attempt was made to identify the solid phase, and although the curve is drawn as smooth the data do not rule out the possibility of a change in hydration in this range.

TABLE II

SOLUBILITY OF HYDRATED ALUMINUM SULFATE

| Temp., °C. | Solubility $Al_2(SO_4)_3$ (wt. %) Undersaturation value | Supersaturation value | Average |
|---|---|---|---|
| 25 | 28.3 | 28.3 | 28.3 |
| 30 | 28.6 | 28.6 | 28.6 |
| 35 | 28.9 | 28.9 | 28.9 |
| 40 | 29.5 | 29.7 | 29.6 |
| 45 | 29.9 | 30.1 | 30.0 |
| 50 | 30.8 | 30.3 | 30.6 |
| 55 | 31.1 | 31.3 | 31.2 |
| 60 | 31.8 | 31.8 | 31.8 |
| 65 | 33.0 | 32.8 | 32.9 |

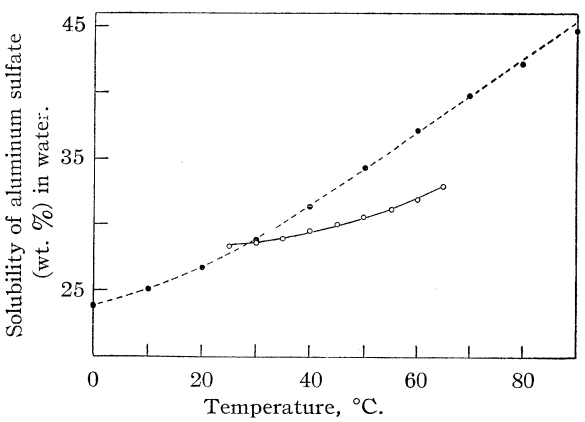



Fig. 2.—Solubility of hydrated $Al_2(SO_4)_3$ in $H_2O$ given as percentage by weight. Broken-line curve represents the values reported by Poggiale.[11]

The solubility curve BC, Fig. 1, shows $Al_2(SO_4)_3 \cdot 9H_2O$ to be the probable solid phase. The average deviation in per cent. $Al_2(SO_4)_3$ by algebraic extrapolation is +0.89. Metastability was encountered in this region as shown by the broken line extending beyond 60.8% sulfuric acid. Behavior of several samples prepared in the range of curve CD indicated that this metastable condition extends to about 65% sulfuric acid.

The curve CD represents solutions in equilibrium with the acid salt $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 12H_2O$. Average deviation in per cent. $Al_2(SO_4)_3$ from the composition of this solid phase as determined by algebraic extrapolation is +0.42. Three acid salts have been reported, $Al_2(SO_4)_3 \cdot H_2SO_4 \cdot 3H_2O$ by E. Baud,[13] $Al_2(SO_4)_3 \cdot 2H_2SO_4 \cdot 10H_2O$ by F. Jeremin,[14] and $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 7H_2O$ by R. Silberberger.[15] The later bisulfate was reported to have been prepared by the addition of aluminum sulfate to cold concentrated sulfuric acid and warming. The acid salt described in the present paper is very similar in physical properties to that reported by Silberberger but differs as to degree of hydration. When filtered and washed with ether the acid sulfate appears as a fine white powder. In contact with water it remains for several hours as a "silky" precipitate gradually decomposing and going into solution. The white powder appears to be slightly deliquescent and changes in moist air to form a paste-like mass which is readily soluble in water.

Beyond the isothermally invariant point *D* anhydrous aluminum sulfate is found to be the solid phase. The average error in per cent. $Al_2(SO_4)_3$ is +0.88. The highest concentration of sulfuric acid studied shows only a trace of dissolved aluminum sulfate. This may be compared with the work of Kendall and Davidson,[16] who report the molar solubility of anhydrous aluminum sulfate in anhydrous sulfuric acid at 25° to be less than 0.01. The amplification of analytical errors caused by failure to obtain a more complete separation of the residue from the solution has contributed greatly to the deviations in the extrapolations. The relatively large range of extrapolations may cast some doubt upon the degree of hydration of phases N and O as stated.

## Summary

The ternary system $Al_2(SO_4)_3$–$H_2SO_4$–$H_2O$ has been investigated at 60°. The four solid phases, $Al_2(SO_4)_3 \cdot 16H_2O$, $Al_2(SO_4)_3 \cdot 9H_2O$, $Al_2(SO_4)_3 \cdot 3H_2SO_4 \cdot 12H_2O$, and anhydrous $Al_2(SO_4)_3$ have been found.

Investigation of the binary system $Al_2(SO_4)_3$–$H_2O$ from 25 to 65° shows lower values of solubility in the higher temperature range than have been previously reported.

RECEIVED SEPTEMBER 7, 1948

(13) E. Baud, *Compt. rend.*, **137**, 494 (1903).
(14) F. Jeremin, *J. Russ. Phys.-Chem., Soc.*, **13**, 468 (1888).
(15) R. Silberberger, *Monatsh.*, **25**, 220 (1904).
(16) Kendall and Davidson, THIS JOURNAL, **43**, 979 (1921).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

# A Comparison of the Long Spacings of Some Soap Hemihydrates

BY J. E. MINOR AND E. C. LINGAFELTER

Values for the cell dimensions of "alpha" sodium palmitate hemihydrate[1] and "alpha" sodium stearate hemihydrate have been published by Buerger.[2] These published values gave an increase in $d_{001}$ value between the palmitate and stearate which was larger than would have been expected. It was therefore thought to be of interest to check the values obtained for the palmitate and stearate, and to extend the series to include sodium myristate and sodium arachidate hemihydrates. An attempt was also made to grow crystals of sodium laurate hemihydrate, but to date no suitable crystals of this substance have been obtained.

## Experimental

The authors are indebted to M. J. Buerger for crystals of sodium arachidate hemihydrate obtained from him. Suggestions for growing crystals of the other hemihydrates were obtained from a publication[3] by de Brettville and Ryer.

The crystals obtained in this Laboratory were grown from sodium soaps produced by titrating the corresponding Eastman Kodak Co. fatty acid dissolved in alcohol with equimolar proportions of alcoholic sodium hydroxide, using phenolphthalein as an outside indicator. The resulting sodium soaps were recrystallized from alcohol before use. A series of analytical tests were run on the Eastman acids used, to determine their freedom from esters, unsaturation, and fatty acids of other molecular weights. Data on the methyl arachidate and arachidic acid from which the sodium arachidate was prepared have been furnished by Dr. F. V. Ryer of the Lever Bros. Company.

The equivalent weights were calculated from acid values run according to Scott's "Standard Methods of Analysis." Saponification values were also run according to Scott's "Standard Methods of Analysis." Iodine numbers required a more specialized technique because of the low percentage of unsaturation present in the fatty acids. Accordingly these determinations were run by M. Yasuda's method[4] using pyridine sulfate dibromide as the halogenating agent.

TABLE I

ANALYTICAL DATA

| Substance | Equiv. wt. | Dev., % | Sapon. value | Dev., % | Iodine no. | Temp., °C. Setting point | Setting point (Francis and Piper)[5] |
|---|---|---|---|---|---|---|---|
| Myristic acid | 228.4 | 0.0 | 245.7 | 1.0 | 0.1 | 52.92 | 53.65 |
| Palmitic acid | 256.6 | .1 | 224.7 | 2.7 | 0.1 | 61.54 | 62.60 |
| Stearic acid | 285.8 | .5 | 204.8 | 3.9 | 1.2 | 68.42 | 69.39 |
| Arachidic acid | | | 172.3(ester) | 0.3 | 0.2(ester) | 74.3(m. p.) | 75.35(m. p.) |

In the first attempt to grow crystals of NaL and NaMy, approximately 0.6% solutions of the compounds in 95% ethyl alcohol were made up, a few grains of sodium chloride were added, and the solutions were placed in a thermostat at 20°. A few tiny crystals of NaMy were obtained, and later proven to be "alpha" form, but no usable crystals of NaL appeared. Approximately 0.2% solutions of NaP, NaSt, and NaL were then made up in 95% ethyl alcohol, a few grains of sodium chloride added to the NaP and NaL solutions, and the solutions were allowed to evaporate slowly at room temperature. The NaL solution produced no single crystals. The NaSt solution produced a large number of single crystals of the "alpha" form. The NaP solution produced a few crystals of a rod shape which were shown by X-ray studies to be different from the "alpha" form. Immediately after these crystals appeared, another crystalline form began to grow, which proved to be "alpha" NaP.

The habit of the NaSt and NaAr crystals corresponds to that described by Buerger[6] for NaSt.

The habit of the NaP crystals corresponds to Buerger's description[6] except that the form (10 $l$) is present to about the same degree as the (11 $l$), making the crystal appearance hexagonal rather than diamond shape. The crystals have good (010) cleavage.

The few NaMy crystals obtained were not sufficiently well developed to obtain crystallographic characteristics.

Data on cell constants were obtained from oscillation photographs for $a_0$ and $b_0$ values, and from equi-inclination Weissenberg photographs for $c_0$ values. CuK radiation with nickel filter was used for all photographs. (Camera diameter = 56.85 mm., obtained by calibration with NaCl, $a_0$ = 5.6394 Å., CuK$\alpha\lambda$ = 1.5418 Å.) Constants of the unit cells appear in Table II.

TABLE II

CONSTANTS OF THE UNIT CELL

| Substance | $a_0$, Å. | $b_0$, Å. | $c_0$, Å. | $\beta$ |
|---|---|---|---|---|
| NaMy·$^1/_2$H$_2$O | 9.32 | 8.00 | 82.63 | 93$^3/_4$° |
| NaP·$^1/_2$H$_2$O | 9.23 | 8.01 | 92.94 | 94°[a] |
| NaSt·$^1/_2$H$_2$O | 9.23 | 8.02 | 103.13 | 93$^3/_4$° |
| NaAr·$^1/_2$H$_2$O | 9.21 | 8.03 | 113.45 | 93$^1/_2$° |

[a] This $\beta$ value was not redetermined, but was taken from values published by Buerger.[2]

## Discussion

The published values[2] for the cell constants of NaP·$^1/_2$H$_2$O and NaSt·$^1/_2$H$_2$O show an increase in $d_{001}$ between the two of 11.02 Å.[7] Since the unit

(1) The following abbreviations are used in this paper for organic radicals:

| Composition | Name | Abbreviation |
|---|---|---|
| $C_{12}H_{23}O_2$ | Laurate | L |
| $C_{14}H_{27}O_2$ | Myristate | My |
| $C_{16}H_{31}O_2$ | Palmitate | P |
| $C_{18}H_{35}O_2$ | Stearate | St |
| $C_{20}H_{39}O_2$ | Arachidate | Ar |

(2) Buerger, *Am. Mineral.*, **30**, 551 (1945).

(3) de Brettville and Ryer, *J. Phys. Chem.*, **48**, 154 (1944).

(4) M. Yasuda, *J. Biol. Chem.*, **94**, 404 (1931–1932).

(5) Francis and Piper, THIS JOURNAL, **61**, 577 (1939).

(6) Buerger, *Proc. Nat. Acad. Sci.*, **28**, 529 (1942).

(7) This value is obtained by using a later value of $c_0$ for NaSt (private communication from M. J. Buerger, $c_0$ = 102.7 kX).

cell is four molecules long in the $c$ direction, this means that an increase of 8 carbon atoms in the chain direction has caused an increase in $d_{001}$ of 11.02 Å. In order for a change of this magnitude to occur, a change of tilt of the order of 7.5° would have to occur between the two compounds. That this difference in tilt actually exists is not probable, since Buerger[2] has shown that the symmetry properties of the two compounds are the same.

Using the cell constants determined in this Laboratory the following increases in $d_{001}$ between the pairs of substances are noted:

| Compounds | $\Delta d_{001}$, Å. |
|---|---|
| NaMy–NaP | 10.26 |
| NaP–NaSt | 10.19 |
| NaSt–NaAr | 10.32 |

Using a least squares approximation on values for $d_{001}$ *vs.* number of carbon atoms in the chain, the most probable value for change in $d_{001}$ is found to be 10.25 Å.

The work of MacArthur[8] on the extension of the C<C link in normal long chain aliphatic compounds indicates that an addition of 8 carbon atoms to a compound of this type should give an increase in chain length of 10.16 Å. MacArthur also lists the data of a number of other workers in this field, and shows that the average of their results would lead to a value of 10.19 Å. (It is not apparent whether the figures published by MacArthur are in kX or Å. units. If the published figures are in kX units, the two results in Å. would then be 10.18 and 10.21, respectively.)

The results of this Laboratory also show a difference of 0.09 Å. between the $a_0$ value for NaMy and the corresponding $a_0$ values for NaP and NaSt. There is no apparent reason for the existence of a real difference in the values, and it is assumed that this difference arises from experimental error since the NaMy crystals obtained were poorly formed.

The agreement in $d_{001}$ increase between pairs of compounds in this series and the agreement with the figures for other normal long chain aliphatic compounds indicates that the long axes of the chains in these compounds are very nearly normal to (001) and that there is little or no difference in tilt in the several crystals. This conclusion is also corroborated by unpublished work in this Laboratory on the hydrazides of $n$-aliphatic acids. In the hydrazides it is found that an increase of 8 carbon atoms in the chain direction leads to an increase in $d_{001}$ of 10.19 Å.

(8) MacArthur, *Proc. Leeds Phil. Lit. Soc., Sci. Sect.*, **4**, pt. 3, 170 (1944).

## Summary

1. The unit cell constants of the hemihydrates of NaMy and NaAr have been determined, and the values for NaP and NaSt redetermined.

2. The increase in $d_{001}$ with increase in chain length has been found to be 1.281 Å. per carbon atom, indicating that the chains are very nearly normal to (001).

RECEIVED AUGUST 10, 1948

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

# The Electrophoretic Properties of Plakalbumin

BY GERTRUDE E. PERLMANN

## Introduction

In a recent note, Linderstrøm-Lang and Ottesen[1] showed that ovalbumin is transformed, by the action of an enzyme from *Bacillus subtilis*, into a protein that crystallizes as rectangular plates from ammonium sulfate. They named this protein plakalbumin.[2] Since the transformation of ovalbumin to plakalbumin, A→P, occurs without serious degradation of the protein,[1] it seemed of interest to compare the electrophoretic behavior of the two materials. Consequently, the preliminary experiments[2] that indicated that plakalbumin differed electrophoretically from its parent substance, ovalbumin, have been extended and the new results are reported below.

## Experimental

Plakalbumin was obtained by incubating a 6% solution of thrice recrystallized ovalbumin[4] in 0.02 ionic strength phosphate buffer at *p*H 6.8 with an enzyme preparation from *B. subtilis*, kindly supplied by Linderstrøm-Lang. After incubation for six hours at 30°, the solution was acidified with hydrochloric acid to *p*H 5.4 and the protein crystallized as rectangular plates by the addition of saturated ammonium sulfate solution.[1]

The electrophoretic experiments were carried out at 0.5° in the apparatus described by Longsworth.[5,6] Unless noted otherwise below, a protein concentration of 1% was used in the experiments and prior to electrophoresis the protein solutions were dialyzed for two to three days against liberal portions of an appropriate buffer. The mobilities were computed from the descending patterns and refer to 0°.

(1) Linderstrøm-Lang and Ottesen, *Nature*, **159**, 807 (1947).

(2) Eeg-Larsen, Linderstrøm-Lang and Ottesen, *Arch. Biochem.*, **19** 340 (1948).

(3) Perlmann, *Nature*, **161**, 720 (1948).

(4) Sørensen and Høyrup, *Compt. rend. Lab. Carlsberg*, **12**, 12 (1917).

(5) Longsworth, *Chem. Reviews*, **30**, 323 (1942).

(6) Longsworth, *Ind. Eng. Chem., Anal. Ed.*, **18**, 219 (1946).

## Results

In Fig. 1 are superimposed the tracings of the patterns obtained after electrophoresis of ovalbumin and plakalbumin in a 0.1 ionic strength phosphate buffer at *p*H 6.8 at a potential gradient of 6 volts per cm. for 9900 seconds. Under these conditions superposition of the patterns permits not only a direct comparison of the relative concentrations of the components but also of their approximate mobilities. It is thus clear from Fig. 1 that although the patterns are similar in appearance the plakalbumin has a lower mobility, $u$, than its parent substance ovalbumin. The actual values are $-5.9 \times 10^{-5}$ and $-5.5 \times 10^{-5}$ cm.$^2$ sec.$^{-1}$ volt$^{-1}$ for the main components, $A_1$ and $P_1$, of ovalbumin and plakalbumin, respectively, and $-4.8 \times 10^{-5}$ and $-4.3 \times 10^{-5}$ for the components $A_2$ and $P_2$. Plakalbumin from a sample of ovalbumin incubated for twenty-four hours gave the same results. Furthermore, as is the case with ovalbumin[7] at *p*H values below 4.0, plakalbumin also migrates over a distance of at least 7.0 cm. in the channel of the electrophoresis cell without resolution of the boundary into more than one peak.

In the preliminary work on plakalbumin it was observed that the relative concentration of the components, $P_1$ and $P_2$, but not their mobilities, changed on repeated crystallization of the freshly prepared protein. However, if the time between successive crystallizations is kept at a minimum and if the plakalbumin is stored as a paste under saturated ammonium sulfate, no significant alteration occurs. On the other hand, prolonged dialysis, or storage of plakalbumin in solution, causes marked changes. Thus, in a solution stored at 3° for ten days, the amount of the slowly moving component, $P_2$, had increased from 16 to 44% at the expense of the faster one, $P_1$. This result may be considered in connection with the observation of the Danish workers that in plakalbumin solutions at *p*H values above 5, even after repeated recrystallizations and dialysis, a slow liberation of non-protein nitrogen occurs.[2]

**Mobilities of Ovalbumin and Plakalbumin at Different *p*H Values.**—Much of this work has been directed toward the determination of the mobilities of the two proteins at various *p*H values. The results of these measurements are presented in Table I, in which the nature and composition of the buffers is listed in the first column while the *p*H of the protein solution in equilibrium therewith is given in column 2. The mobilities listed in this table refer in each case to the fast moving component of the proteins, except for those at *p*H values below 4.0 where the proteins migrate as a single peak. In these cases the mobilities are mean mobilities. A comparison of the figures for plakalbumin, column 3, with those for ovalbumin, column 4, shows that the mobilities of the two proteins at any given *p*H below about 7.0 differ by 0.5 to 0.6 $\times 10^{-5}$, column 5. At *p*H values above *p*H 7.8 the two proteins migrate with the same velocity.

(7) Longsworth, Cannan and MacInnes, THIS JOURNAL, **62**, 2580 (1940).

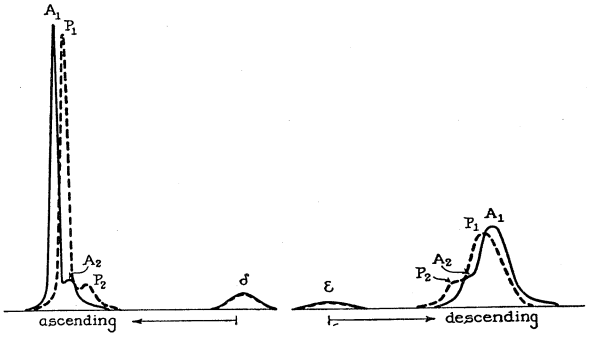



Fig. 1.—Superimposed tracings of electrophoretic patterns of a 1% solution of ovalbumin, —, and plakalbumin, - - -, after electrophoresis in sodium phosphate buffer at *p*H 6.8 and 0.1 ionic strength for 9900 seconds at 6 volts per cm.

TABLE I

MOBILITIES OF PLAKALBUMIN AND OVALBUMIN IN BUFFER SOLUTIONS OF IONIC STRENGTH 0.1

Ac = acetate; Cac = cacodylate; V = diethyl barbiturate

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| | | $u \times 10^5$ | | |
| Buffer | *p*H, 25° | Plakalbumin | Ovalbumin | $\Delta u$ |
| 0.1 *N* HCl—0.5 *N* glycine | 3.10 | 6.54 | 5.95 | 0.59 |
| .1 *N* NaAc—0.5 *N* HAc | 3.91 | 3.25 | 2.71 | .54 |
| .1 *N* NaAc—0.14 *N* HAc | 4.50 | 1.06 | | |
| .1 *N* NaAc—0.1 *N* HAc | 4.64 | 0.29 | −0.25 | .54 |
| .1 *N* NaAc—0.06 *N* HAc | 4.89 | −0.74 | | |
| .1 *N* NaAc—0.01 *N* HAc | 5.65 | −2.91 | −3.50 | .59 |
| .02 *N* NaCac—0.004 *N* HCac —0.08 *N* NaCl | 6.79 | −4.50 | −5.16 | .66 |
| .02 *N* NaV—0.02 *N* HV —0.08 *N* NaCl | 7.82 | −5.62 | −5.65 | |
| .1 *N* NaV—0.02 *N* HV | 8.60 | −5.84 | −5.78 | |
| .1 *N* NaV—0.005 *N* HV | 9.10 | −5.93 | −5.92 | |

**The Behavior of Mixtures of Plakalbumin and Ovalbumin.**—Although the mobility differences below *p*H 7.0 are sufficient to lead one to expect resolution of the ovalbumin and plakalbumin on mixing, attempts in a 0.1 ionic strength phosphate buffer at *p*H 6.8 and in an 0.1 ionic strength hydrochloric acid–glycine buffer at *p*H 3.0 failed. The resulting patterns for the mixture were identical in appearance with those of either protein except that the boundary displacement corresponded to mobility values intermediate between those of the components of the mixture. Resolution is obtained, however, at a *p*H of 4.64, *i.e.*, between their isoelectric *p*H values. This is shown in Fig. 2 where the full line represents the patterns obtained after electrophoresis of a 1.2% solution of a mixture of 33% ovalbumin and 67% plakalbumin at a potential gradient of 6 volts per cm. for 28,800 seconds. The dashed and dotted curves superimposed upon this pattern are those of ovalbumin and plakalbumin, re-

spectively, obtained in separate experiments under identical conditions.

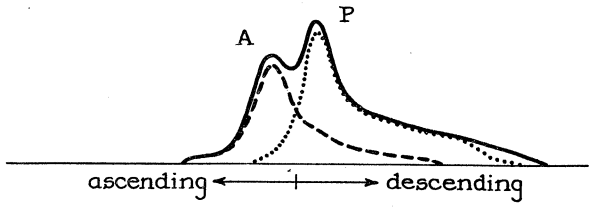



Fig. 2.—Superimposed tracings of electrophoretic patterns of a 1.2% mixture of 33% ovalbumin and 67% plakalbumin —, of a 0.4% solution of ovalbumin - - -, and of a 0.8% solution of plakalbumin . . . . , in 0.1 *N* sodium acetate buffer at *p*H 4.64 at 6 volts per cm. for 28800 seconds.

**Dependence of the Isoelectric *p*H of Plakalbumin upon Ionic Strength in Acetate Buffers.**—As is shown by the data of Table II the isoelectric *p*H of plakalbumin, designated here as *p*I, shifts to higher values at low ionic strength in acetate buffers. The *p*I values at each ionic strength, column 4, were obtained by linear interpolation of the *p*H mobility values listed in the two preceding columns of this table. Owing to the complexity of the electrophoretic patterns of plakalbumin at *p*H values just below the isoelectric *p*H, the first moment of the entire gradient curve of the descending pattern is used for the computation of the mean mobility, reported in Table II.

TABLE II

DEPENDENCE OF THE ISOELECTRIC *p*H ON IONIC STRENGTH

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| | | | *p*I | | |
| $\mu$ | *p*H[a] | $u_p \times 10^5$ | Plakalbumin | Ovalbumin | $\Delta pI$ |
| 0.1 | 4.50 | 1.06 | | | |
| | 4.67 | 0.29 | 4.72 | 4.58 | 0.14 |
| | 4.90 | −0.74 | | | |
| .05 | 4.68 | 0.82 | 4.77 | 4.63 | .14 |
| | 4.88 | −0.75 | | | |
| .02 | 4.73 | 0.7 | 4.82 | 4.68 | .14 |
| | 4.96 | −1.54 | | | |
| .01 | 4.68 | 1.95 | 4.86 | 4.71 | .15 |
| | 4.96 | −1.06 | | | |

[a] *p*H values refer to 0° by applying a correction of 0.02$_5$ to the values measured at 25°.[8]

For comparison, the *p*I values of ovalbumin obtained by Tiselius and Svensson[8] are listed in column 5 of Table II. Except for a constant difference of 0.14 *p*H unit, it is apparent that the isoelectric *p*H of plakalbumin changes with the buffer salt concentration in the same manner as does that of ovalbumin.

The response of plakalbumin to the partial substitution of chloride for acetate in these buffers is also similar to that of ovalbumin; thus if 80% of the acetate ion in a 0.1 *N* buffer is replaced by chloride ion, the isoelectric *p*H of plakalbumin is reduced to 4.58, whereas that of ovalbumin to 4.44, a difference of 0.14 *p*H unit as in the case of the pure acetate buffers, Table II. This displacement of the isoelectric *p*H on substitution of chloride for acetate toward a more acid reaction is comparable with that observed in the case of other proteins.[9]

(8) Tiselius and Svensson, *Trans. Faraday Soc.*, **36**, 16 (1940).

## Discussion

Since there is considerable evidence for a constant proportionality between mobility and the net charge of the protein ion[10,11] it is of interest to compare the change in mobility $\Delta u$, accompanying the A→P transformation, with other properties of these two proteins. Of the many explanations for this change that might be advanced the following is a reasonable one at the present time. It is based, in part, on the observation of Eeg-Larsen, Linderstrøm-Lang and Ottesen[2] that the fragments that are lost by the ovalbumin in the A→P process contain a glutamic and possibly an aspartic acid residue in addition to other amino acid residues that would not have ionizing groups when linked, in the $\alpha$-position, with peptide bonds in the intact protein molecule. In the following discussion the number of ionizing groups that are lost in the A→P process will simply be designated as $a$. If, therefore, ovalbumin can be idealized as peptide chain, $(HOOC)_mR(NH_2)_n$ with $m$ carboxyl groups that dissociate in the region from *p*H 2.0 to 6.5 and $n$ amino groups that dissociate above *p*H 8.5, plakalbumin would be $(HOOC)_{m-a}R'(NH_2)_n$. In strongly acid solution the ovalbumin ion would be $(HOOC)_mR(NH_3^+)_n$ with a net charge, $z$, of $+n$. Under these conditions plakalbumin should have the same net charge as ovalbumin and if the friction coefficients of the two molecules were the same the mobilities should be identical at a given low *p*H. A neutral reaction the ovalbumin ion would be $(^-OOC)_mR(NH_3^+)_n$ with a net charge of $n = m$ and since the mobility is negative at this *p*H one can conclude that $m > n$. Under these conditions the net charge of plakalbumin would be $n - m + a$ and a curve of $z$ against *p*H, as abscissas, for this protein should be above that of ovalbumin except in acid solutions where the two curves approach the common limiting value of $z = n$. If the $a$ carboxyl groups removed in the A→P reaction are strong ones they will lose their protons at *p*H values below the isoelectric zone and ovalbumin will thus have an isoelectric *p*H below that of plakalbumin in which these groups are missing. The experimental observation, Table II, that this is the case thus supports the view that the carboxyl groups that are involved in the A→P transformation are relatively strong ones.

However, the mobility values of plakalbumin

(9) Longsworth and Jacobsen, *J. Phys. and Coll. Chem.*, **53**, 126 (1949)

(10) Abramson, *J. Gen. Physiol.*, **15**, 575 (1931–1932).

(11) Longsworth, *Ann. N. Y. Acad. Sci.*, **41**, 267 (1941).

approach those of ovalbumin at neutrality instead of at acid reactions as the idealized case described above would require. This suggests that the friction coefficients, $f$, of the two proteins are not identical but that for plakalbumin, $f_P$ is enough lower than that for ovalbumin, $f_A$, to compensate for the smaller net negative charge at neutrality. At acid reactions where the net charge of both proteins approaches the common value, $n$, the smaller value of $f_P$, as compared with $f_A$, would lead to the higher mobilities for plakalbumin that are observed.

If at any given $p$H, the values of $u_A$ and $u_P$ refer to the same buffer solvent, the friction coefficients may be defined so that $u_A = z_A/f_A$ and $u_P = z_P/f_P$, where the ratio, $f_A/f_P$, should be independent of the $p$H, the ionic strength and the nature of the buffer ions. At the isoelectric $p$H of plakalbumin, $u_P = z_P = 0$ and since the valence of ovalbumin at this $p$H, *i.e.*, 4.72, is assumed to differ from that of plakalbumin only by the $a$ ionized carboxyl groups that are present in the one protein but missing from the other, $z_A = -a$, and the mobility of ovalbumin, $u_A = -0.6 \times 10^{-5} = a/f_A$ may then be used to estimate the value of $a$. Here $1/f_A$ may be taken as the slope, $3.0 \times 10^{-6}$, of the line that is obtained by plotting[9] as shown in Fig. 3, the mobilities of ovalbumin against the equivalents, $h$, of acid in alkali bound per mole of protein at an ionic strength 0.1 and at the given $p$H.[12] Hence $a = 2$, is in agreement with the result by Eeg-Larsen, Linderstrøm-Lang and Ottesen.[2] In view, however, of the arbitrary nature of the assumptions that have been made in the use of the mobility data for the evaluation of $a$, this agreement should not necessarily be interpreted as confirmation of the chemical analysis. Probably the most that should be said is that the electrophoretic results are not inconsistent with the analytical ones.

In experiments described elsewhere,[3] the author has also observed that plakalbumin differs electrophoretically from the ovalbumin modification reported by MacPherson, Moore and Longsworth.[13] Unpublished results further indicate that their modification is also a product of an enzymatic reaction. It, therefore, appears possible to transform, without serious degradation, a protein like ovalbumin into several other well-defined proteins which differ from each other in at least one property, namely, in their behavior in the electric field.

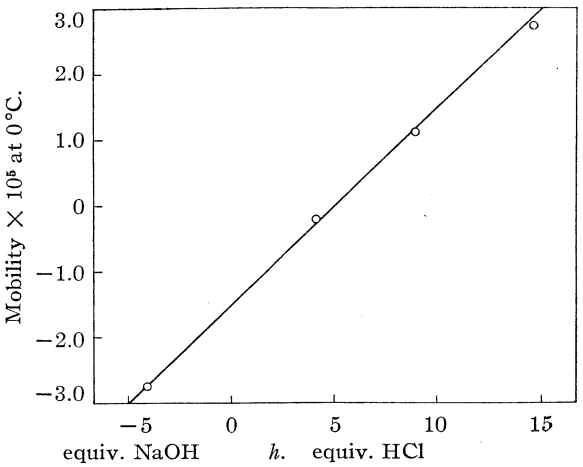



Fig. 3.—Plot for the evaluation of the proportionality factor between mobility and titration increment for ovalbumin.

**Acknowledgment.**—The author is much indebted to Dr. L. G. Longsworth of these Laboratories for suggestions as to the interpretation of the experimental results and also to him and to Dr. D. A. MacInnes for criticism of the manuscript. My thanks go also to Professor K. Linderstrøm-Lang of the Carlsberg Laboratory, Copenhagen, for his constant stimulating interest in this research.

## Summary

The electrophoretic behavior of plakalbumin, a protein derived from ovalbumin by the action of an enzyme from *B. subtilis*, has been compared with that of the parent substance. At $p$H values below about 7.0, the mobilities differ by 0.5 to $0.6 \times 10^{-5}$ whereas at more alkaline reactions plakalbumin and ovalbumin are indistinguishable electrophoretically. The isoelectric $p$H of plakalbumin at all ionic strengths investigated is 0.14 $p$H unit above that of ovalbumin.

NEW YORK, N. Y. RECEIVED DECEMBER 2, 1948

(12) Cannan, Kibrick and Palmer, *Ann. N. Y. Acad. Sci.*, **41**, 243 (1941).

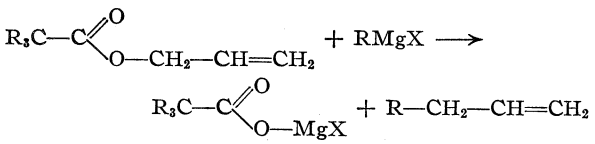
(13) MacPherson, Moore and Longsworth, *J. Biol. Chem.*, **156**, 381 (1944).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

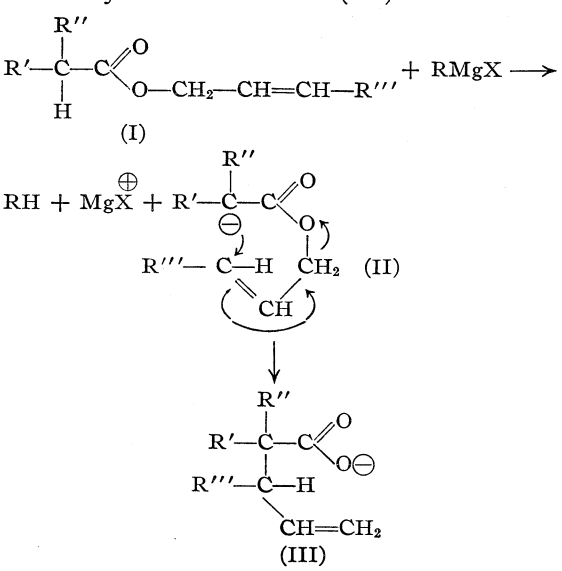
# A New Rearrangement of Allylic Esters

BY RICHARD T. ARNOLD AND SCOTT SEARLES, JR.[1,2]

In an earlier study[3,4,5,6] it was demonstrated that allylic esters of hindered, tertiary carboxylic acids react with the Grignard reagent to give olefins and halomagnesium salts according to the following equation.

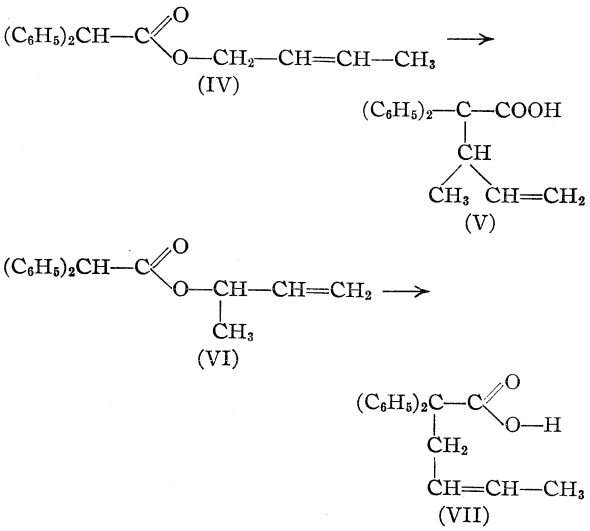


In the event that the allylic ester (I) contains at least one alpha hydrogen atom, the Grignard anion ($R^-$) can act as a base and bring about formation of the anion (II). An intramolecular rearrangement can then occur to produce a thermodynamically more stable anion (III).

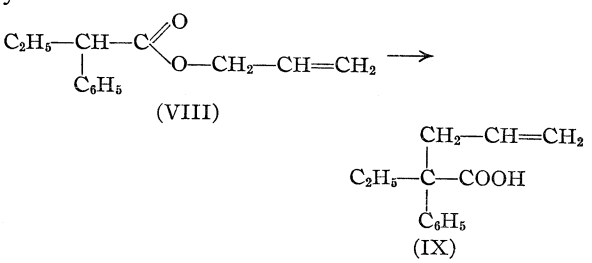


Several examples of this new intramolecular rearrangement have now been observed.[7]

In support of a mechanism involving the transient ring intermediate (II), it has been demonstrated that the allylic system undergoes an alpha-gamma shift during the course of this reaction. Thus, *n*-crotyl diphenylacetate (IV) yields 2,2-diphenyl-3-methylpenten-4-oic acid (V) and isocrotyl diphenylacetate (VI) is transformed into 2,2-diphenylhexen-4-oic acid (VII).



A wide variety of basic reagents (RMgX, NaH, and $R_2N$-MgX) have been employed with varying degrees of success. When R′ and R″ (in I) are aromatic, very satisfactory yields were obtained by the use of Grignard reagents or pulverized sodium hydride. To date, poor results have been observed when R′ = alkyl and R″ = aryl. However, by employing a base of the type $R_2N$-MgX, allyl α-phenylbutyrate (VIII) was converted into 2-ethyl-2-phenylpenten-4-oic acid (IX) in low yields.



**Acknowledgment.**—The authors wish to thank Dr. Ralph Manley and Mr. Jay S. Buckley, Jr., of the General Mills Laboratories for technical aid in connection with certain details of the experimental section. One of us (Scott Searles, Jr.) acknowledges with thanks a du Pont Fellowship for 1946–1947.

## Experimental

**Allyl Diphenylacetate.**—A solution containing allyl alcohol (10 g.) and dry pyridine (15 g.) was added dropwise into a solution of diphenylacetyl chloride (35 g., prepared by means of thionyl chloride on the acid) and chloroform (30 ml.) at 30–50°. After standing several hours at room temperature, the solution was washed with dilute alkali and with water and the chloroform layer was then dried with sodium sulfate. Direct distillation gave allyl diphenylacetate; b. p. 161–162° (3 mm.); yield 28.6 g.

(1) Most of the work reported here has been taken from the Ph.D. thesis of Scott Searles, Jr., University of Minnesota, July, 1947.

(2) Present address, Department of Chemistry, University of Illinois.

(3) Arnold, Bank and Liggett, THIS JOURNAL, **63**, 3444 (1941).

(4) Arnold and Liggett, *ibid.*, **64**, 2875 (1942).

(5) Arnold and Liggett, *ibid.*, **67**, 337 (1945).

(6) Unpublished results by Scott Searles, Jr.

(7) A patent application covering this reaction was filed at the United States Patent Office on December 31, 1947.

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.82; H, 6.15.

**2,2-Diphenylpenten-4-oic Acid.**—(a) A Grignard solution prepared from bromomesitylene (25 g.), magnesium (3.1 g.) and ether (75 ml.) was allowed to react for fifteen hours at 25–35° with a solution composed of allyl diphenylacetate (25 g.) and anhydrous ether (25 ml.). After decomposition of the reaction mixture with slightly acidified ammonium chloride solution, the ether layer was extracted thoroughly with sodium hydroxide solution (5%). Distillation of the ether layer gave mesitylene (9.5 g., 63%) and unchanged allyl diphenylacetate (5.4 g.).

Acidification of the aqueous layer gave 2,2-diphenylpenten-4-oic acid (11.9 g.); m. p. 141.5–141.9°.[8]

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; neut. equiv., 252.3. Found: C, 80.73; H, 6.57; neut. equiv. 252.9.

(b) Allyl diphenylacetate (149 g.) was allowed to react with sodium hydride (18 g.) in boiling toluene in a nitrogen atmosphere for about twenty hours. The cooled mixture was poured into water and the whole shaken vigorously. From the toluene layer there was obtained, by distillation, unused allyl diphenylacetate (56 g.).

Acidification of the alkaline layer gave 2,2-diphenylpenten-4-oic acid which after recrystallization weighed 83.5 g. (56%) and melted at 142–142.5°.

**β-Methylallyl Diphenylacetate.**—Diphenylacetyl chloride (prepared by the action of thionyl chloride on diphenylacetic acid (159 g.)) was dissolved in chloroform (300 ml.). To this was added, at 0–10°, β-methylallyl alcohol (54 g.) dissolved in pyridine (59.5 g.). The solution stood overnight at room temperature and was worked up as described above for the allyl ester. Distillation of the chloroform layer gave the required ester; yield 163 g.; b. p. 153° (1.3 mm.).

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.11; H, 6.82.

**2,2-Diphenyl-4-methylpenten-4-oic Acid.**—β-Methylallyl diphenylacetate (163 g.) was allowed to react with pulverized sodium hydride (24 g.) in boiling toluene (1100 ml.) for twenty-two hours. The cooled mixture was decomposed with water and the aqueous alkaline layer was acidified. Recrystallization of the solid so formed gave pure 2,2-diphenyl-4-methylpenten-4-oic acid; yield 121.5 g. (76%); m. p. 120.5–121.5°.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.99; H, 6.81.

**Isocrotyl Diphenylacetate.**—This ester was prepared by the above described method from methylvinylcarbinol (6 g.), pyridine (7 g.) and diphenylacetyl chloride (15.3 g.) in carbon tetrachloride (30 ml.) as solvent. When the reaction was complete, the mixture was poured into cold water and the organic layer was extracted with sodium hydroxide (5%). Removal of the solvent gave a solid residue which when crystallized from petroleum ether melted at 57–58°; yield 16.4 g. (93%).

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.19; H, 6.81. Found: C, 81.30; H, 7.11.

**2,2-Diphenylhexen-4-oic Acid.**—A solution of mesitylmagnesium bromide was prepared from bromomesitylene (10.75 g.), magnesium (1.3 g.) and ether (50 ml.). To this was added isocrotyl diphenylacetate (11.5 g.) dissolved in ether (50 ml.). A slightly exothermic reaction ensued and after refluxing for thirty minutes, the solution remained at room temperature for forty hours. Decomposition with ammonium chloride solution was followed by extraction of the ether layer with sodium hydroxide (5%). Distillation of the ether solution gave mesitylene (4.6 g., 88.4%) and unused isocrotyl diphenylacetate (0.9 g.).

Upon acidification, the alkaline layer gave 2,2-diphenylhexen-4-oic acid (8.5 g., 74%); m. p. 122.2–122.6°. A mixed melting point determination with diphenylacetic acid gave 108–111°.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.19; H, 6.81; neut. equiv., 266.3. Found: C, 81.47; H, 6.88; neut. equiv., 266.6.

Ozonization of the above unsaturated acid gave acetaldehyde identified as its dimedon derivative.

***n*-Crotyl Diphenylacetate.**—This compound was prepared from *n*-crotyl alcohol (13 g.), pyridine (14.5 g.), diphenylacetyl chloride (34.7 g.) and chloroform (50 ml.) at 0°. The ester boiled at 155–162° (0.1 mm.); yield 22.6 g. (56.5%).

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.19; H, 6.81. Found: C, 80.84; H, 7.10.

**2,2-Diphenyl-3-methylpenten-4-oic Acid.**—This ester (12.5 g.) was treated with a solution of mesitylmagnesium bromide prepared from bromomesitylene (12.0 g.), magnesium (1.5 g.) and ether (75 ml.).

The mixture was refluxed for twelve hours and then allowed to stand at room temperature overnight. Decomposition with ammonium chloride solution gave an ether layer which was extracted with sodium hydroxide solution. From the ether layer, mesitylene (5 g.) was obtained by careful fractionation. Acidification of the alkaline aqueous layer gave a solid acid which was recrystallized from aqueous alcohol; yield 8.2 g. (65.5%); m. p. 138–138.5°.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.19; H, 6.81; neut. equiv., 266.3. Found: C, 81.34; H, 7.10; neut. equiv., 266.5.

Ozonization of the above acid gave formaldehyde which was isolated as its dimedon derivative; yield 52.3%; m. p. 187–188°.

**2-Ethyl-2-phenylpenten-4-oic Acid.**—An ethereal solution of ethylmagnesium bromide (114 ml. of 1.76 *N*) was treated with diethylamine (14.6 ml.). To this was added allyl α-phenylbutyrate (40.8 g.). Heat was evolved and the solution was stirred for three days at room temperature before decomposition with dilute ammonium chloride.

Bicarbonate extraction of the ether layer followed by acidification gave a carboxylic acid which after recrystallization from aqueous methanol gave 2-ethyl-2-phenylpenten-4-oic acid; yield 3.1 g. (7.8%); m. p. 78.5–80°.

*Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90; neut. equiv., 204.3. Found: C, 76.81; H, 7.99; neut. equiv., 204.8.

## Summary

1. It has been shown that allylic esters having at least one aryl group and one hydrogen atom attached to the alpha carbon atom undero intramolecular rearrangement in the presence of many strong basic reagents to give α-allylic substituted acids.

2. The allylic group undergoes an alpha–gamma shift during the course of the reaction.

(8) Ramart, *Compt. rend.*, **178**, 396 (1924).

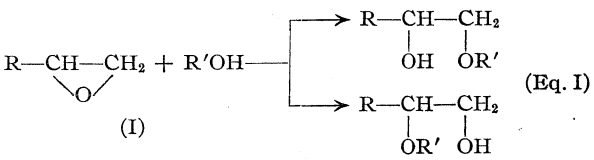
MINNEAPOLIS, MINNESOTA RECEIVED JULY 6, 1948

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

# Chemistry of Epoxy Compounds. VIII.[2] Reaction of Allyl Alcohol with Unsymmetrical Oxirane Compounds. An Electronic Interpretation[2a]

BY DANIEL SWERN, GERALDINE N. BILLEN AND H. B. KNIGHT

When an unsymmetrical oxirane compound (I) reacts with an alcohol (equation I), two isomeric hydroxy ethers can form, depending on which carbon–oxygen bond of the oxirane group is cleaved. The literature on such reactions is voluminous, yet only two cases[3,4] have come to our




(Eq. I)

attention in which the reaction mixture has been carefully fractionated and the structure of the resulting products established. Furthermore, the effects of acidic or alkaline catalysts, and the electronic effect of substituent groups, on the direction of ring opening have been explored only to a limited extent,[3,4,5a,6,7] and in the case of extremely reactive oxirane compounds, notably 3,4-epoxy-1-butene, reaction conditions producing high yields (above 75%) of hydroxy ethers have not been reported, the usual yield being 20 to 68%.[4,5a,8] We have studied the reaction of allyl alcohol with propylene oxide, glycidol, epichlorohydrin, 3,4-epoxy-1-butene and styrene oxide [R-(I) = $CH_3$–, HO–$CH_2$–, Cl–$CH_2$–$CH_2$=CH–, and $C_6H_5$–] in the presence of acidic and alkaline catalysts, and the results of these experiments are described in this paper (Table I). A literature survey on ring opening reactions of this type (equation I) revealed no publications reporting the use of allyl alcohol. After our work was almost complete, however, the preparation of 2-alloxy-1-phenylethanol in 31% yield by the phosphoric acid-catalyzed reaction of allyl alcohol with styrene oxide was reported,[9] although proof of structure was not given.

The procedure which we followed in studying this reaction (equation I) consisted of four steps: (a) Determination of reaction conditions which gave high yields of hydroxy ethers in the presence of alkaline and acidic catalysts (alkaline catalysts could not be employed with epichlorohydrin). The yield was usually determined by distillation of the neutralized reaction mixture through a low hold-up fractionating column of the Vigreux type, which was capable of cleanly separating unreacted allyl alcohol from hydroxy ether and also of separating the latter from di- and polyethers. (b) Redistillation of the hydroxy ether fraction through a low hold-up, highly efficient fractionating column (more than one hundred theoretical plates) in an attempt to separate isomeric hydroxy ethers which might have formed; (c) determination of the identity and purity of the products by well-known means (iodine absorption, per cent. hydroxyl, carbon analysis, etc.); (d) determination of the position of the hydroxyl group, introduced as a result of the ring opening reaction, by one or more chemical diagnostic tests. For example, by oxidation with periodic acid,[10] the α-glycol group was determined in the reaction prod-

TABLE I

CHARACTERISTICS OF HYDROXY ETHERS OBTAINED BY THE REACTION OF ALLYL ALCOHOL WITH UNSYMMETRICAL OXIRANE COMPOUNDS

| Hydroxy ether | B. p. °C. | B. p. Mm. | Carbon, %[a] Calcd. | Carbon, %[a] Found | Hydroxyl, %[b] Calcd. | Hydroxyl, %[b] Found | Iodine No.[c] Calcd. | Iodine No.[c] Found | $n^{30}D$ (Abbe) | $d^{30}_4$ | Molecular refraction Calcd. | Molecular refraction Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1-Alloxy-2-propanol (II) | 71–71.5 | 31 | 62.0 | 61.9 | 14.6 | 14.2 | 218 | 215 | 1.4258 | 0.9112 | 32.61 | 32.65 |
| 2-Alloxy-1-propanol (III) | 77–78 | 30 | 62.0 | 61.8 | 14.6 | 14.4 | 218 | 216 | 1.4298 | 0.9215 | 32.61 | 32.55 |
| 1-Alloxy-3-chloro-2-propanol (IV) | 107–108 | 31 | 47.8 | 47.7 | 11.3 | 11.0 | 168 | 167 | 1.4582 | 1.102 | 37.48 | 37.32 |
| 1-Alloxy-2,3-propanediol (VI) + 2-Alloxy-1,3-propanediol (VII)[d] | 107–109 | 4.3–4.5 | 54.5 | 54.5–54.7 | 25.7 | 24.9–25.2 | 192 | 189 | 1.4583–1.4589 | 1.061 | 34.13 | 34.01–34.05 |
| 2-Alloxy-2-phenylethanol (VIII) | 118–119 | 4.5 | 74.1 | 74.0 | 9.54 | 9.80 | 142 | 142 | 1.5167 | 1.031 | 52.10 | 52.27 |
| 2-Alloxy-1-phenylethanol (IX) | 114–114.5 | 4.6–4.8 | 74.1 | 73.6 | 9.54 | 9.67 | 142 | 142 | 1.5159 | 1.030 | 52.10 | 52.25 |
| 3-Alloxy-4-hydroxy-1-butene (X) | 86–87 | 30–31 | 65.6 | 65.5 | 13.3 | 13.0 | 396 | 393 | 1.4450 | 0.9297 | 36.76 | 36.72 |

[a] Wet combustion method of Van Slyke and Folch [*J. Biol. Chem.*, **136**, 509 (1940)]. [b] Method of Ogg, Porter and Willits [*Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945)]. [c] One-hour Wijs method. [d] 70:30 mixture.

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) For paper VII, see THIS JOURNAL, **70**, 1235 (1948).

(2a) This paper was presented at the 114th meeting of the American Chemical Society held in Washington, D. C., August 30–September 3, 1948. Article not copyrighted.

(3) Chitwood and Freure, THIS JOURNAL, **68**, 680 (1946).

(4) Bartlett and Ross, *ibid.*, **70**, 926 (1948).

(5) (a) Kadesch, *ibid.*, **68**, 41 (1946); (b) Bissinger, *et al.*, *ibid.*, **69**, 2955 (1947).

(6) Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 1038 (1944).

(7) Petrov, *ibid.*, **16**, 1206 (1946).

(8) Petrov, *Acta Univ. Voronegiensis*, **8**, No. 2, 71 (1935); *J. Gen. Chem.* (*U.S.S.R.*), **8**, 131 (1938).

(9) Newman, Magerlein and Wheatley, THIS JOURNAL, **68**, 2112 (1946).

(10) Pohle, Mehlenbacher and Cook, *Oil and Soap*, **22**, 115 (1945).

ucts of allyl alcohol with glycidol. The degree of reaction of benzoyl chloride with the hydroxy ethers obtained from allyl alcohol and epichlorohydrin, styrene oxide and 3,4-epoxy-1-butene was determined under controlled conditions,[5a,11] and the values so obtained were compared with those for related primary and secondary alcohols of known structure. In addition, with the exception of the reaction products of allyl alcohol with epichlorohydrin and glycidol, the time required to dissolve 0.05 g. of metallic sodium in a large molar excess of hydroxy ether was determined. When isomers could be cleanly separated by distillation, the last two tests permitted unequivocal identification of the primary and secondary alcohol (secondary and primary ether, respectively) since the degree of reaction with benzoyl chloride was significantly higher and the time required to dissolve the sodium was significantly lower in the case of the primary alcohol (secondary ether) (Tables II and III). Furthermore, in every instance in which we were able to separate the isomers, and in the few cases reported in the literature, the primary alcohol (secondary ether) had a higher boiling point, density and index of refraction than the secondary alcohol (primary ether).

TABLE II

SOLUTION TIME OF SODIUM[a] IN VARIOUS HYDROXY COMPOUNDS

| Compound | OH | Max. temp. attained during reaction, °C. | Sol. time, minutes |
|---|---|---|---|
| 1-Alloxy-2-propanol (II) | Sec. | 35 | 69 |
| 2-Alloxy-1-propanol (III) | Prim. | 39 | 38 |
| 2-Alloxy-2-phenylethanol (VII) | Prim. | 25 | 240 |
| 2-Alloxy-1-phenylethanol (IX) | Sec. | 25 | >450 |
| 3-Alloxy-4-hydroxy-1-butene (X) | Prim. | 33–38 | 14 to 20 |
| 1-Propanol | Prim. | 56 | 4 |
| 2-Propanol | Sec. | 25 | >480 |
| 2-Propen-1-ol (allyl alcohol) | Prim. | 62 | 1 |
| *n*-Butanol | Prim. | 30 | 11 |
| 2-Buten-1-ol (crotyl alcohol) | Prim. | 46 | 2.3 |
| 2-Methyl-2-propen-1-ol (methallyl alcohol) | Prim. | 49 | 1.6 |
| 3-Buten-2-ol (methyl vinyl carbinol) | Sec. | 25 | 35 |

[a] 0.05 g. (0.00217 mole) of sodium added to 0.0434 mole of hydroxy compound.

TABLE III

DEGREE OF REACTION OF BENZOYL CHLORIDE WITH VARIOUS HYDROXY COMPOUNDS[5a,11]

| Compound | OH | Degree of reaction (expressed as %) |
|---|---|---|
| 1-Alloxy-3-chloro-2-propanol (IV) | Sec. | 11 |
| 2-Alloxy-2-phenylethanol (VIII) | Prim. | 91 |
| 2-Alloxy-1-phenylethanol (IX) | Sec. | 19 |
| 3-Alloxy-4-hydroxy-1-butene (X) | Prim. | 85–94 |
| X + 4-Alloxy-3-hydroxy-1-butene (XI) | [a] | 64–75 |
| 3-Methoxy-4-hydroxy-1-butene[5a] | Prim. | 61–78 |
| 4-Methoxy-3-hydroxy-1-butene[5a] | Sec. | 8–22 |
| 2-Buten-1-ol (crotyl alcohol) | Prim. | 97 |
| 3-Buten-2-ol (methylvinylcarbinol) | Sec. | 17 |

[a] Primary and Secondary. Prepared by the acid-catalyzed reaction of allyl alcohol with 3,4-epoxy-1-butene.

(11) Norris and Haines, THIS JOURNAL, **57**, 1425 (1935).

## Experimental[11a]

**Materials.**—Allyl alcohol, propylene oxide, 3,4-epoxy-1-butene, epichlorohydrin and styrene oxide were the purest commercial products obtainable, and they were distilled (styrene oxide under vacuum) through efficient fractionating columns immediately before use. Glycidol was prepared by the dehydrohalogenation of freshly distilled glycerol α-monochlorohydrin in isopropyl alcohol, substantially as reported by Marple and Evans.[12] A twice-distilled product, b. p. 40° at 2.5 mm., and $n^{25}D$ 1.4292, was employed in the reactions. Oxirane oxygen,[13] calcd., 21.6; found, 21.2.

**Propylene Oxide and Allyl Alcohol. (a) Preparation of 1-Alloxy-2-propanol (II).**—To a stirred solution of 3.2 g. of freshly cut sodium in 290 g. (5 moles) of allyl alcohol in a 500-ml. round-bottom distilling flask at 25°, 29.1 g. (0.5 mole) of propylene oxide was added dropwise. No rise in temperature was observed. The resulting solution was refluxed for one hour, and most of the unreacted allyl alcohol was then separated by distillation at atmospheric pressure (maximum pot temperature, 120°) through a short helix-packed column. Sufficient 6 *N* aqueous sulfuric acid was added to the residual solution at room temperature to neutralize the sodium alloxide, and distillation was continued at about 30 mm. through a Vigreux column 2 feet long and ½ inch in diameter. After recovery of an additional quantity of allyl alcohol, 51 g. (88% yield) of a colorless liquid, b. p. 72–73° at 30–31 mm., $n^{30}D$ 1.4258–1.4264, which was identified as alloxypropanol, was obtained. This was redistilled through a Podbielniak column 90 cm. long and 13 mm. in diameter; 90% of the product boiled at 71–71.5° at 31 mm., $n^{30}D$ 1.4258. The remainder consisted of allyl alcohol and distillation residue. Comparison of the physical properties of the main fraction with those of the products obtained in (b) below indicated that it was 1-alloxy-2-propanol. This was confirmed by the sodium solution test (Table II).

(b) **Preparation of 2-Alloxy-1-propanol (III) and II.**—To a stirred solution of 58.1 g. (1.0 mole) of propylene oxide and 581 g. (10 moles) of allyl alcohol at 25°, 0.58 g. of 95% sulfuric acid was added dropwise. The temperature rose spontaneously from 25 to 30°, and the solution was then refluxed for one hour. (Elimination of the refluxing step caused a considerable reduction in yield.) Sufficient sodium hydroxide was then added to the solution, after it was cooled to room temperature, to neutralize the sulfuric acid, and the solution was distilled through a short helix-packed column. After distillation of the unreacted allyl alcohol at atmospheric pressure, the distillation was completed at 30 mm., yielding 97 g. (84% yield) of a colorless liquid, b. p. 72–75° at 30 mm., $n^{30}D$ 1.4288, which was identified as alloxypropanol. Redistillation through the Podbielniak column gave two distinct fractions, b. p. 71–73° at 30 mm., $n^{30}D$ 1.4258 (II), and b. p. 77–78° at 30 mm., $n^{30}D$ 1.4298 (III). The relative proportions of these fractions (based on hydroxy ether employed as distillation charge) were about 60% of III and 40% of II. The results are summarized in Tables I and II.

(11a) All reactions and distillations were conducted in an atmosphere of nitrogen.

(12) Marple and Evans, U. S. Patent 2,248,635 (1941).

(13) Swern, Findley, Billen and Scanlan, *Anal. Chem.*, **19**, 414 (1947).

**Epichlorohydrin and Allyl Alcohol. Preparation of 1-Alloxy-3-chloro-2-propanol (IV).**—To a stirred solution of 581 g. (10 moles) of allyl alcohol containing 0.92 g. of 95% sulfuric acid at 25°, 92.4 g. (1.0 mole) of epichlorohydrin was added dropwise in five minutes. No rise in temperature was obtained. The solution was refluxed for three hours (a one-hour reflux time caused a considerable reduction in yield) and was then worked up as described under alloxypropanol. Eighty-nine grams (59% yield) of a colorless liquid, b. p. 106–107.5° at 29 to 30 mm., $n^{30}D$ 1.458–1.459, which was identified as alloxychloropropanol, was obtained. Redistillation through the Podbielniak column yielded 1-alloxy-3-chloro-2-propanol (IV), b. p. 107–108° at 31 mm., $n^{30}D$ 1.4582. None of the isomeric 2-alloxy-3-chloro-1-propanol (V) appeared to be present. The results are summarized in Tables I and III.

Alkaline catalysts could not be employed in this system because of the ease with which the chlorine atom in epichlorohydrin was detached. The following alkaline catalysts were tried: potassium hydroxide, sodium hydroxide, sodium, benzyltrimethylammonium hydroxide, trimethylamine and pyridine.

**Glycidol and Allyl Alcohol. Preparation of 1-Alloxy-2,3-propanediol (VI) and 2-Alloxy-1,3-propanediol (VII).**—To a stirred solution of 5.3 g. of sodium in 470 g. (8.1 moles) of allyl alcohol at 25°, 60 g. (0.81 mole) of glycidol was added dropwise. No rise in temperature was observed. The solution was refluxed for three hours, and then worked up as described under alloxypropanol. Seventy-five grams (71% yield) of a colorless liquid, b. p. 104–107° at 3.1 mm., which was identified as alloxypropanediol, was obtained. It was redistilled through the Podbielniak column, b. p. 107–109° at 4.3 to 4.5 mm., $n^{30}D$ 1.4589, but no separation of isomers could be effected. Periodic acid oxidation[10] indicated that the mixed hydroxy ethers consisted of 70 to 75% of VI and 25 to 30% of VII.

Almost identical results (74% yield) were obtained in a similar experiment in which 5.3 g. of 95% sulfuric acid was substituted for the sodium employed above. The catalyst was neutralized with sodium hydroxide. The results are summarized in Table I.

**Styrene Oxide and Allyl Alcohol. (a) Preparation of 2-Alloxy-2-phenylethanol (VIII).**—To a stirred solution of 2.8 g. of sodium in 232 g. (4.0 moles) of allyl alcohol at 25°, 48 g. (0.4 mole) of styrene oxide was added dropwise in five minutes. No rise in temperature was observed over a one-hour period, after which the solution was refluxed for one hour and then worked up as previously described. Fifty-eight g. (81% yield) of a colorless liquid, b. p. 113–117° at 4.5 to 5.0 mm., which was identified as alloxyphenylethanol, was obtained. Redistillation through the Podbielniak column yielded two distinct fractions, b. p. 114° at 4.7 mm., $n^{30}D$ 1.5158, and b. p. 118–119° at 4.5 mm., $n^{30}D$ 1.5167, which were identified as 2-alloxy-1-phenylethanol (IX) and 2-alloxy-2-phenylethanol (VIII), respectively. The latter represented about 90% of the material redistilled.

**(b) Preparation of 2-Alloxy-1-phenylethanol (IX).**—To a stirred solution of 1.2 g. of 95% sulfuric acid and 581 g. (10 moles) of allyl alcohol at 25°, 120 g. (1.0 mole) of styrene oxide was added dropwise in twenty minutes, the temperature being maintained between 25 and 30° by means of an ice–water-bath. The reaction was strongly exothermic. When the exothermic reaction was complete, the solution was refluxed for one hour, and then worked up as described earlier. One hundred and forty-eight grams (83% yield) of a colorless liquid, b. p. 116–118° at 4.8 mm., which was identified as alloxyphenylethanol, was obtained. Redistillation through the Podbielniak column indicated that the product consisted solely of 2-alloxy-1-phenylethanol (IX), b. p. 114–114.5° at 4.6 to 4.8 mm., $n^{30}D$ 1.5159. The results are summarized in Tables I, II and III.

**3,4-Epoxy-1-butene and Allyl Alcohol. Preparation of 3-Alloxy-4-hydroxy-1-butene (X).**—To a stirred solution of 6.5 g. of sodium in 581 g. (10 moles) of allyl alcohol at 25°, 70.1 g. (1.0 mole) of 3,4-epoxy-1-butene was added dropwise in twenty minutes. No rise in temperature was observed. The reaction mixture was allowed to stand for about thirty hours, and then worked up as described earlier. Eighty-five grams (66% yield) of a colorless liquid, b. p. 86–90° at 30 to 32 mm., $n^{30}D$ 1.444, was obtained. This was identified as alloxyhydroxybutene. Redistillation through the Podbielniak column yielded 3-alloxy-4-hydroxy-1-butene (X), b. p. 86–87° at 30 to 31 mm., $n^{30}D$ 1.4449–1.4452.

A similar experiment was conducted in which the 3,4-epoxy-1-butene was added dropwise to allyl alcohol containing 0.70 g. of 95% sulfuric acid as the catalyst. The reaction was extremely exothermic, and the reaction flask had to be kept in an ice-bath to maintain the temperature between 25 and 30° during the addition. After the exothermic reaction was complete, the reaction mixture was stirred at 25 to 30° for one hour (refluxing for one hour resulted in only a 60% yield of hydroxy ether), and then worked up as described earlier. One hundred and one grams (79% yield) of a colorless liquid, b. p. 83–87° at 25 mm., $n^{30}D$ 1.445, which was identified as alloxyhydroxybutene, was obtained. Redistillation through the Podbielniak column gave a main fraction which appeared to be identical (b. p., $d^{30}_4$, $n^{30}D$, etc.) with the product (X) obtained from the alkali-catalyzed experiment, but the benzoyl chloride test suggested that the product from the acid-catalyzed reaction contained some of the secondary alcohol (primary ether) (XI). The results are summarized in Tables I, II and III.

In a smaller scale run, the sulfuric acid catalyst was added dropwise to an uncooled but stirred solution of allyl alcohol and 3,4-epoxy-1-butene. The reaction was vigorously exothermic, and only a 30% yield of hydroxy ether was obtained.

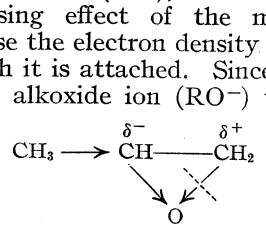
**Sodium Solution Test.**—A freshly cut piece of sodium (0.05 g., 0.00217 mole) was added at 25° to 0.0434 mole of hydroxy compound contained in a test-tube. The test-tube was immediately stoppered with a loosely fitting cork supporting a thermometer which reached to the bottom. The maximum temperature attained during the solution of the sodium, as well as the time required for complete solution, was observed. Solution times could be duplicated within 10 to 20%. The results obtained with some of the hydroxy ethers prepared during this investigation and also with some simple primary and secondary alcohols are shown in Table II.

**Degree of Reaction with Benzoyl Chloride.**—The benzoylation procedure of Kadesch[5a] and Norris and Haines[11] was employed. The results obtained with some of the hydroxy ethers prepared during this investigation and also with some primary and secondary alcohols of known structure are shown in Table III.

**3,5-Dinitrobenzoates.**—Attempts to prepare the 3,5-dinitrobenzoates of the hydroxy ethers by reaction with 3,5-dinitrobenzoyl chloride in pyridine solution yielded oils which could not be induced to crystallize.

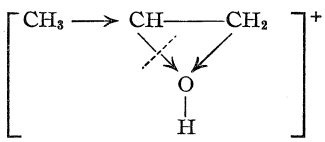
## Discussion

In propylene oxide (XII), the well-known mild electron-releasing effect of the methyl group should increase the electron density of the carbon atom to which it is attached. Since nucleophilic attack by an alkoxide ion ($RO^-$) would be expected to take place preferentially at the carbon atom of lower electron density, namely, at the terminal carbon atom, a secondary alcohol (primary ether) should be obtained. Confirmation of




XII

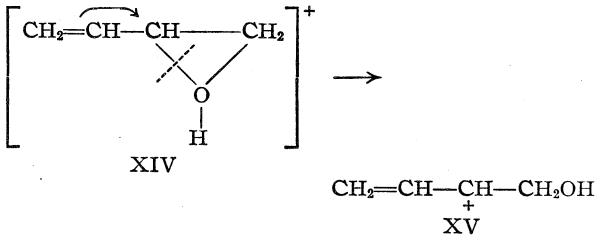
this hypothesis is afforded both by our study of the alkali-catalyzed reaction of allyl alcohol with propylene oxide, in which II is obtained exclusively, and by the work of Chitwood and Freure[3] and Reeve and Sadle,[14] who obtained the secondary alcohol (primary ether) almost exclusively from the alkali-catalyzed reaction of propylene oxide with methanol, ethanol, isopropyl alcohol, *n*-butanol and 2-ethylhexanol. When an acidic catalyst is employed, both carbon–oxygen bonds of the oxirane ring are weakened,[3,15] but because of



XIII

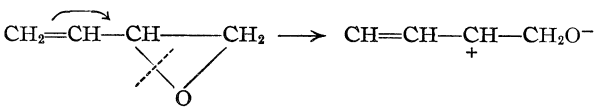
the higher electron density of the carbon atom to which the methyl group is attached, coupled with the repelling effect exerted on the (negative) oxygen atom, this carbon–oxygen bond should be weaker than the other. Cleavage, therefore, should occur as shown in XIII, and a primary alcohol (secondary ether) (III) should be obtained. The hydroxy ethers obtained in the acid-catalyzed reaction of allyl alcohol with propylene oxide consisted mainly of III, as the theory indicates, although II was also obtained in fair yield. The formation of II was not unexpected, since both carbon–oxygen bonds are weakened and the methyl group does not exert a sufficiently powerful electron-releasing effect to cause one carbon–oxygen bond to be so much weaker than the other that preferential cleavage occurs exclusively. As the quantity of acid catalyst is decreased,[3] smaller proportions of primary alcohol (secondary ether) and larger proportions of secondary alcohol (primary ether) form, since the bond-weakening effect diminishes and the electron-releasing effect of the methyl group becomes the major determining factor in influencing the direction of ring opening.

In 3,4-epoxy-1-butene, however, the nature of the catalyst exerted a relatively small effect, the acid-catalyzed reaction yielding a mixture consisting predominantly of the primary alcohol (secondary ether) (X) and the alkali-catalyzed reaction apparently yielding X exclusively. The results of the acid-catalyzed reaction are in agreement with the results previously reported by Kadesch[5a] and by Bartlett and Ross[4] on the acid-catalyzed reaction of 3,4-epoxy-1-butene with methanol. The formation of X in the acid-catalyzed reaction can be explained by assuming the presence of an intermediate carbonium ion, XV,[5a] which should form readily from 3,4-epoxy-1-butene (XIV), since the bond-weakening effect of the strongly electron-releasing vinyl group and the bond-weakening effect of the oxonium ion operate in the same direction. Such an ion should be stabilized as a result of resonance.



XIV XV

The alkali-catalyzed reaction of 3,4-epoxy-1-butene with methanol, however, yields a secondary alcohol (primary ether) predominantly.[4,5a] Since the only difference between our work and that previously reported is the employment by us of allyl alcohol, it can be concluded, perhaps, that allyl alcohol or sodium alloxide enhances the electron-release effect of the vinyl group to such an extent at the precise moment of attack that a considerable bond-weakening effect occurs between the non-terminal carbon atom and the oxirane oxygen atom, yielding an ion as an intermediate (XVI → XVII).

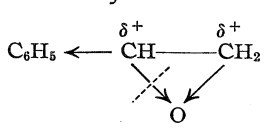


XVI XVII

Nucleophilic attack would occur, of course, at the positive carbon atom, and a primary alcohol would again be obtained.

The ease with which 3,4-epoxy-1-butene and analogous compounds form aldehydes during acid-catalyzed hydration[5,16,17] supports the formulation XIV → XV.

Since the phenyl group can exert either a mild electron-releasing or electron-attracting effect,[18,19,20] the products obtained in the reaction of allyl alcohol with styrene oxide will depend on which effect is taking place. The product obtained in the alkali-catalyzed reaction consisted almost exclusively of primary alcohol (secondary ether) (VIII). The phenyl group, therefore, must exert an electron-attracting effect (XVIII), since formation of the primary alcohol occurs as a result of nucleophilic attack by alkoxide ion on the car-



XVIII

(14) Reeve and Sadle, paper presented at the 113th meeting of the American Chemical Society held in Chicago, Illinois, April, 1948.

(15) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 301.

(16) Pummerer and Reindel, *Ber.*, **66**, 335 (1933).

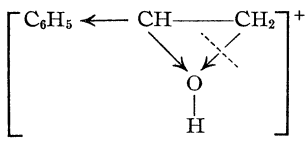
(17) Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **13**, 481 (1943).

(18) Day, "Electronic Mechanisms of Organic Reactions," Stephenson Bros., Philadelphia, Pa., 1947, p. 46.

(19) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 61.

(20) Swern, THIS JOURNAL, **69**, 1692 (1947).

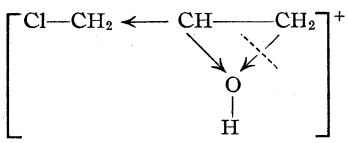
bon atom with the lower electron density, the non-terminal carbon atom in this case. When an acidic catalyst is employed, the lower electron density on the non-terminal carbon atom makes this carbon–oxygen bond stronger than the other because of the increased attraction of the non-terminal carbon atom for the oxygen atom (XIX).



XIX

Since the terminal carbon–oxygen bond is the weaker of the two, the secondary alcohol (primary ether) (IX) should, and does, form in good yield.

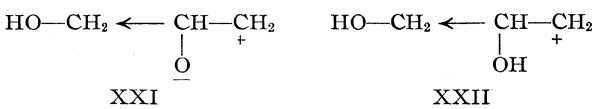
The chloromethyl group in epichlorohydrin (XX) must also exert an electron-attracting effect, since the product obtained when it was treated with allyl alcohol in the presence of sulfuric acid was the secondary alcohol (primary ether) (IV).



XX

The failure to obtain the isomeric primary alcohol (secondary ether) (V) was somewhat surprising, since the chloromethyl group should exert a less powerful electron-attracting effect than the phenyl group.

In the reaction of glycidol with allyl alcohol, the nature of the catalyst was without effect in determining the direction of ring opening. Since the hydroxymethyl group is a strong electron-attracting group, it may be assumed that the ions XXI and XXII exist in alkaline and acidic media, respectively.



XXI XXII

This formulation is analogous to that proposed earlier for 3,4-epoxy-1-butene, except that in glycidol there should be a powerful bond-strengthening effect between the non-terminal carbon atom and the oxirane oxygen atom caused by the strongly electron-attracting hydroxymethyl group, which would favor formation of XXI and XXII.[21] On the basis of this formulation, only α-glycol (VI) should be obtained regardless of the alkalinity or acidity of the systems. The fact that α-glycol formation predominated appears to substantiate the premise, in the main, but the formation of considerable and identical quantities of VII is still without explanation.

**Acknowledgment.**—We are indebted to Frances Cooper and Mary Jane Welsh for the carbon analyses, to R. E. Koos for some of the iodine number and per cent. hydroxyl determinations, and to M. E. Coy for determining the degree of reaction of the hydroxy compounds with benzoyl chloride.

## Summary

The reaction of allyl alcohol with the unsymmetrical oxirane compounds propylene oxide, glycidol, 3,4-epoxy-1-butene, epichlorohydrin and styrene oxide, in the presence of acidic and alkaline catalysts, has been studied. Reaction conditions are described for obtaining good yields (60 to 90%) of hydroxy ethers.

A technique is reported for determining the structure of the hydroxy ethers. This consists in efficient fractional distillation of the reaction products and analysis of the main fractions, followed by the application of one or more chemical diagnostic tests. These include periodic acid oxidation, measurement of the time required to dissolve a known weight of sodium in a large molar excess of hydroxy ether, and determination of the degree of reaction of benzoyl chloride with the hydroxy ether under controlled conditions. When employed under the proper conditions and with suitable substrates, the benzoyl chloride test should be generally applicable in determining whether a hydroxyl group is primary or secondary.

Electronic mechanisms for the reactions have been suggested.

PHILADELPHIA 18, PA. RECEIVED JUNE 25, 1948

(21) After completion of the manuscript, the paper by Vladimirova and Petrov [*J. Gen. Chem.* (*U. S. S. R.*), **17**, 51 (1947); *C. A.*, **42**, 118i] in which an ion similar to XXI was proposed, came to our attention.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE STATE UNIVERSITY OF IOWA]

# The Addition of Bromine to Olefinic Double Bonds. N-Bromoacetamide as a Source of Bromine.[1]

BY ROBERT E. BUCKLES

N-Bromoacetamide has been found to react with several unsaturated compounds to form dibromides in appreciable amounts. Such formations of significant amounts of dibromides of olefins with N-bromoacetamide as the sole source of bromine have not previously been reported.[1a]

In Table I are listed the results of the reactions of various unsaturated compounds with N-bromoacetamide in chloroform. In all cases the reactions were promoted by ultraviolet light or simply by heat. Styrene reacted quite rapidly with the N-bromoacetamide. There was no appreciable bromine color in the reaction mixture. In all the other cases the reaction mixtures maintained a noticeable bromine color, and the olefin seemed to be reacting with the bromine as it formed from the decomposition of the N-bromoacetamide.[2]

TABLE I

MELTING POINTS AND YIELDS OF DIBROMIDES FROM VARIOUS SOURCES

| Olefin | AcNHBr Yield, % | AcNHBr M. p.[a] | AcNHBr + HBr (crude product) Yield, % | AcNHBr + HBr (crude product) M. p.[a] | $Br_2$ M. p.[a] |
|---|---|---|---|---|---|
| Styrene | 34 | 69–71° | 93 | 68–70° | 73–74° |
| | 55[b] | 71–72 | | | |
| Ethyl cinnamate | 48 | 74–75 | 99 | 65–71 | 73–74 |
| Cinnamic acid | 49 | 197–199 | 95 | 183–188 | 198–200 |
| *cis*-Stilbene | 18 | 235–237 | 97 | 85–100 | 110–111 |
| *trans*-Stilbene | 35 | 237–239 | 95 | 234–237 | 235–237 |
| Tolan | 37 | 210–211 | 98 | 167–199 | 210–211 |
| Triphenylethylene[c] | 39 | 112–114 | 99 | 109–112 | 114–115 |

[a] All m. p.'s corrected. [b] Dibromide isolated by distillation. [c] The product was triphenylbromoethylene.

The rapid reaction of styrene whether induced thermally or photochemically usually had an induction period. The liberation of heat which followed the induction period often caused the reaction mixture to boil violently. This behavior of styrene with N-bromoacetamide took place with chloroform, carbon tetrachloride or excess styrene as solvent. The presence of small amounts of alcohol or water in the chloroform or of *p-t*-butylcatechol in the styrene did not change the nature of the reaction. Polystyrene accompanied styrene dibromide as a product only when styrene was used as a solvent. In no case did the reaction give anywhere near a quantitative yield of the solid dibromide.

Styrene reacted with N-bromoacetamide to form dibromide at room temperature in the absence of light when the mixture merely stood overnight. When *cis*-stilbene was treated similarly there was still unchanged N-bromoacetamide after five days. A low yield of *trans*-stilbene dibromide as well as a nearly identical yield of *trans*-stilbene, itself, was obtained from the reaction mixture.

A great deal of difficulty was encountered in the isolation of reaction products which could be traced to the acetamido group of the N-bromoacetamide. It was expected at first that diacetylhydrazine would be the product, but no isolable amount of this compound was formed. The only products successfully identified were small amounts of acetamide and diacetamide hydrobromide or their hydrolysis products. These two compounds, however, have both been isolated as decomposition products of N-bromoacetamide.[2] A small amount of decomposition accompanying the olefin reaction would account for these by-products.

In contrast to these addition reactions with N-bromoacetamide as the sole source of bromine was the formation of dibromides in a much more clean-cut fashion when the unsaturated compounds reacted with N-bromoacetamide in chloroform in presence of excess anhydrous hydrogen bromide. In every case the reaction was carried out so that there was little or no bromine color in the reaction mixture until all the olefin had reacted. In each case, also, the reaction was immediate, and heat was liberated. No external stimulus was necessary for starting the reaction. The yields of crude dibromides are listed in Table I.

## Discussion

N-Bromoamides seem to be capable of supplying either bromine atoms or positive bromine[3] during a reaction. It has been reported[4] that the preferential bromination[5] of the carbon atom adjacent to the double bond is catalyzed by peroxides. Substitution reactions have also been reported for N-bromoacetamide with various olefins[6] as well as for N-bromosuccinimide at the

(1) Presented before the Division of Organic Chemistry of the American Chemical Society, Chicago, Illinois, April 20, 1948.

(1a) Dibromides have recently been reported as the main products of the reactions of N-bromosuccinimide with certain unsaturated compounds: Buchman and Howton, THIS JOURNAL, **70**, 2517 (1948), and Southwick, private communication.

(2) (a) Edgell, Simpson and Buckles, unpublished work; (b) Hantzsch and Dollfus, *Ber.*, **35**, 249 (1902).

(3) Bartlett and Tarbell, THIS JOURNAL, **58**, 466 (1936).

(4) (a) Schmid, *Helv. Chim. Acta.*, **29**, 1144 (1946); (b) Howton, THIS JOURNAL, **69**, 2060 (1947).

(5) Ziegler, Spath, Schaaf, Schumann and Winklemann, *Ann.*, **551**, 80 (1942).

(6) Wohl, *Ber.*, **52**, 51 (1919); Wohl and Jaschinowsky, *Ber.*, **54**, 476 (1921).

$\alpha$-carbon atom of ketones.[7] These reactions are often promoted by ultraviolet light.[7] Reactions of this sort which exhibit catalysis by peroxides or light are generally interpreted[8] as involving bromine atoms and free radical intermediates.

On the other hand N-bromosuccinimide reacts with aromatic hydrocarbons in the presence of anhydrous aluminum chloride to give ring bromination as opposed to the side chain substitution observed with a peroxide catalyst.[4a] N-Bromoacetamide has been reported[9] to be a source of bromine for acid catalyzed olefin addition reactions of olefins in which a hydroxylic solvent is also involved; *e.g.*, water as a solvent giving rise to the bromohydrin as the predominant product. Such reactions are best interpreted[10] as ionic with the bromine behaving as if it were positive.[3]

The formation of dibromide of unsaturated molecules with N-bromoacetamide as the sole source of bromine most likely takes place through free radical intermediates. This interpretation s especially applicable in the case of styrene reacting with N-bromoacetamide because of the induction period followed by an accelerating reaction. The effect of light on the reaction also points to a free radical mechanism. The fact that *cis*-stilbene was isomerized to the *trans* isomer at room temperature in the absence of activating light shows that bromine atoms are available from N-bromoacetamide without the intermediate formation of bromine molecules. Bromine itself reacts with *cis*-stilbene at room temperature in the absence of light to give the *dl*-dibromide as the principle product.[11] On the other hand bromine atoms catalyze the *cis–trans* isomerization of olefins.[8] Thus, it seems reasonable to postulate that in the photochemical reaction N-bromoacetamide first forms a bromine atom (Step 1) which attacks the double bond (Step 2). The resulting radical would be capable of relatively free rotation about the bond that was originally the double bond. It would be expected to react with a N-bromoacetamide molecule to form the dibromide of most stable configuration (Step 3). At the present time it is impossible to say what might happen to the acetamidyl radical, AcNH·.

$$\text{AcNHBr} + h\nu \longrightarrow \text{AcNH}\cdot + \text{Br}\cdot \quad (1)$$

$$>\text{C=C}< + \text{Br}\cdot \longrightarrow >\text{CBr—}\dot{\text{C}}< \quad (2)$$

$$>\text{CBr—}\dot{\text{C}}< + \text{AcNHBr} \longrightarrow >\text{CBr—CBr}< + \text{AcNH}\cdot \quad (3)$$

$$\text{Br}\cdot + \text{AcNHBr} \longrightarrow \text{Br}_2 + \text{AcNH}\cdot \quad (4)$$

$$\text{Br}_2 + h\nu \longrightarrow 2\text{Br}\cdot \quad (5)$$

$$\text{Br}_2 + >\text{CBr—}\dot{\text{C}}< \longrightarrow >\text{CBr—CBr}< + \text{Br}\cdot \quad (6)$$

In the cases where a definite bromine color was observed during the reaction, Steps 4, 5 and 6 must also be considered. No matter what the source of bromine atoms, however, the most stable dibromide isomer would be formed. This was found to be the case when the *meso*-dibromide was the product from either of the stilbene isomers.

The clean-cut reaction of the olefins with N-bromoacetamide in the presence of hydrogen bromide, on the other hand, most likely involves ionic intermediates (ion pairs or triplets in nonpolar solvents). Such addition reactions are best interpreted as involving ionic intermediates, *e.g.*, the bromonium ion,[12] which maintain their steric identity. Only with such an interpretation can the formation of *dl*-dibromide from *cis*-stilbene be explained. Either the conjugate acid of N-bromoacetamide or molecular bromine could act as a source of positive bromine[3] for the usual ionic mechanism of bromine addition.[10]

$$\text{AcNHBr} + \text{HBr} \rightleftharpoons \text{AcNH}_2\text{Br}^+ + \text{Br}^-$$

$$\text{AcNH}_2\text{Br}^+ + \text{Br}^- \longrightarrow \text{AcNH}_2 + \text{Br}_2$$

## Experimental

**N-Bromoacetamide.**—This material was prepared by the reaction of equimolar amounts of acetamide, bromine and potassium hydroxide in a minimum amount of water at 0–5°.[13] The reaction product was dissolved in chloroform and the solution distilled until there was no more water in the distillate. Cooling crystallized the product. The m. p. fell somewhere between 95 and 105° with a range of several degrees. The pure anhydrous N-bromoacetamide has m. p. 108°.[2a] The yields of product were generally around 45%.

**Unsaturated Compounds.**—The styrene (stabilized with *p-t*-butylcatechol) was supplied by Eastman Kodak Co. Thanks are due Mr. Norris G. Wheeler of this Laboratory who prepared the *cis*-stilbene by the decarboxylation of $\alpha$-phenylcinnamic acid.[14]

**Authentic Samples of Dibromides.**—These were all prepared by the action of bromine in either chloroform or carbon tetrachloride on the respective olefins. In the case of triphenylethylene the resulting dibromide lost hydrogen bromide so that triphenylbromoethylene was the product. In all cases except *cis*-stilbene the yields exceeded 80%. The *cis*-stilbene dibromide was generally obtained in about 70% yields with a small amount of *trans*-dibromide.

The m. p.'s of the dibromides check favorably with the accepted values in the chemical literature; they are tabulated in Table I. The capillary m. p. of *meso*-stilbene dibromide from the addition of bromine to *trans*-stilbene, depended on the length of time necessary to heat the sample to the m. p. Only when the sample was placed in the bath preheated to about 210° was decomposition minimized enough for the recorded m. p. of 237° to be observed. Otherwise the m. p. was much lower. On the Maquenne block the m. p. was 254–255° (dec.).

**Reactions of the Unsaturated Compounds with N-Bromoacetamide.**—In most of the experiments 0.005 to 0.02 mole of the unsaturated compound in 15–25 ml. of unpurified commercial chloroform containing 0.75% alcohol was treated with twice as many moles of N-bromoacetamide. In the case of triphenylethylene an equimolar amount was used. The reaction mixture was usually heated gently and illuminated with ultraviolet light. Either sunlight or a Hanovia quartz mercury arc was used as a source of illumination. Usually the solution became

(7) Djerassi and Scholz, *Experientia*, **3**, 107 (1947).

(8) Price, "Mechanisms of Reactions at Carbon–Carbon Double Bonds," Interscience Publishers, New York, N. Y., chap. 3, 1946.

(9) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); Likhosherstov and Alekseev, *J. Gen. Chem.* (*U. S. S. R.*), **3**, 927 (1933); Schmidt, Knilling and Ascherl, *Ber.*, **59**, 1280 (1926).

(10) Footnote 8, chap. 2.

(11) Wislicenus, *Chem. Zentr.*, **72**, I, 464 (1901).

(12) Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

(13) Winstein and Henderson, *ibid.*, **65**, 2196 (1943).

(14) Taylor and Crawford, *J. Chem. Soc.*, 1130 (1934).

light brown in color and remained so for several hours. If an excess of N-bromoacetamide was used the end of the reaction was characterized by a distinct darkening of the bromine color. When no olefin was present the brown color deepened much faster. After several hours of illumination the reaction mixture was filtered and washed with warm water and chloroform. A crystalline product remained if the dibromide was an insoluble one.

The two phase filtrate was shaken, and the water layer was removed. In all cases the aqueous layer contained acetamide and bromide ion, and if it was evaporated to dryness by standing for some time the residue contained ammonium ion and acetic acid as well. In some of the experiments a small amount of a water soluble crystalline product was filtered from the chloroform solution before water was added. This compound proved to be diacetamide hydrobromide[2] of m. p. somewhere in the range 130–139°.

The chloroform solution was distilled at reduced pressure and the dibromide residue was recrystallized from alcohol or alcohol–water. The results of these experiments are given in Table I.

**The Reaction of Styrene with N-Bromoacetamide.**—Several experiments with 0.1 and 0.2 mole of styrene with equivalent amounts of N-bromoacetamide were carried out. In 50 to 100 ml. of unpurified chloroform containing 0.75% ethyl alcohol the reaction was quite violent as soon as it started unless the N-bromoacetamide or the styrene was added portionwise. It was possible to start this violent reaction either by the application of heat to or illumination of the reaction mixture. It made no difference whether the N-bromoacetamide was hydrated or anhydrous. In fact the addition of a mole of water per mole of styrene had no effect on the reaction. In most of these cases the dibromide crystallized from an alcohol solution following the removal of the chloroform. In one case the dibromide was distilled from the residue, b. p. 108–110° (3–4 mm.) (see Table I).

In one experiment 15 ml. of chloroform washed with concentrated sulfuric acid and dried over anhydrous potassium carbonate was distilled into a cooled flask containing 1.4 g. (0.010 mole) of N-bromoacetamide. Two ml. of styrene was then distilled at reduced pressure into the same flask. The reaction exhibited an induction period as before, but the reaction mixture heated up noticeably once it started. A control experiment using unpurified chloroform and styrene stabilized with *p-t*-butylcatechol behaved the same way. Both reactions yielded styrene dibromide.

Similarly 0.01 mole of N-bromoacetamide reacted with styrene alone and with styrene in carbon tetrachloride to give the dibrom de.

At room temperature in the absence of light, a successful reaction of 0.01 mole of N-bromoacetamide with a slight excess of styrene in chloroform was observed only if the reaction mixture stood overnight or longer.

**The Reaction of *cis*-Stilbene with N-Bromoacetamide in the Absence of Light.**—A solution of 1.38 g. (0.010 mole) of N-bromoacetamide in 50 ml. of chloroform was prepared in a Pyrex Lifetime Red Low Actinic glass flask. The solution was cooled, and 0.90 g. (0.005 mole) of *cis*-stilbene was added. The flask was stoppered and the solution was allowed to stand five days at room temperature. The solution was extracted with water. The aqueous phase gave an iodine color when potassium iodide was added. Chloroform was distilled from the organic layer and alcohol was added. Cooling yielded 0.13 g. (8%) of *trans*-stilbene dibromide. The solution was concentrated and cooled and 0.07 g. (8%) of *trans*-stilbene of m. p. 118–120° was isolated. Recrystallization of the *trans*-stilbene from aqueous alcohol yielded crystals of m. p. 122.5–123.5°; no depression when mixed with an authentic sample. Evaporation of the mother liquor gave a little oily residue containing no crystals.

**Reactions of the Unsaturated Compounds with N-Bromoacetamide and Anhydrous Hydrogen Bromide.**—A slight excess of anydrous N-bromoacetamide was added portionwise to a solution of 0.005 mole of the unsaturated compound in 15 ml. of unpurified commercial chloroform which was kept saturated with anhydrous hydrogen bromide. There was an immediate evolution of heat. The N-bromoacetamide was added at a rate such that only local concentrations of bromine were observed by color. At the end of the reaction the bromine color became pronounced and a white precipitate of diacetamide hydrobromide was observed.[2a] The reaction mixture was shaken with water, and the chloroform layer was evaporated on a tared watch glass. The solid residue was weighed and the melting point taken. These data are in Table I. The crude products were recrystallized when necessary and identified by mixed m. p. with authentic samples. When this method of isolation was attempted with the reactions of the olefins with N-bromoacetamide alone, only sticky, viscous liquids were obtained as residues.

## Summary

1. N-Bromoacetamide has been shown to act as the sole source of bromine for addition to the double or triple bonds of certain unsaturated compounds.

2. The reactions of the unsaturated compounds with N-bromoacetamide have been interpreted as involving free radical intermediates.

3. N-Bromoacetamide has been shown to be a source of bromine atoms capable of isomerizing *cis*-stilbene to the *trans* isomer.

4. The reactions of unsaturated compounds with N-bromoacetamide in the presence of anhydrous hydrogen bromide have been interpreted as following the usual polar mechanism of *trans* addition.

IOWA CITY, IOWA RECEIVED MAY 17, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

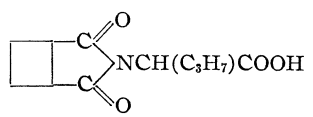
# Studies on Antipodes. VI.[1] The Synthesis of Some Derivatives of Enantiomorphs of Valine[2]

BY FREDERICK N. MINARD[3] AND SIDNEY W. FOX

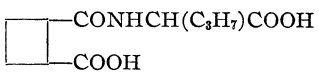
The possible significance of the D-amino acid component in antibiotics has been previously considered.[1a,4] Partly as the result of the finding of inhibition of bacterial growth by D-amino acids[1a,b,d] fundamental relationships involving D-amino acids, proteases, growth, and antibiotics have been suggested. Initial attempts to prepare model antibiotics in this laboratory were based on the knowledge surrounding gramicidin and tyrocidine.[1a] Since that time the penicillins have been shown to be D-amino acid derivatives[5] and the D-amino acid residue has been found to be one critical structural feature in this type.[6] Evidence now exists for the presence of D-amino acid residues in other antibiotics besides gramicidin (D-leucine and D-valine), tyrocidine (D-phenylalanine), and the penicillins (D-penicillamine). These include gramicidin S (D-phenylalanine),[7] bacitracin[8] (D-phenylalanine), and aerosporin[9] (D-leucine and D-$\alpha,\gamma$-diaminobutyric acid). The D-amino acid residue thus appears to be a unit of widespread significance in the comparative biochemistry of antibiotics. The value of the D-amino acid unit may depend upon its contribution to inhibitory action, to non-metabolizability, to cyclizability of the whole molecule,[10] or upon some other function.[11]

All of the above antibiotics are peptides or peptide derivatives. Large natural peptide molecules subjected to treatment resulting in inversion of L-residues have given products which have so far not been found to possess antibacterial activity.[1e] Treatment of "racemized casein" aimed at bringing about cyclization of this material as for the diketopiperazines[12,13] has given products which possess relatively weak antibacterial activity not, however, found in the peptides prior to such treatment.[14]

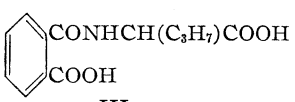
The natural profusion of antibiotics of the D-amino acid derivative class increases interest in chemical attempts to synthesize D-amino acid derivatives with antibacterial activity. Among other working hypotheses for the synthetic approach to the antibiotic problem is the inclusion of strained structures in compounds with groups that may function to attract enzymes. To this end some cyclobutane[15] derivatives (Types I and II) have been prepared and are recorded in this article (Table I). These derivatives contain peptide and carboxyl groups, although not in a relationship such as is found in penicillin or in peptidase substrates.[16] The amino acid residues are L-valine, D-valine, and DL-valine. The *o*-carboxybenzoyl derivatives of the valine isomers (III) are also reported.




I




II




III

The phthaloyl-DL-valine reported in Table I has been recorded earlier by Billman and Harting.[17] The product described here is included for comparative purposes, since it was purified in a different manner. This compound formed a hydrate when crystallized from aqueous solutions. In the case of the corresponding cyclobutane compounds, the optical isomers yielded hydrates from aqueous solution, whereas the racemate did not.

The opening of the ring in the phthaloyl derivatives and the corresponding ring in the cyclobutane analog proceeded very rapidly. Mere warming of the cyclic imides with dilute alkali served to hydrolyze the cyclic imides without appreciable rupture of the remaining peptide linkage.

(1) Earlier papers in this series: (a) Fox, Fling and Bollenback, *J. Biol. Chem.*, **155**, 465 (1944); (b) Fling and Fox, *ibid.*, **160**, 329 (1945); (c) Fling, Minard and Fox, THIS JOURNAL, **69**, 2466 (1947); (d) Kobayashi, Fling and Fox, *J. Biol. Chem.*, **174**, 391 (1948); (e) Fox, Kobayashi, Melvin and Minard, THIS JOURNAL, **70**, 2404 (1948).

(2) Journal Paper No. J-1562 of the Iowa Agricultural Experiment Station, Project 980.

(3) Upjohn Company Fellow, 1946–1949.

(4) Fox, *Can. Med. Assoc. J.*, **56**, 76 (1947).

(5) Committee on Medical Research, O. S. R. D., Washington, and the Medical Research Council, London, *Science*, **102**, 627 (1945).

(6) du Vigneaud, Carpenter, Holley, Livermore and Rachele, *Science*, **104**, 431 (1946).

(7) Synge, *Biochem. J.*, **39**, 363 (1945).

(8) Barry, Gregory and Craig, *J. Biol. Chem.*, **175**, 485 (1948).

(9) Jones, *Biochem. J.*, **42**, lii (1948).

(10) Harris and Work, *Nature*, **161**, 804 (1948).

(11) How the D-amino acid content of antibiotics compares with the content of the same unit in the proteins of the parent organisms cannot be accurately evaluated since there are insufficient data of the latter type.

(12) Fling, Ph.D. thesis, Iowa State College, 1946.

(13) Fruton, THIS JOURNAL, **70**, 1280 (1948).

(14) Fox and Kobayashi, manuscript in preparation.

(15) Kilpatrick and Spitzer, *J. Chem. Phys.*, **14**, 463 (1946).

(16) Greenstein, in Schmidt, "Chemistry of the Amino Acids and Proteins," 2nd ed., Charles C. Thomas, Springfield, Illinois, 1944, pp. 267 and 1080.

(17) Billman and Harting, THIS JOURNAL, **70**, 1475 (1948).

TABLE I

DERIVATIVES OF ISOMERS OF VALINE

| | Empirical formula | M. p. °C. (uncor.) | Nitrogen, % Calcd. | Found | | Neut. equiv. Calcd. | Found | [α]D in abs. EtOH (3% solution) °C. | Rotation |
|---|---|---|---|---|---|---|---|---|---|
| **Acyl derivatives of DL-valine** | | | | | | | | | |
| N,N-Phthaloyl | $C_{13}H_{13}O_4N$ | 102–103 | 5.67 | 5.67 | | 247 | 245 | | |
| N,N-Phthaloyl, monohydrate[a] | $C_{13}H_{15}O_5N$ | 80–81½ | 5.28 | 5.28 | 5.35 | 265 | 262 | | |
| N-(*o*-Carboxybenzoyl) | $C_{13}H_{15}O_5N$ | 171½–172 | 5.28 | 5.27 | 5.27 | 133 | 132 | | |
| N,N-(Cyclobutane-1,2-dicarbonyl) | $C_{11}H_{15}O_4N$ | 102–103½ | 6.22 | 6.20 | 6.18 | 225 | 223 | | |
| N-(2-Carboxycyclobutanecarbonyl) | $C_{11}H_{17}O_5N$ | 178–179 | 5.76 | 5.73 | 5.73 | 122 | 124 | | |
| **Acyl derivatives of L-valine** | | | | | | | | | |
| N-(*o*-Carboxybenzoyl) | $C_{13}H_{15}O_5N$ | 154–155 | 5.28 | 5.23 | | 133 | 136 | 24 | −15.9 ± 0.5° |
| N,N-(Cyclobutane-1,2-dicarbonyl), monohydrate[b] | $C_{11}H_{17}O_5N$ | 92–98 | 5.76 | 5.70 | 5.73 | 243 | 246 | 25 | −76.1 ± 2.8° |
| N-(2-Carboxycyclobutanecarbonyl) | $C_{11}H_{17}O_5N$ | 168–169 | 5.76 | 5.81 | 5.73 | 122 | 123 | 26 | − 7.2 ± 0.4° |
| **Acyl derivatives of D-valine** | | | | | | | | | |
| N-(*o*-Carboxybenzoyl) | $C_{13}H_{15}O_5N$ | 153–154 | 5.28 | 5.26 | 5.28 | 133 | 135 | 27 | +16.2 ± 0.4° |
| N,N-(Cyclobutane-1,2-dicarbonyl), monohydrate[b] | $C_{11}H_{17}O_5N$ | 92–98 | 5.76 | 5.81 | 5.85 | 243 | 246 | 26 | +77.5 ± 3.6° |
| N-(2-Carboxycyclobutanecarbonyl) | $C_{11}H_{17}O_5N$ | 168–169 | 5.76 | 5.71 | 5.70 | 122 | 123 | 27 | + 7.4 ± 0.3° |

[a] By recrystallization of the anhydrous imide from ethanol–water. [b] The anhydrous peptide was hygroscopic and was not obtained.

Preliminary tests of the above compounds on *Lactobacillus arabinosus* and *Escherichia coli* showed neither high antibacterial activity nor antipodal specificity.[18] Activity was found at dilutions of 0.8 mg./ml., but not at half this concentration.

## Experimental

**Preparation of Imides.**—The valine isomer was fused with either phthalic anhydride as previously described[1c,17] or with cyclobutane-1,2-*cis*-dicarboxylic anhydride[19] in equimolar ratio. The phthaloyl-DL-valine was recrystallized from carbon tetrachloride and the cyclobutanedicarbonyl valines were recrystallized from water.

**Hydrolysis of Imides.**—Compounds of Types II and III were prepared as follows: Five grams of the imide was titrated in a 125-ml. Erlenmeyer flask with 2 *N* sodium hydroxide solution to a phenolphthalein end-point. An equal amount of dilute alkali, plus 0.5 ml. excess, was added. The flask was placed in a water-bath (previously at the boiling-point) until the inside temperature reached 70°, and then quickly cooled in an ice-bath. The solution was acidified with concentrated hydrochloric acid solution, and an excess added to precipitate the organic acid. After one hour the product was filtered and dried.

The *o*-carboxybenzoyl derivatives were purified by solution of the dried material in acetone, filtration from undissolved sodium chloride, and addition of carbon tetrachloride to incipient precipitation. The peptides came out slowly and after several such purifications appeared as well-formed crystals.

The carboxycyclobutane derivatives were freed from inorganic matter by solution in anhydrous ethanol. After filtration, several ml. of dry ethyl acetate was added to prevent layering, and then enough hexane to cause incipient precipitation.

Yields were 50–75% for type I compounds, 40–50% for type II, and 60–75% for type III.

(18) Kobayashi and Fox, unpublished experiments.

(19) Buchman, Reims, Skei and Schlatter, THIS JOURNAL, **64**, 2696 (1942).

## Summary

The N-(*o*-carboxybenzoyl), N,N-(cyclobutane-1,2-dicarbonyl), and N-(2-carboxycyclobutanecarbonyl) derivatives of L-, D-, and DL-valine have been prepared and characterized.

AMES, IOWA RECEIVED JULY 19, 1948

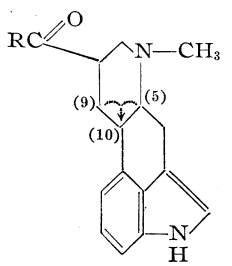
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# Synthetic Analogs of Oxytocic Drugs. I. Phenethyl β-Alanine Derivatives[1]

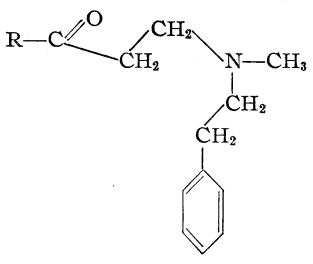
BY RICHARD BALTZLY, VLADIMIR DVORKOVITZ[2] AND ARTHUR P. PHILLIPS

The important natural oxytocic drug ergonovine (ergometrine, ergobasine) has been assigned the structure I (R = $NHCH(CH_3)CH_2OH$[3]) in which the dotted lines indicate the existing uncertainty[4] as to the location of the double bond which is known to shift from the 5-10 to the 9-10 position in transformations between the lysergic and isolysergic acid families of the ergot alkaloids. The contributions of the various portions of the molecule to its physiological activity are not known, although some information is available.

The other ergot alkaloids, in which the group R is replaced by complex cyclic structures, manifest very different physiological behavior, not essentially of an oxytocic character. Stoll and Hofmann[5] have prepared a number of ergonovine analogs and homologs in which 2-amino-1-propanol was replaced by other alkanolamines. A number of these were approximately as active as ergonovine as was α-lysergic acid diethylamide. In contrast to this last finding, Smith and Timmis[6] reported that both ergine and iso-ergine (I, R = $NH_2$) had only vestigial activity. It does not appear that other derivatives of lysergic acid have been tested. The double bond is apparently not of critical importance since Kharasch[7] has claimed therapeutic efficacy for a dihydro-compound. On the other hand, the presence of the double bond in an unfavorable position (as in the isolysergic acid family) abolishes activity.




I




II

Inspection of Formulas I and II shows that lysergic acid (I, R = OH) may be regarded as an N-methyl-N-phenethyl-β-alanine. It is therefore possible to consider a phenethyl-β-alanine alkanolamide as an open-chain model of ergonovine.

A number of phenethyl-β-alanine esters were prepared from N-methylphenethylamines with the intention of transforming them into ethanolamides. While this transformation proved to be unexpectedly tedious and expensive some of the esters themselves showed marked oxytocic activity in laboratory animals. Since the two ethanolamides that have been prepared (compounds IV and XVIII in Table I) appeared to be no more active than the corresponding esters most of our attention was given to the preparation of the latter. It had been hoped that activity could be correlated with structural features. This has been possible only in a general sense. The maximum activity so far observed in this series (5–10% of that shown by ergonovine per unit weight) is manifested by those compounds having two ether substitutions on the phenyl ring. Possibly such substitution of a polar nature may be equivalent roughly to the indole nitrogen in the natural compounds (which would not be cationic under physiological conditions). The activity of the monoalkoxy compounds is perhaps one-tenth that of the di-alkoxy, and the unsubstituted compound (I in Table I) appears inactive. Within the above mentioned classes little differentiation is possible. Differences of less than 100% in potency probably could not be detected by the methods available and the question whether true ergonovine-like action will be manifested in human beings remains to be settled.[8] The secondary amine (XX) and the quaternary salt (XXIV) corresponding to one of the most potent compounds (XXII) showed the same order of activity. The size of the ester alkyl was not critical. On the other hand, the phenolic compounds (II, VI and XIX) were completely inactive. All of these substances showed rather low (in some cases extremely low) toxicities and minimal physiological action of non-oxytocic nature.

The iodinated compounds (VII and VIII) were prepared in the hope that they would partake of the physiological inertness of the parent compound (VI) and would be of interest as radiopaques. Iodination was found, however, to have increased toxicity very considerably.

## Experimental

Physical properties and analytical figures for the phenethyl-β-alanine derivatives are presented in Table I. Analytical results were at times rather unsatisfactory. In general, the most serious error in analysis of amine salts results from difficulty in drying. The present series of compounds presents all the usual complications in drying

(1) The work reported here is a part of a project undertaken in collaboration with a pharmacological group in these Laboratories who will report separately on the pharmacology of the substances described in this paper.

(2) Present address, care of the Diversey Corporation, Chicago, Illinois.

(3) Craig, Shedlovsky, Gould and Jacobs, *J. Biol. Chem.*, **125**, 289 (1938).

(4) Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

(5) Stoll and Hofmann, *Helv. Chim. Acta*, **26**, 944 (1943).

(6) Smith and Timmis, *J. Chem. Soc.*, 1440 (1936).

(7) Kharasch, U. S. Patent 2,086,559.

(8) The physiological action of ergonovine in rabbits and dogs is qualitatively different from that in human beings. These substances behave much like ergonovine with laboratory animals.

TABLE I

SALTS OF N-METHYL-N-PHENETHYL-β-ALANINE DERIVATIVES —$CH_2CH_2NMeCH_2CH_2CORHX$

| Compound | Phenethyl substitutions | R | HX | Crystallizing solvent[b] and crystal habit[a] | M. p., °C.[c] | Empirical formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| I | None | OEt | HBr | AE | 134–135 | $C_{14}H_{22}BrNO_2$ | 53.13 | 53.32 | 7.02 | 6.97 |
| II | 2-OH | OEt | HCl | AE[f] | 155.5–156.5 | $C_{14}H_{22}ClNO_3$ | 58.42 | 58.65 | 7.71 | 7.71 |
| III | 2-OMe | OEt | HCl | Æ[g] | 98–98.5 | $C_{15}H_{24}ClNO_3$ | 59.69 | 59.76 | 8.02 | 8.31 |
| IV | 2-OMe | $NHCH_2CH_2OH$ | $(HOOC)_2$ | Ac. Aq. E.[h] | 128–129 | $C_{17}H_{26}N_2O_7$ | 55.10 | 55.41 | 7.08 | 7.39 |
| V | 3-OEt | OEt | HCl | AE | 101.5 | $C_{16}H_{26}ClNO_3$ | 60.84 | 60.76 | 8.30 | 8.74 |
| VI | 4-OH | OEt | HCl | AE | 136 | $C_{14}H_{22}ClNO_3$ | 58.42 | 58.06 | 7.71 | 7.60 |
| VII | 4-OH, 3,5-$I_2$ | OH | None | Aq | 154 (dec.) | $C_{12}H_{15}I_2NO_3$ | 30.32 | 30.24 | 3.18 | 3.75 |
| VIII | 4-OH, 3,5-$I_2$ | OEt | HCl | A Æ E | 154 (dec.) | $C_{14}H_{20}ClI_2NO_3$ | 31.14 | 31.27 | 3.74 | 3.81 |
| IX | 4-OMe | OMe | HCl | Ac[g] | 139.5–140.5 | $C_{14}H_{22}ClNO_3$ | 58.42 | 58.19 | 7.71 | 8.00 |
| X | 4-OMe, 3-Br | OMe | HCl | Ac E | 134–135 | $C_{14}H_{21}BrClNO_3$ | 45.82 | 46.09 | 5.77 | 5.70 |
| XI | 4-OMe, 3-Br | OEt | HCl | Ac E | 85–88 | $C_{15}H_{23}BrClNO_3$ | 47.28 | 47.60 | 6.09 | 6.01 |
| XII | 4-OMe, β-Me | OEt | HCl | AE | 109 | $C_{16}H_{26}ClNO_3$ | 60.84 | 60.62 | 8.30 | 8.39 |
| XIII | 2,3-$(OMe)_2$ | OEt | $(HOOC)_2$ | Ac[h] | 138.5 | $C_{18}H_{27}NO_8$ | 56.08 | 56.25 | 7.07 | 7.37 |
| XIV | 2-OEt, 3-OMe | OEt | HCl | Æ | 91–92 | $C_{17}H_{28}ClNO_3$ | 59.03 | 59.10 | 8.16 | 8.28 |
| XV | 2,4-$(OMe)_2$ | OEt | $(HOOC)_2$ | Ac[h] | 120.5–121 | $C_{18}H_{27}NO_8$ | 56.08 | 55.94 | 7.07 | 7.15 |
| XVI | 2,5-$(OMe)_2$ | OMe | HCl | M Ac E | 108–109 | $C_{15}H_{24}ClNO_4$ | 56.69 | 57.00 | 7.61 | 7.83 |
| XVII | 2,5-$(OM)_2$ | OEt | HCl | Æ E[f] | 105.5–106.5 | $C_{16}H_{26}ClNO_4$ | 57.91 | 58.14 | 7.90 | 8.17 |
| XVIII | 2,5-$(OMe)_2$ | $NHCH_2CH_2OH$ | $(HOOC)_2$ | Ac Aq E[i] | 153–153.5 | $C_{18}H_{28}N_2O_8$ | 53.98 | 54.02 | 7.05 | 7.48 |
| XIX | 3,4-$(OH)_2$ | OEt | HCl | A Ac E | 96–97.5 | $C_{14}H_{22}ClNO_4$ | 55.34 | 55.30 | 7.31 | 7.42 |
| XX | 3,4-$(OMe)_2$[d] | OMe | HCl | Ac[j] | 121–122 | $C_{14}H_{22}ClNO_4$ | 55.34 | 55.30 | 7.31 | 7.54 |
| XXI | 3,4-$(OMe)_2$ | OMe | HCl | Ac E | 120–122 | $C_{15}H_{24}ClNO_4$ | 56.68 | 56.28 | 7.62 | 7.62 |
| XXII | 3,4-$(OMe)_2$ | OEt | HCl | A Ac E[k] | 139–139.5 | $C_{16}H_{26}ClNO_4$ | 57.91 | 57.94 | 7.90 | 8.04 |
| XXIII | 3,4-$(OMe)_2$ | OEt | HBr | A E | 118 | $C_{16}H_{26}BrNO_4$ | 51.07 | 50.79 | 6.97 | 7.11 |
| XXIV | 3,4-$(OMe)_2$[e] | OEt | I | A Æ E | 113–115 | $C_{17}H_{28}INO_4$ | 46.66 | 46.96 | 6.45 | 6.89 |
| XXV | 3,4-$(OMe)_2$,6-Br | OMe | HCl | Ac E | 138–139 | $C_{15}H_{23}BrClNO_4$ | 45.38 | 45.55 | 5.84 | 6.15 |
| XXVI | 3,4-$(OEt)_2$ | OMe | HCl | Ac E | 111–112 | $C_{17}H_{28}ClNO_4$ | 59.01 | 59.03 | 8.16 | 7.92 |
| XXVII | 3,4-$(OEt)_2$ | OEt | HCl | Ac E | 133–134 | $C_{18}H_{30}ClNO_4$ | 60.04 | 60.18 | 8.41 | 8.27 |
| XXVIII | 3,4-$(OEt)_2$ | $OC_5H_{11}(n)$ | HCl | Ac E | 124–125 | $C_{21}H_{36}ClNO_4$ | 62.72 | 62.47 | 9.03 | 8.87 |
| XXIX | 3,4-O-$CH_2$-O | OEt | $(HOOC)_2$ | Ac Aq[h] | 146.5–147 | $C_{17}H_{23}NO_8$ | 55.27 | 55.46 | 6.28 | 6.49 |

[a] Crystal habit noted only when macroscopically characteristic. [b] A = absolute ethanol, Ac = acetone, Aq = water. Æ = ethyl acetate. M = methanol, E = ether. [c] Melting points uncorrected. [d] Des-N-methyl. [e] Methiodide from base of XXII. [f] Plates. [g] Prisms. [h] Needles. [i] Flat needles. [j] Fine-meshed needles. [k] Needle-prisms.

with the additional disadvantage that β-alanine esters have some tendency to split off acrylic esters.

The general stability of β-alanine derivatives under varying conditions has not been studied thoroughly. We are at present in a position to offer only incidental observations. The salts, as crystalline solids, are not noticeably unstable—only two of the melting points listed in Table I appeared to be accompanied by decomposition. On the other hand, the odor of acrylic esters is usually noticeable when a bottle containing one of these salts is opened. One or two compounds, on standing several years in stoppered bottles, were observed to liquefy and this has been attributed to decomposition. Despite the above, the demethylation reactions leading to the formation of II, VI, and XIX resulted in satisfactory yields. Further, the ester-exchange reactions leading to the formation of XI, XXVII and XXVIII were effectively quantitative and hence could not have been accompanied by significant decomposition. The stability of the free bases appears to be less than that of the salts. Compounds IX and XXI (as bases) were distilled *in vacuo* of 1–5 mm. The boiling points varied from 140–170° and there was obviously considerable decomposition.

The phenethyl-β-alanine esters were prepared from the appropriate secondary amines[9] by reaction either with methyl acrylate or with ethyl β-bromopropionate. The former reaction affords the methyl esters in nearly quantitative yield. In the earlier part of this work the desired ethyl esters were obtained from ethyl bromopropionate and compounds I, III, V, XII–XV, XXII, XXIII and XXIV were first prepared in this way. This reaction, however, is relatively unsatisfactory both on its own merits and in comparison with the excellent methyl acrylate procedure. After it was found that higher esters could be obtained readily by ester exchange from the methyl esters, the us of ethyl bromopropionate was discontinued.

Compounds XIII, XV and XXIX were isolated as acid oxalates, the corresponding hydrochlorides proving uncrystallizable.

**N-Phenethyl-β-alanine Methyl Esters.**—The bases to be transformed were mixed with about two equivalents of methyl acrylate (Eastman Kodak Co. "Practical Grade") in 5–10 volumes of benzene. The solutions were allowed to stand overnight and refluxed thirty to sixty minutes. On cooling, phenyl isocyanate was added in small portions (0.5–1 cc.) until its odor was detectable after standing for ten minutes; usually only 1–2 cc. of phenyl isocyanate was required.[10] Sufficient methanol was then added to combine with excess isocyanate and, after standing about twenty minutes, basic material was extracted with dilute hydrochloric acid. The aqueous solutions were basified with sodium carbonate and the oily bases were taken into ether and dried over potassium carbonate. The ethereal solutions were then run into methanol containing excess hydrogen chloride. In a number of cases the hydrochlorides could be induced to crystallize during this neutralization, never separating as oils or sirups. More often the sirupy layer of hydrochloride had to be worked over considerably before crystallization ensued.

N-Homoveratryl-β-alanine methyl ester hydrochloride (XX) was prepared by hydrogenation of the corresponding N-benzyl derivative with palladized charcoal. The N-benzyl compound, formed by the reaction of the known benzyl homoveratrylamine[11] with methyl acrylate, was

(9) With the exception of the precursor of compound XXV, whose preparation is described, all of these amines were known previously.

(10) This treatment with phenyl isocyanate is probably an unnecessary precaution. In the preparation of analogous substances from β-hydroxyphenethylamines, it appeared better to dispense with this operation, but the products were still obtained in semi-quantitative yields and substantially pure as first isolated.

(11) Buck, THIS JOURNAL, **53**, 2192 (1931).

not obtained analytically pure. Compound XX was also the only isolable product from the reaction of homoveratrylamine with excess methyl acrylate on the steam-bath (homoveratrylamine bis propionic ester had been expected and has subsequently been obtained by variation in reaction conditions).

**Ester Exchange Reactions.**—The methyl ester hydrochlorides to be transformed were dissolved in 10–20 parts by weight of the appropriate higher alcohol and a considerable amount of alcoholic hydrogen chloride. In the preparation of compound XXVII, 3.5 g. of compound XXVI, 100 cc. of absolute ethanol and 10 g. of ethanolic hydrogen chloride (33% by wt.) were refluxed four hours under a fractionating column, solvent being allowed to distil gradually until the volume was about 10 cc. On cooling and dilution with acetone and ether there was obtained 3.5 g. of product melting at 133–134°. The exchange was effectively quantitative.

The corresponding *n*-amyl ester (XXVIII) was recovered in only 70% yield from the reaction of 5 g. of XXVI 50 cc. of *n*-amyl alcohol and 15 cc. of methanolic hydrogen chloride (reflux time, two days with distillation of about half the amyl alcohol) but, since the amyl ester hydrochloride was pure as first isolated it is to be presumed that transformation had been virtually complete.

Compounds XI, XXVII and XXVIII were first prepared from the corresponding methyl esters by the above procedure. Compounds XVII and XXII were prepared in this fashion when additional material was required. It is to be presumed that any of the compounds actually prepared by the ethyl bromopropionate reaction could be obtained more advantageously through the methyl acrylate method followed by ester exchange.

**Preparation of Hydroxyphenethyl-β-alanine Esters.**—Compounds II, VI and XIX were formed by the demethylation of the corresponding methyl ethers (III, IX and XXI) with concentrated hydrochloric acid at 160–165° in glass bombs (four hours of heating). On opening the bombs the solutions were evaporated *in vacuo* and the residual solids were re-esterified by refluxing with ethanolic hydrogen chloride.

In the preparation of the diiodo compounds VII and VIII, the initial product of the demethylation of IX (presumably the acid corresponding to VI) was dissolved in ammonium hydroxide solution and iodinated by addition of a solution of iodine in dioxane.[12] When the disappearance of iodine had become very slow, the solution was evaporated *in vacuo* to small volume. Compound VII (probably a zwitter-ion) crystallized during this evaporation and was purified by crystallization from water. Compound VIII was formed by esterification of VII with ethanolic hydrogen chloride.

**Preparation of the Ethanolamides.**—When the β-alanine esters III and XVI were refluxed with excess ethanolamine compounds IV and XVIII were isolated from the reaction mixtures in poor yield and with difficulty. The analogous reaction with phenethyl glycine esters is very satisfactory and it is apparent that the present process involves decomposition of some sort. From one reaction between ethanolamine and XVI, run in methanol, a picrate was isolated corresponding to about one-third of the starting material. This picrate proved to be that of 2,5-dimethoxyphenethylmethylamine which must have been formed by loss of methyl acrylate from XVI. The methyl acrylate released may have combined with ethanolamine.

Somewhat better results were obtained by the method of Stoll[5]: Ester → hydrazide → azide → ethanolamide. This gave XVIII in about 25% yield. A major difficulty in the application of Stoll's procedure to substances of this type is found in the physical properties of the azide. Stoll's procedure was especially devised for the transformation of lysergic acid hydrazide into alkanolamides of lysergic acid. According to Stoll the azide of lysergic acid can be precipitated from aqueous solution by bicarbonate. The azides corresponding to compounds III and XVI are very soluble in water and salt solutions and are poorly and incompletely extracted therefrom by ether. Furthermore, the extractions prolong the operation which is probably undesirable.

**The Bromophenethyl Derivatives.**—Compound X resulted from the reaction of methyl acrylate with N-methyl-3-bromohomoanisylamine. This secondary amine had been prepared previously[13] by bromination of N-methylhomoanisylamine dissolved in hydrochloric acid. It had been assumed that substitution took place in the 3-position. This has now been confirmed by oxidation (with alkaline permanganate solution) to 3-bromo-4-methoxybenzoic acid. Compound XI was obtained from X by ester exchange.

**N-Methyl-6-bromo-3,4-dimethoxyphenethylamine.**—Bromination of N-methylhomoveratrylamine hydrochloride in aqueous solution proceeded smoothly. After one mol of bromine had been absorbed, the solution was basified, the amine taken into ether, dried over potassium carbonate and transformed to the hydrochloride which crystallized from ethanol–ethyl acetate–ether mixtures; m. p., 152–3°. *Anal.* Calcd. for $C_{11}H_{17}BrClNO_2$: C, 42.49; H, 5.52. Found: C, 42.48; H, 5.28. Substitution was shown to have been in the 6-position by oxidation (permanganate) to the known 6-bromoveratric acid (m. p., 184–185°).

Reaction of the base with methyl acrylate afforded XXV.

**Acknowledgment.**—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel W. Blackman for the performance of the microanalyses here recorded.

## Summary

1. A number of esters of substituted phenethyl-β-alanines have been prepared.

2. Some of these substances show oxytocic activity in laboratory animals.

TUCKAHOE 7, NEW YORK RECEIVED AUGUST 25, 1948

(12) *Cf.* Harington, *Biochem. J.*, **21**, 180 (1927).

(13) Buck, Baltzly and Ardis, THIS JOURNAL, **66**, 311 (1944).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

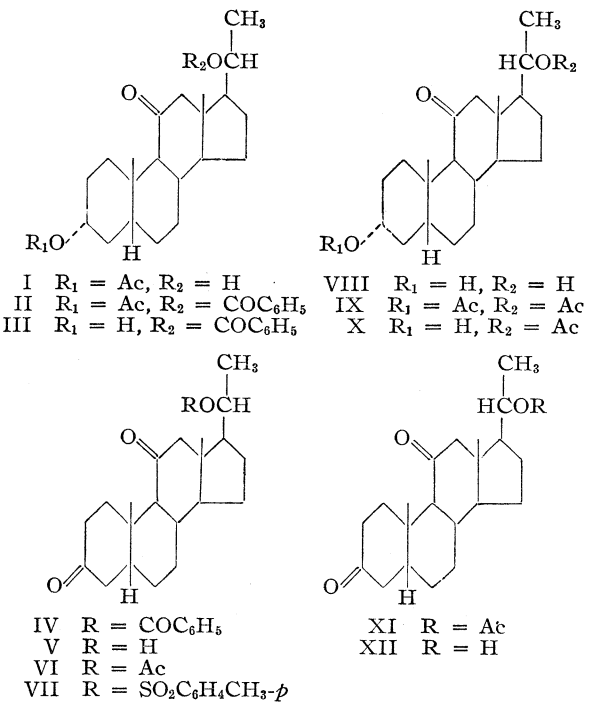
# Stereoisomeric Substituted 11-Keto-20-hydroxypregnanes. I

BY L. H. SARETT

In the course of synthetic studies in this Laboratory in the field of the adrenal steroids[1,2,3,4] a group of substituted 11-keto-20-hydroxypregnanes has been prepared. Some of the reactions which afford members of this group—reduction of a 20-ketopregnane, hydroxylation of a $\Delta^{17}$- or $\Delta^{20}$-pregnene—give both epimers in different but characteristic ratios. In order to illumine regularities peculiar to these reactions, as well as to make a needed nomenclatural integration, we have undertaken the stereochemical correlation of some of these compounds. The results of such an investigation are readily treated in four divisions: first, the correlation of the 11-ketopregnanes bearing the 20-hydroxy (Class A) and the 20,21-dihydroxy (Class B) side chains together with their derivatives which differ only in the substituent at C-3; second, the correlation of 11-ketopregnanes having 17,20-dihydroxy (Class C) and 17,-20,21-trihydroxy (Class D) side chains with their respective derivatives; third, the correlation *inter ipsos* of the four classes; fourth, the linking of this group of compounds with Reichstein's Substances J and O, the adrenal steroids which form the standard of references adopted by Reichstein and co-workers,[5,6,7] for 20-hydroxypregnanes. The present publication is concerned with the first of these divisions. For convenience in reference the results described in the succeeding divisions of this study will be used as the basis for assigning configurational indices to C-20 substituents. The assignment of these indices has been made in such a way as to indicate a very probable configurational correspondence with substances J and O at the C-20 position.

## Class A. Simple 11-Keto-20-hydroxypregnanes

The catalytic reduction of pregnane-3$\alpha$-ol-11,20-dione acetate to pregnane-3$\alpha$,20$\beta$-diol-11-one 3-acetate (I) and the corresponding 3$\alpha$,20$\alpha$-diol (isolated as the diacetate IX)[8] has been described.[3] The corresponding 3-keto derivatives have now been prepared. In the 20$\beta$-series this was accomplished by benzoylating I, partially saponifying the acetate benzoate (II), oxidizing the hydroxy benzoate (III) to the ketobenzoate (IV) and finally hydrolyzing to the ol-dione (V). In the 20$\alpha$-series the 20-monoacetate (X) was obtained by partial saponification[9] of the diacetate (IX). Oxidation then yielded pregnane-20$\alpha$-ol-3,11-dione acetate (XI).




I $R_1$ = Ac, $R_2$ = H
II $R_1$ = Ac, $R_2$ = $COC_6H_5$
III $R_1$ = H, $R_2$ = $COC_6H_5$

VIII $R_1$ = H, $R_2$ = H
IX $R_1$ = Ac, $R_2$ = Ac
X $R_1$ = H, $R_2$ = Ac

IV R = $COC_6H_5$
V R = H
VI R = Ac
VII R = $SO_2C_6H_4CH_3$-*p*

XI R = Ac
XII R = H

An additional source of pregnane-3$\alpha$,20$\alpha$-diol-11-one (VIII) was the alcoholic fraction obtained by diazotization of 20-aminopregnane-3$\alpha$-ol-11-one 3-acetate.[1] After chromatographic separation of the pregnen-3$\alpha$-ol-11-one acetate isomers, which constituted the chief product of the reaction, the crude alcoholic fraction was saponified and the diolone was readily purified by crystallization. In one experiment the 3$\alpha$,20$\beta$-diolone could also be isolated.[10]

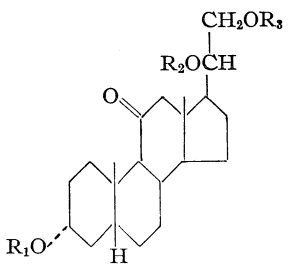
## Class B. 11-Keto-20,21-dihydroxypregnanes

The mixture of pregnen-3$\alpha$-ol-11-one acetate isomers mentioned above has been utilized to prepare pregnane-20$\beta$,21-diol-3,11-dione (XXI) and pregnane-20$\alpha$,21-diol-3,11-dione (XXVIII).[2] If, instead of conversion to the 3-keto derivative, the pregnene mixture was hydroxylated directly, a mixture of three triolones was obtained. These

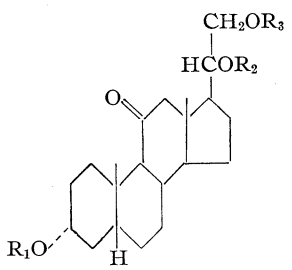
(1) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).
(2) Sarett, THIS JOURNAL, **68**, 2478 (1946).
(3) Sarett, *ibid.*, **70**, 1690 (1948).
(4) Sarett, *ibid.*, **70**, 1454 (1948).
(5) Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940).
(6) von Euw and Reichstein, *ibid.*, **24**, 401 (1941).
(7) Salamon and Reichstein, *ibid.*, **30**, 1616 (1947).
(8) In the cited publication the former compound was named without a configurational index for the 20-hydroxy group; the latter compound was called pregnane-3$\alpha$,20(epi)-diol-11-one. In writing the projection formulas in the present group of papers, a suggestion by Fieser and Fieser, *Experientia*, **4**, 285 (1948), has been followed. According to this suggestion the respective 20$\beta$- or 20$\alpha$-substituent is written on the left or the right of the C-20 carbon atom.
(9) *Cf.* Butenandt and Schmidt, *Ber.*, **67**, 1893 (1934).
(10) Hückel (*Ann.*, **533**, 1 (1938)) has demonstrated that the diazotization of optically active secondary amines with additional centers of asymmetry in the molecule may or may not proceed with retention of configuration.

consisted of the two pregnane-3$\alpha$,20,21-triol-11-one epimers (XIII and XXIII) corresponding to the dioldiones XXI and XXV, and also a 3$\alpha$,17$\alpha$,-20$\beta$-triolone.[11] Separation of XIII and XXIII was effected by chromatography of the 3-acetate acetonides (XIV and XXV). By the usual procedures, XIV and XXV could be converted to the partially acetylated triols, such as the 3-monoacetates (XVI and XXVI) and the 3,21-diacetates (XVII and XXVII).

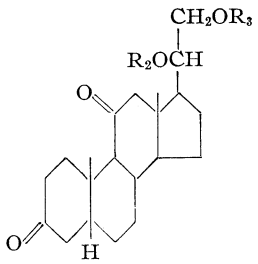
In order to correlate the pair of triolones with the dioldiones one of the former was converted[12] to its acetonide. Oxidation of the latter with N-bromacetamide in dry pyridine–*t*-butanol[13] afforded a nearly quantitative yield of the dioldione acetonide (XX). Hydrolysis and acetylation then yielded the previously described pregnane-20$\beta$,21-diol-3,11-dione diacetate (XXII). That the triolone isomeric with XIII must have the structure pregnane-3$\alpha$,20$\alpha$,21-triol-11-one (XXIII) was shown by oxidation to 3$\alpha$-hydroxy-11-ketoetiocholanic acid. The 3,21-diacetate (XXVII) in the 20$\alpha$-series, which was required for certain rotation data, was prepared through the intermediate acetonide (XXV) and monoacetate (XXVI).



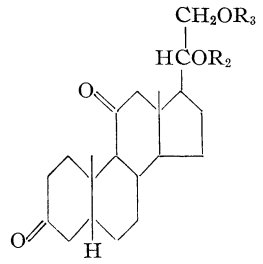
XIII $R_1 = R_2 = R_3 = H$
XIV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$
XV $R_1 = R_2 = R_3 = Ac$
XVI $R_1 = Ac$, $R_2 = R_3 = H$
XVII $R_1 = R_3 = Ac$, $R_2 = H$
XVIII $R_1 = R_3 = Ac$, $R_2 = SO_2C_6H_4CH_3$-*p*
XIX $R_1 = R_2 = Ac$, $R_3 = SO_2C_6H_4CH_3$-*p*



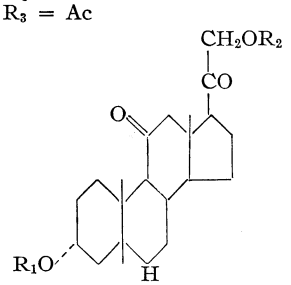
XXIII $R_1 = R_2 = R_3 = H$
XXIV $R_1 = R_2 = R_3 = Ac$
XXV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$
XXVI $R_1 = Ac$, $R_2 = R_3 = H$
XXVII $R_1 = R_3 = Ac$, $R_2 = H$



XX $R_2R_3 = >C(CH_3)_2$
XXI $R_2 = R_3 = H$
XXII $R_2 = R_3 = Ac$



XXVIII $R_2 = R_3 = H$
XXIX $R_2 = R_3$ Ac



XXX $R_1 = R_2 = Ac$
XXXI $R_1 = Ac$, $R_2 = OCH$
XXXII $R_1 = Ac$, $R_2 = H$

The preparation of 11-keto-20,21-dihydroxypregnanes by catalytic reduction of the ketol or ketol acetate gave results similar to those found on reduction of the simple 11,20-diketone. One isomer was the major product and it also belonged to the 20$\beta$-series.[14] Reduction of pregnane-3$\alpha$,21-diol-11,20-dione diacetate (XXX) yielded pregnane-3$\alpha$,20$\beta$,21-triol-11-one 3,21-diacetate (XVII), acetylation of which gave the triacetate (XV).

A second and more convenient method of preparing pregnane-3$\alpha$,20$\beta$,21-triol-11-one 3-acetate (XVI) employed as starting material 21-diazopregnane-3$\alpha$-ol-11,20-dione acetate.[15] This was treated with 90% formic acid, giving the acetate formate (XXXI), which hydrolyzed very rapidly in aqueous methanolic potassium bicarbonate to pregnane-3$\alpha$,21-diol-11,20-dione 3-acetate (XXXII). Catalytic reduction then gave XVI. The partial tosylation of this compound gave an amorphous 21-monotosylate which could be acetylated to give the crystalline diacetate tosylate (XVIII).

## Experimental[16]

**Pregnane-3$\alpha$,20$\beta$-diol-11-one 3-Acetate 20-Benzoate (II).**—A solution of 1.85 g. of pregnane-3$\alpha$,20$\beta$-diol-11-one 3-acetate (I), m.p. 205–206°, in 10 cc. of pyridine was treated with 2.0 cc. of benzoyl chloride and warmed at

(11) The structure of this compound is discussed in Part II.

(12) A slight modification of the method of Fischer and Taube (*Ber.*, **60**, 485 (1927)), using a 5% solution of zinc chloride in acetone, has been found to give excellent results with steroid glycols including the 17,20,21-triols.

(13) Reich and Reichstein (*Helv. Chim. Acta*, **26**, 562 (1943)) have shown that N-bromacetamide in aqueous acetone solution smoothly oxidizes secondary alcohols to ketones. These conditions are unsuitable, however, for molecules containing acid-sensitive functional groups.

(14) This relationship is discussed in Part III.

(15) The preparation of the 3$\beta$-acetoxy isomer of this compound from the corresponding etio acid has been described by Lardon and Reichstein (*Helv. Chim. Acta*, **26**, 747 (1943)).

(16) Melting points were taken on the Kofler micro hot stage and thus represent corrected values. Rotations were taken in acetone, $c$ = 1.0, except where otherwise indicated.

50° for five minutes. The product after recrystallization from alcohol melted at 188–189°; yield, 1.90 g.

*Anal.* Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 75.25; H, 8.60.

**Pregnane-3α,20β-diol-11-one 20-Benzoate (III).**—A solution of 2.05 g. of acetate benzoate (II) in 10 cc. of benzene was treated at 25° with 10 cc. of 1.1 *N* methanolic potassium hydroxide. After eight minutes the solution was neutralized with acetic acid and the benzene removed *in vacuo*, giving the crystalline hydroxybenzoate (III). After recrystallization from dilute alcohol and acetone, it melted at 236–237°; yield, 1.58 g.

*Anal.* Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.74. Found: C, 76.95; H, 8.45.

**Pregnane-20β-ol-3,11-dione Benzoate (IV).**—A solution of 1.55 g. of hydroxybenzoate (III) in 25 cc. of 90% acetic acid was treated at 15° with the solution of 0.80 g. of chromic acid in 16 cc. of 90% acetic acid. After one hour the solution was diluted with water, extracted with benzene, the latter washed with aqueous carbonate and concentrated to dryness *in vacuo*. The keto benzoate after crystallization from ether and from methanol melted at 161–162°; yield, 1.10 g.

*Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.24.

**Pregnane-20β-ol-3,11-dione (V).**—A solution of 1.0 g. of the keto benzoate in 15 cc. of 0.7 *N* methanolic potassium hydroxide was refluxed for forty-five minutes with gradual addition of water. The methanol was then removed *in vacuo*, the aqueous suspension extracted with chloroform, the latter washed with water and concentrated to dryness *in vacuo*. Crystallization from acetone gave 700 mg. of the ol-dione; m. p. 200°, $[\alpha]^{25}D$ + 52.5°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.99; H, 9.40.

**Pregnane-20β-ol-3,11-dione Acetate (VI).**—A sample (22 mg.) of the ol-dione was warmed on the steam-bath for a few minutes with pyridine–acetic anhydride. Addition of water and recrystallization from a small volume of methanol gave the acetate; m. p. 201–203°, $[\alpha]^{25}D$ + 75.5°.

**Pregnane-20β-ol-3,11-dione Tosylate (VII).**—A solution of 498 mg. of 20β-ol-dione in 2.1 cc. of pyridine was treated at 0° with 600 mg. of freshly recrystallized tosyl chloride. After three hours the solution was warmed to room temperature and permitted to stand overnight. After the addition of water, the tosylate was extracted with ether, washed with dilute hydrochloric acid, dilute potassium carbonate and water. Concentration of the ethereal solution and several recrystallizations of the residue from alcohol and ethyl acetate–petroleum ether gave crystals, m. p. 153°; yield, 500 mg.

*Anal.* Calcd. for $C_{28}H_{38}O_5S$: C, 69.11; H, 7.87. Found: C, 68.89; H, 8.10.

The tosylate reacted with refluxing collidine to give a crystalline mixture, m. p. 158–162°, the analysis of which corresponded roughly to a formula of $C_{21}H_{30}O_3$.

**Pregnane-3α,20α-diol-11-one 20-Acetate (X).**—To a solution of 230 mg. of pregnane-3α,20α-diol-11-one diacetate (IX), m. p. 235–236°, in 5 cc. of benzene was added 5 cc. of 1.1 *N* methanolic potassium hydroxide at 25°. After two and one-half minutes, the solution was acidified with acetic acid, concentrated to dryness *in vacuo* and extracted with benzene. The washed benzene solution was concentrated to a small volume and percolated through a column of alumina. Elution with petroleum ether–benzene mixtures removed diacetate and with ether–chloroform the 20-monoacetate (X). The latter weighed 80 mg. after recrystallization from dilute methanol and ether; m. p. 184–185°; $[\alpha]^{25}D$ + 50°.

*Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.36; H, 9.65. Found: C, 73.47; H, 9.48.

**Pregnane-20α-ol-3,11-dione Acetate (XI).**—Oxidation of 53 mg. of the 20α-monoacetate with chromic acid in the usual manner gave 51 mg. of crude crystals which were purified first by the use of Girard reagent T and then by chromatography. Twenty-four milligrams of the pure 20α-ol-dione acetate was obtained; m. p. 135°, $[\alpha]^{25}D$ + 54°. A mixture with pregnane-3α-ol-11,20-dione acetate (m. p. 136°) melted at 110–120°.

**Pregnane-20α-ol-3,11-dione (XII).**—The acetate (23 mg.) was saponified by warming on the steam-bath with dilute methanolic potassium hydroxide (0.5 *N*) for ten minutes. Recrystallization of the product gave 12.5 mg. of the 20α-ol-dione; m. p. 190–192°, $[\alpha]^{25}D$ +69.5° (*c* = 0.5). A mixed m. p. with pregnane-20β-ol-3,11-dione showed a depression of 20°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 76.13; H, 9.52.

**Pregnane-3α,20α-diol-11-one Diacetate (IX) from 20-Aminopregnane-3α-ol-11-one 3-Acetate.**—A portion (7.0 g.) of 20-aminopregnane-3α-ol-11-one acetate was heated with sodium nitrite and pyridine hydrochloride in aqueous pyridine as previously described.[1] Chromatography of the product gave 3.7 g. of unsaturated compounds, eluted with 8:2 petroleum ether–ether and 2.2 g. of material eluted with ether. Several crystallizations of the latter from ether and dilute acetone gave 200 mg. of pregnane-3α,20β-diol-11-one 3-acetate, m. p. 201–204°. A mixed m. p. with an authentic sample (m. p. 204–205°) was 202–204°. The mother liquors of the 3α,20β-diol monoacetate (2.0 g.) were acetylated and the product recrystallized from acetic acid, giving 600 mg. of pregnane-3α,20α-diol-11-one diacetate (IX), m. p. and mixed m. p. 234–235°. Saponification gave the 3α,20α-diol, m. p. and mixed m. p. 219°, $[\alpha]^{25}D$ + 61° (alc.). A number of repetitions of this experiment, using 2.0 equivalents of mineral acid in place of the pyridine hydrochloride yielded only the 3α,-20α-diol monoacetate in the ether eluates (isolated as the diacetate from acetylation).

**Pregnane-3α,20β,21-triol-11-one 3-Acetate 20,21-Acetonide (XIV) and Pregnane-3α,20α,21-triol-11-one Acetate 20,21-Acetonide (XXV).**—The chromatographically purified mixture of pregnene-3α-ol-11-one acetates from the diazotization of 3.0 g. of 20-aminopregnane-3α-ol-11-one 3-acetate amounted to 1.8 g. This material was treated with osmium tetroxide, the osmate esters hydrolyzed with hot aqueous alcoholic sodium sulfite and the product extracted in the usual manner (*e. g.*, ref. 2). The residual crude triols were dissolved in 45 cc. of acetone containing 2.3 g. of anhydrous zinc chloride and the solution permitted to stand overnight. A solution of 3.5 g. of potassium carbonate in 10 cc. of water was added, the mixture was shaken for a few minutes and the supernatant layer decanted. The residue was extracted again with acetone, the extracts combined and concentrated to a small volume after the addition of 5 cc. of a 10% solution of potassium carbonate. The oily precipitate was then extracted with ether, washed with water and concentrated to dryness. The residue (2.0 g.) was heated on the steam-bath with a mixture of 2.0 cc. of pyridine and 1.0 cc. of acetic anhydride for ten minutes, the solvents then removed *in vacuo*, the residue dissolved in 8:2 petroleum ether–benzene and chromatographed over 60 g. of (alkaline) alumina. The fractions eluted with 4:6 petroleum ether–benzene were combined and gave, after several recrystallizations from methanol, 400 mg. of pregnane-3α,20β-21-triol-11-one 3-acetate 20,21-acetonide (XIV); m. p. 137–139°, $[\alpha]^{25}D$ + 63.5°.

*Anal.* Calcd. for $C_{26}H_{40}O_5$: C, 72.20; H, 9.32. Found: C, 72.43; H, 9.38.

Subsequent elution with benzene and recrystallization of the combined eluates gave an equal amount of pregnane-3α,20α,21-triol-11-one 3-acetate 20,21-acetonide (XXV); m. p. 160–162°, $[\alpha]^{25}D$ + 68°.

*Anal.* Calcd. for $C_{26}H_{40}O_5$: C, 72.20; H, 9.32. Found: C, 72.46, 72.34; H, 9.23, 9.30.

Further elution with ether–benzene mixtures gave pregnane-3α,17α,20β-triol-11-one 3,20-diacetate, m. p. 249–250°, $[\alpha]^{25}D$ + 78.5°.

*Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.82. Found: C, 69.06; H, 8.60.

**Pregnane-3α,20β,21-triol-11-one 3-Acetate (XVI).**—A solution of 200 mg. of pregnane-3α,20β,21-triol-11-one 3-acetate 20,21-acetonide, m. p. 136–138°, in 2.0 cc. of acetic acid was diluted with 2.0 cc. of water and the mixture heated at 100° for fifteen minutes. Dilution with water, and extraction with ether followed by concentration of the washed ethereal solution to dryness gave 179 mg. of residue, which was crystallized from a small volume of cold ether, giving fluffy crystals of pregnane-3α,20β,21-triol-11-one 3-acetate; m. p. 121–123°, $[\alpha]^{25}D$ + 66°. The rotation was taken on a sample which had been heated briefly *in vacuo* at 130° to remove solvent of crystallization, which clung tenaciously to the crystals.

**Pregnane-3α,20α,21-triol-11-one 3-Acetate (XXVI).**—This compound was prepared from the corresponding 3-acetate acetonide (XXV) in the same manner. After recrystallization from dilute methanol it melted at 156–158°; $[\alpha]^{25}D$ + 74°.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.22; H, 9.21.

The two epimeric 3-monoacetates (XXVI and XVI) formed a molecular compound, m. p. 188–193°. A sample of this compound was chromatographed and then melted at about 195–197°.

**Pregnane-3α,20β,21-triol-11-one Triacetate (XV).**—Acetylation of pregnane-3α,20β,21-triol-11-one 3-acetate, m. p. 121–123°, with pyridine–acetic anhydride in the usual manner gave the triacetate; m. p. 158–159°, $[\alpha]^{25}D$ + 78°.

*Anal.* Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.11; H, 8.40.

**Pregnane-3α,20α,21-triol-11-one Triacetate (XXIV).**—Acetylation of the corresponding 3α,20α,21-triolone 3-acetate, m. p. 156–158°, gave the triacetate; m. p. 148°, $[\alpha]^{25}D$ + 49.5°.

*Anal.* Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.96; H, 8.17.

**Pregnane-3α,20β,21-triol-11-one (XII).**—Saponification of pregnane-3α,20β,21-triol-11-one triacetate, m. p. 158–159°, gave the readily crystalline triol as heavy prisms from dilute alcohol; m. p. 235°, $[\alpha]^{25}D$ + 53° (alc.).

*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.77. Found: C, 72.03; H, 9.51.

**Pregnane-3α,20α,21-triol-11-one (XXIII).**—Saponification of the 3α,20α,21-triolone triacetate gave the free triolone, m. p. 219–221°, $[\alpha]^{25}D$ + 55°.

*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.77. Found: C, 72.10; H, 9.40.

**Pregnane-3α,20α,21-triol-11-one 3,21-Diacetate (XXVII).**—A solution of 207 mg. of pregnane-3α,20α,21-triol-11-one 3-acetate, m. p. 156–158°, in 0.58 cc. of pyridine containing 58 mg. (1.2 molecular equivalents) of acetic anhydride was left at room temperature overnight. Removal of the solvents *in vacuo* and chromatography of the residue gave 113 mg. of crude diacetate fractions following the elution of 60 mg. of the triacetate, m. p. 148°. Recrystallization from ether–petroleum ether afforded 90 mg. of the 3,21-diacetate; m. p. 136–137°, $[\alpha]^{25}D$ + 67°.

*Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.32; H, 8.99.

**3α-Hydroxy-11-ketoetiocholanic Acid from Pregnane-3α,20α,21-triol-11-one.**—To a solution of 30 mg. of pregnane-3α,20α,21-triol-11-one, m. p. 219–221°, in 3 cc. of methanol was added 0.20 cc. of a 0.200 *N* solution of periodic acid. After standing at room temperature for two hours, the solution was diluted with 5 cc. of water, the methanol removed *in vacuo* and the oily aldehyde extracted with ether. The washed ethereal solution was concentrated to dryness, the residue dissolved in 1.5 cc. of acetone and treated with 0.40 cc. of a 5% aqueous solution of potassium permanganate. After ten minutes a few drops of dilute sulfurous acid was added, the acetone removed *in vacuo* and the crystalline precipitate filtered and washed with water. Recrystallization by concentration in a relatively large volume of acetone gave 3α-hydroxy-11-ketoetiocholanic acid, m. p. 282–286°. A mixed m. p. with an authentic sample (m. p. 289–293°) melted at 282–286°.

**Pregnane-3α,20β,21-triol-11-one 20,21-Acetonide.**—A suspension of 7.75 g. of pregnane-3α,20β,21-triol-11-one (XIII), m. p. 235°, in 300 cc. of acetone containing 15 g. of anhydrous zinc chloride was stirred until all of the crystals dissolved. After twenty hours the solution was treated in the usual manner (see above), giving a residue after removal of ether, which crystallized readily from ether–petroleum ether. The yield was 7.0 g. of acetonide, m. p. 138–141°, with 0.80 g. of a second crop melting slightly lower. Recrystallization of a sample from acetone–petroleum ether raised the m. p. to 141–142°.

*Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.51; H, 9.57.

**Pregnane-20β,21-diol-3,11-dione Acetonide (XX).**—To a solution of 7.0 g. of pregnane-3α,20β,21-triol-11-one acetonide, m. p. 141–142°, in 100 cc. of dry *t*-butyl alcohol was added 5.0 g. of N-bromacetamide (monohydrate) followed by 10 cc. of pyridine. After the bromacetamide had gone into solution, the mixture was permitted to stand at room temperature for eighteen hours, then poured into a separatory funnel containing ether and a solution of 10 g. of sodium sulfite in 60 cc. of water. The mixture was shaken vigorously, the ethereal layer washed with water and concentrated to dryness. Crystallization from dilute alcohol gave 6.2 g. of diol-dione acetonide, which melted at about 163°, partially resolidified and melted again at 171–174°. A sample which was chromatographed and recrystallized from ether–petroleum ether consisted of fine needles, m. p. 168.5–169.0° with transformation into prisms; m. p. 179–180°, $[\alpha]^{25}D$ +55°.

*Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34. Found: C, 74.25; H, 9.14.

**Pregnane-20β,21-diol-3,11-dione Diacetate (XXII) from Pregnane-20β,21-diol-3,11-dione Acetonide (XX).**—A sample of pregnane-20β,21-diol-3,11-dione acetonide, m. p. 169°; 180°, was hydrolyzed with hot dilute acetic acid, the solvents removed *in vacuo* and the residue acetylated in the usual manner. Crystals of pregnane-20β,21-diol-3,11-dione diacetate were obtained, m. p. and mixed m. p. 175°.

**Pregnane-3α,20β,21-triol-11-one 3,21-Diacetate (XVII).**—Pregnane-3α,21-diol-11,20-dione diacetate (XXX) (13.2 g., containing 10% of ether of crystallization) was dissolved in 30 cc. of acetic acid. The solution was concentrated to two-thirds volume *in vacuo* to remove ether, then diluted with 80 cc. of acetic acid and reduced under a pressure of 45 lb. of hydrogen, using 1.0 g. of platinum oxide as catalyst. After 1.0 mole of hydrogen had been consumed the reduction came nearly to a halt. The solution was filtered, concentrated to dryness *in vacuo* and taken up in ether. The ethereal solution was washed with dilute carbonate solution and with water, and concentrated to dryness. Crystallization of the residue from benzene–petroleum ether gave 8.35 g. of the 3α,20β,-21-triolone diacetate. After recrystallization from dilute methanol it melted at 189–190°; $[\alpha]^{25}D$ + 65° (+68° in alcohol).

*Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.21; H, 8.90.

With acetic anhydride–pyridine the diacetate was converted to the 3α,20β,21-triolone triacetate, m. p. 159°. The mother liquors from the reduction product were acetylated and chromatographed. In addition to some starting material (diketone) and 3α,20β,21-triolone triacetate, about 5% of the 3α,20α,21-triolone triacetate, m. p. and mixed m. p. 148°, was isolated. Fractional crystallization of the two isomeric triacetates was facilitated by the fact that the 20β-triacetate was somewhat less soluble in cold ether than the 20α, while the latter was less soluble in cold methanol.

**Pregnane-3α,20β,21-triol-11-one 3,21-Diacetate 20-Tosylate (XVIII).**—A cold solution of 6.25 g. of pregnane-3α,20β,21-triol-11-one 3,21-diacetate in 30 cc. of pyridine was treated with 6.0 g. of recrystallized tosyl chloride. After three days at 0° the solution was diluted with water, extracted with benzene, the benzene layer washed with dilute hydrochloric acid, dilute carbonate and with water, then concentrated to dryness *in vacuo*. Crystallization of the residue from ether gave 7.4 g. of the diacetate tosylate, m. p. 175–176°.

*Anal.* Calcd. for $C_{32}H_{44}O_8S$: C, 65.28; H, 7.53. Found: C, 65.18; H, 7.56.

**Pregnane-3α,21-diol-11,20-dione 3-Acetate 21-Formate (XXI).**—A portion (500 mg.) of 21-diazopregnane-3α-ol-11,20-dione acetate (dec. 117–124°; prepared according to the method of Lardon and Reichstein, ref. 15) was added to 3.5 cc. of 90% formic acid. After three minutes the crystals had dissolved with evolution of nitrogen. The solution was warmed gently on the steam-bath for a few seconds, until a pink color began to replace the pale yellow cast. The solution was then diluted with water, extracted with ether, the ethereal layer washed with alkali and with water and concentrated to dryness. Crystallization from a small volume of ether gave dense prisms of the formate, m. p. 153° after recrystallization from alcohol and from ether. The mother liquor was chromatographed, giving in all 430 mg. of acetate formate.

*Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.02; H, 8.03.

**Pregnane-3α,21-diol-11,20-dione 3-Acetate (XXXII).**—A solution of 170 mg. of the acetate formate, m. p. 153°, in 5 cc. of methanol was treated with a solution of 200 mg. of potassium bicarbonate in 2.0 cc. of water. The mixture was stirred for ten minutes, acidified with a few drops of acetic acid, concentrated to a small volume *in vacuo* and extracted with ether. Evaporation of the washed ethereal solution, followed by crystallization of the residue from a small volume of ether gave 129 mg. of pregnane-3α,21-diol-11,20-dione 3-acetate, m. p. 137–138°.

*Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.69; H, 8.75.

**Pregnane-3α,20β,21-triol-11-one (VI) 3-Acetate from Pregnane-3α,21-diol-11,20-dione 2-Acetate (XXXII).**—The catalytic reduction of 2.48 g. of pregnane-3α,21-diol-11,20-dione 3-acetate, m. p. 137–138°, in 100 cc. of glacial acetic acid, using 1.0 g. of platinum oxide under 45 lb. of pressure was completed in an hour. The filtered solution was concentrated to dryness *in vacuo*, the residue dissolved in ether, washed with alkali and water and concentrated to dryness. Crystallization from a small volume of cold absolute ether gave 2.1 g. of fluffy solvated crystals, m. p. 120–126°. Recrystallization from ethyl acetate–petroleum ether gave a sample of m. p. 100–106° (bubbling). Saponification gave pregnane-3α,20β,21-triol-11-one, m. p. and mixed m. p. 235–236°. For analysis a sample was dried in a weighing pig at 130°.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.55; H, 9.10. Weight loss: 2.18%.

**Acknowledgments.**—The author wishes to express his indebtedness to Dr. Karl Folkers for his active association with this work, to Dr. Everett S. Wallis of Princeton University for valuable suggestions, and to Miss Jean E. Andrews for assistance. The author is indebted to Mr. R. N. Boos and his associates for microanalyses.

## Summary

The preparation and correlation of derivatives of pregnane-3α,20α and β-diol-11-one and the corresponding 3-ketones have been described. Similar correlations in the pregnane-3α,20α and β-21-triol-11-one series have been made.

RAHWAY, N. J. RECEIVED OCTOBER 20, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# Stereoisomeric Substituted 11-Keto-20-hydroxypregnanes. II

BY L. H. SARETT

In Part I of this series[1] the preparation of various derivatives of the stereoisomeric 11-keto-20-hydroxypregnanes and 11-keto-20,21-dihydroxypregnanes was described. Part II deals with the two remaining classes of 11-keto-20-hydroxypregnanes.

## Class C. 11-Keto-17(α),20-dihydroxypregnanes[2]

A useful starting material for the preparation of compounds of this class is pregnane-3α,17α-diol-11,20-dione[3] (I). Since the assignment of the α-configuration to the C-17 hydroxyl was, however, based on indirect evidence, it was felt that more conclusive stereochemical proof was desirable before proceeding to an investigation of the reduction products of this compound. To this end a device employed by von Euw and Reichstein[4] for converting substance P to substance L was used. Pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate,[2] which has been linked[5] sterically with the naturally occurring $\Delta^4$-pregnene-17α,21-diol-3,11,-20-trione (Kendall's compound E), was treated with methylmagnesium iodide, giving 20-methylpregnane-3α,17α,20 (α and β), 21-tetrol-11-one. When periodic acid cleavage of this mixture then yielded I, the α-configuration of the 17-hydroxyl in the latter compound was established.

The catalytic reduction of pregnane-3α,17α-diol-11,20-dione 3-acetate (II) gave both of the epimeric triolones. By benzoylation of the reduction mixture 15% of a highly crystalline 3-acetate 20-benzoate (XII) could be isolated. Upon saponification it yielded the 3α,17α,20α-triolone (VIII) which was identical with that previously obtained[6]

(1) Sarett, THIS JOURNAL, **71**, 1165 (1949).

(2) The formulation of the C-17 hydroxyl group as alpha in the natural series of 17-hydroxypregnanes follows the evidence presented by von Euw and Reichstein (*Helv. Chim. Acta*, **30**, 205 (1947)).

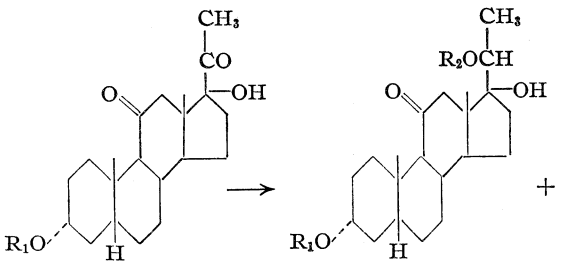
(3) Sarett, THIS JOURNAL, **70**, 1454 (1948).

(4) von Euw and Reichstein, *Helv. Chim. Acta*, **24**, 418 (1941).

(5) A communication describing these results is soon to be published.

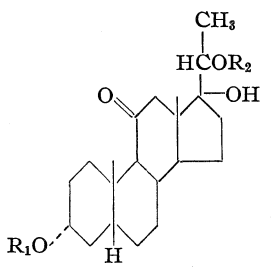
(6) Sarett, THIS JOURNAL, **70**, 1690 (1948).

by hydroxylation of a $\Delta^{17}$-pregnen-3$\alpha$-ol-11-one. The major product of the reduction was best separated by conversion of the reduction mixture to the diacetates. Repeated crystallization then yielded pregnane-3$\alpha$,17$\alpha$,20$\beta$-triol-11-one 3,20-diacetate[7] (V). By saponification the new 3$\alpha$,-17$\alpha$,20$\beta$-triolone (III) was obtained.

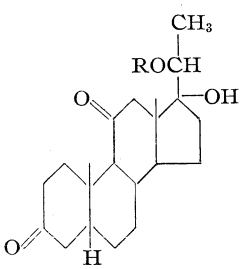


I $R_1$ = H
II $R_1$ = Ac

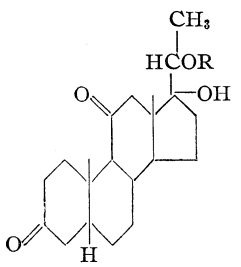
III $R_1$ = $R_2$ = H
IV $R_1$ = H; $R_2$ = Ac
V $R_1$ = $R_2$ = Ac



VIII $R_1$ = $R_2$ = H
IX $R_1$ = $R_2$ = Ac
X $R_1$ = H, $R_2$ = Ac
XI $R_1$ = Ac, $R_2$ = H
XII $R_1$ = Ac, $R_2$ = $C_6H_5CO$
XIII $R_1$ = Ac, $R_2$ = $SO_2C_6H_4CH_3$



VI R = H
VII R = Ac



XIV R = H
XV R = Ac

In order to prepare the 3-keto derivatives corresponding to the triolones III and VIII, the respective 20-monoacetates were required. In the 20$\beta$-series the 20-monoacetate (IV) was readily obtained by partial saponification of the diacetate. Oxidation and hydrolysis then yielded pregnane-17$\alpha$,20$\beta$-diol-3,11-dione (VI). This compound was identical with a pregnane-17,20-diol-3,11-dione previously described in the literature.[8] Pregnane-17$\alpha$,20$\alpha$-diol-3,11-dione (XIV) was derived from the free triolone VIII by partial acetylation. Surprisingly enough, the product which was isolated by chromatography was the 20-monoacetate (X), although doubtless the anticipated 3-monoacetate was also formed. Conversion of X to pregnane-17$\alpha$,20$\alpha$-diol-3,11-dione (XIV) was then carried out as before.

A second method for obtaining derivatives of 11-keto-17,20-dihydroxypregnanes was the hydroxylation of $\Delta^{17}$-11-ketopregnenes. Insofar as the simple preparation of one or both of the dihydroxypregnanes (III and VIII) was concerned, hydroxylation of one of the mixtures of $\Delta^{17}$- and $\Delta^{20}$-pregnenes formed by various reactions was quite satisfactory. It rapidly became apparent, however, that the nature of the products depended so markedly on the nature of the starting mixture that the simple interpretation of the latter as composed of one of the two possible geometrically isomeric $\Delta^{17}$-pregnenes together with the $\Delta^{20}$-pregnene was dubious. Hence a closer examination of the components of these mixtures was undertaken.

The preparation and hydroxylation of a pure $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one (XVI) which melted at 192° have been described.[7] When a crystalline product from the mother liquors of this compound was treated with osmium tetroxide, hydrolyzed and the product acetylated, it was not, however, the 3$\alpha$,17$\alpha$,20$\alpha$-triol diacetate (IX) which was isolated but the epimeric 3$\alpha$,17$\alpha$,20$\beta$-triol diacetate (IV). Only two explanations for these results seemed possible: Either the presence of impurities altered the stereochemical course of the reaction in some unknown way or else a second component reacted with the osmium tetroxide to form IV. In order to test the first possibility, the hydroxylation of mixtures of the pure $\Delta^{17}$-pregnene with coprostanone and also with benzoyl peroxide was carried out. The addition of these substances neither altered the nature of the product (VIII) nor diminished the yield. Hence the second and likelier possibility was explored.

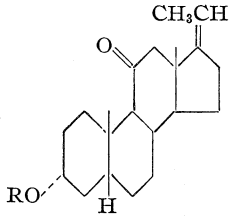
If a second component gave rise to the 3$\alpha$,17$\alpha$,-20$\beta$-triolone, it could only be the geometrically isomeric $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one (XVIa), which upon attack of the osmium tetroxide at the rear of the 17,20 linkage would give a 17$\alpha$,20$\beta$-glycol osmate ester. Attempts to isolate this hypothetical geometrical isomer by chromatography and fractional crystallization of the detosylated mother liquor unfortunately were unsuccessful. The higher melting fractions eventually gave pure XVI, while the lower melting fractions remained mixtures with inconstant properties.

The mixture of pregnenes prepared by diazotization of 20-aminopregnane-3$\alpha$-ol-11-one 3-acetate was then examined. Since only one 3$\alpha$,17,20-triolone was obtained by hydroxylation of this mixture and it was the 17$\alpha$,20$\beta$-isomer (see Part I), it seemed possible that the sought for $\Delta^{17}$-geometrical isomer might be present. Accordingly, the pregnene mixture was submitted to extensive recrystallization. A compound which melted at 154° was isolated in small amount but it appeared

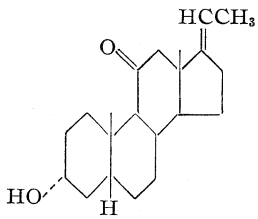
(7) Evidence for the assignment of configuration to the C-20 hydroxyl group is presented in Part III of this series.

(8) Sarett, THIS JOURNAL, **68**, 2478 (1946).

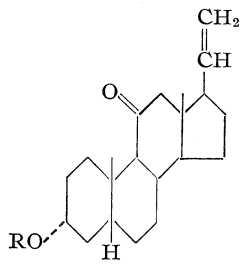
to be identical[9] with $\Delta^{20}$-pregnene-3$\alpha$-ol-11-one (see diagram).



XVI R = H
XVII R = Ac



XVIa



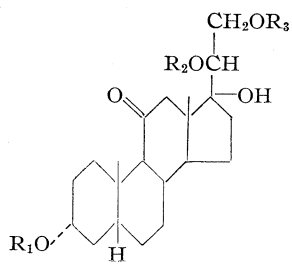
XVIII R = H
XIX R = Ac

When $\Delta^{17}$-21-bromopregnene-3$\alpha$-ol-11-one acetate[10] was reduced with zinc and acetic acid and the product saponified, a compound which gave pregnane-3$\alpha$,20($\alpha$ and $\beta$),21-triol-11-one upon hydroxylation was isolated. Evidently the bromide was reduced as a resonating ion, giving a mixture of isomeric pregnenes of which only the least soluble—the $\Delta^{20}$—was separated. The dehydration of pregnane-3$\alpha$,17$\beta$-diol-11-one acetate with phosphorus oxychloride also gave a mixture of crystalline unsaturates, from which no pure compound was obtained. However, in spite of the failure to obtain a pure sample of the geometrical isomer of $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one, the evidence described appears strongly to indicate its existence in those mixtures which yielded the triolone III on hydroxylation.

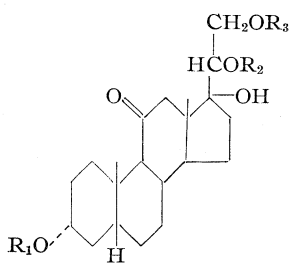
An interesting and perhaps generally useful procedure for the hydrolysis of osmate esters under milder conditions than previously suggested[11] was uncovered in our work on the 17,20-glycols. Since even the relatively gentle conditions described by Criegee and co-workers[11] lead to partial hydrolysis of acetate groups in the molecule, the restoration of such an acetate group must ordinarily be accomplished by preferential esterification. This must be the approach, for example, in the preparation of the 3-monoacetate of a 3,-17,20-triol, in which the protection of the glycol group by an acetonide bridge is not possible. It was found, however, that if the aqueous sodium sulfite solution was added at room temperature to the solution of osmate ester in alcohol containing about 20% of ether, hydrolysis of the osmate linkages occurred far more rapidly than hydrolysis of the acetate group. By this method $\Delta^{17}$-pregnene-3$\alpha$-ol-11 one acetate gave 80% of pregnene-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one 3-acetate (XI). The difference is probably to be ascribed to the physical state of the sodium sulfite, which in the presence of ether separates as a gummy, moderately soluble layer instead of the ordinary nearly insoluble crystals.

## Class D. 11-Keto-17$\alpha$,20,21-trihydroxypregnanes

An important source of members of this class is the $\Delta^{17}$-21-hydroxypregnenes. These have been prepared by the classical allylic rearrangement method[12] and also by the 20-tosylate–collidine reaction.[6] Since the problem of geometrical isomerism arose in connection with the preparation of 17,20-dihydroxypregnanes from $\Delta^{17}$-pregnenes, evidence for this type of isomerism in the 21-hydroxy-$\Delta^{17}$-pregnene series was sought. However, it was found that by either method of preparation only one $\Delta^{17}$-pregnene-3$\alpha$,21-diol-11-one[8] was obtained. Hydroxylation of this compound yielded pregnane-3$\alpha$,17$\alpha$,20$\beta$,21-tetrol-11-one (XX), which could be linked sterically with the previously described pregnane-17$\alpha$,20$\beta$,21-triol-3,11-dione[13] by oxidation of the acetonide (XXIII). The 3,21-diacetate (XXI) was prepared by reduction of pregnane-3$\alpha$,17$\alpha$,21-triol-11,20-dione 3,21-diacetate. Acetylation of the mother



XX $R_1 = R_2 = R_3 = H$
XXI $R_1 = R_3 = Ac$, $R_2 = H$
XXII $R_1 = R_2 = R_3 = Ac$
XXIII $R_1 = H$, $R_2R_3 = >C(CH_3)_2$
XXIV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$



XXV $R_1 = R_2 = R_3 = H$
XXVI $R_1 = R_2 = R_3 = Ac$

(9) The two samples agreed in all properties except the melting points of the acetates. Very likely neither sample was entirely free from isomorphous pregnene-3$\alpha$-ol-11-one isomers.

(10) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(11) See, for example, Criegee, Marchand and Wannowius, *Ann.*, **550**, 99 (1942); Prins and Reichstein, *Helv. Chim. Acta*, **25**, 300 (1942); Criegee, *Ann.*, **522**, 75 (1936).

(12) Ruzicka and Müller, *Helv. Chim. Acta*, **23**, 416 (1939).

(13) This compound was named according to the earlier system of nomenclature pregnane-17$\beta$,20$\beta$,21-triol-3,11-dione.

liquors of XXI, followed by chromatographic separation permitted the isolation of 10% of the epimer (XXVI), pregnane-3α,17α,20α,21-tetrol-11-one triacetate.

## Experimental[14]

**Pregnane-3α,17α-diol-11,20-dione (I) from Pregnane-3α,17α,21-triol-11,20-dione Diacetate.**—A solution of 511 mg. of pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate, m. p. 233–236°, in 40 cc. of warm anhydrous benzene was treated with 20 cc. of an ethereal solution of methylmagnesium iodide prepared from 5 g. of methyl iodide and 0.75 g. of magnesium. The suspension was permitted to stand at room temperature for two days, then poured into 0.1 *N* hydrochloric acid, the benzene layer washed and concentrated to dryness. The residue deposited 160 mg. of poorly formed crystals from a small volume of acetone, which after recrystallization gave 44 mg., m. p. 215–237°. This partially purified product, 20-methylpregnane-3α,17α,20,21-tetrol-11-one, was then dissolved in 3 cc. of methanol, and treated with 1.5 cc. of 0.200 *N* periodic acid. The solution was then concentrated *in vacuo* to half-volume, left at room temperature for three hours, then concentrated to *ca.* 1.5 cc. *in vacuo*. Recrystallization of the precipitate from dilute methanol and from ether gave pregnane-3α,17α,diol-11,20-dione, m. p. 205–207°. A mixed m. p. with an authentic sample, m. p. 206–208°, showed no depression.

**Pregnane-3α,17α,20α-triol-11-one 3-Acetate 20-Benzoate (XII).**—A solution of 250 mg. of pregnane-3α,17α-diol-11,20-dione 3-acetate (II) in 25 cc. of acetic acid was shaken under hydrogen with 300 mg. of platinum oxide until 1.0 mole of hydrogen was consumed. After the usual working up, the residue was dissolved in 2.0 cc. of pyridine and treated with 0.4 cc. of benzoyl chloride. The mixture was left at room temperature overnight, diluted with water, extracted with ether, the ethereal layer washed with dilute hydrochloric acid, dilute carbonate solution and with water. Concentration to dryness gave 350 mg. of residue which deposited 48 mg. of crystals from a small volume of methanol. Recrystallization from chloroform–alcohol and chloroform–ether gave the 3α,17α,20α-triolone acetate benzoate, m. p. 264–265°.

*Anal.* Calcd. for $C_{30}H_{40}O_6$: C, 72.55; H, 8.11. Found: C, 72.88; H, 7.84.

Saponification of a sample of the acetate benzoate gave pregnane-3α,17α,20α-11-one; m. p. 211–212°, $[\alpha]^{25}D$ +23°. A mixed m. p. with an authentic sample gave no depression. It was found that an unsolvated, well-crystallized form could be obtained by crystallization from anhydrous acetone.

*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.79. Found: C, 71.97; H, 9.81.

**Pregnane-3α,17α,20β-triol-11-one 3,20-Diacetate (V) from Pregnane-3α,17α-diol-11,20-dione (I).**—The crude product from the catalytic reduction of 420 mg. of pregnane-3α,17α-diol-11,20-dione was acetylated in the usual manner. After several recrystallizations of the product from dilute acetone, 320 mg. of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate was obtained, m. p. and mixed m. p. 249–250°. Chromatography of the mother liquors gave lower melting mixtures from which no pure 3α,17α,20α-triolone diacetate could be isolated.

**Pregnane-3α,17α,20β-triol-11-one (III).**—Saponification of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate, m. p. 249–250°, afforded the free triolone, m. p. 220° after recrystallization from dilute methanol or acetone–ether. A double melting point of 179°, 220° was occasionally observed; $[\alpha]^{25}D$ +38°.

*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.79. Found: C, 72.04; H, 9.76.

**Pregnane-3α,17α,20β-triol-11-one 20-Acetate (IV).**—To a warm mixture of 10.0 cc. of benzene and 1.0 cc. of methanol was added 565 mg. of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate. The solution was quickly cooled to 25° and treated with 10 cc. of a solution of 1.1*N* methanolic potassium hydroxide. After two and one-half minutes, the potassium hydroxide was neutralized with acetic acid, the solvents removed *in vacuo*, and the residue extracted with chloroform. The washed chloroform extract was concentrated to dryness, the partially crystalline residue dissolved in benzene and chromatographed over 15 g. of acid-washed alumina. After elution of diacetate (ether) 235 mg. of crude 20-monoacetate was eluted with chloroform. Recrystallization from ethyl acetate and dilute methanol gave 180 mg. of the 3α,17α,20β-triolone 20-acetate; m. p. 231–234°, $[\alpha]^{25}D$ + 55°.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.34; H, 9.44.

**Pregnane-17α,20β-diol-3,11-dione 20-Acetate (VII) from Pregnane-3α,17α,20β-triol-11-one 20-Acetate (IV).**—A solution of 17 mg. of the 3α,17α,20β-triolone 20-acetate, m. p. 231–234°, in 1.0 cc. of 90% acetic acid was treated at 15° with 0.30 cc. of 90% acetic acid containing 15 mg. of chromic acid. The solution was allowed to warm to 25° and, after forty-five minutes, water was added to induce crystallization of the product. Recrystallization from methanol gave pregnane-17α,20β-diol-3,11-dione 20-acetate, m. p. 222–224°. Admixture with an authentic specimen, m. p. 222.0–224.5°, showed no depression.[15]

**Pregnane-3α,17α,20α-triol-11-one 20-Acetate (X).**—To 0.60 cc. of pyridine containing 91 mg. of acetic anhydride was added 248 mg. of pregnane-3α,17α,20α-triol-11-one, m. p. 211–212°. After standing at room temperature overnight, the solution was concentrated to dryness *in vacuo*, the residue dissolved in benzene and chromatographed. The fractions eluted with chloroform gave 164 mg. of crystalline 3α,17α,20α-triolone 20-acetate; m. p. 212°, $[\alpha]^{25}D$ +2°.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.65; H, 9.40.

**Pregnane-17α,20α-diol-3,11-dione 20-Acetate (XV).**—A solution of 131 mg. of pregnane-3α,17α,20α-triol-11-one 20-acetate (X) was oxidized with chromic acid in the usual manner. Dilution of the oxidation mixture with water and addition of sufficient solid potassium carbonate to neutralize most of the acetic acid gave a crystalline precipitate, which after recrystallization from dilute methanol and ether afforded 90 mg. of pure 17α,20α-diol-dione 20-acetate; m. p. 182–183°, $[\alpha]^{25}D$ + 12°.

*Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.77; H, 8.53.

**Pregnane-17α,20α-diol-3,11-dione (XIV).**—A solution of 90 mg. of pregnane-17α,20α-diol-3,11-dione 20-acetate, m. p. 182–183°, in a mixture of 3.0 cc. of methanol and 1.0 cc. of 1 *N* aqueous potassium hydroxide was refluxed for three minutes. The methanol was then removed *in vacuo*, the aqueous suspension acidified with a few drops of acetic acid and extracted with chloroform. The washed chloroform solution was concentrated to dryness *in vacuo*, the residue crystallized from ether and again from acetone–ether; m. p. 190–191°, $[\alpha]^{25}D$ +32.5°.

*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.55: H, 9.31.

**Pregnane-3α,17α,20β-triol-11-one Diacetate (IV) from Crude $\Delta^{17}$-Pregnene-3α-ol-11-one.**—The mother liquors obtained from the methanol recrystallizations of $\Delta^{17}$-pregnene-3α-ol-11-one (prepared by treatment of the 3α,20β-diolone acetate tosylate with collidine, followed by saponification of the product) were concentrated to a small volume, diluted with a small volume of water, and left at 0°. A fluffy crystalline precipitate formed, m. p. 130–160°. Since fractional recrystallization of this mixture led only to the isolation of small amounts of the high

(14) Melting points were taken on the Kofler micro hot stage; rotations unless otherwise indicated were taken in acetone, $c$ = 1.0.

(15) These values are characteristic of freshly prepared samples of this compound. Long heating *in vacuo* raises the m. p. as much as 7°.

melting $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one, together with various fractions of inconstant properties, and chromatography likewise gave no appreciable separation, a portion of the crystalline mixture was hydroxylated with osmium tetroxide in the usual manner, and the product acetylated. After chromatography about 25% of the 3$\alpha$,17$\alpha$,20$\beta$-triolone diacetate, m. p. and mixed m. p. 249–250°, was obtained.

**Reaction of Pure $\Delta^{17}$-Pregnene-3$\alpha$-ol-11-one with Osmium Tetroxide in the Presence of:**

**A. Benzoyl Peroxide.**—A solution of 100 mg. of $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one, m. p. 192°, in 20 cc. of absolute ether containing 25 mg. of benzoyl peroxide was treated with 100 mg. of osmium tetroxide followed by 0.05 cc. of pyridine. The precipitated osmate ester was filtered, hydrolyzed and the triol acetylated as usual. Pregnane-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one diacetate, m. p. 228–229°, was obtained in 80% yield.

**B. Acetone.**—Repetition of the reaction, substituting 45 mg. of acetone for the benzoyl peroxide led to the same results.

**C. Coprostanone.**—Substitution of 125 mg. of coprostanone for the benzoyl peroxide gave the same results.

**$\Delta^{20}$-Pregnene-3$\alpha$-ol-11-one (XVIII) from 20-Aminopregnane-3$\alpha$-ol-11-one 3-Acetate.**—One gram of the chromatographically purified mixture of pregnene-3$\alpha$-ol-11-one acetate isomers obtained by diazotization of the 20-amine was saponified by refluxing for fifteen minutes with 20 cc. of 1 *N* methanolic potassium hydroxide. Dilution and cooling of the solution gave 380 mg. of an almost gelatinous crystal mass, m. p. 136–140°. Repeated recrystallization from dilute methanol and ether–petroleum ether raised the melting point to 153–154°; $[\alpha]^{25}D$ +37°. It did not depress the m. p. of $\Delta^{20}$-pregnene-3$\alpha$-ol-11-one (see below). Acetylation gave an acetate, m. p. 115–116°.

The addition of water to the mother liquors of the original saponification product caused the slow deposition of 400 mg. of crystals of the same appearance as the pregnene-3$\alpha$-ol-11-one of m. p. 153°. They melted, however, at 97–99° and, after four recrystallizations, more or less constantly at 116–117°; there was not enough of this material for an analysis of the hydroxylation products.

**$\Delta^{20}$-Pregnene-3$\alpha$-ol-11-one (XVIII) from $\Delta^{17}$-21-Bromopregnene-3$\alpha$-ol-11-one Acetate.**—To a solution of 1.35 g. of $\Delta^{17}$-21-bromopregnene-3$\alpha$-ol-11-one acetate in 10 cc. of acetic acid was added 2.0 g. of zinc dust portionwise, with warming on the steam-bath. After fifteen minutes, the solution was cooled, diluted with water, extracted with ether, the ether layer washed with aqueous carbonate and concentrated to dryness. The residue was refluxed with 1.0 *N* methanolic potassium hydroxide for ten minutes, water added, the methanol removed *in vacuo* and the precipitated product extracted with ether. The residue from the concentration of the ethereal solution weighed 935 mg. and was purified chromatographically, giving 550 mg. of $\Delta^{20}$-pregnene-3$\alpha$-ol-11-one; m. p. 153–154°; $[\alpha]^{25}D$ + 38.5°.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.68; H, 10.12. Found: C, 79.46; H, 10.26.

Acetylation of a sample of this alcohol gave an acetate, m. p. 106°. A mixed m. p. with the $\Delta^{20}$ acetate of m. p. 116° was 109–111°. Refluxing a sample of the alcohol with collidine–collidinium tosylate did not appreciably alter its properties.

Treatment of the $\Delta^{20}$-pregnenolone, m. p. 153–154°, with osmium tetroxide and acetylation of the hydrolysis product in the usual manner gave a mixture of prismatic crystals and clusters of needles, resembling the usual mixture of pregnane-3$\alpha$,20($\alpha$ and $\beta$), 21-triol-11-one triacetate. Recrystallization from methanol gave the pure 3$\alpha$,20$\alpha$,21-triolone triacetate, m. p. and mixed m. p. 147.5–148.5°. Several crystallizations of the mother liquors from ether yielded the 3$\alpha$,20$\beta$,21-triolone triacetate, m. p. and mixed m. p. 157–159°.

**Pregnane-3$\alpha$,17$\beta$-diol-11-one 3-Acetate.**—A solution of 899 mg. of $\Delta^{20}$-pregnene-3$\alpha$,17$\beta$-diol-11-one in 50 cc. of alcohol was shaken under hydrogen with 200 mg. of platinum oxide until absorption of hydrogen ceased. The solution was then filtered, concentrated to a small volume and precipitated as the crystalline hydrate, m. p. 123°; 175–177°, by addition of water. Recrystallization from wet ether did not change the properties. The acetate was prepared by permitting 815 mg. of the diol to stand at room temperature overnight in 2.0 cc. of pyridine and 2.0 cc. of acetic anhydride. It melted at 208–209°; $[\alpha]^{25}D$ + 60°.

*Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.58; H, 9.70.

**Dehydration of Pregnane-3$\alpha$,17$\beta$-diol-11-one 3-Acetate.**—A solution of 800 mg. of pregnane-3$\alpha$,17$\beta$-diol 3-acetate in 4 cc. of pyridine was treated with 0.5 cc. of phosphorus oxychloride and the solution left overnight. Dilution with water, followed by extraction with petroleum ether and concentration of the washed solution gave 680 mg. of a mobile colorless oil which would not crystallize from a small volume of cold methanol, even upon seeding with any of the low melting isomorphous mixtures of pregnene-3$\alpha$-ol-11-one acetate isomers. Saponification of the unsaturated acetate and dilution of the cold methanolic solution gave a flocculent mass which melted at *ca.* 130°. Recrystallizations from dilute methanol gave similar mixtures, m. p. 125–128°.

**Pregnane-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one 3-Acetate (XI).**—To a solution of 900 mg. of $\Delta^{17}$-pregnene-3$\alpha$-ol-11-one acetate, m. p. 122–123°, in 10 cc. of absolute ether was added 800 mg. of osmium tetroxide and 0.4 cc. of pyridine. After five minutes the precipitated osmate ester was redissolved by addition of 45 cc. of alcohol and 5 cc. of benzene. To this solution was added 2.0 g. of sodium sulfite dissolved in 30 cc. of water, and the reddish mixture was shaken for ten minutes at room temperature. The upper layer, which was then nearly colorless, was decanted, the semi-solid lower layer washed with 70% alcohol, the combined alcoholic extracts acidified with a few drops of acetic acid and concentrated to a small volume *in vacuo*. The crystalline precipitate (920 mg.) was filtered, washed with water, and recrystallized from dilute alcohol and acetone–petroleum ether, giving 750 mg. of the 3$\alpha$,17$\alpha$,20$\alpha$-triolone 3-acetate; m. p. 220–223°, $[\alpha]^{25}D$ + 43°.

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.22; H, 9.23.

Upon acetylation a sample gave pregnane-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one 3,20-diacetate, m. p. and mixed m. p. 228–229°.

**Pregnane-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one 3-Acetate 20-Tosylate (XIII).**—A solution of 456 mg. of pregnane-3$\alpha$,17$\alpha$,20$\alpha$-triol-11-one 3-acetate, m. p. 220–223°, in 1.0 cc. of pyridine was treated with 450 mg. of tosyl chloride and left at 0° overnight. After dilution with water, extraction with benzene, washing with dilute hydrochloric acid, dilute sodium carbonate and with water and concentration to dryness *in vacuo*, the tosylate was obtained as prisms from ether; yield, 489 mg. The compound melted with decomposition at temperatures ranging from 145–146° to 158–159°, depending on the rate of heating.

*Anal.* Calcd. for $C_{30}H_{42}O_7S$: C, 65.92; H, 7.73. Found: C, 66.08; H, 7.51.

**$\Delta^{17}$-Pregnene-3$\alpha$,21-diol-11-one from Pregnane-3$\alpha$,-20$\beta$,21-triol 3,21-Diacetate 20-Tosylate.**—A solution of 9.0 g. of pregnane-3$\alpha$,20$\beta$,21-triol-11-one 3,21-diacetate 20-tosylate in 50 cc. of collidine (purified through the hydrobromide), was refluxed for twenty-five minutes. The cooled solution was diluted with ether, cooled with ice and washed with sufficient dilute hydrochloric acid to remove the collidine. The ethereal solution was then washed with dilute sodium carbonate and with water and concentrated to dryness. The residue was dissolved in 50 cc. of benzene–petroleum ether and put on a column of 130 g. of alumina. Elution with 500 cc. of ether gave 6.4 g. of colorless oil, which was saponified by heating with 1 *N* methanolic potassium hydroxide. Dilution of the cooled solution with water gave crystals which after recrystallization from dilute alcohol and acetone–ether yielded 2.6 g. of impure $\Delta^{17}$-pregnene-3$\alpha$,21-diol-11-one.

This was purified through the diacetate, m. p. and mixed m. p. 112–113°. Saponification afforded the diol, m. p. and mixed m. p. 200–201°. Further crystallization of the mother liquors led only to isolation of an additional amount of the same diol.

**Pregnane-3α,17α,20β,21-tetrol-11-one 20,21-Acetonide (XXIII).**—A sample (422 mg.) of $\Delta^{17}$-pregnene-3α,21-diol-11-one diacetate, m. p. 113°, in absolute ether was treated with osmium tetroxide and pyridine, then hydrolyzed with hot aqueous alcoholic sodium sulfite in the usual manner. The filtered and concentrated aqueous suspension was extracted thrice with 50 cc. of chloroform and the chloroform solution concentrated to dryness. The residue (271 mg.) was crystallized from acetone and from alcohol. The crude tetrol melted at 245–255° and was purified through the acetonide; 196 mg. of crude tetrol was dissolved in 10 cc. of a 5% solution of zinc chloride in acetone. After standing at room temperature overnight, the solution was treated with aqueous sodium carbonate, the acetone layer decanted, concentrated to a small volume *in vacuo*, extracted with ether and the product crystallized from ether, giving 170 mg. of the acetonide, m. p. 187°.

*Anal.* Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.82; H, 9.56.

Hydrolysis of a sample of the acetonide with hot aqueous acetic acid gave pure pregnane-3α,17α,20β,21-tetrol-11-one; m. p. 263–264°, $[\alpha]^{25}D$ + 37° (alc.).

**Pregnane-17α,20β,21-triol-3,11-dione Diacetate from Pregnane-3α,17α,20β,21-tetrol-11-one Acetonide (XXIII).**—A solution of 102 mg. of the 3α,17α,20β,21-tetrolone acetonide, m. p. 187°, in 5 cc. of dry benzene was treated with 3 cc. of anhydrous acetone and 300 mg. of aluminum isopropoxide. The mixture was refluxed overnight, then diluted with ether, washed with dilute hydrochloric acid and water and concentrated to dryness. The residue was heated with 1.0 cc. of 75% acetic acid for fifteen minutes, the solvents removed *in vacuo* and the residue heated with a mixture of acetic anhydride–pyridine for five minutes on the steam-bath. The solvents were again removed *in vacuo* and the residue chromatographed giving 20 mg. of the 17α,20β,21-triol-dione diacetate, m. p. 208–210°. A mixed melting point with an authentic sample (m. p. 209–211°) did not show a depression. A total of 65 mg. of the original tetrolone, in the form of its triacetate, m. p. 200–201°, was also obtained from the chromatogram.

**Pregnane-3α,17α,20β,21-tetrol-11-one 3,21-Diacetate (XXI).**—A solution of 2.25 g. of pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate in 75 cc. of acetic acid was shaken with 1.0 g. of platinum oxide under a pressure of 45 lb. of hydrogen until hydrogen uptake nearly ceased (1.0 mole consumed). Filtration of the solution and concentration *in vacuo* to dryness gave a residue which after crystallization from ether and from methanol yielded 1.15 g. of dense prisms. The 3α,17α,20β,21-tetrolone 3,21-diacetate melted at 201–203°; $[\alpha]^{25}D$ + 67°.

*Anal.* Calcd. for $C_{25}H_{38}O_7$; C, 66.54; H, 8.50. Found: C, 66.64; H, 8.74.

**Pregnane-3α,17α,20β,21-tetrol-11-one 3,20,21-Triacetate (XXII).**—The acetylation of a sample of the 3α,17α,-20β,21-tetrolone with pyridine–acetic anhydride gave crystals from dilute methanol; m. p. 201°, $[\alpha]^{25}D$ + 103°.

*Anal.* Calcd. for $C_{27}H_{30}O_8$: C, 65.83; H, 8.18. Found: C, 66.01; H, 7.88.

**Pregnane-3α,17α,20α,21-tetrol-11-one 3,20,21-Triacetate (XXVI).**—The mother liquors from the crystallization of pregnane-3α,17α,20β,21-tetrol-11-one 3,21-diacetate (see above), amounting to 1.15 g., were chromatographed on 40 g. of alumina. Elution with ether–chloroform mixtures with an increasing proportion of chloroform gave oily fractions which were combined and deposited an additional 300 mg. of the 3α,17α,20β,21-tetrolone diacetate from a small volume of ether. The mother liquors from this crystallization were evaporated to dryness and the residue (416 mg.) acetylated with acetic anhydride–pyridine. Dilution of the reaction mixture with water gave 353 mg. of crude 3α,17α,20α,21-tetrolone triacetate. After six recrystallizations from dilute acetone and from methanol, the pure triacetate was obtained; m. p. 213–214°, $[\alpha]^{25}D$ + 18°.

*Anal.* Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.18. Found: C, 65.90; H, 8.19.

**Pregnane-3α,17α,20α,21-tetrol-11-one (XXV).**—Saponification of 30 mg. of the 3α,17α,20α,21-tetrolone triacetate, m.p. 213–214°, followed by concentration of the solution *in vacuo* and extraction of the aqueous suspension with a large volume of chloroform gave 16 mg. of amorphous residue. Crystallization from a small volume of acetone yielded 14 mg. of the tetrolone; m.p. 208–209°, $[\alpha]^{25}D$ + 44° (alc., $c = 0.5$).

**Pregnane-3α,17α,20β,21-tetrol-11-one 3-Acetate 20,-21-Acetonide (XXIV).**—A portion (700 mg.) of pregnane-3α,17α,20β,21-tetrol-11-one 20,21-acetonide was dissolved in a mixture of 2.0 cc. of pyridine and 1.0 cc. of acetic anhydride and heated on the steam-bath for ten minutes. The solvents were removed *in vacuo* and the residue chromatographed over alkaline alumina. Mixtures of ether–petroleum ether eluted 700 mg. of the crystalline acetate acetonide, which melted after recrystallization from benzene–petroleum ether at 190–191°.

*Anal.* Calcd. for $C_{26}H_{40}O_6$: C, 69.62; H, 8.98. Found: C, 69.53; H, 8.91.

**Acknowledgments.**—The author wishes to express his indebtedness to Dr. Karl Folkers for his active association with this work, to Dr. Everett S. Wallis of Princeton University for various suggestions, and to Miss Jean E. Andrews for assistance. The author is indebted to Mr. R. N. Boos and his associates for microanalyses.

## Summary

The preparation and properties of a number of pregnane-3α,17α,20(α and β)-triol-11-one derivatives and correlations with the corresponding 3-keto compounds are described. Similar investigations of the 3α,17α,20(α and β), 21-tetrol-11-one series are described.

RAHWAY, N. J. RECEIVED OCTOBER 20, 1948

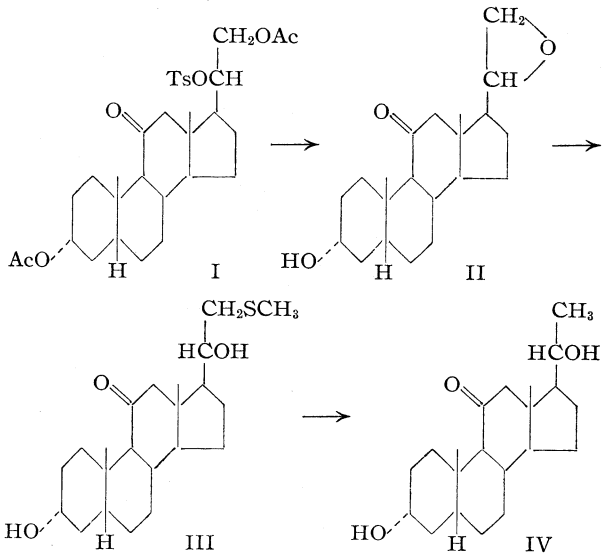
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

# Stereoisomeric Substituted 11-Keto-20-hydroxypregnanes. III

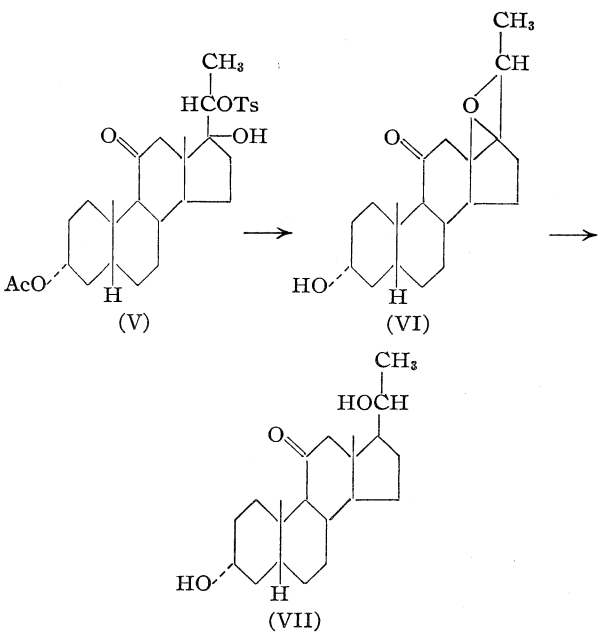
BY L. H. SARETT

In Parts I and II[1,2] of this series, derivatives of 11-ketopregnane with the following side chain substituents have been described: 20-hydroxy (Class A), 20,21-dihydroxy (Class B), 17α,-20-dihydroxy (Class C) and 17α,20,21-trihydroxy (Class D). Within each class the 3α,20α- and 3α,20β-dihydroxypregnanes were linked with the corresponding 3-keto derivatives. Inasmuch as the arbitrary assignment of the α- and β-indices to a pair of 20-hydroxypregnanes in a given class and the repetition of this assignment at random to a pair in a second, a third and a fourth class is unappealing, the stereochemical correlation of the classes among themselves becomes desirable. The elucidation of this problem[3] forms the subject of Part III.

The reference pair for the four classes mentioned above may be conveniently selected from the simplest group, Class A. We designate the pregnane-3α,20-diol-11-one which melts at 237° as the 20β-isomer (VII) and its epimer (IV) as the 20α-form. In order to convert one of the two pregnane-3α,20,21-triol-11-one isomers into a 3α,20-diolone in such a manner that the relative configuration at C-20 might be known with certainty at all stages, a device which has been employed to prepare desoxy sugars was utilized.[4] A pregnane-3α,20,21-triol-11-one in the form of its 3,21-diacetate 20-tosylate (I)[1] was treated with aqueous alkali in acetone solution, giving the oxide (II). Since reactions of this kind proceed with inversion[5] on the carbon atom bearing the tosylate group the C-20 oxygen–carbon linkage is epimeric with that in the original triol. The oxide reacted smoothly with sodium methyl mercaptide to give the thioether (III) in which the configuration at C-20 remained unchanged, the attack of the methyl mercaptide ion having occurred at C-21. Direct treatment of the acetate tosylate with sodium methyl mercaptide also gave the 21-thioether in excellent yield. Evidently, the oxide is an intermediate.[6] Desulfurization[7] of III then gave pregnane-3α,20α-diol-11-one (IV). Hence the original triol is a member of the 20β-series.




The correlation of a member of Class C with the diolone reference pair followed a somewhat similar scheme. The 20-tosylate of one of the epimeric 3α,17α,20-triolones (V)[1] was converted to the oxide (VI), thus inverting the configuration at C-20. Reductive cleavage of the oxide appeared to proceed exclusively at C-17,[8] since




(1) Sarett, THIS JOURNAL, **71**, 1165 (1949).

(2) Sarett, *ibid.*, **71**, 1169 (1949).

(3) The stereochemical correlation of certain allopregnanetetrols of the 17β-hydroxy series with the corresponding triols has recently been accomplished by Salamon and Reichstein (*Helv. Chim. Acta*, **30**, 1616, 1929 (1947)).

(4) Jeanloz, Prins and Reichstein, *Helv. Chim. Acta*, **29**, 371 (1946).

(5) *Inter alia*, Philipps, *J. Chem. Soc.*, 44 (1923); 2565 (1925); Kenyon, Philipps and Taylor, *ibid.*, 173 (1933); Vischer and Reichstein, *Helv. chim. Acta*, **27**, 1332 (1944).

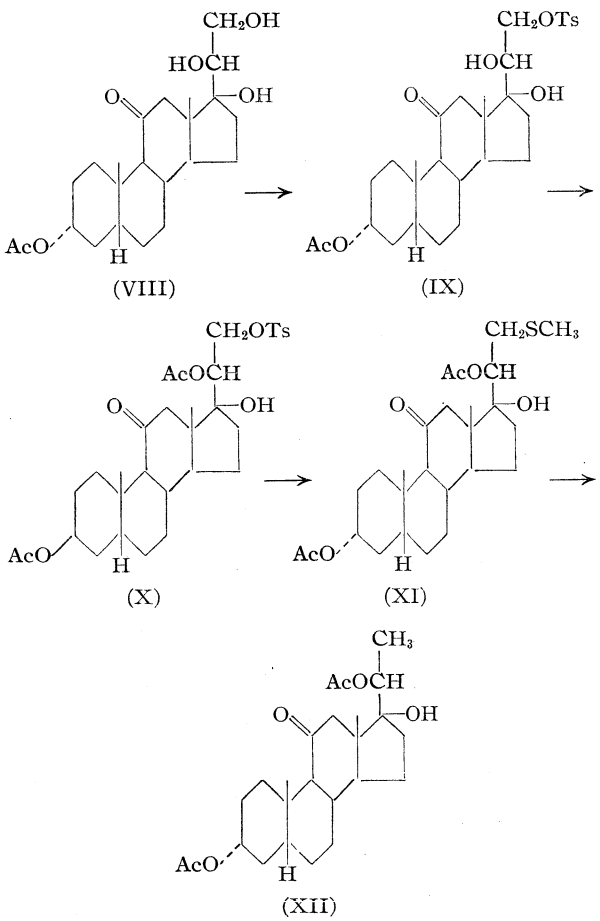
(6) The possibility of a dioxolone type of intermediate such as has been postulated by Winstein, Hass and Buckles (THIS JOURNAL, **64**, 2796 (1942)) in the solvolysis of 1,2-acetate tosylates appears unlikely, considering the strongly basic character of the reaction medium.

(7) Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

(8) *Cf.* Vischer and Reichstein, also Salamon and Reichstein, ref. 5.

pregnane-3$\alpha$,20$\beta$-diol-11-one was the sole product. This series indicated the C-20 hydroxyl group in the original triolone was alpha.

Finally, a pregnane-3$\alpha$,17$\alpha$,20,21-tetrol-11-one[2] was linked with one of the pregnane-3$\alpha$,17$\alpha$,20-triol-11-one epimers. The 3,20-diacetate 21-tosylate of the tetrolone (VIII) was prepared by hydrolysis of pregnane-3$\alpha$,17$\alpha$, 20,21-tetrol-11-one 3-acetate 20,21-acetonide followed by partial tosylation of the tetrolone 3-monoacetate (VIII). Since this derivative (IX) was not crystalline, the 20-hydroxy group was acetylated. Treatment of the tosylate diacetate (X) with sodium methyl mercaptide, followed by reacetylation of the triolone thioether gave the nicely crystalline diacetate (XI) in 89% yield.[9] With Raney nickel the 3$\alpha$,-17$\alpha$,20$\beta$-triolone diacetate (XII) was formed, from which it could be concluded that the parent tetrolone also was a 20$\beta$-hydroxypregnane.




Certain regularities are apparent from the results described above and in Parts I and II. Catalytic hydrogenation of an 11,20-diketopregnane gave predominantly one epimeric form of the 11-keto-20-hydroxypregnane,[10] the $\beta$-form according to our nomenclature. The quantity of $\alpha$-isomer occurring as a by-product increased with the substitution of hydroxyl groups at the 17- and 21-positions but did not exceed about 20%. With osmium tetroxide $\Delta^{17}$-11-ketopregnenes reacted to give glycols, the C-17 hydroxyl of which was invariably alpha[11] and the C-20 hydroxyl usually beta. The 17$\alpha$,20$\alpha$-glycol was obtained from a presumably geometrically isomeric $\Delta^{17}$-pregnene. Confirming the results of other investigators,[12] we have found that hydroxylation of the 20,21-bond is less sterically selective, approximately equal amounts of both C-20 epimers being formed.

With the hope of finding a generally valid criterion for the diagnosis of configuration of the C-20 hydroxyl group, an examination of the molecular rotations of pairs of 11-keto-20-hydroxypregnane epimers was made. Although no particular regularity could be discerned, it presently became apparent that such a differentiation could be made on the basis of another type of rotational comparison. This consisted in the calculation of a characteristic increment or decrement in the molecular rotations of the 20$\beta$- and 20$\alpha$-hydroxypregnanes, respectively, upon acetylation. That the "rule of shift"[13] could be applied to the steroids by analysis of such differences has been shown by Bernstein, Wilson and Wallis.[14] These workers demonstrated that the difference in molecular rotation of a 3$\beta$-hydroxystenol or stanol and its ester was constant and independent of the presence of subsidiary asymmetric centers or functional groups, providing that the latter were sufficiently distant from ring A to prevent the effects of vicinal action. Similarly, Plattner and Heusser[15] found in a study of partially acetylated cholic acid derivatives that the shifts of rotation caused by acetylation at the 3-, 7- and 12-positions were independent of each other. Barton in a series of papers[16] developed this approach (the "Method of Molecular Rotation Differences") and demonstrated its considerable versatility in the steroids and triterpenoids. This method of molecular rotation differences has been very recently applied to certain 20-hydroxypregnanes by Fieser and Fieser.[17] Since we have also carried out comparable calculations, with similar results, an elaboration of the excellent treatment given by these workers is superfluous.

(9) See remarks above on formation of thioether (III). Here, again the oxide is probably the intermediate, but whether or not this is the case, the configuration at C-20 must remain unaltered, since only the C-21 carbon–oxygen bond is broken.

(10) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius (ref. 24) found that catalytic reduction of pregnane-3-ol-20-one's gave only one diol. For a discussion of Marker's system of nomenclature, see below.

(11) *Cf.*, however, Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1112 (1939).

(12) *Inter alios*, Serini, Logemann and Hildebrand, *Ber.*, **72**, 391 (1939); Reich, Montigel and Reichstein, *Helv. Chim. Acta*, **24**, 977 (1941).

(13) Freudenberg, *Ber.*, **66**, 177 (1933).

(14) *J. Org. Chem.*, **7**, 103 (1942).

(15) Plattner and Heusser, *Helv. Chim. Acta*, **27**, 748 (1944).

(16) Barton, *J. Chem. Soc.*, 813 (1945); 512, 1116 (1946).

(17) Fieser and Fieser, *Experientia*, **4**, 285 (1948).

TABLE I

MOLECULAR ROTATIONS OF 11-KETO-20-HYDROXYPREGNANES AND DERIVATIVES

| Class | Substituent at C-3 | C-17 | C-21 | C-20 | Molecular rotation,[a] degrees 20β | 20α | Rotation difference,[b] degrees Δβ | Δα |
|---|---|---|---|---|---|---|---|---|
| A | HOα | Hα | H | HO | +160 (alc.) | +205 (alc.) | | |
| | AcOα | Hα | H | HO | +250 | ... | | |
| | HOα | Hα | H | AcO | ... | +190 | | |
| | AcOα | Hα | H | AcO | +340 | +255 | + 90 | − 15 |
| | O= | Hα | H | HO | +175 | +230 | | |
| | O= | Hα | H | AcO | +280 | +200 | +105 | − 30 |
| B | HOα | Hα | HO | HO | +185 (alc.) | +190 | | |
| | AcOα | Hα | HO | HO | +285 | +290 | | |
| | AcOα | Hα | AcO | HO | +280 | +290 | | |
| | AcOα | Hα | AcO | AcO | +370 | +235 | + 90 | − 55 |
| | O= | Hα | HO | HO | +215 | +240 | | |
| | O= | Hα | AcO | AcO | +320 | +195 | +105 | − 45 |
| | O=, Δ⁴ | Hα | HO | HO | +610 | +610 | | |
| | O=, Δ⁴ | Hα | AcO | AcO | +730 | +570 | +120 | − 40 |
| C | HOα | HOα | H | HO | +135 | + 80 | | |
| | AcOα | HOα | H | HO | ... | +170 | | |
| | HOα | HOα | H | AcO | +215 | + 10 | +80 | − 70 |
| | AcOα | HOα | H | AcO | +340 | +105 | | |
| | O= | HOα | H | AcO | +290 | + 50 | | |
| | O= | HOα | H | HO | +165 | +115 | +120 | − 65 |
| D | HOα | HOα | HO | HO | +175 (alc.) | +160 | | |
| | AcOα | HOα | AcO | AcO | +505 | + 90 | | |
| | AcOα | HOα | AcO | HO | +300 | ... | +205 | −160 |
| | O= | HOα | AcO | AcO | +415 | ... | | |
| | O=, Δ⁴ | HOα | HO | HO | +505 | ... | | |
| | O=, Δ⁴ | HOα | AcO | AcO | +800 | ... | +220 | ... |

[a] Molecular rotation = $M[\alpha]_D/100$ where $M$ = molecular weight and $[\alpha]_D$ = specific rotation; values to nearest 5°. [b] $\Delta\beta$ = molecular rotation of 20β-acetoxypregnane—molecular rotation of corresponding 20β-hydroxypregnane and similarly for $\Delta_\alpha$.

However, a short analysis of the rotational data of the 11-keto-20-hydroxypregnanes described in the present series of papers is not out of place.

Although it has been repeatedly demonstrated that the presence of neighboring asymmetric centers very seriously disturbs the constancy of a molecular rotation difference, we have attempted to apply the method to substituted 20-hydroxypregnanes in as quantitative a manner as possible. From an analysis of the rotational data in Table I, it appears that, independent of the presence of an oxygen function at C-21 or an α-hydroxyl group at C-17, the following rule is valid: In proceeding from the free 20-hydroxypregnane to the acetate, an increment in the molecular rotation may be observed in one of the configurational series while in the epimeric series a decrement is found. In addition, since the difference in rotation between the two 20-hydroxy-pregnanes[18] seems always to be less than the "spreading" effect produced by acetylation, the rotations of the 20-acetates of one configurational series are always greater than those of the other. In Table I, the column headed $\Delta_\beta$ gives the increment in molecular rotation observed upon acetylation of 11-keto-20-hydroxypregnanes having what we have called the β-configuration. Similarly $\Delta_\alpha$ corresponds to the α-series. Although, considering all four classes, $\Delta_\beta$ and $\Delta_\alpha$ vary in magnitude, within a given class their differences from the average do not lie far outside the experimental error.[19,20] Thus the relatively small fluctuation of Δ occurring with the introduction of one adjacent oxygen function is noteworthy. The cause of the great increase in Δ with the introduction of both adjacent oxygen functions (Class D) is not apparent.

Some sample calculations are given

Example 1. Pregnane-3α,20-diol-11-one

$\Delta_\beta = (+340°) - (+250°) = +90°$

$\Delta_\alpha = (+190°) - (+205°) = -15°$

Example 2. Pregnane-3α,20,21-triol-11-one

$\Delta_\beta = (+370°) - (+280°) = +90°$

$\Delta_\alpha = (+235°) - (+290°) = -55°$

Example 3. Pregnane-3α,17α-20,21-tetrol-11-one

$\Delta_\beta = (+505°) - (+300°) = +205°$

$\Delta_\alpha = +90° - [M]_D$ diacetate

(18) Pregnane is used here in a broad sense, to include allopregnane, Δ⁴-pregnene and the like.

(19) A difference of ±2° in the specific rotation is equivalent to an error of about ±8° in the molecular rotation and ±16° in Δ.

(20) The specific rotations taken in alcohol because of low solubility in acetone introduced a small additional error. In an effort to assess this quantity the rotations of five typical substituted pregnanes were measured in both solvents. Those in alcohol had the greater rotations by ±2, +4, +1, +3, and −1°. This small and inconstant difference (*cf.* Barton, Part III, ref. 16) was essentially within the experimental error and was not considered in calculating the values of Δ.

where [M]D diacetate is the molecular rotation of pregnane-3$\alpha$,17$\alpha$,20$\alpha$,21-tetrol-11-one 3,21-diacetate. This quantity may be estimated by adding to the molecular rotation of the free tetrol, the contributions from acetylation at C-3 and C-21. The former, taken as the average of a number of rotation differences of 3$\alpha$-hydroxy- and acetoxypregnanes is +90°.[21] If the latter be borrowed from a comparison of the rotations of a pair of 3,21-diacetates with the corresponding 3-monoacetates (Table I, Class B), according to which the rotation change produced by acetylation of a C-21 hydroxyl is negligible, the calculation may then be completed

$$\Delta_\alpha = (+90°) - [(+160°) + (+90°) + (0°)] = -160°$$

If the assumption is made that the rotational changes described above are at least qualitatively valid for 20-hydroxypregnanes[18] independent of the presence of an 11-keto group or C-3-hydroxyl configuration, a significant steric comparison may be made between this group of compounds and certain naturally occurring adrenal steroids. In particular, Reichstein's substance J, the C-20-hydroxyl of which has been arbitrarily defined as beta by Prins and Reichstein[22] and substance O, its C-20 epimer, may be linked with the present series. When this calculation is performed, it may be seen that J and O qualitatively follow the criteria for the 20$\beta$- and 20$\alpha$-configurations, respectively. On this basis, the assignment of those 20-hydroxypregnanes which we have called beta to the same steric series as substance J has been made.

Allopregnane-3$\beta$,17$\alpha$-20-triol (substance J)[23]

$$\Delta = (+100°) - (-25°) - (-15°) = +150°$$

Allopregnane-3$\beta$,17$\alpha$,20-triol (substance O)[23]

$$\Delta = (-125°) - (-40°) - (-15°) = -70°$$

Another convention which has been used to designate epimeric 20-hydroxypregnanes is that of Marker and co-workers.[24] According to this system those 20-hydroxypregnanes occurring as urinary metabolites are given the alpha index and their epimers, produced in high yield by catalytic reduction of 20-ketopregnanes, the beta-designation. From the combined results of Butenandt and Schmide–Thomé[25] and Prins and Reichstein (ref. 23), who, in essence, converted substance J into the diol called according to Marker's nomenclature allopregnane-3$\beta$,20$\beta$-diol without disturbing the asymmetry at C-20, it is apparent that Marker's convention is also in agreement with those of Reichstein. In order further to test the rule of configuration described above, the rotation of the pregnane-3$\alpha$,20-diols was compared with those of the corresponding diacetates.[26] Using the value [$\alpha$]D+27° (alc.),[27] or [M]D+85°, for the rotation of the 3$\alpha$,20$\alpha$-diol (Marker's nomenclature) together with our experimental values for the rotations of the 3$\alpha$,20$\beta$-diol, and the two diacetates, the two $\Delta$ values may be calculated

Pregnane-3$\alpha$,20$\beta$-diol

$$\Delta = (+275°) - (+90°) - (+90°) = +105°$$

Pregnane-3$\alpha$,20$\alpha$-diol

$$\Delta = (+165°) - (+85°) - (+90°) = -10°.$$

These $\Delta$'s agree well with the $\Delta_\beta$ of +90° and the $\Delta_\alpha$ of −15° found in the 11-ketodiol series. From these results it appears that the rotational rule rests on substantial ground.

Consideration of this rule reveals no *a priori* likelihood of its precise application to the 17$\beta$,20-dihydroxypregnanes, since the validity of the principal of optical superposition, upon which such a prediction must be based, is dubious in this system of adjacent asymmetric centers. That the "Rule of Shift," however, might find application in some manner not necessarily related to that in the 17$\alpha$,20-dihydroxypregnane series, appears quite possible. Indeed, Reich, Montigel and Reichstein (ref. 12) have pointed out that in a series of three sterically correlated epimeric pairs of 17$\beta$,20-dihydroxypregnane derivatives, the fully acetylated compounds of the 20 "$\beta$"-group[28] all have the higher rotations. However, an examination of the rotations of all of the pertinent 17$\beta$-triols, tetrols and their acetates[29] shows that, unfortunately, no simple regularity based upon the "Rule of Shift" exists.

## Experimental[30]

**20$\alpha$,21-Oxidopregnane-3$\alpha$-ol-11-one** (II).—A solution of 1.10 g. of pregnane-3$\alpha$,20$\beta$,21-triol-11-one 3,21-diacetate 20-tosylate (I) m. p. 176–177°, in 35 cc. of 0.50 *N* methanolic potassium hydroxide was permitted to stand at 30° for two hours. Concentration of the solution *in vacuo* gave a crystalline precipitate which yielded after several recrystallizations from dilute acetone 400 mg. of the oxide; m. p. 173–174°, [$\alpha$]$^{25}$D + 50°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.58; H, 9.40.

**Pregnane-3$\alpha$,20$\alpha$-diol-21-thiol-11-one Methyl Thioether (III)**

**A. From 20$\alpha$,21-Oxidopregnane-3$\alpha$-ol-11-one** (II).—A solution of 183 mg. of the 20$\alpha$,21-oxide, m. p. 173–174°, in 2.0 cc. of methanol containing 300 mg. of sodium methyl mercaptide was refluxed for one hour. The solution was diluted with water and extracted with ether. Concentration of the washed ethereal solution to dryness and recrystallization of the residue from a small volume of ether

(21) Plattner and Heusser (ref. 15) found +91° (alc.) and Barton (ref. 16) found +83° (all solvents).

(22) Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940).

(23) Calculated from data of Prins and Reichstein, ref. 22. The value for the conversion of the C-3 $\beta$-hydroxyl to acetate was taken as −15° (Barton, Part III, ref. 16).

(24) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, THIS JOURNAL, **59**, 2291 (1937).

(25) Butenandt and Schmide–Thomé, *Ber.*, **72**, 1960 (1939).

(26) We are indebted to Dr. K. Dobriner and to Dr. T. F. Gallagher of the Sloan–Kettering Institute for samples of these compounds.

(27) Beall, *Biochem. J.*, **31**, 35 (1937).

(28) The indices in the 17$\beta$,20-diol and 17$\beta$,20,21-triol series were assigned arbitrarily and, while they agree with each other (Salamon and Reichstein, ref. 3), they do not necessarily agree with those used in the 17$\alpha$,20-diol and 17$\alpha$,20, 21-triol series.

(29) Data collected by Salamon and Reichstein, ref. 3.

(30) Melting points were taken on the Kofler micro hot stage. Rotations were taken in acetone, $c$ = 1.0, unless otherwise indicated.

yielded 171 mg. of the thioether, m. p. 147–148°. When the thioether was dissolved in a small volume of methanol, dense prisms of a solvated form quickly appeared, which lost solvent at *ca.* 140°, resolidified and remelted at 146–147°.

*Anal.* Calcd. for $C_{22}H_{36}O_3S$: C, 69.42; H, 9.54. Found: C, 69.46; H, 9.24.

**B. From Pregnane-3α,20β,21-triol-11-one 3,21-Diacetate 20-Tosylate (I).**—Treatment of 140 mg. of the tosylate with sodium methyl mercaptide in the manner described above and two crystallizations of the product from methanol yielded 60 mg. of the thioether (III), m. p. and mixed m. p. 141°, 147°.

**Pregnane-3α,20α-diol-11-one (IV) from Pregnane-3α,-20α-diol-21-thiol-11-one Methyl Thioether (III).**—To a suspension of 3 g. of Raney nickel in 25 cc. of 80% alcohol was added an alcoholic solution of 102 mg. of the thioether (III). The mixture was warmed on the steam-bath for ten minutes, filtered and concentrated to dryness *in vacuo*. The crystalline residue (65 mg.) was acetylated in the usual manner and the product oxidized with 50 mg. of chromic acid in 90% acetic acid to convert any 11-hydroxy compound to the 11-ketone. Addition of water to the acetic acid solution gave 60 mg. of crystals. After recrystallization from alcohol the 3α,20α-diolone diacetate had m. p. 235–237°. A mixed m. p. with an authentic sample showed no depression. Saponification of the diacetate gave pregnane-3α,20α-diol-11-one, m. p. and mixed m. p. 221°. A sample (15 mg.) of the diolone was oxidized with chromic acid (15 mg.) in 90% acetic acid and yielded pregnane-3,11,20-trione, m. p. and mixed m. p. 161–163°.

**17α,20β-Oxidopregnane-3α-ol-11-one (VI).**—To a solution of 350 mg. of pregnane-3α,17α,20α-triol-11-one 3-acetate 20-tosylate (V) in 6 cc. of acetone was added 4 cc. of 1 *N* aqueous potassium hydroxide. After two and one-half hours at room temperature the solution was concentrated *in vacuo* to a small volume, extracted with ether and the washed ethereal solution concentrated to dryness. The residue was dissolved in a small volume of methanol, water was added to turbidity and the solution then chilled to 0°. The difficultly crystalline hydrate of the oxide slowly separated. It decomposed (loss of solvent of crystallization) at about 102–105°. After several recrystallizations from cold dilute methanol, the crystals melted at 103–112°; $[\alpha]_D$ +54.5° ($c$ = 0.5) (not corrected for water of crystallization). For analysis a sample was dried in a weighing pig at 110°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.76; H, 9.30. Loss in weight on drying: 2.2%.

**Pregnane-3α,20β-diol-11-one (VII) from 17α,20β-Oxidopregnane-3α-ol-11-one (IV).**—A solution of 30 mg. of 17α,20β-oxidopregnane-3α-ol-11-one in 50 cc. of alcohol with 1/4 teaspoonful of Raney nickel was shaken in a bomb under hydrogen at 120° for two hours. The cooled solution was filtered, concentrated nearly to dryness *in vacuo* and the residue dissolved in acetone. The acetone solution was filtered to remove traces of inorganic matter, the solution concentrated to dryness and the residue crystallized from dilute alcohol. The diol melted at 236–237° and did not depress the m. p. of an authentic sample of pregnane-3α,20β-diol-11-one. Acetylation gave the 3α,-20β-diolone diacetate, m. p. and mixed m. p. 161.5–162.0°.

**Pregnane-3α,17α,20β,21-tetrol-11-one 3-Acetate (VIII).**—A solution of 600 mg. of pregnane-3α,17α,20β,21-tetrol-11-one 3-acetate 20,21-acetonide, m. p. 190–191°, in 1 cc. of warm acetic acid was treated with 1 cc. of water and the mixture heated on the steam-bath for fifteen minutes. Water was added and the suspension extracted with three 25-cc. portions of chloroform. The chloroform solution was washed with a little sodium carbonate solution, then with water and concentrated to dryness *in vacuo*. The tetrolone monoacetate was obtained as a white amorphous powder; yield, 471 mg.

**Pregnane-3α,17α,20β-21-tetrol-11-one 3,20-Diacetate 20-Tosylate (X).**—The 471 mg. of amorphous pregnane-3α,17α,20β,21-tetrol-11-one 3-acetate was dissolved in 2.0 cc. of pyridine and treated with 280 mg. of freshly recrystallized tosyl chloride (1.28 molecular equivalents). The solution was kept at room temperature overnight, then diluted with water and extracted with chloroform. The chloroform solution was washed successively with dilute hydrochloric acid, dilute sodium bicarbonate and water, then concentrated to dryness *in vacuo* at 20°. The amorphous residue was sparingly soluble in ether and weighed 671 mg. (103%). The amorphous 21-monotosylate (IX) was next converted to the 3,20-diacetate (X) by heating on the steam-bath with a mixture of 2.0 cc. of acetic anhydride and 1.5 cc. of pyridine for six minutes. The solution was cooled, and carefully diluted with water, giving 420 mg. of the crystalline diacetate tosylate. Recrystallization from chloroform–ether gave prisms, m. p. 145° (dec.). Another crystalline form, m. p. 140° (dec.), could be obtained by crystallization from methanol.

*Anal.* Calcd. for $C_{32}H_{44}O_9S$: C, 63.55; H, 7.33. Found: C, 63.27; H, 7.52.

**Pregnane-3α,17α,20β-triol-21-thiol-11-one 3,20-Diacetate Methyl Thioether (XI).**—A solution of 200 mg. of the tosylate (X), m. p. 145° (dec.), in 4 cc. of methanol containing 600 mg. of sodium methyl mercaptide was refluxed for one hour. Dilution with water and removal of the methanol *in vacuo* gave hydrated crystals which could not be recrystallized from organic solvents. These crystals were combined with the amorphous product obtained by extraction of the mother liquors with chloroform, giving 160 mg. of crude reaction product, which contained some extraneous sulfur compounds. This material was acetylated with pyridine–acetic anhydride in the usual manner and dilution of the reaction mixture with water then gave 140 mg. (89%) of the diacetate, m. p. 191–194°. Recrystallization from methanol gave a product melting at 194–196°.

*Anal.* Calcd. for $C_{26}H_{40}O_6S$: C, 64.98; H, 8.39. Found: C, 65.18; H, 8.42.

**Pregnane-3α,17α,20β-triol-11-one Diacetate (XII) from Pregnane-3α,17α,20β-triol-21-thiol 3,20-Diacetate Methyl Thioether.**—A solution of 28 mg. of the thioether (XI) in 10 cc. of alcohol was refluxed with 0.5 teaspoonful of Raney nickel for ten minutes, the nickel removed by centrifugation, and the solvent removed *in vacuo*. The crystalline residue was dissolved in ether and recrystallized by concentration. The product, which melted at 233–245°, was best separated from a small amount of high melting impurity (11-hydroxy analog(?)) by chromatography over 3 g. of alumina. The eluates obtained with 1:1 ether–petroleum ether through ether were combined and recrystallized from a small volume of ethyl acetate. The pregnane-3α,17α,20β-triol-11-one diacetate then had m. p. 248–249°. A mixed melting point with an authentic sample (m. p. 249–250°) showed no depression.

**Rotations of Pregnanediols.**—Pregnane-3α,20α-diol, +27° (alc.); pregnane-3α,20β-diol (m. p. 239°), +25° (alc.); pregnane-3α,20α-diol diacetate (m. p. 180.5–182.0°), +41°; pregnane-3α,20β-diol diacetate (m. p. 112–113°), +68°.

**Acknowledgments.**—The author wishes to express his indebtedness to Dr. Karl Folkers for his active association with this work, to Dr. Everett S. Wallis of Princeton University for various suggestions, and to Miss Jean E. Andrews for assistance. The author is indebted to Mr. R. N. Boos and his associates for microanalyses.

## Summary

The stereochemical correlation of the 11-ketopregnane-3α,20,21-triols, the 11-ketopregnane-3α,-17α,20-triols, and the 11-ketopregnane-3α,17α,20,-21 tetrols with the 11-ketopregnane 3α,20-diols is

described. Analysis of the rotations of various 11-keto-20-hydroxypregnanes by the "Method of Molecular Rotation Differences" shows certain regularities independent of the presence of oxygen functions at the C-17 or C-21 positions.

RAHWAY, N. J. RECEIVED OCTOBER 20, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Senecio Alkaloids: α- and β-Longilobine from *Senecio longilobus*

BY ROGER ADAMS AND T. R. GOVINDACHARI

The investigations[1] on *Senecio* alkaloids, of which nearly forty have been isolated so far, have brought to light the striking similarities of many members belonging to this group. Essentially, most of these alkaloids are alkamine esters, in which a pyrrolizidine base carrying two hydroxyls is esterified with aliphatic acids either on one or both hydroxyls. While the heterocyclic component has proved to be retronecine in a large number of cases, the acid fragments exhibit a bewildering variety. These necic acids, although many of them are isomeric, differ widely in melting point, optical rotation, etc., and only in a few cases has the acid moiety been found to be common to two different alkaloids.

The work presented here comprises an investigation of the alkaloids of *Senecio longilobus*, a plant to which a large percentage of the West Texas cattle losses may probably be attributed rather than to the loco plant. Manske[2] was the first to isolate a product from this source which he designated as longilobine. It became apparent very early in the course of the work that longilobine was not a single entity, but a mixture of at least two components. It has been known for a long time that many species of *Senecio* elaborate more than one alkaloid and several alkaloids have been isolated from the same species by fractional crystallization procedures.[3,4] In some instances, however, the attempts at separation of such mixtures have failed completely.[5,6]

Manske has reported longilobine to be $C_{18}H_{23}O_5N$ and the acid obtained by hydrolysis $C_{10}H_{14}O_5$, although his analytical data did not agree satisfactorily with these empirical formulas. The analysis of a sample of longilobine prepared in this Laboratory suggested the same formula as proposed by Manske but likewise was not as close to the theoretical as might be expected of a pure product. In spite of several crystallizations a constant melting point and specific rotation were not reached and the values obtained did not coincide with those reported by Manske.

It has been suggested[3a,6] that these alkaloids are difficult to burn and often gave low values for carbon. It seemed more likely that some other alkaloid with lower carbon content was associated with the $C_{18}H_{23}O_5N$ alkaloid and that this could not be effectively removed by crystallization.

The use of chromatographic adsorption methods for the separation and purification of alkaloids has been a well-established procedure but no application of chromatography has been made so far in the case of the *Senecio* alkaloids. The chromatography of colorless substances presents a difficult problem and many ingenious ways have been devised to locate the invisible zones.[7] Mention may be made of the use of the ultraviolet lamp,[8] the brush method,[9] the use of fluorescent adsorbents[10] and the use of total reflection on a thick glass plate[11] for the detection of boundaries.

They proved unsatisfactory for the separation of the constituents of the crude alkaloid from *Senecio longilobus* for various reasons. Preliminary tests indicated that the "brush method" might have been successfully applied if a further careful study had been undertaken. Investigations along these lines were abandoned when it was found that two main fractions corresponding to $C_{18}H_{23}O_5N$ and $C_{18}H_{25}O_6N$ could be separated easily on a column of alumina by a simple empirical procedure. The criterion of purity was set as a constant optical rotation, which did not change or lead to fractions having higher and lower optical rotations on further adsorption and fractional elution. The liquid chromatogram method, combined with the examination of the column cut into portions arbitrarily, proved sufficiently useful for the purpose.

An initial treatment of the crude alkaloid with alumina was used for effecting a preliminary separation of products before the usual chromatographic procedure. Longilobine with a specific

(1) For a detailed discussion, the following papers may be consulted: (a) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939); (b) Adams, Hamlin, Jelinek and Phillips, *ibid.*, **64**, 2760 (1942); (c) Adams, Carlin and Rogers, *ibid.*, **64**, 571 (1942). The authors also had access to a chapter on *Senecio* alkaloids contributed by Dr. N. J. Leonard, University of Illinois, to a forthcoming monograph on alkaloids, under the editorship of Dr. R. H. F. Manske.

(2) Manske, *Can. J. Res.*, **17B**, 1 (1939).

(3) (a) de Waal and Onderstepoort, *J. Vet. Sci. Animal Ind.*, **16**, 149 (1941); (b) **12**, 155 (1939).

(4) Barger and Blackie, *J. Chem. Soc.*, 584 (1937).

(5) Barger and Blackie, *ibid.*, 743 (1936).

(6) Manske, *Can. J. Res.*, **14B**, 8 (1936).

(7) Zechmeister, *Annals New York Academy of Sciences*, **49**, 149 (1948).

(8) Karrer and Schöpp, *Helv. Chim. Acta*, **17**, 693 (1934); Winterstein and Schön, *Z. physiol. Chem.*, **230**, 139 (1939).

(9) Zechmeister, Cholnoky and Ujhelyi, *Bull. soc. chim. Biol.*, **18**, 1885 (1936).

(10) Brockmann and Volpers, *Ber.*, **80**, 77 (1947).

(11) Claesson, *Nature*, **159**, 708 (1947).

TABLE I

PURIFICATION OF α-LONGILOBINE[a]

6 g. of α-fraction (2.8 g. of sp. rot. −116° and 3.2 g. of sp. rot. −110°) in 150 ml. chloroform was poured onto 12 × 2 cm. column of alumina (30 g.) and the alumina washed with 800 ml. of chloroform

| Filtrate | | | Alumina (ext. with methyl alcohol) |
|---|---|---|---|
| First 400 ml. 4.94 g. (−118.5°) | Second 400 ml. 0.24 g. (−111°) | Bottom half 0.15 g. | Top half 0.5 g. |

Solution in 50 ml. chloroform poured onto 12 × 2 cm. column of alumina (30 g.)

| | | |
|---|---|---|
| First 400 ml. 3.8 g. (−123.8°)[b] | Second 300 ml. 0.2 g. | Alumina (ext. with methyl alcohol) |

| | |
|---|---|
| Top half 0.4 g. | Bottom half 0.4 g. |

0.5 g. in 10 ml. chloroform on 16 cm. × 1 cm. alumina (15 g.) column—washed with chloroform

| First 150 ml. | 50 ml. | 50 ml. | 50 ml. | 50 ml. | 100 ml. | 100 ml. |
|---|---|---|---|---|---|---|
| nil. | 0.142 g. (−123.2°) | 0.126 g. (−124.6°) | 0.095 g. (−124.4°) | 0.046 g. (−123.8°) | 0.021 g. | trace |

[a] Figures in parentheses denote the specific rotation of the sample in chloroform. [b] This product was crystallized twice from ethanol. The product had a rotation in chloroform $[\alpha]^{25}D$ −125.2°. Further chromatographing of this fraction was employed to demonstrate a constant optical rotation.

TABLE II

PURIFICATION OF β-LONGILOBINE[a]

4 g. of β-fraction (1.8 g. of sp. rot. −66.5° and 2.2 g. of sp. rot. −72.5°) in 100 ml. chloroform was poured onto 7.5 × 4.5 cm. column of alumina (100 g.) and the alumina washed with 3500 ml. of chloroform

| Filtrate | Alumina (eluted with N-acetic acid, basified, extracted with chloroform) |
|---|---|
| 3500 ml. 0.54 g. (−106.5°) | 2.62 g. (−66.3°) |

Solution in 50 ml. of chloroform poured onto 1 × 3.5 cm. column of alumina (25 g.)—washed with chloroform

| First 500 ml. | 500 ml. | 250 ml. | Alumina (eluted with N-acetic acid, basified, extracted with chloroform) |
|---|---|---|---|
| 0.616 g. (−70.5°) | 0.19 g. (−70.0°) | 0.04 g. (−62.5°) | 1.54 g. (−65°) |

Solution in 25 ml. of chloroform—column 62.5 × 1 cm.—50 g. of alumina—developed with chloroform and chloroform–ethyl alcohol

| 200 ml. $CHCl_3$ | 250 ml. $CHCl_3$ | 100 ml. $CHCl_3$ | Alumina column cut in ten portions and eluted with N-acetic acid, basified, extracted with chloroform |
|---|---|---|---|
| nil. | (1% EtOH) nil. | (2% EtOH) trace | |

| 1 (top) | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| 0.075 g. (−69°) | 0.132 g. (−68°) | 0.154 g. (−68°) | 0.161 g. (−67°) | 0.194 g. (−64.5°) | 0.097 g. (−64.5°) | 0.237 g. (−52.2°) | 0.185 g. (−49.5°)[b] | 0.11 g. (−48.9°)[b] | Trace |

[a] Figures in parentheses denote the specific rotation of the sample in chloroform. [b] A mixture of samples 8 and 9 were combined and recrystallized from ethanol. The product had a rotation in chloroform $[\alpha]^{28}D$ −48.6°.

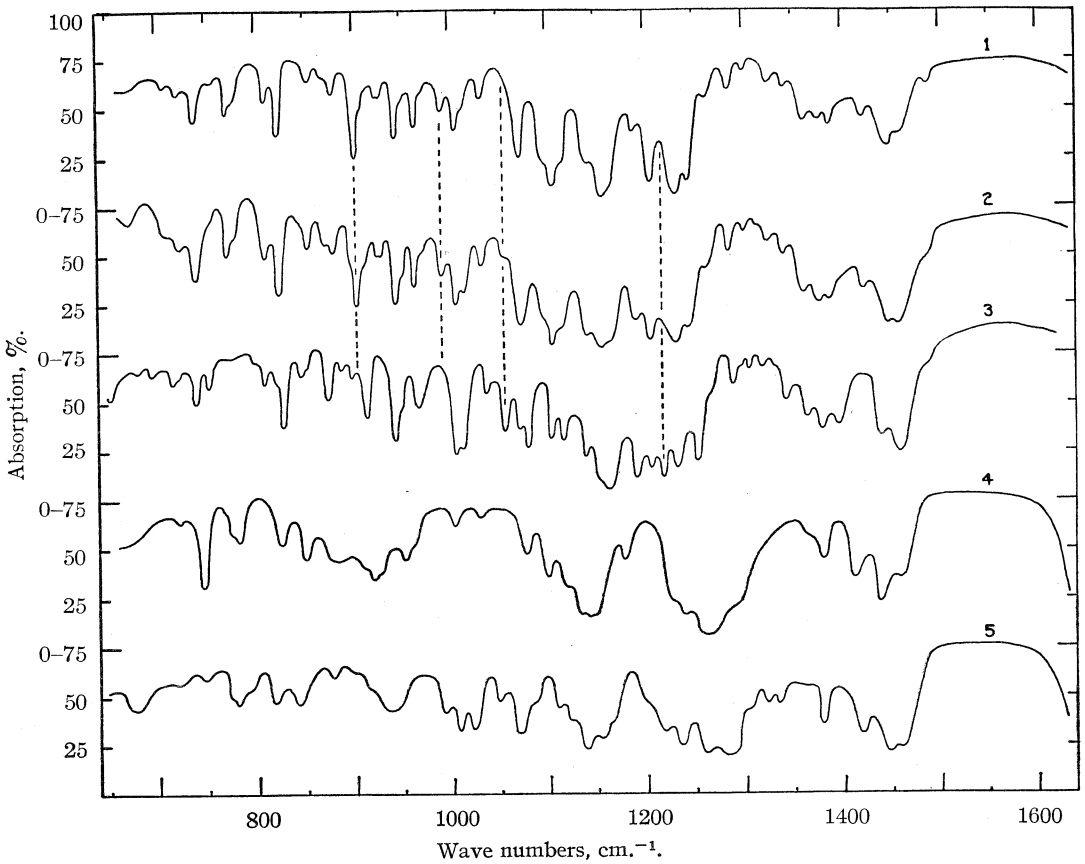


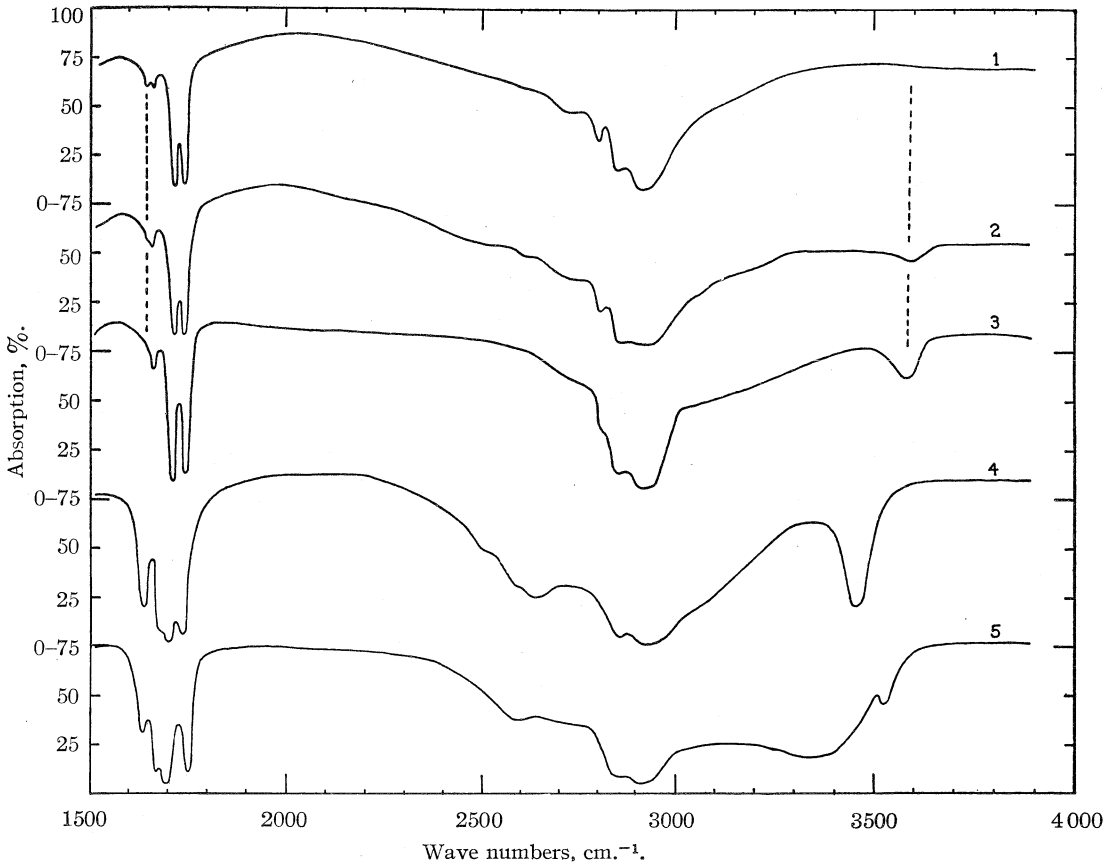

Fig. 1.—Infrared absorption spectra; all spectra are of crystalline solids ground up in Nujol between rock salt plates: 1, $\alpha$-longilobine; 2, crude longilobine; 3, $\beta$-longilobine; 4, $\alpha$-longinecic acid; 5, $\beta$-longinecic acid.

rotation of $-91°$ was stirred with chloroform and alumina for thirty minutes. The filtrate from the alumina had a specific rotation in chloroform of $-116°$. The alumina was eluted with ether and the solvent was found to contain very little product. This was followed by elution with methanol from which solvent material of specific rotation $-66.5°$ was obtained.

The purification of the higher rotating fraction designated as $\alpha$-longilobine was achieved by two passages of a solution in chloroform through alumina columns. The $\alpha$-longilobine passed with the solvent into the filtrate and the impurities were retained on the adsorbent. The pure $\alpha$-longilobine was obtained by evaporation of the chloroform and after crystallization from ethanol had a specific rotation of $-125.2°$ in chloroform at 28°. It melted at 217–218° and the analysis was in good agreement with the empirical formula $C_{18}H_{23}O_5N$.

The lower rotating fraction, called $\beta$-longilobine, was also chromatographed several times, first through short columns then through a long narrow alumina column in chloroform as solvent. The first operation eliminated practically all of the $\alpha$-longilobine. The subsequent operations served for the isolation of $\beta$-longilobine in optically pure state. A certain amount of a third alkaloid was obviously present (probably riddelliine) which was more strongly adsorbed than $\beta$-longilobine. As a consequence, the optically pure product was usually obtained from the lower quarter of the column. Pure $\beta$-longilobine had a specific rotation of $-48.6°$ in chloroform. It melted at 207–208° and analyzed correctly for $C_{18}H_{25}O_6N$.

The infrared spectra of $\alpha$- and $\beta$-longilobine were complementary and when combined were essentially identical with that of crude longilobine. They are shown in Chart I. Both $\alpha$- and $\beta$-longilobine show the same two frequencies at 1740 cm.$^{-1}$ and 1717 cm.$^{-1}$ indicating that the molecules must have virtually identical carbonyl linkages. The former is in the region where normal esters, six-membered lactones, cyclopentanones and some acids are found. The latter lies in the region where conjugated esters or six-membered lactones, ketones and acids are found. Both the alkaloids contain the carbon–carbon double bond absorptions at about 1664 cm.$^{-1}$. In addition, $\alpha$-longilobine has a second absorption at 1645 cm.$^{-1}$. Certain absorptions appearing in the low frequency region and common to both seem to be due to the retronecine part of the




molecule, *e.g.*, those at 738 cm.$^{-1}$, 824 cm.$^{-1}$, and 1006 cm.$^{-1}$. The characteristic bands used in identification of α-longilobine were those at 992 cm.$^{-1}$ and 902 cm.$^{-1}$ and of β-longilobine at 1055 cm.$^{-1}$ and the hydroxyl band at 3590 cm.$^{-1}$.

Crude longilobine on hydrolysis furnished retronecine and an acid which was difficult to purify. Pure α-longilobine on hydrolysis yielded retronecine and an acid melting at 114–115° which analyzed correctly for $C_{10}H_{14}O_5$. The acid was dibasic and on heating *in vacuo* was converted to a glassy mass, possibly by lactonization. β-Longilobine gave on hydrolysis retronecine and an acid melting at 146–147°, which analyzed correctly for $C_{10}H_{16}O_6$. On direct titration two carboxyls were indicated.

The infrared spectra of the two acids (Chart I) show many similarities and differences. Both contain the same strong absorption band between 1675 cm.$^{-1}$ and 1700 cm.$^{-1}$, which could be due to acid or keto carbonyl absorption. In addition, the α-acid shows another carbonyl absorption at 1735 cm.$^{-1}$ and the β-acid at 1750 cm.$^{-1}$. These two bands could be due to the carbonyl of an acid, ester, or lactone. The carbon–carbon double bond stretching frequency at 1637 cm.$^{-1}$ appears in both spectra.

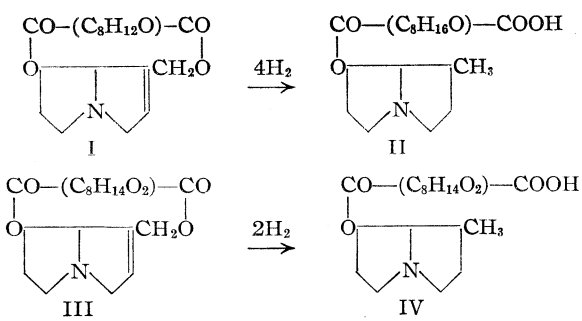
The α-acid shows a single strong hydroxyl frequency at 3452 cm.$^{-1}$. The β-acid appears to have two hydroxyl frequencies, one at 3350 cm.$^{-1}$ and the other at 3525 cm.$^{-1}$. The latter corresponds to the hydroxyl frequency found in β-longilobine itself at 3585 cm.$^{-1}$. The consistently high frequency of this band (above 3500 cm.$^{-1}$) both in β-longilobine and in β-longinecic acid probably indicates that the hydroxyl group is in a hindered position, preventing inter-molecular and intra-molecular bonding. It seems unlikely that these hydroxyl absorptions could be due to an acid hydroxyl group, since few cases are known in which a solid acid gives an absorption in this region. Structural work on α- and β-longinecic acids are under way.

On hydrogenation in the presence of Raney nickel catalyst, α-longilobine furnished a single product in quantitative yield, taking up two mole equivalents of hydrogen. This tetrahydro-α-longilobine is a crystalline compound possessing the physical properties of an amino acid and on hydrolysis furnished retronecanol and an acid identical with α-longinecic acid obtained by direct hydrolysis of the alkaloid with barium hydroxide. It is, therefore, evident that hydrogenation in the presence of Raney nickel as catalyst cleaves one ester linkage in the alkaloid and saturates the retronecine double bond, but leaves the unsaturation in the acid part of the molecule unaffected.

On the other hand, when α-longilobine was

hydrogenated in the presence of platinum-oxide catalyst, four mole equivalents of hydrogen were taken up and a single product was obtained in excellent yield. This product was amorphous and could not be crystallized. It showed the physical properties of an amino acid and on hydrolysis yielded retronecanol and an acid which could not be induced to solidify. The additional two moles of hydrogen taken up in the presence of platinum-oxide catalyst must therefore be accounted for by unsaturation in the acid moiety of the alkaloid. The intermediates obtained in the hydrogenation with either catalyst were certainly amino acids and there is a striking similarity in the behavior of α-longilobine on hydrogenation to riddelliine.[1b] With the structure of retronecine and retronecanol established[12] the general structural formula for α-longilobine may be indicated as I and the reduction product resulting from the absorption of four moles of hydrogen as II.

β-Longilobine in the presence of platinum-oxide catalyst absorbs merely two mole equivalents of hydrogen to give a single product in excellent yield. This product like those from α-longilobine appears to be an amino acid, since it is easily soluble in water and ethanol but insoluble in ether and other non-polar solvents. It was amorphous and could not be crystallized. On hydrolysis, retronecanol was obtained and an acid, m.p. 146°, identical with that from β-longilobine by hydrolysis with baryta. The two moles of hydrogen have obviously been used in hydrogenolysis and saturation of the retronecine double bond. The acid portion is saturated or contains no easily reduced unsaturation. The formula for β-longilobine may be designated as III and its reduction product as IV.




The authors are grateful to Mrs. J. L. Johnson for determination and interpretation of infrared spectra.

## Experimental

**Extraction of Longilobine from Senecio longilobus.**—The powdered plant material (whole plant) was extracted continuously in a Soxhlet for twenty-four to thirty hours with ethanol. The alkaloid was isolated as previously described for riddelliine.[1b] The residue from the chloroform extract was once recrystallized from methanol. The yield of longilobine from 27 lb. of dried material was 29.8 g. (0.24%). The product melted at 203–204° (cor.) with sintering from 197°. It was recrystallized thrice from absolute ethanol and then melted at 209–210° (cor.). This was the sample analyzed.

*Rotation:* (once recrystallized product) 0.2819 g. made up to 10 ml. in chloroform at 30° gave $\alpha_D$ −2.565°; *l*, 1; $[\alpha]^{30}D$ −91°.

*Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.86; H, 6.91; N, 4.2. Found: C, 63.88; H, 7.12; N, 3.98.

**Hydrolysis of Crude Longilobine.**—One gram of crude longilobine (once crystallized) was refluxed with 2 g. of barium hydroxide octahydrate in 7 ml. of water for one hour. The necine and necic acid portions were isolated as in the case of riddelliine.[1b] Retronecine hydrochloride in yield of 0.41 g. was obtained. Crystallization from ethanol gave a product, m.p. 162–163° (cor.), which did not depress the melting point of an authentic specimen of retronecine hydrochloride from monocrotaline.[1a]

*Anal.* Calcd. for $C_8H_{13}O_2N\cdot HCl$: C, 50.11; H, 7.36; Cl, 18.51. Found: C, 50.24; H, 7.16; Cl, 18.49.

The retronecine was also identified by conversion to diacetylretronecine picrate prepared from the base according to the directions of Barger, *et al.*[12a] The m.p. was 143° (cor.).

*Anal.* Calcd. for $C_{12}H_{17}O_4N\cdot C_6H_3O_7N_3$: N, 11.95. Found: N, 11.91.

The necic acid portion weighed 0.61 g. and was an amber-colored oil which could not be induced to crystallize.

**Chromatographic Procedure.**—Alumina[13] was used exclusively as the adsorbent in these experiments. The columns were packed dry with the adsorbent and washed with pure solvent before introducing the substance. Chloroform was found to be the ideal solvent. The α-longilobine was eluted from the column by washing with chloroform or with a mixture of chloroform and ethanol (one to two per cent.). In many early experiments, the β-longilobine was eluted by extracting the alumina residue with methanol. A purer product was obtained in better yield by stirring the alumina, after removal from the column, with fifteen to twenty parts of normal acetic acid, filtering from the alumina, basifying the filtrate with ammonia and extracting with chloroform. This was the preferred procedure in all later experiments.

The chloroform extract of the several "cuts," either from the filtrate or from the alumina, was distilled and the residue was made up to a known volume in pure chloroform. An aliquot portion was transferred to a tared watch glass and the amount of material in each fraction determined by evaporation. Another portion was utilized for determining the rotation. From these data, the specific rotation of each fraction was calculated.

**Preliminary Separation of α- and β-Longilobine.**—A solution of 5 g. of crude longilobine ($[\alpha]^{30}D$ −91°) in 150 ml. of dry chloroform was stirred for thirty minutes with 10 g. of freshly ignited alumina. The alumina was allowed to settle and the chloroform was decanted off through a filter paper. The process was repeated with two 150-ml. portions of chloroform (filtrate A).

The alumina was stirred with a total of 500 ml. of absolute ether in three lots and the ether decanted off (filtrate B).

The alumina was then stirred with a total of 500 ml. of methanol in five portions (filtrate C).

Filtrate A gave 2.9 g. of material. *Rotation:* 0.0521 g. made up to 2 ml. in chloroform at 30° gave $\alpha_D$ −3.02°; *l*, 1; $[\alpha]^{30}D$ −116°.

Filtrate B gave 0.1 g. of material. This was discarded.

Filtrate C gave 1.8 g. of material. *Rotation:* 0.0694 g. made up to 2 ml. in chloroform at 30° gave $\alpha_D$ −2.3°; *l*, 1; $[\alpha]^{30}D$ −66.2°.

Further purification of the two main fractions from

(12) Adams and Leonard, THIS JOURNAL, **66**, 257 (1944).

(12a) Barger, *et al.*, *J. Chem. Soc.*, 11 (1935).

(13) Activated alumina, Grade F 20, made by Aluminum Ore Co., East St. Louis, Illinois, was found to be quite satisfactory.

filtrates A and C was achieved as shown in Tables I and II.

**α-Longilobine.**—From absolute ethanol, m. p. 217–218° (cor.). *Rotation:* 0.0412 g. made up to 2 ml. in chloroform at 25° gave $\alpha_D$ −2.58°; *l*, 1; $[\alpha]^{25}D$ −125.2°.

*Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.86; H, 6.91; N, 4.2. Found: C, 65.21; H, 7.00; N, 4.37.

**α-Longilobine Methiodide.**—The methiodide was prepared by warming the alkaloid in chloroform solution with an excess of methyl iodide. After removing the chloroform, the product was twice recrystallized from ethanol with the addition of a few drops of water; white crystals, m. p. 240° (cor.).

*Rotation:* 0.0151 g. made up to 1 ml. in water at 28° gave $\alpha_D$ −1.06°; *l*, 1; $[\alpha]^{28}D$ −70.1°.

*Anal.* Calcd. for $C_{18}H_{23}O_5N{\cdot}CH_3I$: C, 48.0; H, 5.48; N, 2.95; I, 26.4. Found: C, 47.92; H, 5.64; N, 3.17; I, 26.51.

**β-Longilobine.**—From absolute ethanol, m. p. 207–208° (cor.). *Rotation:* 0.0367 g. made up to 2 ml. in chloroform at 28° gave $\alpha_D$ −0.89°; *l*, 1; $[\alpha]^{28}D$ −48.6°.

*Anal.* Calcd. for $C_{18}H_{25}O_6N$: C, 61.5; H, 7.12; N, 3.98. Found: C, 61.41; H, 7.28; N, 4.15.

**β-Longilobine Methiodide.**—This was prepared in the same manner as the α-longilobine derivative. After two recrystallizations from ethanol containing water, the product melted at 256° (cor.).

*Rotation:* 0.0168 g. made up to 1 ml. in water at 28° gave $\alpha_D$ −0.40°; *l*, 1; $[\alpha]^{28}D$ −23.8°.

*Anal.* Calcd. for $C_{18}H_{25}O_6N{\cdot}CH_3I$: C, 46.25; H, 5.68; N, 2.88. Found: C, 46.02; H, 5.93; N, 2.81.

**α-Longinecic Acid.**—A mixture of 0.5 g. of α-longilobine, 1 g. of barium hydroxide octahydrate and 7 ml. of water was refluxed for one hour. The necine and necic acid portions were isolated by the usual procedure. The yield of retronecine hydrochloride was 0.205 g. (72%), m. p. 163–164° (cor.).

The yield of α-longinecic acid was 0.289 g. (80%). This was recrystallized from absolute ether, with addition of petroleum ether to incipient turbidity. The product melted at 114–115° (cor.). By titration it was shown to be dibasic.

*Anal.* Calcd. for $C_{10}H_{14}O_5$: C, 56.08; H, 6.54; neut. equiv., 107. Found: C, 56.16; H, 6.34; neut. equiv., 103.9.

*Rotation:* 0.0249 g. made up to 1 ml. in water at 28° gave $\alpha_D$ −0.33°; *l*, 1; $[\alpha]^{28}D$ −13.25°.

On heating α-longinecic acid, water was evolved and a glassy product resulted which could possibly be a lactone. It could not be purified.

*Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.12. Found: C, 59.77; H, 6.58.

**β-Longinecic Acid.**—From 0.5 g. of β-longilobine by a similar hydrolysis, 0.19 g. (66.5%) of retronecine hydrochloride, m. p. 163–164°, was obtained. The yield of β-longinecic acid was 0.26 g. (78.6%). The acid was less soluble in absolute ether than α-longinecic acid. It was recrystallized by dissolving in a large volume of ether, concentrating to a small volume, adding a few drops of petroleum ether and rubbing with a glass rod. The recrystallized acid melted at 146–147° (cor.). Direct titration of β-longinecic acid indicated dibasicity. By adding excess of alkali, permitting to stand overnight and back titrating with standard hydrochloric acid, three carboxyls were indicated (Calcd. 77.3. Found 83.9).

*Anal.* Calcd. for $C_{10}H_{16}O_6$: C, 51.8; H, 6.95; neut. equiv., 116. Found: C, 51.58; H, 7.00; neut. equiv., 115.9.

*Rotation:* 0.0298 g. made up to 1 ml. in water at 28° gave $\alpha_D$ −0.27°; *l*, 1; $[\alpha]^{28}D$ −9.06°.

**Hydrogenolysis of α-Longilobine (Raney Nickel Catalyst). Tetrahydro-α-longilobine.**—A solution of 0.4 g. of α-longilobine in 15 ml. of ethanol and 2.5 ml. of water was hydrogenated at slightly over atmospheric pressure in the presence of approximately 0.5 g. of Raney nickel. A total of two mole equivalents of hydrogen were absorbed during three hours, after which no more hydrogen was taken up. The catalyst was filtered off and the solvent removed *in vacuo*. The residue was a colorless crystalline solid in a yield of 0.4 g. It was fairly soluble in water, more soluble in ethanol and acetic acid and insoluble in ether. It was best crystallized from a small volume of water, m. p. 190–191° (cor.). *Rotation:* 0.0187 g. made up to 2 ml. with water at 28° gave $\alpha_D$ −0.61°; *l*, 1; $[\alpha]^{28}D$ −65.2°.

*Anal.* Calcd. for $C_{18}H_{27}O_5N$: C, 64.10; H, 7.81. Found: C, 63.95; H, 7.96.

**Hydrolysis of Tetrahydro-α-longilobine.**—A mixture of 0.2 g. of tetrahydro-α-longilobine and 0.5 g. of barium hydroxide octahydrate in 5 ml. of water was refluxed for one hour and cooled. After saturating with carbon dioxide, the solution was filtered and made acid to congo red. Continuous extraction with ether for twenty-four hours and removal of solvent yielded an oil which solidified on rubbing. Recrystallization from ether–petroleum ether (b. p. 30–60°) gave a solid which melted at 114°. The melting point of a mixture of this product with α-longinecic acid gave no depression.

The aqueous solution remaining after ether extraction was made alkaline with sodium hydroxide and extracted with ether. After drying the ether extract with anhydrous magnesium sulfate and distilling the ether, a solid remained which was converted to a picrate with aqueous picric acid. The picrate, after recrystallization from water, melted at 211° and was identical with an authentic specimen of retronecanol picrate.

**Hydrogenolysis of α-Longilobine (Platinum Oxide Catalyst).**—A solution of 0.5 g. α-longilobine in 15 ml. of absolute ethanol and 1.5 ml. of acetic acid was hydrogenated at slightly over atmospheric pressure in the presence of 0.05 g. of platinum oxide catalyst. A total of four mole equivalents of hydrogen was absorbed. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was a glassy mass which could be broken down to a brittle powder; yield, 0.51 g. (quant.). If the acetic acid was omitted, the residue was an amorphous solid in nearly the same yield. Attempts to crystallize the product were unsuccessful. Accurate analysis was not possible because of the extreme hygroscopicity of the material.

A solution of 0.5 g. of the above material in 20 ml. of a 10% aqueous solution of sodium hydroxide was refluxed for one hour and cooled. The solution was repeatedly extracted with ether, the ether extract dried over anhydrous magnesium sulfate and the ether distilled. The residue was an oil which solidified on keeping in the desiccator. On recrystallization from petroleum ether (b. p. 30–60°), a white crystalline solid was obtained, m. p. 95–96° (cor.) identical with an authentic specimen of retronecanol.

The aqueous layer in acidification and continuous extraction with ether gave 0.25 g. of an amber-colored liquid which did not solidify.

**Hydrogenolysis of β-Longilobine.**—When 0.5 g. of β-longilobine was similarly hydrogenated in the presence of 0.05 g. of platinum oxide catalyst, only two mole equivalents of hydrogen were taken up. After filtration of catalyst and removal of solvent, a glassy mass was left behind which was converted to an amorphous powder on treatment with ether. This material (0.45 g.) was insoluble in ether and easily soluble in water and ethanol. On dissolving in absolute ethanol and adding absolute ether, the material separated as an oil which solidified on rubbing. This solid melted at 55–60°, forming a voluminous foam. Attempts to purify the material for analysis were unsuccessful.

A solution of 0.4 g. of the above material in 4 ml. of water was refluxed for one hour with one gram of barium hydroxide octahydrate. The acid portion was isolated by saturating with carbon dioxide, filtering the barium carbonate, acidifying the filtrate and extracting continuously with ether; yield, 0.21 g. After two recrystalliza-

tions from ether–petroleum ether mixture, the acid melted at 146° (cor.) and was identical with β-longinecic acid, obtained by direct hydrolysis of β-longilobine. The basic portion was isolated in the usual way and proved to be retronecanol identified conveniently as the picrate, m. p. 211°.

## Summary

1. The alkaloid from *Senecio longilobus*, first isolated by Manske, has been shown to be a mixture of two components designated as α- and β-longilobine, whose empirical formulas are $C_{18}H_{23}O_5N$ and $C_{18}H_{25}O_6N$, respectively. The separation was achieved by an empirical chromatographic procedure, combining the liquid chromatogram method and examination of the column. The course of the chromatogram was followed by determining the specific rotations of the different fractions and the two main components were rechromatographed until a constant specific rotation was attained.

2. On hydrolysis α-longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{14}O_5$, designated as α-longinecic acid.

3. Similarly β-longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{16}O_6$, designated as β-longinecic acid.

4. On reduction with hydrogen and Raney nickel, α-longilobine absorbs two moles of hydrogen to form tetrahydro-α-longilobine which has the properties of an amino acid and on hydrolysis yields retronecanol and α-longinecic acid. With platinum oxide as catalyst four moles of hydrogen are absorbed, yielding an amorphous product which gives on saponification retronecanol and an oily acid which was not purified.

5. β-Longilobine absorbs only two moles of hydrogen in the presence of platinum oxide as catalyst, yielding an amorphous product which gives on hydrolysis retronecanol and β-longinecic acid.

6. Both α- and β-longilobine are shown to be cyclic diesters, from one mole of retronecine and one mole of a dibasic acid, each of the two hydroxyls in retronecine being utilized.

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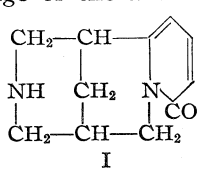
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Condensation Reactions of N-Substituted Pyridones[1]

BY ROGER ADAMS AND ANTHONY W. SCHRECKER

A consideration of possible methods for the synthesis of cytisine[2] (I) leads to the necessity of further knowledge of the activity of a 6-methyl



I

group in N-substituted 2-pyridones. This communication is devoted primarily to the description of the reactivity of the ring-substituted methyl group in 1,6-dimethyl-2-pyridone. It includes also the results of a similar study of 1,4-dimethyl-2-pyridone. 6-Methyl-2-pyridone-1-β-propionitrile and ethyl 6-methyl-2-pyridone-1-acetate were synthesized and preliminary experiments on pyridocoline formation were attempted. The activity of the methyl group in 2-acetamido-6(and 4)-methylpyridine is also described.

The ability of such compounds as 2-picoline to undergo condensation reactions with carbonyl compounds has been attributed to the double bond linking the nitrogen with the carbon atom carrying the methyl group.[3] A molecule carrying such a structural unit can undergo an electromeric shift permitting formation of a carbanion and subsequent condensation with a carbonyl group.[4] No such double bond appears in the formula of a compound such as 1,6-dimethyl-2-pyridone (IIa). If N-alkylpyridones are, however, resonance hybrids of an uncharged and a betaine (IIb) structure, as postulated by Arndt and Kalischek,[5] and the carbanion (III) is stabilized by resonance, then the requirement for base-catalyzed condensation reactions should be fulfilled. Replacement of the 6-methyl group by a carbethoxymethyl group would render the compound somewhat similar in its behavior to a β-keto ester and replacement by a cyanomethyl group similar to a β-carbonylated nitrile, such as ethyl cyanoacetate. Such compounds should form sodium enolates which react with alkyl and acyl halides. These predictions have been realized experimentally.

The predictions were supported by the experiments of Kaslow and Cook[6] who demonstrated the reactivity of the 4-methyl group in 1,4-dimethylcarbostyril toward ethyl oxalate. The condensation product was readily transformed into 1-methyl-4-carbostyrilacetonitrile, which underwent condensation with benzaldehyde.

The starting materials, 1,6-dimethyl-2-pyridone

(1) From a thesis presented by Anthony W. Schrecker to the Graduate College of the University of Illinois, August, 1948, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

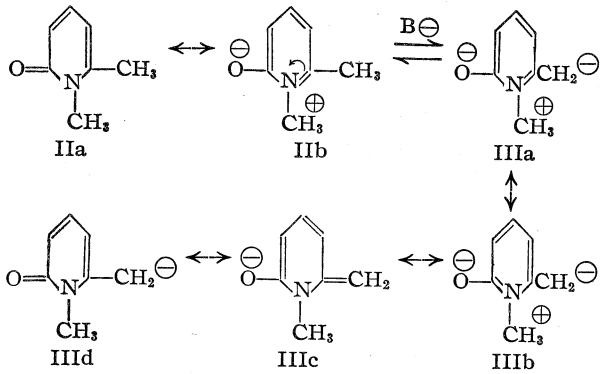
(2) Späth and Galinovsky, *Ber.*, **66**, 1338 (1933).

(3) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

(4) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 130.

(5) Arndt and Kalischek, *Ber.*, **63**, 587 (1930).

(6) Kaslow and Cook, THIS JOURNAL, **67**, 1969 (1945).



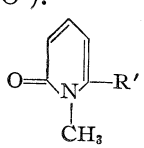

(II) and 1,4-dimethyl-2-pyridone, were prepared from the sodium salts of 6-methyl-2-pyridone and 4-methyl-2-pyridone by alkylation with dimethyl sulfate. They were low-melting, water-soluble compounds, which was to be expected from a consideration of the physical properties of the previously characterized 1-methyl-2-pyridone[7] and 1,4,6-trimethyl-2-pyridone.[8] Mumm[9] has described a product reputed to be 1,6-dimethyl-2-pyridone. He obtained it in a series of reactions starting with diethyl 2,6-dimethylpyridine-3,5-dicarboxylate and reported it to melt at 352° and to be difficultly soluble in water. The physical properties and chemical reactions of the compound, m. p. 56.5–58°, described in the present paper, prove conclusively that this substance is actually 1,6-dimethyl-2-pyridone.

1,6-Dimethyl-2-pyridone underwent condensation with ethyl oxalate in the presence of potassium or sodium ethoxide to form the yellow potassium or sodium salt of ethyl 1-methyl-2-pyridone-6-pyruvate in 95% yield, from which the free ester (IV) was obtained by acidification. The same reaction proceeded at a somewhat lower rate with 1,4-dimethyl-2-pyridone to give the potassium salt (84% yield) and from it ethyl 1-methyl-2-pyridone-4-pyruvate. Hydrolysis of the esters gave 1-methyl-2-pyridone-6-pyruvic acid (V) and 1-methyl-2-pyridone-4-pyruvic acid.

The pyruvic acids underwent oxidative decarboxylation when treated with aqueous sodium hydroxide and hydrogen peroxide to give respectively 1-methyl-2-pyridone-6-acetic acid (VI) (84–87% yield) and 1-methyl-2-pyridone-4-acetic acid (46–59% yield). The former was also obtained when the pyruvic ester instead of the acid was treated with hydrogen peroxide in aqueous sodium hydroxide, though in lower yield. The oxidation took a different course when the potassium salt of ethyl 1-methyl-2-pyridone-6-pyruvate was treated with hydrogen peroxide, and one mole of dilute sodium hydroxide was added only after some time. None of the 6-acetic acid was obtained, but 1-methyl-2-pyridone-6-carboxylic acid[10] (VII) was formed in a 58% yield. 1-Methyl-2-pyridone-6-acetic acid (VI), m. p. 188°, and 1-methyl-2-pyridone-6-carboxylic acid (VII), m. p. 260°, decompose at their melting points with loss of carbon dioxide to give, respectively, 1,6-dimethyl-2-pyridone and 1-methyl-2-pyridone. Consideration of the betaine structure of pyridones (IIb) shows that the former acid is somewhat analogous to a β-keto acid, the latter to an α-keto acid.

By treatment of 1-methyl-2-pyridone-6-pyruvic acid (V) with hydroxylamine or by alkaline hydrolysis of the oximino ester prepared similarly from the pyruvic ester (IV), 1-methyl-2-pyridone-6-(α-oximino)-propionic acid (VIII) was readily formed and this was converted in 93% yield to 1-methyl-2-pyridone-6-acetonitrile (IX) by pyrolysis. By alkaline hydrolysis of the nitrile the 6-acetic acid (VI) results. Ethyl 1-methyl 2-pyridone-6-acetate (X), formed by esterification of the corresponding acid (VI), and 1-methyl-2-pyridone-6-acetonitrile (IX) condensed with benzyl chloride in the presence of ethanolic sodium ethoxide, the former to give ethyl 1-methyl-2-pyridone-6-(α-benzyl)-acetate (XI, R = $C_6H_5CH_2$-) in 61% yield and the latter to give the corresponding nitrile in 42% yield. On hydrolysis, the ethyl 1-methyl-2-pyridone-6-(α-benzyl)-acetate as well as the nitrile gave the corresponding acid (XII, R = $C_6H_5CH_2$-) which melted at 155° with evolution of carbon dioxide and formation of 1-methyl-6-phenethyl-2-pyridone (XIII, R = $C_6H_5CH_2$-). An analogous condensation of ethyl 1-methyl-2-pyridone-6-acetate with *n*-butyl bromide or better *n*-butyl iodide gave the α-*n*-butyl derivative (XI, R = $C_4H_9$-) which was hydrolyzed and decarboxylated to 6-*n*-amyl-1-methyl-2-pyridone (XIII, R = $C_4H_9$-).

The sodium derivative of ethyl 1-methyl-2-pyridone-6-acetate also reacted with acetyl chloride to give in 38% yield a β-keto ester (XI, R = $CH_3CO$-) which was an oil. It was not purified, but hydrolyzed and decarboxylated directly with formation of 6-acetonyl-1-methyl-2-pyridone (XIII, R = $CH_3CO$-).



| R′ = | R′ = |
|---|---|
| IV, $CH_2COCOOEt$ | IX, $CH_2CN$ |
| V, $CH_2COCOOH$ | X, $CH_2COOEt$ |
| VI, $CH_2COOH$ | XI, $CHRCOOEt$ |
| VII, COOH | XII, $CHRCOOH$ |
| VIII, $CH_2C(=NOH)COOH$ | XIII, $CH_2R$ |

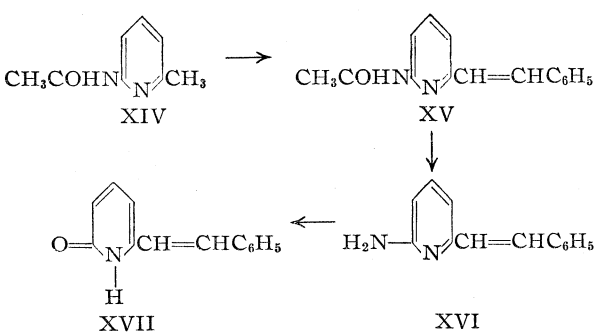
Condensation of 1,6-dimethyl-2-pyridone with *m*-nitrobenzaldehyde in the presence of acetic anhydride gave only about 1% yield of 1-methyl-6-(*m*-nitrostyryl)-2-pyridone, in contrast to a 90% yield obtained in the reaction of *m*-nitrobenzaldehyde with 2-picoline.[11] In view of the unsatisfactory result of the attempts to prepare condensation products of pyridone homologs with alde-

(7) Binz and Räth, *Ann.*, **489**, 107 (1931).
(8) Hantzsch, *Ber.*, **17**, 2903 (1884).
(9) Mumm, *Ann.*, **443**, 272 (1925).
(10) Späth and Koller, *Ber.*, **56**, 880 (1923).
(11) Shaw and Wagstaff, *J. Chem. Soc.*, 77 (1933).

hydes, the possibility of obtaining such compounds by an indirect route was investigated.

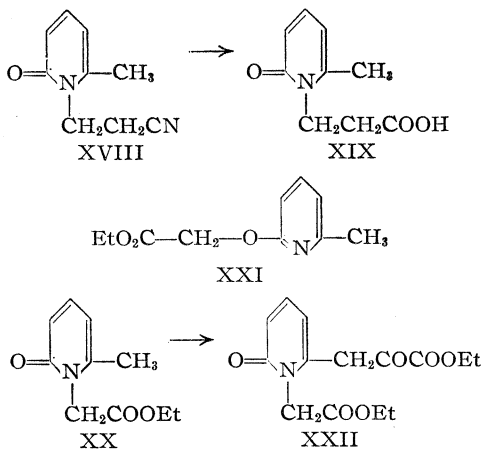
2-Acetamido-6-methylpyridine (XIV) was condensed with benzaldehyde in the presence of acetic anhydride to give 6-acetamido-2-stilbazole (XV) in 12% yield. A yield of 87% is reported in the condensation of benzaldehyde with 2-picoline.[11] The acetamidostilbazole was hydrolyzed in hydrochloric acid and the 6-amino-2-stilbazole (XVI) purified by taking advantage of the low solubility of its hydrochloride in cold 20% hydrochloric acid. Diazotization of the amino compound gave a 48% yield of 6-hydroxy-2-stilbazole (6-styryl-2-pyridone) (XVII). When the same series of reactions was carried out with 2-acetamido-4-methylpyridine, a 14% yield of 2-amino-4-stilbazole resulted. In this case the intermediary acetamido compound was not isolated but the reaction mixture hydrolyzed directly by boiling with hydrochloric acid. Diazotization of the aminostilbazole gave a 36% yield of 2-hydroxy-4-stilbazole(4-styryl-2-pyridone). In the formation of 2-amino-4-stilbazole there was isolated from the condensation a yellow crystalline by-product, m. p. 234–235°, the structure of which was not determined.

6-Methyl-2-pyridone condenses in the same manner as 2-pyridone[12] in presence of alkaline




catalysts with acrylonitrile to form 6-methyl-2-pyridone-1-β-propionitrile (XVIII). This product was hydrolyzed to the corresponding acid (XIX). Esterification of the acid by the usual methods failed to give a pure product. On distillation the oily esters were unstable and decomposed into 6-methyl-2-pyridone and acrylic esters. The nitrile (XVIII), which can be readily purified since it is a crystalline solid, also decomposes on distillation. All attempts to cause a ring closure between the carbalkoxy group and the 6-methyl group in the esters of XIX in order to obtain a bicyclic molecule more closely resembling cytisine were unsuccessful.

The stable ethyl 6-methyl-2-pyridone-1-acetate (XX) was prepared by the reaction of 6-methyl-2-pyridone sodium with ethyl bromoacetate. A 70% yield resulted, with 5% of the corresponding 2-pyridyl ether (XXI) as a by-product. Ethyl oxalate condensed with ethyl 6-methyl-2-pyridone-1-acetate (XX) to form probably ethyl 1-carbethoxymethyl-2-pyridone-6-pyruvate (XII), but no bicyclic product which might result from the elimination of two moles of ethanol.




Attempts to introduce halogen into the 6-methyl group of 6-methyl-2-pyridone failed. Bromination invariably resulted in ring substitution.

## Experimental

**6-Methyl-2-pyridone.**—A solution of 108 g. of 2-amino-6-methylpyridine (b. p. 209–210°) in a cold mixture of 111 ml. of concd. sulfuric acid and 830 ml. of water was placed in an ice–salt-bath. With mechanical stirring a solution of 73 g. of 97% sodium nitrite in 140 ml. of water was introduced through a dropping funnel, the orifice of which reached nearly to the bottom of the beaker, at such a rate that the temperature of the reaction mixture did not rise above 5°. To complete the reaction, it was stirred for an additional hour below 10° and finally heated on a steam-bath until the temperature reached 90°.

The yellow solution was made alkaline by adding 205 g. of anhydrous potassium carbonate and evaporated to dryness on the steam-bath. The residue was powdered in a mortar and then extracted exhaustively with boiling benzene. The extract was clarified with Norit, filtered hot, concentrated to a volume of about 500 ml. and allowed to cool in an icebox. The yellow crystals were collected on a Büchner funnel and, after drying, weighed 95.3 g. By working up the mother liquor, an impure product was obtained which after recrystallization from benzene weighed 5.9 g. The over-all yield was thus 101.2 g. (92.8%). The material as initially obtained and after crystallization from benzene melted at 158–159° (cor.). By recrystallization from acetone or by distillation, b. p. 282° (760 mm.), colorless prismatic needles of the same melting point resulted.

This compound was first described by Errera[13] who obtained it by decarboxylation of 6-methyl-2-pyridone-3,5-dicarboxylic acid. He reported a melting point of 159°. A somewhat similar procedure was described by Seide,[14] who also reported the same melting point.

**6-Methyl-2-pyridone Sodium.**—The diazotized solution of 108 g. of 2-amino-6-methylpyridine was heated to boiling and neutralized by the addition of 568 g. of barium hydroxide octahydrate dissolved in 1500 ml. of boiling water. Barium sulfate was removed by filtration on a Büchner funnel and extracted several times with boiling water. The combined filtrate and washings, after addition of 50 ml. of 25% aqueous sodium hydroxide, were evaporated to dryness and the residue extracted exhaus-

(12) Adams and Jones, THIS JOURNAL, **69**, 1803 (1947).

(13) Errera, *Ber.*, **33**, 2969 (1900).

(14) Seide, *J. Russ. Phys.-Chem. Soc.*, **50**, 534 (1918).

tively with hot 95% ethanol. Cooling of the extract caused the separation of yellowish leaflets. Recrystallization from 95% ethanol served for purification. The product formed colorless glittering leaflets. The yield was 115.5 g. (88%), after drying *in vacuo* at 100°; m. p. 290°.

The sodium salt is very soluble in water, moderately soluble in ethanol, difficultly soluble in acetone and insoluble in ether.

*Anal.* Calcd. for $C_6H_6ONNa$: Na, 17.54. Found: Na, 17.48.

**1,6-Dimethyl-2-pyridone (II).**—This product was prepared in a manner similar to that used for the preparation of 1-methyl-2-pyridone from 2-pyridone potassium.[7]

In a 2-l. round-bottomed flask fitted with reflux condenser and dropping funnel, 98.7 g. of 6-methyl-2-pyridone was dissolved in a warm, freshly prepared solution of 21.0 g. of sodium in 250 ml. of methanol. After cooling to room temperature, 130 g. of dimethyl sulfate was added with shaking during a period of fifteen minutes. After refluxing on a water-bath for two hours, the solution was made strongly alkaline by adding 220 g. of 25% aqueous sodium hydroxide and steam-distilled until the odor of the by-product, 2-methoxy-6-methylpyridine, had disappeared from a sample of the distillate. After cooling to room temperature, sodium sulfate was removed from the steam-distillation residue by filtration on a Büchner funnel and the filter-cake washed with two 75-ml. portions, then with four 50-ml. portions of chloroform. The successive chloroform washings were used to extract the filtrate. After drying over potassium carbonate, the solvent was removed under reduced pressure and the product distilled, b. p. 110° (2 mm.). The yield was 82 g. (74%). The distillate solidified to a colorless crystalline mass which was recrystallized from dry ether; deliquescent plates, m. p. 56.5–58°.

The compound is very soluble in water, ethanol, chloroform and benzene, moderately soluble in ether, insoluble in petroleum ether. Its aqueous solutions are neutral.

*Anal.* Calcd. for $C_7H_9ON$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.40; H, 7.33; N, 11.36.

Attempts to prepare this compound by alkaline hydrolysis of the product from methyl iodide and 2-amino-6-methylpyridine according to the procedure of Chichibabin and Konovalova[15] gave only a 23% yield. The use of dimethyl sulfate on α-picoline followed by the action of alkaline ferricyanide[16] failed to give any product.

**1,6-Dimethyl-2-pyridone Hydrochloride.**—This hydrochloride was prepared in absolute ether with dry hydrogen chloride. After several recrystallizations from absolute ethanol, it formed colorless prismatic needles, m. p. 202–203° (cor.). The compound had to be dried at room temperature, as it sublimes readily at 75° (3 mm.).

*Anal.* Calcd. for $C_7H_{10}ONCl$: C, 52.67; H, 6.32; N, 8.78; Cl, 22.21. Found: C, 52.75; H, 6.30; N, 8.92; Cl, 22.31.

**1,6-Dimethyl-2-pyridone Picrate.**—The picrate was obtained by the usual procedure. It was purified by crystallization from 95% ethanol and formed long yellow needles, m. p. 134–136° (cor.).

*Anal.* Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.32; H, 3.43; N, 15.91. Found: C, 44.53; H, 3.58; N, 15.84.

**4-Methyl-2-pyridone.**—This product was synthesized in a manner similar to that described for converting 2-amino-6-methylpyridine to 6-methyl-2-pyridone. Two runs of 54 g. of 2-amino-4-methylpyridine were diazotized, combined and then made alkaline by adding 210 g. of anhydrous potassium carbonate. After evaporation on a steam-bath, the nearly dry residue was extracted several times with a total of 1 l. of boiling ethanol. The brown extract was freed from ethanol under reduced pressure and the residue distilled. The 4-methyl-2-pyridone boiled at 186–187° (12 mm.) and solidified in the receiver to a colorless crystalline mass which was recrystallized from benzene and washed with petroleum ether (b. p. 30–60°). The yield was 85.1 g. (78%) of large colorless prisms, m. p. 130° (cor.).

Seide[17] reported a melting point of 130° and a boiling point of 307–309° (atm. press.).

**1,4-Dimethyl-2-pyridone.**—This compound was prepared in a manner analogous to the preparation of 1,6-dimethyl-2-pyridone from 6-methyl-2-pyridone. The crude reaction product, obtained from 85.1 g. of 4-methyl-2-pyridone by methylation, addition of base, steam-distillation and extraction of the residue with chloroform, was distilled *in vacuo*, b.p. 110° (1 mm.). The yield was 73.6 g. (77%). The product solidified in the receiver to a colorless mass, which after crystallization from dry ether formed colorless needles, m. p. 59°. It is somewhat deliquescent, though less so than 1,6-dimethyl-2-pyridone.

*Anal.* Calcd. for $C_7H_9ON$: C, 68.27; H, 7.37. Found: C, 68.05; H, 7.52.

**1,4-Dimethyl-2-pyridone Hydrochloride.**—This compound was prepared by saturating a solution of the base in a little absolute ethanol with dry hydrogen chloride, while cooling in ice water, and then adding dry ether. Recrystallization was accomplished from ethanol–ether; small colorless needles, m. p. 173–174° (cor.).

*Anal.* Calcd. for $C_7H_{10}ONCl$: Cl, 22.21. Found: Cl, 22.22.

**1,4-Dimethyl-2-pyridone Picrate.**—The picrate crystallized from 95% ethanol as yellow needles, m. p. 168–169° (cor.).

*Anal.* Calcd. for $C_{13}H_{12}O_8N_4$: N, 15.91. Found: N, 15.84.

**Ethyl 1-Methyl-2-pyridone-6-pyruvate (IV).**—A procedure was employed somewhat similar to one described for quinaldine.[18]

(a) **Potassium Ethoxide.**—A solution of potassium ethoxide was prepared by adding cautiously through a dropping funnel 69 ml. of absolute ethanol to 10.55 g. of potassium previously covered with 60 ml. of absolute ether and finally refluxing the mixture until the potassium had completely dissolved. After cooling to room temperature a solution of 39.5 g. of anhydrous ethyl oxalate in 250 ml. of absolute ether was added and the slightly yellow solution allowed to stand at room temperature for ten minutes. Then 30.75 g. of 1,6-dimethyl-2-pyridone was introduced and the flask stoppered securely and shaken until the dimethylpyridone had dissolved. The potassium salt of the keto ester started to separate immediately as a dense yellow powder. The mixture was allowed to stand at room temperature for three days, after which the potassium salt was collected on a Büchner funnel, washed with a liberal amount of absolute ether and dried in a vacuum desiccator over phosphorus pentoxide. The yield was 61.8 g. (94.7%).

Recrystallization from absolute ethanol gave yellow microcrystals, m. p. 310–320°, with decomposition.

*Anal.* Calcd. for $C_{11}H_{12}O_4NK$: C, 50.56; H, 4.63; N, 5.36; K, 14.96. Found: C, 51.19; H, 4.90; N, 5.55; K, 14.76.

Conversion to the free ester was accomplished by adding 61.8 g. of the crude potassium salt gradually to a well-stirred ice-cold solution of 27 g. of concd. sulfuric acid in 450 ml. of water. The yellow microcrystalline precipitate was collected on a Büchner funnel, washed with cold water, suspended in 300 ml. of cold water, refiltered, washed again and dried. The yield of ester was 42.8 g. (81.1% based on potassium salt, 76.8% based on dimethylpyridone). After recrystallization from 95% ethanol it formed small yellow needles; m. p. 175–176° (cor.). The product is very difficultly soluble in water; soluble in ten parts of boiling ethanol.

*Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.39; H, 5.79; N, 6.23.

(15) Chichibabin and Konovalova, *Ber.*, **54**, 814 (1921).

(16) Prill and McElvain, *Org. Syntheses*, Coll. Vol. II, p. 419.

(17) Seide, *Ber.*, **57**, 791 (1924).

(18) Wislicenus and Kleisinger, *ibid.*, **42**, 1140 (1909).

(b) **Sodium Ethoxide.**—By use of sodium ethoxide prepared from sodium hydride in absolute ether and absolute ethanol, following the procedure just described, a 95% yield of sodium salt and from it a yield of 85% of ester (based on sodium salt) was obtained.

When the same procedure was applied to condensations of ethyl oxalate with 2-picoline, 6-methyl-2-pyridone or 2-acetamido-6-methylpyridine, no pyruvic esters could be obtained.

**Ethyl 1-Methyl-2-pyridone-4-pyruvate.**—The procedure described for making ethyl 1-methyl-2-pyridone-6-pyruvate was used. The potassium salt of the keto ester separated only very gradually as a dense yellow powder. It was collected on a Büchner funnel after standing for four and one-half days at room temperature, washed with absolute ether and dried over phosphorus pentoxide in a vacuum desiccator. The yield was 84%.

Conversion to the free ester was carried out by adding 12.0 g. of the potassium salt to a mixture of 5.25 g. of concd. sulfuric acid in 55 ml. of water, 30 g. of chopped ice and 100 ml. of chloroform, which was agitated by an efficient mechanical stirrer. The chloroform layer was decanted and the aqueous phase extracted with 50 ml. of chloroform. It was then made nearly neutral by adding with stirring 3.5 ml. of 28% aqueous ammonia in 30 ml. of water and again extracted with 50 ml. of chloroform. The combined chloroform solutions were washed twice with a small amount of water, filtered and concentrated to a volume of 49 ml., then diluted with 200 ml. of petroleum ether (b. p. 30–60°). The ester separated as small yellow crystals, which were filtered and washed with petroleum ether (b. p. 30–60°) after standing for three hours in the icebox. The yield was 8.1 g. (79% based on potassium salt, 67% based on dimethylpyridone). The ester crystallized from acetone or from ethanol–benzene as small colorless needles, m. p. 157–158° (cor.). The product is very soluble in ethanol and chloroform, moderately soluble in acetone, sparingly soluble in benzene, insoluble in water and petroleum ether.

*Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87. Found: C, 59.14; H, 5.89.

When the potassium salt was converted into the free ester by the method described under the preparation of ethyl 1-methyl-2-pyridone-6-pyruvate, the yield based on the potassium salt was only 56%.

The condensation was also effected by the use of sodium ethoxide in a similar manner. The over-all yield was 65%.

**1-Methyl-2-pyridone-6-pyruvic Acid (V).**—A mixture of 22.3 g. of 6% sulfuric acid and 2.23 g. of ethyl 1-methyl-2-pyridone-6-pyruvate was boiled under reflux for one-half hour with mechanical stirring. At first the ester dissolved, then after several minutes the acid started to separate. The mixture was allowed to stand in the icebox for several hours, the acid collected on a filter, washed with cold water and dried. There was obtained 1.78 g. (91%) of yellowish-white fine small needles. After recrystallization from water the acid melted at 239–240° (cor.) with effervescence.

*Anal.* Calcd. for $C_9H_9O_4N$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.06; H, 4.78; N, 7.21.

**1-Methyl-2-pyridone-4-pyruvic Acid.**—The hydrolysis of the ester was carried out as described for the analogous 6-pyruvic ester. The product was obtained in 55% yield. It was purified by recrystallization from 50% acetic acid; small pale yellow needles, m. p. 246° (cor.) with effervescence.

*Anal.* Calcd. for $C_9H_9O_4N$: C, 55.38; H, 4.65. Found: C, 55.31; H, 4.88.

### 1-Methyl-2-pyridone-6-acetic Acid (VI)

(a) **From 1-Methyl-2-pyridone-6-pyruvic Acid.**—A solution of 1.95 g. of the keto acid in 18 ml. of ice-cold 10% aqueous sodium hydroxide was cooled in an ice–salt-bath and shaken vigorously, while 3.3 ml. of 30% hydrogen peroxide diluted with 5 ml. of water was added at such a rate that the temperature did not rise above 0°. The solution, which at first was yellow but became colorless after some time, was kept in the icebox for forty-eight hours. A little powdered manganese dioxide was then added to cause decomposition to excess hydrogen peroxide and the mixture left in the icebox for another hour. Manganese dioxide was removed by filtration and washed with a little water and the combined filtrate and washings were acidified to congo red by the cautious addition of concd. hydrochloric acid. Crystals separated from the blue solution which, when heated, turned red, then yellowish. After boiling for several minutes, the mixture was cooled and allowed to stand in the icebox to complete crystallization. The pinkish crystals were collected on a filter and washed with ice-cold water; 1.46 g. (87%). By recrystallization from water the acid formed colorless crystals, m. p. 188° (cor.) with effervescence.

*Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.54; H, 5.33; N, 8.25.

When 0.3 g. of the acid was heated at its melting point, it formed 1,6-dimethyl-2-pyridone with evolution of carbon dioxide. The dimethylpyridone was identified as the picrate; yellow needles from ethanol; m. p. 134–136°.

(b) **From Ethyl 1-Methyl-2-pyridone-6-pyruvate.**—To 0.446 g. of the keto ester was added a mixture of 3.6 ml. of 10% aqueous sodium hydroxide, 0.7 ml. of 30% hydrogen peroxide and 2 g. of ice. After standing for fourteen hours in the icebox, 0.3 ml. of 30% hydrogen peroxide was added to the still slightly yellow solution, which then was allowed to stand in the icebox for another twenty-four hours. A little powdered manganese dioxide was added to the now colorless solution, which was filtered after several minutes and acidified to congo red with concd. hydrochloric acid. When heated, the blue solution turned tan-colored. Cooling caused crystals to separate which were washed with ice-cold water after standing for some time in an ice-bath. The yield was 0.18 g. (54%) of colorless crystals, m. p. 186.5° (cor.) with effervescence.

**1-Methyl-2-pyridone-4-acetic Acid.**—This acid was prepared in a manner similar to the 6-acetic acid analog. From 3.9 g. of 1-methyl-2-pyridone-4-pyruvic acid 1.98 g. (59%) of product resulted. It was purified by crystallization from water; colorless needles, m. p. 184° (cor.) with effervescence.

*Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; neut. equiv., 167.2. Found: C, 57.50; H, 5.57; neut. equiv., 167.7.

**1-Methyl-2-pyridone-6-carboxylic Acid (VII).**—To 10.4 g. of the potassium salt of ethyl 1-methyl-2-pyridone-6-pyruvate was added 92 g. of ice, followed by 14 ml. of 30% hydrogen peroxide and the solution kept in the icebox for one and one-half hours. An ice-cold solution of 1.8 g. of sodium hydroxide in 10 ml. of water was added and, after forty-two hours in the ice-box, excess hydrogen peroxide was decomposed by adding a little manganese dioxide. The mixture was allowed to stand in the ice-box for another hour, filtered and acidified with 7.5 ml. of concd. hydrochloric acid, which caused the blue solution to turn brown. Tan crystals separated immediately; they were filtered after standing for two hours in the icebox, 3.55 g. (58%). The acid was purified by dissolving it in dilute aqueous sodium carbonate, boiling the solution with Darco, then filtering and acidifying with dilute hydrochloric acid and recrystallizing the precipitate twice from glacial acetic acid. It formed colorless needles, m. p. 260° (cor.) with effervescence. Späth and Koller[10] reported m. p. 247–248° for the compound as prepared by methylation of 6-hydroxypyridine-2-carboxylic acid.

*Anal.* Calcd. for $C_7H_7O_3N$: C, 54.90; H, 4.61. Found: C, 54.87; H, 4.79.

A small quantity of the acid was melted in a small tube and the liquid distilled. The distillate was dissolved in ether and an ethereal solution of mercuric chloride added. The colorless needles of the mercuric chloride double salt of 1-methyl-2-pyridone, m. p. 127°, as reported by Späth and Koller, resulted.

**Methyl 1-Methyl-2-pyridone-6-acetate.**—A mixture of 0.55 g. of 1-methyl-2-pyridone-6-acetic acid, 14 ml. of

methanol and 0.5 ml. of concd. sulfuric acid was boiled under reflux for two hours, cooled, poured into an excess of aqueous potassium carbonate and the resulting solution extracted several times with chloroform. Addition of petroleum ether (b. p. 30–60°) to the chloroform solution which had been concentrated to a small volume caused the separation of 0.46 g. (77%) of crystals. Recrystallization from ether–petroleum ether (b. p. 30–60°) yielded small colorless needles, m. p. 102°.

*Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.90; H, 6.01; N, 8.06.

**Ethyl 1-Methyl-2-pyridone-6-acetate (X).**—A mixture of 17.6 g. of 1-methyl-2-pyridone-6-acetic acid, 500 ml. of absolute ethanol and 6 ml. of concd. sulfuric acid was boiled under reflux for two hours. After addition of 50 ml. of benzene, the solution was distilled slowly for one hour on the steam-bath until about half volume was reached and then concentrated under reduced pressure to a volume of about 110 ml. Upon adding carefully 20 g. of anhydrous potassium carbonate, then 50 g. of chopped ice, followed by 200 ml. of water, and extracting of the solution with eight 25-ml. portions of chloroform, a chloroform solution was obtained. This was dried, concentrated to about 30 ml. and diluted with 100 ml. of petroleum ether (b. p. 30–60°) which caused the deposition of 17.8 g. of colorless needles, m. p. 100–101° (cor.). Another 0.5 g. of less pure product was obtained from the filtrate, giving a total yield of 18.3 g. (89%). Recrystallization of the first crop from dry ether did not cause modification of the melting point.

The ester was very soluble in water, benzene and chloroform, moderately soluble in ether, sparingly soluble in petroleum ether.

*Anal.* Calcd. for $C_9H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.59; H, 6.61; N, 7.12.

The ester failed to undergo condensation with aromatic aldehydes in the presence of piperidine or with ethyl oxalate in the presence of potassium ethoxide.

**Ethyl 1-Methyl-2-pyridone-6-(α-oximino)-propionate.**—A solution of 15.0 g. of ethyl 1-methyl-2-pyridone-6-pyruvate and 15 g. of hydroxylamine hydrochloride in 75 ml. of pyridine and 75 ml. of absolute ethanol was refluxed for four hours on the steam-bath. The hot solution was filtered to remove a small amount of impurity and the filtrate freed from solvents by distillation under reduced pressure. The yellowish gelatinous residue was triturated with 75 ml. of cold water. White crystals separated which were collected on a filter, washed with water and dried. The yield was 13.8 g. (86%). The ester was purified by crystallization from 95% ethanol; colorless needles, m. p. 198° (cor.).

*Anal.* Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.49; H, 6.15; N, 11.86.

**1-Methyl-2-pyridone-6-(α-oximino)-propionic Acid (VIII)**

(a) **By Hydrolysis of the Oximino Ester.**—A solution of 8.91 g. of the oximino ester in 45 ml. of 2 *N* aqueous sodium hydroxide was boiled under reflux for one hour and twenty minutes. A small amount of impurity was removed by filtration, 10 ml. of water being used for washing flask and filter. The combined yellow filtrate and washings were cooled in an ice-bath and acidified with 9 ml. of concd. hydrochloric acid. Small colorless needles separated; 7.49 g. (95%), m. p. 182° (cor.) with decomposition. Purification by crystallization from 50% acetic acid did not change the melting point.

*Anal.* Calcd. for $C_9H_{10}O_4N_2$: C, 51.43; H, 4.80. Found: C, 51.31; H, 4.87.

(b) **By Action of Hydroxylamine on 1-Methyl-2-pyridone-6-pyruvic Acid.**—To 19.5 g. of the keto acid was added an ice-cold solution of 14.75 g. of 95% sodium hydroxide in 60 ml. of water, followed by an ice-cold solution of 10.42 g. of hydroxylamine hydrochloride in 20 ml. of water. The mixture was shaken to dissolve the acid, then allowed to stand at 30° for forty-three hours. A small amount of impurity was removed by filtration and the yellow filtrate, which was cooled in an ice-bath to 5°, acidified by the addition of 33 ml. of concd. hydrochloric acid. Small colorless needles separated, which were filtered after standing for several hours in the icebox, washed with ice-cold water and, when dried, melted at 182° (cor.) with decomposition. The yield was 19.15 g. (91%).

**1-Methyl-2-pyridone-6-acetonitrile (IX).**—A distilling flask containing 19.1 g. of 1-methyl-2-pyridone-6-(α-oximino)-propionic acid was heated cautiously with a free flame. The solid melted with copious evolution of carbon dioxide and water. The residue was then distilled under reduced pressure, b. p. 168° (1 mm.), as a yellow oil which solidified in the receiver. The yield was 12.5 g. (93%). After recrystallization from benzene–ether and a second vacuum-distillation the product formed colorless needles, m. p. 95.5–96.5°, very soluble in water, ethanol and acetone, moderately soluble in benzene, sparingly soluble in ether.

*Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44. Found: C, 64.78; H, 5.33.

The nitrile failed to condense with ethyl carbonate. With benzaldehyde in the presence of pyridine and piperidine, a yellow condensation product, m. p. 260–262° (cor.), formed in a high yield, but could not be obtained in analytically pure form.

The nitrile was readily hydrolyzed by boiling with dilute ethanolic sodium hydroxide for three hours. After acidification 1-methyl-2-pyridone-6-acetic acid, m. p. 187° (cor.) with effervescence, resulted in 86% yield.

**Ethyl 1-Methyl-2-pyridone-6-(α-benzyl)-acetate (XI, R = $C_6H_5CH_2$).**—To a solution of 0.084 g. of sodium in 2 ml. of absolute ethanol was added 0.69 g. of ethyl 1-methyl-2-pyridone-6-acetate, followed by 0.45 ml. of benzyl chloride. The mixture was refluxed on the steam-bath for twenty-one hours with exclusion of moisture. Another 0.2 ml. of benzyl chloride was added and refluxing continued for three hours until the reaction mixture was neutral. After steam-distillation to remove excess benzyl chloride, the oil which had separated from the residue was dissolved in ether. The ether solution was washed twice with dilute aqueous sodium carbonate, dried over potassium carbonate and concentrated to a volume of about 3 ml., which caused colorless crystals to separate. Crystallization was completed by adding 30 ml. of petroleum ether (b. p. 30–60°) and chilling in an ice-bath for one hour. The solid weighed 0.62 g. (61%). After two recrystallizations from 35% ethanol it formed small colorless needles, m. p. 104–105° (cor.), very soluble in benzene and ethanol, moderately soluble in ether, insoluble in water.

*Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.74; H, 6.96; N, 4.80.

**1-Methyl-2-pyridone-6-(α-benzyl)-acetic Acid (XII, R = $C_6H_5CH_2$-).**—To 1.0 g. of sodium hydroxide dissolved in 2 ml. of water and 5 ml. of ethanol was added 0.74 g. of the ester and the solution refluxed for two hours. After cooling and acidification to congo red with dilute hydrochloric acid, colorless crystals separated. The yield of material was 0.59 g. (88%). It was purified by dissolving in dilute aqueous ammonia, filtering (Darco) and reprecipitating it with dilute hydrochloric acid; small colorless needles, m. p. 155° (cor.) with effervescence.

*Anal.* Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.15; H, 5.88.

**1-Methyl-6-phenethyl-2-pyridone (XIII, R = $C_6H_5$-$CH_2$-).**—In a vacuum-sublimation apparatus 0.1 g. of 1-methyl-2-pyridone-6-(α-benzyl)-acetic acid was heated carefully in an oil-bath. At approximately 150° the crystals melted with evolution of carbon dioxide. When gas evolution had ceased, the temperature was raised slowly to 180°, maintained there for five minutes and again decreased to 150°. When the pressure was reduced to 2 mm., the material distilled and solidified on the cold finger. Redistillation at 2 mm. gave small colorless needles, m. p. 95.5–96.5°, soluble in ether, difficultly soluble in water.

*Anal.* Calcd. for $C_{14}H_{15}ON$: C, 78.84; H, 7.09. Found: C, 79.05; H, 6.99.

**1-Methyl-2-pyridone-6-($\alpha$-benzyl)-acetonitrile.**—To a solution of 0.23 g. of sodium in 4 ml. of absolute ethanol was added dropwise with mechanical stirring and exclusion of moisture a solution of 1.48 g. of 1-methyl-2-pyridone-6-acetonitrile in 5 ml. of absolute ethanol and 5 ml. of dry benzene, followed by 1.3 ml. of benzyl chloride in 5 ml. of dry benzene. The dark mixture was stirred at room temperature for fifteen minutes, then at the refluxing temperature for fifteen hours. Water was added and the brown benzene layer extracted several times with water, dried over potassium carbonate and boiled with Darco. The yellow filtrate was heated, diluted with petroleum ether (b. p. 30–60°) until it became cloudy, and filtered rapidly. Cooling and scratching with a glass rod caused separation of light tan-colored crystals. The yield was 1.0 g. (42%). After recrystallization from dilute ethanol, then from benzene–ether, the nitrile formed small colorless leaflets, m. p. 132° (cor.).

*Anal.* Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.71; H, 5.66; N, 11.11.

The nitrile was hydrolyzed by 62% sulfuric acid or preferably by dilute ethanolic potassium hydroxide to form the corresponding acid, m. p. 155°, previously described.

**Ethyl 1-Methyl-2-pyridone-6-($\alpha$-*n*-butyl)-acetate (XI, R = $C_4H_9$-).**—To a solution of 0.51 g. of sodium in 10 ml. of absolute ethanol was added 4.30 g. of ethyl 1-methyl-2-pyridone-6-acetate, followed by 3.5 ml. of *n*-butyl iodide. The orange-colored solution was refluxed with exclusion of moisture on the steam-bath for twenty hours, after which time it was no longer alkaline. Solvent and unreacted butyl iodide were evaporated on the steam-bath under reduced pressure; then 20 ml. of water was added to dissolve sodium iodide. The oil was dissolved in ether and the solution washed twice with aqueous sodium bicarbonate, then thrice with water and dried. Removal of the solvent and fractionation under reduced pressure gave 3.6 g. (65%), b. p. 159–160° (2 mm.). After another distillation the product was a pale yellow oil, $n^{20}D$ 1.5180. It solidified to colorless crystals on cooling in Dry Ice–acetone.

*Anal.* Calcd. for $C_{14}H_{21}O_3N$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.87; H, 8.58; N, 5.81.

The reaction was carried out also with *n*-butyl bromide, but somewhat less satisfactory results were obtained.

**Hydrolysis and Decarboxylation of Ethyl 1-Methyl-2-pyridone-6-($\alpha$-*n*-butyl)-acetate.**—A mixture of 0.59 g. of the ester and 0.93 g. of 33% aqueous sodium hydroxide was heated on the hot-plate until a homogeneous solution resulted, then on the steam-bath for one hour. The solution was diluted with 1 ml. of water, cooled in an ice-bath and acidified by the addition of 0.7 ml. of concd. hydrochloric acid. The 1-methyl-2-pyridone-6-($\alpha$-*n*-butyl)-acetic acid separated as a viscous oil which could not be induced to solidify. This oil was dissolved in chloroform, the solution washed with water, then concentrated to a small volume and placed in the terminal bulb of a three-bulb microdistillation tube. Chloroform was removed and the residue heated in an oil-bath. The acid decomposed at 150° with evolution of carbon dioxide. The temperature was slowly raised to 185° and maintained there for five minutes. The residue was then distilled into the other bulbs in a vacuum (below 1 mm.) by placing the tube partly in an air-bath heated at 90°. The 6-*n*-amyl-1-methyl-2-pyridone (XIII, R = $C_4H_9$-) was obtained as a colorless oil; $n^{20}D$ 1.5250 (after redistillation).

*Anal.* Calcd. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.26; H, 10.06; N, 8.41.

**6-Acetonyl-1-methyl-2-pyridone (XIII, R = $CH_3CO$-).**—To 0.31 g. of sodium hydride and 10 ml. of absolute ether in a 50-ml. round-bottomed flask provided with a mechanical stirrer and a reflux condenser fitted with a calcium chloride tube, was added 0.77 ml. of absolute ethanol diluted with 10 ml. of absolute ether. As soon as the sodium hydride had been transformed completely into sodium ethoxide, 2.52 g. of ethyl 1-methyl-2-pyridone-6-acetate was added and the mixture refluxed with stirring for fifteen minutes. After cooling in an ice-bath, 0.97 ml. of acetyl chloride, diluted with 10 ml. of absolute ether, was added in one lot. The yellow suspension turned colorless and sodium chloride separated. Stirring was continued for five minutes while keeping the flask in the ice-bath, then for two hours at the boiling point of ether. The slightly acid reaction mixture was extracted with aqueous sodium bicarbonate, then with water. The ethereal solution, after drying, was treated with petroleum ether (b. p. 30–60°) to cause the separation of an oil which partly solidified at 6°, but became liquid again at room temperature. The ether and petroleum ether were evaporated and the residual oil freed from traces of solvent in a vacuum desiccator. The yield of $\beta$-keto ester, which was not further purified, was 1.16 g. (38%).

A mixture of 0.97 g. of the crude keto ester and 15 ml. of concd. hydrochloric acid was boiled under reflux on the steam-bath for twenty-two hours. The solution was concentrated under reduced pressure to a small volume, made alkaline by the addition of a large excess of saturated aqueous sodium carbonate and extracted twice with chloroform. The extract was boiled with Darco and the yellow filtrate evaporated on the steam-bath. When petroleum ether (b. p. 30–60°) was added, the oil solidified to pale yellow crystals. The yield was 0.18 g. (27% based on the crude keto ester, 10% based on starting material). The ketone crystallized from benzene as almost white needles, m. p. 135.5–136.5° (cor.). After distillation in a vacuum-sublimation apparatus (bath 150°, 5 mm.) it formed colorless oblong leaflets, m. p. 136.5–137.5° (cor.), very soluble in water and acetone.

*Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71. Found: C, 65.62; H, 6.83.

**6-Acetonyl-1-methyl-2-pyridone *p*-Nitrophenylhydrazone.**—A solution of 55 mg. of the ketone and of 60 mg. of *p*-nitrophenylhydrazine in 2 ml. of glacial acetic acid was boiled under reflux for thirty minutes. After dilution with water, 79 mg. (79%) of small yellow needles separated. After two recrystallizations from 95% ethanol, the product melted at 209–210° (cor.) with blackening.

*Anal.* Calcd. for $C_{15}H_{16}O_3N_4$: C, 59.99; H, 5.37. Found: C, 60.14; H, 5.42.

**1-Methyl-6-*m*-nitrostyryl-2-pyridone.**—A mixture of 2.1 g. of 1,6-dimethyl-2-pyridone, 2.58 g. of *m*-nitrobenzaldehyde and 1.77 g. of acetic anhydride was heated in an oil-bath at 175–180° for twenty hours. The black oil was dissolved in 30 ml. of methanol, the solution boiled with 0.2 g. of Norit for five minutes and filtered, diluted with 3 ml. of concd. hydrochloric acid and 20 ml. of water and boiled on the hot plate to remove methanol. The yellow solution, in which a black-brown oil was suspended, was cooled to room temperature and extracted with benzene to remove tar and unreacted aldehyde. The benzene phase was extracted twice with dilute hydrochloric acid. The combined light yellow acid solutions were boiled for two minutes and made alkaline with 25% aqueous sodium carbonate. A yellow microcrystalline precipitate separated; 0.05 g. (1.1%). It was purified by dissolving in 2 ml. of boiling ethanol, filtering from a black impurity and diluting with 30 ml. of water. The solid was recrystallized from benzene–petroleum ether, then from 95% ethanol, and formed small yellow crystals, m. p. 216–218° (cor.).

*Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.56; H, 4.77; N, 11.04.

**6-Acetamido-2-stilbazole (XV).**—A mixture of 15.0 g. of 2-acetamido-6-methylpyridine,[14] 10.6 g. of benzaldehyde and 5.1 g. of acetic anhydride was boiled under reflux for thirty hours. The reaction mixture was steam-distilled to remove unreacted benzaldehyde, of which 50% was recovered as the semicarbazone. The residue from the steam-distillation was diluted with water to 250 ml., acidified with hydrochloric acid, treated with Norit and Celite to remove a tarry impurity and filtered through a

Büchner funnel. The yellow filtrate was rendered alkaline by adding aqueous ammonia. A yellow oil separated which was dissolved in ether. After drying and removal of the ether, the residue was dissolved in a small amount of chloroform and the solution diluted with petroleum ether. A solid separated which was dissolved in dilute hydrochloric acid, filtered from a tarry impurity; then ice was added to the solution, followed by an excess of aqueous ammonia. A yellow flocculent mass separated which was filtered and washed with ice-cold water. It was then dissolved in 95% ethanol, the solution boiled with Norit, filtered hot and diluted with hot water until a precipitate started to form. When cooled slowly, a yellow solid separated weighing 2.94 g. (12.3%). After one recrystallization from benzene–petroleum ether (b. p. 90–110°) and one recrystallization from 70% ethanol, the compound formed colorless needles, m. p. 149–150° (cor.).

*Anal.* Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.85; H, 6.15; N, 11.86.

**6-Amino-2-stilbazole Hydrochloride.**—A solution of 4.2 g. of 6-acetamido-2-stilbazole in 70 ml. of concd. hydrochloric acid and 70 ml. of water was boiled under reflux for three hours, then cooled and allowed to stand in the icebox overnight. The hydrochloride was collected on a filter, washed with ice-cold 20% hydrochloric acid, then with ether and dried; yield 3.98 g. (97%), m. p. 249–252° (cor.). It was recrystallized from ethanol to form yellow needles of the same melting point.

*Anal.* Calcd. for $C_{13}H_{13}N_2Cl$: C, 67.09; H, 5.63; N, 12.04; Cl, 15.24. Found: C, 67.02; H, 5.72; N, 12.12; Cl, 15.37.

**6-Amino-2-stilbazole (XVI).**—A solution of 0.67 g. of the hydrochloride in a small amount of water was made alkaline with aqueous ammonia. A pale yellow oil separated which solidified rapidly on standing; yield 0.54 g. (96%). It was purified by crystallization from benzene–petroleum ether (b. p. 90–110°); small colorless prismatic needles, m. p. 110°.

*Anal.* Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.74; H, 6.09; N, 14.46.

**6-Hydroxy-2-stilbazole (6-Styryl-2-pyridone) (XVII).**—To a warm solution of 0.165 g. of 6-amino-2-stilbazole in 0.1 ml. of concd. sulfuric acid and 3 ml. of water was added 0.07 g. of powdered sodium nitrite. A brown flocculent mass separated. After boiling the mixture for five minutes, an excess of aqueous ammonia was added and boiling continued for two minutes. The red-brown powder was removed by filtration and treated with hot dilute aqueous potassium hydroxide. A black tarry impurity was removed by filtration and the yellow filtrate buffered with Dry Ice. The hydroxystilbazole separated as a yellow oil which rapidly solidified. The yield was 0.08 (48%). Two recrystallizations from 95% ethanol (Norit) yielded small yellow needles, m. p. 210–211° (cor.).

*Anal.* Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.67; H, 5.77; N, 7.52.

**2-Amino-4-stilbazole.**—A mixture of 8.0 g. of 2-acetamido-4-methylpyridine,[17] 6.3 g. of benzaldehyde and 2.7 g. of acetic anhydride was refluxed under nitrogen for forty-six hours. The dark oil, to which 15 ml. of concd. hydrochloric acid had been added, was steam-distilled to remove unreacted benzaldehyde. To the residue, consisting of a dark sticky mass and about 50 ml. of an aqueous solution, was added 50 ml. of concd. hydrochloric acid. The mixture was heated to boiling and filtered from a brown solid, which was then boiled with 50 ml. of concd. hydrochloric acid and refiltered.

The combined filtrates were boiled with Norit and filtered. The clear dark yellow solution was boiled under reflux for three hours, diluted with 50 ml. of water and refluxed for an additional four hours. When cooled, a yellow flocculent precipitate separated. It was collected on a filter, dissolved in boiling ethanol, the solution made alkaline with aqueous ammonia and diluted with water. The tan flocculent precipitate was dissolved in 50 ml. of concd. hydrochloric acid, the solution boiled with Norit, filtered hot and diluted with 50 ml. of boiling water. After standing for three hours in the icebox, the material which had separated was isolated by filtration, washed with cold water and dissolved in 50 ml. of hot ethanol; to the boiling solution was added 4 ml. of 28% aqueous ammonia in 10 ml. of ethanol, then water, until crystallization started, and the mixture allowed to stand in the icebox. The tan-colored leaflets of the aminostilbazole weighed 1.52 g. (14.5%). After two recrystallizations from 95% ethanol it formed pale yellow glittering leaflets, m. p. 216–217° (cor.).

*Anal.* Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.76; H, 6.09; N, 14.23.

The solid, which proved to be insoluble when the original reaction mixture was extracted with hydrochloric acid, was digested with ice-cold acetone, then with boiling concd. hydrochloric acid and refiltered. It was then dissolved in 70 ml. of boiling ethanol, the solution filtered and heated with 40 ml. of concd. hydrochloric acid. Upon slow dilution with 100 ml. of boiling water a yellow flocculent solid separated. After dissolving in ethanol and adding aqueous ammonia to the boiling solution, yellow microcrystals formed. The product (0.29 g.) was recrystallized from ethanol–methyl ethyl ketone; small yellow needles, m. p. 234–235° (cor.).

Analysis did not serve to identify the product.

*Anal.* Found: C, 84.26; H, 5.59; N, 6.87.

**2-Hydroxy-4-stilbazole (4-Styryl-2-pyridone).**—A solution of 2.4 g. of 2-amino-4-stilbazole in 1.5 ml. of concd. sulfuric acid and 10 ml. of glacial acetic acid was stirred and cooled in an ice–salt-bath, which caused separation of the sulfate. It was diazotized by the gradual addition of 1.0 g. of sodium nitrite in 2 ml. of water. The mixture was then allowed to come to room temperature and treated with small portions of solid sodium nitrite until it gave a positive reaction with starch–iodide paper (ten minutes). Addition of 100 ml. of water caused separation of a tan-colored flocculent solid. The suspension was heated to 90° and made alkaline with aqueous ammonia. The solid was removed by filtration, dissolved in 100 ml. of boiling ethanol, a tan-colored impurity removed by filtration and the filtrate allowed to stand in the icebox. The greyish-brown crystals were collected and weighed 0.86 g. (36%). By repeated recrystallizations from 95% ethanol (Darco), yellowish prismatic needles, m. p. 238–239° (cor.), resulted.

*Anal.* Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.71; N, 7.45.

**6-Methyl-2-pyridone-1-β-propionitrile (XVIII).**—An intimate mixture of 42.5 g. of 6-methyl-2-pyridone and 1.3 g. of 6-methyl-2-pyridone sodium was heated under reflux on a steam-bath with 22.8 g. of acrylonitrile. The mixture was shaken frequently until it had liquefied, which took about ten minutes, then heated for twenty more minutes. After addition of 1 ml. of glacial acetic acid in 110 ml. of boiling benzene, the solution was filtered hot from sodium acetate and allowed to cool in the icebox. Tan crystals separated, which were collected on a filter and washed with a small amount of ice-cold benzene. The yield was 52.5 (81% based on total methylpyridone, 83% based on free methylpyridone). It was recrystallized from methyl ethyl ketone to give colorless prisms, m. p. 109–110° (cor.), very soluble in water, moderately soluble in benzene, acetone and methyl ethyl ketone, insoluble in petroleum ether.

*Anal.* Calcd. for $C_9H_{10}ON_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.88; H, 6.20; N, 17.13.

Other catalysts, such as 50% aqueous potassium hydroxide, powdered sodium hydroxide, Triton B (with addition of dioxane) gave satisfactory results, although the yield of product was slightly less.

Pyrolysis of the nitrile in a small distilling flask gave acrylonitrile and 6-methyl-2-pyridone, showing the reversibility of this reaction.

**6-Methyl-2-pyridone-1-β-propionic Acid (XIX).**—A solution of 18.4 g. of the propionitrile in 92 ml. of water

and 6 ml. of concd. sulfuric acid was refluxed for three hours. When cooled in the icebox, colorless crystals separated; the yield was 18.9 g. (92%). After recrystallization from water, then from acetone, the acid formed colorless plates or prisms, m. p. 165–166° (cor.).

*Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.73; H, 6.24; N, 7.82.

Many experiments were performed to prepare the esters of this acid. None gave satisfactory results. An oil which could not be distilled without decomposition into acrylic ester and 6-methyl-2-pyridone always resulted. The methods employed were alcoholysis of the corresponding nitrile, condensation of 6-methyl-2-pyridone sodium with ethyl β-bromopropionate, esterification of the acid with hydrogen chloride and ethanol, reaction of the silver salt of the acid with methyl or ethyl iodide, attempted condensation of 6-methyl-2-pyridone with ethyl acrylate, the action of diazomethane on the acid.

The crude oil obtained in many of these experiments was treated with reagents such as potassium, potassium ethoxide, and sodium hydride in an attempt to eliminate ethanol or methanol from the ester grouping and 6-methyl group in order to obtain a pyridocoline ring. All experiments failed.

**Ethyl 6-Methyl-2-pyridone-1-acetate (XX) and 2-Carbethoxymethoxy-6-methylpyridine (XXI).**—To a solution of 2.3 g. of sodium in 50 ml. of absolute ethanol and 20 ml. of dry benzene was added 10.9 g. of 6-methyl-2-pyridone, followed by 18 g. of ethyl bromoacetate. The mixture was refluxed in a boiling water-bath for two hours; then ethanol, benzene and most of the unreacted ethyl bromoacetate were removed on the steam-bath under reduced pressure. After addition of 100 ml. of hot water, the mixture was steam-distilled. The steam-distillate from which a heavy oil had separated was extracted with chloroform and the extract dried over potassium carbonate. Chloroform was removed under reduced pressure and the residual oil distilled *in vacuo*. The 2-carbethoxymethoxy-6-methylpyridine boiled at 132° (15 mm.), $n^{20}D$ 1.4909. The yield was 1 g. (5%).

*Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71. Found: C, 61.56; H, 6.88.

The residue of the steam-distillation was made alkaline by the addition of 2 g. of potassium carbonate and extracted with chloroform in a continuous extractor. The extract was dried over potassium carbonate and freed completely from chloroform by heating on the steam-bath under reduced pressure. The ethyl 6-methyl-2-pyridone-1-acetate remained as a brown liquid which on cooling solidified to a tan-colored solid. The yield was 13.7 g. (70%). It was dissolved in hot benzene, the solution boiled with Norit, filtered and diluted with petroleum ether (b. p. 30–60°) until incipient cloudiness. When cooled in the ice-box, 11.7 g. (60%) of crystals separated. They were dissolved in cold acetone, a colorless impurity removed by filtration and the filtrate diluted with petroleum ether (b. p. 30–60°). Repeated recrystallizations gave colorless needles, m. p. 81–82°. The ester was purified for analysis by vacuum-sublimation.

*Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.41; H, 6.44; N, 7.04.

**6-Methyl-2-pyridone-1-acetic Acid.**—A mixture of 1.24 g. of the ester (XX) and 7.4 ml. of 35% aqueous potassium hydroxide was boiled under reflux for thirty minutes. The solution was filtered, diluted with 10 ml. of water and acidified by the addition of 5.7 ml. of concd. hydrochloric acid. The colorless prisms were collected on a filter after standing in an ice-box overnight; yield 0.68 g. (64%). The acid was purified from ethanol; m. p. 229° (cor.) with effervescence.

*Anal.* Calcd. for $C_8H_9O_3N$: N, 8.38. Found: N, 8.77.

The same compound was made as follows. To a solution of 2.18 g. of 6-methyl-2-pyridone in 4.62 g. of hot 50% aqueous potassium hydroxide was added 1.98 g. of chloroacetic acid and the mixture boiled on the hot plate for two minutes. The solid which formed was dissolved by adding 2 ml. of water and boiling was continued for three more minutes. When cooled, the mixture solidified to a crystalline mass. It was dissolved in 7 ml. of hot water and acidified by the addition of 1.8 ml. of concd. hydrochloric acid. Cooling to room temperature and scratching the wall of the container with a glass rod caused separation of colorless crystals; yield 0.4 g. (12%). After washing with a little acetone, the remaining 0.3 g. was recrystallized from boiling water, then ethanol; m. p. 229° (cor.) with effervescence.

**Ethyl 1-Carbethoxymethyl-2-pyridone-6-pyruvate (XXII).**—To a solution of 0.76 g. of potassium in 4.3 ml. of absolute ethanol and 9 ml. of absolute ether was added at 0° 2.84 g. of ethyl oxalate, then after ten minutes 3.48 g. of ethyl 6-methyl-2-pyridone-1-acetate, followed by 15 ml. of dry benzene and 26 ml. of absolute ether. The flask was flushed with nitrogen, tightly stoppered and allowed to stand at room temperature for nineteen hours. In a short time the potassium salt started to separate as a yellow powder and the solution turned at first bright yellow, then orange, finally dark red-brown. The potassium salt of the condensation product was collected on a Büchner funnel, washed with absolute ether and weighed 2.42 g. (41%).

The potassium salt was stirred into a mixture of 0.5 ml. of concd. sulfuric acid and 20 g. of ice. A yellow oil separated which rapidly solidified. The ester was collected on a filter, washed with water and dried. It weighed 1.61 g. (30.6%). It was purified by crystallization from 95% ethanol (Norit); small lemon-yellow leaflets, m. p. 137–138°.

*Anal.* Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.90; H, 5.73; N, 4.84.

**Reaction of 6-Methyl-2-pyridone with N-Bromosuccinimide.**—A mixture of 2.18 g. of 6-methyl-2-pyridone, 7.12 g. of N-bromosuccinimide and 0.25 g. of benzoyl peroxide in 60 ml. of carbon tetrachloride was boiled under reflux for thirty minutes. Succinimide was removed by filtering the hot mixture and washing with boiling carbon tetrachloride. The combined filtrate and washings were evaporated to dryness and the residue recrystallized from 95% ethanol. The product consisted of 1.2 g. of colorless needles, which after recrystallization melted at 254–255° (cor.). Admixture of an authentic sample of 3,5-dibromo-6-methyl-2-pyridone did not depress the melting point.

**2-Amino-5-bromo-6-methylpyridine.**—A solution of 10.8 g. of 2-amino-6-methylpyridine in 47 g. of 20% sulfuric acid was cooled in ice water and 18.7 g. of bromine was added dropwise over fifteen minutes with continuous swirling. It was then shaken at room temperature until a colorless solution resulted (about fifteen minutes). cooled again in ice water and made alkaline by adding 80 g. of ice-cold aqueous 20% sodium hydroxide. A partly crystalline, partly oily white mass separated which solidified completely after standing for several hours in the ice-box. The crude product weighed 14.6 g. (78%). Recrystallization from petroleum ether (b. p. 90–110°) in which the contaminants are very soluble, gave 9.3 g. (50%) of long silky colorless needles, m. p. 83–84°. The analytical sample was prepared by vacuum-sublimation.

*Anal.* Calcd. for $C_6H_7N_2Br$: N, 14.98; Br, 42.73. Found: N, 15.00; Br, 42.76.

**2-Amino-3,5-dibromo-6-methylpyridine.**—To a solution of 10.8 g. of 2-amino-6-methylpyridine in 47 g. of 20% sulfuric acid was added with continuous swirling 32 g. of bromine. The temperature was maintained below 35° by occasional immersion in ice water. The mixture was heated on the steam-bath for two hours, then allowed to stand in the icebox overnight. The white crystalline sulfate was collected on a filter and washed with ice-cold 20% sulfuric acid, then with acetone. The yield was 24.6 g. (78%).

The sulfate was added in small portions with stirring to 50 g. of ice-cold 10% aqueous sodium hydroxide and the mixture allowed to stand in the icebox for several hours. The colorless crystals weighed 17.15 g. (82.5% based on sulfate). After recrystallization from 95% ethanol, the

base formed short colorless prismatic needles, m. p. 144° (cor.).

*Anal.* Calcd. for $C_6H_6N_2Br_2$: C, 27.09; H, 2.27; N, 10.53; Br, 60.10. Found: C, 27.31; H, 2.33; N, 10.63; Br, 59.93.

**5-Bromo-6-methyl-2-pyridone.**—A solution of 8.4 g. of 2-amino-5-bromo-6-methylpyridine in 40 g. of ice-cold 20% sulfuric acid was diazotized below 10° by adding dropwise a solution of 3.3 g. of sodium nitrite in 7 ml. of water. The sulfate of the pyridone separated during the reaction. The paste was diluted with 30 ml. of water and the suspension heated on the steam-bath for five minutes. A solution of 9 g. of potassium carbonate in 15 ml. of water was added with stirring and the yellow suspension heated to boiling, then allowed to stand in the icebox. The yield of tan needles was 6.9 g. (82%). The compound was recrystallized from 95% ethanol, then from benzene to form colorless needles, m. p. 204° (cor.). The analytical sample was prepared by vacuum-sublimation.

*Anal.* Calcd. for $C_6H_6ONBr$: N, 7.45; Br, 42.50. Found: N, 7.28; Br, 42.50.

**3,5-Dibromo-6-methyl-2-pyridone.**—A warm solution of 13.3 g. of 2-amino-3,5-dibromo-6-methylpyridine in 54 g. of 20% sulfuric acid was cooled rapidly in an ice-salt bath with efficient stirring to cause separation of very small crystals, then diazotized by adding dropwise a solution of 3.7 g. of sodium nitrite in 10 ml. of water. The mixture became pasty as the sulfate of the pyridone separated. The suspension obtained by adding 300 ml. of water was heated to boiling and made alkaline by adding slowly with stirring a solution of 13 g. of potassium carbonate in 50 ml. of water. The yield of colorless crystals was 12.9 g. (97%). After recrystallization from ethanol-benzene and then from 95% ethanol, colorless needles, m. p. 254–255° (cor.), resulted. Errera[13] reported m. p. 238–239°.

## Summary

1. In order to devise methods by which cytisine might be synthesized, a further knowledge of the activity of a 6-methyl group in 1-substituted 2-pyridones was required. It has been shown that the 6-methyl group in 1,6-dimethyl-2-pyridone condenses readily with ethyl oxalate in presence of potassium or sodium ethoxide to give the corresponding pyruvate. The same is true of the 4-methyl group in 1,4-dimethyl-2-pyridone.

2. These pyruvic esters were saponified to the corresponding acids and these by means of alkali and hydrogen peroxide degraded to the corresponding 1-methyl-2-pyridone-6(or 4)-acetic acids. The 6-pyruvic ester was converted directly in one step to the 6-acetic acid with alkali and hydrogen peroxide. Its potassium salt, however, by treatment with hydrogen peroxide, gave 1-methyl-2-pyridone-6-carboxylic acid.

3. Pyrolysis of 1-methyl-2-pyridone-6-(α-oximino)-propionic acid, obtained by reaction of the 6-pyruvic acid and hydroxylamine or by hydrolysis of the oximino ester, gave the 6-acetonitrile which could be alkylated with alkyl halides in the presence of sodium ethoxide. In the same way the 6-acetic ester, obtained from the acid, was alkylated with benzyl chloride and *n*-butyl iodide and acylated with acetyl chloride, the resulting products saponified and the corresponding acids decarboxylated by pyrolysis. 1-Methyl-6-phenethyl-2-pyridone, 6-*n*-amyl-1-methyl-2-pyridone and 6-acetonyl-1-methyl-2-pyridone were thus obtained.

4. 1,6-Dimethyl-2-pyridone condensed with *m*-nitrobenzaldehyde in presence of acetic anhydride to give a very low yield of 1-methyl-6-*m*-nitrostyryl-2-pyridone.

5. 2-Acetamido-6(or 4)-methylpyridine condensed with benzaldehyde to give 2-acetamido-6(or 4)-stilbazole, from which by saponification of the acetyl group and diazotization, 6- or 4-styryl-2-pyridone resulted.

6. 6-Methyl-2-pyridone condensed with acrylonitrile in presence of alkaline catalysts to give 6-methyl-2-pyridone-1-β-propionitrile, which was hydrolyzed to the corresponding acid. 6-Methyl-2-pyridone sodium condensed with bromoacetic ester to give ethyl 6-methyl-2-pyridone-1-acetate which in turn condensed with ethyl oxalate to form a pyruvate.

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[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

# Hyperconjugation. III. Relative Rates of Bromination of Twelve Monoalkylbenzenes

BY ERNST BERLINER AND FRANCES BERLINER

The relative rates of bromination of toluene, ethylbenzene, *i*-propylbenzene and *t*-butylbenzene in aqueous acetic acid at 25° are 100, 76, 44 and 23, respectively.[1] A competitive bromination study of toluene and *t*-butylbenzene has confirmed the order for the latter two compounds.[2] These results have been explained by hyperconjugation involving the hydrogen atoms on the carbon atom alpha to the benzene ring.[1,2,3] In the work presented here the above order of reactivity is confirmed and investigation of the relative rates of bromination of monoalkylbenzenes is extended to include both propylbenzenes, all four butylbenzenes, and four of the eight amylbenzenes. The results are considered in the light of hyperconjugation.

**Method.** The procedure adopted for measuring the relative rates of bromination was similar to that used by De la Mare and Robertson.[1] The relative rates were calculated by comparing the times necessary for ten per cent. reaction of bro-

(1) De la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).
(2) Berliner and Bondhus, THIS JOURNAL, **68**, 2355 (1946).
(3) Baker and Nathan, *J. Chem. Soc.*, 1844 (1935).

mine with the hydrocarbon. However, in the present investigation the reactions were conducted with a ten-fold excess of hydrocarbon and in the presence of excess sodium acetate. Sodium acetate increased the rates considerably and made it possible to conclude the reactions in a much shorter time.[4] In view of the work of Robertson, De la Mare and Johnston[1,5] it has seemed justified to assume that the order of the reaction with respect to bromine is the same for all monoalkylbenzenes.[6]

## Experimental Part

### Preparation of Materials

**Glacial Acetic Acid.**—C. P. acetic acid ("Niacet") was purified according to the method of Orton and Bradfield,[7] m. p. 16.4–16.5°. The "85% acetic acid" was prepared by adding 15 parts by volume of water from a buret to 85 parts of the above acetic acid, measured in a volumetric flask. The stock solution was kept in an amber bottle.

**Bromine.**—C. P. bromine was used without purification.

**Sodium Acetate.**—J. T. Baker C. P. Analyzed anhydrous sodium acetate was used without purification. The 0.15 *M* solution contained 6.1530 g. of sodium acetate in 85% acetic acid made up to volume in a 500-ml. flask.

Table I records the monoalkylbenzenes which were prepared for this study, their properties and the methods of synthesis.

TABLE I

PREPARATION AND PROPERTIES OF MONOALKYLBENZENES

| Hydrocarbon | Boiling point °C. | Mm. | $n^{25}D$ | Acetamino derivatives,[a] m. p., °C. |
|---|---|---|---|---|
| Toluene[b] | 109.8–110.1 | 750 | 1.4930 | |
| Ethylbenzene[b] | 135.9–136.9 | 760 | 1.4930 | |
| *n*-Propylbenzene[c] | 158.9–159.2 | 766 | 1.4893 | Mono 97.3–97.8<br>Di 206.7–207.7 |
| *i*-Propylbenzene[b] | 151.9–152 | 754 | 1.4885 | Mono 105–106 |
| *n*-Butylbenzene[d,e] | 183–183.1<br>182–183 | 766[d]<br>764[e] | 1.4872[d]<br>1.4872[e] | Mono 104–104.8<br>Di 216.4–217.4 |
| *i*-Butylbenzene[f] | 171.8–172 | 759 | 1.4840 | Mono 130.8–131.5<br>Di 210.3–211.3 |
| *s*-Butylbenzene[g] | 172.2–172.3 | 751 | 1.4877 | Mono 123.7–124.3 |
| *t*-Butylbenzene[h] | 168–168.4 | 763 | 1.4901 | Mono 170.8–171.8 |
| *n*-Amylbenzene[i] | 203.5–203.8 | 753 | 1.4859 | Mono 101.6–102.2 |
| Neopentylbenzene[j] | 185.5–185.8 | 755 | 1.4850 | Mono 164.5–165.5<br>Di 245.9–246.9 |
| 2-Methyl-3-phenylbutane[k] | 189–190 | 755 | | Mono 147.3–147.9 |
| *t*-Amylbenzene[l] | 188–189.5 | 755 | 1.4909 | |

[a] Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937); **60**, 1476 (1938); **65**, 2470 (1943). The melting points of the derivatives must be taken as indications of the identity rather than the purity of the hydrocarbons. [b] A C. P. chemical grade was purified with cold concentrated sulfuric acid according to Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, Boston, 1941, p. 364. [c] Prepared in 79% yield (b. p. 158–160° (758 mm.)) from 0.6 mole of propiophenone by a Wolff–Kishner reduction as modified by Huang–Minlon, THIS JOURNAL, **68**, 2487 (1946). [d] Prepared in 78% yield by a Clemmensen reduction (with stirring) of butyrophenone. [e] Prepared by a Wurtz reaction of bromobenzene and *n*-butyl bromide ("Organic Syntheses," **25**, 11(1945)). [f] Prepared in 79% yield (b. p. 170–172°) from 189 g. of *i*-butyrophenone, see ref. in (*c*). The *i*-butyrophenone was prepared in 81% yield (b. p. 66–67 (2 mm.)) from 300 g. of aluminum chloride suspended in 1200 ml. of thiophene-free benzene and 168 g. of *i*-butyryl chloride in 200 ml. of thiophene-free benzene at ice-bath temperature (Schmidt, Hopp and Schoeller, *Ber.*, **72**, 1893 (1939); Hennion and Auspos, THIS JOURNAL, **65**, 1603 (1943)); m. p. dinitrophenylhydrazone 161.3–162.8°. [g] Prepared according to Price and Lund, THIS JOURNAL, **62**, 3105 (1940), using three times their amounts and letting the reaction mixture stand overnight, yield 70% (b. p. 170–173°). [h] Prepared as previously described, see ref. 2. [i] Prepared in 80% yield (b. p. 202–203° (750 mm.)) from 0.8 mole of *n*-valerophenone, see ref. in (*c*); $n^{20}D$ 1.4878 for the pure sample. The valerophenone was prepared as described for *i*-butyrophenone in 77.5% yield (b. p. 81.2° (2 mm.)); m. p. dinitrophenylhydrazone 166–167°. [j] Prepared by the method of Bygden, *Ber.*, **45**, 3479 (1912), from benzylmagnesium chloride and *t*-butyl chloride. The yield was raised from 39 to 57.5% by adding benzene to the reaction mixture and refluxing it for several hours, b. p. 185.1–185.9° (755 mm.), $n^{25}D$ 1.4855, $n^{20}D$ 1.4875, m. p. monoacetamino derivative 164.9–165.8°. The diacetamino derivative melted between 236° and 242° after three crystallizations and was not pure. This sample was later found to contain small amounts of *p*-*t*-butyltoluene (see last paragraph of the experimental part) and was repurified in the following manner. Thirty-five milliliters of the hydrocarbon was treated with 10% of bromine in a brown bottle in the presence of a catalytic amount of iodine; after three days a trace of iron was added and the reaction mixture was heated briefly to 50° to complete the bromination. The product was washed and fractonally distilled affording the sample of neopentylbenzene recorded in the table, $n^{20}D$ 1.4870. [k] Prepared by catalytic reduction of 2-methyl-3-phenylbutene-2 in the presence of Adams catalyst at room temperature. The reduction proceeded slowly and never exceeded 75% of the theoretical. The olefin was prepared in about 45% yields from 0.5 mole of acetophenone and *i*-propylmagnesium chloride (Ipatieff, Pines and Schmerling, THIS JOURNAL, **60**, 353 (1938); Klages, *Ber.*, **36**, 3688 (1903)). [l] Prepared in 60% yield from 2 moles of *t*-amyl alcohol and 10 moles of thiophene-free benzene by the method of Huston, Fox and Binder, *J. Org. Chem.*, **3**, 252 (1938), $n^{20}D$ of pure sample 1.4928.

All of the samples recorded in Table I were purified with cold concentrated sulfuric acid, or with aqueous potassium permanganate (agitated overnight at room temperature) followed by sulfuric acid, prior to final fractionations from metallic sodium. The ice-cold concentrated sulfuric acid extracted acid-darkening material from the reaction products regardless of the method of synthesis, and whereas it alone is effective in removing rapidly brominated impurities from the hydrocarbons, treatment with permanganate had to be followed by washing with sulfuric acid. It is believed that the ice-cold sulfuric acid did not cause any rearrangement. Of all of the compounds described above, only the purity of the 2-methyl-3-phenylbutane is questionable. Bromination of several samples was erratic, and there was never a sufficient amount available for rigorous purification.

The following samples were generously supplied by the Sun Oil Company, Norwood, Pennsylvania, the Phillips

(4) The increase in rate produced by sodium acetate may be due to the formation of a more active brominating agent or may be connected with the removal of a proton from the activated complex by the acetate ion, the strongest base in the system. See also Bennett, Brand, James, Saunders and Williams, *J. Chem. Soc.*, 474 (1947).

(5) Robertson, De la Mare and Johnston, *J. Chem. Soc.*, 276 (1943); De la Mare and Robertson, *ibid.*, 100 (1948).

(6) In the bromination of aromatic compounds in acetic acid the order with respect to bromine is dependent on the temperature, the dilution and the type of compound. In the present case it is probably between two and three (see ref. 1 and 5). The bromination of benzene in benzene as a solvent is also kinetically of a higher order with respect to bromine. Bruner, *Z. physik. Chem.*, **41**, 513 (1902); Price, THIS JOURNAL, **58**, 2101 (1936).

(7) Orton and Bradfield, *J. Chem. Soc.*, 983 (1927).

Petroleum Company, Bartlesville, Oklahoma, and the Universal Oil Products Company, Riverside, Illinois: toluene, 99.7% pure; ethylbenzene, 99.82%; ethylbenzene, 99.3%; *n*-propylbenzene 99.0%; *i*-propylbenzene, 98%; *n*-butylbenzene 99.5%; *i*-butylbenzene, 99.8%; *s*-butylbenzene, 99.2%; *s*-butylbenzene, 98%; *s*-butylbenzene; *t*-butylbenzene, 99.9%; *t*-butylbenzene, 99.76%; *t*-butylbenzene, 98%. Each sample was redistilled from metallic sodium immediately before use.

All samples of hydrocarbons used in the bromination study were stored in amber bottles over sodium wire.

## General Procedure

The bromination experiments were conducted as follows in a room provided with black curtains and lighted with a red lamp. To 20 ml. of an 85% acetic acid solution, 0.4 *M* in hydrocarbon and 0.15 *M* in sodium acetate, contained in a blackened bottle and brought to 25 ± 0.05° in a thermostat, was added 20 ml. of an 85% acetic acid solution, 0.04 *M* in bromine and 0.15 *M* in sodium acetate.[8] The solutions were mixed and a 5-ml. portion was immediately withdrawn and analyzed for bromine iodimetrically with 0.04 *M* sodium thiosulfate, contained in a microburet graduated to 0.01 ml., using starch as an indicator. This reading was taken as the zero point. The thiosulfate solution was prepared for each run from a 0.1000 *M* stock solution. A freshly prepared 6% solution of potassium iodide was used for each titration. A blank was run simultaneously with each reaction in order to provide corrections for loss of bromine by evaporation. The loss occurred only during sampling and became rather large and irregular after four or five samples had been withdrawn. In order to reduce to a minimum the corrections for loss of bromine by evaporation, preliminary studies were made for each monoalkylbenzene in which six to eight readings were taken in order to establish the approximate time for 10% reaction of bromine. Then subsequent runs were made for each compound in which only four readings were taken, one to establish the zero point, two shortly before 10% reaction, and one shortly after 10% reaction, in order to determine accurately the 10% reaction time. The error, introduced chiefly through the uncertainty of the blank, was about ±1% of the final reaction time. The results were well reproducible. Due to the volatility of the bromine the initial concentration usually deviated slightly from 0.02 *M*, but corrections for this deviation were applied to the final results and never amounted to more than a few minutes. A large number of check runs was made for each monoalkylbenzene and all samples listed above were used, although some were found to contain small amounts of rapidly brominated impurities. Results obtained with such samples were discarded. A rapidly brominated impurity was easily recognized by the large deviation of the initial titer from the blank. Small amounts of impurities which are brominated more slowly than the hydrocarbons would not have affected the rates. All compounds were studied independently by each investigator; a total of about 200 runs was made. Some results of a typical study (*n*-propylbenzene) are listed below. (The blanks found were on the average 0.15, 0.25, 0.35 for each successive opening.)

Sample I (synthetic)

| Time | Sodium thiosulfate, ml. of 0.04 *M* | Reaction, % |
|---|---|---|
| 0 | 4.951 | ... |
| 240′ | 4.598 | 6.83 |
| 325′ | 4.507 | 8.46 |
| 420′ | 4.420 | 10.02 |
| | 10%, 419 minutes | |
| 0 | 4.972 | ... |
| 340′ | 4.510 | 8.99 |
| 390′ | 4.469 | 9.61 |
| 440′ | 4.422 | 10.36 |
| | 10%, 416 minutes | |
| | Sample II (99.0% pure) | |
| 0 | 4.900 | ... |
| 325′ | 4.459 | 8.70 |
| 400′ | 4.395 | 9.80 |
| 440′ | 4.353 | 10.45 |
| | 10%, 412 minutes | |
| 0 | 4.902 | ... |
| 290′ | 4.501 | 7.87 |
| 370′ | 4.422 | 9.28 |
| 440′ | 4.357 | 10.40 |
| | 10%, 415 minutes | |

The sample of neopentylbenzene, prepared by the method of Bygden (Table I, ref. *j*) was found kinetically to contain a by-product, although the impurity was not brominated rapidly enough to show a deviation of the initial titer from the blank. The sample showed a 10% reaction time of about 400 minutes, almost identical with *n*-propylbenzene (415 minutes). A comparison of the time/% reaction curves for the two compounds up to 15% reaction showed, however, that they were not identical in shape. The neopentyl curve rose more rapidly and slowed down appreciably after 10%, suggesting that the sample contained an impurity, present to the extent of about 1%, which was brominated more rapidly than neopentylbenzene. A 5-ml. sample of the impure neopentylbenzene was oxidized with potassium permanganate[9] in aqueous pyridine and afforded a small amount of *p*-*t*-butylbenzoic acid, m. p. after crystallization from dilute alcohol 165–166°. Mixed melting point with an authentic sample of *p*-*t*-butylbenzoic acid[10] showed no depression. The formation of *p*-*t*-butyltoluene from benzylmagnesium chloride and *t*-butyl chloride is similar to the recently reported formation of *p*-ethyltoluene from benzylmagnesium chloride and ethyl sulfate.[11]

## Results and Discussion

In Table II are recorded the compounds that were brominated and the times required for 10% reaction of each. Table III summarizes some of the pertinent relative rates.

The members of Series I (first column of Table III) fall in an order demanded by the Baker–Nathan effect and identical with that obtained by De la Mare and Robertson.[1] Under the present experimental conditions the differences in relative rates of bromination of the four compounds (100:70:40:18) are larger than those obtained by the latter investigators (100:76:44:23). That the solvent composition (the presence of sodium acetate) should influence the spacing of the rates is not unreasonable and was discussed in a previous communication.[12] The relative rates of bro-

(8) The amylbenzenes required more dilute solutions since they were not sufficiently soluble for the preparation of 0.4 *M* solutions in 85% acetic acid. The bromine solution was therefore concentrated accordingly so that after mixing the concentrations of bromine and hydrocarbon were still 0.02 and 0.2 *M*, respectively.

(9) Nightingale, Radford and Shanholtzer, THIS JOURNAL, **64**, 1662 (1942).

(10) Prepared by Mrs. Lucille Altschul.

(11) Burtle and Shriner, THIS JOURNAL, **69**, 2059 (1947). It is possible that the rearrangement which occurred during the preparation of neopentylbenzene was due to the higher temperature employed through the use of benzene, and does not occur when ether is used.

(12) Berliner and Bondhus, *ibid.*, **70**, 854 (1948).

TABLE II

TEN PER CENT. REACTION TIMES FOR BROMINATION OF MONOALKYLBENZENES

| Alkylbenzene | Time in minutes for 10% reaction |
|---|---|
| Toluene | 230 |
| Ethylbenzene | 330 |
| *n*-Propylbenzene | 415 |
| *i*-Propylbenzene | 570 |
| *n*-Butylbenzene | 390 |
| *i*-Butylbenzene | 620 |
| *s*-Butylbenzene | 710 |
| *t*-Butylbenzene | 1300 |
| *n*-Amylbenzene | 440 |
| Neopentylbenzene | 1110 |
| 2-Methyl-3-phenylbutane | (800) |
| *t*-Amylbenzene | 1000 |

TABLE III

RELATIVE RATES OF BROMINATION OF MONOALKYLBENZENES

| R | Series I Ph–R | Series II $PhCH_2$–R | Series III $PhCHRCH_3$ |
|---|---|---|---|
| Methyl | 100 | 100 | 100 |
| Ethyl | 70 | 80 | 80 |
| *i*-Propyl | 40 | 53 | (71) |
| *t*-Butyl | 18 | 30 | |

mination of the two propylbenzenes and the four butylbenzenes also follow the general pattern of the Baker–Nathan effect, *i. e.*, are dependent on the number of hydrogen atoms available on the alpha carbon atom for conjugation with the benzene ring. Thus *n*-propylbenzene with two alpha hydrogen atoms is brominated faster than *i*-propylbenzene with only one (100:73). The four butylbenzenes fall in the order *n*-butyl > *i*-butyl > *s*-butyl > *t*-butyl (100:63:55:30). The difference between *i*-butyl and *s*-butylbenzene, although in accord with the theory, is not very large. On the other hand, the difference between the normal and the iso compound seems quite pronounced, where on the basis of the Baker–Nathan effect *per se* no statement could have been made regarding a difference as both compounds carry the same number of hydrogen atoms on the carbon atom alpha to the ring and have, moreover, identical molecular weights. Series II (second column of Table III) affords a more comprehensive example of the same type. This series corresponds to Series I with a methylene group placed between the ring and the variable alkyl group. The rates of bromination decrease in the order R = methyl > ethyl > *i*-propyl > *t*-butyl, *i. e.*, the order of reactivity corresponds to that for Series I, although the relative rates can no longer be accounted for by the Baker–Nathan effect. A similar situation exists for Series III (last column of Table III).[13]

(13) These series are not the only cases in which the number of hydrogen atoms alpha to the ring is not the decisive factor. *i*-Butylbenzene (two hydrogens) clearly reacts slower than *i*-propylbenzene (one hydrogen), and neopentylbenzene is brominated appreciably slower than *t*-amylbenzene, in spite of a difference of two hydrogen atoms.

Since the relative reactivities of the members of Series II (and Series III) cannot be accounted for on the basis of the number of hydrogen atoms on the carbon atom next to the benzene ring, as all four compounds have two such hydrogen atoms, the determining factor might conceivably be the extent of carbon–carbon hyperconjugation, the electrostatic inductive effect, or the size and polarizabilities of the four alkyl groups. Neopentylbenzene in all cases then should react the most rapidly,[14] ethylbenzene the least, and the total order of reactivity for the series should be exactly the reverse of the order actually obtained. Increasing steric hindrance in the *ortho* positions with increasing size of the alkyl group *might* account for the observed order and therefore merits consideration. Moreover, there has been a recent demonstration that the rates of propylation of alkylbenzenes can be accounted for by such an hypothesis.[15]

Toluene, on bromination in excess toluene as a solvent, yields 60.3% *para* and 39.7% *ortho* product.[16] That the ratio will not be appreciably changed in another solvent can be assumed and is borne out by experiments of Ingold, *et al.*[17] If one assumes the least favorable case, that *t*-butylbenzene affords *no ortho* substitution, a comparison of only the *para* positions shows that toluene reacts $5.7 \times 60/100 = 3.42$ times faster than *t*-butylbenzene in the *para* position.[18] Thus steric hindrance can account for only a fraction of the difference in rates of bromination of the two sterically extreme members of Series I. It must therefore contribute even less to the other relative rates of the series.[19]

(14) If carbon–carbon hyperconjugation were the determining factor, contributions like $ArCH_2\ominus\oplus C(CH_3)_3$ would make neopentylbenzene the most reactive.

(15) Condon, THIS JOURNAL, **70**, 2265 (1948).

(16) Holleman, *Chem. Rev.*, **1**, 187 (1924–1925).

(17) Ingold, Lapworth, Rothstein and Ward, *J. Chem. Soc.*, 1959 (1931); Bird and Ingold, *ibid.*, 918 (1938).

(18) Actually some *ortho* substitution in bromination of *t*-butylbenzene does occur. Kozak (*Bull. Akad. Sci. Cracow*, 407 (1906); *Chem. Zentr.*, **78**, I, 1787 (1907)) prepared *o*-*t*-butyltoluene by a Wurtz–Fittig reaction of the bromination product of *t*-butylbenzene. The rate of bromination of toluene in the *para* position relative to that of *t*-butylbenzene is therefore greater than 3.42. In the nitration of *t*-butylbenzene 23% *ortho* and 77% *para* substitution has been reported (Craig, THIS JOURNAL, **57**, 195 (1935)).

(19) Schramm (*Ber.*, **18**, 1272 (1885); *Monatsh.*, **9**, 842 (1888)) has demonstrated the formation of *ortho* products in the bromination of ethylbenzene and cumene. However, the only existent numerical data for *ortho*–*para* ratios of ethylbenzene, cumene and *t*-butylbenzene were obtained in preparative nitration (see data quoted by Le Fevre (*J. Chem. Soc.*, 980 (1933)) and see also Sterling and Bogert (*J. Org. Chem.*, **4**, 20 (1939)), Mayes and Turner (*J. Chem. Soc.*, 500 (1929)) and Craig (ref. 18). The data show qualitatively that *para* substitution increases successively in the four compounds of Series I as *ortho* substitution decreases. Since bromination affords more *para* substitution in general than nitration (about 20% for toluene), one can tentatively assign to the four compounds, on the basis of the nitration data, the *ortho*–*para* ratios 40/60, 30/70, 20/80, and 10/90 in bromination. Using these data the relative reactivities for the four compounds in the *para* positions become 100:81:54:27 as compared with the original 100:70:40:18. These corrected relative rates are numerically very close to the relative rates obtained in Series II (100:80:53:30) and Series III (100:80:(71)). However, as the *ortho*–*para* ratios assigned to the members of Series I are only approximate, one cannot attach great significance to the similarity of the numerical values for the relative rates in the three series.

If steric hindrance is not decisive in Series I, it cannot be decisive in Series II where the branching occurs on a carbon atom once removed from the benzene ring.[20] The contributions from steric factors to the reactivities of the compounds of series II can, as a first approximation, be assumed to be the same. The relevant data in the literature are not very extensive, but the data that exist point toward little difference in the *ortho–para* ratios for the members of this series.[21] In the alpha-methyl series (III) steric hindrance also probably has an insignificant effect on the relative rates. The data on the third compound of Series III, however, are less accurate than those for all other compounds and this series will not be considered further.

One is, therefore, left with a situation in which neither steric effects, first-order hyperconjugation of the carbon–hydrogen bonds, carbon–carbon hyperconjugation nor the electrostatic inductive effect can account for the observed decrease in rates of Series II. The experimental facts, apart from any theories, demonstrate the following. The four alkyl groups methyl, ethyl, *i*-propyl, *t*-butyl, attached directly to the benzene ring, release electrons into the ring (or accommodate a positive charge in the transition state) in the order methyl > ethyl > etc. If a methylene group is placed between the alkyl group and the benzene ring, the effect of these alkyl groups passes through the methylene group in the same order. It is reasonable to assume that whatever causes the four alkyl groups to act as they do in Series I is also responsible for the relative rates in Series II and that this effect is transmitted through the saturated methylene group, contrary to accepted views. If it is correct that the differences in rate in the first series are due to hyperconjugation of the carbon–hydrogen bonds, and there seem to be enough indications that this is the case, one is forced to conclude that the second series is also affected by a similar type of hyperconjugation and that the relative rates depend on the number of hydrogen atoms on the beta carbon atom. A second-order hyperconjugation involving the beta hydrogens as is shown in Fig. 1 is therefore tentatively suggested to account for the relative rates of bromination of the compounds of Series II. The structures would clearly account for the experimentally observed facts, provided that only the number of hydrogen atoms on the *beta* carbon atom

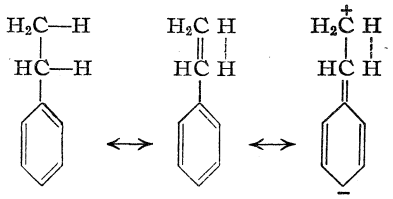


Fig. 1.

determines the stability of the transition state (when the number of *alpha* hydrogen atoms is constant). This type of hyperconjugation must be less important than hyperconjugation involving *alpha* hydrogens, for otherwise ethylbenzene would be brominated faster than toluene and isopropylbenzene would be brominated faster than *n*-propylbenzene, whereas the reverse is true. On the other hand, *n*-butylbenzene with two *beta* hydrogen atoms is brominated faster than isobutylbenzene with only one as previously pointed out, and the difference may be attributed at least in part to a difference in hyperconjugation involving the beta hydrogens. Although it is true that second-order hyperconjugation is supposed to be insignificant (although ever present),[22] it is, in this case, enhanced by conjugation with the benzene ring. Similar forms have been suggested for bibenzyl (where two rings are available for conjugation) and for geranylamine hydrochloride (where a single bond is flanked by two double bonds) to account for the shortening of the central carbon–carbon bond.[23] In looking for other possible explanations the following suggest themselves. There is the possibility of structures of type $ArCH_2^{\oplus}\ \ominus R$ which would withdraw electrons from the ring and account for the order, but such a possibility is not supported by any other evidence. Steric inhibition of resonance due to a lack of coplanarity is not expected to be a decisive factor, nor is it assumed that the observed order is due to a change in mechanism of the substitution by bromine. However, none of these factors can be ruled out completely on the basis of the available experimental evidence.

It is noteworthy that the order of the rates of bromination of the alkylbenzenes of Series II is identical with that of $S_N1$ displacement reactions on the corresponding halides (ethyl bromide, *n*-propyl bromide, etc.).[24,25] The order for the $S_N1$ reactions has been ascribed by Benfey[25] to hyperconjugation of the hydrogen atoms on the beta carbon atoms. $S_N1$ reactions, like aromatic substitution, are electron demanding and go through a positively charged transition state. Although the reactions of the alkyl halides are different from

(20) Note the related case of "classical" steric hindrance in 2,4,6-trimethylbenzoic acid and its esters, and the absence of steric hindrance in the corresponding phenylacetic acid: Meyer and Sudborough, *Ber.*, **27**, 1580 (1894); Watson, "Modern Theories of Organic Chemistry," Oxford University Press, 2nd ed., 1941, pp. 246 ff.

(21) *Nitration* of *n*-propylbenzene affords the *ortho* isomer to about the same extent as ethylbenzene (Baddeley and Kenner, *J. Chem. Soc.*, 303 (1935)). The presence of the *ortho* isomer in the *bromination* of the former has been demonstrated through oxidation to *o*-bromobenzoic acid (Schramm, Ref. 19). Furthermore, all normal alkylbenzenes afford a dinitro product with great ease (*o*/*p*), and with the amylbenzenes having two hydrogen atoms next to the ring, including neopentylbenzene, appreciable *ortho* substitution occurs (Ipatieff and Schmerling, Table I, ref. *a*).

(22) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 86–87.

(23) Jeffrey, *Proc. Roy. Soc.* (*London*), **A183**, 388 (1945); **A188**, 222 (1947); Bateman and Jeffrey, *J. Chem. Soc.*, 211 (1945); Robertson, *Ann. Reports*, **42**, 54 (1946).

(24) Dostrovsky and Hughes, *J. Chem. Soc.*, 157 (1946), and following papers.

(25) Benfey, THIS JOURNAL, **70**, 2163 (1948).

those of the alkylbenzenes, in that in the latter the alkyl groups are far removed from the seat of the reaction, it would seem plausible that alkyl groups exhibit the same electronic effect in both alkyl halides and alkylbenzenes. Granted the similarity, it is then perhaps no coincidence that *t*-amylbenzene is brominated faster than *t*-butylbenzene where *t*-amyl chloride is hydrolyzed faster than *t*-butyl chloride.[26] In the case of the two tertiary alkylbenzenes it may mean that in the complete absence of alpha hydrogen atoms carbon–carbon hyperconjugation takes precedence—an hypothesis which will be further tested.

*n*-Butylbenzene is brominated faster than *n*-propylbenzene to a small but definite extent. The result, tested on two different samples, indicates an apparent anomaly, particularly in view of the fact that *n*-amylbenzene is brominated slower than *n*-propylbenzene.[27] This anomality of the *n*-butyl group is manifested in other reactions and equilibria such as the strengths of aliphatic acids[28] and amines,[29] the enolization of phenyl alkyl ketones[30] and the basic dissociation constants of *p*-alkyldimethylanilines and their reactions with methyl iodide.[31] In the last two cases the order is methyl

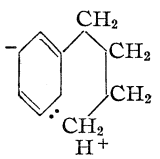



Fig. 2.

(26) Hughes and MacNulty, *J. Chem. Soc.*, 1283 (1937).

(27) The relative rates of bromination of the normal alkyl series, toluene, ethylbenzene, *n*-propylbenzene, *n*-butylbenzene and *n*-amylbenzene, are 100, 70, 55, 59 and 52, respectively.

(28) Dippy, *Chem. Rev.*, **25**, 189 (1939); *J. Chem. Soc.*, 1222 (1938).

(29) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

(30) Evans, *J. Chem. Soc.*, 785 (1936); Evans and Gordon, *ibid.*, 1434 (1938).

(31) Davies, *ibid.*, 1865 (1938). The author assigns the anomality to the *n*-propyl rather than the *n*-butyl group: also ref. 32.

> ethyl > *n*-butyl > *n*-propyl > *i*-butyl. The anomalous effect has variously been attributed to a field effect,[31,32] or chelation and hydrogen bonding[28,30] resulting from the interaction of the terminal hydrogen atoms with the functional group. In the case of *n*-butylbenzene (and higher alkylbenzenes) chelation, if it occurs, might be pictured in terms of hyperconjugation structures as shown in Fig. 2. Such additional hyperconjugation should increase the rate of bromination and the amount of meta product.[33]

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## Summary

The relative rates of bromination of twelve monoalkylbenzenes are toluene 100, ethylbenzene 70, *n*-propylbenzene 55, *i*-propylbenzene 40, *n*-butylbenzene 59, *i*-butylbenzene 37, *s*-butylbenzene 32, *t*-butylbenzene 18, *n*-amylbenzene 52, neopentylbenzene 21, 2-methyl-3-phenylbutane 29, *t*-amylbenzene 23. A second-order hyperconjugation involving beta hydrogen atoms is suggested to account for part of this order of relative rates.

Neopentylbenzene prepared from benzylmagnesium chloride and *t*-butyl chloride contains some *p*-*t*-butyltoluene.

BRYN MAWR, PA. RECEIVED SEPTEMBER 21, 1948

(32) Ayling, *ibid.*, 1014 (1938).

(33) The possibility of accounting for the anomalous effect of the *n*-butyl group by hyperconjugation structures of the above type was suggested by one of the Referees of this paper, who proposed structures involving second-order hyperconjugation throughout the *n*-butyl group.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

# The Effect of Benzoyl Peroxide on the Bromination of Methylthiophenes by N-Bromosuccinimide[1]

BY KARL DITTMER, ROBERT P. MARTIN, WERNER HERZ[2] AND STANLEY J. CRISTOL

In the course of our work dealing with the synthesis of possible amino acid antagonists, we had occasion to study the reaction of 2- and 3-methylthiophenes with N-bromosuccinimide. Of particular interest was the preparation of thiophene intermediates which could be used in the synthesis of β-3-thienylalanine.

Steinkopf and co-workers[3,4] reported that they obtained side chain bromination in the reaction of bromine with 2- and 3-methylthiophenes only after the thiophene ring had been completely brominated.

Buu-Hoi and Lecocq[5] obtained brominated side-chain derivatives of α-methylnaphthalene, 2-methylfuran and 2,5-dimethylfuran by the reaction with N-bromosuccinimide. With 2,5-dimethylthiophene the yields were lower because of the greater ease of nuclear substitution in the thiophene ring.

The results of Schmid and Karrer[6] on the catalytic effect exerted by benzoyl peroxide in initiating and maintaining the free radical formation necessary for side-chain bromination of toluene by N-bromosuccinimide suggested the possibility of introducing a bromine atom into the side chain of 2- and 3-methylthiophene without ring bromination.

Recently Campaigne and LeSuer[7] prepared 3-bromomethylthiophene by treating 3-methylthiophene with N-bromosuccinimide in the presence of benzoyl peroxide. We have obtained similar results. In this paper we wish to report on the effect of benzoyl peroxide on the bromination of 2- and 3-methylthiophenes by one and two molar equivalents of N-bromosuccinimide.

When 2-methylthiophene (I) was treated with one equivalent of N-bromosuccinimide without benzoyl peroxide, a good yield of monobromo-2-methylthiophene was obtained by distillation of the crude product. This material was about 66% 2-methyl-5-bromothiophene (III) and 34% 2-thenyl bromide (II). With benzoyl peroxide present the major fraction consisted primarily of 2-thenyl bromide (II) (84%), but contained some 2-methyl-5-bromothiophene (III). The composition of these fractions was estimated by analysis for total bromine and for hydrolyzable bromine, the latter being a measure of side chain bromination. These conclusions were confirmed by fractional distillation analysis.

In the absence of benzoyl peroxide, 3-methylthiophene reacted with one molar equivalent of N-bromosuccinimide to form a mixture of monobromo-3-methylthiophenes which consisted of approximately 90% 2-bromo-3-methylthiophene (XII) and 10% 3-thenyl bromide (XIII); with benzoyl peroxide the monobromomethylthiophene fraction contained 90% 3-thenyl bromide and 10% 2-bromo-3-methylthiophene.[8]

The reaction between 2-methylthiophene and two molar equivalents of N-bromosuccinimide formed a fraction which analyzed correctly for dibromomethylthiophene. Fractional bromine analysis indicated that this sample was practically pure 2-bromomethyl-5-bromothiophene (IV). Benzoyl peroxide did not significantly change the yield or composition of this product. The structure of 2-bromomethyl-5-bromothiophene (IV) was proved by conversion to 5-bromo-2-thenylacetamidomalonate (VI) and 5-bromo-2-thenylacetamidocyanoacetate (VII).

When 3-methylthiophene was treated with two molar equivalents of N-bromosuccinimide, a fraction of dibromomethylthiophenes was obtained which contained about 20% 2-bromo-3-bromomethylthiophene (XIV) and 80% 2,5-dibromo-3-methylthiophene (XV). The possibility of the presence of some 2,4-dibromo-3-methylthiophene is not completely ruled out. The addition of benzoyl peroxide gave a dibromo-3-methylthiophene fraction which consisted of about 84% 2-bromo-3-bromomethylthiophene (XIV) and 16% 2,5-dibromo-3-methylthiophene (XV). In one experiment evidence was obtained which indicated that some 3-thenylidine bromide was also formed. The structure of 2-bromo-3-bromomethylthiophene (XIV) was established by condensation with acetamidomalonate to form 2-bromo-3-thenylacetamidomalonate (XVI). A free alpha position was indicated by the ease with which it formed a chloromercuri derivative.

Most of the compounds formed were stable enough to permit distillation *in vacuo*. All 2-thenyl bromide derivatives lost hydrogen bromide and polymerized into tarry masses within a few days even though they were stored in the cold.

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(3) Steinkopf, *Ann.*, **513**, 281 (1934).

(4) Steinkopf and Jacob, *ibid.*, **515**, 273 (1935).

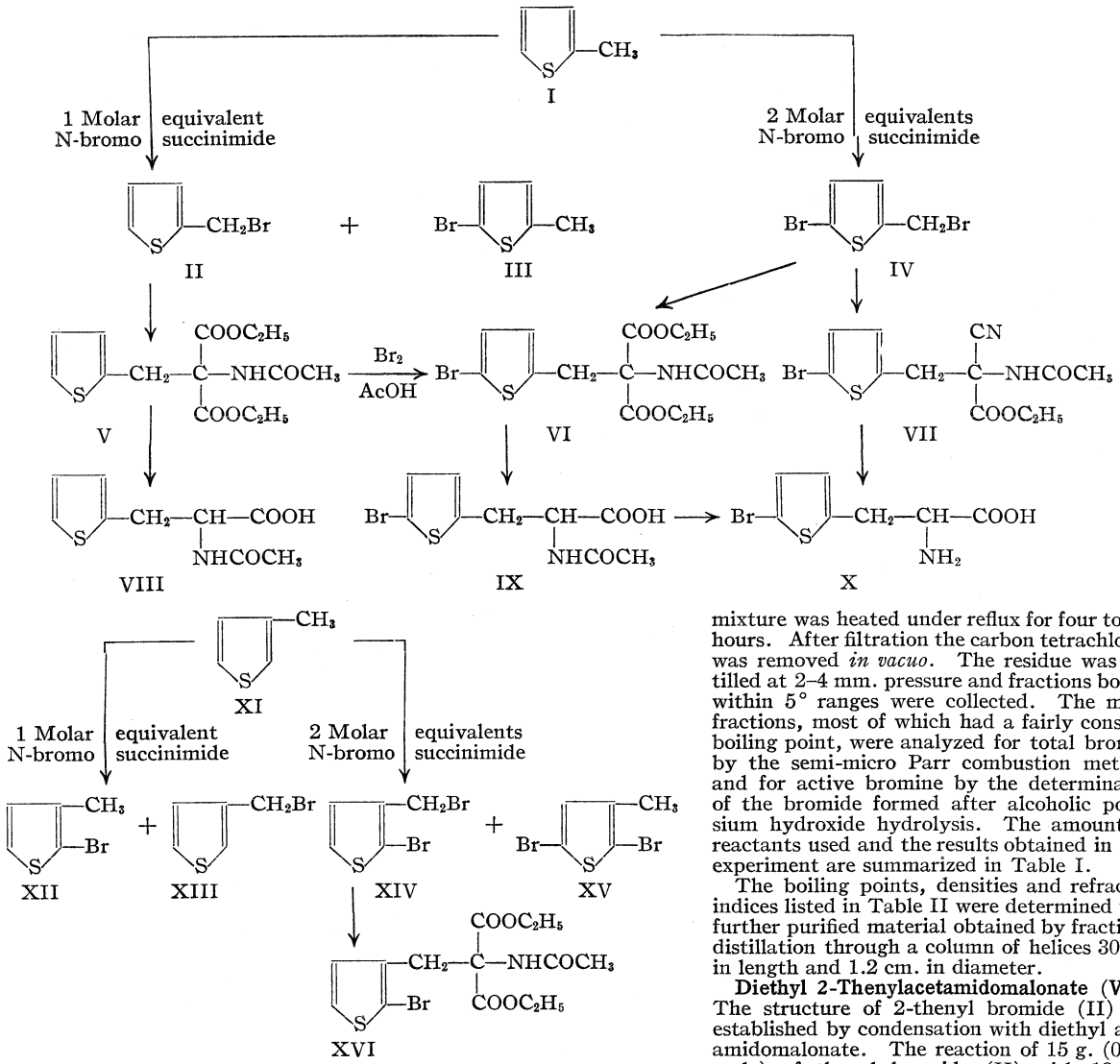
(5) Buu-Hoi and Lecocq, *J. Chem. Soc.*, 830 (1946), and *Compt. rend.*, **222**, 1441 (1946).

(6) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(7) Campaigne and LeSuer, THIS JOURNAL, **70**, 1555 (1948).

(8) In an earlier attempt when a different sample of N-bromosuccinimide was used, only traces of side chain-brominated material were obtained from 2-methyl- and 3-methylthiophenes. This misleading result prompted the preparation of 2-bromo-3-thenyl bromide with two molar equivalents of N-bromosuccinimide. The 2-bromo-3-thenyl bromide has been used for the preparation of β-3-thienylalanine.[9]

(9) Dittmer, THIS JOURNAL, **70**, 1205 (1948).




This ease of decomposition was not observed with any of the 3-thenyl bromide derivatives.

**Acknowledgment.**—The authors wish to thank Mr. T. D. Waugh of the Arapahoe Chemicals, Inc., for a gift of N-bromosuccinimide, and Mr. G. A. Harrington of the Socony-Vacuum Oil Company for generous gifts of the 2- and 3-methylthiophene used in these experiments. The authors also wish to thank Mrs. Philippa Szerwo of this department for the analyses reported in this paper.

## Experimental

**Reaction of Methylthiophenes with N-Bromosuccinimide.**—All of the brominations were conducted with from 0.13 to 0.40 mole of either 2- or 3-methylthiophene with either one or two molar equivalent amounts of N-bromosuccinimide suspended in 50 to 100 ml. of dry carbon tetrachloride. When benzoyl peroxide was used, between 0.10 and 0.25 g. per 0.1 mole of methylthiophene was added when the reaction started and, after ten minutes of refluxing, an additional 0.10 g. was added. Each reaction mixture was heated under reflux for four to five hours. After filtration the carbon tetrachloride was removed *in vacuo*. The residue was distilled at 2–4 mm. pressure and fractions boiling within 5° ranges were collected. The major fractions, most of which had a fairly constant boiling point, were analyzed for total bromine by the semi-micro Parr combustion method, and for active bromine by the determination of the bromide formed after alcoholic potassium hydroxide hydrolysis. The amounts of reactants used and the results obtained in each experiment are summarized in Table I.

The boiling points, densities and refractive indices listed in Table II were determined with further purified material obtained by fractional distillation through a column of helices 30 cm. in length and 1.2 cm. in diameter.

**Diethyl 2-Thenylacetamidomalonate (V).**—The structure of 2-thenyl bromide (II) was established by condensation with diethyl acetamidomalonate. The reaction of 15 g. (0.084 mole) of thenyl bromide (II) with 18.2 g. (0.084 mole) of diethyl acetamidomalonate in 100 ml. of absolute ethanol containing 1.9 g. (0.084 gram atom) of sodium after three hours reflux, followed by concentration, yielded 18.0 g. (67%) of diethyl 2-thenylacetamidomalonate (V), m. p. 115–116°, which was identical with the same compound prepared previously[10] from 2-chloromethylthiophene.

**N-Acetyl-β-2-thienylalanine (VIII).**—Hydrolysis of 5 g. (0.016 mole) of V by the method of Snyder and co-workers[11] gave 2.9 g. (85%) of N-acetyl-β-2-thienylalanine (VIII). The white needles obtained on recrystallization from hot water melted at 130°.

*Anal.* Calcd. for $C_9H_{11}NO_3S$: N, 6.57. Found: N, 6.44.

**Diethyl 2-(5-Bromo)-thenylacetamidomalonate (VI).**—The reaction of 13 g. (0.05 mole) of 2-bromomethyl-5-bromothiophene (IV) with a solution of 50 ml. of absolute ethanol containing 1.15 g. (0.05 gram atom) of sodium and 10.8 (0.05 mole) of diethyl acetamidomalonate yielded 12 g. (0.03 mole, 60%) of slightly-colored product (VI). White needles, m. p. 108°, were obtained by decolorizing

(10) Dittmer, Herz and Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

(11) Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 310 (1945).

TABLE I

DATA ILLUSTRATING THE COMPOUNDS PRESENT IN THE MAJOR DISTILLATION FRACTIONS OBTAINED BY THE BROMINATION OF 2- AND 3-METHYLTHIOPHENES WITH ONE AND TWO MOLAR EQUIVALENTS OF N-BROMOSUCCINIMIDE WITHOUT AND WITH ADDED BENZOYL PEROXIDE

| Reactants: 2-Methylthiophene moles | Reactants: N-Bromosuccinimide moles | Benzoyl peroxide: grams | Benzoyl peroxide: millimoles | Major fractions obtained: B. p. °C. | B. p. Mm. | Yield, g. | Bromine analyses, % Active | Bromine analyses, % Total | Compounds present (relative amounts in each fraction) |
|---|---|---|---|---|---|---|---|---|---|
| 0.2 | 0.2 | 0 | | 66–70 | 3[a] | 25.3 | 15.6 | 45.1[b] | 2-Methyl-5-bromothiophene (66%); 2-Thenyl bromide (34%) |
| .2 | .2 | 0.7 | 2.9 | 75–80 | 3[a] | 22.8 | 38.0[e] | 44.9[b] | 2-Thenyl bromide (84%); 2-Methyl-5-bromothiophene (16%) |
| .13 | .26 | 0 | | 84–87 | 2[a] | 16.8 | 29.2[c] | 62.1[d] | 2-Bromomethyl-5-bromothiophene (nearly pure) |
| .13 | .26 | 0.3 | 1.2 | 82–87 | 2[a] | 16.9 | 32.0[c] | 61.5[d] | 2-Bromomethyl-5-bromothiophene (nearly pure) |
| 3-Methylthiophene | | | | | | | | | |
| 0.22 | 0.22 | 0 | | 57–60 | 4[a] | 10.1 | 5.0 | 44.0[b] | 2-Bromo-3-methylthiophene (90%); 3-Thenyl bromide (10%) |
| .28 | .28 | 0.7 | 2.9 | 68–73 | 4[a] | 24.0 | 40.0[e] | 45.0[b] | 3-Thenyl bromide (90%); 2-Bromo-3-methylthiophene (10%) |
| .2 | .4 | 0 | | 26–30 | 2[f] | 10.7 | 1.8 | 44.8[b] | 2-Bromo-3-methylthiophene (nearly pure) |
| | | | | 50–80 | 2[f] | 15.6 | 7.0 | 62.2[d] | 2,5-Dibromo-3-methyl thiophene (77%); 2-Bromo-3-bromomethylthiophene (23%) |
| .4 | .8 | 0.45 | 1.9 | 34–37 | 2 | 10.2 | 3.1 | 44.0[b] | 2-Bromo-3-methylthiophene (nearly pure) |
| | | | | 70–73 | 2[f] | 31.0 | 26.1[c] | 62.3[d] | 2-Bromo-3-bromomethylthiophene (84%); 2,5-Dibromo-3-methylthiophene (16%) |

[a] These distillations were made in an all-glass Claisen distilling apparatus with no refluxing and considerable overheating of the vapors. [b] Total bromine calculated for monobromomethylthiophenes, 45.2%. [c] Active bromine calculated for bromomethylbromothiophenes, 31.1%. [d] Total bromine calculated for dibromomethylthiophenes, 62.2%. [e] Active bromine for thenyl bromides, 45.2%. [f] These distillations were made through a column of helices 30 cm. in length.

TABLE II

PHYSICAL PROPERTIES OF MONO- AND DI-BROMO COMPOUNDS OF 2- AND 3-METHYLTHIOPHENES

| Compound, thiophene- | Formula | Bromine, % Total Calcd. | Bromine, % Total Found | Bromine, % Active Calcd. | Bromine, % Active Found | Boiling point °C. | Boiling point Mm. | $d^{20}_{20}$ | $n^{20}D$ |
|---|---|---|---|---|---|---|---|---|---|
| 2-Methyl-5-bromo- | $C_5H_5SBr$ | 45.2 | 45.1 | 0.0 | 0.5 | 29 | 1.8 | 1.552 | 1.5687 |
| 2-Bromomethyl-[f] | $C_5H_5SBr$ | 45.2 | 44.6 | 45.2 | 40.4[a] | 55 | 1.5 | 1.605 | 1.6050 |
| 2-Bromomethyl-5-bromo-[c] | $C_5H_4SBr_2$ | 62.2 | 62.7 | 31.1 | 28.7 | 71 | 1.2 | 2.022 | 1.6406 |
| 2-Bromo-3-methyl-[d] | $C_5H_5SBr$ | 45.2 | 44.0 | 0.0 | 0.3 | 27 | 1.8 | 1.571 | 1.5714 |
| 3-Bromomethyl-[e,g] | $C_5H_5SBr$ | 45.2 | 45.8 | 45.2 | 40.6[b] | 50 | 1.5 | 1.616 | 1.6035 |
| 2,5-Dibromo-3-methyl-[d] | $C_5H_4SBr_2$ | 62.2 | 62.4 | 0.0 | 3.1 | 55 | 2 | 1.972 | 1.6126 |
| 2-Bromo-3-bromomethyl- | $C_5H_4SBr_2$ | 62.2 | 62.7 | 31.1 | 32.0 | 78 | 2 | 2.025 | 1.6363 |

[a] Still contains 2-methyl-5-bromothiophene. [b] Still contains 2-bromo-3-methylthiophene. [c] Previously prepared by Steinkopf.[3] [d] Previously described by Steinkopf and Jacob.[4] [e] Campaigne and LeSuer[7] prepared this compound: b. p. 75–78 (1 mm.), $d_4^{20}$ 1.635, $nD^{20}$ 1.604. [f] M. p. −10°. [g] M. p. −9°.

an acetone solution of the product, concentrating, chilling and diluting with water.

*Anal.* Calcd. for $C_{14}H_{18}BrNO_5S$: C, 42.86; H, 4.62; N, 3.57. Found: C, 42.5; H, 5.05; N, 3.60.

The same compound (VI) was also obtained by brominating diethyl 2-thenylacetamidomalonate (V).[10] A solution of 5.0 g. (0.031 mole) of bromine in 50 ml. of glacial acetic acid was slowly added with stirring to 10 g. (0.032 mole) of diethyl 2-thenylacetamidomalonate dissolved in 60 ml. of glacial acetic acid and 25 ml. of water. Dilution with water yielded 11.4 g. (0.029 mole, 91%) of nearly white needles. On recrystallization from 40% ethanol, the compound VI melted at 107–108°; mixed melting point with the first sample, 107–108°.

**N-Acetyl-β-2-(5-bromo)-thienylalanine (IX).**—Eleven and three-tenths gram (0.029 mole) of VI, hydrolyzed as in the preparation of VIII above, gave 7.9 g. (94%) of IX. The product melted at 177° after recrystallization from 20% ethanol.

Bromination of 1 g. of VIII in the manner described above gave 0.75 g. of IX, m. p. 177°.

*Anal.* Calcd. for $C_9H_{10}BrNO_3S$: N, 4.79; neut. equiv., 292. Found: N, 4.82; neut. equiv., 295.

**Ethyl 2-(5-Bromo)-thenylacetamidocyanoacetate (VII).**—Thirteen grams (0.05 mole) of IV was added to 50 ml. of absolute ethanol containing 1.15 g. (0.05 gram atom) of sodium and 8.5 g. (0.05 mole) of ethyl acetamidocyanoacetate. A reaction occurred immediately and a precipitate appeared. The mixture was refluxed for one and one-half hours. The alcohol was evaporated *in vacuo* and 50 ml. of water was added to the residue. The water was evaporated *in vacuo;* the residue was again diluted with 100 ml. of water and chilled for two days. Seventeen grams of dark colored material separated. The product was dissolved in 75 ml. of acetone and treated repeatedly with charcoal until the color of the solution had become a light orange. The solution was concentrated to 40 ml. in a vacuum and chilled for a day. The yield of yellow crystals was 5.2 g. An additional 5.7 g. was recovered from the mother liquor, giving a total of 10.9 g. (0.03 mole, 60%). Recrystallization from 30% ethanol yielded shiny white plates of VII, m. p. 116.5–117°.

*Anal.* Calcd. for $C_{12}H_{13}BrN_2O_3S$: N, 8.12. Found: N, 8.04.

**β-2-(5-Bromo)-thienylalanine (X).**—A solution obtained by the hydrolysis of 7.2 g. (0.025 mole) of IX with 40 ml. of 10% sodium hydroxide for four hours was treated with charcoal, filtered, diluted with 50 ml. of ethanol, neutralized with concentrated hydrochloric acid to *p*H 6 and chilled. One and two-tenths grams of nearly white plates separated. The mother liquor was evaporated to dryness *in vacuo*, triturated with 30 ml. of water and

filtered. The residue was washed with a little water, ethanol and ether and weighed 1.2 g. Acidification of the filtrate yielded 3.6 g. of unhydrolyzed starting material. The yield of crude amino acid (X), 2.4 g., was therefore 78% of the material which reacted.

The product was dissolved in 25 ml. of hot water containing 3 ml. of concentrated hydrochloric acid, treated with charcoal, filtered, diluted with 30 ml. of ethanol while hot and neutralized with concentrated ammonium hydroxide. The pure amino acid separated on cooling. It melted at 235–238° (capillary) with decomposition and at 256° on a Dennis melting point bar. Another recrystallization did not change the melting point when taken in a capillary tube, but raised the melting point on the bar to 262°.

*Anal.* Calcd. for $C_7H_8BrNO_2S$: N, 5.60. Found: N, 5.47.

The amino acid was also obtained when 5 g. of VII was refluxed with 50 ml. of 10% sodium hydroxide for eighteen hours. The hot solution was treated with charcoal, filtered, neutralized to *p*H 6 with concentrated hydrochloric acid and cooled. The precipitate, when purified as before, yielded 1.3 g. of X. Another 280 mg. was recovered by working up the mother liquors.

Two hundred and fifty milligrams of X, when treated with the calculated amount of sodium hydroxide and phenyl isocyanate in the usual manner,[12] yielded 300 mg. of the α-phenylureido derivative of X. Recrystallization from 30% ethanol gave white plates, m. p. 166–167° (capillary), 172–173° on the Dennis melting point bar.

*Anal.* Calcd. for $C_{14}H_{13}BrN_2O_3S$: neut. equiv., 369. Found: neut. equiv., 367.

Four hundred and twenty milligrams of the N-carbobenzoxy derivative of X was obtained by treating 500 mg. of X with the calculated amounts of sodium hydroxide and carbobenzoxy chloride. Recrystallization from dilute ethanol gave white crystals, m. p. 109–110°.

*Anal.* Calcd. for $C_{15}H_{14}BrNO_4S$: neut. equiv., 384. Found: neut. equiv., 390.

**Diethyl 3-(2-Bromo)-thenylacetamidomalonate (XVI).**—Four grams (0.0156 mole) of the lachrymatory material (XIV) obtained by the bromination of 3-methylthiophene with two molar equivalents of N-bromosuccinimide was added to 40 ml. of absolute ethanol containing 0.36 g. (0.0156 gram atom) of sodium and 3.38 g. (0.0156 mole) of diethyl acetamidomalonate. The mixture was refluxed for three hours, cooled and diluted with some water. After evaporation to dryness *in vacuo*, more water was added and the mixture was again evaporated to dryness *in vacuo*. The residue was diluted with a little water, chilled, filtered and washed with water. The yield of slightly-colored product was 5.5 g. (90%). Recrystallization from 50% ethanol gave shiny white plates of XVI, m. p. 84.5–85°.

*Anal.* Calcd. for $C_{14}H_{18}BrNO_5S$: C, 42.86; H, 4.62; N, 3.57. Found: C, 43.0; H, 4.27; N, 3.38.

This compound (XVI) formed a chloromercuri derivative, m. p. 216°.

## Summary

The effect of benzoyl peroxide on the bromination of 2-methyl- and 3-methylthiophene by the action of N-bromosuccinimide has been investigated.

When one molar equivalent of N-bromosuccinimide was permitted to react with 2-methylthiophene, the product was mainly 2-methyl-5-bromothiophene with some 2-thenyl bromide. The addition of benzoyl peroxide to this reaction mixture resulted in the formation of mostly 2-thenyl bromide.

When two molar equivalents of N-bromosuccinimide were allowed to react with 2-methylthiophene, the main product was 2-bromomethyl-5-bromothiophene. Benzoyl peroxide did not affect the yield of 2-bromomethyl-5-bromothiophene. The 2-bromomethyl-5-bromothiophene was condensed with ethyl acetamidocyanoacetate and diethyl acetamidomalonate to yield solid derivatives which were characterized and hydrolyzed to β-2-(5-bromo)-thienylalanine.

When one molar equivalent of N-bromosuccinimide was permitted to react with 3-methylthiophene in the absence of benzoyl peroxide, the product was mainly 2-bromo-3-methylthiophene, whereas in the presence of benzoyl peroxide 3-bromomethylthiophene was the chief product.

When two molar amounts of N-bromosuccinimide were reacted with 3-methylthiophene in the absence of benzoyl peroxide, the main product was 2,5-dibromo-3-methylthiophene with some 2-bromo-3-bromomethylthiophene. The addition of benzoyl peroxide resulted in the formation of mainly 2-bromo-3-bromomethylthiophene and some 2,5-dibromo-3-methylthiophene. The 2-bromo-3-bromomethylthiophene was characterized and converted to the diethyl 2-bromo-3-thenylacetamidomalonate.

BOULDER, COLORADO RECEIVED[13] AUGUST 7, 1948

(12) Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," 5th ed., Julius Springer Verlag, Berlin, 1931, p. 517.

(13) Original manuscript received November 24, 1947.

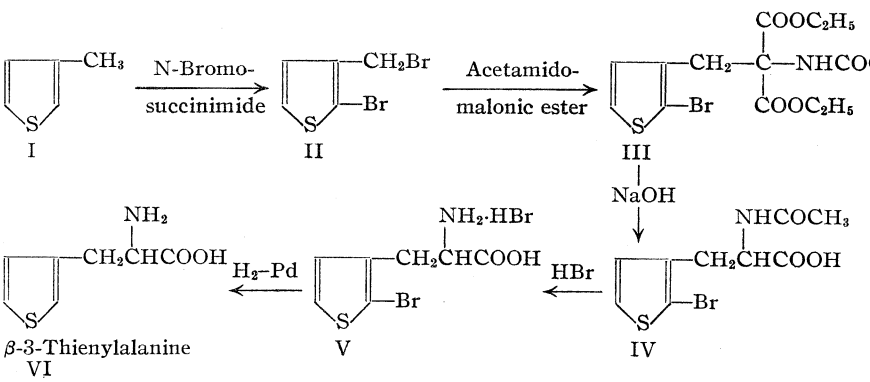
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

# The Synthesis and Microbiological Properties of β-3-Thienylalanine, a New *anti*-Phenylalanine[1,2]

BY KARL DITTMER

That β-2-thienylalanine is an antagonist of phenylalanine has been demonstrated by du Vigneaud and co-workers.[3] This inhibitory physiological action is brought about by the interchange of a vinylene group for an aromatic sulfide, a structural change which has also produced antagonists of nicotinic acid[4] and thiamine.[5]

As part of a large research program designed to further establish what structural changes consistently yield metabolite antagonists and what changes do not, the preparations of other heterocyclic amino acids related to phenylalanine have been completed in this Laboratory. Clark and Dittmer[6] found that β-2-furylalanine is about one-third as good a phenylalanine antagonist as β-2-thienylalanine. Herz, Dittmer and Cristol[7] prepared β-2-pyrrylalanine and, although not obtained in pure form, found that it is an antiphenylalanine.




Since all of these β-2-heterocyclic alanines were active as antagonists of phenylalanine it seemed important to determine what influence the position of the alanine side chain would have on the antiphenylalanine activity of the thiophene analog. To determine which of the two possible isomers of thienylalanine is the better antagonist, the β-3-thienylalanine was prepared by the reactions.

During a study of the bromination of 3-methylthiophene with N-bromosuccinimide, 2-bromo-3-(bromomethyl)-thiophene (II) was obtained in good yield.[8,9] The condensation with diethyl acetamidomalonate resulted in a 73% yield of diethyl (2-bromo-3-thenyl)-acetamidomalonate (III). Pure samples of β-(2-bromo-3-thienyl)-alanine hydrobromide (V) were most easily obtained if the condensation product (III) was converted to the water insoluble N-acetyl intermediate (IV) which was then hydrolyzed with hydrobromic acid to yield V. The removal of the bromine with hydrogen in the presence of palladium catalyst on charcoal according to the method of Mozingo and co-workers[11] was tried on compounds III, IV and V. Best results were obtained when the bromine was removed from β-(2-bromo-3-thienyl)-alanine hydrobromide (V).

The structure of β-3-thienylalanine (VI) could be inferred by its synthesis from 3-methylthiophene (I), it was strengthened by analysis, and established by oxidizing it with alkaline permanganate to 3-thiophenecarboxylic acid which showed no depression of the melting point with an authentic sample of 3-thiophenecarboxylic acid.

β-3-Thienylalanine was tested for its inhibitory action on the growth of *Saccharomyces cerevisiae*, strain 139, and an unidentified strain of *Escherichia coli*.

## Experimental

**N-Acetyl-β-(2-bromo-3-thienyl)-alanine (IV).**—Partial hydrolysis of 8.66 g. (0.022 mole) of diethyl (2-bromo-3-thenyl)-acetamidomalonate (III), prepared as previously described,[8] was accomplished by heating under reflux for four hours with 50 ml. of 10% sodium hydroxide.[12] The reaction mixture was acidified to *p*H 3 with hydrochloric acid and heated for one hour. It was treated with Darco, filtered and cooled overnight. The yield of fairly pure N-acetyl-β-(2-bromo-3-thienyl)-alanine (IV) was 2.72 g. (45%). Recrystallization from water yielded a pure crystalline product, m. p. 148–149°.

(1) This work was supported in part by a research contract with the Office of Naval Research.

(2) Presented in part at the 113th meeting of the American Chemical Society at Chicago, April, 1948.

(3) du Vigneaud, McKennis, Simmonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

(4) Erlenmeyer, Block and Kiefer, *Helv. Chim. Acta*, **25**, 1066 (1942).

(5) Woolley and White, *J. Exp. Med.*, **78**, 489 (1943).

(6) Clark and Dittmer, *J. Biol. Chem.*, **173**, 313 (1948).

(7) Herz, Dittmer and Cristol, THIS JOURNAL, **70**, 504 (1948).

(8) Dittmer, Martin, Herz and Cristol, *ibid.*, **71**, 1201 (1949).

(9) Early in the bromination studies we obtained primarily 2-bromo-3-(bromomethyl)-thiophene which was employed in the synthesis of β-3-thienylalanine here described. Through a personal communication we learned that Campaigne synthesized β-3-thienylalanine from 3-thenyl bromide. We have likewise obtained β-3-thienylalanine by that more convenient method.[10]

(10) Campaigne, Bourgeois, Garst, McCarthy, Patrick and Day, THIS JOURNAL, **70**, 2611 (1948).

(11) Mozingo, Harris, Wolf, Hoffhine, Easton and Folkers, *ibid.*, **67**, 2092 (1945).

(12) Snyder, Shekleton and Lewis, *ibid.*, **67**, 310 (1945).

*Anal.* Calcd. for $C_9H_{10}O_3BrNS$: N, 4.79; neut. equiv., 292. Found: N, 4.59; neut. equiv., 289.

**β-(2-Bromo-3-thienyl)-alanine Hydrobromide (V).**—With vigorous stirring 3.6 g. (0.012 mole) of IV and 150 ml. of 10% hydrobromic acid solution were heated for four hours. The hydrobromic acid and water were removed *in vacuo*. The residue was dissolved in ethyl alcohol; the solution was treated with Darco and filtered; and ethyl acetate was added to induce crystallization. Upon cooling and the addition of more ethyl acetate, 2.42 g. (61% yield) of white crystalline hydrobromide (V) was obtained.

*Anal.* Calcd. for $C_7H_9Br_2O_2NS$: N, 4.23; neut. equiv., 331. Found: N, 4.18; neut. equiv., 330.

**β-3-Thienyl-DL-alanine (VI).**—To 2 g. of reduced palladium on charcoal catalyst in 30 ml. of 50% aqueous methanol was added 1.05 g. (0.0032 mole) of β-(2-bromo-3-thienyl)-alanine hydrobromide (V). The catalyst was prepared and reduced at 60 cm. of mercury pressure according to Mozingo and co-workers.[11] During the first ten minutes of shaking at room temperature 64 ml. (STP) of hydrogen at 1.6 atmospheres pressure was absorbed which represents 90% of the theoretical amount required to debrominate V. After shaking another hour the theoretical amount of hydrogen was used. The catalyst was removed by filtration. The filtrate was concentrated to dryness *in vacuo*, dissolved in 5 ml. of water and again taken to dryness. The β-3-thienylalanine hydrobromide was dissolved in 10 ml. of absolute ethanol; the solution was treated with Darco, filtered, and the filtrate was exactly neutralized with 10 *N* ammonium hydroxide. Crystals began to form almost immediately and after cooling, 330 mg. (61% yield) of β-3-thienylalanine (VI) was collected. This sample gave a negative Beilstein test and a positive ninhydrin reaction. β-3-Thienylalanine was recrystallized by dissolving in a small amount of absolute ethanol containing a slight excess of hydrobromic acid. After the solution had been treated with Darco the hydrobromic acid was exactly neutralized with 10 *N* aqueous ammonium hydroxide. The crystals were washed with absolute alcohol and dried, melting point 244–248° in a capillary when placed into the bath at 240°.

*Anal.* Calcd. for $C_7H_9O_2NS$: C, 49.10; H, 5.30; N, 8.18. Found: C, 48.98; H, 5.65; N, 8.34.

The position of the side chain was established by oxidizing the β-3-thienylalanine to 3-thiophenecarboxylic acid. To 40 ml. of water containing 1.8 g. of sodium hydroxide was added 256 mg. (0.0015 mole) of β-3-thenylalanine and 1.0 g. of potassium permanganate. The reaction mixture was heated to boiling and kept warm for two hours. After cooling, the manganese dioxide was removed by filtration and the filtrate was acidified and extracted with ether. The ether solution was dried with sodium sulfate and then concentrated to a small amount of oil which soon crystallized. The solid was dissolved in 1 ml. of hot water; the hot solution was treated with Darco, filtered and cooled overnight. The yield of 3-thiophenecarboxylic acid was 110 mg. (57%), m. p. 137–138°. Mixed melting point with an authentic sample of 3-thiophenecarboxylic acid, was 137–138°, whereas, when mixed with 2-thiophenecarboxylic acid the melting point was 120–124°.

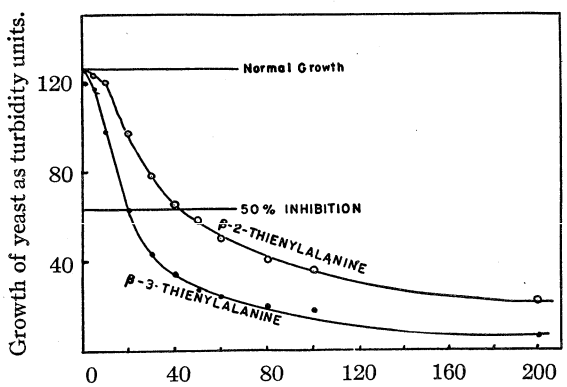



Fig. 1.—A comparison of the properties of two isomeric thienylalanines as yeast growth inhibitors.

**Microbiological Tests.**—The methods of comparing the inhibitory properties of β-3-thienylalanine with the antiphenylalanine properties of β-2-thienylalanine on the growth of *Saccharomyces cerevisiae*, strain 139, and on an unidentified strain of *Escherichia coli* were the same as previously described.[6]

The curve in Fig. 1 illustrates the relative potency of the two thienylalanines as growth inhibitors of *S. cerevisiae*. It will be observed that 20.0 micrograms of β-3-thienyl-DL-alanine per 7.5 ml. of medium inhibited growth to 50% of normal, whereas for the same degree of inhibition 42.5 micrograms of β-2-thienyl-DL-alanine were required. Figure 2 illustrates that phenylalanine completely reversed the toxicity of β-3-thienylalanine. In addition to phenylalanine, tryptophan, leucine, isoleucine and valine also reversed the toxicity of β-3-thienylalanine. These are the same amino acids which nullified the toxicity of β-2-thienylalanine.[13] β-(2-Bromo-3-thienyl)-alanine (V) did not inhibit the growth of yeast when tested up to a concentration of 1 mg. per 7.5 ml.

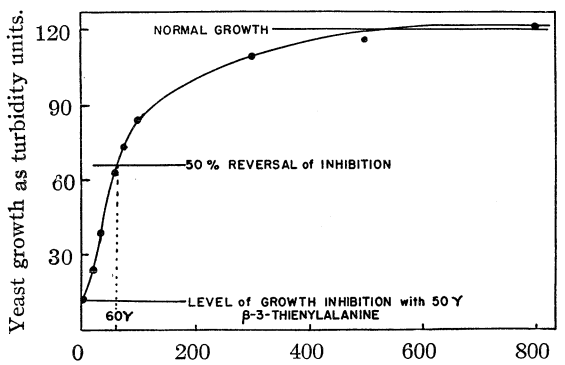



Fig. 2.—Nullification of the β-3-thienylalanine inhibition of the growth of *S. cerevisiae*.

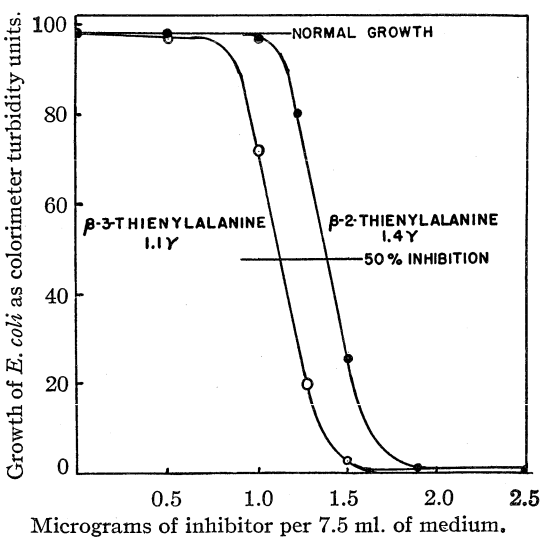



Fig. 3.—A comparison of the properties of two isomeric thienylalanines as inhibitors of *E. coli*.

(13) Dittmer, Ellis, McKennis and du Vigneaud, *J. Biol. Chem.*, **164**, 761 (1946).

When increasing amounts of β-3-thienyl-DL-alanine were added to the medium in which *E. coli* grew well, it completely inhibited the growth and was about 30% more effective than β-2-thienylalanine. This is illustrated by the data of Fig. 3. The toxicity on the growth of *E. coli* was also prevented by phenylalanine.

## Discussion

The results of previous work[3,6,7,13] show that the replacement of the benzene ring in phenylalanine by the thiophene, furan or pyrrole ring results in the formation of antagonists of phenylalanine. Of these three antagonists the thiophene analog was probably the most active. The results described in this paper indicate that when the alanine side chain is in the 3-position the antagonist is more potent than if it is in the 2-position. These results suggest that if the best antagonist of a compound which contains a phenyl ring is to be designed it would be most likely obtained by replacing the phenyl group by a thiophene ring with the side chain in the 3-position.

**Acknowledgment.**—The author wishes to acknowledge the very excellent assistance of Mr. Robert P. Martin in the chemical phase of this work, and of Mrs. Charmion McMillan and Mrs. Virginia Janda for the microbiological tests. The analyses were made by Mrs. Philippa Szerwo of this department. The author also wishes to thank Mr. G. A. Harrington of the Socony–Vacuum Oil Company for a generous gift of 3-methylthiophene.

## Summary

β-3-Thienyl-DL-alanine was synthesized by alkaline hydrolysis of diethyl (2-bromo-3-thenyl)-acetamidomalonate, yielding N-acetyl-β-(2-bromo-3-thienyl)-alanine. The N-acetyl derivative was converted to the β-(2-bromo-3-thienyl)-alanine hydrobromide by acid hydrolysis. The bromine was removed by hydrogenation in the presence of palladium on charcoal catalyst, yielding pure β-3-thienylalanine.

This new isostere of phenylalanine was tested for its inhibitory properties on the growth of *Saccharomyces cerevisiae*, strain 139, and on an unidentified strain of *Escherichia coli*. For yeast, the β-3-thienylalanine was about twice as active as β-2-thienylalanine. It was about 30% more effective against *E. coli*. In each instance the toxicity was reversed by phenylalanine.

BOULDER, COLORADO RECEIVED AUGUST 17, 1948

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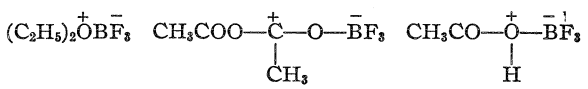
[CONTRIBUTION NO. 701 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# Further Studies in the Acylation of Thiophene and Furan in the Presence of Boron Fluoride Complexes[1]

BY ROBERT LEVINE, JOHN V. HEID[2] AND MARTIN W. FARRAR

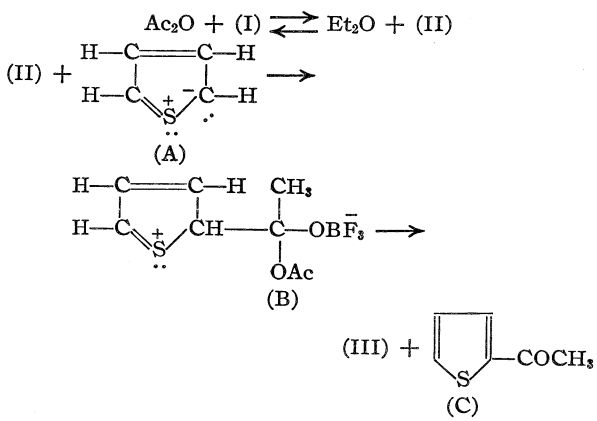
In an earlier paper[3] from this Laboratory it was reported that high yields of 2-thienyl and 2-furyl ketones are obtained when thiophene and furan are acylated with anhydrides in the presence of catalytic amounts of boron fluoride etherate as the condensing agent.

In the present work, we were interested in investigating the course of these acylations. In this discussion, the boron fluoride complexes will be referred to as follows



| (I) | (II) | (III) |
|---|---|---|
| Etherate | Complex with acetic anhydride | Complex with acetic acid |

The following scheme indicates a possible reaction mechanism whereby catalytic amounts of (I) could result in high yields of the heterocyclic ketones. The acylation of thiophene with acetic anhydride is taken as an example.



The first step in the reaction probably involves the interaction between acetic anhydride and (I) to give (II). This reactive intermediate then condenses with thiophene (A), to give the complex of (II) and thiophene (B), which then decomposes to produce (III) and 2-thienyl methyl ketone (C). We postulate that the acylating agent is (II) and the actual condensing agent (the catalyst) is (III). As this complex of acetic acid and boron fluoride (III) is formed it functions as (I) did in the first step of the reaction and is con-

(1) Presented before the Organic Division of the American Chemical Society, St. Louis Meeting, September, 1948.

(2) Present address: Mellon Institute, Pittsburgh, Pa.

(3) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

tinually being recycled. Hence catalytic amounts of (I) could result in high yields of ketone.[4]

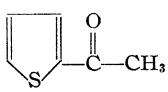
Some support of the mechanism proposed above would be available if the acylations of thiophene and furan could be effected using a complex of boron fluoride and a carboxylic acid as the condensing agent. Therefore, thiophene and furan were acylated with acetic, propionic and *n*-butyric anhydrides in the presence of catalytic amounts of (III). High yields of the 2-acyl derivatives of thiophene and furan were obtained. These yields compare favorably with those obtained in the same acylations using (I) as the condensing agent,[3] and hence it is felt that the above mechanism represents the actual course of the reaction.[5]

We then prepared 2-thienyl methyl (51%), ethyl (55%), *n*-propyl (69%), and phenyl (38%) ketones by acylating thiophene with the appropriate acid chlorides in the presence of (I) as the condensing agent.

The direct acylation of thiophene with acetic acid in the presence of two boron fluoride complexes was then studied. Two types of experiments were performed. In the first experiment one equivalent of boron fluoride etherate was allowed to react with equivalents of thiophene and glacial acetic acid. It was anticipated that the following reactions would occur.

(a) $BF_3.Et_2O + CH_3COOH \rightleftharpoons Et_2O + BF_3.CH_3COOH$

(b)  $+ BF_3.CH_3COOH \longrightarrow$




Apparently, under the conditions employed, the equilibrium of reaction (a) lies largely to the left, since only 7% of 2-thienyl methyl ketone was obtained. In the second experiment, in which the preformed complex of boron fluoride and acetic acid was allowed to react with thiophene (reaction b), a 25% yield of the ketone was obtained. Earlier, Hartough and Kosak[6] reported the direct acylation of thiophene and furan with carboxylic acids in the presence of phosphorus pentoxide in fair to good yield.

Finally, 2,5-dimethylfuran was acylated with acetic, propionic and *n*-butyric anhydrides in the presence of catalytic amounts of boron fluoride etherate to give the corresponding 3-acyl-2,5-dimethylfurans in good yields. One of these, 3-acetyl-2,5-dimethylfuran, was prepared in high yield by Hurd and Wilkinson,[7] by the interaction of 2,5-dimethylfuran and acetic anhydride in the presence of a catalytic amount of stannic chloride as the condensing agent.

(4) It should be pointed out that in the acylations involving propionic and *n*-butyric anhydrides, the actual condensing agent is probably the complex of boron fluoride and the corresponding carboxylic acid.

(5) Although no study was made of the use of the complexes of boron fluoride and propionic and *n*-butyric acids as condensing agents, yields comparable to those obtained with (III) would probably have been obtained had such experiments been performed.

(6) Hartough and Kosak, THIS JOURNAL, 69, 3098 (1947).

## Experimental

**Acylation of Thiophene and Furan with Anhydrides in the Presence of the Complex of Boron Fuoride and Acetic Acid. General Procedure.**—The apparatus used in these experiments consisted of a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a reflux condenser (protected from atmospheric moisture by a drying tube filled with Drierite), and a thermometer so that the temperature of the reaction mixture could be recorded. One mole of furan (68 g.), or thiophene (84 g.), and 1.15 moles of the appropriate anhydride were placed in the flask. To the rapidly stirred solution of furan and anhydride, cooled to 0° in an ice-bath, or of thiophene and anhydride at room temperature, 18.5 g. of the complex of boron fluoride and acetic acid was added all at once. The temperature of the reaction mixture rapidly rose to 100–115° and then dropped to room temperature over a period of about fifteen minutes. Stirring was continued for one-half hour longer and then about 200 ml. of water was added to hydrolyze the reaction mixture. The contents of the reaction flask were made basic with sodium carbonate solution, extracted with ether, and the ethereal phase dried over Drierite. The solvent was distilled at atmospheric pressure and the residue distilled in vacuum. From 75–92% yield of the ketones were obtained. The m. p. of the semicarbazones agreed with those reported previously.[3]

**Acylation of Thiophene with Acid Chlorides in the Presence of Boron Fluoride Etherate. General Procedure.**—The apparatus used was the same as that described above except that a hydrogen chloride trap was attached to the top of the condenser. The thiophene (1.5 moles) and acid chloride (0.5 mole) were placed in the flask, and 14 g. of boron fluoride etherate was added all at once. The reaction mixture was then refluxed until the evolution of hydrogen chloride was practically complete (one to two hours). The reaction mixture was then worked up as described above.

**The Acylation of 2,5-Dimethylfuran with Anhydrides in the Presence of Boron Fluoride Etherate. General Procedure.**—The reactions were carried out exactly as described above for the acylation of furan with anhydrides in the presence of the complex of boron fluoride and acetic acid, except that boron fluoride etherate (14 g.) was used as the condensing agent and that the 2,5-dimethylfuran and the anhydrides were at room temperature when the catalyst was added.

In this way the following 3-acyl-2,5-dimethylfurans were prepared: 3-acetyl (65%), b. p. 95° (23 mm.), oxime, m. p. 75–76°[7]; 3-propionyl (63%), b. p. 105–108° (23 mm.). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.05; H, 7.89. Found: C, 71.07; H, 7.74; 2,4-dinitrophenylhydrazone, m. p. 171–172°; 3-*n*-butyryl (60%), b. p. 115–117° (23 mm.). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.54; H, 8.77; 2,4-dinitrophenylhydrazone, m. p. 146–147°.

**The Direct Acylation of Thiophene with the Complex of Boron Fluoride and Acetic Acid.**—Thiophene (64 g., 0.76 mole) and 200 ml. of carbon disulfide were placed in the apparatus described above, and heated to 45°. Forty-nine grams (0.38 mole) of the complex of boron fluoride and acetic acid was then added over a two-hour period. The reaction mixture was then refluxed for one hour longer and worked up as described above for the other acylations. Upon distillation, there was obtained 12.2 g. (25.4%) of 2-acetylthiophene, b. p. 79–80° (7 mm.).

**Acknowledgment.**—The authors are very grateful to Dr. P. E. Cholet of the General Chemical Division of the Allied Chemical and Dye Corpora-

(7) Hurd and Wilkinson, *ibid.*, 70, 740 (1948).

tion for supplying the complex of boron fluoride and acetic acid, and to E. I du Pont de Nemours and Company for contributing the furan used in this investigation.

## Summary

Thiophene and furan have been acylated with several aliphatic acid anhydrides in the presence of the complex of boron fluoride and acetic acid to give high yields of the corresponding 2-acyl derivatives.

Thiophene has been acylated with four acid chlorides in the presence of boron fluoride etherate in fair yields.

The direct acylation of thiophene with the complex of boron fluoride and acetic acid has given only a low yield of 2-thienyl methyl ketone.

PITTSBURGH, PA. RECEIVED OCTOBER 11, 1948

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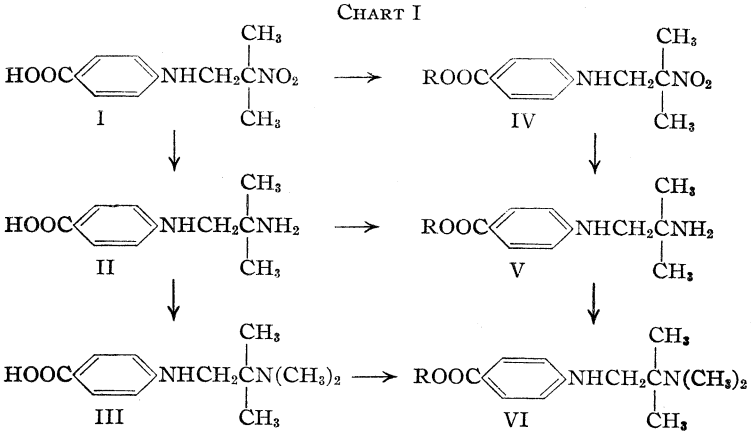
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DEPAUW UNIVERSITY]

# Esters of Nitrogen-substituted *p*-Aminobenzoic Acid

BY J. M. FULMER AND HOWARD BURKETT

In 1942 it was suggested by Dr. H. G. Johnson[1] that from *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] (I) (see Chart I) alkyl *p*-(2-dialkylamino-2-methylpropylamino)-benzoates (VI, R = alkyl) be prepared and tested for local anesthetic activity. He synthesized *p*-(2-amino-2-methylpropylamino)-benzoic acid[2] (II) by the catalytic hydrogenation of I.

CHART I




The authors have made a number of esters (IV, V, VI) in which R is methyl, ethyl, *n*-propyl and γ-diethylaminopropyl, according to the equations shown. Methyl *p*-(2-amino-2-methylpropylamino)-benzoate (V, R = $CH_3$) was prepared in good yield both from the hydrogenation of the corresponding nitro-ester (IV, R = $CH_3$) and by the esterification of the acid (II). Using methyl sulfate, attempts to methylate the primary amine group in the acid (II) or the ester (V, R = $CH_3$) to give III or VI (R = $CH_3$), respectively, failed. However, no reactions were tried at elevated pressures. Use of the methylation procedure described by Clarke, *et al.*,[3] gave good yields in both cases.

All of the esters were prepared by direct esterification, except the γ-diethylaminopropyl esters, which were synthesized by the reaction of γ-diethylaminopropyl chloride on the sodium salt of the appropriate acid. The ethyl and *n*-propyl esters of VI were obtained only in poor yields by esterification. It was found in the case of the ethyl ester that better yields were obtained by the methylation of V (R = $C_2H_5$).

The pharmacological properties of these compounds are being studied by Graam, Ott and Schultz, who plan to publish their report in the *Journal of Pharmacology and Experimental Therapeutics*.

**Acknowledgment.**—The authors thank Dr. Jerome Martin for his suggestions and Commercial Solvents Corporation for the financial aid which made this investigation possible. The authors also thank Commercial Solvents Corporation for running all high-pressure hydrogenations and analyses.

## Experimental

**Procedure A. Ethyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.**—To a mixture of 25 g. of *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] and 150 ml. of ethanol was added 2 ml. of concd. sulfuric acid, with shaking. After refluxing for twelve hours, the reaction mixture was cooled and filtered. Two recrystallizations from ethanol yielded 15.7 g. (56%) of ester, m. p. 137–138°.

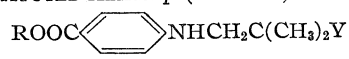
The methyl and *n*-propyl esters, as noted in Table I, were prepared in a similar manner. They were recrystallized from methanol and *n*-propanol, respectively.

**Procedure B. γ-Diethylaminopropyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.**—To a suspension of 29.0 g. (0.12 mole) of finely powdered *p*-(2-nitro-2-methylpropylamino)-benzoic acid in 150 ml. of ethanol was added 72.5 ml. (0.12 mole) of a 1.660 *N* solution of sodium hydroxide in ethanol. After a few minutes, 19.8 g. (0.132 mole) of γ-diethylaminopropyl chloride, along with 50 ml. of ethanol, was added. After refluxing for four and one-half hours, the solution was filtered hot, collecting 7.0 g. of sodium chloride (theory was 7.0 g.). The filtrate was cooled overnight in the refrigerator. Filtration, followed by washing with ethanol and drying, gave 33.2 g. of the ester, m. p. 110–110.5°. Evaporation

(1) Private communication.
(2) H. G. Johnson, THIS JOURNAL, **68**, 14 (1946).
(3) Clarke, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).

TABLE I

SUBSTITUTED ALKYL *p*-(N-AMINO)-BENZOATES



| R | Y | Procd.[e] yield, % | M. p., °C. | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|
| $CH_3$ | $NO_2$ | A90 | 132.5–134 | 11.11 | 11.44 |
| $C_2H_5$ | $NO_2$ | A56 | 137–138 | 10.50 | 10.15 |
| $CH_3CH_2CH_2$ | $NO_2$ | A51 | 103–104 | 10.00 | 10.17 |
| $(C_2H_5)_2N(CH_2)_3$ | $NO_2$ | B94 | 110–110.5 | 11.97 | 12.03 |
| $CH_3$ | $NH_2$ | D82 | 79–80 | 12.61 | 12.60 |
| $CH_3$ | $NH_2$ | C92[a] | | | |
| $C_2H_5$ | $NH_2$ | C74 | 65.5–66.5 | 11.87 | 12.09 |
| $CH_3CH_2CH_2$ | $NH_2$ | C81 | Oil | 11.20 | 11.51 |
| $(C_2H_5)_2N(CH_2)_3$ | $NH_2$ | B58 | 20–22 | 13.09 | 12.97 |
| $(C_2H_5)_2N(CH_2)_3$ | $NH_2$ | D84 | 18–20 | | |
| H | $(CH_3)_2N$ | E68 | 238 (dec.)[b] | 11.87 | 11.73 |
| $CH_3$ | $(CH_3)_2N$ | C60 | 90.5–91.5 | 11.20 | 10.74[c] |
| $CH_3$ | $(CH_3)_2N$ | E68 | 90.5–91.5 | | |
| $C_2H_5$ | $(CH_3)_2N$ | E66 | 70–71 | 10.60 | 10.57 |
| $C_2H_5$ | $(CH_3)_2N$ | C12 | 72–73 | | |
| $CH_3CH_2CH_2$ | $(CH_3)_2N$ | C35[d] | 65.5–66.5 | 10.08 | 10.33 |
| $(C_2H_5)_2N(CH_2)_3$ | $(CH_3)_2N$ | B92 | 38–39 | 12.03 | 12.56 |

[a] This is the hydrochloride, m. p., 166–168° (dec.). [b] The hydrochloride melts at 256° (dec.). [c] Analysis after further drying: Calcd. for C, 67.20; H, 8.70. Found: C, 67.40; H, 8.39. [d] Yields for other runs of this compound were much lower. [e] Letter preceding percentage yield represents procedure followed.

to one-fourth volume, adding water and cooling gave an additional 6.4 g. (94% yield).

The other γ-diethylaminopropyl esters (V and VI, R = $(C_2H_5)_2N(CH_2)_3$) were prepared in a similar way with the following exceptions. After refluxing, the solvent was removed under reduced pressure, water was added and the product was extracted with ether. After washing the ether solution with dilute sodium carbonate solution, the ether was evaporated. Solid esters were recrystallized from petroleum ether.

**Procedure C. Methyl *p*-(2-Amino-2-methylpropylamino)-benzoate.**—A suspension of 9 g. of finely divided *p*-(2-amino-2-methylpropylamino)-benzoic acid[2] in 100 ml. of methanol was saturated with dry hydrogen chloride, finally with cooling in ice. After standing at room temperature overnight, the reaction mixture was refluxed for twenty minutes. After cooling in the refrigerator, the mixture was filtered and washed with methanol, yielding 11.7 g. of the hydrochloride of the ester, V (R = $CH_3$).

A portion of the hydrochloride was dissolved in water. Upon adding sodium hydroxide, the ester, m. p. 79–80.5°, precipitated.

Other esters required refluxing for a longer time (up to twenty-four hours) in order to get satisfactory yields. In most cases the product was isolated as described in the last paragraph under Procedure B.

**Procedure D. Methyl *p*-(2-Amino-2-methylpropylamino)-benzoate.**—A solution of 130 g. of methyl *p*-(2-nitro-2-methylpropylamino)-benzoate in 1000 ml. of methanol, to which was added 10 g. of Raney nickel, was hydrogenated at 100° and 1000 p.s.i. After filtering off the catalyst, the methanol was distilled and the remaining liquid distilled under reduced pressure. There was obtained 94.5 g. of the ester, b. p. 160–161° at 1 mm., which solidified upon standing, m. p. 79–81°.

γ-Diethylaminopropyl *p*-(2-nitro-2-methylpropylamino)-benzoate was hydrogenated in benzene. The amine was purified by washing with aqueous sodium hydroxide, drying over anhyd. sodium carbonate and removing the solvent under reduced pressure.

**Procedure E. *p*-(2-Dimethylamino-2-methylpropylamino)-benzoic Acid.**—To 41.6 g. (0.2 mole) of *p*-(2-amino-2-methylpropylamino)-benzoic acid was added 50 ml. of formalin and 52 ml. of 98% formic acid. In about fifteen minutes the flask was placed in an oil-bath heated to 140° and the mixture was allowed to reflux for four hours. After adding 24 ml. of concd. hydrochloric acid to the hot reaction mixture, it was evaporated to dryness under reduced pressure with warming on the steam-bath. After adding 50 ml. of warm water and cooling in the refrigerator, the mixture was filtered and the solid washed with water, yielding 37.1 g. of the hydrochloride of the acid, m. p. 256° (dec.).

A sample of the hydrochloride was dissolved in boiling water and sufficient 20% aqueous sodium hydroxide was added to make the solution faintly basic. Filtering and washing with hot water gave the free acid, m. p. 238° (dec.).

Esters prepared in this manner were purified as in Procedure C.

## Summary

A number of esters of *p*-(2-nitro-2-methylpropylamino)-, *p*-(2-amino-2-methylpropylamino)- and *p*-(2-dimethylamino-2-methylpropylamino)-benzoic acid have been prepared.

GREENCASTLE, INDIANA RECEIVED NOVEMBER 15, 1948

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Ring Substituted Benzoylacrylic Acids as Antibacterial Agents

BY FRED. K. KIRCHNER, JOHN HAYS BAILEY AND CHESTER J. CAVALLITO

In an investigation of model antimicrobial compounds containing unsaturated lactone or carbonyl structures, one of the types which appeared to be of interest because of its solubility and activity against both gram positive and gram negative bacteria was benzoylacrylic acid. Worrall[1] has reported antibacterial activity of methyl and propyl esters of the acid and Rinderknecht, *et al.*,[2] have observed activity of the acid as well as the *p*-chloro-, 2,4-dichloro- and *p*-acetamido derivatives.[2,3]

Observations have been made relative to some non-ionic antibiotics that the degree of activity against gram positive bacteria was associated with the lipophilic properties of the compound.[4,5] It was of interest to determine whether this relationship could be shown with the anionic benzoylacrylic acids.

Para alkyl-substituted β-benzoylacrylic acids

(1) Worrall, "Med. World" (London), 1946, 2 pp., *C. A.*, **41**, 6598 (1947).

(2) Rinderknecht, Ward, Bergel and Morrison, *Biochem. J.*, **41**, 463 (1947).

(3) British Patent 588,108; *C. A.*, **42**, 329 (1948).

(4) Small, Bailey and Cavallito, THIS JOURNAL, **69**, 1710 (1947).

(5) Cavallito and Bailey, *J. Bact.*, in press.

have been prepared with substituent groups ranging from methyl to dodecyl. A marked increase in activity against gram positive bacteria resulted up to approximately the nonyl derivative, beyond which there was a decrease. The *p*-methoxy and ethoxy derivatives were of the same order of activity as the methyl and ethyl compounds. The 2,4-dihydroxy derivative was prepared with some difficulty and was found to be less active than benzoylacrylic acid. The *m*-nitro-, *p*-chloro- and *p*-bromobenzoylacrylic acids were only moderately active.

The benzoylacrylic acids prepared were presumably all of the *trans* form.[6] Orientation in the benzene ring was determined by hypobromite oxidation of the benzoylacrylic acids to the corresponding alkylbenzoic acids.

Unsaturated lactones and other carbonyl derivatives have been indicated to inhibit growth by reaction with biologically essential —SH and possibly amino groups.[7,8] It was thus of interest to determine the nature of the reaction of cysteine with benzoylacrylic acid. An amphoteric reaction product was obtained and it appeared to be a simple addition product of cysteine to the —CO—CH=CH—COOH system to yield the —CO—$CH_2$—CH(SR)—COOH type of derivative. The cysteine derivative retained considerable antibacterial activity which is believed to result from the ease of dissociation of the addition product to regenerate benzoylacrylic acid.

The low activity of 2,4-dihydroxybenzoylacrylic acid is believed to result from interruption of the conjugated system by chelation involving the carbonyl and the 2-hydroxy group. It would be of interest to determine whether the alkyl substituted phenylglyoxylic acids of Hunsberger and Amstutz[9] would be more active if devoid of the orthohydroxy group.

With the lichesterinic acid type of antibiotic[10] it was found that the unsaturated structure was subordinate to the surface-active properties in contributing to antibacterial activity. The higher alkyl-substituted benzoylacrylic acids, on the other hand, have been found to be relatively poor surface tension depressants. The importance of the double bond in contributing to antibacterial activity was demonstrated by *p*-hexylbenzoylacrylic acid which was approximately one-hundred fold as active as *p*-hexylbenzoylpropionic acid.

## Experimental[11]

**Phenyl Alkyl Ketones.**—Except for propiophenone, which was purchased, the ketones were prepared through the Friedel–Crafts reaction. The acid chlorides were prepared according to Bauer's recommendation.[12]

**Alkyl Benzenes.**—Toluene, and ethyl and isopropyl benzene, were purchased and redistilled before use. The *t*-butylbenzene was prepared by the method of Norris and Sturgis.[13] The remaining *n*-alkyl benzenes were obtained by the Wolff–Kishner reduction of the phenyl *n*-alkyl ketones, using the Huang-Minlon modification.[14]

The constants previously reported[15] for *n*-decylbenzene were determined on a substance whose structure was questioned. Reduction of the *n*-nonyl phenyl ketone gave *n*-decylbenzene of b. p. 115–116° (2 mm.), and $n^{25}D$ 1.4816.

*Anal.* Calcd. for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.17; H, 11.76.

**β-(4-Alkylbenzoyl)-acrylic Acids.**—The methyl derivative was prepared using an excess of toluene as a solvent.[16] The other alkyl derivatives were prepared by the following general procedure. In a suitably equipped flask, cooled with an ice-bath, were placed 0.20 mole of the alkyl benzene, 0.21 mole of powdered maleic anhydride, and 300 ml. of dry carbon disulfide. There was added in small portions with stirring a total of 0.42 mole of anhydrous aluminum chloride. When the addition was complete the ice-bath temperature was maintained for twenty minutes longer, whereupon the ice-bath was removed and stirring was continued at room temperature for four hours. The flask then was warmed gently for two hours, with continued stirring.

At the end of this period the cooled reaction mixture was decomposed with 300 g. of ice and 10 ml. of concentrated hydrochloric acid. The resulting mixture was steam-distilled and the yellow residue was taken up in ether and the ether solution dried with Drierite.

After removing the Drierite and ether, the yellow residue was recrystallized from a hot benzene–Skellysolve B mixture, or from hot Skellysolve B alone. In this manner there was obtained the compounds listed in Table I.

With the isopropyl and the *t*-butyl derivatives the above procedure was modified at one point. When the aluminum chloride addition was completed, the stirring was continued for four hours at ice-bath temperature, then two hours at room temperature.

The orientation of the substituents in the benzene ring was determined by the sodium hypobromite oxidation[17] of the acrylic acids to known alkylbenzoic acids, and comparison of their constants. The melting point of 4-*n*-octylbenzoic acid was found to be 98–99°, in close agreement with Zaki and Fahim. Beran[18] had reported a melting point of 139°. Melting points for the 4-*n*-nonyl-, 4-*n*-decyl- and 4-*n*-dodecylbenzoic[19] acids were not found in the literature; therefore, we are reporting the following values based on analytically pure samples.

4-*n*-Nonylbenzoic acid, m. p. 96–97° (cor.)

*Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.38; H, 9.56.

4-*n*-Decylbenzoic acid, m. p. 95–96° (cor.)

*Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.53; H, 9.77.

4-*n*-Dodecylbenzoic acid, m. p. 93–95° (cor.)

*Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.60; H, 10.42. Found: C, 78.44; H, 10.20.

The above acids, oxidized with potassium permanganate, gave terephthalic acid, identified through its methyl ester, m. p. 140°.

(6) Lutz and Scott, *J. Org. Chem.*, **13**, 284 (1948).

(7) Cavallito and Haskell, THIS JOURNAL, **67**, 1991 (1945).

(8) Geiger, *Arch. Biochem.*, **16**, 423 (1948).

(9) Hunsberger and Amstutz, THIS JOURNAL, **70**, 671 (1948).

(10) Cavallito, Fruehauf and Bailey, *ibid.*, **70**, 3724 (1948).

(11) In the experimental section physical constants and analyses are reported only for those compounds which have not been reported previously, and for those whose preparation or properties differ from that found in the literature.

(12) Bauer, *Oil and Soap*, **23**, 1 (1946).

(13) Norris and Sturgis, THIS JOURNAL, **61**, 1413 (1939).

(14) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(15) Francis, *Chem. Rev.*, **42**, 144 (1948).

(16) von Pechmann, *Ber.*, **15**, 881 (1882).

(17) Zaki and Fahim, *J. Chem. Soc.*, 307 (1942).

(18) Beran, *Ber.*, **18**, 139 (1885).

(19) Balle, Wagner and Nold, U. S. Patent 2,195,198, report the preparation of a *n*-dodecylbenzoic acid, but give no melting point.

TABLE I

ANALYTICAL, PHYSICAL AND ANTIBACTERIAL PROPERTIES

| $RC_6H_4COCH=CHCOOH$ R | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | M. p., °C.[a] | Surface tension,[b] dynes per cm. | Minimum bacteriostatic[c] concn. as moles per ml. × $10^4$ *Staphylococcus aureus 209* | *Cl. perfringens* | *M. tuberculosis H37Rv* | *E. coli* | *K. pneumoniae* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hydrogen[i] | 68.18 | 68.00 | 4.58 | 4.53 | 93–94 | 72.6 | 7.5 | 12.5 | 25.0 | 25 | 100 |
| 4-Methyl | 69.46 | 69.52 | 5.30 | 5.34 | 139–140 | 70.4 | 5 | 12.5 | 7.5 | 25 | 75 |
| 4-Ethyl | 70.57 | 70.72 | 5.93 | 5.77 | 105–106 | 72.1 | 1 | 3.75 | 5.0 | 25 | 75 |
| 4-*n*-Propyl | 71.54 | 71.54 | 6.46 | 6.67 | 87–89 | 70.2 | 0.5 | 3.75 | 1.0 | 25 | 75 |
| 4-*n*-Butyl | 72.39 | 72.39 | 6.94 | 6.67 | 90–91 | 72.1 | 0.1 | 1.25 | 0.5 | 25 | 75 |
| 4-*n*-Amyl | 73.15 | 72.91 | 7.37 | 7.56 | 81–82 | 66.0 | 0.075 | 1.25 | 0.1 | 50 | 50 |
| 4-*n*-Hexyl | 73.82 | 73.83 | 7.74 | 7.72 | 86–87 | 68.0 | 0.05 | 3.75 | 0.05 | 25 | 75 |
| 4-*n*-Heptyl | 74.42 | 74.64 | 8.08 | 8.26 | 79–80 | 60.0 | 0.025 | 0.05 | 0.01 | 10 | >10 |
| 4-*n*-Octyl | 74.97 | 75.07 | 8.39 | 8.26 | 77–78 | 50.1 | 0.0075 | 0.0375 | 0.005 | 10 | >10 |
| 4-*n*-Nonyl | 75.46 | 75.78 | 8.67 | 8.55 | 82–83 | 33.8 | 0.025 | 0.025 | 0.01 | ... | ... |
| 4-*n*-Decyl | 75.91 | 75.81 | 8.92 | 8.78 | 82–83 | 34.6 | 0.025 | 0.0025 | 0.0075 | ... | ... |
| 4-*n*-Dodecyl | 76.70 | 76.76 | 9.37 | 9.13 | 81–82 | 53.6 | <0.01[h] | <0.05[h] | <0.01[h] | ... | ... |
| 4-*i*-Propyl | 71.54 | 71.58 | 6.46 | 6.57 | 95–98 | 72.6 | 0.5 | 0.25 | 5.0 | 10 | 50 |
| 4-*t*-Butyl[j] | 72.39 | 72.17 | 6.94 | 7.06 | 123–125 | 72.0 | 0.25 | 0.125 | 5.0 | 25 | 50 |
| 4-Methoxy | 64.07 | 64.20 | 4.89 | 5.01 | 129–131 | .. | 10.0 | 2.5 | 10 | 25 | 75 |
| 4-Ethoxy | 65.44 | 65.31 | 5.49 | 5.20 | 141–145 | .. | 2.5 | 2.5 | 10 | 25 | 75 |
| 4-Hexyloxy | 69.54 | 69.55 | 7.30 | 7.41 | 118–119 | .. | 0.25 | 0.5 | 0.5 | >10 | >10 |
| 4-Chloro[d] | 57.02 | 56.99 | 3.35 | 3.34 | 156–157 | .. | 2.5 | 3.75 | 10 | 25 | 50 |
| 4-Bromo[e] | 47.09 | 47.15 | 2.77 | 2.77 | 159–160 | .. | 2.5 | 3.75 | 7.5 | 25 | 50 |
| 3-Nitro[f] | 54.30 | 54.58 | 3.19 | 3.19 | 190–192 | .. | 50 | 25.0 | 50.0 | 100 | >100 |
| 2,4-Dihydroxy | 57.69 | 57.43 | 3.87 | 4.17 | 195 | .. | >100 | >100 | >100 | >100 | >100 |
| Cysteine deriv. of benzoylacrylic acid[g] | 52.51 | 52.62 | 5.08 | 5.14 | 160–161 (dec.) | | 25 | 12.5 | 50 | 25 | >100 |
| β-4-*n*-Hexylbenzoyl propionic acid | 73.25 | 73.42 | 8.46 | 8.51 | 97–98 | 67.8 | 5 | 12.5 | 0.25 | >100 | 100 |

[a] Corrected. [b] Solvent is 0.1 molar potassium phosphate buffer of *p*H 7; solvent surface tension = 72.0 dynes per cm. Measurements made with a Du Nouy interfacial tensiometer at 27°. Concentration of acids = $7 \times 10^{-3}$ moles per ml. [c] The bactericidal activity is approximately one-tenth the bacteriostatic power. [d] Calcd.: Cl, 16.84. Found: Cl, 16.90. [e] Calcd.: Br, 31.33. Found: Br, 30.90. [f] Calcd.: N, 6.33. Found: N (Kjeldahl), 6.01. [g] Calcd.: N, 4.71. Found: N (Kjeldahl), 4.70. [h] Lack of solubility prevented attaining a bacteriostatic concentration. [i] Fieser and Fieser, THIS JOURNAL, **57**, 1679 (1935). [j] Price, *et al.*, *J. Org. Chem.*, **7**, 517 (1942).

**β-(2,4-Dihydroxybenzoyl)-acrylic Acid.**[20]—In a round-bottom flask were placed 40 g. (0.4 mole) of resorcinol, 40 g. (0.41 mole) of powdered maleic anhydride, and 600 ml. of freshly-distilled nitrobenzene. A solution of 108 g. (0.81 mole) of anhydrous aluminum chloride in 300 ml. of nitrobenzene was added dropwise to the stirred solution over a period of ninety minutes, keeping the temperature of the reaction mixture between 20–30°. When the addition was complete stirring was continued for three hours longer, maintaining the temperature at 50–60°. At the end of this period the stirring was discontinued and the reaction allowed to cool to room temperature and stand overnight.

To the reaction mixture was added 300 ml. of ice-cold 12% hydrochloric acid solution and the mixture was stirred for three hours while keeping the temperature at 0–10°. At the end of this period the supernatant liquors were decanted from the brown, viscous mass which had formed. The latter was washed several times with benzene, then crystallized from 60% ethanol. A second smaller crop of the product was obtained by concentrating and cooling the nitrobenzene liquor. The orange-colored product was dried at 100° to give a lemon-yellow compound of m. p. 195°, yield 20–25%.

Catalytic hydrogenation of the unsaturated acid with platinum catalyst gave β-(2,4-dihydroxybenzoyl)-propionic acid, m. p. 199–200°, previously reported by Desai and Shroff.[21]

**Other β-Substituted Benzoylacrylic Acids.**—The 4-methoxy,[22] 4-ethoxy,[23] 4-chloro,[24] 4-bromo,[25] and 3-nitro[26] compounds were prepared according to procedures in the literature.

The hexyloxy compound was prepared according to the method used for the *n*-alkyl derivatives with a slight modification. After the addition of the aluminum chloride was complete, the reaction mixture became so viscous that it was allowed to stand at room temperature for five hours. At the end of this period the solvent was decanted and the viscous mass decomposed with ice and concentrated hydrochloric acid. The required hexyloxybenzene[27] was prepared according to a procedure given by Vogel.[28]

(20) Bogert and Ritter, *Proc. Nat. Acad. Sci. Washington*, **10**, 363 (1924); *cf.* Thomas "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Pub. Corp., N. Y., 1941, p. 581. In the original article the authors make no mention of an attempt to prepare this acid. However, the article in Thomas states that Bogert and Ritter had obtained only fumaric acid in attempting to condense resorcinol with maleic anhydride in the presence of aluminum chloride and carbon disulfide.

(21) Desai and Shroff, *J. Univ. Bombay*, **10**, Pt. 3, 97 (1941).

(22) Dave and Nargund, *ibid.*, **7**, Pt. 3, 191 (1938).

(23) Rice, THIS JOURNAL, **46**, 2319 (1924).

(24) Rinderknecht, *et al.*, *Biochem. J.*, **41**, 463 (1947).

(25) Kohler and Woodward, THIS JOURNAL, **58**, 1933 (1936).

(26) Bogert and Ritter, *ibid.*, **47**, 526 (1925).

(27) Tronow and Ladigina, *Ber.*, **62**, 2844 (1929).

(28) Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., N. Y., 1948, p. 641.

The hexyloxy compound was oxidized[17] to the known 4-*n*-hexyloxybenzoic acid.[29]

**β-(4-*n*-Hexylbenzoyl)-propionic Acid.**—This compound was prepared in the same manner as the majority of the aroylacrylic acids. The compound was oxidized[17] to the known 4-*n*-hexylbenzoic acid.

**Reaction Product of β-Benzoylacrylic Acid with Cysteine.**—Three grams (0.017 mole) of β-benzoylacrylic acid was dissolved in 12 ml. of water and the solution adjusted to *p*H 7 with aqueous sodium hydroxide solution. A solution of 2.68 g. (0.017 mole) of cysteine hydrochloride in 12 ml. of water was treated with aqueous sodium hydroxide until the *p*H was 7. The solutions were mixed and allowed to stand overnight.

The mixture had become slightly yellow and the *p*H was 7.3. Dilute hydrochloric acid was added dropwise until *p*H 2 was reached. The white precipitate was filtered off, washed several times with water, then recrystallized from 60% ethanol solution.

**Antibacterial Tests.**—The compounds were tested as growth inhibitors of *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae* in nutrient broth by the serial dilution method using as an inoculum, 1 ml. of a 1:1000 dilution of a twenty-four hour culture of the test organism and a final volume of 5 ml. in each tube. Incubation was for eighteen hours at 37°. Tests with *Clostridium perfringens* and *Mycobacterium tuberculosis* H37Rv were conducted as previously described.[10] To avoid fluctuations in susceptibility of the test organisms, all compounds of a series were tested against a single organism at the same time and benzoylacrylic acid was used as a reference test compound for series of tests conducted on different days.

**Acknowledgment.**—The authors wish to express their appreciation for the analytical determinations and the corrected melting points which were carried out under the direction of Mr. M. E. Auerbach in the Analytical Laboratories of this Institute. We are indebted to Dr. F. C. Nachod and his staff for the surface-tension measurements. We are appreciative also of the technical assistance given by Mrs. G. W. Schraver during the course of this investigation.

(29) Jones, *J. Chem. Soc.*, 1874 (1935).

## Summary

1. A number of substituted β-aroylacrylic acids were prepared and their antibacterial activity determined *in vitro*.

2. With the *n*-alkyl series there was a noticeable increase in activity against gram positive bacteria as the length of the alkyl chain was increased, the $C_9$ chain being approximately the optimum chain length. The antibacterial activity appears to result from the presence of the highly conjugated benzoylacryl- system which may react with biologically essential —SH groups; the lipophilic ring substituents quantitatively increase the activity against gram positive bacteria.

3. The following 4-*n*-alkylbenzoic acids are considered to be reported for the first time: *viz.*, *n*-nonyl, *n*-decyl and *n*-dodecyl.

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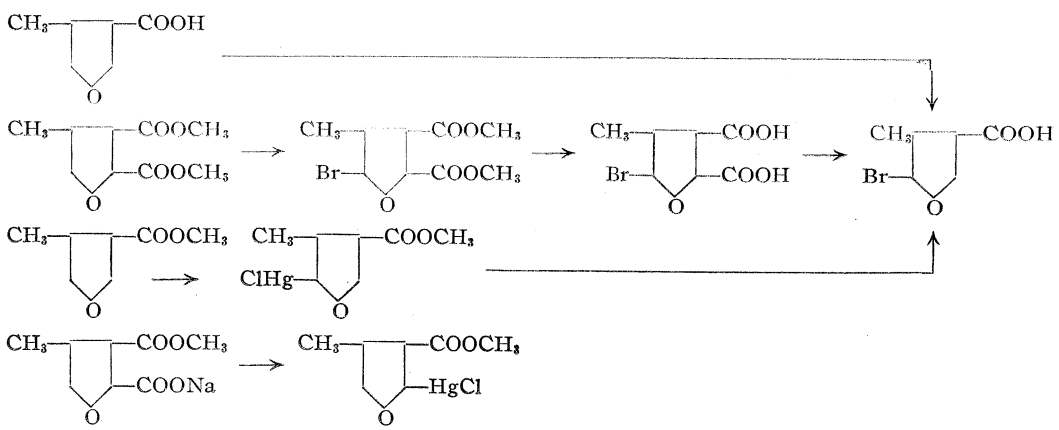
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Orientation in the Furan Nucleus. XII. 3-Methyl-4-furoic Acid and Some of its Derivatives

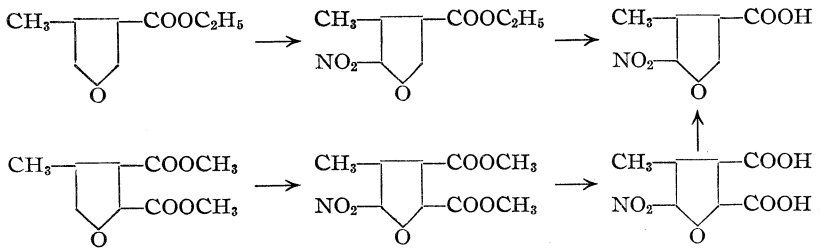
BY HENRY GILMAN AND ROBERT R. BURTNER[1]

In a previous paper dealing with orientation of β-substituted furans[2] the prediction was made on the basis of evidence then available that nuclear substitution of 3-methyl-4-furoic acid would involve replacement of hydrogen on the 2-position. The validity of this assumption as regards bromination of the acid, mercuration of the methyl ester, and nitration of the ethyl ester has now been established by a sequence of reactions as shown.



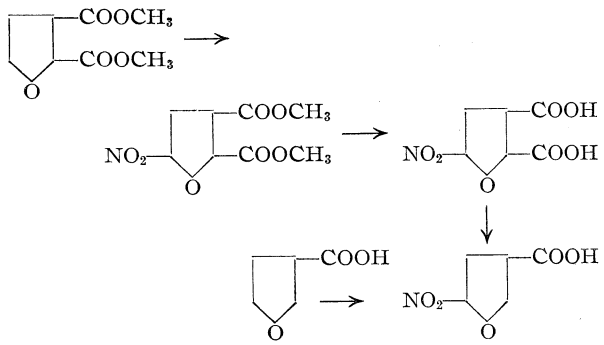

(1) Present address: G. D. Searle & Co., Chicago, Ill.

(2) Gilman and Burtner, THIS JOURNAL, **55**, 2903 (1933).



The above transformations are based on the nominal yields of products isolated from these somewhat sensitive compounds.

In addition, the position of the nitro group in 2-nitro-4-furoic acid[2] has been definitely established in the following manner



## Experimental Part

**2-Bromo-3-methyl-4-furoic acid.**—Nine and six-tenths grams (0.06 mole) of bromine was added dropwise to a stirred solution of 6.3 g. (0.05 mole) of 3-methyl-4-furoic acid[3] in 40 ml. of acetic acid at 15–20°. The reaction mixture was then stirred for twelve hours at laboratory temperature, placed under reduced pressure for one hour to remove excess bromine and finally poured onto 250 g. of ice. The crude product was filtered, crystallized from hot water and sublimed in vacuum to yield 2 g. of the acid melting at 163–164°.

*Anal.* Calcd. for $C_6H_5O_3Br$: Br, 39.02. Found: Br, 39.11.

**Methyl 2-Chloromercuri-3-methyl-4-furoate.**—A solution of 2.5 g. (0.017 mole) of methyl 3-methyl-4-furoate in 10 ml. of ethanol was added to a solution of 4.6 g. (0.017 mole) of mercuric chloride and 2.88 g. (0.034 mole) of anhydrous sodium acetate in 100 ml. of water. The mixture was stirred for twelve hours, filtered to remove a flocculent white precipitate and the filtrate gently refluxed with stirring for four hours. Filtration of the cooled mixture yielded a second crop of the crude mercurial. Both fractions were combined and crystallized from ethanol to give 2 g. of the desired material, which melted at 175°.

*Anal.* Calcd. for $C_7H_7O_3ClHg$: Hg, 53.49. Found: Hg, 53.18.

**Conversion of Methyl 2-Chloromercuri-3-methyl-4-furoate to 2-Bromo-3-methyl-4-furoic Acid.**—One and two-tenths grams (0.0075 mole) of bromine was added to a stirred suspension of 1.8 g. (0.005 mole) of the mercurial in 15 ml. of acetic acid at laboratory temperature. There was a mild heat effect, and the mercurial dissolved. The solution was stirred for three hours, diluted with 400 ml. of water and the excess bromine reduced with sulfur dioxide. The mixture was then saturated with hydrogen sulfide, refluxed for one hour and filtered hot to remove the mercuric sulfide. Ether extraction of the cold filtrate yielded a yellow crystalline solid, which after crystallization from water melted at 161°. A mixed melting point determination proved this acid to be identical with that described above.

**2-Bromo-3-methylfuran-4,5-dicarboxylic Acid.**—Six and four-tenths grams (0.04 mole) of bromine was added dropwise at 20° to a stirred solution of 4.4 g. (0.022 mole) of dimethyl 3-methylfuran-4,5-dicarboxylate[3] in 25 ml. of chloroform. The mixture was stirred for three hours longer after which the solvent and excess bromine were removed under reduced pressure. The residual crystals, after being washed with a small amount of ether, melted at 131–132°. Saponification was effected by refluxing for three hours with an alcoholic solution of potassium hydroxide. Removal of the solvent followed by solution of the residue in water and acidification yielded 1.5 g. of a colorless acid melting at 257° with gas evolution.

*Anal.* Calcd. for $C_7H_5O_5Br$: Br, 32.13. Found: Br, 31.5.

**Decarboxylation of 2-Bromo-3-methylfuran-4,5-dicarboxylic Acid.**—A solution of 1.1 g. (0.004 mole) of the bromo acid, 1.2 g. (0.004 mole) of mercuric chloride and 0.25 g. of sodium hydroxide in 40 ml. of water was refluxed for one hour, by which time carbon dioxide evolution had ceased. The mixture was made alkaline to phenolphthalein with sodium hydroxide, filtered and the filtrate acidified. After dilution with water to a volume of 200 ml. and saturation with hydrogen sulfide the mixture was boiled briefly, filtered and the filtrate chilled. The product thus obtained was recrystallized from water to yield 0.3 g. of an acid which melted at 165°. A mixed melting point determination showed this acid to be identical with that obtained by direct bromination of 3-methyl-4-furoic acid.

**3-Methyl-4-carbomethoxy-5-furoic Acid.**—A solution of 12 g. (0.06 mole) of dimethyl 3-methylfuran-4,5-dicarboxylate and 3.4 g. (0.06 mole) of potassium hydroxide in 60 ml. of methanol was refluxed until it was no longer alkaline to phenolphthalein. After removal of the solvent under reduced pressure the residue was dissolved in 15 ml. of water, acidified and the crude product filtered. Crystallization from 50% ethanol and finally from benzene gave 8.5 g. of the desired product melting at 119.5°.

*Anal.* Calcd. for $C_8H_8O_5$: C, 55.10; H, 4.08; neut. equiv., 184. Found: C, 55.01; H, 4.36; neut. equiv., 182.7.

**3-Methyl-4-carbomethoxy-5-chloromercurifuran.**—Four grams (0.021 mole) of 3-methyl-4-carbomethoxy-5-furoic acid was dissolved in 40 ml. of water containing 0.84 g. (0.021 mole) of sodium hydroxide and added to a solution of 5.7 g. (0.021 mole) of mercuric chloride in 100 ml. of water. After standing for one and one-half hours the mixture was filtered and the filtrate refluxed with stirring for thirty minutes at which point carbon dioxide evolution had ceased. The precipitate, obtained by filtering the chilled reaction mixture, was extracted with boiling methanol for one and one-half hours. The chilled extract yielded a small amount of an unidentified white crystalline solid which decomposed at 235–240°. After a week's storage in the refrigerator the alcoholic filtrate was evaporated to yield a pale yellow crystalline material which upon recrystallization from methanol melted at 141–142°. A mixture of this mercurial with the isomeric 5-chloromercuri derivative melted at 122°.

*Anal.* Calcd. for $C_7H_7O_3ClHg$: Hg, 53.49. Found: Hg, 53.08.

**2-Nitro-3-methyl-4-furoic Acid.**—A solution of 9 g. (0.06 mole) of ethyl 3-methyl-4-furoate in 12 ml. of acetic anhydride was added dropwise with stirring at −10° to a nitrating mixture prepared in the customary manner from 18.9 g. (0.3 mole) of nitric acid (sp. gr. 1.51) and 30 ml. of acetic anhydride. The mixture was stirred for

(3) Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

thirty minutes longer at −10° and then poured onto 150 g. of ice. The excess acid was carefully neutralized with 40% sodium hydroxide and the mixture extracted with ether. The extract was immediately treated with 20 ml. of pyridine and allowed to stand for twelve hours in the refrigerator. Removal of the solvent and acidification of the residue with an excess of ice cold 10% hydrochloric acid gave the crude ester, which after crystallization from methanol, weighed 5 g. and melted at 42°.

*Anal.* Calcd. for $C_8H_9O_5N$: C, 48.24; H, 4.52. Found: C, 48.15; H, 4.71.

The ester was hydrolyzed by refluxing for two hours with a solution of 10 g. of sulfuric acid and 25 ml. of water. The acid melted at 194° after crystallization from water.

*Anal.* Calcd. for $C_6H_5O_5N$: C, 42.10; H, 2.92. Found: C, 41.93; H, 3.08.

This acid may also be obtained by direct nitration of 3-methyl-4-furoic acid. Twelve and one-half grams of the acid was added portionwise at −15° to a stirred nitrating mixture prepared from 36.6 g. of nitric acid (sp. gr. 1.51) and 78 ml. of acetic anhydride. The mixture was stirred for one hour longer at −10°, poured onto 500 g. of ice and extracted with ether. The solvent was evaporated and the crude product crystallized from water to give 4.2 g. of the acid melting at 193°.

**2-Nitro-3-methylfuran-4,5-dicarboxylic Acid.**—Five grams of dimethyl 3-methylfuran-4,5-dicarboxylate was added in small portions with stirring at −10° to a nitrating mixture composed of 7.9 g. of nitric acid (sp. gr. 1.51) and 12 ml. of acetic anhydride. Stirring was continued for one hour at −10°, followed by dilution with ice, extraction and treatment with pyridine as previously described. The crude nitro ester was hydrolyzed by refluxing for seven hours with a solution of 10 g. of sulfuric acid and 25 ml. of water. After treatment with decolorizing charcoal the hot filtrate was chilled to give the crude acid. Crystallization from benzene yielded 1.5 g. of the acid melting at 218°.

*Anal.* Calcd. for $C_7H_5O_7N$: C, 38.88; H, 2.31; neut. equiv., 108. Found: C, 38.78; H, 2.81; neut. equiv., 107.3.

**Decarboxylation of 2-Nitro-3-methylfuran-4,5-dicarboxylic Acid.**—One-tenth gram of the dicarboxylic acid contained in a long, narrow test-tube was heated in a metal-bath at 225°. Carbon dioxide was evolved, and a white crystalline solid condensed on the upper walls of the tube. This material melted at 194° and showed no depression in melting point when mixed with samples of 2-nitro-3-methyl-4-furoic acid previously described.

**Dimethyl 2-Nitrofuran-4,5-dicarboxylate.**—A solution of 6.2 g. (0.033 mole) of dimethyl furan-2,3-dicarboxylate[4] in 9 ml. of acetic anhydride was added dropwise at −10° to a stirred nitrating mixture prepared from 10.3 g. (0.16 mole) of nitric acid (sp. gr. 1.51) and 15.6 ml. of acetic anhydride. The mixture was stirred for an additional hour at −10°, poured onto ice, neutralized with caustic solution, extracted with ether and the extract treated with 20 ml. of pyridine. After twelve hours of storage in the refrigerator the solvent was removed and the residue suspended in an excess of ice-cold 10% hydrochloric acid. The crude product thus obtained was crystallized from methanol to give 5.1 g. of the nitro ester melting at 97°.

*Anal.* Calcd. for $C_8H_7O_7N$: C, 41.92; H, 3.05. Found: C, 42.15; H, 3.79.

**Decarboxylation of 2-Nitrofuran-4,5-dicarboxylic Acid.**—Four grams of the above ester was hydrolyzed by refluxing for four hours with a solution of 12 g. of sulfuric acid and 24 ml. of water. The chilled hydrolysate was washed once with chloroform to remove any unchanged ester and then extracted thoroughly with ether. Evaporation of the solvent yielded the crude 2-nitrofuran-4,5-dicarboxylic acid, which after crystallization from a mixture of ether and benzene melted at about 225° with gas evolution.

This material contained in a long, narrow test-tube was heated in a metal-bath at 235°. Carbon dioxide was evolved and a white crystalline solid deposited on the upper part of the tube. Resublimation followed by crystallization from water afforded an acid melting at 137°, which was identical with that obtained by the direct nitration of 3-furoic acid.[2]

## Summary

Bromination of 3-methyl-4-furoic acid, mercuration of the methyl ester, and nitration of the ethyl ester result in substitution in the 2-position. The structure of 2-nitro-4-furoic acid has been established.

(4) Asahina, *et al.*, *Acta Phytochim.*, **2**, 1 (1924).

AMES, IOWA RECEIVED OCTOBER 11, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# The Ultraviolet Absorption Spectra of Aliphatic Sulfides and Polysulfides[1]

JOHN E. BAER[2] AND MARVIN CARMACK

Various organic polysulfides, $RS_xR'$, have been prepared in which R and R′ are simple alkyl groups.[3] Recently interest has been aroused in the 2-chloroethyl polysulfides in connection with the characterization of the by-products of the manufacture of mustard gas by the Levinstein process.[4,5] Other aliphatic polysulfides of particular interest are the Thiokol types of elastomers and possible intermediates in the vulcanization of rubber.

In view of the differing opinions regarding the manner of attachment of the sulfur atoms in the organic polysulfides, new methods for the recognition of different types of linkages are of interest, particularly methods which do not alter the polysulfide groups chemically.

We have found that aliphatic polysulfides have intense and characteristic ultraviolet absorption

(1) The essential material of this paper was presented before the Organic Division of the American Chemical Society at the National Meeting in Chicago, Illinois, April 22, 1948. It is from the Ph.D. dissertation of John E. Baer, accepted by the Faculty of the Graduate School of Arts and Sciences of the University of Pennsylvania, June, 1948.

(2) Abbott Laboratories Fellow, 1946–1947. Present address: Department of Chemistry, Carleton College, Northfield, Minnesota.

(3) R. Connor, "Organic Chemistry," (ed. H. Gilman), John Wiley and Sons, New York, N. Y., ed. 2, 1943, Vol. I, p. 864.

(4) Fuson, Price, Burness, Foster, Hatchard and Lipscomb, *J. Org. Chem.*, **11**, 487 (1946).

(5) Macy, Jarman, Morrison and Reid, *Science*, **106**, 355 (1947).

spectra. The locations of the peaks and the intensities differ widely depending upon the number of sulfur atoms in the polysulfide function. Consequently, the preliminary results suggest that spectrometric measurements may afford a convenient method for the qualitative identification of different types of polysulfides. In some cases, also, absorption spectrometry may be applied to the analysis of mixtures.

We were led to investigate the absorption spectra of polysulfides by the following considerations. (1) Simple mercaptans and alkyl sulfides, unlike most organic compounds containing no multiple linkages, show a characteristic sharp absorption band in the far ultraviolet region (near 200 mμ).[6] Appearance of such a peak indicates that the unshared electrons of the sulfur atom can be excited by frequencies of light possessing about the same energy as those which excite the carbon-carbon double bond. (2) Many chemical analogies between the —S̈— and the —C=C— groups have been observed and classified under the general term, isosterism, based upon similarities in the electronic systems. (3) Resonance forms of compounds containing the —S̈— function have been postulated[7] in which the sulfur atom expands its valence shell to ten or more electrons; such assumptions are considered necessary to account for dipole moments and other physical and chemical properties of certain sulfur-containing compounds.

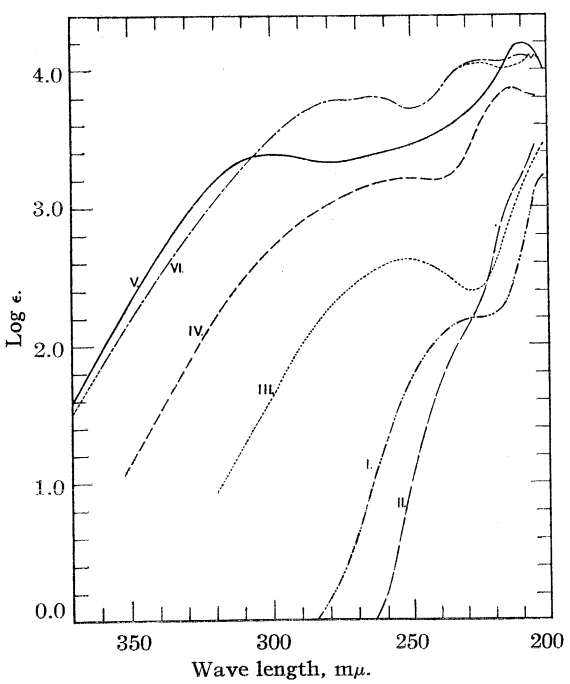



Fig. 1.—Curve I, *n*-hexadecyl mercaptan; II, *n*-hexadecyl sulfide; III, *n*-hexadecyl disulfide; IV, *n*-hexadecyl trisulfide; V, *n*-hexadecyl tetrasulfide; VI, sulfur ($S_8$) in hexane and alcohol (except dotted portion below 230 mμ showing deviation in alcohol).

The facts cited above lead one to expect that, in the disulfides and polysulfides, the groupings of linked sulfur atoms will behave optically somewhat like conjugated systems of carbon–carbon double bonds, as, for example, in the conjugated polyene hydrocarbons. That is, the peak of light absorption will increase in intensity and shift toward longer wave lengths as the number of conjugated sulfur atoms in the functional group increases. Some evidence of conjugation between sulfide groups and other functional groups containing double bonds has been noted in other connections in This Laboratory.[8]

Crystalline *n*-hexadecyl trisulfide and *n*-hexadecyl tetrasulfide[9] were chosen as particularly suitable reference compounds. Since these two compounds can be readily synthesized in good yields by straightforward methods and give the ordinary indications of homogeneity (sharpness and reproducibility of melting points and constancy of composition), there is little reason to doubt their true polysulfide nature and freedom from contamination with elementary sulfur. Furthermore, *n*-hexadecyl disulfide, *n*-hexadecyl sulfide, and *n*-hexadecyl mercaptan are all available and are well-defined, low-melting crystalline solids,[10] readily soluble in paraffinic solvents in which ultraviolet absorption spectra are relatively little complicated by solvent effects.

Figure 1 shows the absorption spectra of RSH (I) (R = $n$-$C_{16}H_{33}$), $R_2S$ (II), $R_2S_2$ (III), $R_2S_3$ (IV), $R_2S_4$ (V), and $S_8$ (VI) in hexane. The mercaptan and sulfide have spectra very similar to other simple alkyl compounds with these functional groups.[6,8] The mercaptan spectrum shows the typical shoulder at 225 mμ which has been noted with other mercaptans.[1] The absorption maxima for I and II lie just beyond the limits accessible to measurement with the instrument and solvent used. The disulfide (III) exhibits a fairly intense new peak at 252 mμ (log ε 2.63), an indication of conjugation between the unshared electrons on the two sulfur atoms.[11]

The trisulfide (IV) has two maxima: 251 mμ (log ε 3.22) and 213 mμ (log ε 3.87). The absorp-

(6) (a) Purvis, Jones and Tasker, *J. Chem. Soc.*, **97**, 2287 (1910); (b) Hantzsch, *Ber.*, **52**, 1544 (1919); **58**, 612 (1925); (c) Gibson, Graham and Reid, *J. Chem. Soc.*, **123**, 874 (1923); (d) Houston, Canning and Graham, *ibid.*, 965 (1935); (e) Ley and Arends, *Z. physik. Chem.*, **B15**, 311 (1932); (f) Price, *J. Chem. Phys.*, **3**, 256 (1935); (g) Mohler and Sorge, *Helv. Chim. Acta*, **23**, 1200 (1940); Mohler, *ibid.*, **20**, 287, 1188 (1937).

(7) Schomaker and Pauling, THIS JOURNAL, **61**, 1769 (1939).

(8) Fehnel and Carmack, *ibid.*, **71**, 84, 231 (1949).

(9) Clayton and Etzler, *ibid.*, **69**, 974 (1947).

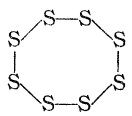
(10) (a) Collin, Hilditch, Marsh and McLeod, *J. Soc. Chem. Ind.* **52**, 272T (1933); (b) Flaschentröger and Wannschaff, *Ber.*, **67**, 1121 (1934).

(11) Ethyl disulfide has an absorption band with a maximum at 249 mμ (log ε 2.63) (ref. 6e). Cystine has also been reported to exhibit a similar peak, Anslow and Foster, *J. Biol. Chem.*, **97**, 37 (1932).

tion is much more intense for the trisulfide than for the disulfide.[12]

The tetrasulfide (V) shows two maxima: 300 mμ (log ε 3.39) and 209 mμ (log ε 4.19). The whole absorption curve for the tetrasulfide is more intense than that of the trisulfide, and the first peak is shifted markedly toward the visible region compared with the trisulfide.

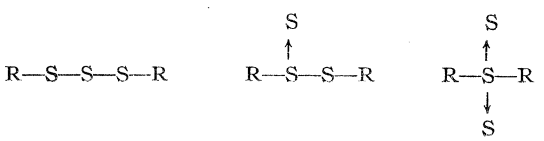
The absorption spectrum of solutions of molecular sulfur is of interest not only to permit an evaluation of its contribution to the absorption of mixtures in which it may be present, but also because the ordinary $S_8$ molecule provides a structural model in which the mode of attachment of multiple units of sulfur atoms has been established by independent methods[13] and in which even the geometric relationships are well defined. The structure is considered to be a puckered eight-membered ring, as represented by formula VI.



(VI)

Curve VI of Fig. 1 shows the spectra of solutions of sulfur as determined in both hexane and ethyl alcohol. Curves in the two solvents are identical over a wide range, but differ slightly at short wave lengths. Several peaks and plateaus of high intensity are so broad and tend to merge to such an extent that the determination of the exact locations of the maxima is difficult. It may be noted that the absorption spectra of $S_8$ and of *n*-hexadecyl tetrasulfide have certain features in common: namely, both are nearly congruent from the visible region to approximately 320 mμ, and extinction values are of the same order of magnitude through the whole range investigated.

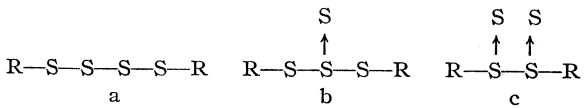
Several structures have been suggested for organic trisulfides (VIIabc)[3,4,5,14,15]; most authorities have favored the linear formulation (VIIa).[3,4]



VII

Recent studies of methyl trisulfide[15] by means of electron diffraction support the linear formulation.

A number of possible structures can be written for tetrasulfides, but the three formulas most seriously considered have been VIIIabc.



VIII

In the conjugated diphenylpolyene series, $C_6H_5(CH{=}CH)_nC_6H_5$, a relationship has been found between the value of $n$ and $\lambda^2$ for the first absorption band.[16] It might be expected that chains of sulfur atoms connected linearly as in the series R–(–S–)$_n$R would show a regular shift of absorption maxima with increasing values of $n$, and that attachment of sulfur atoms along the chain in a non-linear fashion (as in VIIbc and VIIIbc) would be revealed by irregularities which could be correlated with structure.[17]

The correlation of structure with spectra in the polysulfide series is obviously very complicated, and many more compounds will need to be prepared before the relationships can be fully interpreted. It seems likely, for example, that steric relationships among the sulfur atoms of a polysulfide group may have an important influence upon the spectra. Zechmeister, LeRosen, Schroeder, Polgar and Pauling[18] have shown that in the carotenoid polyenes the stereochemical configurations have important, and predictable, influences upon the spectra. Similarly, in the polysulfides it may be expected that rigid polysulfide structures may have somewhat different spectra than acyclic polysulfides for which many stereochemical configurations are possible. The synthesis of other polysulfides, including the cyclic, is under investigation. Determinations of the spectra at lower temperatures may perhaps permit a sharper resolution of the absorption peaks.[19]

(12) That the trisulfide and disulfide should both have one peak at almost the same wave length (251–252 mμ) should probably not be considered particularly significant. The more intense peak of IV centering at 213 mμ has its foot superimposed upon the lower first absorption band, and this makes it difficult to estimate the location of the true center of the first absorption band. If merging of the broad bands did not occur to such an extent, it seems likely that the first band of the trisulfide would have a maximum somewhat nearer the visible region than the first band of the disulfide.

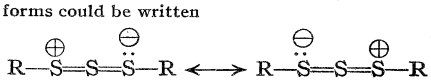
(13) Yost and Russell, "Systematic Inorganic Chemistry," Prentice–Hall, New York, N. Y., 1944, p. 277. Molecular extinction values were calculated on the basis of the molecular formula $S_8$ and it was assumed that the molecular state in solutions at room temperature is the same as in the crystalline state.

(14) Westlake, Mayberry, Whitlock, West and Haddad, THIS JOURNAL, **68**, 748 (1946).

(15) Donohue and Schomaker, *J. Chem. Phys.*, **16**, 92 (1948).

(16) For an excellent recent discussion of this and other similar correlations of structure and spectra, *cf.*, Maccoll, *Quarterly Reviews of the Chemical Society (London)*, **1**, No. 1, 16–58 (1947), especially p. 45.

(17) The assumption of an analogy between the optical behavior of polyene chains and linear polysulfide chains implies that polarization can occur by a transfer of charge along the chain of sulfur atoms. Polarization of the molecule can occur if one sulfur atom accepts an extra pair of electrons from its adjoining neighbor (thus expanding its valence shell to ten electrons). For example, in a linear trisulfide the polar forms could be written



The non-linear structures of polysulfides are generally written with semipolar bonds between the chain sulfur and the extra sulfur atoms, implying a permanent polarization of the molecule; however, if expansion of the sulfur valence shell is possible, then a large number of resonance forms can be written for the non-linear as well as for the linear structures.

(18) Zechmeister, LeRosen, Schroeder, Polgár and Pauling, THIS JOURNAL, **65**, 1941 (1943).

(19) Scott, Sinsheimer and Loofbourow, *Science*, **107**, 302 (1948).

## Experimental

**Preparation and Purification of Compounds.**—*n*-Hexadecyl mercaptan purchased from the Connecticut Hard Rubber Company, m.p. 18°,[10b] was distilled at 0.6 mm., b.p. 135–140°. The middle cut was used for the spectrometric determination and for some of the other preparations described below. Analyses for carbon, hydrogen, and sulfur were satisfactory. ***n*-Hexadecyl sulfide** was prepared by the reaction of *n*-hexadecyl bromide[20] with sodium sulfide in alcohol; after recrystallization from 95% alcohol–hexane, colorless crystals, m.p. 58.2–58.5° (reported m.p. 57.5°[21]); analyses for carbon and hydrogen agreed with theory. ***n*-Hexadecyl disulfide** was prepared from *n*-hexadecyl mercaptan by oxidation with iodine in alcohol according to Collin *et al.*[10a]; recrystallization from acetone gave colorless needles, m.p. 55–55.5° (reported m.p. 54°[10a]). The sample for spectrometric analysis was recrystallized again from glacial acetic acid; analyses for carbon, hydrogen and sulfur agreed with the theoretical. ***n*-Hexadecyl trisulfide** was prepared from *n*-hexadecyl mercaptan and freshly redistilled sulfur dichloride according to the procedure of Clayton and Etzler[9]; recrystallization of the product from hexane–acetone gave colorless crystals, m.p. 42.0–42.6° (reported m.p. 41.2–41.9°[9]); analyses for carbon and hydrogen agreed with the theoretical. ***n*-Hexadecyl tetrasulfide** was prepared from *n*-hexadecyl mercaptan and sulfur monochloride according to the procedure of Clayton and Etzler[9]; recrystallization of the product three times from hexane–acetone gave a faintly yellow crystalline product, m.p. 36.8–37.2° (reported m.p. 35.9–36.5°[9]); analyses for carbon and hydrogen agreed with the theoretical. All preparations were repeated to verify the reproducibility of results. **Sulfur** (commercial, sublimed) was twice recrystallized from alcohol, m.p. 119° (capillary).

**Determination of Ultraviolet Absorption Spectra.**—The hexane used as a solvent in most of the determinations was purified by washing with 10% fuming sulfuric acid, followed by washing with aqueous sodium bicarbonate and water, then distillation through a Vigreux column. The spectrum of sulfur was determined in Commercial Solvents Gold Shield Absolute Alcohol as well as in hexane. Differences in the spectra in the two solvents were only observed at wave lengths below 230 mμ. Measurements were made in the Beckman Model DU Quartz Spectrophotometer in 1-cm. quartz cells. Values of log ε in the range 1–2 were measured at $10^{-2}$ *M* concentration, log ε 2–3 at $10^{-3}$ *M*, log ε 3–4 at $10^{-4}$ *M*, etc. Wave bands did not exceed 2.3 mμ. Most curves were checked on two different preparations of the same compound.

**Mixed Melting Point Determinations.**—It was of interest to determine whether mixtures of the various polysulfides would show depressions of melting point. For each of the several pairs of compounds, four simultaneous capillary melting point observations were made: specimens of each pure compound, a 2:1 mixture, and a 1:2 mixture of the two. The mixture of 1 disulfide: 2 trisulfide showed a 1°-depression below the m.p. of the pure trisulfide. The mixtures of the disulfide and tetrasulfide melted over wide ranges between the limits for the pure compounds. Mixtures of the trisulfide and tetrasulfide melted over ranges at intermediate values.

**Acknowledgment.**—Analyses of all compounds were made by Mrs. Sarah Miles Woods.

## Summary

The ultraviolet absorption spectra of *n*-hexadecyl mercaptan, *n*-hexadecyl sulfide, *n*-hexadecyl disulfide, *n*-hexadecyl trisulfide, and *n*-hexadecyl tetrasulfide were determined in hexane solution. The spectra of sulfur in hexane and in ethanol solutions were determined. The spectra of the polysulfides have been shown to vary markedly with the sulfur content of the functional group. Spectrometry may be useful in the qualitative identification and quantitative estimation of various organic polysulfides.

PHILADELPHIA 4, PENNSYLVANIA

RECEIVED AUGUST 23, 1948

(20) Purchased from Halogen Chemicals, Inc., Columbia, S. C.

(21) Fridau, *Ann.*, **83**, 16 (1852).

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[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

# The Synthesis of tris-(Hydroxymethyl)-methylnitramine and Other Compounds Related to tris-(Hydroxymethyl)-aminomethane[1]

BY JAMES CASON[2] AND FRANKLIN S. PROUT[2a]

In connection with studies on nitramines carried out in this country and Canada it became desirable to study the absorption spectra of an aliphatic nitramine and the isomeric nitrosohydroxylamine. The present communication describes the synthesis of such an isomeric pair. The study of the absorption spectra is reported separately by other authors.[3]

Although there have been prepared, in the aromatic series, nitramines isomeric with known nitrosohydroxylamines[4] there appears to be no report of the preparation and isolation in a pure condition of such an isomeric pair in the aliphatic series. In fact, there have been reported only a limited number of aliphatic nitrosohydroxylamines which are sufficiently stable to permit isolation in a pure state. tris-(Hydroxymethyl)-methylnitrosohydroxylamine has been prepared by Piloty and Ruff,[5] starting with tris-(hydroxymethyl)-nitromethane, and this preparation has been repeated by us with some modifications.

The method first investigated for the preparation of the previously unknown tris-(hydroxy-

(1) This paper is based entirely on work done for the Office of Scientific Research and Development under Contract OEMsr-790 with Vanderbilt University.

(2) Present address, Department of Chemistry, University of California, Berkeley.

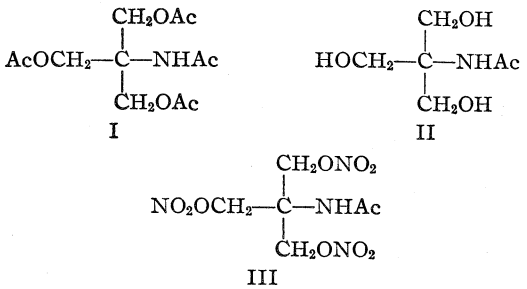
(2a) Present address, Department of Chemistry, De Paul University, Chicago, Illinois.

(3) Carmack and Leavitt, THIS JOURNAL, **71**, 1221 (1949).

(4) Hantzsch, *Ber.*, **31**, 177 (1898); **38**, 1000 (1905); Bamberger, *ibid.*, **27**, 363 (1894); **31**, 577 (1898); Bradfield and Orton, *J. Chem. Soc.*, 915 (1929); Marvel, "Org. Syn.," Coll. Vol. I, 177 (1941); Thiele, *Ann.*, **376**, 256 (1910); Neubauer, *ibid.*, **298**, 200 (1897).

(5) Piloty and Ruff, *Ber.*, **30**, 1656 (1897).

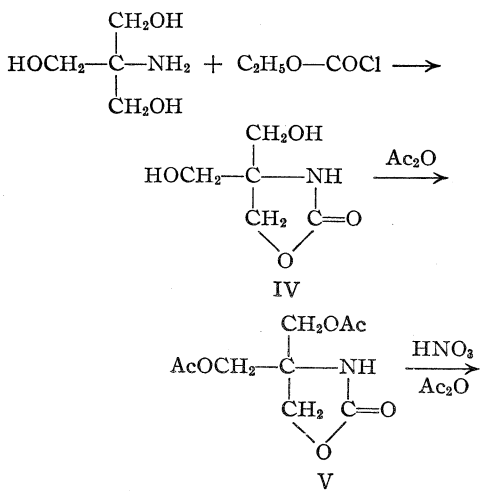
methyl)-methylnitramine (VII) involved nitration of tetraacetyl tris-(hydroxymethyl)-aminomethane (I), but this route was unsuccessful for



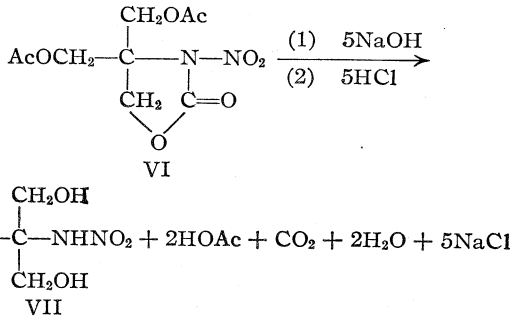
this amide resisted nitration by mixed acid, 98% nitric acid or nitric acid in acetic anhydride. The only product isolated from these attempted nitrations was starting material.

An attempt was also made to prepare the related tris-(nitroxymethyl)-methylnitramine, but it was found that nitration of N-acetyl-tris-(hydroxymethyl)-aminomethane (II) failed to affect the amide group; the only product isolated was N - acetyl - tris - (nitroxymethyl) - aminomethane. Two later attempts to obtain tris-(nitroxymethyl)-methylnitramine were also unsuccessful. The alkaline hydrolysis of 3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone,[6] as well as nitration of tris-(hydroxymethyl)-methylnitramine failed to yield any isolable product.

A successful synthesis of tris-(hydroxymethyl)-methylnitramine (VII) was finally worked out, starting with 4,4-bis-(hydroxymethyl)-oxazolidone[6] (IV). The steps involved are outlined in the accompanying chart.



(6) 4,4-bis-(Hydroxymethyl)-oxazolidone and 3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone were first prepared at Cornell University as a part of the investigation carried out under an OSRD contract and directed by Dr. A. T. Blomquist. The 3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone was obtained by Blomquist by nitration of the oxazolidone, IV, with mixed acid, while nitration with 98% nitric acid gave the 4,4-bis-(nitroxymethyl) derivative. Publication of this work is planned for the near future (private communication, 11-18-48, from A. T. Blomquist).



Nitration of 4,4-bis-(acetoxymethyl)-oxazolidone (V) with a mixed acid containing excess sulfur trioxide resulted in nitrolysis of the acetyl groups to give 3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone[6]; however, nitration with 98% nitric acid in acetic anhydride proceeded smoothly to give 3-nitro-4,4-bis-(acetoxymethyl)-oxazolidone (VI). Alkaline hydrolysis of the latter compound at room temperature gave a 77% yield of the desired tris - (hydroxymethyl) - methylnitramine (VII).

## Experimental[7]

**tris-(Hydroxymethyl)-methylhydroxylamine** was obtained only after some modification of the method of Piloty and Ruff.[5] In the best procedure, a solution of 10 g. of tris-(hydroxymethyl)-nitromethane (recrystallized from nitromethane, m. p. 158–162°, with gassing) and 45 g. of crystalline aluminum sulfate in 300 cc. of water was stirred at 0–2° while 360 g. of 2.5% sodium amalgam was added during forty-five minutes. The mixture was stirred an additional forty-five minutes at the same temperature. After removal of aluminum hydroxide and mercury by filtration, the filtrate was concentrated to dryness *in vacuo* at a bath temperature of 50–60°. The residue was extracted at 100° with one 50-cc. portion and three 25-cc. portions of butanol. On standing overnight in the refrigerator, there crystallized from this extract 3.2 g. (35.2%) of heavy blades, m. p. 139–140°, with softening at 128°. On concentrating the butanol filtrate *in vacuo* a slightly waxy second crop weighing 0.4 g. was obtained. This hydroxylamine is not hygroscopic in moist air and it reduces Fehling solution instantly in the cold.

The product obtained as above contains a trace of sulfate, for its aqueous solution gives a slight cloudiness with barium hydroxide; however, this should be no disadvantage for use in preparation of the nitrosohydroxylamine. Piloty and Ruff[5] recommend removing sulfate by crystallization from alcohol containing "enough" barium hydroxide; however, in our hands, this procedure gave a product of lower melting point.

**tris-(Hydroxymethyl)-methylnitrosohydroxylamine.**[5]—A solution of 1.00 g. of the above-described hydroxylamine in 15 cc. of 0.484 *N* hydrochloric acid was cooled in an ice–salt-bath and treated with 0.504 g. of sodium nitrite in 4 cc. of water. The mixture was left in the cooling-bath for five minutes then the water was removed *in vacuo* at a bath temperature of 50–60°. The residue was dried *in vacuo* for one hour at this temperature then extracted at 50° with butanol (20, 10, 5 cc.). The extract was concentrated *in vacuo* at a bath temperature of 55–60°, then allowed to stand overnight in the refrigerator. There was obtained 0.66 g. (54.5%) of small, white dense crystals, m. p. 123–138° with continuous gassing.

The substance burns with a flash of brown fumes and does not reduce Fehling solution in the cold. It shows no evidence of decomposition on warming briefly in butanol or ethanol to 80°. Approximate solubilities at room tem-

(7) All melting points corrected.

perature are 2.5 g. per 100 cc. in ethanol and 0.6 g. per 100 cc. in butanol. It is very soluble in water, but not hygroscopic in moist air. The melting point behavior was unchanged by additional crystallization from butanol or ethanol. Since Piloty and Ruff[5] give the melting point as 147°, two samples were analyzed; sample NB-I-50B was recrystallized four times, sample NB-I-51 was recrystallized once.

*Anal.* Calcd. for $C_4H_{10}O_5N_2$: C, 28.92; H, 6.07. Found: (Sample NB-I-51) C, 29.05; H, 6.51; (Sample NB-I-50B) C, 29.21; H, 6.28.

**Tetraacetyl tris-(Hydroxymethyl)-aminomethane[8] (I).**—To a mixture of 415 cc. of acetic anhydride and 1 g. of sodium acetate was added 121 g. of commercial tris-(hydroxymethyl)-aminomethane (m. p. 146–161°). The amine went into solution rapidly, with evolution of heat, and the mixture soon refluxed so violently that external cooling was necessary. After spontaneous refluxing had ceased (longer heating is unnecessary) acetic acid was removed *in vacuo* and the residue was treated with Norit in benzene and crystallized at 0° from 700 cc. of benzene. The product so obtained was bulky and soft, and removal of benzene on the filter was exceedingly difficult; weight, 179.3 g., m. p. 97–107°. This product was crystallized from 200 cc. of acetic acid-400 cc. of ether, then from 125 cc. of acetic acid–300 cc. of ether; yield of soft white needles, 107.8 g., m. p. 114.0–114.5° (literature,[8] 115°). By systematically working up the mother liquors there was obtained an additional 57.5 g., m. p. 114.0–114.5°; total yield, 56%.

When this substance was prepared from pure tris-(hydroxymethyl)-aminomethane (m. p. 170.4–171.8°) the yield was not greatly improved, but pure material was obtained after one crystallization. Sodium acetate may be omitted if the reaction mixture is heated on a steam-bath for several hours.

**N-Acetyl-tris-(hydroxymethyl)-aminomethane (II).**—Tetraacetyl tris-(hydroxymethyl)-aminomethane (72.3 g.) was dissolved at room temperature in 800 cc. of 0.9844 *N* sodium hydroxide. After this mixture had remained at room temperature for three hours there was added an amount of standard hydrochloric acid equivalent to the alkali used. Water was removed *in vacuo* and the residue was extracted at 50° with 300 cc. of ethanol in four portions. After addition of 200 cc. of nitromethane, filtration of precipitated salt and concentration to 300 cc. there crystallized 11.5 g. of monoacetyl derivative, II, m. p. 131.3–133.4°. From the mother liquor was obtained 8.26 g. of product, m. p. 130–134°, total yield, 48.4%. This substance crystallizes with considerable difficulty. A sample crystallized from nitromethane for analysis melted at 133.6–134.0°.

*Anal.* Calcd. for $C_6H_{13}O_4N$: C, 44.16; H, 8.03. Found: C, 44.28; H, 8.13.

Attempts to prepare this compound in other ways were unsuccessful. When an aqueous solution of tris-(hydroxymethyl)-aminomethane was treated at room temperature with one mole equivalent of acetic anhydride, practically no crystalline monoacetyl derivative could be isolated from the reaction mixture. When a sample of tetraacetyl tris-(hydroxymethyl)-aminomethane was boiled with absolute ethanol containing a trace of anhydrous hydrogen chloride the starting material was essentially unaffected, and when the amount of hydrogen chloride was increased the material recovered was the hydrochloride of tris-(hydroxymethyl)-aminomethane, m. p. 150.0–150.8° (gas). Täuber[9] gives the melting point of this substance as "about 149°."

**N-Acetyl-tris-(nitroxymethyl)-aminomethane (III).**—A 4.08-g. sample of monoacetyl compound, II, was added during ten minutes, at 5–9°, to a mixture of 12.6 g. of 98% nitric acid and 12.8 g. of acetic anhydride. After the mixture had been stirred for four hours at 15–20° it was poured on 75 g. of cracked ice and the precipitate was collected and washed with water. The product was treated with sodium bicarbonate in 50 cc. of acetone and precipitated with 150 cc. of water. The oil which separated was seeded and the resulting crystallizate collected and dried; yield 6.26 g. (80.8%): m. p. 89.6–91.0°. This substance is crystallized with much difficulty. According to the best method discovered, 0.50 g. of nitrate was dissolved in 50 cc. of acetone and the solution diluted with 200 cc. of water. The recovery of slender needles was 0.16 g., m. p. 90.3–90.6°. The substance decomposes slowly at room temperature and rapidly at 56°; it was dried at 35° *in vacuo* for two hours for analysis. The analytical values show that only three nitro groups entered the molecule.

*Anal.* Calcd. for $C_6H_{10}O_{10}N_4$: C, 24.17; H, 3.38. Found: C, 24.69; H, 3.49.

Nitration of II with mixed acid gave water-soluble products at elevated temperatures and a poor yield of the trinitroxy compound at lower temperatures.

**4,4-bis-(Hydroxymethyl)-oxazolidone (IV)** was prepared by a slight modification of the procedure described by Blomquist.[6] To a solution of 121 g. of tris-(hydroxymethyl)-aminomethane (recrystallized, m. p. 167.6–170.6°) in 200 cc. of water was added, during two hours, at 5–10°, 124.8 g. (15% excess) of ethyl chlorocarbonate. During the last half of this addition there was added concurrently 46 g. of sodium hydroxide in 400 cc. of water. After addition was complete the cooling bath was removed and stirring continued for two hours, then solvent was removed as completely as possible *in vacuo* at a bath temperature of 55–65°. The residue was extracted with 550 cc. of absolute ethanol, and the residue obtained after removal of ethanol *in vacuo* was crystallized from methanol. Additional crops of product were obtained by addition of butanone and concentration. The total yield of IV was 100.3 g. (68%) distributed in five crops of melting point varying from 107.9–109.2° to 93–104°. One additional crystallization gave essentially pure material from low-melting crops; the best sample melted at 109.5–110.7°.

When only one equivalent of ethyl chlorocarbonate was used the yield was lower and there was difficulty in completely separating small amounts of the less-soluble starting material.

**4,4-bis-(Acetoxymethyl)-oxazolidone (V).**—A mixture of 29.4 g. of 4,4-bis-(hydroxymethyl)-oxazolidone (IV), 44.8 g. of acetic anhydride and 0.2 g. of sodium acetate was heated under reflux for five minutes, then concentrated to a sirup *in vacuo*. The mixture was seeded[10] and allowed to stand overnight, then ground under 50 cc. of ether. There was collected 39.4 g. (85.4%) of nearly colorless product melting at 57–68°. Three crystallizations from ethanol gave hard irregular plates melting at 69.0–70.4°.

*Anal.* Calcd. for $C_9H_{13}NO_6$: C, 46.75; H, 5.67. Found: C, 47.00; H, 5.66.

**3-Nitro-4,4-bis-(acetoxymethyl)-oxazolidone (VI).**—To a mixture of 16.6 g. of 98% nitric acid and 13.3 g. of acetic anhydride there was added during ten minutes, at 3–8°, 16.9 g. of 4,4-bis-(acetoxymethyl)-oxazolidone (V) as a sirup (crystalline material had not been obtained at that time). After stirring for two hours at 20–25° the homogeneous mixture was poured on 150 g. of cracked ice. The white precipitate, after collecting and drying, weighed 9.3 g., m. p. 89.4–90.8°. After three crystallizations from methanol there was obtained 7.11 g. of heavy elongated prisms melting at 97.1–97.8°.

*Anal.* Calcd. for $C_9H_{12}N_2O_8$: C, 39.14; H, 4.38. Found: C, 38.81; H, 4.63.

When V was nitrated with a mixed acid containing 5% excess sulfur trioxide the acetyls were nitrolyzed to some extent and the only product isolated was a slightly impure sample of **3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone,**[6] m. p. 120.6–123.2°. A pure sample, prepared as de-

(8) Piloty and Ruff, *Ber.*, **30**, 2066 (1897).

(9) Täuber, *Z. Krystallographie und Mineralogie*, **33**, 87.

(10) During early runs, persistent and varied efforts failed to induce crystallization of this substance; however, a sample which had stood for several weeks at room temperature was found crystalline.

scribed by Blomquist for comparison, melted at 124.3–124.9°. The mixed m. p. was 121–124°.

When 3-nitro-4,4-bis-(nitroxymethyl)-oxazolidone was hydrolyzed as described below in the preparation of tris-(hydroxymethyl)-methylnitramine, no product could be isolated from the reaction mixture.

**tris-(Hydroxymethyl)-methylnitramine (VII).**—A 4.42-g. sample of the nitro derivative, VI, was stirred mechanically with 116.5 cc. of 0.9844 *N* sodium hydroxide for two hours, mild cooling being used at first to prevent the temperature from rising above 35°. The solid dissolved after about one hour. The solution was treated with an amount of standard hydrochloric acid exactly equivalent to the sodium hydroxide used, then concentrated to dryness *in vacuo* (bath, 50–65°). The crystalline residue was extracted at about 50° with 125 cc. of butanol in three portions (extraction at 100° with nitromethane caused considerable decomposition). After filtration of salt the butanol solution was concentrated to dryness *in vacuo* (bath, 53–65°), leaving 2.84 g. of crude nitramine containing some salt, m. p. 114–117° (gas). One crystallization from nitromethane gave 2.04 g. (77%) of material melting at 123–125°. After two additional crystallizations from nitromethane very large striated blades and plates were obtained, m. p. 124–126° (gas), varying somewhat with rate of heating. The analytical sample, Code No. IV-20, was ground and dried *in vacuo* at 80°.

*Anal.* Calcd. for $C_4H_{10}N_2O_5$: C, 28.92: H, 6.07; mol. wt., 166.1. Found: C, 29.00; H, 6.26; mol. wt., 165.3 (by titration).

This nitramine is very soluble in water, moderately soluble in alcohol and essentially insoluble in acetone and ether. It shows no evidence of decomposition during crystallization.

When tris-(hydroxymethyl)-methylnitramine was nitrated at −5°, using a slight excess of 98% nitric acid in acetic anhydride, there was evolution of gas during the reaction, and the water-insoluble product which was obtained crystallized very slowly. Attempted recrystallization caused further decomposition, and no pure product could be obtained.

## Summary

There has been prepared tris-(hydroxymethyl)-methylnitramine and the isomeric, previously known tris - (hydroxymethyl) - methylnitrosohydroxylamine. The preparation of several related compounds from tris-(hydroxymethyl)-aminomethane is also described.

NASHVILLE, TENN. RECEIVED AUGUST 23, 1948

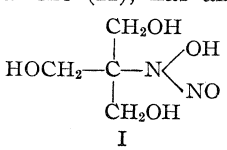
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

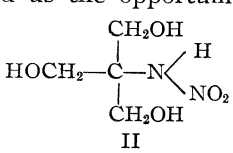
# The Ultraviolet Absorption Spectra of tris-(Hydroxymethyl)-methylnitrosohydroxylamine, tris-(Hydroxymethyl)-methylnitramine, and their Salts[1,2]

BY MARVIN CARMACK AND J. J. LEAVITT[3]

The synthesis by Cason and Prout[4] of tris-(hydroxymethyl)-methylnitrosohydroxylamine (I) and its isomer, tris-(hydroxymethyl)-methylnitramine (II), has afforded us the opportunity




I




II

to investigate the ultraviolet absorption spectra of the primary nitramine and the isonitramine (nitrosohydroxylamine) chromophores in the rare, if not unique, situation in which both isomeric compounds are of the aliphatic series and isolable as reasonably stable crystalline compounds. In many of the more readily prepared nitrosohydroxylamine compounds, the presence of aromatic groups complicates the interpretation of the ultraviolet absorption spectra.

As was hoped, ultraviolet spectrometry proved useful in studying the nature of the functional groups in certain nitramines or isonitramines of ambiguous structure which have been reported in the literature, as for example, "methylenebisisonitramine," prepared by the Traube reaction.[2,5,6]

Kortüm and Finckh[7] have published the ultraviolet absorption spectra of nitramide and methylnitramine in dilute hydrochloric acid and of dimethylnitramine in water. They also reported the spectra of hyponitrous acid in dilute hydrochloric acid, and of sodium hyponitrite, nitrohydroxylamine, and methylnitrosohydroxylamine in dilute sodium hydroxide. The alkylnitramines were measured only in neutral or acidic solution, while methylnitrosohydroxylamine was, unfortunately, measured only in alkaline solution; hence, the spectra of the two types of isomeric compounds are not directly comparable, and it is difficult from the data of Kortüm and Finckh to evaluate the suitability of spectrometry as a means of distinguishing one functional group from the other.

The spectrometric curves for tris-(hydroxyl-

(1) This paper is based upon work carried out for the Office of Scientific Research and Development under Contract OEMsr-646, between the National Defense Research Committee and the University of Pennsylvania.

(2) R. Norman Jones and G. Denis Thorn have made a comprehensive study of the ultraviolet absorption spectra of nitramines and related compounds, including methylenebisisonitramine obtained by the Traube reaction. They will publish their results elsewhere (private communication).

(3) Present address: Calco Chemical Division, American Cyanamid Company, Bound Brook, N. J.

(4) Cason and Prout, THIS JOURNAL, **71**, 1218 (1949).

(5) Traube, *Ber.*, **27**, 1509, 3291 (1894); *cf.* also Wieland, *ibid.*, **61**, 2382 (1928).

(6) G. F. Wright and collaborators have studied the Traube product, methylenebisisonitramine, and will publish the results of their findings elsewhere (private communication).

(7) Kortüm and Finckh, *Z. physik. Chem.*, **48B**, 32 (1940).

methyl)-methylnitrosohydroxylamine (I) in water and in 0.25 *N* sodium hydroxide solutions are shown in Fig. 1. Curves for tris-(hydroxymethyl)-methylnitramine (II) in water, in *N* sodium hydroxide, and in *N* hydrochloric acid are shown in Fig. 2. For comparison, curves for methylnitramine in *N* hydrochloric acid and for potassium methylnitramine in 0.5 *N* potassium hydroxide are shown in Fig. 3. Data on the extinction values at the absorption peaks are summarized in Table I.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF COMPOUNDS

| Compound and solvent | $\epsilon_{max.}$, mμ. | $\epsilon_{max.} \times 10^{-3}$ |
|---|---|---|
| tris-(Hydroxymethyl)-methylnitroso-hydroxylamine (I) | | |
| in water | 229 | 6.0 |
| in 0.25 *N* sodium hydroxide | 249 | 8.73 |
| tris-(Hydroxymethyl)-methyl-nitramine (II) | | |
| in water | 235 | 6.97 |
| in *N* sodium hydroxide | 236 | 8.07 |
| in *N* hydrochloric acid | 234 | 6.19 |
| Methylnitramine (potassium salt) | | |
| in *N* hydrochloric acid[8] | 230 | 7.01 |
| in *N* potassium hydroxide | 228.5 | 7.60 |

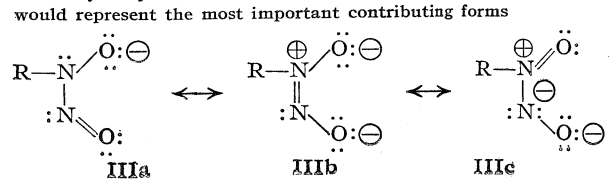
The spectra of the nitramines in water are very similar to the spectrum of tris-(hydroxymethyl)-methylnitrosohydroxylamine (I) in water. The differences in both the intensities and wave lengths of the absorption peaks are small and of the same order as those among homologous members of a series derived from one chromophore group.

A striking difference was observed between the nitramines and the isonitramine in alkaline solution. Upon the formation of the salt of the nitrosohydroxylamine (I) in alkali, it was noted that not only did the absorption peak increase in intensity, but the position of the maximum shifted 20 mμ toward the visible. In contrast, the nitramines showed only very slight shifts in the positions of their maxima although the extinction values at the maxima for the nitramines increased as the medium was varied from aqueous acid to water to dilute alkali.

The magnitude of the shift of the absorption peak for the isonitramine is sufficiently great to serve as a means of distinguishing the isonitramine (nitrosohydroxylamine) functional group from the nitramine.[9]

(8) Kortüm and Finckh (ref. 7) published a spectrum of methylnitramine in dilute hydrochloric acid, but the absorption maximum of their curve was apparently obtained by extrapolation.

(9) Kortüm and Finckh (ref. 7) proposed for the anion of methylnitrosohydroxylamine a resonating structure, of which IIIa and IIIb would represent the most important contributing forms



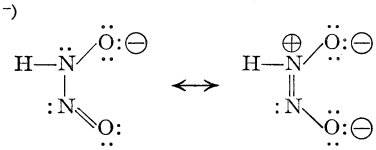
IIIa IIIb IIIc

## Experimental

**Materials.**—tris-(Hydroxymethyl)-methylnitrosohydroxylamine (I) was kindly supplied to us by Dr. James Cason[4] (his Sample No. NB-I-50B which had been recrystallized four times). When received in this Laboratory the sample had a well-defined crystalline appearance. The spectrum was determined immediately after receipt in order to minimize the possibility of deterioration upon storage. Solutions were freshly made up to appropriate concentrations immediately before being measured. Another sample of I (NB-I-51) gave similar results except that slightly lower extinction values were obtained at the maximum. tris-(Hydroxymethyl)-methylnitramine was also furnished to us by Dr. Cason (his Sample No. IV-20, m. p. 124–126°). The sample of potassium methylnitramine was provided through the courtesy of Dr. A. T. Blomquist, Cornell University.

**Ultraviolet Absorption Spectral Measurements.**—All spectrometric measurements were made on dilute aqueous solutions in 1-cm. quartz cells in the Beckman Quartz Spectrophotometer, Model DU.[10] Appropriate dilution, kept the readings within the range of 10–80% transmission. In the case of potassium methylnitramine, curves were determined in several concentrations of potassium hydroxide as well as in water alone. Although the curves were similar in appearance and location of the peak on the wave length scale, the value of $\epsilon_{max.}$ varied from 7.21 ×

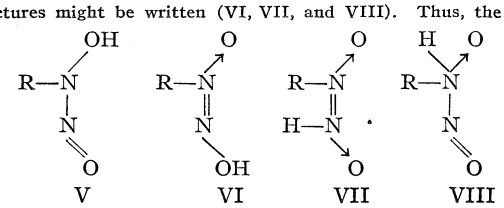
These are analogous to the important resonance forms of the tautomeric structure favored by Kortüm and Finckh for the hyponitrite ion ($HN_2O_2^-$)



IVa IVb

They pointed out that the spectra of the hyponitrite ion and of methylnitrosohydroxylamine in alkaline solutions are very similar. It would be interesting to know whether hyponitrous acid and free methylnitrosohydroxylamine show similar spectra in neutral and acidic solutions and whether the magnitude of the shift on passing from neutral to basic medium is similar for hyponitrous acid and for the alkylnitrosohydroxylamines. Kortüm and Finckh did not extend their measurements of the solution of hyponitrous acid sufficiently far into the ultraviolet region to reach the absorption maximum, and they did not report the spectrum of the methylnitrosohydroxylamine in neutral or acidic solution.

For the free isonitramines, the general structural formula V is preferred because it does not involve a separation of charges; it is used to represent the crystalline compound prepared by Cason and Prout (I). It may be pointed out, however, that three other structures might be written (VI, VII, and VIII). Thus, the hydrogen atom could conceivably be attached to either of the oxygen atoms or either of the nitrogen atoms. Structure VII would be least probable, since it involves two positive charges on the adjacent nitrogen atoms. Kortüm and Finckh considered only the structure V. The possibility that a tautomeric equilibrium between two or more forms exists in solution must also be considered. In any case, only one resonating anion would be expected. The shift of the absorption peak upon formation of the salt from the isonitramine suggests that the distribution of electrical charges is different in the free parent isonitramine and in the salt anion.



V VI VII VIII

(10) We gratefully acknowledge the technical assistance of Mr. P. W. Wilcox and Mr. Joseph L. Ciminera of the Research Laboratory, Sharp and Dohme, Glenolden, Pennsylvania, in the determination of the absorption spectra.

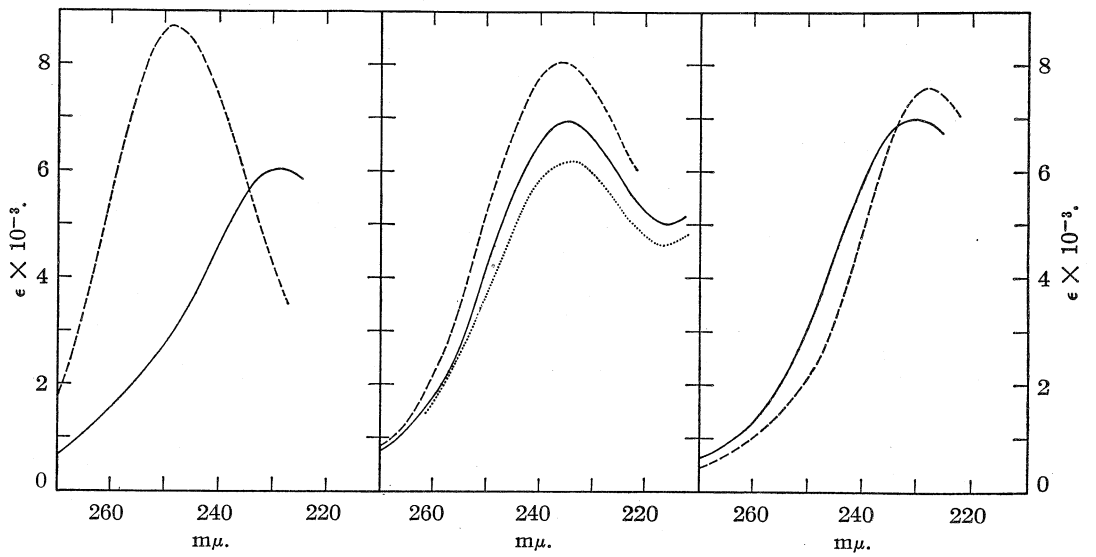



Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Solid curve: tris-(hydroxymethyl)-methylnitrosohydroxylamine in water; dash curve, same in 0.25 *N* NaOH.

Fig. 2.—Solid curve: tris-(hydroxymethyl)-methylnitramine in water; dash curve, same in *N* NaOH; dotted curve: same in *N* HCl.

Fig. 3.—Solid curve: methylnitramine in *N* HCl; dash curve, same in 0.5 *N* KOH.

$10^3$ in water to $7.60 \times 10^3$ in 0.5 *N* potassium hydroxide. No further increase of $\epsilon_{max.}$ was noted in *N* potassium hydroxide. The spectrum of free methylnitramine was obtained by dissolving potassium methylnitramine in a large excess of dilute hydrochloric acid.

## Summary

The ultraviolet absorption spectrum of tris-(hydroxymethyl) - methylnitrosohydroxylamine in neutral aqueous solution is similar in location and intensity to that of tris-(hydroxymethyl)-methylnitramine and methylnitramine in neutral, aqueous solution. In aqueous alkaline solution the absorption of the nitrosohydroxylamine is greatly intensified and the maximum shifts 20 mμ toward the visible region. The spectra of the alkylnitramines are intensified by conversion into the salts but the location of the maximum remains almost unchanged. This differing behavior in alkaline medium affords a means of distinguishing nitramines from isonitramines (nitrosohydroxylamines).

PHILADELPHIA 4, PENNSYLVANIA

RECEIVED AUGUST 23, 1948

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[CONTRIBUTION FROM DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

# The Separation of Choline Esterase, Mucoprotein, and Metal-Combining Protein into Subfractions of Human Plasma[1a,b,c]

BY D. M. SURGENOR, L. E. STRONG,[1d] H. L. TAYLOR,[1e] R. S. GORDON, JR., AND D. M. GIBSON[1f]

A system for the separation of the protein components of human plasma has been described in an earlier paper in this series.[2] The fractions so obtained contain groups of proteins of somewhat similar solubility characteristics, each of which is susceptible of further purification. Many of the components so isolated, either in

(1a) This work was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council, which included a grant from the American College of Physicians. From August, 1941, to July, 1946 it was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. Since then it has been aided by a grant recommended by the Panel on Hematology of the National Institute of Health.

(1b) This paper is Number XX in the series "Preparation and Properties of Serum and Plasma Proteins" from the Department of Physical Chemistry, Harvard Medical School.

(1c) This paper is Number 75 in the series "Studies on the Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

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(1e) Present address, Michigan State Department of Health, Bureau of Laboratories, Lansing, Michigan.

(1f) Present address, Wesley Memorial Hospital, Chicago, Illinois.

(2) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, THIS JOURNAL, **68**, 459 (1946).

pure or concentrated form, have been found of physiological importance and some of them of clinical use. This was true of Fraction I which contains fibrinogen and the antihemophilic globulin[3]; of Fraction II which contains various antibodies, and of Fraction III which contains the isoagglutinins, prothrombin and the fibrinolytic enzyme precursor, plasminogen.[4]

Fraction IV, originally separated to render the albumin in Fraction V as pure as possible, has since been removed in two steps (2), Fraction IV-1 separated the $\alpha_1$-lipoprotein under conditions of lower ethanol concentration than were required to precipitate the whole Fraction IV. The remainder of this fraction, IV-4, contained those proteins soluble in 0.062 mole fraction (18 per cent.) ethanol[5] at *p*H 5.2 and $-5°$,—used for the precipitation of Fraction IV-1—and insoluble in 0.163 mole fraction (40%) ethanol at *p*H 5.8 at the same temperature. It comprised slightly more than 7% of the plasma proteins. In addition to a small amount of albumin which separated with this fraction, it was composed mainly of $\alpha_2$- and $\beta_1$-globulins. It has been routinely prepared free of pressor or depressor activity, and has been injected intravenously without untoward reactions.[6]

A number of labile components have also been recognized in Fraction IV-4. These include $\alpha_1$-lipoprotein, $\alpha_2$ carbohydrate-containing globulins, and hypertensinogen. It was early recognized that "precipitation of Fraction IV-4 by 0.163 mole fraction ethanol at *p*H 5.8 and $-5°$ led to the destruction of hypertensinogen and presumably of other labile components of the fraction without, however, destroying gross molecular structure."[7] Attempts to isolate certain of these components from Fraction IV-4 in their native states, particularly the various $\alpha$-globulins, have thus far met with only moderate success. The new method of fractionation now being developed should yield more satisfactory preparations of these and of other labile components of plasma.[8]

This communication is concerned with the separation of Fraction IV-4 of human plasma into subfractions in which have been concentrated certain of the more stable physiologically important components. These include plasma choline esterase and the $\beta_1$ metal-combining globulin.[9,10]

These subfractions have been used for certain clinical investigations,[11,12,13] and have been the starting materials for chemical studies, to be reported later, on the purification and crystallization of the metal-combining globulin[14] and on the further concentration and purification of plasma esterase.[15]

## II. Materials and Methods

Fraction IV-4 used in these studies came from three sources. The major part was from substandard or outdated dried plasma being fractionated in the interest of recovering albumin, $\gamma$-globulin, and other stable protein components of proven therapeutic or prophylactic value for distribution by the American Red Cross.[16] Some was prepared from fresh plasma at the Harvard Pilot Plant during the war. Finally, this fraction was made available from the fresh plasma fractionated at the Division of Biologic Laboratories, Massachusetts Department of Public Health, from blood collected by the American Red Cross.[17]

**Carbohydrate analyses** were performed by a modification by the method of Sørensen and Haugaard.[18] An equimolar mixture of galactose and mannose was used as the standard.[19] To 1 ml. of solution, containing 0.02 to 0.10 mg. of hexose, in a colorimeter cuvette, was added 5 ml. of 0.1% orcinol in 67 volume per cent. sulfuric acid. After heating for exactly ten minutes in an 80° bath, the tubes were chilled rapidly in an ice-bath. The solutions were kept in the dark and read within an hour against a protein-free blank in a Klett photoelectric colorimeter using Corning glass filters number 5031 and 3389 (420 to 580 m$\mu$). A series of standard tubes, containing varying amounts of the galactose–mannose standard, were always read at the same time as the unknowns.

**Hexoseamine** determinations were carried out by the method of Elson and Morgan,[20] as adapted by Rimington.[21] Glucoseamine was used as the standard.

**Metal-combining capacities** were measured by a modification of the method of Schade.[9,10] Determinations were carried out in *p*H 7.4 sodium diethyl barbiturate buffer of ionic strength 0.1, using a standard solution of ferrous ammonium sulfate (200 $\gamma$ Fe/ml.). The solutions were allowed to stand sixty minutes and their extinctions were read in the Beckman spectrophotometer against an iron-free blank at 460 m$\mu$.[22]

**Solubility studies** with plasma choline esterase were made with small sized aliquots of a standard solution of the enzyme, adjusted to the desired *p*H, ethanol concentration, and ionic strength; the total amount of protein in the system was the same throughout. After equilibration for twenty-four hours at the desired temperature, the precipitates were removed by centrifugation in a refrigerated angle centrifuge. The supernatant solutions were dried

(3) J. T. Edsall, R. M. Ferry and S. H. Armstrong, Jr., *J. Clin. Invest.*, **23**, 557 (1944).

(4) J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., THIS JOURNAL, **71**, 541 (1949).

(5) Ethanol concentrations are given in mole fraction and volume per cent. at 25°.

(6) C. A. Janeway and F. L. Plachte, Report to the Subcommittee on Blood Substitutes, Division of Medical Sciences, National Research Council, March 14, 1943; Bull. Blood Subst., pp. 1335 and 1400.

(7) Ref. 2, pp. 469–470.

(8) E. J. Cohn, personal communication.

(9) A. L. Schade and L. Caroline, *Science*, **104**, 340 (1946).

(10) D. M. Surgenor, B. A. Koechlin and L. E. Strong, *J. Clin. Invest.*, **28**, 73 (1949).

(11) R. D. Barnard and J. W. Mentha, *Science*, **107**, 195 (1948).

(12) C. E. Rath and C. A. Finch, *J. Clin. Invest.*, **28**, 79 (1949).

(13) G. E. Cartwright and M. M. Wintrobe, *J. Clin. Invest.*, **28**, 86 (1949).

(14) B. A. Koechlin, in preparation.

(15) D. M. Surgenor and D. Ellis, in preparation.

(16) These preparations were carried out at E. R. Squibb and Son, New Brunswick, New Jersey, and released by the American Red Cross for these investigations.

(17) These preparations were obtained through the courtesy of Drs. Getting, G. Edsall and Mulford.

(18) M. Sørensen and G. Haugaard, *Compt. rend. trav. lab. Carlsberg*, **19**, No. 12, p. 1 (1933).

(19) L. F. Hewitt, *Biochem. J.*, **33**, 1496 (1939).

(20) L. E. Elson and W. T. J. Morgan, *Biochem. J.*, **27**, 1824 (1933).

(21) C. Rimington, *Biochem. J.*, **34**, 931 (1940).

(22) We wish to acknowledge the collaboration of Dr. Schade during this work. Periodic microbiological assays of iron-binding capacity, performed under his direction, served as a check on the spectrophotometric determination which, because of its facility, was of great use in guiding the fractionation.

from the frozen state to remove ethanol, and redissolved in water for analysis.[23]

Other methods and the equipment used in this Laboratory for the fractionation of proteins in ethanol–water mixtures of controlled *p*H, ionic strength, temperature, and protein concentration have been described elsewhere.[2]

We are glad to acknowledge the assistance of M. M. Hasson, B. J. Learned and W. O'Donnell during this investigation, as well as that of M. J. E. Budka for the electrophoretic analyses and C. G. Gordon and P. M. Baker, under the direction of J. L. Oncley, for the ultracentrifugal analyses.

## III. System of Fractionation

The conditions that have been found effective for the optimum separation of proteins from each other, in the five variable system here employed, have evolved slowly and are always subject to further modification. The lability of some of the components imposed limits on the conditions deemed acceptable. The precipitation of certain components in Fraction IV-4 rather than in Fraction IV-1 or V was considered evidence of protein–protein interactions. When purified, many of the proteins in Fraction IV-4 proved to be isoelectric and of low solubility near or below *p*H 5.0.

Electrophoretic analyses, assays for plasma esterase activity and metal-combining capacity were the principal analytical tools employed. Since a well-planned scheme of fractionation concentrates unknown, as well as known, components, it was hoped that an inclusive subfractionation of Fraction IV-4 would be obtained. This was indeed the case for several components for which no assay was carried out but which were later recognized in one or another subfraction. Because of the possible clinical utilization of some of these components, the number of subfractions was maintained as small as possible and those procedures were adopted which were suitable for large-scale processing.

**Fraction IV-5+6.**—When a solution of Fraction IV-4 was dialyzed against a buffer of low ionic strength, or diluted to 1% protein concentration (ionic strength 0.005) at 0°, a euglobulin precipitated. The minimum solubility of this precipitate, largely $\alpha_1$-lipoprotein, was near *p*H 5.0. This precipitate contained 85 to 90% of the lipid, measured as cholesterol, in Fraction IV-4. The supernatant solution contained albumin, $\alpha_2$- and $\beta_1$-globulins; all of the esterase and metal-combining activity.

Although all of the esterase could be precipitated from this solution at *p*H 5.2 by adding ethanol to a concentration of 0.062 mole fraction (18%), a large amount of albumin and $\beta_1$-globulin were precipitated as well. An attempt was therefore made to find conditions under which the albumin and $\beta_1$-globulin remained soluble while the esterase remained insoluble. On increasing the ionic strength at 0.062 mole fraction ethanol, the solubility of the impurities increased more rapidly than did the esterase. Moreover, on lowering the *p*H to 4.7, the impurities became more soluble. At a *p*H near *p*H 4.4, the esterase as well as the other proteins dissolved. This behavior was reminiscent of the principle[24] that acid to the isoelectric points of the proteins in a fraction, the tendency to interaction diminished and more satisfactory separations were achieved. Thus, at *p*H 4.7, ionic strength 0.02 and 0.062 mole fraction (18%) ethanol at −5°, the esterase was precipitated with a minimum of impurities.

Since the subsequent separation of the esterase involves many additional steps, considerable advantage was gained by proceeding directly to the conditions just described, for the precipitation of the esterase. A large subfraction, Fraction IV-5+6, was obtained, which contained the same components that were found in the earlier two subfractions. This reduced the number of steps and removed the limitation on protein concentration imposed by the low ionic strength necessary to precipitate the $\alpha_1$-lipoprotein, thus making it possible to use increased protein concentrations throughout.

**Fraction IV-5.**—In the subfractionation of Fraction IV-5+6 the lipoprotein was separated into Fraction IV-5 by employing the conditions previously found to precipitate this component: *p*H 4.9, and ionic strength 0.002 at 0°. The low ionic strength was attained at a protein concentration of 2.5%, instead of the 1% protein previously employed. The further treatment of Fraction IV-5+6 was intended to separate the plasma esterase, as well as to recover the serum albumins and $\beta_1$ metal-combining globulin in this fraction.

**Fraction IV-6.**—The solution from which Fraction IV-5 was separated was essentially free of lipid, measured as cholesterol. Solubility experiments on the protein remaining in the supernatant showed that the choline esterase had a minimum solubility near *p*H 4.9 (Fig. 1). At this *p*H, in 0.062 mole fraction (18%) ethanol, the solubility of the enzyme increased almost a thousand fold on increasing the ionic strength from 0.02 to 0.10. On lowering the *p*H, the inactive protein dissolved more readily than the esterase. At *p*H 4.4, ionic strength 0.02 and 0.062 mole fraction ethanol, all of the esterase was precipitated into Fraction IV-6 while a considerable fraction of the protein remained soluble.

**Fraction IV-7.**—The solution from which Fraction IV-5+6 separated consisted mainly of albumin and $\beta_1$-globulin. All of the protein in solution could be precipitated, without changing the *p*H or ionic strength, by raising the ethanol concentration to 0.163 mole fraction (40%). However, the $\beta_1$ metal-combining globulin could be precipitated in a smaller fraction (IV-7)

(23) We are indebted to Dr. Ralph W. Brauer, and, more recently, to Dr. Avram Goldstein for the plasma esterase assays which they kindly carried out in the Department of Pharmacology, Harvard Medical School.

(24) A. A. Green, THIS JOURNAL, **60**, 1108 (1938).

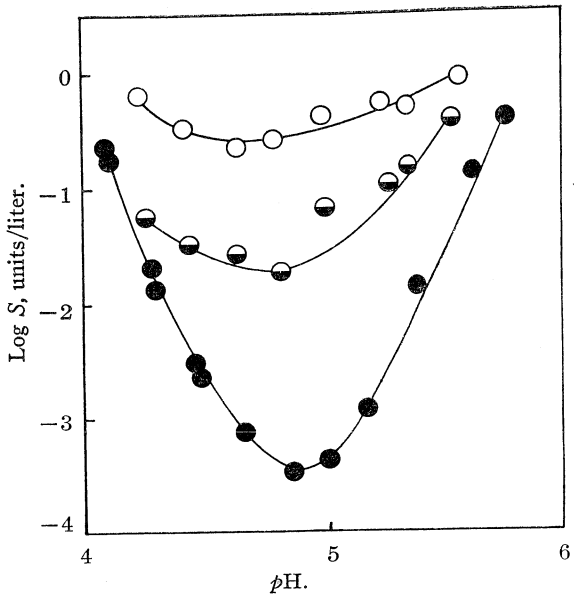



Fig. 1.—Solubility of plasma choline esterase in Fraction IV−5+6 in 0.062 mole fraction ethanol at −5°: ○, Γ/2 = 0.10; ◒, Γ/2 = 0.05; ●, Γ/2 = 0.02 [*cf.* footnote (a) of Table IV for definition of unit of enzyme activity].

formed at *p*H 5.9, ionic strength 0.09 and 0.163 mole fraction ethanol.

**Fraction IV-8.**—The albumin remaining in solution after removal of Fraction IV-7, could be precipitated, as Fraction IV-8, by lowering the *p*H to 4.9. This fraction contained only small amounts of globulins.

**Fraction IV-9.**—The solution, after the precipitation of Fraction IV-8, was essentially free of protein. That remaining in solution after precipitation of Fraction IV-6, was mainly albumin and $\beta_1$-globulin. These were precipitated together, as Fraction IV-9, by adjusting the *p*H to 5.2 and increasing the ethanol concentration to 0.091 mole fraction (25%) ethanol.

The detailed procedures for carrying out the separation of Fractions IV-5, IV-6, IV-7, IV-8 and IV-9 from Fraction IV-4 are given below. These have been tentatively recommended to the American Red Cross to make these fractions available for clinical studies.

### Subfractionation of Fraction IV-4

Fraction IV-4 separated from human plasma by method (6)[25] is the starting material for this preparation.[26] Each kg. of paste is suspended in 8.5 liters of water and ice. The resulting suspension is adjusted to *p*H 4.7, ionic strength 0.02 and 18% ethanol. This requires, for each liter of suspension, 26 millimoles of sodium acetate buffer diluted to 167 ml. with water, and 500 ml. of 53.3% ethanol. The buffer consists of the amount of *p*H 4 acetate buffer necessary to adjust the *p*H, together with sufficient *p*H 4.7 acetate buffer[27] so that the total amount of sodium acetate in the two buffers is 26 millimoles. The diluted buffers and then the ethanol should be added, with vigorous stirring, through capillary jets. The rate of addition should be 80–100 ml. per jet per minute.[28] During the addition of the ethanol the suspension should be kept at the freezing point until a temperature of −5° is reached, and then maintained at −5° throughout the remainder of the addition.

**Precipitate IV-5+6** is removed by centrifugation at −5°. The fraction may be further separated as described below, or dried from the frozen state. The latter is conveniently done after resuspending the paste in 2 or 3 volumes of water and ice.

The supernatant solution is brought to *p*H 5.9–6.0, ionic strength 0.09 and 40 per cent. ethanol. The *p*H is adjusted with sodium bicarbonate[29] and sodium chloride is added to make a total of 114 millimoles of sodium bicarbonate and sodium chloride for each liter of supernatant. The combined salts are added in 50 ml. of water, after which 437 ml. of 95% ethanol is introduced. The reagents are added through capillary jets, as before, but the rate of addition of the ethanol should be somewhat slower, *i. e.*, 40–50 ml. per jet per minute. The temperature is maintained at −5° throughout the addition.[30]

**Precipitate IV-7** is a concentrated source of the metal-combining globulin. The fraction is removed by centrifugation at −5°. It should be dissolved in 3 volumes of water and ice, and dried from the frozen state.

The albumin remaining in solution is precipitated by adjusting the *p*H to 4.9 with *p*H 4 sodium acetate buffer. The buffer should be adjusted with 95% ethanol so that it has an ethanol concentration of 40%. It should be added through capillary jets at the rate of 50 ml. per jet per minute, keeping the temperature constant at −5° and the ethanol concentration at 40%.

**Precipitate IV-8** is obtained by centrifuging at −5°. The paste should be redissolved in 3 volumes of ice and water, adjusted to *p*H 6.0–6.5, and dried from the frozen state. The supernatant solution may be discarded.

### Subfractionation of Fraction IV-5+6

The IV-5+6 paste[26] is resuspended in 9 volumes of ice and water.[31] This gives a protein concentration of 2.5 per cent., ionic strength 0.002 and 1% ethanol. The *p*H is adjusted with sodium bicarbonate to 4.9 and the suspension should be stirred at least two hours at 0°.

**Precipitate IV-5** is removed by centrifugation at 0° at a sufficiently slow rate to give a clear supernatant solution.[32] This fraction is largely $\alpha_1$-lipoprotein; when derived from dried plasma or dried fractions thereof, it is largely denatured. It may be resuspended in water and dried from the frozen state.

The solution is next brought to 18% ethanol, *p*H 4.4 and ionic strength 0.02. This requires 29 millimoles of ace-

(25) Ref. 2, p. 470.

(26) Storage at −5° of plasma esterase fractions in paste (containing ethanol) will generally result in loss of esterase activity in approximately a month. No appreciable loss of activity has been detected on storage of the dry powder. It is therefore advisable to use the wet paste immediately, or, if this is not possible, to dry the fraction from the frozen state and store the powder in the cold.

(27) W. C. Boyd, THIS JOURNAL, **67**, 1035 (1945).

(28) If dried Fraction IV-4 is used as the starting material, these same conditions will be attained by suspending each 300 g. of powder in 8.7 liters of water. Each liter will require 26 millimoles of the required buffers, diluted to 110 ml. with water, and 556 ml. of 53.3% ethanol.

(29) This is a difficult *p*H adjustment because of the solubility of carbon dioxide in the solution. Thorough equilibration is necessary. The *p*H should be determined with a sample which has been diluted with 3 volumes of 0.02 *M* NaCl without shaking or aerating the solution.

(30) Starting with 2 kg. of IV-4 paste, which is approximately the amount derived from 100 liters of plasma, the volume at this point in the procedure will be 40 liters.

(31) If dry powder is used, each 250 g. should be suspended in 10 liters of water at 0°. It is unnecessary to adjust the ethanol concentration.

(32) In certain cases, for example, in the preparation of the $\alpha_2$-mucoprotein, it is of advantage to clarify this solution. This can be done by suspending 0.25% of washed standard super-cel and filtering at 0° through Hormann type D-7 pads.

tate buffers, diluted to 50 ml., and 500 ml. of 53.3% ethanol for each liter of solution.[33] The buffers include the amount of *p*H 4 acetate buffer needed to lower the *p*H to 4.4 and enough *p*H 4.4 acetate buffer so that the total amount of sodium acetate in the two buffers is 29 millimoles. The diluted buffers and then the ethanol should be added through capillary jets at the rate of 80–100 ml. per jet per minute. During the addition of the ethanol the temperature should be kept at the freezing point until −5° is reached, and maintained at −5° thereafter. The suspension should be stirred at least two hours, and then centrifuged as soon as possible.[34]

**Precipitate IV-6** may be further subfractionated immediately, or resuspended in 2 volumes of ice and water, adjusted to *p*H 5 with sodium bicarbonate, and dried from the frozen state.

Finally, the supernatant solution is adjusted to *p*H 5.2 and 25% ethanol. This requires, for each liter, the necessary amount of sodium bicarbonate, diluted to 25 ml. with water, and 106 ml. of 95% ethanol. The bicarbonate and ethanol should be added through capillary jets as before, maintaining the temperature at −5° throughout.

**Precipitate IV-9** may be redissolved in 3 volumes of ice and water, and dried from the frozen state.

## IV. Distribution and Properties of Protein Components in Fraction IV-4 and its Subfractions

As in previous studies,[2,4] we have made use of chemical and physical measurements at our disposal to characterize the various components. The distribution of nitrogen and the actual yields of total protein have been determined by direct analysis of the separated subfractions and are given in Table I.

TABLE I

ESTIMATED DISTRIBUTION OF NITROGEN AND PROTEIN INTO SUBFRACTIONS OF FRACTION IV-4

| Fraction | Total nitrogen[a] | Per cent. of total protein | $\left(\frac{\text{g. protein}}{\text{g. nitrogen}}\right)$ |
|---|---|---|---|
| IV-4 | 100 | 100 | 7.1[b] |
| IV-5+6 | 59.8 | 61.8 | 7.3 |
| IV-7 | 14.8 | 13.8 | 6.6[c] |
| IV-8 | 14.0 | 12.4 | 6.3 |
| Supernatant soln. | 4.2 | 3.8 | 6.4 |
| Total | 92.8 | 91.8 | |

[a] Based on averages from direct analysis of precipitates in two runs. [b] From ref. 2, Table VII, p. 473 [c] Measurement made by J. L. Oncley, G. Scatchard and A. Brown, *J. Phys. and Coll. Chem.*, **51**, 184(1947).

From these data, and the results of the electrophoretic analyses,[35] the yields of the electrophoretic components in the subfractions have been calculated. The yields are presented in Tables II and III. The limitations in the quantitative interpretation of electrophoretic Schlieren diagrams, discussed in a previous paper in this series,[36] were quite apparent, especially in the determination of $\alpha$-globulins. Indeed, we have found the electrophoretic technique of but limited use in characterizing fractions containing high percentages of $\alpha_2$-globulins. The protein components of interest have been most readily followed during subfractionations by means of assays for lipid, carbohydrate, plasma esterase and iron-binding capacity. Results of certain experiments suggesting the distribution of lipoprotein, carbohydrate-rich proteins, plasma esterase and metal-combining globulin are reported in Table IV.

(33) If dry Fraction IV-5+6 were used, each liter of solution requires 535 ml. of 53.3% ethanol.

(34) Although serum esterase has proved to be among the more stable of the plasma proteins at acid *p*H, it is advisible to expose solutions of the enzyme to acid conditions for as short a time as possibe.

(35) Electrophoretic analyses have not been corrected for refractive index increments.

(36) S. H. Armstrong, Jr., M. J. E. Budka and K. C. Morrison, THIS JOURNAL, **69**, 416 (1947).

TABLE II

ESTIMATED DISTRIBUTION OF PROTEINS INTO SUBFRACTIONS OF FRACTION IV-4[a]

| Fraction | Albumin | $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | Total |
|---|---|---|---|---|---|---|
| | Per cent. of subfraction | | | | | |
| IV-4[b] | 30 | 17 | 24 | 28 | 1 | 100 |
| IV-5+6 | 15 | 17 | 44 | 23 | 1 | 100 |
| IV-7 | 13 | 1 | 7 | 76 | 3 | 100 |
| IV-8 | 91 | 3 | 3 | 3 | | 100 |
| | Grams per liter of plasma recovered in subfractions | | | | | |
| IV-4[b] | 1.5 | 0.9 | 1.1 | 1.6 | 0.1 | 5.2 |
| IV-5+6 | 0.5 | 0.5 | 1.4 | 0.7 | 0.1 | 3.2 |
| IV-7 | 0.1 | <0.1 | <0.1 | 0.6 | <0.1 | 0.7 |
| IV-8 | 0.7 | <0.1 | <0.1 | <0.1 | 0 | 0.7 |
| Total | 1.3 | 0.5 | 1.4 | 1.3 | 0.1 | 4.6 |

[a] The strong interactions of the $\alpha$-globulins resulted in low apparent values for $\alpha_1$-globulins and correspondingly high apparent values for $\alpha_2$-globulins as determined from the Schlieren diagrams. [b] These values were obtained from three preparations of Fraction IV-4 used in this work, and have been used rather than the previously published values for Fraction IV-4 (ref. 2, Table IX, p. 479) in preparing this table, since the fraction obtained from outdated dried plasma or from fresh plasma in which acid citrate dextrose, "ACD," was used as the diluent, usually contained more albumin, and was therefore correspondingly larger in size, than Fraction IV-4 from fresh citrated plasma.

TABLE III

ESTIMATED DISTRIBUTION PROTEINS INTO SUBFRACTIONS OF FRACTION IV-5+6

| Fraction | Albumin | $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | Total |
|---|---|---|---|---|---|---|
| IV-5+6 | 15 | 17 | 44 | 23 | 1 | 100 |
| IV-5 | 8 | 73 | 14 | 4 | 1 | 100 |
| IV-6 | 6 | 11 | 77 | 6 | | 100 |
| IV-9 | 30 | 0 | 28 | 41 | 1 | 100 |
| | Grams per liter of plasma recovered in subfractions | | | | | |
| IV-5+6 | 0.5 | 0.5 | 1.4 | 0.7 | 0.1 | 3.2 |
| IV-5 | <0.1 | 0.5 | 0.1 | <0.1 | <0.1 | 0.6 |
| IV-6 | 0.1 | 0.1 | 0.8 | <0.1 | 0 | 1.0 |
| IV-9 | 0.3 | 0 | 0.3 | 0.5 | <0.1 | 1.1 |
| Total | 0.4 | 0.6 | 1.2 | 0.5 | <0.1 | 2.7 |

**Fraction IV-5.**—The $\alpha_1$-lipoprotein separated in this fraction was largely denatured. Cholesterol determinations and qualitative observations, however, led to the conclusion that this component was probably identical with the $\alpha_1$-lipoprotein which separated into Fraction IV-1.

**Fraction IV-6.**—This complex fraction contained at least two carbohydrate-rich $\alpha_2$-globulins,

TABLE IV

ESTIMATED DISTRIBUTION OF CARBOHYDRATE, CHOLESTEROL, IRON-BINDING CAPACITY AND PLASMA CHOLINE ESTERASE IN SUBFRACTIONS

| Fraction | Carbohydrate, % | Cholesterol, % | Units plasma[a] esterase/g. | Iron-binding capacity, mg. Fe/g. |
|---|---|---|---|---|
| Plasma | (1.16)[b] | 2.3[b] | 1.5-2.0 | 0.04[c] |
| IV-4 | 2.9[b,d] | 1.7[b] | 20 | .30 |
| IV-5+6 | 3.1 | 2.1 | 32[e] | .24 |
| IV-5 | | 5.3 | | |
| IV-6 | 3.8 | | 45 | |
| IV-7 | 2.3 | <0.1 | <1 | .85 |
| IV-8 | 0.4 | <0.1 | 0 | .05 |
| IV-9 | 1.7 | | 1 | .44 |

[a] Assays for esterase activity were made on appropriate dilutions of the enzyme, by measuring in the Warburg apparatus, at 37°, the release of carbon dioxide from a solution of sodium bicarbonate buffered at *p*H 7.4 with carbon dioxide. Acetylcholine, 0.0805 molar, was used as the substrate. We have used the unit of esterase activity as that amount of enzyme which would split 1 millimole of acetylcholine per hour under the above conditions. [b] Values taken from Table VIII, ref. 2, p. 474. [c] Based on estimates of the amount of metal-combining protein in plasma. This agrees quite well with the value obtained by direct analysis of plasma. [d] Higher values have been obtained using the carbazole reaction, by F. B. Seibert, M. L. Pfaff and M. V. Seibert, *Arch. Biochem.*, **18**, 279 (1948). [e] Plasma esterase represents only a minor part of the protein in this fraction, and its properties cannot therefore be deduced from the properties of this fraction.

in addition to plasma choline esterase. From the results of studies now in progress[15] which indicate that the pure enzyme may have an activity of at least 15,000 times its activity in plasma, it has been estimated that less than 1 per cent. of the protein in the fraction was esterase.

**Fraction IV-7.**—The main component of this fraction was the metal-combining globulin, so designated because of certain *in vitro* evidence that it is capable of binding other metals as well as iron.[10,14,37] Subsequent purification and crystallization of this component[14] has proved that the $\beta_1$-globulin which separated with Fraction IV-4, and was further concentrated in Fraction IV-7, is indeed the component responsible for the iron-binding capacity of the serum.[9]

Of the impurities in Fraction IV-7, the $\alpha_2$-globulin, although rich in carbohydrate, has been distinguished from the $\alpha_2$-globulins of Fraction IV-6 by its ability to bind bilirubin. This property was not shared by the $\alpha_2$-globulins of Fraction IV-6.[38]

Fraction IV-7, rather than the crystallized $\beta_1$ metal-combining globulin obtained therefrom, has been recommended to the American Red Cross as the most convenient source of metal-combining globulin for clinical investigation.[10,12,13]

(37) This component has been called "siderophyllin" by Schade [A. L. Schade, R. W. Reinhart and H. Levy, *Arch. Biochem.*, **20**, 170 (1949)] and "transferrin" by Holmberg and Laurell (C. G. Holmberg and C.-B. Laurell, *Acta Chem. Scand.*, **I**, 944 (1947)).

(38) N. H. Martin, THIS JOURNAL, **71**, 1230 (1949).

**Fraction IV-8.**—Recovery of the albumins in Fraction IV-4 and their addition to those in Fraction V[2] represents an additional yield of 2%. The albumins in Fraction IV-8 were similar in ultracentrifugal behavior and in ability to bind hematin,[39] to the albumins separated into Fraction V. No differences between them have yet been observed.

## V. Studies with the $\alpha_2$-Mucoprotein

Protein-bound carbohydrate is distributed rather generally throughout the globulins in the plasma. Of the various components isolated from plasma, only the crystallized serum albumin was free of carbohydrate.[40] The highest concentration of bound carbohydrate was found in Fraction IV-4.[41]

The carbohydrate-rich proteins fall into two classes, the mucoproteins and the glycoproteins.[42] Examples of these are the mucoprotein fraction from guinea pig serum, associated with one of the components of complement,[43] and the glycoprotein from horse serum, associated with albumin.[44] Mucoproteins have been characterized by euglobulin properties, high viscosity in solution, and a tacky behavior when precipitated. Glycoproteins have often appeared to be pseudoglobulins, resembling the albumins in their solubility properties.

In the course of the studies with Fraction IV-4 we have recognized members of both classes of carbohydrate-rich proteins. These were largely separated, with the $\alpha_2$-globulins, into Fraction IV-6 by the procedures just described. The results of some studies with an $\alpha_2$-mucoprotein are outlined here; studies on the glycoproteins will be the subject of a later communication.

The mucoprotein has proved to be extremely labile under conditions of acid *p*H. Preparations derived from Fraction IV-6, which was precipitated at *p*H 4.4, were usually partially denatured, as evidenced by a large amount of fast-sedimenting, inhomogeneous material in the ultracentrifuge.[45] It therefore seemed necessary to prepare mucoprotein by means of separations which did not involve the use of acidities below *p*H 5. In this

(39) M. Rosenfeld, in preparation.

(40) E. J. Cohn, W. L. Hughes, Jr., and J. H. Weare, THIS JOURNAL, **69**, 1753 (1947).

(41) Ref. 2, Table VIII.

(42) The nature of the carbohydrate moiety has received considerable attention and the carbohydrate content has been the principal means of characterization. The presence of glucoseamine was early demonstrated by H. W. Bywaters [*Biochem. Z.*, **15**, 322 (1909)]. The evidence indicates a polysaccharide of the composition glucoseamine:mannose:galactose [C. Rimington, *Biochem. J.*, **34**, 931 (1940)]; ref. 19.

(43) L. Pillemer, E. E. Ecker, J. L. Oncley and E. J. Cohn, *J. Exp. Med.*, **74**, 297 (1941).

(44) T. L. McMeekin, THIS JOURNAL, **62**, 3393 (1940).

(45) It is difficult to decide, on the basis of ultracentrifugal behavior, whether a part of this denatured material was already present in the starting material because of the small amount that would have been present in Fraction IV-4.

way, it was hoped to obtain the native protein, although in lower yield and of less purity. Considerable difficulty was encountered in freeing the preparations of the euglobulin lipoprotein, as well as of the last traces of metal-combining globulin, which seemed to interact strongly with the mucoprotein.

## Experimental

Purified $\alpha_2$-mucoprotein was prepared by a series of separations involving varying conditions of *p*H, ionic strength, ethanol concentration, protein concentration and temperature. (1) Fraction IV-4 was resuspended and adjusted to *p*H 5.2, ionic strength 0.02, 18% ethanol, 2% protein and −5°. (2) The precipitate, which contained all the $\alpha_1$-lipoprotein, $\alpha_2$-globulins, together with some albumin and $\beta_1$ metal-combining globulin, was brought to *p*H 5.0, ionic strength 0.001, 1.5% protein and 0°. The euglobulin precipitate, largely lipoprotein, was discarded. (3) Crude mucoprotein was precipitated by adjusting the solution to *p*H 5.1, ionic strength 0.005, 10% ethanol and −3°. The esterase and more soluble $\alpha_2$-glycoproteins remained in solution under these conditions. (4) $\beta_1$ Metal-combining globulin was removed from the crude mucoprotein precipitate by resuspending and adjusting the conditions to *p*H 6.1, ionic strength 0.02, 19% ethanol, 1.2% protein and −5°. The mucoprotein, which remained soluble under these conditions, was reprecipitated (5) by returning to the first set of conditions: *p*H 5.2, ionic strength 0.02, 17% ethanol and −5°. The precipitate contained 6% of the protein from Fraction IV-4.

Further purification was effected (6) by reprecipitation of the mucoprotein at *p*H 5.1, ionic strength 0.003, 10% ethanol, 0.3% protein and −3°. (7) The precipitate was redissolved in water at a protein concentration of 0.5% and filtered through a Seitz type S-3 pad under pressure to remove the slight turbidity due to some residual lipoprotein in the preparation. The product was 82 per cent. $\alpha_2$-globulin by electrophoresis, the impurities being albumin (6%) $\alpha_1$-globulin (8%), and $\beta_1$-globulin (4%).

In the ultracentrifuge three poorly resolved components were observed: (a) about 10% sedimenting much like albumin and $\beta_1$ metal-combining globulin ($s$ = 4.5 to 5.5), (b) 15 to 25%, quite heterogeneous, sedimenting rapidly ($s$ = 12 to 20), and (c) the third and principal component (65 to 75 per cent.) sedimenting with $s$ = 6 to 9, depending on the protein concentration. The extrapolated value at infinite dilution was near $s$ = 11. This behavior is somewhat like that to be expected of a highly asymmetrical molecule, but more homogeneous preparations must be studied before this can be definitely proved.

The results of dry weight, nitrogen, and carbohydrate determinations are summarized in Table V. The hexose–hexoseamine ratio was close

TABLE V

PROPERTIES OF PURIFIED MUCOPROTEIN

| | |
|---|---|
| g. protein/g. nitrogen | 6.90 |
| g. hexose/g. protein | 0.0435 |
| g. hexoseamine/g. protein | 0.0284 |
| Hexose/hexoseamine | 1.53 |

to 3 to 2, instead of 2 to 1.[40] This may be due to the fact that our preparation was not pure.

The protein could be dried from the frozen state; it was insoluble in water and soluble in dilute sodium chloride, acetate, or bicarbonate. On boiling solutions up to 2% in concentration for four hours, there was no visible change. The protein was precipitated, however, with 7% trichloroacetic acid.

The mucoprotein had a marked accelerating effect on the sedimentation rate of erythrocytes which was accompanied by rouleau formation. Added to whole blood in concentrations of 0.5 g. per 100 ml., the mucoprotein increased the rate 2.5-fold over the control. Fibrinogen, which is the principal component affecting erythrocyte sedimentation rates,[46] produced a 5-fold acceleration in the same concentration. Other fractions tested, including Fraction IV-4, had no effect, or diminished the rate.

## Summary

Under controlled conditions of *p*H, temperature, ethanol, salt and protein concentrations, Fraction IV-4 of human plasma has been separated into a series of subfractions into which were concentrated plasma choline esterase, carbohydrate-rich $\alpha_2$-globulins, both glycoprotein and mucoprotein, the $\beta_1$-metal-combining globulin and albumins. These subfraction are of use in chemical physiological and clinical studies and as intermediates in the purification and crystallization of the various protein components.

RECEIVED NOVEMBER 4, 1948

(46) R. Fåhraeus, *Acta med. scand.*, **55**, 1 (1921); S. J. Gray and E. B. Mitchell, *Proc. Soc. Exptl. Biol. Med.*, **51**, 403 (1942); K. Meyer, E. Hahnel and R. R. Feiner, *ibid.*, **58**, 36 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

# Preparation and Properties of Serum and Plasma Proteins. XXI. Interactions with Bilirubin[1,2]

BY NICHOLAS H. MARTIN[3]

Many of the small molecules circulating in the blood are "bound" to one or another of the protein components of the plasma. Among these is bilirubin, one of the intermediates of porphyrin metabolism. Bennhold,[4] using the electrophoretic techniques available to him in 1932, demonstrated that, in icteric serum, bilirubin migrated with the albumin fraction. Pedersen and Waldenström[5] made similar observations in the course of ultracentrifugal studies. Since then it has been assumed that the "bound" bilirubin in the blood serum was attached to the circulating albumins.[6]

In recent years a number of components of human plasma have been isolated in highly purified form. These include crystallized human serum albumins, a crystallized $\beta_1$ metal-combining globulin and electrophoretically pure $\gamma$-globulins. In addition, a number of $\alpha$-globulins and of other $\beta$-globulins have been concentrated in various fractions.[7] This investigation was undertaken to study the interactions of bilirubin with these proteins.

## Materials[8]

**Human Serum Albumin.**—Three different preparations were used. The first had been recrystallized five times from ethanol–water mixtures containing chloroform.[9] Another preparation had been recrystallized as a mercury compound.[10] The third preparation was made from crystallized serum albumin by guanidination of the free amino groups by reaction with methyl isourea, according to a modification of the method of Greenstein.[11] The modified, or guanidinated, preparation had approximately fifty-four of its amino groups replaced with guanidine groups.[12]

**Bovine serum albumin** was Armour's crystallized preparation.

**$\alpha_1$-Globulin.**—This globulin was concentrated from Fraction V-1 of human plasma. It was the component responsible for the indirect van den Bergh reaction[13] and, as isolated, already contained stably-bound bilirubin.[14]

**$\alpha_2$-Globulins.**—The first preparation was isolated from Fraction IV-6[15] and was 97% $\alpha_2$-globulin by electrophoresis. It contained approximately 6% carbohydrate. A second preparation was isolated from Fraction IV-7 and was 74% $\alpha_2$-globulin by electrophoresis. It was estimated to contain 3% carbohydrate.[16]

**$\beta_1$ Metal-Binding Globulin.**—This protein was purified from fraction IV-7 and crystallized from ethanol–water mixtures.[16]

**$\gamma$-Globulin** was 98% pure by electrophoresis.[17]

**Bilirubin** (Armour Laboratories) was isolated from ox bile. In chloroform, ethylene dichloride and acetone it had a well-defined absorption maximum at 450 m$\mu$ with a molecular extinction coefficient of 55,300. This is in good agreement with the value of 54,900 given by Heilmeyer.[18]

## Methods

Dissolved in 0.01 *N* sodium hydroxide at room temperature, the bilirubin had an ill-defined absorption maximum lying between 425 and 440 m$\mu$ whose height tended to decrease rapidly on standing. Preservation at 0° in the absence of light delayed but did not inhibit degradation. Advantage was taken of the ability of ascorbic acid to stabilize solutions of bilirubin.[19] Solutions were prepared by dissolving weighed amounts of bilirubin in 0.01 *N* sodium hydroxide at 0°, and immediately adding phosphate buffer containing sufficient ascorbate so that the final ratio of ascorbate to bilirubin was twenty to one. The extinction of solutions prepared in this manner decreased about 10% in forty-eight hours while the peak remained reasonably well defined at 430 to 435 m$\mu$ (Fig. 1). That ascorbic acid did not interfere with the interactions being studied was indicated by the fact that, within the experimental error, no difference was observed in the amount of bilirubin interacting with albumin in the presence or absence of ascorbate. Furthermore, in weight concentrations of ascorbate of from 5 to 30-fold the bilirubin concentration appeared to have no apparent effect on the extent of the interaction.

(1) This paper is Number 77 in the series "Studies on Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

(2) This work was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council which included a grant from the American College of Physicians. From August, 1941, to July, 1946, it was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. Since then it has been aided by a grant recommended by the Panel on Hematology of the National Institute of Health.

(3) Research Fellow in Pediatrics, Harvard Medical School, 1946–1947. Present address: St. George's Hospital Medical School, University of London, England.

(4) H. Bennhold, *Ergeb. inn. Med. Kinderheilk.*, **42**, 273 (1932).

(5) K. O. Pedersen and J. Waldenström, *Z. physiol. Chem.*, **245**, 152 (1937).

(6) I. Snapper and W. M. Bendien, *Acta. Med. Scand.*, **98**, 77 (1938).

(7) E. J. Cohn, L. E. Strong, W. L. Hughes, Jr., D. J. Mulford, J. N. Ashworth, M. Melin and H. L. Taylor, THIS JOURNAL, **68**, 459 (1946).

(8) The proteins used in these studies were, with the exception of the bovine serum albumin, prepared in the Department of Physical Chemistry during the course of investigations leading to the isolation and purification of the protein components of plasma. Acknowledgment is made to the various members of the department for making these components available. The bovine serum albumin was obtained through the courtesy of Dr. J. D. Porsche of the Armour Laboratories.

(9) E. J. Cohn, W. L. Hughes, Jr., and J. H. Weare, THIS JOURNAL, **69**, 1753 (1947).

(10) W. L. Hughes, Jr., *ibid.*, **69**, 1836 (1947).

(11) J. P. Greenstein, *J. Biol. Chem.*, **109**, 529 (1925).

(12) H. A. Saroff, W. L. Hughes, Jr., and A. L. Carney, in preparation. Earlier studies on this reaction were carried out by Hughes in 1940–1941. See *Chem. Revs.*, **28**, 395 (1941), footnote 10, p. 413.

(13) E. J. Cohn, *Blood*, **3**, 471 (1948).

(14) The purification of the albumin in Fraction V is described in reference 7. Fraction V-1 is that part of Fraction V which was insoluble at 10% ethanol, $\Gamma/2$ 0.01 and *p*H 4.7 at −5°. We are indebted to Dr. G. Derouaux for the preparation of Fraction V-1.

(15) D. M. Surgenor, L. E. Strong, H. L. Taylor R. S. Gordon, Jr., and D. M. Gibson, THIS JOURNAL, **71**, 1223 (1949).

(16) B. A. Koechlin, in preparation.

(17) J. L. Oncley, M. Melin, D. A. Richert, J. W. Cameron and P. M. Gross, Jr., THIS JOURNAL, **71**, 451 (1949).

(18) L. Heilmeyer, *Biochem. Z.*, **232**, 229 (1931).

(19) A. Lambrecht and G. Barac, *Bull. soc. chim. biol.*, **21**, 1171 (1939).

**Electrophoretic measurements** were carried out in the apparatus of Tiselius,[20] using the 11-cm. analytical cell. The electrophoretic migration of the protein solutions containing bilirubin was studied and in those fractions which were not homogeneous it was possible to observe with which component or components the bilirubin traveled, thus obtaining confirmatory evidence of the interaction observed by other techniques.

**Dialysis experiments** were carried out in two chambered systems across cellophane membranes. The solutions were kept at 0° in the absence of light and oxygen. Equilibration was aided by repeated inversion of the tubes. The outer chamber contained bilirubin dissolved in aqueous buffer, stabilized with ascorbate, as described, and in contact with solid bilirubin. The inner chamber contained albumin dissolved in the same buffer. A control experiment in which the inner chamber contained the buffer without protein, was run simultaneously. It was thus possible to compensate for losses of bilirubin due to its instability, as well as for losses in handling. Equilibrium was considered to be attained when the concentrations of bilirubin inside and outside the membranes were the same in the control experiment. Because of the instability of the bilirubin the experiments were not run longer than forty-eight hours. Attempts to avoid dialysis were unsuccessful due to difficulties in determining free and bound bilirubin directly.

***p*H measurements** were made with a glass electrode.

**Absorption spectra** were measured with a Beckman spectrophotometer using quartz cells.

## Results

### 1. Studies on the Interaction of Bilirubin with Serum Albumin

**a. Spectrophotometry.**—Within the range of concentration used in this work, bilirubin, either alone or in the presence of protein, was found to obey Beer's law. In aqueous phosphate buffer the molecular extinction coefficient at 435 to 440 mμ was 46,700, taking 584 as the molecular weight of bilirubin, and was independent of *p*H between *p*H 7.0 and *p*H 8.5. In the presence of crystallized human or bovine serum albumin the absorption maximum was displaced to 460 mμ (Fig. 1), while the extinction coefficient remained the same. The wave length of the maximum, and the extinction coefficient of bilirubin in the presence of albumin, were also independent of *p*H between *p*H 7.0 and 8.5. The characteristic shift in the absorption maximum of bilirubin, resulting from the addition of albumin, was taken as evidence of interaction. No such shift occurred when the albumin was replaced by γ-globulin.

**b. Electrophoresis.**—Further evidence of interaction was obtained when a solution of albumin to which bilirubin had been added was analyzed in the electrophoresis apparatus of Tiselius. The pigment was found to migrate in sharp coincidence with and at the same mobility as the albumin peak. In the presence of γ-globulin, no such clearly defined pigment boundary was observed. Attempts to follow the migration of the bilirubin in the absence of protein were unsuccessful.

**c. Dialysis Experiments.**—The results of dialysis studies with crystallized human serum albumin are summarized in Table I. Under these experimental conditions, and within the limits of *p*H and concentrations studied, it was found that between 2 and 3 moles of bilirubin interacted with each mole of albumin. Human serum albumin crystallized as the mercury compound behaved in the same manner. However, the guanidinated albumin was found to bind only approximately half a mole of bilirubin per mole.

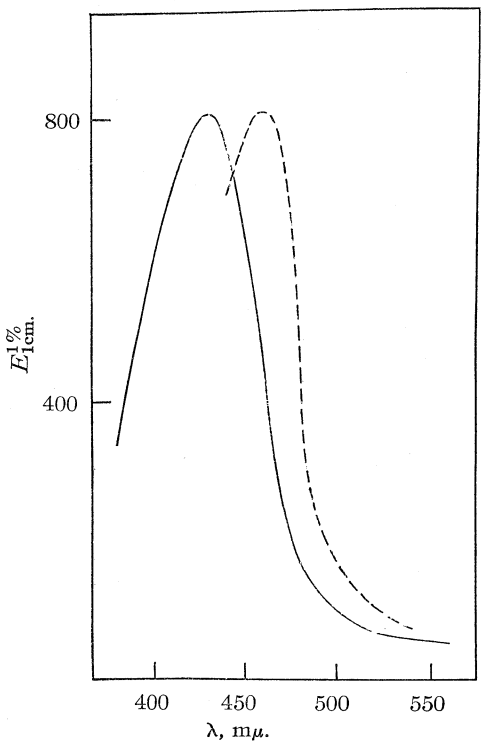



Fig. 1.—Absorption spectra of bilirubin alone and in the presence of excess albumin. *Solid line:* bilirubin, 1 mg./100 ml.; ascorbic acid 20 mg./100 ml. in *p*H 7.8, Γ/2 0.1 phosphate. *Dashed line:* Same in presence of 250 mg./100 ml. human serum albumin.

TABLE I

INTERACTION OF ALBUMINS AND BILIRUBIN IN Γ/2 0.10 PHOSPHATE BUFFER AT 0°

| | Protein system at *p*H 7.4 | | Protein system at *p*H 7.6 | | Protein system at *p*H 7.9 | |
|---|---|---|---|---|---|---|
| | inside bag | outside bag | inside bag | outside bag | inside bag | outside bag |
| Volume, ml. | 5 | 45 | 5 | 45 | 5 | 45 |
| Concn. of albumin: mg./100 ml. | 330 | 0 | 600 | 0 | 600 | 0 |
| Concn. of bilirubin: mg./100 ml. | 5.3 | 0.1 | 13.4 | 1.0 | 19.6 | 2.7 |
| Absorption maximum mμ | 460 | 435 | 460 | 435 | 460 | 435 |
| Concn. of bound bilirubin: mg./100 ml. | 5.2 | ... | 12.4 | ... | 16.9 | ... |
| Moles bilirubin bound per mole albumin | 1.9 | ... | 2.5 | ... | 3.3 | ... |

**d. Range of Stability of the Complex.**—A bilirubin–albumin complex prepared at *p*H 7.6

(20) A. Tiselius, *Trans. Faraday Soc.*, **33**, 524 (1937).

TABLE II

INTERACTIONS OF BILIRUBIN WITH PURIFIED HUMAN SERUM PROTEINS AT *p*H 7.6, Γ/2 = 0.10 PHOSPHATE BUFFER

| | Composition by electrophoresis in mg./100 ml. | | | | | | Bound bilirubin mg./g. protein | Bilirubin assumed to be bound to albumin mg./g. | Bilirubin apparently bound to globulin mg./g. |
|---|---|---|---|---|---|---|---|---|---|
| | Albumin | Globulins $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | $\gamma$ | | | |
| Albumin, crystallized | 500 | ... | ... | ... | ... | ... | 21.1 | 21.1 | 0 |
| $\alpha_1$-Globulin from Fraction V-1 | 100 | 250 | 100 | 50 | ... | ... | 16.4 | 4.2 | 12.2 |
| $\alpha_2$-Globulin from Fraction IV-6 | 5 | ... | 485 | 10 | ... | ... | 2.8 | 0.2 | 2.6 |
| $\alpha_2$-Globulin from Fraction IV-7 | 40 | 30 | 370 | 60 | ... | ... | 11.4 | 1.8 | 9.6 |
| $\beta_1$ Metal-combining globulins, crystallized from Fraction IV-7 | ... | ... | ... | 500 | ... | ... | 0.1 | 0 | 0 |
| $\gamma$-Globulin from Fraction II | Trace | ... | ... | ... | ... | 500 | Trace | Trace | Trace |

and containing 2 moles of bilirubin per mole of albumin was examined over a *p*H range of 8 to 3.5. The absorption maximum remained constant at 460 mμ betwen *p*H 8 and 5. Dissociation, as evidenced by a gradual return of the maximum to 435 mμ and precipitation of bilirubin, occurred near *p*H 4.5.[21] This is approximately the same range as was found by Klotz for the interactions of bovine serum albumin with methyl orange and azosulfathiazole.[22,23] Further, Stenhagen and Teorell have shown that albumin and "yellow pigment" migrated together in electrophoresis between *p*H 4.18 and 8.0.[24]

## 2. Studies on the Interaction of Bilirubin with the Serum Globulins

When the interaction of bilirubin with some of the globulin-containing fractions of human plasma was studied, it was observed that in certain cases more bilirubin was bound by the protein than could readily be accounted for by the amounts of albumin present in the fractions. This was confirmed, in the case of Fraction IV-7, by observing the electrophoretic behavior of the fraction in the presence of bilirubin. This experiment suggested that the bilirubin was bound to the $\alpha_2$-globulin, as well as to the albumin present in the fraction. The main component, $\beta_1$ metal-combining globulin, did not bind bilirubin under these conditions.

Accordingly, dialysis studies were made with a number of fractions rich in $\alpha$-, $\beta_1$- and $\gamma$-globulins. The results are given in Table II. Since the molecular weights of some of these components are not known, the data have been calculated on a gram basis. In the fourth column, the amount of bilirubin that would normally be bound to the albumin in the fraction has been calculated. The difference between this and the total bound bilirubin (column 3) has been taken as a measure of the binding capacity of the globulin components present. This involves the assumption that the albumin present in these fractions behaved normally with respect to its interaction with bilirubin. It does not preclude the possibility of other phenomena which might give rise to interactions with bilirubin.

The results indicate that neither $\gamma$-globulin nor the $\beta_1$ metal-combining globulin bind, if any, not more than traces of bilirubin. The $\alpha_1$-globulin from Fraction V-1 bound nearly four times as much bilirubin as would be anticipated from the amount of albumin present as impurity. Indeed, it is possible that the pure $\alpha_1$-globulin from this fraction may be capable of binding more bilirubin per gram than albumin. Of the $\alpha_2$-globulins studied, that isolated from Fraction IV-7 bound more bilirubin than the $\alpha_2$-globulin from Fraction IV-6.[25]

## Summary

From the present study it would appear that crystallized serum albumin forms a complex with bilirubin which is stable over a *p*H range including but extending well beyond physiological limits. The amount of this complex that formed was diminished when the free amino groups had been guanidinated by methyl isourea. Quantitative data suggest that, within the limits of bilirubin and protein concentration and in the range of *p*H used, the composition of the complex is of the order of 3 moles of bilirubin to 1 mole of albumin.

The studies on the interaction of bilirubin with fractions containing high proportions of $\alpha$-globulins suggest that complex formation can take place between $\alpha$-globulins and bilirubin. This is most marked with the $\alpha_1$-globulin isolated from Fraction V-1 but is evident with the $\alpha_2$-globulins isolated from Fractions IV-6 and IV-7 as well. The crystallized $\beta_1$ metal-combining globulin and the $\gamma$-globulin examined did not appear to interact with bilirubin to any significant extent.

BOSTON, MASS. RECEIVED[26] JULY 30, 1948

(21) It is possible that the dissociation of the complex was favored, at *p*H 4.5, by the extremely low solubility of bilirubin.

(22) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

(23) I. M. Klotz, *ibid.*, **68**, 2299 (1946).

(24) E. Stenhagen and T. Teorell, *Nature*, **141**, 415 (1938).

(25) Since this paper was completed we have learned of studies on the state of bilirubin in serum now being conducted by Dr. Ulrich Westphal at the University of Tübingen in Germany (French Zone). Dr. Westphal states: "Electrophoresis diagrams using the Philpot method (by courtesy of Dr. E. Wiedemann, Basel) demonstrate that bilirubin when added to human serum, is bound partly to the albumins, and partly to the $\alpha_2$ globulin fraction."

(26) Original manuscript received March 12, 1947.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF CASE INSTITUTE OF TECHNOLOGY]

# Equilibria in Saturated Salt Solutions. IV. The Quaternary System $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75°

BY WILLIAM J. LIGHTFOOT AND CARL F. PRUTTON

In previous papers[1,2,3] the isotherms for the ternary systems at 35 and 75° and for the quaternary system at 35° were reported for the system $CaCl_2$–$MgCl_2$–KCl–$H_2O$.

## Experimental Method

The experimental methods used were identical with those employed in the earlier papers. Temperature at which solutions and solid phases were brought into equilibrium was 75 ± 0.02°. The three methods of identification for the solid phases employed in the earlier work[3] were used.

**The Quaternary System.**—The data for the quaternary system at 75° are given in Table I. In Fig. 1 the upper portion of the quaternary tetrahedral figure is shown schematically. The relative proportions of the saturation surfaces are indicated. The same characteristic of magnesium chloride solutions that was noted in the ternaries and quaternary at 35° is found here: carnallite remains almost insoluble in solutions saturated for $MgCl_2 \cdot 6H_2O$. Tachydrite solutions dissolve considerably more carnallite, particularly as the saturated solution becomes richer in calcium chloride. This ability of tachydrite solutions to dissolve more carnallite is more pronounced than at 35°. The presence of the field of a new compound, $2KCl \cdot CaCl_2 \cdot 2H_2O$, decreases the range of existence of carnallite appreciably.

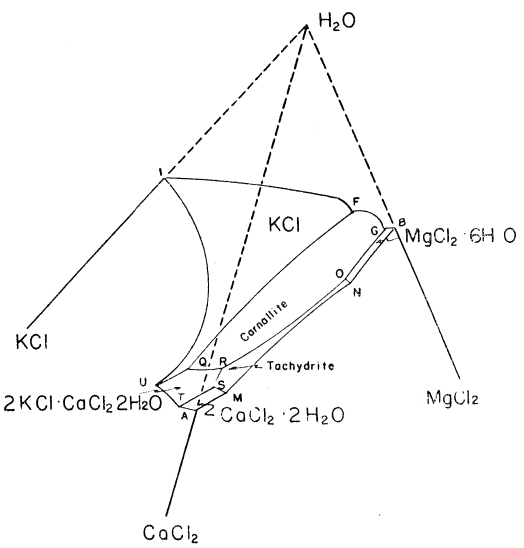



Fig. 1.—The system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75°, upper portion of tetrahedron.

The saturation surface of $MgCl_2 \cdot 6H_2O$ has been reduced so that it now covers a very small part of the diagram. The area of saturation of $CaCl_2 \cdot 2H_2O$ is the second smallest with tachydrite and $2KCl \cdot CaCl_2 \cdot 2H_2O$ coming next in size, each with about the same area. Again KCl and carnallite occupy the largest areas in the diagram. However, the field of carnallite no longer extends from one side almost to the other.

With the introduction of a new solid phase, $2KCl \cdot CaCl_2 \cdot 2H_2O$, the relationships in the quaternary diagram have been altered considerably. Where at lower temperatures, $CaCl_2 \cdot 4H_2O$ and carnallite were in equilibrium along a portion of the isotherm, the presence of the new phase completely separates $CaCl_2 \cdot 2H_2O$ from carnallite. No formation of a quaternary compound was found at 75°.

In Fig. 2 the quaternary isotherm has been projected on the $MgCl_2$–KCl–$H_2O$ plane. Points F, G, M, N, T, and U are the respective invariant points of the associated ternary systems. Area IFQU, is the saturation surface of KCl; FGORQ, that of carnallite, $KCl \cdot MgCl_2 \cdot 6H_2O$; NOGB, that of $MgCl_2 \cdot 6H_2O$; MNORS, that of tachydrite, $CaCl_2 \cdot 2MgCl_2 \cdot 12H_2O$; AMST, that of $CaCl_2 \cdot 2H_2O$; and RSTUQ, that of $2KCl \cdot CaCl_2 \cdot 2H_2O$.

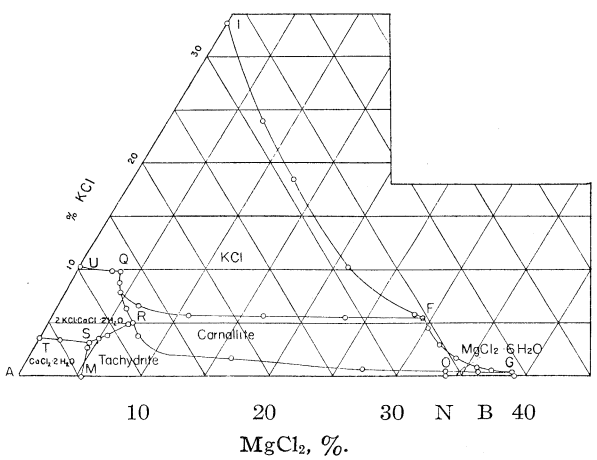



Fig. 2.—Equilibria in the quaternary system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75°, projection on the $MgCl_2$–KCl–$H_2O$ plane.

The curve FQ is the intersection of the KCl surface with the carnallite surface, and all points on it represent equilibrium between the two solid phases, KCl and carnallite, and saturated solution. GO represents solutions saturated with carnallite

(1) Lightfoot and Prutton, THIS JOURNAL, **68**, 1001 (1946).
(2) Lightfoot and Prutton, *ibid.*, **69**, 2098 (1947).
(3) Lightfoot and Prutton, *ibid.*, **71**, 1236 (1949).

TABLE I

THE QUATERNARY SYSTEM $MgCl_2$–$CaCl_2$–KCl–$H_2O$ AT 75°

| Point or line | Saturated solution, Weight per cent. $MgCl_2$ | $CaCl_2$ | KCl | Wet residue, $MgCl_2$ | $CaCl_2$ | KCl | Jänecke projection, weight, % $MgCl_2$ | $CaCl_2$ | Solid phase |
|---|---|---|---|---|---|---|---|---|---|
| F | 29.26 | ... | 5.57 | | | | 84.01 | ... | Carnallite + KCl |
| FQ | 23.14 | 8.56 | 5.56 | | | | 62.10 | 22.97 | Carnallite + KCl |
| FQ | 16.71 | 18.07 | 5.61 | | | | 41.37 | 44.74 | Carnallite + KCl |
| FQ | 10.89 | 27.57 | 5.85 | | | | 24.58 | 62.22 | Carnallite + KCl |
| FQ | 6.39 | 36.76 | 6.73 | 12.99 | 21.46 | 25.80 | 12.81 | 73.70 | Carnallite + KCl |
| FQ | 4.48 | 41.95 | 7.81 | | | | 8.26 | 77.34 | Carnallite + KCl |
| FQ | 3.85 | 44.63 | 8.80 | | | | 6.72 | 77.92 | Carnallite + KCl |
| Q | 3.49 | 46.28 | 9.70 | | | | | | Carnallite + KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| Q | 3.44 | 46.34 | 9.70 | | | | | | Carnallite + KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| Q | 3.49 | 46.32 | 9.70 | 6.83 | 33.82 | 26.93 | | | Carnallite + KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| Q mean | 3.47 | 46.31 | 9.70 | | | | 5.83 | 77.86 | Carnallite + KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| G | 38.86 | ... | 0.32 | | | | 99.18 | ... | Carnallite + $MgCl_2 \cdot 6H_2O$ |
| GO | 36.20 | 4.26 | 0.38 | 37.18 | 3.03 | 4.37 | 88.64 | 10.43 | Carnallite + $MgCl_2 \cdot 6H_2O$ |
| O | 33.64 | 8.38 | 0.40 | | | | | | Carnallite + $MgCl_2 \cdot 6H_2O$ + Tachydrite |
| O | 33.69 | 8.40 | 0.38 | | | | | | Carnallite + $MgCl_2 \cdot 6H_2O$ + Tachydrite |
| O | 33.66 | 8.42 | 0.39 | 36.16 | 6.29 | 4.11 | | | Carnallite + $MgCl_2 \cdot 6_2HO$ + Tachydrite |
| O mean | 33.68 | 8.40 | 0.39 | | | | 79.30 | 19.78 | Carnallite + $MgCl_2 \cdot 6H_2O$ + Tachydrite |
| OR | 26.95 | 16.96 | 0.67 | | | | 60.45 | 38.04 | Carnallite + Tachydrite |
| OR | 16.12 | 32.00 | 1.58 | 19.73 | 28.15 | 3.75 | 32.43 | 64.39 | Carnallite + Tachydrite |
| OR | 7.92 | 44.90 | 3.68 | | | | 14.02 | 79.47 | Carnallite + Tachydrite |
| R | 6.76 | 46.44 | 5.11 | | | | | | Carnallite + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| R | 6.73 | 46.46 | 5.12 | 16.19 | 31.25 | 14.98 | | | Carnallite + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| R | 6.79 | 46.40 | 5.11 | | | | | | Carnallite + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| R mean | 6.76 | 46.43 | 5.11 | | | | 11.60 | 79.64 | Carnallite + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| RQ | 5.58 | 46.69 | 6.25 | 11.51 | 31.19 | 25.95 | 9.54 | 79.78 | Carnallite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| T | ... | 57.66 | 3.59 | | | | ... | 94.14 | $CaCl_2 \cdot 2H_2O$ + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| TS | 1.85 | 55.23 | 3.35 | 1.08 | 59.95 | 6.83 | 3.06 | 91.40 | $CaCl_2 \cdot 2H_2O$ + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| M | 5.28 | 52.58 | ... | | | | 9.13 | 90.87 | $CaCl_2 \cdot 2H_2O$ + Tachydrite |
| MS | 4.66 | 52.47 | 2.65 | 9.21 | 53.02 | 1.54 | 7.80 | 87.77 | $CaCl_2 \cdot 2H_2O$ + Tachydrite |
| S | 4.56 | 52.45 | 3.08 | | | | | | $CaCl_2 \cdot 2H_2O$ + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| S | 4.54 | 52.54 | 3.06 | | | | | | $CaCl_2 \cdot 2H_2O$ + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| S | 4.54 | 52.55 | 3.06 | 9.63 | 46.60 | 6.65 | | | $CaCl_2 \cdot 2H_2O$ + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| S mean | 4.55 | 52.51 | 3.07 | | | | 7.57 | 87.33 | $CaCl_2 \cdot 2H_2O$ + Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| SR | 4.51 | 52.29 | 3.19 | | | | 7.52 | 87.16 | Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| SR | 4.97 | 51.21 | 3.44 | 6.55 | 45.18 | 15.19 | 8.34 | 85.89 | Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| SR | 5.44 | 50.06 | 3.81 | | | | 9.17 | 84.40 | Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| SR | 6.68 | 46.63 | 5.02 | | | | 11.45 | 79.94 | Tachydrite + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| U | ... | 51.20 | 10.33 | | | | ... | 83.21 | KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| UQ | 2.71 | 47.32 | 9.84 | 1.49 | 39.94 | 32.06 | 4.53 | 79.04 | KCl + $2KCl \cdot CaCl_2 \cdot 2H_2O$ |
| N | 33.91 | 8.31 | ... | | | | 80.32 | 19.68 | Tachydrite + $MgCl_2 \cdot 6H_2O$ |

and $MgCl_2 \cdot 6H_2O$; RQ, carnallite and $2KCl \cdot CaCl_2 \cdot 2H_2O$; UQ, KCl and $2KCl \cdot CaCl_2 \cdot 2H_2O$; TS, $CaCl_2 \cdot 2H_2O$ and $2KCl \cdot CaCl_2 \cdot 2H_2O$; SR, tachydrite and $2KCl \cdot CaCl_2 \cdot 2H_2O$; MS, $CaCl_2 \cdot 2H_2O$ and tachydrite; and NO, $MgCl_2 \cdot 6H_2O$ and tachydrite.

There are four isothermal invariant points in the system, R, S, Q, and O. The three solid phases in equilibrium with saturated solution at each point are: at Q, KCl, carnallite and $2KCl \cdot CaCl_2 \cdot 2H_2O$; at S, $CaCl_2 \cdot 2H_2O$, tachydrite, and $2KCl \cdot CaCl \cdot 2H_2O$; and at O, $MgCl_2 \cdot 6H_2O$, tachydrite, and carnallite.

In Figs. 3 and 4, the quaternary relationships have been projected on the $CaCl_2$–KCl–$H_2O$ and the $CaCl_2$–$MgCl_2$–$H_2O$ planes respectively. In the projection on the $CaCl_2$–KCl–$H_2O$ face there appears to be an overlapping of the KCl and carnallite surfaces. This is due only to the method of projection. The saturation curves can be readily distinguished from one another. The projection on the $CaCl_2$–$MgCl_2$–$H_2O$ plane is perhaps the

clearest in that there is no overlapping or superimposing of the different curves.

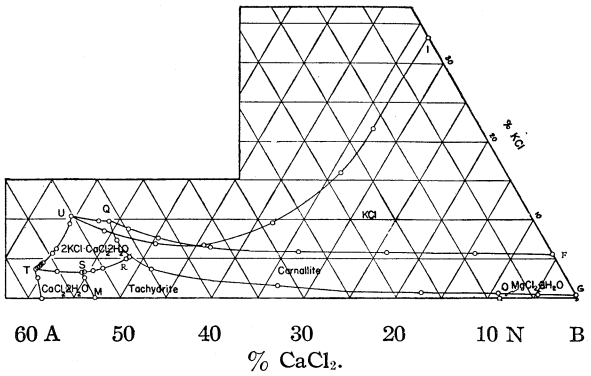



Fig. 3.—Equilibria in the system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75° projected on the $CaCl_2$–KCl–$H_2O$ plane.

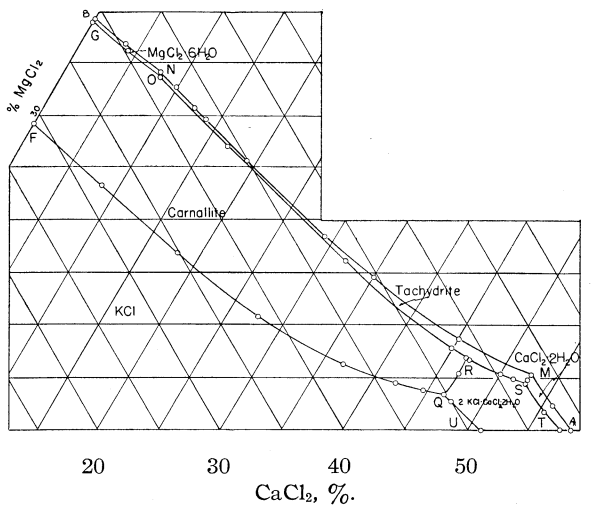



Fig. 4.—Equilibria in the quaternary system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75°, projection on the $CaCl_2$–$MgCl_2$–$H_2O$ plane.

The data on the quaternary system at 75° are given in Table I on a water free basis, and have been plotted in Figure 5, which gives the Jänecke projection. The coexistent solid phases are connected by straight lines, the triangles formed represent the three solid phases which are in equilibrium at the invariant points. The notations are consistent with those used in the other projections. Comparison with the similar type of diagram at 35° shows that all areas in general have increased except $MgCl_2 \cdot 6H_2O$. The main difference is that saturated solutions dissolve more KCl.

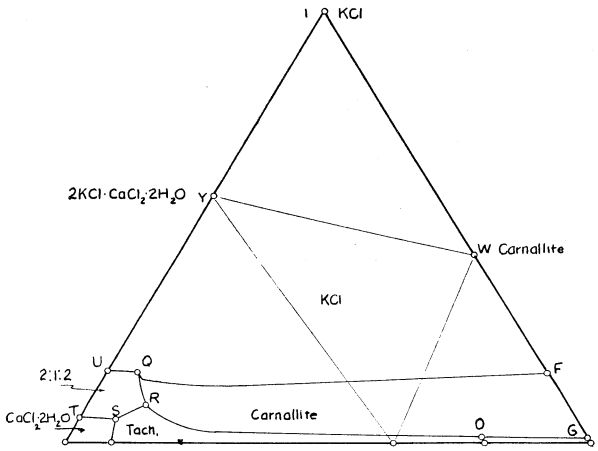



Fig. 5.—Quaternary system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75°, Jänecke projection.

## Summary

1. The isotherm for the quaternary system $CaCl_2$–$MgCl_2$–KCl–$H_2O$ at 75° has been determined.

CLEVELAND HEIGHTS, OHIO RECEIVED AUGUST 25, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF CASE INSTITUTE OF TECHNOLOGY]

# Equilibria in Saturated Salt Solutions. V. The Quinary System $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$ at 35°

BY TED A. MEYER, CARL F. PRUTTON AND WILLIAM J. LIGHTFOOT

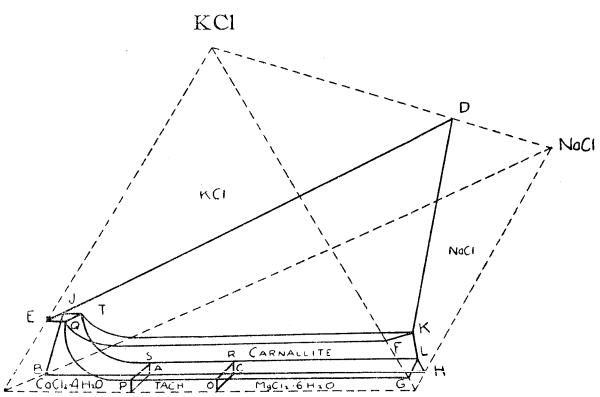
Invariant points in the quinary system $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$; in the quaternary systems $CaCl_2$–KCl–NaCl–$H_2O$, $MgCl_2$–KCl–NaCl–$H_2O$ and $CaCl_2$–$MgCl_2$–NaCl–$H_2O$; and in the ternary systems $CaCl_2$–NaCl–$H_2O$, $MgCl_2$–NaCl–$H_2O$ and KCl–NaCl–$H_2O$ were determined at 35° to supplement the existing data. Data for the remaining associated ternary systems and quaternary system are found in the papers of Lightfoot and Prutton.[1,2] Seidell[3] gives references to most of the other published data on these systems

## Experimental Method

Calcium chloride tetrahydrate was made by neutralizing C. P. hydrochloric acid with C. P. calcium carbonate and subsequent crystallization at 35°. Magnesium chloride hexahydrate was made by reaction of C. P. hydrochloric acid with distilled magnesium and the crystallization of the chloride at room temperature. A. C. S. grade potassium and sodium chlorides were used without further purification.

Samples of different over-all composition were made up for each invariant point, and it was possible to obtain analyses of fixed composition on these separate solutions that were within the limits for the experimental methods involved. Solid phases were checked by microscopic examination.

The samples were agitated three to five days in the usual manner in bottles in a thermostat maintained at 35 ± 0.02° to attain equilibrium. Each sample was seeded with the appropriate solid phase. Sampling and analytical methods for the determination of total chloride, calcium and potassium contents were identical with those used by Lightfoot and Prutton.[1] Magnesium was calculated by difference in all cases. Sodium was determined as uranyl zinc sodium acetate on a separate sample of saturated solution.




$CaCl_2$ $MgCl_2$

Fig. 1.—The quinary system $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$ at 35°.

(1) Lightfoot and Prutton, THIS JOURNAL, **68**, 1001 (1946).

(2) Lightfoot and Prutton, *ibid.*, **70**, 4112 (1948).

(3) Seidell, "Solubilities of Inorganic and Metal Organic Compounds," Vol. I, third ed., D. Van Nostrand, New York, N. Y., 1940.

## Experimental Results

Table I gives the data for the quinary system $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$ at 35°. As it becomes increasingly difficult to graphically represent phase equilibria as the number of components increases, a schematic three dimensional figure probably offers the clearest conception of the relationships existing. In Fig. 1 the three dimensional model for the quinary system is shown schematically as a regular tetrahedron.

Each line forming the sides of the tetrahedron represents equilibria in the ternary system composed of the two salts at the ends of the line and water. Each face represents the equilibria in a given quaternary system. This last face is a projection by the Jänecke method of the equilibria in a quaternary tetrahedron on the base of the tetrahedron. Unfortunately in such a projection, there is no satisfactory method for representing water content of the saturated solutions and everything must be dealt with on a zero per cent. water basis. Each Jänecke projection of the quaternary systems forms the sides of the quinary tetrahedron. Equilibria in the quinary system are represented by points within the body of the tetrahedron.

A point on the line joining potassium chloride and magnesium chloride would represent a saturated solution of magnesium chloride and potassium chloride in equilibrium with one or two solid phases. At point F the two solid phases would be potassium chloride and carnallite, $KCl \cdot MgCl_2 \cdot 6H_2O$. At a point between F and G there would be only one solid phase, carnallite.

Within the area bounded by potassium chloride, F, K and D, a point would represent a saturated solution containing potassium chloride, magnesium chloride, and sodium chloride in equilibrium with potassium chloride as the solid phase. Along the line DK, the solid phases potassium chloride and sodium chloride would be present. At point K, a quaternary isothermal invariant point, the three phases, carnallite, potassium chloride and sodium chloride would exist. This same relationship holds true for the other quaternary faces.

In the quinary system, a point within the volume bounded by FGLKTQPOSR, the carnallite volume, would be a saturated solution containing potassium chloride, magnesium chloride, sodium chloride, calcium and chloride in equilibrium with one solid phase, carnallite. A point

TABLE I

THE QUINARY SYSTEM $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$ AT 35°

| Point | Saturated solution, Weight % $MgCl_2$ | $CaCl_2$ | KCl | NaCl | Solid phase |
|---|---|---|---|---|---|
| D | ... | ... | 12.35 | 19.93 | KCl + NaCl |
| D | ... | ... | 12.34 | 19.88 | KCl + NaCl |
| H | 35.96 | ... | ... | 0.32 | $MgCl_2 \cdot 6H_2O$ + NaCl |
| H | 35.93 | ... | ... | 0.33 | $MgCl_2 \cdot 6H_2O$ + NaCl |
| G | 36.17 | ... | 0.14 | ... | $MgCl_2 \cdot 6H_2O$ + carnallite[a] |
| F | 27.33 | ... | 3.81 | ... | KCl + carnallite |
| N | 18.18 | 26.68 | ... | ... | $MgCl_2 \cdot 6H_2O$ + tachydrite[b] |
| M | 6.20 | 45.03 | ... | ... | $CaCl_2 \cdot 4H_2O\alpha$ + tachydrite |
| B | ... | 51.33 | ... | 0.33 | $CaCl_2 \cdot 4H_2O\alpha$ + NaCl |
| B | ... | 51.31 | ... | 0.33 | $CaCl_2 \cdot 4H_2O\alpha$ + NaCl |
| E | ... | 50.45 | 6.48 | ... | $CaCl_2 \cdot 4H_2O\alpha$ + KCl |
| K | 27.87 | ... | 1.98 | 1.45 | Carnallite + KCl + NaCl |
| K | 27.88 | ... | 2.02 | 1.45 | Carnallite + KCl + NaCl |
| L | 35.88 | ... | 0.09 | 0.33 | $MgCl_2 \cdot 6H_2O$ + carnallite + NaCl |
| L | 35.86 | ... | 0.09 | .33 | $MgCl_2 \cdot 6H_2O$ + carnallite + NaCl |
| Q | 1.02 | 49.76 | 6.46 | ... | Carnallite + KCl + $CaCl_2 \cdot 4H_2O\alpha$ |
| P | 5.91 | 45.30 | 0.99 | ... | Carnallite + $CaCl_2 \cdot 4H_2O\alpha$ + tachydrite |
| O | 18.07 | 26.74 | 0.23 | ... | Carnallite + $MgCl_2 \cdot 6H_2O$ + tachydrite |
| J | ... | 49.75 | 6.77 | .33 | $CaCl_2 \cdot 4H_2O\alpha$ + KCl + NaCl |
| J | ... | 49.69 | 6.79 | .33 | $CaCl_2 \cdot 4H_2O\alpha$ + KCl + NaCl |
| A | 6.53 | 44.67 | ... | .28 | $CaCl_2 \cdot 4H_2O\alpha$ + tachydrite + NaCl |
| A | 6.48 | 44.73 | ... | .28 | $CaCl_2 \cdot 4H_2O\alpha$ + tachydrite + NaCl |
| C | 18.46 | 26.52 | ... | .32 | $MgCl_2 \cdot 6H_2O$ + tachydrite + NaCl |
| C | 18.51 | 26.45 | ... | .32 | $MgCl_2 \cdot 6H_2O$ + tachydrite + NaCl |
| T | 1.41 | 48.83 | 6.28 | .32 | $CaCl_2 \cdot 4H_2O\alpha$ + carnallite + KCl + NaCl |
| T | 1.34 | 48.77 | 6.25 | .32 | $CaCl_2 \cdot 4H_2O\alpha$ + carnallite + KCl + NaCl |
| R | 17.41 | 27.18 | 0.21 | .26 | $MgCl_2 \cdot 6H_2O$ + carnallite + tachydrite + NaCl |
| R | 17.50 | 27.10 | .21 | .26 | $MgCl_2 \cdot 6H_2O$ + carnallite + tachydrite + NaCl |
| S | 6.17 | 44.70 | .97 | .28 | $CaCl_2 \cdot 4H_2O\alpha$ + carnallite + tachydrite + NaCl |
| S | 6.21 | 44.72 | .97 | .28 | $CaCl_2 \cdot 4H_2O\alpha$ + carnallite + tachydrite + NaCl |

[a] Carnallite = $KCl \cdot MgCl_2 \cdot 6H_2O$. [b] Tachydrite = $CaCl_2 \cdot 2MgCl_2 \cdot 12H_2O$.

on the three dimensional surface within the tetrahedron bounded by FKTQ would have the solid phases, carnallite and potassium chloride. Along the line KT the solid phases would be carnallite, potassium chloride, and sodium chloride; along JT, $CaCl_2 \cdot 4H_2O\alpha$, potassium chloride, and sodium chloride; along QT, $CaCl_2 \cdot 4H_2O\alpha$, carnallite, and potassium chloride. These three lines join at point T, a quinary isothermal invariant point, where the four solid phases, carnallite, $CaCl_2 \cdot 4H_2O\alpha$, potassium chloride and sodium chloride are co-existent.

The same relationships can be reasoned for the other volumes, surfaces, lines and points in the quinary figure.

Literature values for the sodium chloride content of the invariant points of the systems studied are not in good agreement with each other and, in general, are higher than the values given in Table I. This might be explained by the fact that many of these investigations were carried out prior to the development of the zinc uranyl acetate method for sodium.

The most striking feature of the data of this investigation is the constancy of the sodium chloride values at the invariant points in which $CaCl_2 \cdot 4H_2O\alpha$ or $MgCl_2 \cdot 6H_2O$ appear as solid phases. These values range from 0.26 to 0.33%. Concentration of sodium chloride at other points is significantly higher.

## Summary

1. The isothermal invariant points in the quinary system $CaCl_2$–$MgCl_2$–KCl–NaCl–$H_2O$ were determined at 35°.

2. The isothermal invariant points in the quaternary systems $CaCl_2$–KCl–NaCl–$H_2O$ and $CaCl_2$–$MgCl_2$–NaCl–$H_2O$ were determined at 35°.

3. The isothermal invariant points in the ternary systems $CaCl_2$–NaCl–$H_2O$, $MgCl_2$–NaCl–$H_2O$ and KCl–NaCl–$H_2O$ were determined at 35°.

CLEVELAND HEIGHTS 18, OHIO

RECEIVED AUGUST 27, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE GEORGE WASHINGTON UNIVERSITY AND THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1242]

# The Photochemical Iodine-Sensitized *cis–trans* Isomerization of Dichloroethylene

BY ROSCOE G. DICKINSON,[1] RICHARD F. WALLIS[2] AND REUBEN E. WOOD[3]

The kinetics of a number of *cis–trans* isomerization reactions occurring in the presence of iodine can be interpreted in terms of a mechanism involving catalysis by iodine atoms.[4] We have studied the photochemical iodine-sensitized isomerization of *cis*- and *trans*-dichloroethylene and find that the kinetics of this reaction are compatible with such a mechanism.

**Acknowledgment.**—This study was begun and pursued by Dickinson and Wood during the academic year 1939–1940. The experiments made at that time were rate measurements on the above-named reaction carried out in decalin solutions. Fairly consistent results were obtained for specific rate constants and their temperature coefficients, and kinetics in agreement with those reported in this paper were indicated. However, side reactions involving the iodine occurred appreciably in the experiments in decalin solutions, as shown by decreases in concentration of free iodine during the runs; the results of those experiments could not, therefore, be interpreted in terms of the kinetics of the isomerization reaction so precisely and straightforwardly as should be possible with experiments involving no considerable side reactions.

During the academic year 1947–1948 new experiments were carried out the description and results of which are presented in this paper. The other two authors take responsibility for this publication but we have taken the liberty to include Professor Dickinson's name with ours in recognition of his proposal of and important contributions to this research.

## Experimental Details

**Apparatus.**—The work mentioned above showed that temperatures above 100° would be required to obtain convenient photochemical isomerization rates even with intense illumination. It also showed that the available intensity of illumination would have to be high in order to permit adequate exploration of temperature coefficients of rate constants and the effect of reduced light intensity, while operating in a temperature range below that at which thermal isomerization would be a factor seriously complicating the interpretation of the data. These two facts led to the choice of the radial illumination system[5] shown in Figs. 1 and 2. In this apparatus a cylindrical light source and a cylindrical reaction vessel are placed with axes at the conjugate foci of an elliptical reflector.

The light source selected was a 400-watt type A-H-1 mercury vapor lamp manufactured by the General Electric Company. This lamp has a convenient cylindrical shape and emits an intense light with the maximum of the spectral distribution curve located in the green. It has a glass envelope and emits practically no radiation of wavelengths shorter than 3200 Å. The mercury vapor pressure is a little over 1 atm. when the lamp is operating at full intensity, the arc appearing to be an almost white, pencil-like beam about 16 cm. long.

Although the lamp is designed for operation in open air, it was found necessary to have a light filter solution flowing around the lamp. This change in operating conditions did not, however, affect its performance materially. A pyrex glass tube about 8 cm. in diameter was placed around the lamp and held in position by rubber stoppers cut to size. Outlet and inlet tubes for the light filter solution were placed in the top and bottom stoppers, respectively. Cooling of the filter solution was effected by forcing it through a spiral condenser by means of an all-glass centrifugal pump. A thermometer was placed in the line so that the temperature of the filter solution leaving the lamp could be observed. The speed of the motor driving the pump was always adjusted so that the temperature shown by this thermometer remained at 68 ± 5°. This was done because the absorption spectrum of the filter is somewhat temperature dependent.

The elliptical reflector consisted of side, top, and bottom pieces made of chromium-plated brass. The side piece was bent into an elliptical shape and held in position by three brass templates. The top and bottom pieces were bolted to the upper and lower templates. The reflector was disassembled and dusted from time to time during the course of the research. No evidence of dulling or tarnishing appeared.

A brass tube directed toward the lamp was soldered into the wall of the reflector. An RCA Type 922 vacuum photocell was mounted in a light-tight box attached to the end of this brass tube. The photocell was connected in series with a 22.5-volt "B" battery and a microammeter (a suitably shunted and calibrated galvanometer was used in the experiments at reduced light intensity). The stated characteristics of this photocell and the light intensities involved were such that the current through the circuit should have been and is assumed to have been directly proportional to the light intensity. This system was used to observe the constancy of light intensity during runs and to evaluate the relative intensities in the various runs. Reduced intensities were obtained by wrapping a piece of blackened Monel metal wire cloth around the jacket of the lamp. Wire cloth screens of two different coarsenesses were used.

In "blank" runs, solutions of dichloroethylene containing no iodine were illuminated without filtration of the light other than that effected by the glass in the light path. A change in dielectric constant of the solutions equivalent to significant amounts of isomerization was observed in these runs. A light filter which would prevent photo-

(1) See acknowledgment.

(2) Present address: Department of Chemistry, Catholic University of America, Washington 17, D. C.

(3) Department of Chemistry, George Washington University, Washington 6, D. C.

(4) (a) The photochemical iodine-sensitized isomerization of *cis*- into *trans*-cinnamic acid: A. Berthoud and Ch. Urech, *J. chim. phys.*, **27**, 291 (1930). (b) The thermal iodine-catalyzed isomerization of *cis*- into *trans*-cinnamic acid: R. G. Dickinson and H. Lotzkar, THIS JOURNAL, **59**, 472 (1937). (c) The thermal iodine-catalyzed isomerization of *cis*- and *trans*-dichloroethylene: R. E. Wood and R. G. Dickinson, *ibid.*, **61**, 3259 (1939). (d) The thermal iodine-catalyzed isomerization of *cis*- and *trans*-dibromoethylene: R. M. Noyes and R. G. Dickinson, *ibid.*, **65**, 1427 (1943). (e) A study of isomerization and exchange reactions in solutions of *cis*- and *trans*-diiodoethylene containing radioactive iodine, both in the presence and absence of illumination: R. M. Noyes, R. G. Dickinson and V. Schomaker, *ibid.*, **67**, 1319 (1945).

(5) W. A. Noyes, Jr., and P. A. Leighton, "The Photochemistry of Gases," Reinhold Publishing Corporation, New York, N. Y., 1941, p. 25.

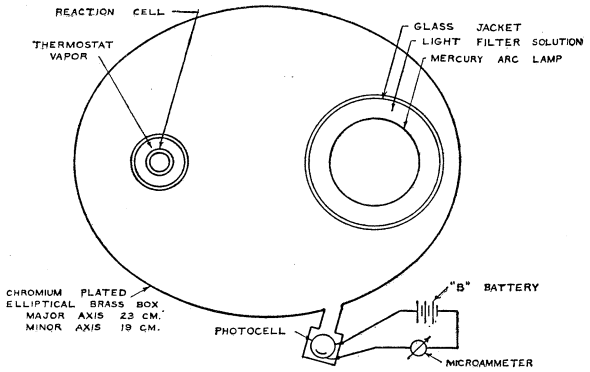



Fig. 1.—Horizontal section through illumination apparatus.

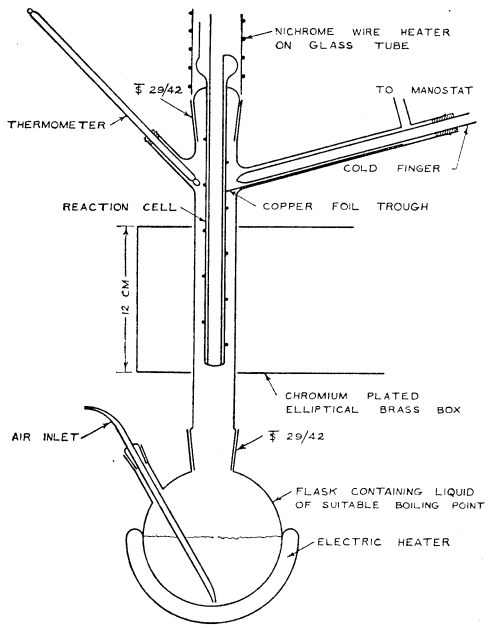



Fig. 2.—Vapor thermostat and reaction cell.

chemical reaction in the absence of iodine was sought and found. It is an aqueous solution of $^1/_2$ formula weight of cupric chloride and 1 formula weight of calcium chloride per liter of solution. Incidentally, a cupric sulfate solution was unsatisfactory; these two solutions differ significantly in absorption spectrum only in that the chloride solution absorbs more strongly in the violet and near-ultraviolet. *cis*- and *trans*-dichloroethylene and their benzene solutions were shown by means of a Beckman ultraviolet spectrophotometer to absorb weakly in the 3200 to 3700 Å. range.

The reaction cell is shown in Figs. 2 and 3. The high vapor pressures of the reaction solutions and the necessity for continuous measurement of their temperatures were principal factors influencing the design of the cell. Preliminary tests demonstrated that the cell, which was constructed of Pyrex glass tubing, could withstand an internal pressure of at least 8 atm. From a theoretical standpoint it was advantageous to have the solution in the form of a thin cylindrical lamina with axis passing through the focus of the elliptical reflector. A sheet of bright aluminum foil was wrapped around the thermometer as shown in Fig. 3 so that no radiation would fall directly on the thermometer and so that the light paths would represent as much vertical symmetry as possible.

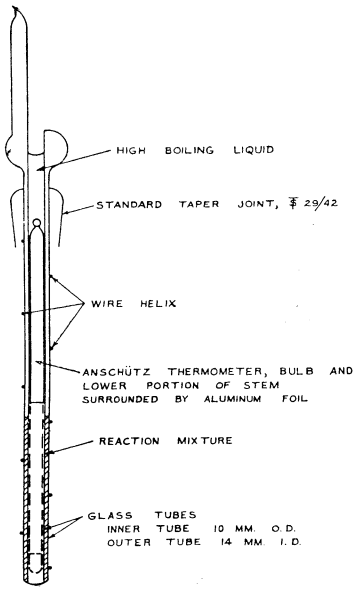



Fig. 3.—Reaction cell.

The method of thermostating the reaction solution is shown in Fig. 3. Because the cell was heated appreciably by the radiation focused on it, it was necessary to direct a flow of condensate over the outside of the cell by means of a copper foil trough and a wire helix wound on the cell. The condensate flowed smoothly over the glass; it seems probable that any inconstancy of light paths caused by irregularities of flow had a negligible effect on the rate measurement. The desired temperatures were obtained and maintained by suitable choice of the boiling liquid and by adjustment of the manostate controlling the boiling pressure. The temperature at the center of the reaction cell was measured by an Anschütz thermometer and was maintained constant within $\pm 0.2°$ during an experiment. The thermometer was immersed in decalin to ensure good thermal conduction to the inner wall of the reaction cell. The thermometer was calibrated at 100, 110 and 118° with boiling water, toluene, and acetic acid, respectively.

The temperature at the center of the reaction cell was consistently 4 or 5° higher than that of the thermostat vapor. This difference doubtless represents in part thermal gradients across the two cell walls and intervening solution, in part superheating of the condensate flowing over the outer wall. The thermal gradient across the inner wall would be expected to be smaller than that across the outer wall; it would be zero if all the radiation were absorbed before reaching the inner wall, neglecting heat conduction vertically through the inner wall to outside the illuminated zone. The thermal gradient in the bulk of the reaction solution, too, is probably small because of convection currents. So, in tabulations and calculations, we have treated the temperatures measured at the center of the reaction cell as the temperatures of the reaction solutions. We estimate the temperature uncertainties as follows: the true solution temperatures corresponding to calculated rate constants are not greater than, and are not more than 1° less than those recorded; the true differences in temperatures between runs, the basis of the activation energy calculation, are within a few tenths of a degree of those indicated by the recorded data.

To prevent the reaction mixture from refluxing from the upper part of the reaction vessel (outside the thermostat), this part of the reaction vessel was heated a little above the temperature of the thermostat by an electric heating coil wound on a slip-over glass tube. No condensate or iodine vapor was visible in this part of the reaction vessel once thermal equilibrium had been established. The portion of the reaction vessel extending above the reflecting

box was shielded from the direct rays of the lamp. Wood and Stevenson[6] obtained evidence that the rate of the thermal isomerization of the 1,2-dichloroethylenes catalyzed by iodine in the vapor phase is of the same order of magnitude as the rate in liquid solutions when comparable concentrations are used. From the foregoing considerations we believe that the isomerization in the vapor phase in this work was negligible.

As in previous work on the isomerization of the 1,2-dihaloethylenes,[4c,d,e] the analytical method was based on the difference in dielectric constant between the *cis* and *trans* isomer. The heterodyne circuit employed to measure dielectric constants was similar to that described by Hudson and Hobbs[7] and was operated at 1.7 megacycles. The liquid dielectric condenser (dielectric cell) is shown in Fig. 4. The amount of solution required to fill it was somewhat less than the 5 ml. used in the photo-chemical reaction cell. The gold-plated brass tubes were soldered to the glass members by applying a platinum film to the glass with a platinizing solution which is described by Strong.[8] The platinic chloride required was prepared by heating chloroplatinic acid at 110° until no more vapors were evolved. Water from a thermostat maintained at 24.7° was circulated around the dielectric cell while measurements were being made.

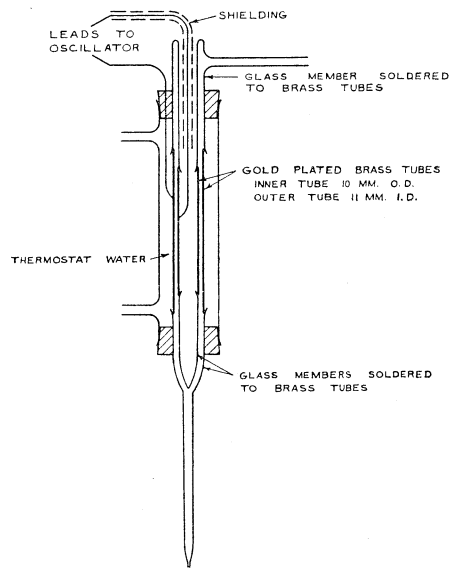



Fig. 4.—Dielectric cell.

**Chemical.**—It seemed desirable in the photochemical experiments to use one of the solvents which had been used in the thermal experiments.[4c] Decalin was tried first because its relatively low vapor pressure at convenient reaction temperatures would permit the use of flat-windowed photochemical reaction cells of conventional design. However, the earlier experiments as well as some carried out since this research was resumed indicate that in the decalin solutions there is a slow but appreciable side reaction. This may be a photochemical reaction between iodine and decalin itself or between iodine and impurities in the decalin which are not removed by reasonably careful purification.

Decalin was therefore abandoned and benzene was used as the solvent in all the isomerization experiments tabulated below. This more volatile solvent was permissible in the tubular reaction cell. Eastman Kodak Co. "White Label" benzene was cooled while being stirred, until about half frozen. The remaining liquid was poured off and discarded. The solid benzene thus obtained had a melting point of 5.5°. It was dried over anhydrous calcium chloride and distilled in an apparatus from which moisture was excluded. The solvent so prepared did not react with iodine under conditions corresponding to those of the isomerization experiments. The only evidence of any side reaction in the runs represented by the quantitative data reported here was the occasional appearance of a small ring of brownish coloration on the reaction vessel where the reaction solution meniscus had been.

*cis*- and *trans*-dichloroethylenes were obtained in 90–95% purity from the Columbia Organic Chemicals Company, and from the Westvaco Chlorine Products Company. The liquids were distilled through a packed column under an atmosphere of dry carbon dioxide. The boiling ranges of the final products were less than 0.1°. Exactly 10.00 mole per cent. solutions of the pure *cis*- and *trans*-dichloroethylenes in benzene were prepared by weighing and were stored under carbon dioxide in closed vessels designed to permit withdrawal of the solution without admission of air.

Merck "Reagent" grade iodine was sublimed from a mixture with Merck "Reagent" grade potassium iodide and was then resublimed. An 0.0602 mole per cent. iodine solution in benzene was prepared.

**Procedure.**—The following procedures were followed in the majority of the experimental runs; exceptions will be described below. Manipulations involved in filling and sealing the reaction cell were carried out under carbon dioxide to exclude oxygen. Between runs the reaction cell was filled with chromic acid cleaning solution to remove any materials which might influence the reaction. The chromic acid was removed by repeated washing with water and then twice with acetone. The residual solvent was pumped off.

Pure dry carbon dioxide was passed through the cell for a few minutes, after which the cell was stoppered and weighed. In the case of the runs with dilute iodine solutions, a suitable volume of benzene solution of iodine was pipetted into the cell which was then reweighed. Iodine crystals were added directly to the cell for the experiments with concentrated iodine solutions. In either case sufficient solution of one of the dichloroethylenes was next added to make a total of 5 ml. of reaction solution. A final weighing of the reaction cell was made, after which additional carbon dioxide was passed through the upper part of the cell to remove any vapors which might pyrolyze. The stream of carbon dioxide was not permitted to reach down to the reaction solution, however, so no fractionation of the latter is believed to have occurred; the results of blank experiments supported this assumption. The cell was then sealed off. At the start of these operations the mercury vapor lamp and the thermostat heater were turned on so that they would be at operating temperatures by the time everything else was ready to start the run.

The filled and sealed reaction cell was put into place in the apparatus and the starting time noted. Reference marks on both members of the ground glass joint supporting the cell made it possible to orient the cell in exactly the same manner for each run, a precaution which seemed advisable since the axis of the cell and that of the ground glass joint did not exactly coincide. The heater for the vapor portion of the cell was clamped into place. Thermal equilibrium was practically achieved within five minutes. Light intensity readings were taken at fifteen-minute intervals throughout the run. The run was concluded by turning off the light and removing the cell from the thermostat. When the solution had cooled it was transferred to a test-tube containing a clean coil of copper wire to remove iodine: this method of removing iodine had been shown[4c] not to produce isomerization.

After the solution had become free of iodine, its dielectric constant was measured and from it together with the knowledge of the total dichloroethylene concentration the concentrations of *cis*- and *trans*-dichloroethylene in it were

(6) R. E. Wood and D. P. Stevenson, THIS JOURNAL, **63**, 1650 (1941).

(7) B. E. Hudson, Jr., and M. E. Hobbs, *Rev. Sci. Instruments*, **13**, 140 (1942).

(8) J. Strong, "Procedures in Experimental Physics," Prentice-Hall, Inc., New York, N. Y., 1938, p. 152.

calculated. Such calculations were based on the assumption that, over the concentration ranges used, the dielectric constant is a linear function of the mole fractions of *cis*- and *trans*-dichloroethylene present in the solution. This assumption was tested and found valid for the two-component system comprising solutions of *cis*-dichloroethylene from 7 to 10 mole per cent. in benzene, it was also tested and found valid for the three-component system comprising benzene solutions of *cis*- and *trans*-dichloroethylene in which the total dichloroethylene concentration was kept at 10 mole per cent.

## Calculations

The conditions and results of the rate experiments are summarized in Tables I, II and III. The first part of this discussion will attempt to show how the specific rate constants, tabulated in the last column of each table, were calculated from the data, and to indicate how they are related to the interpretation of the results in terms of an iodine atom catalysis. The line of argument will be to derive, on the basis of the proposed mechanism, the equations for certain quantities ($k$'s) the values of which should be constant or should have a predicted dependence on the experimental parameters if the proposed mechanism is compatible with the data.

The proposed mechanism is[4]

$$C + I \rightleftarrows CI \qquad (1)$$

$$CI \rightleftarrows TI \qquad (2)$$

$$TI \rightleftarrows T + I \qquad (3)$$

where C and T represent the *cis* and *trans* isomers, respectively, I is atomic iodine, and CI and TI are complexes. On this basis one can write for the over-all reaction

$$-d(C)/dt = k_1(I)(C) - k_2(I)(T) \qquad (4)$$

in which $k_1$ and $k_2$ are specific rate constants for the forward and reverse *cis* to *trans* isomerization (note that $k_1$ and $k_2$ do not refer to reactions 1 and 2 above). This is an expression for the local rate of isomerization. In the case of photochemical experiments the rate will vary from place to place in the solution because of varying light intensity and consequently varying iodine atom concention (it is assumed that recombination of iodine atoms occurs before they have diffused appreciably). The over-all rate of isomerization will be the average local rate.

Because of the uniformity of C and T concentrations throughout the solution, which it is reasonable to assume because of the slowness of isomerization compared to probable stirring processes, the over-all isomerization rate should be given by

$$-\overline{d(C)/dt} = k_1\overline{(I)}(C) - k_2\overline{(I)}(T) \qquad (5)$$

Here $-\overline{d(C)/dt}$ represents the over-all net rate of conversion of *trans* to *cis* dichloroethylene, and $\overline{(I)}$ represents the average concentration of iodine atoms throughout the reaction solution.

If one now considers isomerization experiments of the kind reported here in which $\overline{(I)}$ remains essentially constant throughout a given experiment and which start with only the *cis* or only the *trans* isomer, equation (5) can be integrated. Representing by $\alpha$ the fraction of dichloroethylene in the *cis* form at the time $t$ and letting $K$ be the equilibrium constant $(trans)_{eq}/(cis)_{eq}$, the integration leads to the expressions for $k_1$

$$k_1 = -\frac{K}{t(I)(K+1)} \ln \frac{(K+1)\alpha - 1}{K} \qquad (6)$$

which applies to experiments in which the initial dichloroethylene is all *cis*, and

$$k_1 = -\frac{K}{t(I)(K+1)} \ln [1 - (K+1)\alpha] \qquad (7)$$

which applies to experiments in which the initial dichloroethylene is all *trans*. $k_2$ has been eliminated from these equations by $K = k_1/k_2$.

It remains to get expressions for $\overline{(I)}$ in terms of the experimental parameters. In addition to reactions 1, 2, and 3 one must consider processes by which iodine atoms are produced from molecular iodine and also the recombination of the atoms to form the molecule, *i. e.*

| | | |
|---|---|---|
| The photochemical dissociation | $I_2 + h\nu \longrightarrow 2I$ | (8) |
| The thermal dissociation | $I_2 \longrightarrow 2I$ | (9) |
| Recombination | $2I \longrightarrow I_2$ | (10) |

It is understood that energy and momentum requirements may be satisfied by particles not symbolized in these expressions. The usual treatment of rate expressions based on processes 1, 2, 3, 8, 9, and 10 leads to the following implicit expression for (I), the local steady-state iodine atom concentration

$$\phi i + k_9(I_2) = k_{10}(I)^2 \qquad (11)$$

where $\phi$ is the quantum yield for process 8, $i$ is the local rate of light absorption in einsteins liters$^{-1}$ seconds$^{-1}$, and $k_9$ and $k_{10}$ are the specific rate constants of processes 9 and 10, respectively.

The azimuthal variation of $i$ throughout the reaction vessel will not affect the form of rate expressions to be derived under the assumptions that the light enters and leaves the cell radially and that the isomer concentrations are at all times uniform throughout the solution. Therefore, since quantum yields are not calculated, it is not necessary to consider the azimuthal variation further.

The radial relations follow from applications of Beer's and Lambert's laws. Let $r$ be the distance from the axis of the reaction cell to the point in the solution where the rate of light absorption is $i$, and let $r_0$ and $r_1$ be the distances from the cell axis to the inner and outer boundaries of the solution, respectively. Let $\epsilon$ be a molal absorption coefficient of iodine for a particular wave length and let $I_0$ be the rate at which light enters the outer surface of the solution (in einsteins per second). It can be shown that the rate of light absorption per unit volume in a thin cylindrical shell of solution of radius $r$ is given by

$$i = \frac{I_0}{V}(I_2)\epsilon(r_1 - r_0)[\exp(-\epsilon(I_2)(r_1 - r)) + m\exp(-\epsilon(I_2)(r_1 + r - 2r_0))] \qquad (12)$$

In this equation $V$ is the total volume of the reaction solution, $m$ is a fraction which takes account of the loss of light which occurs at the aluminum reflectors. The derivation involves approximations which are good when $r_0$ is considerably larger than $r_1 - r_0$. These are thought to be satisfactory approximations for the cell used in this work.

A combination of equations 11 and 12 gives

$$(\mathrm{I}) = \sqrt{\frac{1}{k_{10}}\left\{k_9(\mathrm{I}_2) + \phi\left[\frac{I_0}{V}(\mathrm{I}_2)\epsilon(r_1 - r_0)\right][\exp(-\epsilon(\mathrm{I}_2)(r_1 - r)) + m\exp(-\epsilon(\mathrm{I}_2)(r_1 + r2 - r_0))]\right\}} \quad (13)$$

The average value of the iodine atom concentration, $\overline{(\mathrm{I})}$, is needed to evaluate the specific rate constant, $k_1$ (equation 7). Thus

$$\overline{(\mathrm{I})} = \frac{1}{r_1 - r_0}\int_{r_0}^{r_1}(\mathrm{I})\,dr \quad (14)$$

This expression for $\overline{(\mathrm{I})}$ can be integrated for several cases of interest. For the case of purely thermal isomerization $I_0$ is zero and only the first term under the radical sign in equation 13 remains, in this case $(\mathrm{I}) = \sqrt{k_9/k_{10}[(\mathrm{I}_2)]}$. On the other hand, the experiments reported here were carried out so that the rate of thermal isomerization should be small compared to the photochemical rate. The approximate evaluation of $\overline{(\mathrm{I})}$ for such experiments is done by neglecting the first (thermal) term in equation 13. In making this evaluation, it is convenient to treat separately two cases: the case in which the iodine concentration is low enough so that only a fairly small fraction of the incident light is absorbed in passing through the reaction solution, and the case in which the iodine concentration is high enough so that most of the light is absorbed in passing through the solution.

In the case of pale solutions in which the absorption of light approaches zero the sum of the exponential terms in equation 13 approaches $1 + m$ giving

$$\overline{(\mathrm{I})} = (\mathrm{I}) = \sqrt{\frac{\phi I_0(\mathrm{I}_2)\epsilon}{V}(r_1 - r_0)(1 + m)} \quad (15)$$

When this expression for $\overline{(\mathrm{I})}$ is put into equations 6 and 7 and constants are lumped together, expressions are obtained for $k_p$, the apparent pale solution photochemical specific rate constant for the *cis* and *trans* isomerization

$$k_p = -\frac{K}{t(K+1)\sqrt{I_0(\mathrm{I}_2)}}\ln\frac{(K+1)\alpha - 1}{K} \quad (16c)$$

equation 16c applying to experiments starting with *cis* and no *trans* isomer, and

$$k_p = -\frac{K}{t(K+1)\sqrt{I_0(\mathrm{I}_2)}}\ln[1 - (K+1)\alpha] \quad (16t)$$

equation 16t applying to experiments starting with *trans* and no *cis* isomer. By plotting values of $k_p$ against $(\mathrm{I}_2)$ and extrapolating to $(\mathrm{I}_2) = 0$ the best value of the true pale-solution photochemical specific rate constant should be obtained. It should be stated that since the thermal and photochemical rates both are proportional to $\sqrt{(\mathrm{I}_2)}$ in pale solutions, neglecting the thermal isomerization is as good an approximation for solutions having very small light absorption as for moderately absorbing solutions—a little better, in fact.

Although equations 16 have been derived for the case of monochromatic light, equations of the same form apply to polychromatic light provided that any variations of the intensity of incident light do not involve variation in the relative intensities of the various light components. Tables I and II show the pale solution results. In these tables the $k_p$'s are calculated from equations 16 where the $I_0$ values are in arbitrary units representing relative values as indicated by the photocell output. Most of these specific rate constants are plotted against the iodine concentration in Fig. 5. It can be seen that the $k_p$'s vary only a little with ten-fold variation in $(\mathrm{I}_2)$ and that their variation is in the direction that would be expected, in view of the approximations made in getting equations 16 from equation 13, if the reaction mechanism is indeed a simple iodine atom catalysis.

Equation 13 is also the starting point for the treatment of deep-colored solutions. In this case the second exponential term in that equation approaches zero. Then, still neglecting the thermal term and putting the residue of equation 13 into equation 14 and integrating, one gets

$$\overline{(\mathrm{I})} = \text{constant} \times \sqrt{I_0/(\mathrm{I}_2)} \quad (17)$$

On the basis of this equation, the photochemical rate in deep-colored solutions should vary inversely with $\sqrt{(\mathrm{I}_2)}$. Since the thermal rate should vary directly with $\sqrt{(\mathrm{I}_2)}$, in the very deep-colored solutions the thermal rate can become appreciable compared to the photochemical even though the temperature is such that this is not the case with paler solutions. The exact treatment of cases where both thermally and photochemically produced iodine atoms are present in effective quantities is complicated. However, if one makes the approximation that the photochemical reaction occurs appreciably only in a thin layer[9] on the outside of the reacting solution then convenient equations, equations 18c and 18t, can be derived for calculating the photochemical specific rate constant. Since at the temperatures and light intensities of these experiments the thermal isomerization has any relative importance only in the most deeply colored solutions, that approxi-

(9) A fuller discussion of this treatment as well as of a number of other aspects of this research can be found in a thesis entitled, "The Kinetics of the Photochemical Isomerization of Dichloroethylene Catalyzed by Iodine," submitted to the George Washington University in 1948 by Richard Fisher Wallis.

mation should be good where there is an appreciable thermal effect. Where there is no appreciable thermal effect expressions 18c and 18t for the photochemical specific rate constant reduce to just the forms that would follow from equation 17 without using the thin-layer assumption. Therefore, equations 18 may be used on all of the experiments with deep-colored solutions. In these equations, $\mathbf{k_p}$ is the photochemical specific rate constant in deep-colored solutions, $k_T$ is the thermal specific rate constant (called $k_1$ by Wood and Dickinson[4c]). Values for $k_T$ to use in equations 18 were calculated from the data of Wood and Dickinson.

$$\mathbf{k_p} = -\sqrt{\frac{(I_2)}{I_0}}\left\{\left[\frac{K}{t(K+1)}\ln\frac{(K+1)\alpha-1}{K}\right]-k_T\sqrt{(I_2)}\right\} \quad (18c)$$

$$\mathbf{k_p} = -\sqrt{\frac{(I_2)}{I_0}}\left\{\left[\frac{K}{t(K+1)}\ln\left[1-(K+1)\alpha\right]\right]-k_T\sqrt{(I_2)}\right\} \quad (18t)$$

Equation 18c applies to experiments in which the initial dichloroethylene is all *cis* and equation 18t to those in which it is all *trans*. Available data and the fact the polychromatic light was used do not permit a simple calculation of the numerical value to be expected for the ratio of the pale-solution photochemical specific rate constant, $k_p$, to the deep-colored-solution photochemical specific rate constant, $\mathbf{k_p}$.

## Results and Conclusions

The data and calculated $k_p$'s for the pale-solution experiments are presented in Tables I and II. In Fig. 5 these $k_p$'s (except those for the experiments to which footnotes a, b, and d of Table I refer) have been plotted against $(I_2)$. This graph shows that at a given temperature the $k_p$'s decrease by only about 10% with a tenfold increase in $(I_2)$. Both the comparative constancy of the $k_p$'s and the direction of their change with change in iodine concentration are, in the light of the preceding derivations, compatible with the proposed mechanism. It is to be noted that the light intensities as well as concentrations differed among the experiments the results of which are plotted. Table VII presents the data and calculated $k_p$'s for the experiments with deep-colored solutions. Again, the comparative constancy of the $k_p$'s with an eight-fold variation in $(I_2)$ is compatible with the proposed mechanism.

The numbers of the runs tabulated in Tables I, II and III indicate chronological order of the experiments. All of the isomerization experiments carried out except blanks and the preliminary experiments are included in these tables. It can be seen that the second, third and fourth runs gave low $k_p$'s. In these three cases the reaction cell had been rinsed with solvent but had not been cleaned with chromic acid before filling. In the first run and in all runs after the fourth a

TABLE I

RATE MEASUREMENTS AT 120.6° WITH DILUTE IODINE SOLUTIONS

| Run | Mole % total $C_2H_2Cl_2$ | Mole fraction $I_2 \times 10^4$ | Duration, hours | Dielect. constant at end | Fraction *cis* in $C_2H_2Cl_2$ at end | Light intensity, arb. units | $k_p$, arb. units |
|---|---|---|---|---|---|---|---|
| 1-C | 8.09 | 1.150 | 5.50 | 2.579 | 0.864 | 5.07 | 1.44 |
| 2-T[a] | 9.33 | 0.410 | 5.50 | 2.345 | .196 | 5.08 | 1.08 |
| 3-T[a] | 8.06 | 1.168 | 5.50 | 2.371 | .296 | 5.15 | 1.06 |
| 4-C[a] | 9.01 | 0.593 | 5.50 | 2.636 | .915 | 5.20 | 1.05 |
| 5-C | 8.05 | 1.173 | 5.50 | 2.575 | .858 | 5.23 | 1.48 |
| 6-T | 9.04 | 0.576 | 5.50 | 2.386 | .302 | 5.05 | 1.56 |
| 7-C | 9.06 | .567 | 5.50 | 2.626 | .886 | 5.03 | 1.60 |
| 8-T | 9.61 | .231 | 5.50 | 2.352 | .209 | 5.08 | 1.56 |
| 9-T | 9.82 | .110 | 6.00 | 2.337 | .171 | 5.10 | 1.62 |
| 10-C[b] | 7.33 | 1.01 | 6.00 | 2.545 | .852 | 4.94 | 1.60 |
| 15-C[b] | 7.51 | 0.74 | 5.50 | 2.560 | .874 | 5.07 | 1.59 |
| 16-T | 9.50 | .302 | 5.50 | 2.366 | .244 | 5.08 | 1.63 |
| 17-T | 9.12 | .542 | 6.50 | 2.342 | .194 | 1.36 | 1.50 |
| 18-T | 9.13 | .525 | 6.00 | 2.354 | .222 | 2.05 | 1.60 |
| 19-T | 9.44 | .337 | 6.50 | 2.348 | .203 | 2.13 | 1.62 |
| 20-C | 8.25 | 1.049 | 7.00 | 2.601 | .904 | 1.24 | 1.48 |
| 29-C[d] | 9.05 | 0.571 | 5.50 | 2.653 | .954 | 5.12 | 0.54 |
| 30-T[d] | 9.03 | .585 | 5.50 | 2.326 | .156 | 5.12 | 0.69 |
| 31-C[d] | 9.05 | .575 | 5.25 | 2.626 | .888 | 4.65 | 1.67 |
| 32-C[d] | 9.04 | .573 | 5.50 | 2.632 | .902 | 4.96 | 1.30 |
| 33-C[d] | 9.05 | .572 | 5.50 | 2.628 | .893 | 5.03 | 1.47 |
| 34-T[d] | 9.82 | .106 | 5.00 | 2.320 | .132 | 4.90 | 1.52 |
| 35-T[d] | 9.62 | .228 | 5.00 | 2.338 | .177 | 5.21 | 1.40 |
| 36-C[d] | 8.10 | 1.144 | 5.00 | 2.585 | .877 | 5.00 | 1.37 |

Initial isomer indicated by C (for *cis*) or T (for *trans*) following run number. [a] Cell not cleaned with chromic acid before run. [b] Reaction mixture boiled, then frozen, and cell evacuated before sealing off. [d] "Wall" surface tripled by putting glass capillary tubes in reaction cell.

TABLE II

RATE MEASUREMENTS AT 100.0 AND 110.3° WITH DILUTE IODINE SOLUTIONS

| Run | Mole % total $C_2H_2Cl_2$ | Mole fraction $I_2 \times 10^4$ | Duration, hours | Dielect. constant at end | Fraction *cis* in $C_2H_2Cl_2$ at end | Light intensity, arb. units | $k_p$, arb. units |
|---|---|---|---|---|---|---|---|
| 21-C | 8.30 | 1.020 | 6.00 | 2.601 | 0.899 | 5.20 | 0.92 |
| 22-T | 9.04 | 0.589 | 6.00 | 2.356 | .229 | 5.45 | 0.93 |
| 23-C | 9.64 | .217 | 7.25 | 2.667 | .929 | 5.23 | 1.06 |
| 24-T | 9.82 | .108 | 7.00 | 2.318 | .128 | 5.13 | 0.98 |
| 25-T | 9.07 | .557 | 6.00 | 2.335 | .178 | 5.11 | .70 |
| 26-C | 8.28 | 1.036 | 7.25 | 2.605 | .912 | 5.16 | .64 |
| 27-T | 9.62 | 0.234 | 7.50 | 2.320 | .135 | 5.11 | .64 |
| 28-T | 9.83 | 0.102 | 8.00 | 2.311 | .112 | 5.11 | .74 |

Runs 21-C to 24-T inclusive at 110.3°. Runs 25-T to 28-T inclusive at 100.0°.

TABLE III

RATE MEASUREMENTS AT 120.6° WITH CONCENTRATED IODINE SOLUTIONS

| Run | Mole % total $C_2H_2Cl_2$ | Mole fraction $I_2 \times 10^3$ | Duration, hours | Dielect. constant at end | Fraction *cis* in $C_2H_2Cl_2$ at end | Light intensity arb. units | $k_p$, arb. units |
|---|---|---|---|---|---|---|---|
| 11-T | 9.96 | 3.15 | 5.00 | 2.436 | 0.387 | 5.10 | 0.00101 |
| 12-C | 9.98 | 1.93 | 5.50 | 2.635 | .825 | 5.08 | .00098 |
| 13-C | 9.92 | 8.10 | 5.50 | 2.659 | .885 | 5.05 | .00106 |
| 14-T | 9.85 | 16.2 | 5.50 | 2.365 | .233 | 4.91 | .00103 |

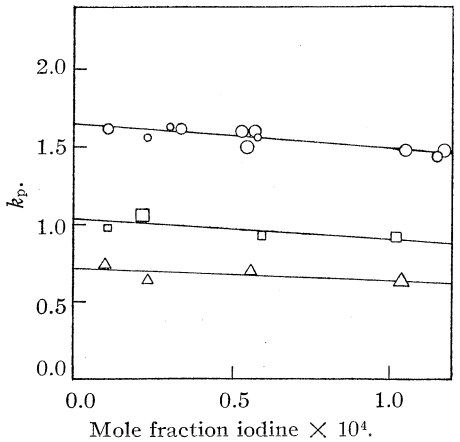



Fig. 5.—Variation of rate constants with iodine concentration for pale solutions: O, 120.6°; □, 110.3°; △, 100.0°.

soaking with chromic acid was part of the preparation of the cell.

Two other runs gave markedly low values of $k_p$, namely, runs 29 and 30 which are the first two of a series of eight in which the glass surface in contact with the reaction solution was approximately tripled by putting thin-walled glass tubing (melting-point tubes) into the solution space in the reaction vessel. This series of experiments was to test the homogeneity of the reaction, a test that seemed especially appropriate in view of the three anomalous results, mentioned in the preceding paragraph, which were obtained when the reaction vessel had not been vigorously cleaned. It seems most probable that the anomalous values obtained in runs 29 and 30 (as compared to all the other $k_p$'s in Table I and particularly as compared to the values from runs 31 through 36) like the $k_p$'s from runs 2, 3 and 4, involve faulty manipulation and are invalid. It is difficult to clean, rinse and dry thoroughly a set of capillary tubes entrapped and largely immobilized in a small reaction vessel such as we used. The only difference in technique between the earlier and later runs of the series 29 through 36 was in the care and extent of these operations. We did not feel justified in omitting runs 2, 3, 4, 29 and 30 from the tables because the probability of their invalidity is based on *a posteriori* considerations. But assuming them to be invalid, the agreement of the $k_p$'s from runs 31 through 36 with the other $k_p$'s in Table I is evidence that the reaction studied is homogeneous. It is not strange that the average value of $k_p$ in the experiments with capillary tubes should be a little different from the others. It is perhaps remarkable that it is so nearly the same since no correction was attempted for the disturbing effect that the capillary tubing would have on stirring processes and on the optical system..

Only two experiments remain to be mentioned specifically, runs 10 and 15. These were carried out to show that rigorous exclusion of oxygen had no appreciable effect on the rate of isomerization. In these experiments a solution of *cis*-dichloroethylene and iodine in benzene was put into the reaction vessel, part of the solution was boiled off, the remainder was frozen while being pumped on by a vacuum pump, and then the system was sealed off. The mixture was melted and part of the solution was poured into a side arm which was then sealed off, the rest of the solution in the sealed-off reaction cell being used in the isomerization run. The solution in the side arm was analyzed colorimetrically and by a dielectric constant measurement to determine the initial iodine and dichloroethylene concentrations in the reaction cell.

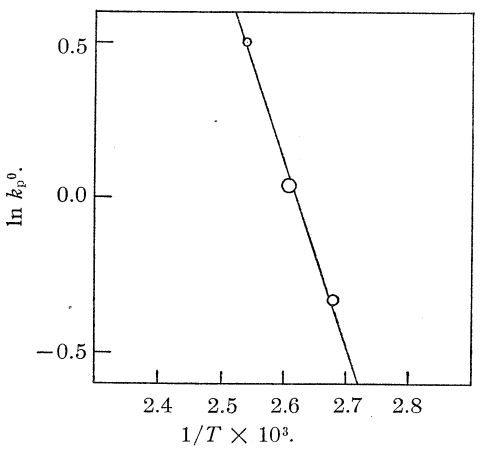



Fig. 6.—Temperature dependence of rate constants for pale iodine solutions.

In Fig. 6 in $k_p^0$ is plotted against $1/T$. $k_p^0$ is the experimental value of $k_p$ at the temperature in question extrapolated (Fig. 5) to zero iodine concentration. From the slope of this curve and a consideration of probable experimental errors the Arrhenius activation energy $Q_p$ of the photochemical iodine-sensitized isomerization can be estimated as $Q_p = 11{,}900 \pm 700$ cal. mole$^{-1}$ ($d \ln k_p^0/dT = Q_p/RT^2$). Wood and Dickinson[4c] give 31,200 cal. mole$^{-1}$ as the corresponding activation energy for the thermal iodine-catalyzed isomerization. The difference between these two quantities should be half the heat of dissociation of molecular iodine in these solutions. The difference is 19,300 cal. mole$^{-1}$. This is in good agreement with the value of 19,400 calculated by Dickinson and Lotzkar[4b] from the cinnamic acid isomerization data. Half the heat of dissociation of gaseous iodine, 18,100 cal. mole$^{-1}$ calculated[4b] from spectroscopic data may also be compared. The similarity of this last figure to the 19,300 calculated from the thermal and photochemical rate experiments would seem to constitute evidence favoring an atom catalysis as distinguished from some other mechanisms which might be proposed and which would be compatible with the other experimental

facts. Other evidence against the ion catalysis possibility is mentioned by Wood and Dickinson.


## Summary

The photochemical iodine-sensitized *cis–trans* isomerization of dichloroethylene in benzene solutions has been studied. Isomerization rates have been measured for various light intensities, iodine concentrations, temperatures, and area of glass surface in contact with the solution. The results indicate that the reaction is homogeneous under the experimental conditions and that a mechanism involving catalysis of the isomerization by iodine atoms is probable.

A value for the activation energy of this photochemical reaction has been calculated from the results of these experiments.


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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# Effect of Structure on Reactivity.[1] II. Influence of Solvents on Ammonolysis of Esters

BY MAXWELL GORDON,[2] JOHN G. MILLER AND ALLAN R. DAY

In the first investigation of this series[3] the electron release effects of alkyl and aryl groups in the ammonolysis of esters were studied. All of the reaction media employed contained about 18% water because it had been found that most esters will not react appreciably with ammonia in anhydrous dioxane or methanol over a period of several weeks at room temperature. The question of the effect of water on the ammonolysis of esters is subject to more difference of opinion[4] than any other phase of this work. On the basis of the references cited,[4] the work in this paper probably offers the first general method for the ammonolysis of esters in the absence of water.

From the earlier investigations and from the work in this laboratory, it may be stated that in general simple esters will not react with ammonia at a useful rate in anhydrous media. The notable effect of water on the rate of ammonolysis suggested that the use of hydroxylated organic solvents might also promote the ammonolysis of esters. Investigation of a series of such solvents has shown this assumption to be correct. Certain of the glycols and related compounds were found to be more effective than water. Furthermore, the results show the same qualitative structure–reactivity correlations as those reported in the first paper[3] for aqueous solutions.

## Experimental

The experimental method employed for ammonolysis in this investigation was identical with that used in the first paper of this series.[3] At this point in the work it became apparent that the choice of dioxane as a diluent was particularly fortunate, since it was found that ammonolysis proceeds more slowly in dioxane than in any other solvent tested. On this account dioxane could reasonably be used as a diluent in evaluating the catalytic effects of other solvents.

In addition to the compounds used in the previous work,[3] the following were employed: ethylene glycol, b.p. 72° at 1 mm., $n^{20}$D 1.4316; diethylene glycol, 101° at 1 mm., 1.4472 at 20°; trimethylene glycol, 88° at 1 mm., 1.4398 at 20°; ethylene glycol monomethyl ether, 43° at 20 mm., 1.4074 at 20°; diethylene glycol monomethyl ether, 68° at 1 mm., 1.4264 at 27°; glycerol, 1.4729 at 20°; propylene glycol, 65° at 1 mm., 1.4293 at 27°; ethylene glycol monoacetate, 61° at 1 mm., 1.4278 at 20°; 1,3-butanediol, 74° at 0.5 mm., 1.4410 at 20°; isobutylene glycol, 58° at 1 mm., 1.4350 at 20°. The anhydrous ammonia used was controlled with a steel needle valve and metered by means of a bubble counter.

## Results

The promoting effect of water on the ammonolysis of ethyl acetate was found to be dependent on its concentration. Thus with no water present there was no measurable ammonolysis in 400 hours, with 5 moles of water/l. the rate constant was 0.000220 l. mole$^{-1}$ hour$^{-1}$, with 10 moles of water/l., 0.000450, and with 20 moles of water/l., 0.000750. The concentration of ammonia was 0.809–1.172 moles/l. The lack of ammonolysis in the anhydrous diluent (dioxane) is notable. Further preliminary measurements revealed that other solvents similarly showed an increase in rate of ammonolysis beyond the point where the ammonia–catalyst ratio is 1:1. Other solvents tried were methanol, *t*-butanol, ethylene glycol and glycerol.

Because of the striking effects of the various

(1) From a thesis submitted in December, 1947, by M. Gordon to the Department of Chemistry and Chemical Engineering of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) National Institute of Health Predoctoral Research Fellow, 1946–1948.

(3) Gordon, Miller and Day, THIS JOURNAL, **70**, 1946 (1948).

(4) Fischer and Dilthey, *Ber.*, **35**, 844 (1902); McKenzie and Wren, *J. Chem. Soc.*, 311 (1908); Morrell, *ibid.*, 2701 (1914); Blair, THIS JOURNAL, **48**, 37 (1926); Grant and Hinshelwood, *J. Chem. Soc.*, 1351 (1933); Hughes and Ingold, *ibid.*, 252 (1935); Haworth, Haslop, Salt and Smith, *ibid.*, 222 (1944).

solvents used in the preliminary work and in view of the desirability of making the comparisons on the basis of the number of moles of solvent added, the experiments summarized in Table I were performed. Here, in the ammonolysis of methyl acetate, the data shown are for systems containing ten moles of water/l. in each case and five moles of additional solvent. In all instances the reaction mixtures were made up to volume with dioxane. The use of water was required because some of the solvents will not promote ammonolysis in the absence of water. The particular sample in which water was the additional solvent contained, of course, a total of fifteen moles of water/l.

In these experiments the rate constants were measured over rather long periods of time and, in general, showed a slight decrease as the reaction progressed, similar to the behavior reported in the previous investigation.[3] For comparison of the catalytic effects of the solvents, Table I lists the rate constants at the half-time in each case.

The order of listing in this table shows the relative catalytic effects of the solvents. Similar results were obtained in the ammonolysis of ethyl acetate, methyl benzoate and methyl lactate.

The values for per cent. ammonolysis for most of the experiments summarized in Table I are plotted against time in Fig. 1. Two of the curves 6 and 10, are important reference curves, the latter representing the behavior of the system containing the same constituents as all the rest, without any additional solvent, while the former shows the effect of additional water. Between these curves are found those of all the solvents which have a lower catalytic effect, mole for mole, than water. It is in these solvents that ammonolysis would not be expected to proceed appreciably in the absence of water. This conclusion was verified experimentally when ammonolysis failed to take place in anhydrous methanol or *t*-butanol.

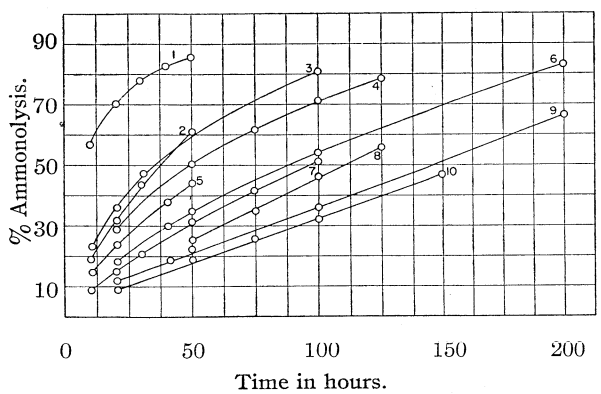



Fig. 1.—Effect of additional solvent on the ammonolysis of methyl acetate: 1, glycerol; 2, diethylene glycol; 3, ethylene glycol; 4, propylene glycol; 5, diethylene glycol monomethyl ether; 6, water (15 moles/l.): 7, ethylene glycol monoethyl ether; 8, *t*-butanol; 9, methanol; 10, water (10 moles/l.) All concentrations are 5 moles/l. with the exception of water.

TABLE I

EFFECT OF ADDITIONAL SOLVENT ON AMMONOLYSIS[a] OF METHYL ACETATE AT 30°

| Additional solvent | *k* | Additional solvent | *k* |
|---|---|---|---|
| None | 0.0014 | Water | 0.00391 |
| Methanol | .00172 | Diethylene glycol–monomethyl ether | .00527 |
| *t*-Butanol | .0025 | Propylene glycol | .00600 |
| 1,3-Butanediol | .00262 | Ethylene glycol | .0100 |
| Trimethylene glycol | .00330 | Diethylene glycol | .0100 |
| Ethylene glycol monoethyl ether | .00339 | Glycerol | .0285 |
| Isobutylene glycol | .0038 | | |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.463–2.537 moles/l.

Of course, ammonolysis of most esters would not be anticipated in anhydrous dioxane since replacement of a portion of dioxane by any of the other solvents tested resulted in an increase in rate, thus showing dioxane to be at the bottom of the scale of catalytic activity. Ethylene glycol monoethyl ether and trimethylene glycol lie below the level of water in catalytic activity, but are so close to it that they would be expected to promote ammonolysis in the absence of water. This conclusion was verified experimentally. All of the solvents corresponding to the curves above that of 15 moles of water/l. would be expected to promote ammonolysis readily in the absence of water, and this was found to be the case.

To corroborate the results shown in Table I and Fig. 1, the ammonolysis of methyl acetate was studied in the following anhydrous solvents at 30°: ethylene glycol, diethylene glycol, propylene glycol and trimethylene glycol. The concentration of ester was 0.7 mole/l. and that of the ammonia was 2.52 to 2.61 moles/l. Due to the high viscosity of these glycols, the experimental error was higher than in the experiments in which dioxane or alcohol diluent was used and the downward drift of the constants was slightly more pronounced. For this reason, only the values of the reaction constants measured at twenty hours reaction time are reported here: 0.0421, 0.0286, 0.0175, and 0.00216 l. mole$^{-1}$ hour$^{-1}$, respectively.

A more complete representation of the experiments is shown in Fig. 2 where the per cent. ammonolysis in each case is plotted over a period of time. This graph shows the variety of solvents in which ammonolysis can take place under anhydrous conditions. These results verify the prediction made in discussion of Table I, that solvents which exert a catalytic activity in the ammonolysis of esters equal to or greater than that of water would cause ammonolysis to proceed in

the absence of water. The relative catalytic effects of these anhydrous solvents follow the same order as that found with ten moles of water/l. present in each case.

The effect of sodium hydroxide on the ammonolysis of methyl acetate at 30° is shown by the two experiments reported in Table II. The concentration of sodium hydroxide was 0.07 mole/l. in one run, and the base was absent in the other. Ten moles of water/l. was present in each case. Dioxane was used as the diluent. The application of the second analytical method for ammonia described earlier[3] showed that about 50% of the ester was hydrolyzed. Without additional comment at this point, we note that the extent of hydrolysis prevents practical application of the use of sodium hydroxide in ammonolysis.

TABLE II

EFFECT OF SODIUM HYDROXIDE ON THE AMMONOLYSIS[a] OF METHYL ACETATE AT 30°

| Concn. of NaOH | Hours 1 | 25 | 50 | 75 | 100 |
|---|---|---|---|---|---|
| None | | | | | |
| % Ammonolysis | | 10.5 | 18.8 | 25.8 | 33.3 |
| Rate constant | | 0.00185 | 0.00178 | 0.00176 | 0.00148 |
| 0.07 Mole NaOH/l. | | | | | |
| % Ammonolysis | 14.5 | 27.5 | 39.0 | 44.0 | 47.0 |
| Rate constant | 0.0705 | 0.00600 | 0.00350 | 0.00205 | 0.00145 |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.276–2.474 moles/l.

The values found for the relative rates, using the rate for methyl acetate (0.0418) as unity, for the ammonolysis of acetates in anhydrous ethylene glycol are listed in Table III.

TABLE III

AMMONOLYSIS[a] OF ACETATES IN ANHYDROUS ETHYLENE GLYCOL AT 30°

| Ester | Relative rate |
|---|---|
| Phenyl acetate | 17.9 |
| Vinyl acetate | 4.33 |
| Methyl acetate[b] | 1.00 |
| *n*-Amyl acetate | 0.91 |
| Isobutyl acetate | .87 |
| Isopropyl acetate | .65 |
| *s*-Butyl acetate | .21 |
| α-Naphthyl acetate | .18 |
| β-Naphthyl acetate | .18 |
| *t*-Butyl acetate | .036 |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.411–2.416 moles/l. [b] The rates for methyl, ethyl, *n*-propyl, *n*-butyl and benzyl acetates were practically the same in anhydrous ethylene glycol.

The values found for the relative rates, using the rate for methyl benzoate (0.00280) as unity, for the ammonolysis of benzoic acid esters in anhydrous ethylene glycol are shown in Table IV.

The values found for the relative rates, using the rate for methyl lactate (0.599) as unity, for the ammonolysis of lactic acid esters in anhydrous ethylene glycol are listed in Table V.

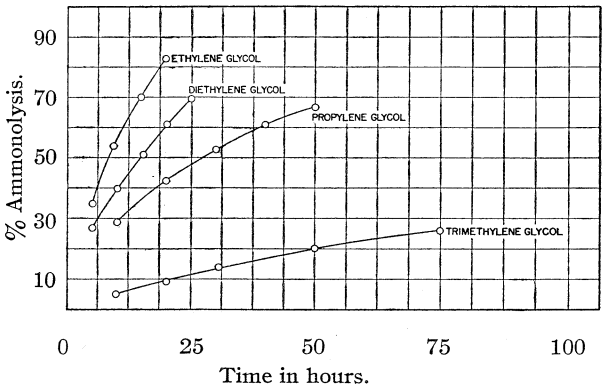



Fig. 2.—Ammonolysis of methyl acetate in anhydrous solvents.

TABLE IV

AMMONOLYSIS[a] OF BENZOATES IN ANHYDROUS ETHYLENE GLYCOL AT 30°

| Ester | Relative rate |
|---|---|
| Phenyl benzoate | 1.01 |
| Methyl benzoate | 1.00 |
| Ethyl benzoate | 0.92 |
| Benzyl benzoate | .82 |
| *n*-Propyl benzoate | .64 |
| Isopropyl benzoate | .30 |
| *t*-Butyl benzoate | .057 |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.385 moles/l.

TABLE V

AMMONOLYSIS[a] OF LACTATES IN ANHYDROUS ETHYLENE GLYCOL AT 30°

| Ester | Relative rate |
|---|---|
| Methyl lactate | 1.00 |
| Allyl lactate | 0.91 |
| Ethyl lactate | .88 |
| *n*-Propyl lactate | .70 |
| *n*-Butyl lactate | .57 |
| *n*-Amyl lactate | .55 |
| Isobutyl lactate | .47 |
| Isopropyl lactate | .22 |
| *s*-Butyl lactate | .21 |
| *n*-Butyl hydracrylate[b] | .038 |
| *t*-Butyl lactate | .016 |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.458 moles/l. [b] Inserted for comparison with *n*-butyl lactate.

Table VI lists similar data, using the rate for methyl acetate as unity, for the ammonolysis of methyl esters of various acids in anhydrous ethylene glycol. It should be noted that in the case of methyl crotonate principally addition to the double bond, with very little ammonolysis, took place. These results confirm those obtained in aqueous dioxane solution.[3]

In the ammonolysis of four homologous series of esters in anhydrous ethylene glycol the same general effects were noted as were observed earlier in aqueous dioxane–ammonia solutions.[3] Of course, most of the esters ammonolyzed much

TABLE VI

AMMONOLYSIS[a] OF METHYL ESTERS IN ANHYDROUS ETHYLENE GLYCOL AT 30°

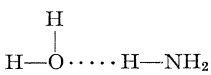
| Ester | Relative rate |
|---|---|
| Methyl formate | 66.4 |
| Methyl lactate | 14.3 |
| Methyl acetate | 1.00 |
| Methyl phenylacetate | 0.85 |
| Methyl propionate | .650 |
| Methyl crotonate | .25 |
| Methyl isobutyrate | .13 |
| Methyl benzoate | .08 |
| Methyl trimethylacetate | .003 |

[a] Concentration of ester 0.7 mole/l., concentration of ammonia 2.510 moles/l.

more rapidly in ethylene glycol solution than in aqueous dioxane. The only characteristic feature about the ammonolysis of esters in anhydrous ethylene glycol (Tables III, IV, V and VI) was the much smaller difference in reactivity between the different esters. While ammonolysis in anhydrous ethylene glycol has excellent possibilities for the preparation of amides, it should not be used in comparative studies without using a diluent such as dioxane to avoid the manipulative difficulties in working quantitatively with viscous solutions.

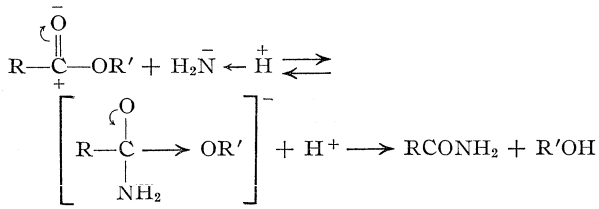
## Discussion

The mechanism of activation of the ammonia pictured earlier for water[3] is probably also in effect



with the alcohols. While the free amide ion is not postulated in any case, polarization of the hydrogen–nitrogen bond in the case of water and some of the other solvents is sufficient to make the ammonia molecule more reactive as a nucleophilic agent.

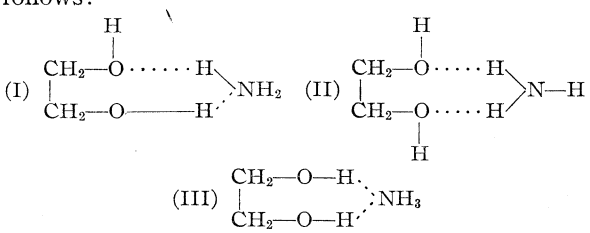
The effect of sodium hydroxide on the ammonolysis of methyl acetate (Table II) is strong evidence for the mechanism of ammonolysis involving addition of an amide ion, rather than molecular ammonia.



The presence of hydroxyl ions would favor the formation of amide ions and the precipitous initial rate of ammonolysis in sodium hydroxide solution bears this out. The rate constants drop off after 10% reaction. This would be expected from the low concentration of sodium hydroxide used and its consumption by the competing hydrolysis.

The catalysis by water and the other solvents continues increasingly even beyond the point where there is a 1:1 ratio of solvent to ammonia. This points to the association of only a fraction of the solvent molecules with ammonia. It is difficult, therefore, to assign a specific structure to the ammonia–solvent complex in most cases. However, for purposes of discussion of relative effects, a simple addition complex involving one molecule of ammonia and one of solvent will be considered.

In view of the results obtained for the ammonolysis of esters in various media a cyclic structure for the complex of ammonia with ethylene glycol, one of the most active of catalysts, seems probable. The three possible structures for this hydrogen-bonded complex are as follows:



In formula (I) for this complex the two hydrogen bonds are probably of unequal strength. Spectroscopic evidence has been found by Gordy[5] for this conclusion. In his studies Gordy used methanol containing a deuterium atom in the hydroxyl group, and he measured the shift in O–D infrared absorption as a result of hydrogen bonding to various compounds. From these data he concluded that the acceptor properties of the amine hydrogen are much weaker than those of the hydroxyl hydrogen. Huggins[6] has likewise emphasized the improbability of strong hydrogen bonds being formed through an amine hydrogen. From these investigations it is apparent that the N–H · · · · O bond is weaker than the N · · · · H–O bond in Formula I.

Formula II of the ammonia–ethylene glycol complex, although present in smaller amounts than Formula I due to its weak bonds, is probably the more active in ammonolysis because it contains two N–H · · · · O bonds which are the ones making a $NH_2^-$ ion available. However, a strong bond is not necessary to implement the mechanism of ammonolysis. All that is needed is an attractive force which will polarize the covalent nitrogen–hydrogen bond sufficiently. In form (II) both hydrogen–nitrogen bonds involved would be weakened somewhat, and it is statistically possible for fission of either bond to occur upon approach of the nitrogen to the carbonyl carbon of the ester.

In ammonolysis it is not necessary to postulate that the nitrogen–hydrogen bond breaks before the nitrogen–carbon bond is formed. These

(5) Gordy, *J. Chem. Phys.*, **7**, 93 (1939).

(6) Huggins, *J. Org. Chem.*, **1**, 407 (1936).

bonds could be broken and formed simultaneously,[7] after the nucleophilic center in the ammonia complex and the electrophilic center of the ester have approached one another through the action of electrostatic forces or by random motion.

An additional form of the ammonia–ethylene glycol complex may be drawn (III), but it was ruled out for two reasons: first, because it is difficult to see how it could contribute to the formation of potential amide ions and, second, because of the unlikelihood of two hydrogen bonds forming on a single nitrogen. In this connection Huggins[6] has stated that attempts to find two O–H $\cdots$ N bridges to the same nitrogen were unsuccessful.

The reasons for the postulate of a cyclic and not a linear hydrogen bonded ammonia–solvent complex are obvious from the data. The monohydric alcohols, for which no simple cyclic hydrogen bonded structure is possible, show a comparatively low order of catalytic activity. The 1,2-glycols and glycerol, on the other hand, exhibit an increase in catalytic effect that is far out of proportion to the additional molecular concentration of hydroxyl groups introduced. For example, the rate of ammonolysis of methyl acetate in the presence of 5 moles of ethylene glycol/l. is over five times the rate in a similar molecular concentration of methanol. The disproportionate increase in the catalytic activity of glycerol over ethylene glycol is probably due to the combination of inter- and intramolecular hydrogen bonded complexes with ammonia which are possible.

Trimethylene glycol, which differs from ethylene glycol only by one $CH_2$ group, has a catalytic activity only one-third that of ethylene glycol. Similarly 1,3-butanediol has a much lower order of catalytic activity than would be anticipated. In fact, on the basis of equivalent molecular concentrations of hydroxyl groups, the catalytic activity of these 1,3-glycols is of the order of magnitude of methanol. This phenomenon points very strongly to a structure like (II), containing a seven-membered ring, for the ethylene glycol–ammonia complex. A similar structure for trimethylene glycol or 1,3-butanediol would require an eight-membered ring, which is less likely on steric grounds. Wall and Claussen have stated,[8] on the basis of spectrographic evidence, that the most stable rings involving hydrogen bonds contain six or seven atoms, including the hydrogen. These numbers are greater by one than those usually given for rings involving only ordinary electron pair types of bonds.

Substitution of one of the hydrogens in ethylene glycol by an ethyl group reduced the catalytic activity in ammonolysis to one-third of the former value. The fact that ethylene glycol was three times as effective as ethylene glycol monoethyl ether indicates that the hydroxyl oxygen is much more effective in promoting hydrogen bonding, and hence ammonolysis, than the ether oxygen. Independent confirmation for these results was obtained by Gordy[9] from measurements of the shift in the infrared absorption spectra of hydroxyl groups. The shift in the oxygen–deuterium absorption maximum of $CH_3OD$ was more than twice as great in propylene glycol as in dioxane.

Gordy further stated that a cyclic ether is not as effective an electron donor solvent as an open chain ether. Errera[10] and Freymann[11] similarly commented on the comparatively low associating ability of dioxane. Their observations corroborate the results of this laboratory on the very low order of catalytic activity of dioxane. In this particular instance there is the additional steric factor which makes ring formation, involving the two ether oxygens of dioxane, improbable.

From all of the foregoing experiments we may generalize that the grouping –O–C–C–O– is the basic one involved in most of the pronounced catalytic effects noted in this study. If the groups attached to the terminal ends of the oxygens are hydrogens, the greatest activity is observed. Conversion of the hydroxyl oxygens to ether oxygens reduces the catalytic activity, particularly if the ether grouping is part of a ring. In diethylene glycol, which was found to have the same catalytic effect on ammonolysis as ethylene glycol, two hydroxyl groups are present, but they are separated by five atoms, the center one being an ether oxygen. In this molecule the possibility of bonding of ammonia to either half of the molecule increases its catalytic activity to the point where it equals that of ethylene glycol.

The catalytic activity of diethylene glycol monomethyl ether was about half that of diethylene glycol, showing again the reduced catalytic activity of the ether oxygen when compared with the hydroxyl oxygen. However, diethylene glycol monomethyl ether showed about 55% greater catalytic activity than ethylene glycol monoethyl ether, indicating that the ether oxygen must make some contribution, if a small one, to the catalytic activity of the solvent.

On the basis of the relative catalytic effects of methanol and *t*-butanol on the ammonolysis of esters, it might be anticipated that propylene glycol, containing a secondary alcohol group, would show a greater catalytic activity than ethylene glycol. A similar conclusion might be reached for the relative catalytic effects of trimethylene glycol and 1,3-butanediol, or ethylene glycol and isobutylene glycol.

In this Laboratory the catalytic effect of propylene glycol was found to be 40% less than that of ethylene glycol. Empirical confirmation for these

(7) London, *Z. Elektrochem.*, **35**, 552 (1929).

(8) Wall and Claussen, THIS JOURNAL, **61**, 2679 (1939).

(9) Gordy, *J. Chem. Phys.*, **8**, 170 (1940).

(10) Errera, Gaspart and Sack, *ibid.*, **8**, 63 (1940).

(11) Freymann, *Compt. rend.*, **204**, 41 (1937).

results can be obtained from the work of Gordy and Stanford[12] and Wall and Claussen.[8] These investigators found that there was no intramolecular hydrogen bonding in ethylene glycol, while in propylene glycol the internal association was noted in the shift in the oxygen–deuterium absorption band. Therefore these investigators concluded that ethylene glycol shows a greater proton attracting ability than propylene glycol.

Similarly, it was found in this Laboratory that ethylene glycol had greater catalytic activity in ammonolysis than isobutylene glycol, and it was ound that the effect of trimethylene glycol was greater than 1,3-butanediol. From all of these results on glycols a generalization is apparent. All symmetrical glycols have a greater catalytic activity in ammonolysis than the corresponding unsymmetrical glycols due to the presence of intramolecular hydrogen bonding in the latter. Thus: $CH_2OHCH_2OH > CH_3CHOHCH_2OH > (CH_3)_2COHCH_2OH$, and $CH_2OHCH_2CH_2OH > CH_3CHOHCH_2CH\ OH$. In other words, in unsymmetrical glycols the intramolecular hydrogen bonding results in a reduced over-all ability to associate with ammonia or other compounds. The more basic an atom, the more readily it acts as an acceptor for hydrogen; the more acidic the atom, the more readily it acts as a proton donor. Therefore in a glycol the greater the difference in electronegativities of the oxygens, the greater will be the intramolecular hydrogen bonding. The relative effects of ethylene glycol, propylene glycol, and isobutylene glycol, noted above, agree with these predictions. Wall and Claussen[8] postulated intramolecular hydrogen bonding in propylene glycol, in preference to intermolecular bonding, because of the small change in the frequency of hydroxyl absorption encountered upon dilution o' carbon tetrachloride solutions of propylene glycol.

Consideration was given the possibility that catalysis of the ammonolysis of esters by ethylene glycol takes place through ester interchange.

(1) $CH_3COOCH_3 + CH_2OHCH_2OH \longrightarrow CH_3COOCH_2CH_2OH + CH_3OH$

(2) $CH_3COOCH_2CH_2OH + NH_3 \longrightarrow CH_3CONH_2 + CH_2OHCH_2OH$

Demonstration that either of these two steps proceeds more slowly than the ammonolysis of methyl acetate in the presence of ethylene glycol rules out the mechanism involving ester interchange. The first of these steps was too difficult to study experimentally. The second step was followed experimentally, and the ammonolysis of β-hydroxyethyl acetate ($k = 0.00700$) was found to proceed more slowly than the ammonolysis of methyl acetate ($k = 0.0100$) in the presence of ethylene glycol. In addition, the ammonolysis of β-hydroxyethyl acetate was much slower in ethylene glycol than would be anticipated in comparison with other esters.

It should not be inferred from the above discussion that a sharp demarcation exists between those solvents which catalyze ammonolysis in the absence of water and those which do not. On the basis of experimental evidence the ammonolysis of all esters may be said to proceed in all solvents although the extent of reaction in some cases is too small to be measurable with any degree of accuracy. Justification for this statement is found in the behavior of phenyl acetate in various ammonia solutions. Phenyl acetate ammonolyzed completely in the presence of water in about half an hour. This ester was then shown to undergo ammonolysis almost completely in anhydrous dioxane or alcohol in about twenty-four hours. In comparison, the ammonolysis of methyl acetate takes place to the extent of only a few per cent. in anhydrous dioxane or alcohol over a period of three months. The magnitude of the experimental error involved in working with anhydrous solutions of alcohol or dioxane, particularly the latter, is so great that the results are of value in qualitative comparisons only. Experimental error in these cases is due to the low solubility o' ammonia in these solvents, and to the volatility of the solvents themselves.

**Acknowledgment.**—The authors wish to express their thanks to the following companies for supplying solvents used in this study: Carbide and Carbon Chemicals Corporation, Eastman Kodak Company, Shell Development Company, and Joseph E. Seagram and Sons, Inc.

## Summary

A general method has been developed for the ammonolysis of esters in the absence of water.

The catalytic effect of water and other solvents on the ammonolysis of esters has been found to increase with concentration, even beyond the point where the ammonia–catalyst ratio is 1:1.

The relative catalytic effects of solvents on the ammonolysis of esters has been investigated and the following order of reactivity was determined: glycerol > ethylene glycol, diethylene glycol > propylene glycol > diethylene glycol monomethyl ether > water > isobutylene glycol > ethylene glycol monoethyl ether > trimethylene glycol > 1,3-butanediol > *t*-butanol > methanol > dioxane.

A mechanism has been postulated for the ammonolysis of esters in various solvents.

PHILADELPHIA, PENNSYLVANIA RECEIVED MARCH 2, 1948

(12) Gordy and Stanford, *J. Chem. Phys.*, **9**, 204, 215, 440 (1941).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

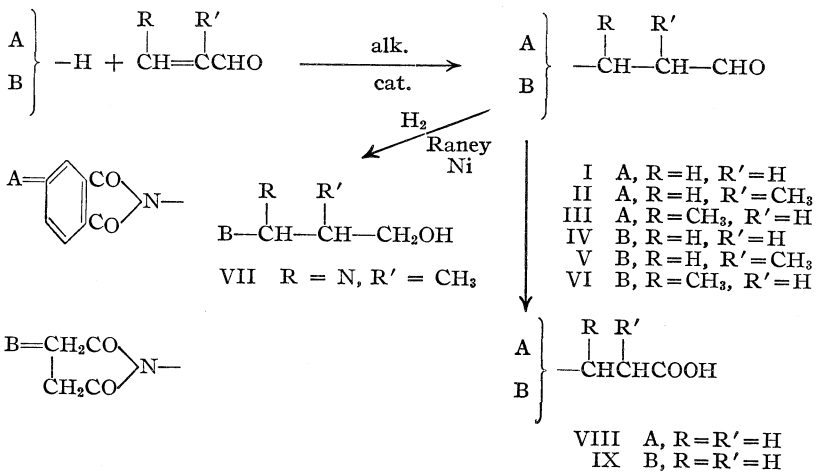
# 1,4 Addition Reactions. III. The Addition of Cyclic Imides to α,β-Unsaturated Aldehydes. A Synthesis of β-Alanine Hydrochloride[1]

BY OWEN A. MOE AND DONALD T. WARNER

Previous publications[2,3] from this Laboratory have disclosed the 1,4 addition of malonate systems to acrolein. Since the 1,4 addition of imides to α,β-unsaturated aldehydes has not been reported, this paper describes the reaction of cyclic imides, such as phthalimide and succinimide with acrolein and alkyl substituted acroleins such as, methacrolein (α-methylacrolein) and crotonaldehyde.

The addition reactions involving phthalimide and acrolein, methacrolein and crotonaldehyde proceeded smoothly in the presence of a minute quantity of alkaline catalyst to yield the aldehydo compounds I, II and III, respectively. The adducts were characterized as the phenylhydrazones and the 2,4-dinitrophenylhydrazones.

Radde[4] attempted the preparation of phthalimidopropionaldehydes by the reduction of the corresponding acid chlorides. However, Radde observed that this reduction reaction was only applicable for the α-phthalimido acid chlorides and not for the β, γ and δ compounds.




The 1,4 addition of succinimide to acrolein, methacrolein and crotonaldehyde yielded the aldehydo compounds IV, V and VI, respectively.

The crude reaction products from the succinimide series were obtained in good yields, but they were liquids which resisted crystallization or distillation. Therefore, it was necessary to determine the proportion of the aldehydo compounds (1,4 addition products) by other methods. This was accomplished by means of derivative formation and reduction experiments. Some of the aldehydo derivatives were obtained in yields in excess of 80%. It was observed that the lowest yield of derivative occurred when crotonaldehyde was used as the unsaturated aldehyde.

If 1,2 addition had occurred, the presence of unsaturation in the reaction product could be readily determined by low pressure hydrogenation employing palladium on charcoal as the catalyst. In an experiment designed to determine this possibility (using methacrolein–succinimide reaction product) it was found that less than 5% of the theoretical amount of hydrogen had been consumed after one hour. However, when acetic acid, ethyl cyanoacetate and piperidine[5] were added to the same reaction mixture, and hydrogenation was resumed, 67% of the theoretical amount of hydrogen was taken up in one hour, indicating the predominant presence of the aldehydo compound.

The reduction of the crude α-methyl-β-succinimidopropionaldehyde in the presence of Raney nickel catalyst yielded 2-methyl-3-succinimido-1-propanol VII which in turn was characterized as the crystalline 3,5-dinitrobenzoate melting at 104–105°.

Oxidation by permanganate of β-phthalimidopropionaldehyde I yielded β-phthalimidopropionic acid VIII which was identical with an authentic sample. The substituted propionic acid was readily converted to β-alanine hydrochloride by means of acid hydrolysis.

Permanganate oxidation of β-succinimidopropionaldehyde IV yielded β-succinimidopropionic acid IX melting at 131–132°.

## Experimental

**β-Phthalimidopropionaldehyde, I.**—Phthalimide (44.1 g.) was added to an alcoholic solution containing 110 cc. of absolute ethanol and 0.15 g. of sodium. The resulting reaction mixture was stirred at room temperature and the greater portion of the phthalimide remained suspended in the reaction mixture. A solution containing 25 cc. of acrolein and 15 cc. of absolute ethanol was added dropwise over a twenty-minute period and the reaction temperature increased to 51°. The reaction mixture was stirred for an additional half hour when a substantially clear solution resulted. After standing overnight, the re-

(1) Paper No. 94, Journal Series, General Mills, Inc., Research Department.

(2) Moe and Warner, THIS JOURNAL, **70**, 2763 (1948).

(3) Warner and Moe, *ibid.*, **70**, 3470 (1948).

(4) Radde, *Ber.*, **55**, 3174 (1922).

(5) Alexander and Cope, THIS JOURNAL, **66**, 886 (1944).

action mixture was neutralized by the addition of the requisite quantity of glacial acetic acid. After filtration, the ethanol was removed by distillation under reduced pressure, yielding a viscous oil. Benzene (100 cc.) was added and the concentration *in vacuo* was repeated, yielding a semi-solid residue. The addition of benzene (100 cc.) yielded a pasty solid which was collected by filtration. Sixteen grams were obtained melting at 108–115°, and concentration of the filtrate yielded an additional quantity of solid which was not investigated further. Since this crude product proved difficult to purify by crystallization, a portion of it was placed in a round bottom flask and heated in an oil-bath under reduced pressure (15 mm.) until a clear melt was obtained. Fine needle-like crystals collected on the cool sides of the flask. These crystals melted at 119–120°.

*Anal.* Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.43; N, 6.90. Found: C, 65.20; H, 4.34; N, 7.03.

The phenylhydrazone melted at 121.5–122.5° after crystallization from ethanol.

*Anal.* Calcd. for $C_{17}H_{15}O_2N_3$: C, 69.60; H, 5.15; N, 14.33. Found: C, 69.41; H, 5.15; N, 14.73.

The 2,4-dinitrophenylhydrazone melted at 209–210° after crystallization from aqueous acetone.

*Anal.* Calcd. for $C_{17}H_{13}O_6N_5$: C, 53.26; H, 3.42; N, 18.28. Found: C, 53.24; H, 3.55; N, 18.33.

**α-Methyl-β-phthalimidopropionaldehyde.**—Phthalimide (14.7 g.) was suspended in an alcoholic solution consisting of 110 cc. of absolute ethanol and 0.04 g. of sodium. Methacrolein (7.4 g.) was added dropwise with no apparent increase in the reaction temperature. Reaction mixture was heated at 40–50° for a period of two hours when a substantially clear solution resulted. After neutralization, the ethanol was removed by concentration *in vacuo* and 21.3 g. of the reaction product resulted as an oil.

The crude phenylhydrazone was obtained in 80% yield and melted at 116–119°. An analytical sample was prepared by crystallization from ethanol and it melted at 119–121°.

*Anal.* Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.35; H, 5.58; N, 13.68. Found: C, 69.88; H, 5.38; N, 13.63.

The crude 2,4-dinitrophenylhydrazone (70%) melted at 184–187°. An analytical sample which melted at 193–194° was prepared by crystallization from ethanol–acetone (50–50).

*Anal.* Calcd. for $C_{18}H_{15}O_6N_5$: N, 17.63. Found: N, 17.68.

**β-Methyl-β-phthalimidopropionaldehyde.**—This reaction was accomplished essentially as described in the previous case employing recrystallized phthalimide (29.4 g.) and freshly redistilled crotonaldehyde (15.66 g.). The reaction product (42 g.) was a brown pasty solid melting at 93–103°. A portion of this solid was recrystallized three times from Skelly C and melted at 105–108°.

*Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.36; H, 5.1; N, 6.4. Found: C, 66.62; H, 5.1; N, 6.6.

The crude phenylhydrazone (45%) melted at 98–100°. Purification by crystallization from ethanol yielded an analytical sample melting at 98–99°.

*Anal.* Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.35; H, 5.58; N, 13.68. Found: C, 70.21; H, 5.60; N, 13.88.

The crude 2,4-dinitrophenylhydrazone (40%) melted at 170–172°. Recrystallization from acetone yielded an analytical sample melting at 180.5–181°.

*Anal.* Calcd. for $C_{18}H_{15}O_6N_5$: C, 54.4; H, 3.8; N, 17.6. Found: C, 54.63; H, 3.9; N, 17.84.

**β-Succinimidopropionaldehyde, II.**—Succinimide[6] (29.7 g.) was added to an alcoholic solution containing 50 cc. of absolute ethanol and 0.05 g. of sodium. The resulting suspension was cooled to 6° in an ice-bath. The cooling bath was removed and acrolein (16.8 g.) was added dropwise. The reaction temperature increased very rapidly to 31° and this temperature was maintained by varying the rate of addition of the acrolein. After the addition of the aldehyde was complete, the reaction mixture was stirred for an additional thirty-five minute period when a clear, water-white solution resulted. After standing for two and a half hours, the reaction mixture was neutralized with glacial acetic acid. Concentration *in vacuo* yielded a very viscous oil (44.3 g.) which resisted crystallization.

A portion of the crude aldehydo compound yielded a semicarbazone (75%) melting at 189–193°. An analytical sample was prepared by two crystallizations from aqueous ethanol and it melted at 201–202.5°.

*Anal.* Calcd. for $C_8H_{12}O_3N_4$: C, 45.3; H, 5.7; N, 26.4. Found: C, 45.34; H, 5.56; N, 26.64.

The *p*-nitrophenylhydrazone (61%) melted at 213–215°. After purification by crystallization from ethanol–acetone, it melted at 221–223°.

*Anal.* Calcd. for $C_{13}H_{14}O_4N_4$: C, 53.8; H, 4.8; N, 19.3. Found: C, 53.5; H, 4.8; N, 19.45.

The 2,4-dinitrophenylhydrazone (60% crude) melted at 183.5–184.5° after crystallization from 50 volume % ethanol–acetone solution.

*Anal.* Calcd. for $C_{13}H_{13}O_6N_5$: C, 46.56; H, 3.9; N, 20.89. Found: C, 47.05; H, 4.34; N, 20.68.

**α-Methyl-β-succinimidopropionaldehyde, V.**—Succinimide (9.9 g.) was added to an alcoholic solution containing 55 cc. of absolute ethanol and 0.05 g. of sodium. Methacrolein (7.04 g.) was added dropwise and the reaction temperature increased from 20 to 31°. The resulting clear reaction mixture was stirred for three hours and then neutralized with glacial acetic acid. Concentration *in vacuo* yielded 15.8 g. of an oily product which resisted crystallization.

The 2,4-dinitrophenylhydrazone which was obtained in 86% yield melted at 196.5–197° after crystallization from acetone.

*Anal.* Calcd. for $C_{14}H_{15}O_6N_5$: C, 48.13; H, 4.32. Found: C, 48.52; H, 4.59.

The *p*-nitrophenylhydrazone (80%) melted at 184–185° after crystallization from acetone.

*Anal.* Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.26; H, 5.3; N, 18.42. Found: C, 55.22; H, 5.3; N, 18.42.

**Low Pressure Reduction of Reaction Product, V.**—The above crude reaction product (15.4 g.) was dissolved in 60 cc. of ethanol. Palladium on charcoal (0.5 g.) was added and the reduction was carried out at initial pressure of 32.5 pounds of hydrogen. After one hour, less than 5% of the theoretical amount of hydrogen had been consumed. The attempted reduction was interrupted at this point and 1 cc. of glacial acetic acid, 11.3 g. of ethyl cyanoacetate and 0.4 g. of piperidine were added. The reduction was again resumed at 32 pounds pressure. After one hour, 67% of the theoretical amount of hydrogen had been consumed. No attempt was made to characterize this simultaneous condensation–reduction product.

**2-Methyl-3-succinimido-1-propanol, VII.**—The crude β-methyl-β-succinimidopropionaldehyde (12.5 g.) was dissolved in 75 cc. of absolute ethanol. Raney nickel catalyst was added and the reduction was carried out at 70–80° at an initial pressure of 800 pounds of hydrogen. When the reduction was complete, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. A light yellow viscous oil resulted. The crude carbinol (1.9 g.) was mixed with 3,5-dinitrobenzoylchloride in a conventional manner. The resulting 3,5-dinitrobenzoate (0.93 g.) melted at 104–105° after crystallization from ethanol.

*Anal.* Calcd. for $C_{15}H_{15}O_8N_3$: C, 49.32; H, 4.14; N, 11.50. Found: C, 49.84; H, 4.23; N, 11.76.

**β-Methyl-β-succinimidopropionaldehyde, VI.**—This reaction was accomplished essentially as described in the

(6) The 1,4 addition reactions involving Eastman Kodak Co. White Label succinimide did not proceed under the reaction conditions described. This may be due possibly to the presence of acidic components; hence recrystallized succinimide was employed in all experiments.

previous case employing recrystallized succinimide (7.7 g.) and freshly redistilled crotonaldehyde (5.8 g.) and the reaction temperature increased from 28 to 34°. Concentration *in vacuo* yielded 12.8 g. of crude reaction product.

The crude aldehydo compound was converted to the 2,4-dinitrophenylhydrazone (40%) which melted at 165–166° after crystallization from an ethyl acetate–acetone solution.

*Anal.* Calcd. for $C_{14}H_{15}O_6N_5$: C, 48.13; H, 4.32; N, 20.06. Found: C, 48.35; H, 4.38; N, 20.32.

**Preparation of β-Succinimidopropionic Acid, IX.**—The crude β-succinimidopropionaldehyde (15.5 g., viscous oil) was dissolved in 30 cc. of warm water. Approximately 1.5 cc. of 10% aqueous sodium hydroxide solution was added, and the resulting solution was cooled to 8°. An aqueous solution of potassium permanganate consisting of 300 cc. of water and 10.5 g. of permanganate was added in portions. The temperature increased rapidly to 14° but was maintained at approximately 10° by continued cooling. After the oxidation was complete, the manganese dioxide was removed by filtration, and the excess permanganate was destroyed with dilute sodium bisulfite solution. The clear reaction solution was concentrated *in vacuo* yielding a viscous oil. The residual oil was extracted with ether, and after drying over anhydrous sodium sulfate the ether was removed by distillation. The residual oil rapidly crystallized on cooling and the crystalline product melted at 124–128°. Further extraction of the syrup with ethyl acetate gave additional crude product. The total yield (2.15 g.) was low. Recrystallization from absolute ethanol yielded needle-like crystals melting at 131–132°.

*Anal.* Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18; neut. equiv., 171. Found: C, 49.03; H, 5.34; N, 8.00; neut. equiv., 177.

**Conversion of β-Phthalimidopropionaldehyde to β-Alanine Hydrochloride.**—The crude β-phthalimidopropionaldehyde I was oxidized by permanganate essentially as discussed in the previous case. Concentration *in vacuo* yielded a white crystalline material which was collected by filtration, washed with water and dried. The N-phthalyl-β-alanine VIII thus obtained melted at 139–141°. Recrystallization from absolute ethanol increased the melting point to 141–142°. When the N-phthalyl-β-alanine was recrystallized from water, it melted at 149.5–151°. The melting point of the N-phthalyl-β-alanine was not depressed when mixed with an authentic sample.[7]

Two and five-tenths grams of the recrystallized N-phthalyl-β-alanine was refluxed with 25 cc. of 20% hydrochloric acid for a period of eighteen hours. Upon cooling, the phthalic acid crystallized from the reaction solution, and after filtration the filtrate was evaporated *in vacuo* to yield a crystalline residue. Recrystallization from isopropyl alcohol yielded β-alanine hydrochloride (0.51 g.) as fine needles melting at 120–121.5°. An additional crystallization increased the melting point to 121.5–123°.

## Summary

1. The 1,4 addition of cyclic imides, such as phthalimide and succinimide, to acrolein, methacrolein and crotonaldehyde has been described.

2. A new synthesis of β-alanine, using β-phthalimidopropionaldehyde as the starting material, has been described.

(7) Schöberl, *Ann.*, **542**, 274 (1939).

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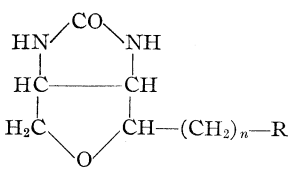
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# Furan and Tetrahydrofuran Derivatives. X.[1] The Synthesis of the Sulfonic Acid Analogs of Oxybiotin and Homoöxybiotin

BY KLAUS HOFMANN, ANNA BRIDGWATER AND A. E. AXELROD[2]

In connection with our studies on the relationships of chemical structure and biological activity in the biotin and oxybiotin series,[3] it seemed desirable to replace the carboxyl group in *dl*-oxybiotin (I) by a sulfonic acid moiety and to test the biological activity of the resulting compound. Recently we have shown that *dl*-homoöxybiotin (II) has the ability to antagonize the growth-promoting effects of *dl*-oxybiotin for yeast. It was of interest to determine whether the sulfonic acid analog (IV) would possess greater antagonistic potency than homoöxybiotin (II). This communication describes the synthesis of the two sulfonic acids (III and IV). A brief account of the biological activities of these acids and of several of the intermediates obtained during their preparation will also be presented.




| | *n* | R |
|---|---|---|
| (I) | 4 | COOH |
| (II) | 5 | COOH |
| (III) | 4 | $SO_3H$ |
| (IV) | 5 | $SO_3H$ |

The methods used to prepare *dl*-hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII), the key intermediate in the synthesis of III, were those recently developed in this Laboratory for the preparation of similar compounds.[3,4,5,6] Starting material for the present study was 2-furanpropanol (V)[3] which was transformed into 2-furanpropyl chloride (VI) by a modification of the procedure of Gilman.[7] This chloride, on treatment with potassium cyanide followed by hydrolysis, was converted into 2-furanbutyric acid (VII), which was then esterified. The resulting ethyl 2-furanbutyrate (VIII), upon reduction with sodium and alcohol, yielded the desired 2-furanbutanol (IX). Condensation of IX with diethylacetylenedicarboxylate, followed by partial hydrogenation and thermal decomposi-

(1) A preliminary report of some of the work herein described has appeared in THIS JOURNAL, **69**, 1550 (1947).

(2) The authors wish to express their appreciation to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and to the Buhl Foundation for their generous support of this study.

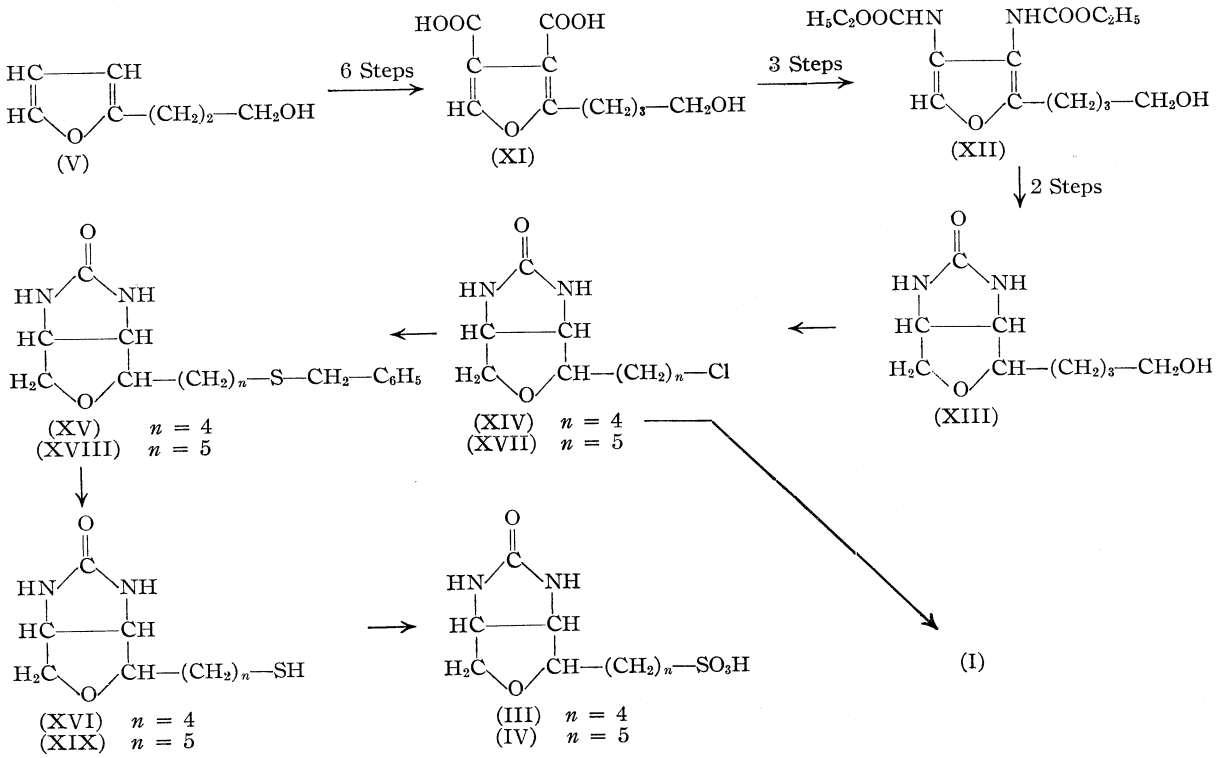
(3) Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, **69**, 191 (1947).

(4) Hofmann, *ibid.*, **67**, 421 (1945).

(5) Hofmann and Bridgwater, *ibid.*, **67**, 1165 (1945).

(6) Hofmann, *ibid.*, **67**, 1459 (1945).

(7) Gilman and Hewlet, *Rec. trav. chim.*, **51**, 93 (1932).




tion,[4,8] gave 3,4-dicarbethoxy-2-furanbutanol which was transformed into 3,4-dicarboxy-2-furanbutanol (XI) by alkaline hydrolysis. The acetate of XI, by a modified Curtius degradation,[6] was converted into 3,4-dicarbethoxyamino-2-furanbutanol (XII).

It should be noted that the transformation of a tri-substituted furan such as XII into the corresponding tetrahydro derivative creates three assymetric carbon atoms within the molecule, and four racemic 3,4-diamino-2-tetrahydrofuranbutanols may theoretically be expected. Stereochemically this situation parallels that of the 3,4-dicarbethoxyamino-2-tetrahydrofuranpentanols.[9] Catalytic hydrogenation of XII resulted in the formation of a mixture of reduction products, which were separated into an ether-soluble and an ether-insoluble fraction. The ether-insoluble material, containing the desired *cis*-3,4-dicarbethoxyamino-2-tetrahydrofuranbutanol, upon treatment with barium hydroxide[5] yielded a hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII) which on the basis of evidence presented below has the same spatial configuration as *dl*-oxybiotin (I).

Treatment of XIII with thionyl chloride[3] gave the corresponding chloride (XIV), which upon reaction with potassium cyanide and hydrolysis was transformed into *dl*-oxybiotin (I). Therefore, derivatives which are prepared from XIII by modification of the side chain also have the same stereochemical configuration as *dl*-oxybiotin. Condensation in absolute alcohol of the chloride (XIV) with sodiobenzylmercaptide gave the benzyl thioether (XV), which upon reduction with sodium and alcohol was converted into the mercaptobutanol (XVI). Attempts to cleave the thioether (XV) with sodium in liquid ammonia failed, probably because of the insolubility of the compound in the liquid ammonia. Oxidation with dilute barium permanganate of the mercaptobutanol (XVI) gave the desired sulfonic acid (III) in excellent yield. Oxidation of XVI with bromine according to Levene[10] gave the same sulfonic acid in poor yields.

A similar series of reactions was used in the preparation of the sulfonic acid (IV). *dl*-Hexahydro-2-oxo-4-(5-chloropentyl)-1-furo(3,4)-imidazole (XVII),[3] through the benzyl thioether (XVIII), was converted into the mercaptopentanol (XIX), which on oxidation with barium permanganate yielded the desired sulfonic acid (IV). Both sulfonic acids were characterized in the form of their crystalline barium salts.

The microbiological activity of compounds III, IV, XV, XVI, XVIII and XIX was determined with *Lactobacillus arabinosus* and *Saccharomyces cerevisiae* as the test organisms. In conformity with earlier observations which showed that the substitution of carboxyl groups by sulfonic acid groups in biologically active molecules led to antagonists, the sulfonic acid analog of oxybiotin (III) was also found to possess antagonistic activity against *d*-biotin and *dl*-oxybiotin (molar-inhi-

(8) Hofmann, THIS JOURNAL, **66**, 51 (1944).
(9) Hofmann, *ibid.*, **71**, 164 (1949).
(10) Levene, Mori and Mikeska, *J. Biol. Chem.*, **75**, 347 (1927).

bition ratio[11] toward *d*-biotin and *dl*-oxybiotin for *S. cerevisiae* = 1,500,000 and 16,000, respectively).

Two intermediates in the synthesis of the sulfonic acid (III), namely, the benzyl thioether (XV) and the mercaptobutanol (XVI), proved to be rather active antagonists. Thus, compound XV possessed a molar-inhibition ratio toward *d*-biotin and *dl*-oxybiotin of 740,000 and 9,300, respectively, when *S. cerevisiae* was used as the test organism.

In contrast to *dl*-homoöxybiotin (II), which is an effective oxybiotin antagonist for yeast, the corresponding sulfonic acid analog (IV) possessed slight growth-stimulating activity both for *L. arabinosus* and *S. cerevisiae*. Compounds XVIII and XIX also had stimulatory activity for *L. arabinosus*. They were inhibitory, however, when tested with *S. cerevisiae*.

A complete description of the biological activities of the above compounds, especially their inhibitory action toward pathogenic organisms, will be published elsewhere.

## Experimental[12,13]

**2-Furanbutyric Acid (VII).**—To a three-neck flask, equipped with a dropping funnel and a stirrer with a mercury seal, were added 300 g. of 2-furanpropanol (V)[3] and 312 g. of dimethylaniline. The flask was cooled in an ice–salt-bath, and 306 g. of thionyl chloride in 180 cc. of dry chloroform was added dropwise with stirring. The inside temperature was kept at 0–10° throughout the operation. The mixture was stirred for one hour, poured on crushed ice, and extracted with chloroform. The chloroform extracts were washed with 2 *N* hydrochloric acid, water and 2 *N* potassium carbonate, and were dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue on distillation yielded 218 g. (63% of the theoretical yield) of 2-furanpropyl chloride (VI) as a colorless liquid which boiled at 80–92° at 13 mm. To a solution of 71 g. of (VI) in 700 cc. of 95% alcohol, 36 g. of potassium cyanide dissolved in 75 cc. of water were added, and the mixture refluxed for twenty-two hours. The solution was concentrated to one-third of its volume, 215 cc. of 5 *N* potassium hydroxide was added, and refluxing was continued for nine hours. Most of the alcohol was removed by distillation and the solution was extracted with ether. It was then acidified with 18 *N* sulfuric acid to congo red and re-extracted with ether. The ether extracts were washed with water, dried over sodium sulfate, and the ether removed on the steam-bath. The residue, on distillation, yielded 46 g. (60% of the theoretical yield) of 2-furanbutyric acid as a colorless liquid which boiled at 94–117° at 0.03 mm.

*Anal.* Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.53; H, 6.71.

**Anilide of 2-Furanbutyric Acid.**—A mixture of 3.0 g. of the above acid and 6.0 g. of freshly distilled aniline was heated to 170–175° for seventeen hours. The anilide was isolated in the usual manner, and was sublimed at 140° and 0.02 mm. Recrystallization of the sublimate from a mixture of petroleum ether and ether yielded shiny white crystals which melted at 62–64°.

*Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.31; H, 6.59; N, 6.11. Found: C, 72.81; H, 6.90; N, 6.03.

**2-Furanbutanol (IX).**—The furanbutyric acid (VII) (175 g.) was esterified with cold ethanolic hydrochloric acid and the ester isolated in the usual manner; 179 g. (87% of the theoretical yield) of ethyl 2-furanbutyrate (VIII), which boiled at 119–122° and 23 mm. was obtained. The ester (VIII) (60 g.) was reduced with sodium and ethanol as described previously,[4] and 36 g. (78% of the theoretical yield) of 2-furanbutanol was obtained as a colorless liquid which boiled at 115–117° at 18 mm.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.62. Found: C, 68.50; H, 8.25.

**α-Naphthylurethan of 2-Furanbutanol.**—This derivative was prepared in the usual manner and following recrystallization from a mixture of petroleum ether (b. p. 30–60°) and ether melted at 71–73°.

*Anal.* Calcd. for $C_{19}H_{19}O_3N$: C, 73.80; H, 6.19; N, 4.53. Found: C, 73.82; H, 6.16; N, 4.71.

**3,4-Dicarboxy-2-furanbutanol (XI).**—Fifty grams of 2-furanbutanol (IX) and 67 g. of diethylacetylene dicarboxylate were heated on the steam-bath overnight. The cooled mixture was dissolved in 300 cc. of ethyl acetate and hydrogenated at room temperature and atmospheric pressure in the presence of 8 g. of a palladium-on-barium sulfate catalyst[14] until one mole of hydrogen had been absorbed. The catalyst was removed by filtration, the ethyl acetate was evaporated *in vacuo*, and the residue heated to 190–200° at 16 mm. until the evolution of ethylene had ceased, and distilled *in vacuo;* 86.8 g. (86% of the theoretical yield), of 3,4-dicarbethoxy-2-furanbutanol (X) was obtained, which boiled at 156–161° at 0.02 mm. Saponification of the above material with a mixture of 500 cc. of methanol and 250 cc. of 5 *N* potassium hydroxide followed by acidification gave 67.3 g. (96% of the theoretical yield) of 3,4-dicarboxy-2-furanbutanol (XI) which was recrystallized from a mixture of methanol and ethyl acetate; m. p. 126–127°.

*Anal.* Calcd. for $C_{10}H_{12}O_6$: C, 52.63; H, 5.31. Found: C, 52.59; H, 5.54.

**3,4-Dicarboxy-2-furanbutanol Acetate.**—To 57.5 g. of 3,4-dicarboxy-2-furanbutanol (XI) in 235 cc. of dry pyridine was added slowly 150 cc. of acetic anhydride. After standing overnight, the solvents were removed *in vacuo*, the residue was dissolved in ethyl acetate, and the solution washed with 2 *N* hydrochloric acid and water, and extracted with several portions of 10% sodium bicarbonate. The combined bicarbonate extracts were acidified with concentrated hydrochloric acid to congo red and the desired compound re-extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulfate, and the solvent removed *in vacuo*. The crystalline residue of 3,4-dicarboxy-2-furanbutanol acetate was repeatedly washed with petroleum ether (b. p. 30–60°) and dried over phosphorus pentoxide; 61.3 g. (90% of the theoretical yield) of crystals was obtained, which upon recrystallization from ether melted at 89–90°.

*Anal.* Calcd. for $C_{12}H_{14}O_7$: C, 53.35; H, 5.22. Found: C, 53.04; H, 4.99.

**3,4-Dicarbethoxyamino-2-furanbutanol (XII).**—To a suspension of 50 g. of the above acetate in 250 cc. of dry ether was added, in small amounts, with cooling and shaking, a total of 87 g. of phosphorus pentachloride. Shaking was continued until most of the phosphorus pentachloride had disappeared, and the ether was removed *in vacuo* at a bath temperature of 95–100°. Dry benzene (100 cc.) was added to the residue with subsequent removal, and this procedure was repeated twice more. The residue was dissolved in 500 cc. of ether and stirred vigorously in an ice-bath for two hours with a solution of 48 g. of sodium azide in 130 cc. of water. The ether layer was separated, the aqueous layer reëxtracted with fresh ether, and the combined ether extracts washed with 10% sodium bicarbonate and water and finally dried over freshly desiccated sodium sulfate. The dried solution was filtered through a fluted

(11) The ratio of the molar concentration of the antagonist to that of *d*-biotin or *dl*-oxybiotin, at which *complete* inhibition of growth results.

(12) All melting points are corrected.

(13) The microanalyses were performed in our Microanalytical Laboratory by Mr. George L. Stragand.

(14) Schmidt, *Ber.*, **52**, 409 (1919).

filter filled with sodium sulfate, and the ether was removed *in vacuo* at a bath temperature of 20°. The resulting oily azide was dissolved in 500 cc. of absolute alcohol and decomposed under nitrogen as described in a previous communication.[15] The resulting solution was cooled to 0° and 370 cc. of *N* sodium hydroxide was added with stirring. After standing overnight the alcohol was removed *in vacuo*, the residue was diluted with water and extracted with ether. The ether extracts were washed with three 100-cc. portions of water, dried over sodium sulfate, and the solvent evaporated on the steam-bath. The oily residue crystallized on standing and gave 30 g. (52% of the theoretical yield) of ether-washed crystals which melted at 77–79°. No further purification was necessary for the next step. A sample for analysis was recrystallized from ether.

*Anal.* Calcd. for $C_{14}H_{22}O_6N_2$: C, 53.49; H, 7.05; N, 8.90. Found: C, 53.31; H, 6.75; N, 9.26.

***dl*-Hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII).**—A solution of 50 g. of (XII) in 800 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 75 g. of a palladium-on-barium sulfate catalyst[14] until 2 moles of hydrogen had been absorbed (reaction complete in approximately two hours). The catalyst was removed by filtration, the glacial acetic acid was evaporated *in vacuo*, and the residual oil dissolved in 100 cc. of ether. Washing of the ethereal solution with 100 cc. of 10% sodium bicarbonate resulted in the separation of an oily layer which contained the desired *cis* isomer of 3,4-dicarbethoxyamino-2-tetrahydrofuranbutanol. This oil was separated, dissolved in ethyl acetate, the solution dried over sodium sulfate, and the ethyl acetate removed *in vacuo*. A 10% solution of $Ba(OH)_2 \cdot 8H_2O$ (2.8 liters) was added to the residue and the mixture stirred at 90° for four hours. Isolation in the usual manner[3,6] gave 12 g. of crystals of XIII (37% of the theoretical yield) which upon recrystallization from dioxane melted at 156–157°.

*Anal.* Calcd. for $C_9H_{16}O_3N_2$: C, 53.98; H, 8.05; N, 13.99. Found: C, 54.12; H, 7.81; N, 13.80.

***dl*-Hexahydro-2-oxo-4-(4-chlorobutyl)-1-furo-(3,4)-imidazole (XIV).**—The butanol (XIII) (2 g.) was placed in a round-bottomed flask surrounded with ice, 5 cc. of ice-cold thionyl chloride was added at once and the solution was kept at room temperature for approximately twelve hours. The reaction product was isolated in the usual manner[3] and recrystallized from ethyl acetate; 1.33 g. (61% of the theoretical yield) of prisms melting at 124–126° was obtained.

*Anal.* Calcd. for $C_9H_{15}O_2N_2Cl$: C, 49.38; H, 6.90; N, 12.80; Cl, 16.22. Found: C, 49.16; H, 6.84; N, 12.54; Cl, 16.27.

***dl*-Oxybiotin (I).**—To a solution of 3.5 g. of the above chloride (XIV) in 100 cc. of 95% alcohol a solution of 2 g. of potassium cyanide in 4 cc. of water was added, and the mixture refluxed for twenty-four hours. The solvents were removed *in vacuo*, 1 *N* sodium hydroxide (100 cc.) was added to the residue, and refluxing continued for twelve hours. A slow stream of carbon dioxide was passed into the solution for thirty minutes and the resulting precipitate of silica removed by filtration through a layer of Filter-Cel. The clear filtrate was concentrated to a small volume *in vacuo* and was then acidified to congo red with concentrated hydrochloric acid. The resulting *dl*-oxybiotin (2.1 g.) (69% of the theoretical yield) was purified by crystallization from water. The compound was by mixed melting point and biological activity identical with *dl*-oxybiotin prepared by another method.[6]

***dl*-Hexahydro-2-oxo-4-(4-benzylthiobutyl)-1-furo-(3,4)-imidazole (XV).**—A stock solution of sodiobenzylmercaptide was prepared by dissolving 1.2 g. of sodium in a mixture of 19 cc. of absolute ethanol and 6 cc. of benzyl mercaptan.

To a solution of 442 mg. of the chloride (XIV) in 10 cc. of absolute ethanol 1.1 cc. of the above sodiobenzylmercaptide solution was added, and the mixture refluxed for two hours. The ethanol was removed *in vacuo*, the residue dissolved in ethyl acetate, and the solution washed with several portions of water, dried over sodium sulfate, and the ethyl acetate removed *in vacuo*. The oily residue solidified on standing, and the crystals were washed with ether and purified by recrystallization from dilute methanol; 410 mg. (66% of the theoretical yield) of silky needles were obtained which melted at 76–79°.

*Anal.* Calcd. for $C_{16}H_{22}O_2N_2S$: C, 62.73; H, 7.24; N, 9.14; S, 10.46. Found: C, 62.54; H, 6.96; N, 9.31; S, 10.32.

**Sulfone of XV.**—To a solution of 100 mg. of (XV) in 2 cc. of glacial acetic acid, 1 cc. of 30% hydrogen peroxide (Superoxol) was added, and the mixture kept at room temperature for twelve hours. The solvents were removed and the crystalline residue dried over potassium hydroxide *in vacuo*. Recrystallization of the substance from absolute ethanol gave 90 mg. (82% of the theoretical yield) of prisms melting at 189–190°.

*Anal.* Calcd. for $C_{16}H_{22}O_4N_2S$: C, 56.80; H, 6.55; N, 8.27; S, 9.48. Found: C, 57.03; H, 6.64; N, 7.95; S, 9.22.

Recrystallization of the sulfone from aqueous methanol gave needles of the half hydrate melting at 95–100°.

*Anal.* Calcd. for $C_{16}H_{22}O_4N_2S \cdot {}^1/_2H_2O$: C, 55.32; H, 6.62. Found: C, 55.11; H, 6.64.

***dl*-Hexahydro-2-oxo-1-furo-(3,4)-imidazole-4-(4-butane Sulfonic Acid) (III).**—To 4 g. of sodium which was placed in a round-bottomed flask, a solution of 500 mg. of the above thioether (XV) in 50 cc. of absolute ethanol was added at once and the mixture refluxed until all of the sodium had dissolved. Absolute alcohol (200 cc.) was then added and carbon dioxide was passed into the solution for one hour. The sodium carbonate was removed by filtration and the filter cake was repeatedly washed with absolute ethanol. The combined filtrate and washings were evaporated to dryness *in vacuo* in a stream of carbon dioxide, and the residue extracted with three 25-cc. portions of hot ethyl acetate. The combined ethyl acetate extracts were filtered and evaporated to dryness *in vacuo* under carbon dioxide. The resulting crystalline *dl*-hexahydro-2-oxo-4-(4-mercaptobutyl)-1-furo-(3,4)-imidazole (XVI), 185 mg. (52% of the theoretical yield), was used for the next step without further purification. The compound gave a strong nitroprusside test. To a solution of the above thiopentanol (XVI) (390 mg.) in 39 cc. of water which was cooled in an ice-bath, a 0.01 *M* solution of barium permanganate was added slowly with stirring until the pink color remained for twenty minutes. (Approximately 174 cc. of the solution was required.) The mixture was heated on the steam-bath, and 2 cc. of methanol was added in order to decompose the excess of permanganate. The manganese dioxide was removed by filtration and the clear filtrate was concentrated to dryness *in vacuo*. The crystalline residue was suspended in hot 95% alcohol and water was added until all of the barium salt had dissolved. Upon the addition of more hot 95% alcohol, the barium salt of the sulfonic acid crystallized; 485 mg. (81% of the theoretical yield) of colorless needles were obtained, which were purified by recrystallization from dilute ethanol.

*Anal.* Calcd. for $C_9H_{15}O_5N_2SBa/2$: C, 32.53; H, 4.55; N, 8.44: S, 9.66; Ba, 20.69. Found: C, 32.58; H, 4.74; N, 8.18; S, 9.43; Ba, 20.33.

***dl*-Hexahydro-2-oxo-4-(5-benzylthiopentyl)-1-furo-(3,4)-imidazole (XVIII).**—To a solution of 538 mg. of *dl*-hexahydro-2-oxo-4-(5-chloropentyl)-1-furo(3,4)imidazole (XVII)[3] in 5 cc. of absolute ethanol, 1.3 cc. of the above-mentioned sodiobenzylmercaptide solution was added and the mixture was refluxed for two hours. The benzyl thioether was isolated as described for the preparation of the lower homolog (XV). Recrystallization from dilute methanol yielded 639 mg. (86% of the theoretical yield) of needles which melted at 66–68°.

*Anal.* Calcd. for $C_{17}H_{24}O_2N_2S$: C, 63.73; H, 7.55;

(15) Hofmann and Bridgwater, THIS JOURNAL, **67**, 738 (1945).

N, 8.74; S, 10.00. Found: C, 63.24; H, 7.36; N, 8.89; S, 10.30.

**Sulfone of (XVIII).**—A sample of the thioether (XVIII) (200 mg.) was oxidized with Superoxol as described for the preparation of the lower homolog. Recrystallization from methanol gave 190 mg. (87% of the theoretical yield) of needles melting at 169–170°.

*Anal.* Calcd. for $C_{17}H_{24}O_4N_2S$: C, 57.95; H, 6.86; N, 7.94; S, 9.10. Found: C, 57.79; H, 6.59; N, 7.93; S, 9.17.

***dl*-Hexahydro-2-oxo-4-(5-mercaptopentyl)-1-furo-(3,4)-imidazole (XIX).**—Five hundred milligrams of the above thioether (XVIII) were cleaved with sodium in absolute ethanol as described for the lower homolog (XV); 250 mg. (70% of the theoretical yield) of the desired material, m. p. 92–94°, was obtained which was purified by recrystallization from ethyl acetate. The substance gave a strong nitroprusside test.

*Anal.* Calcd. for $C_{10}H_{18}O_2N_2S$: C, 52.15; H, 7.88; N, 12.15; S, 13.90. Found: C, 52.35; H, 7.58; N, 11.82; S, 14.67.

***dl*-Hexahydro-2-oxo-1-furo-(3,4)-imidazole-4-(5-pentane Sulfonic Acid) (IV).**—To an ice-cold solution of 200 mg. of the above thiopentanol (XIX) in 10 cc. of water and 1 cc. of acetone, a 0.01 *M* solution of barium permanganate was slowly added with stirring until the solution remained pink for thirty minutes (approximately 76 cc.). The excess of permanganate was destroyed by the addition of 2 cc. of methanol and heating on the steam-bath, and the solution was filtered and concentrated to dryness *in vacuo*. The residue was dissolved in a small amount of water, acetone was added until the solution became cloudy and the barium salt of the sulfonic acid crystallized out. Two hundred fifteen milligrams (71% of the theoretical yield) of the crystalline salt was obtained. The compound was purified by recrystallization from dilute acetone.

*Anal.* Calcd. for $C_{10}H_{17}O_5N_2SBa/2$: C, 34.70; H, 4.95; N, 8.09; S, 9.27; Ba, 19.86. Found: C, 34.37; H, 5.20; N, 8.14, S, 9.30; Ba, 19.60.

## Summary

1. The sulfonic acid analogs of oxybiotin and homoöxybiotin have been prepared.

3. These compounds, as well as several intermediates in their synthesis, were capable of antagonizing the growth-promoting activity of biotin and oxybiotin for several microörganisms.

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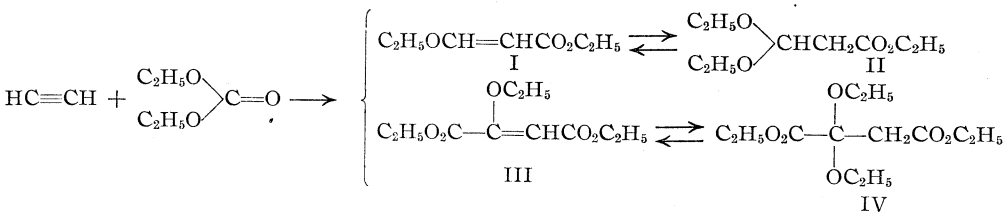
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[CONTRIBUTION FROM ROHM & HAAS COMPANY]

# Condensation of Acetylenes. Acetylene and Alkyl Carbonates

BY W. J. CROXALL AND H. J. SCHNEIDER

Although alkyl carbonates in the presence of strong bases have been successfully used to introduce the carbalkoxy group into the anions of esters,[1,2,3] ketones[4] and nitriles[5,6] there appears to be no record of the acylation of an acetylene with an alkyl carbonate. This paper describes the results obtained with acetylene and alkyl carbonates.




Preliminary work demonstrated that when ethyl carbonate in the presence of alcohol-free sodium ethoxide was contacted with acetylene at 80° and two to five psi gage pressure, absorption of acetylene occurred over a period of six to eight hours. After neutralization with aqueous acetic acid, distillation of the reaction mixture gave two fractions. The main fraction was a mixture of ethyl β-ethoxyacrylate (I) and ethyl β,β-diethoxypropionate (II). The higher boiling fraction was mostly ethyl α,α-diethoxysuccinate (IV) containing a small amount of ethyl ethoxymaleate (III). The over-all reaction may be represented schematically as follows:

Excess of ester was found to give higher yields of the products and when a twenty to one molar ratio of ethyl carbonate to sodium ethoxide was used, the yields (calculated as mole per cent.) varied between 55–60% based on the ethyl carbonate and acetylene and 175–200% based on the sodium ethoxide. Lower ratios of carbonate to ethoxide gave progressively poorer yields so that when a two to one ratio was used only traces of the products were obtained along with a large amount of non-distillable residue.

Further investigation showed that basic agents other than sodium ethoxide (Method A) were suitable as condensation agents. Sodium acetylide (Method C), disodium acetylide (Method D), and benzyltrimethylammonium ethoxide (Method E) were successfully employed in this reaction with various alkyl carbonates. Table I lists the experiments using these agents with various alkyl carbonates. In all the experiments the yield values

(1) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2056 (1941).

(2) Hauser, Abramovitch and Adams, *ibid.*, **64**, 2714 (1942).

(3) Walker, Levine, Kibler and Hauser, *ibid.*, **68**, 672 (1946).

(4) Wallingford, Homeyer and Jones, *ibid.*, **63**, 2252 (1941).

(5) Wallingford, Jones and Homeyer, *ibid.*, **64**, 576 (1942).

(6) Levine and Hauser, *ibid.*, **68**, 760 (1946).

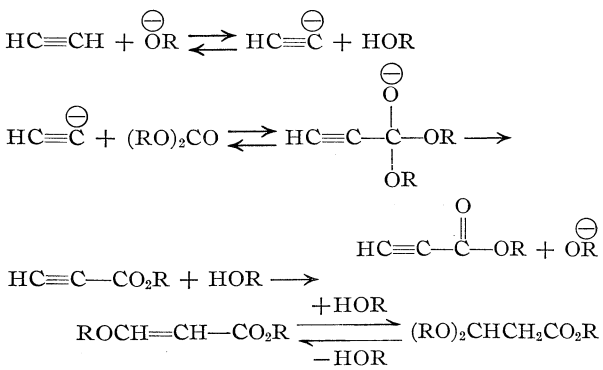
based on the condensation agents were over one hundred per cent. indicating the reaction to be catalytic. Table II lists the physical constants of the products obtained from the various alkyl carbonates.

With sodium alkoxide, a reaction temperature of 80–85° was found to be preferable. Lower temperatures gave slow rates of acetylene absorption, whereas higher temperatures, while increasing the absorption rate, decreased the yields due to nondistillable residues. The initial rate of acetylene absorption with the sodium alkoxides was slow and did not increase appreciably for two to four hours, after which the rate increased and a slightly exothermic reaction occurred over a two-hour period. The rate then became increasingly slow. However, the addition of 0.125 to 0.25 mole of ethyl β-ethoxyacrylate per mole of alkoxide (Method B) to the carbonate, before pressurizing with acetylene, eliminated this induction period so that the absorption of acetylene started immediately. Of all the agents used, sodium alkoxides in general gave the poorest yields.

Mono and disodium acetylide were more active agents than the sodium alkoxides. Reaction with acetylene occurred exothermically at 30–45°, the yields were higher and the amount of the alkyl dialkoxysuccinate fraction was larger than when alkoxides were used. Considerable care was necessary in using these materials with various carbonates; on one occasion when allyl carbonate was mixed with monosodium acetylide, a violent explosion occurred.

Benzyltrimethylammonium methoxide and ethoxide were prepared as alcoholic solutions from benzyltrimethylammonium chloride and the corresponding sodium alkoxide.[7] They were isolated from these solutions by filtration and evaporation under reduced pressure as viscous liquids whose compositions corresponded to equimolecular ratios of quaternary alkoxide to alcohol. Yields were highest with these agents, reaction with acetylene occurring rapidly at room temperature.

The condensation of alkyl carbonates with acetylene is thought to proceed through a series of acid-base type reactions which may be represented by the following ionic mechanisms



(7) Meisenheimer, *Ann.*, **397**, 295 (1913).

The first step is the establishment of an equilibrium between acetylene and acetylide ion. It is probable that the equilibrium favors the products on the left-hand side due to (a) the solubility of acetylene in the alkyl carbonate[8] and (b) the stronger acidity of alcohol as compared to acetylene.[9] However, any acetylide ion formed in this equilibrium reacts (see Method C) according to the second step with the alkyl carbonate to give an intermediate ionic complex which releases an alkoxide ion to form an alkyl propiolate. The postulated ionic complex is similar to that advanced by Hauser and Renfrow for the Claisen condensation of esters.[10]

The third step is the addition of alcohol to the alkyl propiolate to give alkyl alkoxyacrylate and alkyl dialkoxypropionate.[11] Although in none of the experiments was it possible to isolate propiolates, their transitory existence seems likely. Their known reactivity with alcohols in the presence of basic catalysts suggests that they immediately react to form the alcohol adducts, namely, the alkoxyacrylate and dialkoxypropionate.[11]

It is therefore evident that in this mechanism the driving force which is capable of shifting the initial equilibrium between acetylene and acetylide ion is represented by the last step in which the alkyl propiolate is converted to the alkyl alkoxyacrylate and the alkyl dialkoxypropionate. The equilibrium existing between acrylate and propionate is undoubtedly in favor of the propionate since only small amounts of acrylate are isolated. That the last step affects the initial equilibrium is partially demonstrated in Method B where alkyl alkoxyacrylate is added to the alkyl carbonate at the beginning of the condensation. In this case, reaction with acetylene starts immediately and no induction period occurs. This procedure presumably removes alcohol in the initial equilibrium to give the alkyl dialkoxypropionate, and allows the formation of acetylide ion.

A possible route for the formation of alkyl alkoxymaleate and alkyl dialkoxysuccinate is indicated in the next formulas.

In this mechanism the alkyl propiolate first undergoes an acid-base exchange and then a series of reactions similar to those outlined for the acrylate and propionate, the intermediate in this case being the alkyl acetylenedicarboxylate. As in the proposed mechanism for the acrylate and propionate, no intermediate acetylenedicarboxylic ester was isolated but only the alcohol addition products of this ester.[11,12]

With disodium acetylide (Method D) it is thought that an initial attack by two molecules of

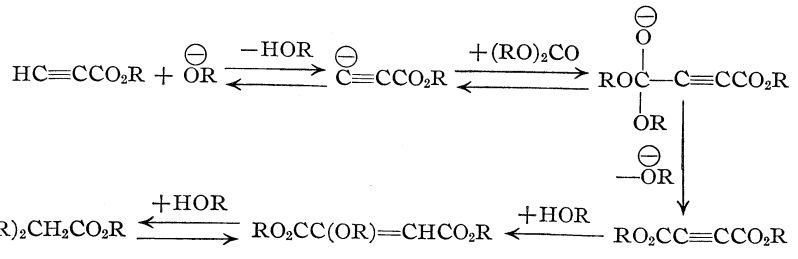
(8) The amount of acetylene required to saturate ethyl carbonate at 40° and five psi gage pressure was found to be 0.5%.

(9) Nieuwland and Vogt, "The Chemistry of Acetylene," Reinhold Publishing Corp., New York City, 1945, state on page 45, . . . the oxyradicals of alcohols and phenols appear to be capable of displacing the ethynyl group. . . .

(10) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937).

(11) Ingold, *J. Chem. Soc.*, **127**, 1203 (1925).

(12) Michael and Bucher, *Ber.*, **29**, 1792 (1896); (see also ref. 11).




alkyl carbonate produces an intermediate doubly charged ionic complex which releases two alkoxide ions to give directly the acetylenedicarboxylic ester. Further condensation with acetylene would then follow the routes indicated above for acrylate-propionate and maleate-succinate formation.

**Acknowledgment.**—The authors wish to thank Dr. R. Connor for his helpful suggestions and encouragement. The analyses were carried out under the direction of Dr. E. L. Stanley and Mr. C. W. Nash.

## Experimental

**Materials.**—Methyl carbonate was obtained from Pittsburgh Plate Glass Company, Columbia Chemicals Division, and the ethyl carbonate was obtained from U. S. Industrial Chemicals, Inc. Both carbonates were fractionated before use. The higher alkyl carbonates were prepared by alcoholysis of ethyl carbonate with the appropriate alcohol using sodium ethoxide as a catalyst.

**Acetylene and Ethyl Carbonate with Sodium Ethoxide.**—Method A—The general procedure herein described is representative of all the condensations carried out with acetylene. The others differ only in the type of condensation agent used.

In a 5-liter, 3-necked flask, equipped with a reflux condenser and a gas tight stainless steel stirrer whose blades scraped the bottom of the flask, was placed 800 g. of anhydrous ethanol. While stirring, 57.5 g. (2.5 moles) of clean sodium cut in quarter-inch cubes was added over a period of one hour. The excess ethanol was removed by distillation under vacuum to give white powdered sodium ethoxide. The vacuum was broken by admitting dry nitrogen and 2950 g. (25 moles) of diethyl carbonate was added. In order to remove the last traces of ethanol from the ethoxide–ethyl carbonate mixture, distillation under reduced pressure was continued until a total of 1134 g. of distillate was obtained which consisted of 898 g. of ethyl carbonate and 236 g. of ethanol. Additional ethyl carbonate, 898 g., was then added to the flask so that the final charge was 25 moles of carbonate to 2.5 moles of ethoxide. The flask was then equipped with a thermometer, a gas inlet tube extending below the surface of the liquid and a gas outlet tube which was connected to an open end mercury manometer. With stirring, the mixture was heated to 80°, and acetylene which had been washed with water and concd. sulfuric acid and dried with soda lime was pressed in at five psi gage pressure. The absorption of acetylene was very slow at the start and did not increase appreciably for three hours, at which point the absorption rate began to increase and heating was not necessary. The temperature was held at 80–85° by periodic cooling. A total of 192 g. (7.37 moles) of acetylene was absorbed in seven hours. During the last two hours, the absorption rate was very slow and heating was necessary to maintain the temperature at 80°. The mixture was cooled to room temperature and 653 g. (2.5 moles) of aqueous 23% acetic acid was added. The upper oil layer was separated, the aqueous layer extracted with ether and the extract combined with the oil layer. Distillation through a short packed column, after removal of ether, ethanol and 1620 g. (14 moles) of ethyl carbonate, gave (a) 915 g. of material b. p. 63–65° (2 mm.) and (b) 25 g. of material b. p. 65–110° (2 mm.). There was 223 g. of nondistillable residue.

Fraction (a) had a saponification equivalent of 182. Treatment of a portion of this fraction with a 1% solution of sodium in ethanol gave ethyl $\beta,\beta$-diethoxypropionate, b. p. 65° (2 mm.); $n^{25}D$ 1.4108[13]; saponification equivalent 192 (calcd. 190).

*Anal.* Calcd. for $C_9H_{18}O_4$: C, 56.86; H, 9.46. Found: C, 56.90; H, 9.91.

Distillation of a part of fraction (a) from 0.5% of sodium bisulfate gave ethanol and ethyl $\beta$-ethoxyacrylate, b. p. 60° (1.8 mm.); $n^{20}D$ 1.4471; saponification equivalent 145 (calcd. 144).[14]

*Anal.* Calcd. for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found: C, 57.96; H, 8.50.

Therefore, from the original saponification equivalent (182), fraction (a) was 87% ethyl $\beta,\beta$-diethoxypropionate and 13% ethyl $\beta$-ethoxyacrylate. These percentages check those obtained from a known index of refraction–composition graph. The yield of the propionate–acrylate fraction calculated on a mole per cent. basis was 50.0% on the carbonate consumed, 69.9% on the acetylene and 200% on the sodium ethoxide.

From 600 g. of fraction (b), obtained from a number of runs, there was obtained on fractionation through a two-foot glass helices packed column, 74 g. of ethyl $\beta,\beta$-diethoxypropionate, $n^{20}D$ 1.4106; 9 g. of an intermediate fraction, b. p. 65° (2 mm.) −85° (0.1 mm.), $n^{20}D$ 1.4195; 377 g. of ethyl $\alpha,\alpha$-diethoxysuccinate, b. p. 85° (0.1 mm.), $n^{20}D$ 1.4305, saponification equivalent 131.5 (calcd. 131) and 106 g. of a higher fraction, b. p. 85° (0.1 mm.) to 98° (0.5 mm.).

*Anal.* Calcd. for $C_{12}H_{22}O_6$: C, 54.96; H, 8.39. Found: C, 54.95; H, 8.11.

The ethyl $\alpha,\alpha$-diethoxysuccinate was characterized by hydrolysis with aqueous hydrochloric acid to ethyl oxalacetate according to the method of Michael and Bucher.[12] Treatment of the crude oxalacetate with a copper acetate solution gave the copper salt of ethyl oxalacetate which on recrystallization from anhydrous ethanol formed fine needles, m. p. 156°.[15]

The higher boiling material (106 g.) was refractionated to give 45 g. of ethyl ethoxymaleate, b. p. 97–98° (0.5 mm.); $n^{20}D$ 1.4562; saponification equivalent 108 (calcd. 108).

*Anal.* Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.39. Found: C, 55.59; H, 7.27.

The ethyl ethoxymaleate was characterized by hydrogenation over Raney nickel at 30° and 1500 psi gage pressure to ethyl ethoxysuccinate, b. p. 92–93° (2 mm.); $n^{20}D$ 1.4217[16]; saponification equivalent 108 (calcd. 109).

*Anal.* Calcd. for $C_{10}H_{18}O_5$: C, 55.05; H, 8.25. Found: C, 55.01; H, 8.00.

**Acetylene and Ethyl Carbonate with Sodium Ethoxide and Ethyl $\beta$-Ethoxyacrylate.**—Method B—In a similar experiment there was added before the introduction of acetylene, 0.25 mole of ethyl $\beta$-ethoxyacrylate. On heating to 80° and pressurizing to five psi gage with acetylene, the absorption of acetylene started immediately, heating was discontinued and periodic cooling was necessary to

(13) Dyer and Johnson, THIS JOURNAL, **56**, 222 (1934).

(14) Auwers, *Ber.*, **44**, 3521 (1911).

(15) Wislicenus and Endres, *Ann.*, **321**, 373 (1902), report m. p. 155–156°.

(16) Material prepared according to the method of Purdie, *J. Chem. Soc.*, **39**, 348 (1881), had $n^{20}D$ 1.4220.

TABLE I

ALKYL CARBONATES AND ACETYLENE

| Carbonate | Moles carbonate | Moles condensation agent | Moles acetylene | Method | Yield, Moles: Acrylate | Propionate | Succinate | Moles %[e]: $(RO)_2CO$ | $C_2H_2$ |
|---|---|---|---|---|---|---|---|---|---|
| Methyl | 25.0 | 2.5 | 8.2 | A[a] | 0.04 | 1.89 | 0.93 | 42.3 | 35.0 |
| Methyl | 15.0 | 0.5 | 2.8 | C | 0.06 | 0.48 | 0.94 | 47.5 | 52.8 |
| Methyl | 5.0 | 0.25 | 1.14 | D | 0.00 | 0.27 | 0.49 | 50.0 | 66.0 |
| Methyl | 6.9 | 0.23 | 1.18 | E | 0.01 | 0.30 | 0.58 | 79.1 | 75.4 |
| Ethyl | 20.0 | 1.0 | 2.92 | A | 0.15 | 1.42 | 0.48 | 53.0 | 70.5 |
| Ethyl | 20.0 | 1.0 | 3.20 | B | 0.13 | 1.13 | 0.29 | 45.0 | 48.5 |
| Ethyl | 10.0 | 0.5 | 1.50 | C | 0.06 | 0.54 | 0.46 | 72.0 | 71.0 |
| Ethyl | 5.0 | 0.25 | 1.05 | D | 0.06 | 0.52 | 0.10 | 97.0 | 54.2 |
| Ethyl | 25.0 | 0.50 | 3.69 | E | 0.23 | 1.37 | 1.05 | 86.0 | 71.9 |
| *n*-Butyl | 3.0 | 0.50 | 1.20 | A[b] | 0.28 | 0.29 | 0.00[d] | 33.3 | 47.5 |
| 2-Ethylbutyl | 1.5 | 0.25 | 0.73 | A[c] | 0.06 | 0.43 | 0.00[d] | 81.6 | 67.5 |
| 2-Ethylhexyl | 3.0 | 0.50 | 0.83 | C | 0.28 | 0.44 | 0.00[d] | 29.0 | 87.5 |
| *n*-Decyl | 2.5 | 0.50 | 0.88 | A[a] | 1.01 | 0.00 | 0.00[d] | 41.6 | >100 |

[a] $NaOCH_3$ used as catalyst. [b] $NaOC_4H_9$ used as catalyst. [c] $NaOC_8H_{17}$ used as catalyst. [d] Unable to obtain pure by distillation and therefore calculated as loss. [e] The yields are expressed as mole per cent. of the total products based on the reactants consumed.

TABLE II

PHYSICAL CONSTANTS OF COMPOUNDS OBTAINED FROM ALKYL CARBONATES AND ACETYLENE

| Compound | B. p. (uncor.) °C. | Mm. | $n^{20}D$ | $d^{20}_{20}$ | Formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H | Sapon. equiv. Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3OCH{=}CHCO_2CH_3$ | 56 | 18 | 1.4500 | 1.0801 | $C_5H_8O_3$ | 51.72 | 6.89 | 51.19 | 7.05 | 116 | 116 |
| $(CH_3O)_2CHCH_2CO_2CH_3$ | 77 | 20 | 1.4095 | 1.0445 | $C_6H_{12}O_4$ | 48.65 | 8.11 | 48.70 | 7.88 | 148 | 147 |
| $(CH_3O)_2C(CO_2CH_3)CH_2CO_2CH_3$ | 92 | 2 | 1.4335 | 1.1964 | $C_8H_{14}O_6$ | 46.60 | 6.80 | 46.46 | 7.04 | 103 | 103 |
| $(CH_3O)C(CO_2CH_3){=}CHCO_2CH_3$ | 89–90 | 0.9 | M. p. 40°C. | | $C_7H_{10}O_5$ | 48.28 | 5.74 | 48.29 | 5.68 | 87 | 87 |
| $n$-$C_4H_9OCH{=}CHCO_2C_4H_9$ | 110 | 3 | 1.4505 | 0.9465 | $C_{11}H_{20}O_3$ | 66.00 | 10.00 | 66.12 | 9.64 | 200 | 194 |
| $(n$-$C_4H_9O)_2CHCH_2CO_2C_4H_9$ | 133 | 3 | 1.4278 | 0.9268 | $C_{15}H_{30}O_4$ | 65.69 | 10.95 | 66.04 | 11.46 | 274 | 274 |
| $(C_6H_{13}O)_2CHCH_2CO_2C_6H_{13}$[a] | 177–180 | 3 | 1.4412 | 0.9094 | $C_{21}H_{42}O_4$ | 70.39 | 11.73 | 70.87 | 11.83 | 358 | 359 |
| $C_8H_{17}OCH{=}CHCO_2C_8H_{17}$[b] | 192–203 | 4 | 1.4566 | 0.9080 | $C_{19}H_{36}O_3$ | 73.08 | 11.54 | 73.59 | 12.33 | 312 | 312 |
| $(C_8H_{17}O)_2CHCH_2CO_2C_8H_{17}$[b] | 195–198 | 1 | 1.4470 | 0.8912 | $C_{27}H_{54}O_4$ | 73.30 | 12.21 | 73.20 | 12.16 | 442 | 438 |
| $n$-$C_{10}H_{21}OCH{=}CHCO_2C_{10}H_{21}$ | 200 | 0.1[c] | 1.4489 | 0.8930 | $C_{23}H_{44}O_3$ | 75.00 | 11.96 | 74.27 | 12.46 | 368 | 364 |

[a] 2-Ethylbutyl $\beta,\beta$-di-(2-ethylbutoxy)-propionate. [b] 2-Ethylhexyl $\beta$-(2-ethylhexoxy)-acrylate and 2-ethylhexyl $\beta,\beta$-(di-2-ethylhexoxy)-propionate. [c] Falling film still.

maintain the temperature at 80–85°. Over a period of three hours, 4 moles of acetylene was absorbed.

**Acetylene and Ethyl Carbonate with Monosodium Acetylide.**—Method C—Sodium acetylide (0.54 mole) was prepared in liquid ammonia according to the method of Hennion.[17] The liquid ammonia was allowed to evaporate and the last traces were removed by warming under reduced pressure. Rapidly there was added, with stirring and cooling, 1350 g (15.0 moles) of methyl carbonate.[18] The carbonate–acetylide suspension was warmed to 40° and acetylene was pressed in at five psi gage pressure. The absorption of acetylene started immediately and cooling was necessary to maintain the temperature below 45°. A total of 49 g. (1.93 mole) of acetylene was absorbed in four hours.

**Acetylene and Ethyl Carbonate with Disodium Acetylide.**—Method D—To 0.25 mole of disodium acetylide[19] there was added cautiously 590 g. (5 moles) of ethyl carbonate.[18] Acetylene was pressed in at five psi gage pressure until a total of 29.5 g. (1.1 mole) of acetylene had been absorbed in two hours. The temperature was maintained at 35–40°.

**Acetylene and Ethyl Carbonate with Benzyltrimethylammonium Ethoxide.**—Method E—Benzyltrimethylammonium ethoxide was prepared in a manner similar to the method used by Meisenheimer[7] for the preparation of tetramethylammonium ethoxide. From 238 g. (0.43 mole) of a 35.2% ethanolic solution of benzyltrimethylammonium ethoxide there was obtained by evaporation at 40° under reduced pressure (5–1 mm.), 103 g. of the ethoxide containing an equivalent of ethanol. To this was added 1520 g. (12.9 moles) of ethyl carbonate and then 65 g. (2.5 moles) of acetylene over a period of two hours while a temperature of 40–45° was maintained by cooling.

(17) Hennion, *Proc. Indiana Acad. of Sci.*, **47**, 116 (1938).

(18) Unless sufficient agitation was maintained and adequate cooling provided, violent exothermic reactions occurred at this stage. In one case when dipotassium acetylide was used a violent explosion occurred.

(19) "Inorganic Syntheses," **2**, 80 (1946).

## Summary

1. Acetylene condenses with alkyl carbonates in the presence of basic condensation agents to produce alkyl $\beta$-alkoxyacrylates, alkyl $\beta,\beta$-dialkoxypropionates, alkyl alkoxymaleates and alkyl $\alpha,\alpha$-dialkoxysuccinates.

2. A mechanism has been proposed to account for the course of this reaction.

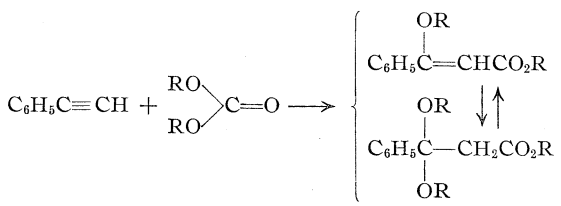
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[CONTRIBUTION FROM ROHM & HAAS COMPANY]

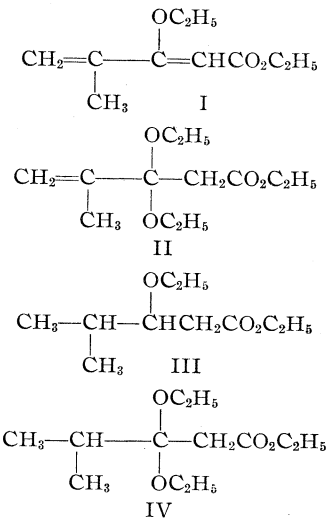
# Condensation of Acetylenes with Esters. Mono Substituted Acetylenes and Alkyl Carbonates[1]

BY W. J. CROXALL AND MARIAN F. FEGLEY

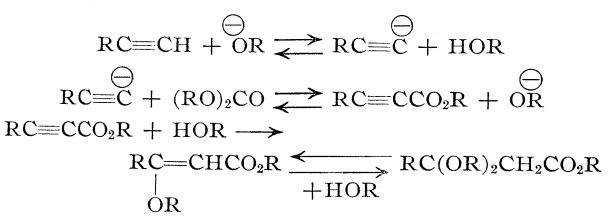
The nature of the products obtained from acetylene and alkyl carbonates[1] suggested that similar results might be obtained with substituted acetylenes. Our first experiments involved sodium phenylacetylide and ethyl carbonate and it was found that when these reactants were used in equimolecular amounts intractable oils were obtained as reported earlier by Nightingale and Wadsworth.[2] However when ethyl carbonate in the presence of a basic condensation agent such as sodium phenylacetylide was treated with phenylacetylene, there was formed in good yield ethyl β-phenyl-β-ethoxyacrylate and ethyl β-phenyl-β,β-diethoxypropionate. The yield data indicated that sodium phenylacetylide functioned as a catalyst. Sodium ethoxide and benzyltrimethylammonium ethoxide were also used successfully as the basic condensation agents for this reaction in place of sodium phenylacetylide. Extension of this work to methyl carbonate gave the corresponding methyl analogs. The over-all reaction may be represented as



Similar results were obtained with an alkeneyne. Ethyl carbonate and 2-methyl-1-butene-3-yne in the presence of either sodium ethoxide or benzyltrimethylammonium ethoxide gave three fractions on distillation. The first fraction was shown to be a mixture consisting chiefly of 2-methyl-3-ethoxy-4-carbethoxy-1,3-butadiene (I) containing a small amount of 2-methyl-3,3-diethoxy-4-carbethoxy-1-butene (II). This mixture when heated with a catalytic amount of sodium bisulfate gave ethanol and the pure butadiene ester (I) which was hydrogenated to the known 2-methyl-3-ethoxy-4-carbethoxybutane (III).[3] The second fraction was the butene ester (II) which on acid hydrolysis produced methyl isopropenyl ketone. Distillation of the ester (II) from a trace of sodium bisulfate gave the butadiene ester (I) and ethanol. Butene ester (II) gave on hydrogenation 2-methyl-3,3-diethoxy-4-carbethoxybutane (IV) which on acid hydrolysis yielded methyl isopropyl ketone. The third fraction was a high boiling oil which could not be distilled without decomposition. It was not characterized.



These reactions are thought to proceed throug a mechanism similar to that advanced for acety - ene and alkyl carbonates[1] and may be represented in a condensed form as



It is to be noted that this mechanism requires that the acetylene possess at least one acetylenic hydrogen atom. Actually, experiment showed that methylphenylacetylene gave no reaction.

**Acknowledgment.**—We wish to thank Dr. R. Connor for his advice and assistance. The analyses were carried out under the direction of Dr. E. L. Stanley and Mr. C. W. Nash. Miss R. Lookabaugh carried out the preparation of a number of intermediates used in this work and Mr. H. J. Schneider performed the experiment on methylphenylacetylene.

## Experimental

**Phenylacetylene with Methyl and Ethyl Carbonates.**—In a 1-liter, 3-necked flask equipped with a Hershberg stirrer, a dropping funnel and a soda lime tube there was prepared 0.5 mole of sodamide[4] in liquid ammonia. To the sodamide in liquid ammonia was added 51 g. (0.5 mole) of phenylacetylene, the ammonia allowed to evaporate at

(1) For the first paper of this series, see Croxall and Schneider, THIS JOURNAL, **70**, 1257 (1948).

(2) Nightingale and Wadsworth, *ibid.*, **69**, 1183 (1947).

(3) Linstead, *J. Chem. Soc.*, 2503 (1929).

(4) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2121 (1934).

room temperature and the last traces removed at the water pump. The flask was then equipped with a reflux condenser topped with a soda lime tube and with vigorous stirring and cooling there was added 590 g. (5 moles) of ethyl carbonate. After the exothermic reaction had subsided, the mixture was heated to 80° and 204 g. (2 moles) of phenylacetylene was added over a one-hour period, the temperature being maintained at 70–80° by periodic cooling. After being heated for ten hours at 65–75°, the reaction mixture was cooled to room temperature and neutralized with 130 g. of aqueous 23% acetic acid. The oil layer was separated, washed with 200 ml. of water, dried over anhydrous potassium carbonate and distilled through a short packed column. After removal of ethanol and 265 g. of ethyl carbonate there was obtained (a) 75 g. of material b. p. 135° (2 mm.); $n^{20}D$ 1.5202 and (b) 370 g. of material b. p. 135–148° (2 mm.); $n^{20}D$ 1.5274. Both fractions *a* and *b* were carefully refractionated to give pure ethyl β-phenyl-β-ethoxyacrylate, b. p. 101–102.5° (0.4 mm.); $n^{20}D$ 1.5320[5]; saponification equivalent 216 (calcd. 220) and ethyl β-phenyl-β,β-diethoxypropionate, b. p. 86–89° (0.24 mm.); $n^{20}D$ 1.4920[6]; saponification equivalent 253 (calcd. 266). From the saponification equivalents, the combined fractions *a* and *b* correspond to 93% ethyl β-phenyl-β-ethoxyacrylate and 7% ethyl β-phenyl-β,β-diethoxypropionate. The yield of acrylate–propionate mixture was 73% based on the ethyl carbonate consumed, 80% on phenylacetylene and 400% on sodium.

In a similar experiment in which sodium ethoxide was substituted for sodium phenylacetylide, there was obtained 64% of the acrylate and 36% of the propionate. The yield was 46% based on the ethyl carbonate consumed, 76% on phenylacetylene and 152% on sodium ethoxide.

From a condensation reaction maintaned at 30–40°, methyl carbonate (1.9 moles), phenylacetylene (0.5 mole) and 0.2 mole of benzyltrimethylammonium methoxide (containing an equivalent of methanol)[1] there was obtained 38% methyl-β-phenyl-β-methoxyacrylate,[5,7] b. p. 101° (0.25 mm.); $n^{20}D$ 1.5507; saponification equivalent 192 (calcd. 192) and 62% methyl β-phenyl-β,β-dimethoxypropionate,[6] b. p. 85–88° (1 mm.); $n^{20}D$ 1.4997; saponification equivalent 213 (calcd. 224). The yield was 63% based on the methyl carbonate consumed, 80% on phenylacetylene and 208% on benzyltrimethylammonium methoxide.

**2-Methyl-1-butene-3-yne with Ethyl Carbonate.**—To 1.5 moles of sodium ethoxide and 1414 g. (12 moles) of ethyl carbonate in a 2-liter, 3-necked flask equipped with a dropping funnel, a gas-tight stainless steel stirrer whose blades scraped the bottom of the flask and a reflux condenser which was connected to an open end mercury manometer, there was added 204 g. (3.1 moles) of 2-methyl-1-butene-3-yne[8] over a period of four hours, the temperature being maintained at 70–80°. The mixture was heated at the above temperature six additional hours, cooled and neutralized with aqueous 23% acetic acid. Fractionation of the organic layer through a short packed column gave after removing ethanol and 866 g. (7.3 moles) of ethyl carbonate, (a) 189 g. of material, b. p. 73–80.5° (2 mm.); $n^{20}D$ 1.4490–1.4527, 34 g. of an intermediate fraction, b. p. 80.5–100° (2 mm.) and (b) 216 g. (30%) of a constant boiling fraction, b. p. 100–103° (1 mm.); $n^{20}D$ 1.4520, which proved to be 2-methyl-3,3-diethoxy-4-carbethoxy-1-butene (II). *Anal.* Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.61; H, 9.53. There was also obtained 90 g. of a higher boiling material, b. p. 91–195° (1–4 mm.) which distilled with decomposition and was discarded.

In a similar experiment in which the condensation was carried out at 30–45°, there was obtained from 14 moles of ethyl carbonate, 3.8 moles of 2-methyl-1-butene-3-yne and 0.9 mole of benzyltrimethylammonium ethoxide (containing an equivalent of ethanol),[1] 1289 g. (10.9 moles) of unreacted ethyl carbonate, 289 g. of fraction *a*, 108 g. of fraction *b* and 170 g. of the high boiling fraction.

**2-Methyl-3-ethoxy-4-carbethoxy-1,3-butadiene (I).**—All attempts to fractionate cut *a* to obtain a pure compound were unsuccessful. However, by fractionating a toluene (100 g.) solution of fraction *a* (50 g.) in the presence of sodium bisulfate (0.25 g.) there was obtained 32 g. of an ethanol–toluene mixture, b. p. 76–110° (9.36% ethanol by hydroxyl determination) and 41 g. of the pure butadiene ester (I), b. p. 65–66° (1.7 mm.); $n^{20}D$ 1.4690; saponification equivalent 185 (calcd. 190).

*Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.18; H, 8.75. Found: C, 65.06; H, 8.74.

**2-Methyl-3-ethoxy-4-carbethoxybutane (III).**—In a high pressure hydrogenation bomb was placed 66 g. (0.36 mole) of (I) and 4 g. of Raney nickel. This mixture was treated with hydrogen at 1300 psi and 70–78° to give 56 g. of the butane ester (II), b. p. 81–81.5° (10 mm.); $n^{20}D$ 1.4175; saponification equivalent 189 (calcd. 188).[3]

**2-Methyl-3,3-diethoxy-4-carbethoxy-1-butene (II).**—The pure butene ester (II) (fraction *b*) was characterized as follows. To 32 g. (0.14 mole) was added 23 ml. of aqueous 15% hydrochloric acid and 24 ml. of 95% ethanol. The mixture was allowed to stand ninety hours, refluxed for thirty minutes, cooled, neutralized with potassium carbonate, extracted with ether and dried over anhydrous potassium carbonate. After removing ether, fractionation gave 20 g. of an ethanol-water azeotrope, b. p. 76–78°, 14 g. of an intermediate fraction, b. p. 78–94° and 24 g. of crude methyl isopropenyl ketone, b. p. 94–99°. These last two fractions gave a semicarbazone which on recrystallization from ethanol-water melted at 173.5–175°. A mixed melting point with an authentic sample of the semicarbazone was 172.5–174°.

Fractionation of 30 g. (0.13 mole) of (II) and 50 g. of toluene in the presence of 0.5 g. of sodium bisulfate gave 11 g. of an ethanol–toluene fraction, b. p. 76–110° (98% yield of ethanol by hydroxyl determination) and 20 g. of the butadiene ester (I), b. p. 102° (12 mm.); $n^{20}D$ 1.4688.

**2-Methyl-3,3-diethoxy-4-carbethoxybutane (IV).**—Hydrogenation of 40 g. (0.17 mole) of the butene ester (II) dissolved in 80 ml. of ethanol over 20 g. of Raney nickel at 1300 psi and 80° gave 31 g. of the butane ester (IV), b. p. 85–87° (1 mm.); $n^{20}D$ 1.4308.

*Anal.* Calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.25; H, 10.38.

Acid hydrolysis of this ester gave methyl isopropyl ketone whose 2,4-dinitrophenylhydrazone melted at 116–117° and did not depress an authentic sample.

## Summary

1. Phenylacetylene condenses with alkyl carbonates in the presence of basic condensation agents to produce alkyl β-phenyl-β-alkoxyacrylates ($C_6H_5C(OR)=CHCO_2R$) and alkyl β-phenyl-β,β-dialkoxypropionates ($C_6H_5C(OR)_2CH_2CO_2R$).

2. 2-Methyl-1-butene-3-yne condenses with ethyl carbonate under similar conditions to give chiefly 2-methyl-3-ethoxy-4-carbethoxy-1,3-butadiene ($CH_2=C(CH_3)C(OC_2H_5)=CHCO_2C_2H_5$) and 2-methyl-3,3-diethoxy-1-butene ($CH_2=C(CH_3)C(OC_2H_5)_2CH_2CO_2C_2H_5$).

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(5) Moureu, *Bull. soc. chim.*, [3] **31**, 509 (1904); see also ref. 7.
(6) Moureu, *ibid.*, [3] **31**, 493 (1904).
(7) v. Auwers, *Ann.*, **413**, 274 (1917).
(8) Carothers and Coffman, THIS JOURNAL, **54**, 4074 (1932).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE HILTON-DAVIS CHEMICAL COMPANY, DIVISION OF STERLING DRUG, INC.]

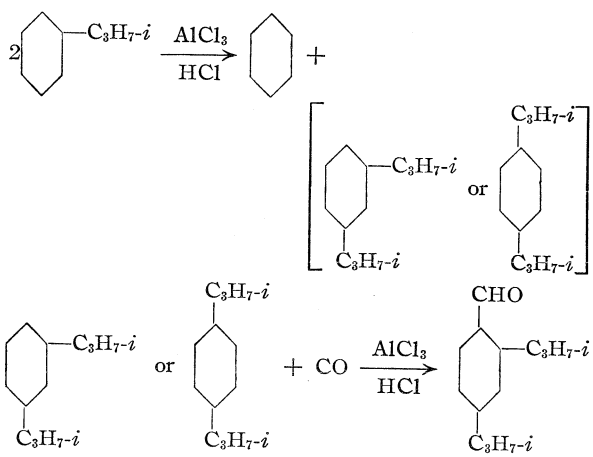
# The Gattermann–Koch Reaction. The Formylation of Isopropylbenzene under Pressure

BY NATHAN N. CROUNSE[1]

Although a description of the high pressure formylation of benzene utilizing the Gattermann–Koch reaction is available,[2] there are only patent reports[3,4,5] on the pressure formylation of an alkylbenzene. The high pressure formylation of isopropylbenzene and the side reactions have been studied. The reaction of isopropylbenzene and carbon monoxide under pressure with aluminum chloride and hydrogen chloride as catalysts gives chiefly *p*-isopropylbenzaldehyde, small amounts of benzaldehyde and 2,4-diiospropylbenzaldehyde.

The addition of hydrogen chloride was found necessary, and since water is also required,[2,6] it was attempted to add them as hydrochloric acid. The yield of *p*-isopropylbenzaldehyde was increased from 33% when only dry hydrogen chloride was used to 37% with no decrease in the time of absorption of carbon monoxide. To distribute water evenly on the aluminum chloride, twenty-mesh aluminum chloride was raked occasionally in the open air for two hours.[7] This treatment decreased the time of absorption from seven to three hours, and raised the yield to 45%.

The role of benzene, the solvent in the formylation,[8] has never been analyzed. The amount of benzene used can affect the yield of 2,4-diisopropylbenzaldehyde, formation of which could occur through the reactions shown.




The first reaction is known.[9] The diisopropylbenzenes must then be formylated according to the second equation since no diisopropylbenzenes are isolated from the reaction. The first reaction is reversible,[10] hence increasing the amount of benzene should reduce the yield of diisopropylbenzenes and preserve the isopropylbenzene. Increasing the amount of benzene 50% raised the yield of *p*-isopropylbenzaldehyde from 45 to 54%.

The effect of excess aluminum chloride on formylation has been shown.[2,11] A considerable excess of aluminum chloride utilized all the isopropylbenzene without increasing the yield of *p*-isopropylbenzaldehyde. By dropping the ratio of aluminum chloride to isopropylbenzene from 1.31 to 1.10, the yield of *p*-isopropylbenzaldehyde rose from 54 to 60%.

The formation of 2,4-diisopropylbenzaldehyde could also have been effected by alkylation of *p*-isopropylbenzaldehyde with isopropylbenzene and aluminum chloride. *p*-Isopropylbenzaldehyde can be alkylated with isopropyl chloride and aluminum chloride.[5] However, simulating formylation conditions but omitting carbon monoxide yielded neither a diisopropylbenzaldehyde nor benzaldehyde.

The lower boiling by-product of the reaction was benzaldehyde which could be formed by dealkylation of *p*-isopropylbenzaldehyde. *p*-Isopropylbenzaldehyde, benzene, aluminum chloride, and hydrogen chloride were processed together, but only the starting materials were recovered. Hence the benzaldehyde is formed probably by the action of carbon monoxide on benzene.

The higher boiling by-product, an aldehyde, was assumed to be 2,4-diisopropylbenzaldehyde, previously mentioned without proof of structure.[5] Its structure was determined here by oxidation to 2,4-diisopropylbenzoic acid, and characterization of the latter as its amide through mixed melting points.[12] The aldehyde was also characterized as a 2,4-dinitrophenylhydrazone. The formation of 2,4-diisopropylbenzaldehyde is in accord with the observation made when *m*- and *p*-xylenes are formylated to give 2,4-dimethylbenzaldehyde.[8,13,14]

(1) Present address: The Christ Hospital Institute for Medical Research, Cincinnati, Ohio.

(2) Holloway and Krase, *Ind. Eng. Chem.*, **25**, 497 (1933).

(3) German patent 281,212 [*Frdl.*, **12**, 169] [*C. A.*, **9**, 1830 (1915)].

(4) Meuly, U. S. Patents 2,158,518–9 [*Chem. Zentr.*, **109**, I, 3388 (1938)].

(5) Knorr and Weissenborn, U. S. Patent 1,776,154 [*C. A.*, **24**, 5307 (1930)].

(6) Olson, U. S. Patent 1,935,914 [*C. A.*, **28**, 778 (1934)].

(7) No originality is claimed for this treatment. Information came to the writer that a German plant activated aluminum chloride in this way. This technique may benefit other Friedel–Craft acylations.

(8) Gattermann and Koch, *Ann.*, **347**, 347 (1906).

(9) Heise and Tohl, *ibid.*, **270**, 155 (1892).

(10) Boedtker and Halse, *Bull. soc. chem.*, [4] **19**, 444 (1916).

(11) Hey, *J. Chem. Soc.*, 2476 (1931).

(12) Newton, THIS JOURNAL, **65**, 320 (1943).

(13) Francesconi and Mundici, *Gazz. chim. ital.*, **32**, II, 467 (1902) [*J. Chem. Soc. Abs.*, **84** [I], 426 (1903)].

(14) Mundici, *Gazz. chim. ital.*, **34**, II, 114 (1904) [*J. Chem. Soc. Abs.*, **86** [I], 897 (1904)].

As in the case of benzene[2] cuprous chloride was found unnecessary as a carrier for high pressure formylation.

A pressure of 500 p. s. i. was used here. However, when the same conditions were used at 30 p. s. i., no carbon monoxide was absorbed in seven hours. The poor agitation of the rocking autoclave may be more noticeable at low pressure than at high.

## Procedures

**p-Isopropylbenzaldehyde.**—To a mixture of 210 g. (1.75 moles) of isopropylbenzene and 315 g. (4.05 moles) of benzene saturated with hydrogen chloride in a lead-lined rocking autoclave,[15] was added 255 g. (1.92 moles) of aluminum chloride (technical) which previously had been ground to pass 20-mesh and exposed in a one-inch layer to air for two hours with frequent stirring. The autoclave was then purged with carbon monoxide (commercial) from a cylinder and carbon monoxide added to a pressure of 500 p. s. i. at 25–30°. After the pressure dropped to 300 p. s. i., it was again raised to 500 p. s. i. This was repeated until no drop occurred (two and one-half hours) whereafter the pressure was maintained for an hour longer.

The reaction mixture was poured onto 2500 g. of ice acidified with 5 cc. of concentrated hydrochloric acid and separated. The oil layer was washed with 500-cc. portions of water and 5% sodium carbonate solution, and filtered to break the emulsion. After separation the oil layer was washed twice with 500-cc. portions of water.

The oil was charged to a round-bottom flask headed by a 36-inch fractionating column packed with glass helices. Distillation was continued under atmospheric pressure until the pot temperature reached 131°, the distillate being benzene. Then, under a vacuum of 135 mm., 40.5 g. of isopropylbenzene (b. p. 95° at 135 mm.) were recovered. Distillation at 35 mm. gave 11 g. of benzaldehyde (b. p. 83–88° at 35 mm.) contaminated with a small amount of isopropylbenzene, 126 g. of *p*-isopropylbenzaldehyde (b. p. 131–135° at 35 mm.), 60.3% yield based on the recovered isopropylbenzene, and 25 g. of 2,4-diisopropylbenzaldehyde. A residue of about 25 g. remained.

The *p*-isopropylbenzaldehyde reduced Tollens reagent. Oxidation with alkaline potassium permanganate gave *p*-isopropylbenzoic acid, m. p. 115°.[16] Calcd.: neut. equiv., 164. Found: neut. equiv., 162.

Benzaldehyde was characterized as its phenylhydrazone, m. p. 156°. A mixed melting point with an authentic specimen suffered no depression.

The higher boiling aldehyde was redistilled. Fifteen g. was recovered: $n^{20}D$ 1.5241, $d^{20}_4$ 0.9461, b. p. 127° (13 mm.).

*Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.10; H, 9.47. Found: C, 82.14; H, 9.45.

**Oxidation of Diisopropylbenzaldehyde.**—Oxidation of diisopropylbenzaldehyde with alkaline potassium permanganate gave low yields of 2,4-diisopropylbenzoic acid, m. p. 107–107.5°.[17] Calcd.: neut. equiv., 206. Found: neut. equiv., 204. Newton[12] records a melting point of 107.5–108.5°.

**2,4-Diisopropylbenzamide.**—Half a gram of the above acid was treated with an excess of thionyl chloride[18] and then converted to the amide; melting point 156.5°. A mixed melting point with a sample prepared by Newton's[12] method showed no depression.

**2,4-Dinitrophenylhydrazone of 2,4-Diisopropylbenzaldehyde.**—One gram of 2,4-diisopropylbenzaldehyde was treated with 2 g. of 2,4-dinitrophenylhydrazine in alcohol.[19] The yield of red needles, m. p. 156.5–157.5°, was 2.5 g. (90% yield). The product was dissolved in 20 cc. of cold benzene. Addition of 15 cc. of low boiling petroleum caused the precipitation of 2.2 g. of tiny red needles, m. p. 156.5–157.5°.

*Anal.* Calcd. for $C_{19}H_{22}O_4N_4$: N, 15.20. Found: N, 15.00.

**Attempted Alkylation of *p*-Isopropylbenzaldehyde with Isopropylbenzene.**—To a mixture of 225 g. of benzene and 74 g. of isopropylbenzene, saturated with hydrogen chloride, 80 g. of aluminum chloride was added and then 74 g. of *p*-isopropylbenzaldehyde in forty-five minutes at 24–27°. After stirring for two hours, the mixture was poured onto 800 g. of ice and separated. The oil layer was washed with water, 5% sodium carbonate solution, and again with water. Distillation through a 3-ft. column packed with helices gave benzene, isopropylbenzene, and *p*-isopropylbenzaldehyde in 90% recoveries. The small residue showed no evidence of 2,4-diisopropylbenzaldehyde.

**Attempted Dealkylation of *p*-Isopropylbenzaldehyde.**—The conditions of the experiment recorded above were repeated omitting the 74 g. of isopropylbenzene. Only the starting materials were recovered.

## Summary

A study has been made of some factors in the pressure formylation of isopropylbenzene. The structure and mode of formation of the by-products of the reaction have been discussed.

CINCINNATI, OHIO RECEIVED DECEMBER 10, 1948

(15) American Instrument Company, Silver Springs, Md.; lead-lined at Hilton-Davis.

(16) Meyer, *J. prakt. Chem.*, [2] **34**, 100 (1886), reports the melting point as 116–117°.

(17) Niedzielski and Nord, *J. Org. Chem.*, **8**, 147 (1943). These authors report the formation of diisopropylbenzaldehydes through application of the Gattermann reaction to both isopropylbenzene and *m*-diisopropylbenzene. The corresponding acids melt at 186° and 190°, respectively; the 2,4-dinitrophenylhydrazones melt at 133° and 143°.

(18) McElvain, THIS JOURNAL, **53**, 1173 (1931).

(19) Allen, *ibid.*, **52**, 2955 (1930).

[CONTRIBUTION FROM ABBOTT LABORATORIES]

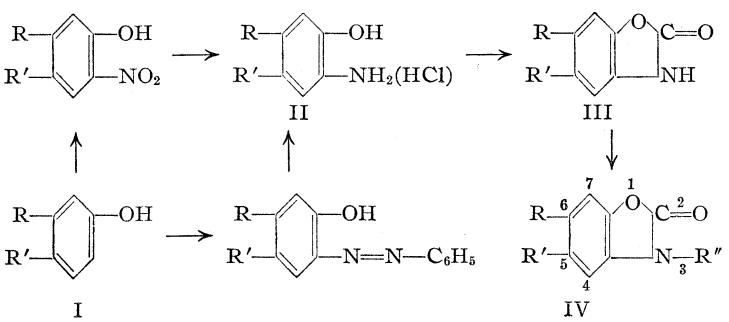
# The Analgesic Activity of Some Benzoxazolone Derivatives[1]

BY W. J. CLOSE, BURRIS D. TIFFANY AND M. A. SPIELMAN

Lespagnol and his co-workers[2] were the first to indicate that compounds of the benzoxazolone type may affect the central nervous system. Inasmuch as benzoxazolone is structurally related to 2,4-oxazolidinedione which forms the nucleus of a number of compounds with analgesic and anticonvulsant activity,[3] it seemed desirable to make an extensive search among benzoxazolone derivatives for possible therapeutic application.

The compounds included in this study were N-alkyl, N-acyl, and N-dialkylaminoalkyl derivatives of benzoxazolone and various nuclear substituted derivatives. It was found that a majority of these compounds are capable of inducing mild analgesia in animals.

The preparation of the benzoxazolones required the use of various *o*-aminophenols (II) as intermediates. These were prepared generally through nitration of the corresponding phenol (I), followed by catalytic reduction. In certain cases it was considered more expedient to couple the phenol with benzenediazonium chloride and to reduce the resulting azo derivative chemically. Most of the aminophenols were very sensitive to air oxidation; these were isolated and used in the form of their hydrochlorides.




Usually, the *o*-aminophenol salts were converted to benzoxazolone derivatives (III) by fusion with urea. Though this reaction represents one of the oldest methods of making benzoxazolones,[4] it has received little attention,[5] possibly because it was associated with a poor yield. We have found, however, that yields of 76–90% can be obtained by moderating the temperature and time of reaction. In one case (5,6-dimethylbenzoxazolone) the urea fusion technique failed to give satisfactory yields and the less convenient phosgene method was employed. 6-Chlorobenzoxazolone was prepared in good yield directly from benzoxazolone by chlorination.

The alkylation of the parent benzoxazolones to produce N-substituted derivatives (IV) required considerable experimentation to secure satisfactory results. The use of an alkyl halide in methanolic potassium hydroxide as suggested in the literature[6] usually gave very low yields. By substituting the higher-boiling Cellosolve (glycol monoethyl ether) for methanol, yields of 62–76% were obtained except when secondary halides were used. Somewhat higher yields (generally 80–95% for normal halides) could be obtained by the use of Cellosolve as the solvent and its sodium alkoxide as the basic condensing agent; this method was used for approximately half of the preparations.

Acylation of the benzoxazolones was accomplished easily by treatment of the compound or its sodium salt with acetic anhydride.

## Experimental[7]

### Preparation of Substituted Phenols

***p*-Propylphenol.**—*p*-Propylanisole[8] (289 g.) was demethylated by refluxing three days with a mixture of 450 cc. of 48% hydrobromic acid and 450 cc. of acetic acid into which dry hydrogen bromide was bubbled during the first two hours of reaction. The yield of product was 245 g. (93%); b. p. 79–80° (0.75 mm.).[8]

***p*-Amylphenol.**—The following modification of the procedure of Sandulesco and Girard,[9] using a large excess of aluminum chloride, was found to give a three-fold increase in the amount of the desired *p*-hydroxyvalerophenone: Seventy-two grams of phenol dissolved in 144 cc. of nitrobenzene was added to 205 g. of aluminum chloride in 400 cc. of nitrobenzene at 10–12° with stirring. The mixture was treated with 85 g. of valeryl chloride by dropwise addition at 5–10° with stirring. After standing overnight the mixture was poured onto ice and concentrated hydrochloric acid, the layers were separated, and the nitrobenzene layer was extracted with dilute sodium hydroxide. The oil obtained by neutralizing the basic extract was taken up in ether and fractionated to give 108 g. (87%) of the *p*-isomer; b. p. 150–160° (0.6 to 0.8 mm.).

The ketone was reduced by the Clemmensen procedure to give an 85% yield of *p*-amylphenol boiling at 103–107° (1.4 mm.).[10]

(1) Presented in part at the 113th meeting of the American Chemical Society in Chicago, April 20, 1948.

(2) Lespagnol, Durbet and Mongy, *Compt. rend. soc. biol.*, **135**, 1255 (1941); Lespagnol and Lefebvre, *Bull. soc. chim.*, **12**, 386 (1945).

(3) Spielman, THIS JOURNAL, **66**, 1244 (1944); Spielman and Everett, *ibid.*, **70**, 1021 (1948).

(4) Sandmeyer, *Ber.*, **19**, 2656 (1886).

(5) The fusion of the free aminophenol with urea was used to prepare benzoxazolone in 35% yield by Bywater, Coleman, Kamm and Merritt, THIS JOURNAL, **67**, 905 (1945). Since the inauguration of the present work, Williams [*Biochem. J.*, **41**, 4 (1947)] has reported a 76% yield from the fusion of the free base and urea by a procedure similar to ours.

(6) Ransom, *Am. Chem. J.*, **23**, 33 (1900).

(7) Microanalyses by E. F. Shelberg and staff. High pressure hydrogenations by M. Freifelder.

(8) Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 520 (1945).

(9) Sandulesco and Girard, *Bull. soc. chim.*, [4] **47**, 1309 (1930).

(10) Ref. 9, p. 1310.

### Preparation of Substituted ortho-Aminophenols

**2-Amino-4-methylphenol.**—2-Nitro-4-methylphenol[11] was dissolved in absolute alcohol and reduced with Raney nickel at 75° under a hydrogen pressure of 1000 pounds. After removal of the catalyst by filtration and evaporation of the solvent, the basic residue was treated with a slight excess of alcoholic hydrogen chloride. Anhydrous ether was then added to precipitate the hydrochloride in 90% yield; m. p. 222–224° (dec.).[12]

**2-Amino-4-propylphenol.**—A modification of the Baranger[11] procedure gave 83% of 2-nitro-4-propylphenol; b. p. 92–96° (0.85 mm.); $n^{25}D$ 1.5574.

*Anal.*[13] Calcd. for $C_9H_{11}NO_3$: N, 7.7. Found: N, 7.7.

Catalytic reduction as described above gave 98% of the aminopropylphenol hydrochloride; m. p. 245–252° (dec.).

*Anal.* Calcd. for $C_9H_{13}NO \cdot HCl$: N, 7.5. Found: N, 7.6.

**2-Amino-4-amylphenol.**—A solution of 51 cc. of concentrated nitric acid in 100 cc. acetic acid was cooled to −10° and 65 g. of *p*-amylphenol dissolved in 65 cc. of acetic acid was added with stirring over a period of two hours. The temperature was maintained below −5° during the addition. The reaction mixture was immediately poured into a mixture of ice and 160 g. of 10% sodium hydroxide, and extracted with benzene. The benzene extract was steam distilled and the oil so obtained was distilled to give 61.8 g. (75%) of 2-nitro-4-amylphenol; b. p. 100–105° (0.5 mm.); $n^{25}D$ 1.5253.

*Anal.* Calcd. for $C_{11}H_{15}NO_3$: N, 6.7. Found: N, 6.9.

The nitro derivative was reduced as described above to give 84% of the hydrochloride which melted at 194° after recrystallization from alcohol.

*Anal.* Calcd. for $C_{11}H_{17}NO \cdot HCl$: N, 6.5. Found: 6.5.

The free base, obtained by neutralization of the hydrochloride and recrystallization from petroleum ether, melted at 128°.

*Anal.* Calcd. for $C_{11}H_{17}NO$: N, 7.8. Found: N, 8.0.

**2-Amino-4,5-dimethylphenol.**—2-Benzeneazo-4,5-dimethylphenol[14] was reduced by sodium hydrosulfite in basic solution to give 77% of aminophenol melting at 171–175°.[15]

**2-Amino-4-methoxyphenol.**—One mole of diazotized aniline was added over a period of 1.5 hours to a solution of 124 g. of hydroquinone monomethyl ether dissolved in 1200 cc. of water containing 120 g. of sodium hydroxide. The temperature was maintained at −5 to 0° during the addition. The mixture was filtered, and the filtrate acidified to yield 202 g. (89%) of 2-benzeneazo-4-methoxyphenol; m. p. 69–72°. A pure sample was prepared as dark red needles from alcohol; m. p. 72.5–73.5°.

*Anal.* Calcd. for $C_{13}H_{12}N_2O_2$: N, 12.3. Found: N, 12.5.

The azo derivative was reduced by dissolving 100 g. in 1 l. of water containing 100 g. of sodium hydroxide. The solution was warmed on the steam-bath and sodium hydrosulfite was added in portions with stirring until the color was discharged. The aniline formed was extracted with ether; neutralization of the basic solution precipitated the aminophenol which was filtered rapidly, pressed as dry as possible on the filter plate, and immediately triturated with ethereal hydrogen chloride to give 57.5 g.; m. p. 205–212° (dec.). An additional 7.8 g., m. p. 197–205°, isolated from the aqueous filtrate by ether extraction and precipitation with ethereal hydrogen chloride brought the yield to 85%. The hydrochloride could be recrystallized only with considerable loss. An analytically pure sample was obtained from alcohol, using Norit. The m. p. was 210–213° (dec., pyrex tube evacuated to 0.5 mm.). Roberts and co-workers[16] reported a m. p. of 171° for the product obtained by the reduction of 2-nitro-4-methoxyphenol.

*Anal.* Calcd. for $C_7H_9NO_2 \cdot HCl$: N, 8.0. Found: N, 7.8.

### Preparation of Parent Benzoxazolones

The urea-fusion method (Method A), which was used for the preparation of most of the parent compounds, is illustrated by the preparation of 5-propylbenzoxazolone. Benzoxazolones not prepared by fusion with urea were synthesized as described below. The properties of all the compounds are given in the accompanying table.

**Method A. 5-Propylbenzoxazolone.**—2-Amino-4-propylphenol (470 g.) was intimately mixed with 300 g. of urea and heated in an oil-bath at 180° for two hours. The reaction mixture was cooled somewhat and acidulated water was added. The oil which separated was taken up in ether, concentrated and distilled. The product (348 g., 79%) boiled at 180–182° (0.8 mm.) and solidified in the receiver.

**5,6-Dimethylbenzoxazolone.**—A suspension of 34.2 g. of 2-amino-4,5-dimethylphenol and 59 g. of anhydrous potassium acetate in 600 cc. of ethyl acetate was treated dropwise with 30 g. of phosgene in 400 cc. of ethyl acetate with vigorous stirring. After refluxing briefly, water was added and the ethyl acetate layer separated. After washing with water and 5% hydrochloric acid, the solvent was removed. The residue of crude product was best purified by dissolving in boiling 10% NaOH and cooling in ice. The sodium salt which precipitated was suspended in water and acidified. By reworking the basic filtrate, a total of 27.6 g. (68%) of material melting at 173–177° was obtained.

**6-Chlorobenzoxazolone.**—Benzoxazolone (50 g.) was dissolved in 500 cc. of acetic acid, cooled in ice, and treated with 32 cc. of sulfuryl chloride with stirring. After standing overnight at room temperature, the solution was warmed on the steam-bath for one hour, cooled, and poured into water. A total of 51.3 g. (81%), m. p. 189–194°, was obtained.

The position of the chloro group was demonstrated by cleavage of the oxazolone ring with sodium hydroxide to give a chloroaminophenol. Purification of the product gave prismatic needles, m. p. 152–154° (dec.). The melting point was undepressed when mixed with a sample of 2-amino-5-chlorophenol, m. p. 152–154°, prepared according to Theilacker.[17]

### Alkylation of Benzoxazolones

The following examples illustrate the two general methods used to convert the parent benzoxazolones into N-substituted derivatives. The accompanying table lists the compounds prepared by these methods together with their properties.

**Method B. 3-*iso*-Amyl-5-propylbenzoxazolone.**—5-Propylbenzoxazolone (6.2 g.) was dissolved in 60 cc. of 0.84 *N* KOH in Cellosolve. *iso*-Amyl iodide[18] (9.3 cc.) was added and the mixture was refluxed for six hours. The liquid was decanted from the precipitate of potassium iodide and concentrated under reduced pressure. The residue was taken up in benzene and water; the benzene layer was separated and washed with 5% sodium hydroxide and water. After removal of the benzene, the product was distilled to give 5.7 g. (66%); b. p. 148–150° (0.8 mm.).

**Method C. 3-Amyl-5-methoxybenzoxazolone.**—A small flask was fitted with a reflux condenser, stirrer, dropping funnel, and short gas inlet tube. A slow stream of nitrogen was passed through the inlet tube during the course of reaction. Thirty cc. of Cellosolve (purified by distillation from sodium dissolved in Cellosolve) was introduced into the flask, and 1.6 g. of sodium was dissolved

(11) Baranger, *Bull. soc. chim.*, [4] **49**, 1217 (1931).

(12) Wagner, *Ber.*, **7**, 1270 (1874).

(13) No analyses reported in original preparation.

(14) (a) Diepolder, *Ber.*, **42**, 2918 (1909); (b) **44**, 2498 (1911).

(15) Ref. 14a, p. 2920; ref. 14b.

(16) Roberts, de Worms and Clark, *J. Chem. Soc.*, 198 (1935).

(17) Theilacker, *Ber.*, **71B**, 2070 (1938).

(18) There appeared to be no advantage in using iodides in place of bromides. Bromides were used exclusively in Method C.

TABLE I

PROPERTIES OF BENZOXAZOLONE DERIVATIVES

| Substituents Nuclear | Nitrogen | B. p.,[a] °C. | Mm. | $n^{25}D$[a] | M. p.,[a] °C. | Formula | Nitrogen, % Calcd. | Found | Prep. meth. | Yield, % | Act.[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| None | H[c] | ..... | | .... | 139–140 | ..... | .. | .. | A | 88 | .... |
| None | $CH_3$[d] | ..... | | .... | 83–84 | ..... | .. | .. | ..[d] | .. | ± |
| None | $n$-$C_4H_9$ | 129–130 | 1.3 | 1.5316 | ..... | $C_{11}H_{13}NO_2$ | 7.3 | 7.3 | B | 62 | 0 |
| None | $i$-$C_4H_9$ | ..... | | .... | 63.5–65[e] | $C_{11}H_{13}NO_2$ | 7.3 | 7.3 | B | 76 | 0 |
| None | $n$-$C_5H_{11}$ | 140–142 | 1.0 | 1.5268 | ..... | $C_{12}H_{15}NO_2$ | 6.8 | 6.9 | ..[f] | 40 | 0 |
| None | $i$-$C_5H_{11}$ | 112–113 | 0.4 | 1.5248[g] | 40–40.5[e] | $C_{12}H_{15}NO_2$ | 6.8 | 6.8 | C | 90 | +++[h] |
| None | $s$-$C_5H_{11}$ | 132–134 | 1.3 | 1.5280 | ..... | $C_{12}H_{15}NO_2$ | 6.8 | 7.0 | B | 40 | ++ |
| None | Acetyl[i] | ..... | | .... | 92–94 | ..... | .. | .. | ..[i] | 66 | 0 |
| None | Allyl[j] | 112–114 | 0.5 | 1.5536 | ..... | $C_{10}H_9NO_2$ | 8.0 | 8.1 | C | 66 | 0 |
| None | ....[k] | ..... | | .... | 171–173[k] | $C_{13}H_{19}ClN_2O_2$ | 10.3 | 10.3 | C | 66 | ++ |
| 5-$CH_3$ | H[l] | ..... | | .... | 128–129 | ..... | .. | .. | A | 79 | 0 |
| 5-$CH_3$ | $n$-$C_4H_9$ | 138–140 | 1.2 | 1.5300 | ..... | $C_{12}H_{15}NO_2$ | 6.8 | 7.0 | B | 67 | ++ |
| 5-$CH_3$ | $i$-$C_4H_9$ | ..... | | .... | 61–62[e] | $C_{12}H_{15}NO_2$ | 6.8 | 7.1 | B | 70 | ± |
| 5-$CH_3$ | $n$-$C_5H_{11}$ | 136–138 | 0.8 | 1.5239 | ..... | $C_{13}H_{17}NO_2$ | 6.4 | 6.5 | B | 65 | + |
| 5-$CH_3$ | $i$-$C_5H_{11}$ | 142–143 | 1.3 | 1.5230 | ..... | $C_{13}H_{17}NO_2$ | 6.4 | 6.3 | B | 65 | ± |
| 5-$CH_3$ | $s$-$C_5H_{11}$ | 130–133 | 1.2 | 1.5251 | ..... | $C_{13}H_{17}NO_2$ | 6.4 | 6.6 | B | 54 | .... |
| 5-$n$-$C_3H_7$ | H | ..... | | .... | 66.5–68[m] | $C_{10}H_{11}NO_2$ | 7.9 | 7.7 | A | 79 | 0 |
| 5-$n$-$C_3H_7$ | $n$-$C_4H_9$ | 164–167 | 1.0 | 1.5196 | ..... | $C_{14}H_{19}NO_2$ | 6.0 | 6.1 | C | 95 | +++[h] |
| 5-$n$-$C_3H_7$ | $i$-$C_4H_9$ | 141–144 | 1.2 | 1.1597 | ..... | $C_{14}H_{19}NO_2$ | 6.0 | 6.1 | B | 65 | ++ |
| 5-$n$-$C_3H_7$ | $n$-$C_5H_{11}$ | 162–164 | 1.4 | 1.5157 | ..... | $C_{15}H_{21}NO_2$ | 5.7 | 5.7 | B | 66 | ++ |
| 5-$n$-$C_3H_7$ | $i$-$C_5H_{11}$ | 148–150 | 0.8 | 1.5167 | ..... | $C_{15}H_{21}NO_2$ | 5.7 | 5.9 | B | 66 | 0 |
| 5-$n$-$C_3H_7$ | $s$-$C_5H_{11}$ | 148–151 | 1.1 | 1.5197 | ..... | $C_{15}H_{21}NO_2$ | 5.7 | 5.9 | B | 38 | + |
| 5-$n$-$C_5H_{11}$ | H | ..... | | .... | 62–64[n] | $C_{12}H_{15}NO_2$ | 6.8 | 6.8 | A | 90 | .... |
| 5-$n$-$C_5H_{11}$ | $CH_3$ | ..... | | .... | 55–56.5[n] | $C_{13}H_{17}NO_2$ | 6.4 | 6.5 | ..[o] | 96 | .... |
| 5-$n$-$C_5H_{11}$ | $n$-$C_3H_7$ | 167–170 | 2.0 | 1.5180 | ..... | $C_{15}H_{21}NO_2$ | 5.7 | 5.8 | C | 94 | 0 |
| 5-$n$-$C_5H_{11}$ | $i$-$C_4H_9$ | 146–148 | 0.6 | 1.5144 | ..... | $C_{16}H_{23}NO_2$ | 5.4 | 5.3 | C | 90 | + |
| 5-$n$-$C_5H_{11}$ | $n$-$C_5H_{11}$ | 178–180 | 1.4 | 1.5115 | ..... | $C_{17}H_{25}NO_2$ | 5.1 | 5.0 | C | 93 | 0 |
| 5,6-di$CH_3$ | H | ..... | | .... | 177–178[p] | $C_9H_9NO_2$ | 8.6 | 8.4 | ..[q] | 68 | ++ |
| 5,6-di$CH_3$ | $C_2H_5$ | ..... | | .... | 86–87[r] | $C_{11}H_{13}NO_2$ | 7.3 | 7.3 | ..[s] | 73 | ++ |
| 5,6-di$CH_3$ | $n$-$C_4H_9$ | ..... | | .... | 68–69[t] | $C_{13}H_{17}NO_2$ | 6.4 | 6.3 | C | 80 | 0 |
| 5,6-di$CH_3$ | $i$-$C_5H_{11}$ | ..... | | .... | 50–51[u] | $C_{14}H_{19}NO_2$ | 6.0 | 6.2 | C | 86 | ++ |
| 5-$CH_3O$ | H | ..... | | .... | 170–172[v] | $C_8H_7NO_3$ | 8.5 | 8.2 | A | 76 | ++ |
| 5-$CH_3O$ | $i$-$C_4H_9$ | ..... | | .... | 57–58[w] | $C_{12}H_{15}NO_3$ | 6.3 | 6.2 | C | 87 | ++ |
| 5-$CH_3O$ | $n$-$C_5H_{11}$ | 168–172 | 1.4 | 1.5299 | ..... | $C_{13}H_{17}NO_3$ | 6.0 | 5.8 | C | 92 | ++ |
| 5-$CH_3O$ | Acetyl | ..... | | .... | 102–103[p] | $C_{10}H_9NO_4$ | 6.8 | 6.7 | ..[q] | 95 | ++ |
| 6-Cl | H | ..... | | .... | 194–195[x] | $C_7H_4ClNO_2$ | 8.3 | 8.3 | ..[q] | 81 | .... |
| 6-Cl | $CH_3$ | ..... | | .... | 104–105[x] | $C_8H_6ClNO_2$ | 7.6 | 7.6 | ..[o] | 85 | 0 |
| 6-Cl | $i$-$C_3H_7$ | ..... | | .... | 91–92[r] | $C_{10}H_{10}ClNO_2$ | 6.6 | 6.4 | C | 40 | + |
| 6-Cl | $i$-$C_5H_{11}$ | 157–163 | 1.0 | 1.5308[g] | 46–47[y] | $C_{12}H_{14}ClNO_2$ | 5.8 | 5.9 | C | 62 | +++ |

[a] Data for analytically pure sample. [b] The symbols express the increase in pain threshold according to the following scale: 0 = none; ± = doubtful; + < 10%; ++ = 10–20%; +++ = 20–30%. [c] Bywater, Coleman, Kamm and Merritt, THIS JOURNAL, **67**, 905 (1945). [d] Ransom, *Am. Chem. J.*, **23**, 33 (1900). [e] Prisms from pentane. [f] Reaction carried out using potassium hydroxide in ethylene glycol. [g] Data on supercooled liquid. [h] Tested in human volunteers with lower results. [i] Kalckhoff, *Ber.*, **16**, 1828 (1883). [j] Reported by Lespagnol, Durbet and Mongy, *Compt. rend. soc. biol.*, **135**, 1255 (1941), with no details given. [k] Diethylaminoethyl hydrochloride; two crystallographic forms; lower form obtained as prisms from acetone–alcohol, m. p. 140–147° with resolidification and conversion to higher form. [l] Upson, *Am. Chem. J.*, **32**, 17 (1904). [m] Needles from pentane. [n] Needles from petroleum ether. [o] Reaction carried out using sodium methoxide and dimethyl sulfate in methanol. [p] Needles from alcohol. [q] Specific preparation described in text. [r] Needles from alcohol-petroleum ether. [s] Prepared with sodium ethoxide and diethyl sulfate in ethanol. [t] Two crystallographic forms; lower form obtained as prisms from petroleum ether, m. p. 61–63° with resolidification and conversion to higher form. [u] Needles from dilute alcohol. [v] Prisms from alcohol. [w] Prisms from alcohol–petroleum ether. [x] Leaflets from alcohol. [y] Leaflets from petroleum ether.

in the solvent. 5-Methoxybenzoxazolone (9.9 g.) was stirred into the solution, followed by 9.6 cc. of *n*-amyl bromide.[18] The solution was refluxed for one hour, then retreated with 0.69 g. of sodium dissolved in 10 cc. of Cellosolve (solution prepared under nitrogen) and 4.8 cc. of bromide. Refluxing was continued for one hour.

The reaction mixture was acidified with acetic acid and concentrated under reduced pressure. The residue was treated with ether and water. The separated ether layer was washed with water, 5% sodium hydroxide, 5% hydrochloric acid, and water. The ether was removed and the residue was distilled to give 13.0 g. (92%); b. p. 166–174° (1.0 mm.).

### Acylation of Parent Benzoxazolones

N-Acetyl derivatives of two benzoxazolones were prepared (see table). The following procedure gave the best results.

**3-Acetyl-5-methoxybenzoxazolone.**—A solution of 1.6 g. of sodium in 50 cc. of methanol was prepared and 9.9 g. of

5-methoxybenzoxazolone was added. The solvent was removed under reduced pressure and the dry solid residue was treated with 25 cc. of acetic anhydride. The mixture was swirled thoroughly and allowed to stand for ten minutes, after which it was poured into water. The product was filtered to give 11.8 g. (95%); m. p. 100–103°.

### Pharmacologic Evaluation

The compounds were tested for analgesic activity in dogs by a modification of the method of Andrews and Workman.[19] These determinations were carried out by Dr. R. K. Richards and Mr. K. E. Kueter of our laboratories to whom we express our thanks. Doses of 100–200 mg./kg. were used, at which level toxic symptoms rarely appeared. Several of the derivatives raised the pain threshold 10–20%; a few 20–30%. The best compounds, therefore, have an activity comparable to that of aspirin, which gives a 15–20% increase in 100 mg./kg. doses. They are much weaker analgesics than Demerol, which is capable of raising the pain threshold 30–40% in 15 mg./kg. quantities. Pharmacologic data for all of the benzoxazolones tested are included in the table.

(19) Andrews and Workman, *J. Pharmacol.*, **73**, 99 (1941).

## Summary

1. The synthesis of approximately forty N-alkyl, N-acyl, and N-dialkylaminoalkyl derivatives of benzoxazolone and nuclear substituted benzoxazolones is described.

2. About two-thirds of the derivatives induced mild analgesia in dogs.

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[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Streptomycin. XII. Streptamine Isomers from *meso*-Inositol

BY A. E. O. MENZEL,[1] M. MOORE AND O. WINTERSTEINER

In 1915 Griffin and Nelson,[2] in a study of the action of acetyl bromide on *meso*-inositol, obtained besides other products two isomeric dibromotetraacetoxycyclohexanes, melting at 225 and 130°, respectively, which Müller[3] had previously prepared from *meso*-inositol in a slightly different manner. In the absence of information on the position of the bromine atoms the higher-melting isomer was arbitrarily termed α-, and the lower melting isomer, β-. Soon after the structure of streptamine had been established,[4,5] we began an investigation of the aminolysis of these compounds and of the corresponding dibromotetrols (of which only the β-isomer had been previously described[2]), in the hope to arrive, if not at streptamine itself, at some isomers of it. While Griffin and Nelson were unable to effect amination of the β-dibromotetraacetoxycyclohexane by treatment with liquid ammonia at room temperature, we found that both the α- and the β-dibromotetrol reacted with aqueous ammonia at 100° with the formation of diamines. The crude products were isolated as picrates, which in both cases could be separated into a methanol-soluble fraction (I) and a much smaller methanol-insoluble fraction (II). The four picrate fractions were purified by recrystallization and converted to dihydrochlorides. The two pairs of diamines thus obtained are designated here for convenient reference as α- and β-diamines I, and α- and β-diamines II, the Greek letters signifying derivation from the corresponding dibromotetrol isomers, and the Roman numerals derivation from the methanol-soluble and methanol-insoluble picrate fraction, respectively. They were converted into suitable acyl derivatives for comparison with each other and with streptamine.

As could be anticipated from the properties of the salts and acyl derivatives of streptamine, the crystal shape and melting point data were of limited value as criteria for establishing identity or non-identity because the new compounds were generally microcrystalline and melted or decomposed over a considerable range. This was for instance the case with the dipicrates, sulfates, N,N′-diacetates and hexaacetates of α-diamine I and β-diamine I, respectively. Notwithstanding these limitations the picrates, sulfates and hexaacetates showed such close correspondence of their properties that identity of the parent diamines was at first suspected. Subsequently, however, certain differences in melting point behavior were observed with the N,N′-diacetates and the hexabenzoates. Particularly with the latter pair these discrepancies could not be dismissed as being due to accidental causes, because both compounds, in contradistinction to the acetyl derivatives, exhibited fairly well-defined melting points. Thus, while the β-hexabenzoate melted at 262–263°, it was not possible to raise the melting point of the α-hexabenzoate beyond 252–255°, and a small but distinct depression (251–253°) was observed in mixture. Furthermore, the X-ray diffraction patterns[6] of the two compounds were quite dissimilar, but the significance of this finding is not quite clear in view of the fact that the pattern given by the α-hexabenzoate raised some doubt as to its completely crystalline character (*cf.* Experimental). Nevertheless, we believe that the weight of the evidence is against identity, and that α-di-

(1) Present address: Roosevelt Hospital, W. 59th St., New York 19, N. Y.

(2) E. G. Griffin and J. M. Nelson, THIS JOURNAL, **37**, 1552 (1915).

(3) H. Müller, *J. Chem. Soc.*, **91**, 1788 (1907).

(4) R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

(5) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell and W. A. Strong, *Science*, **103**, 540 (1946).

(6) We are greatly indebted to Prof. G. L. Clark, of the Department of Chemistry, University of Illinois, for these measurements.

amine I and β-diamine I should be considered as separate entities. It was not vital for the purpose of this investigation to establish this point more conclusively.

There can be little doubt that neither of the isomers is identical with streptamine, since the N,N′-diacetates, hexaacetates and hexabenzoate of the latter all exhibit much higher melting points than the corresponding derivatives of the two diamines.

The dihydrochlorides of both isomers consumed, as expected, 6 moles of periodic acid while the N,N′-diacetates consumed 2 moles. This parallels the results obtained with streptamine and its N,N′-diacyl derivatives.[4,5] The amino groups in either diamine could therefore be in 1,3- or 1,4-position to each other.

The dihydrochlorides of α-diamine II and β-diamine II could be secured in small amounts only, since the yields of the purified methanol-insoluble picrates were poor and in some runs insignificant. Of acyl derivatives only the N,N′-diacetates were prepared. Both products melted sharply at 268–269° after slight sintering at 265°, and did not depress each other's melting point, whereas admixture of streptamine N,N′-diacetate gave a marked depression. It is therefore highly probable that these two diamines are identical. Identity with either of the diamines I is excluded not only by the different melting point properties of the dihydrochlorides and N,N′-diacetates of the latter, but also by the results obtained by the periodic acid method. The dihydrochlorides of the "α-" as well as of the "β-" diamine II consumed the expected 6 moles, but the N,N′-diacetates consumed 3 moles, indicating that the amino groups occupy vicinal positions. The fact that the isomeric α- and β-dibromotetrols give rise to the same diamine must be ascribed to the formation, in the initial phase of the amination reaction, of a common intermediate, *i. e.*, an epoxide.

The investigation had to be discontinued at this point for extraneous reasons so that no effort could be made to obtain further information on the structure of the diamines I and of the isomeric dibromotetrols. It might be mentioned in this connection that the application of the periodate method to the bromine compounds gave a definitive result only with the β-isomer, which in slow reaction consumed 3 moles of periodic acid and hence appears to carry the bromine atoms at adjoining carbon atoms. In the case of the α-dibromotetrol the oxidative attack was evidently complicated by side reactions. Consumption came to a standstill at 4 moles whereas no more than 3 moles could be consumed if the oxidation were confined to glycol groupings.

## Experimental

**α- and β-Dibromotetrahydroxycyclohexane.**—*meso*-Inositol was subjected to the reaction with acetyl bromide as described by Griffin and Nelson.[2] For the separation of the reaction products we followed in general their procedure of fractional crystallization, and were able to isolate most of the compounds reported by them, *e. g.*, α-dibromotetraacetoxycyclohexane, m. p. 222–223°[7]; β-dibromotetraacetoxycyclohexane, m. p. 128–129°; monobromopentaacetoxycyclohexane, m. p. 240–241°; dibromodiacetoxydihydroxycyclohexane, m. p. 220–222°; and β-dibromocyclohexanetetrol m. p. 214–216°. However, the yields of these compounds, as well as the proportion of the two dibromotetraacetoxy isomers, varied markedly from run to run. The purification of the α-isomer was greatly facilitated by chromatographing the crude product in benzene solution on aluminum oxide. For instance, the sirupy reaction product obtained from 50 g. of *meso*-inositol was taken up in hot absolute ethanol (1.4 l.). The resulting crystalline mass was filtered off from the hot solution, washed and dried (19.5 g.), then dissolved in benzene and chromatographed on a column (35 × 480 mm.) of acetic acid-washed alumina. Continued washing with benzene (2.1 l.) eluted crystalline material, which on recrystallization from ethyl acetate–ethanol (1:9) yielded slightly impure α-dibromotetraacetoxycyclohexane, m. p. 218–222° (10.9 g.). Subsequent elution with benzene–ethanol (9:1) removed from the column the chief contaminant of this fraction, monobromopentaacetylcyclohexane. The original alcoholic mother liquor on concentration yielded a second crop of crystals consisting mainly of β-dibromotetraacetoxycyclohexane (after recrystallization 10.4 g., m. p. 126–128°). A third crop of crystals obtained from this mother liquor was treated with hot chloroform. From the chloroform-insoluble fraction crude dibromodiacetoxydihydroxycyclohexane (9.2 g.) was isolated, while the chloroform-soluble fraction afforded an additional amount (1 g.) of α-dibromotetraacetoxycyclohexane m. p. 219–221°. The identity of the purified preparations was in all cases confirmed by analysis.

It was found preferable to secure **β-dibromocyclohexanetetrol** by acid hydrolysis of its tetraacetate rather than by direct isolation. A solution of the tetraacetate in about 20 parts of a 1:1 mixture consisting of ethanol and 2 *N* hydrochloric acid was boiled on the steam-bath for five hours and then concentrated to a small volume *in vacuo*. The excess hydrochloric acid was removed by twice repeating the distillation after the addition of absolute ethanol. The residue was taken up in warm ethanol, and the tetrol was precipitated by the addition of excess ether. After recrystallization from acetone it melted at 214–216° (dec.) after softening at 210°, yield, 58–65%.

*Anal.* Calcd. for $C_6H_{10}O_4Br_2$: C, 23.55; H, 3.29; Br, 52.2. Found: C, 23.14; H, 3.50; Br, 51.9.

The hitherto undescribed **α-dibromocyclohexanetetrol** was prepared from the tetraacetate in the same manner. The crude product was triturated with dry ether, and the insoluble part recrystallized from methanol–benzene or ethyl acetate–chloroform; prisms, m. p. 186–188°. The melting point of a mixture with the β-isomer was 175–180°. The solubility properties were similar to those of the β-isomer (readily soluble in water, moderately in methanol or ethanol, sparingly in acetone, insoluble in benzene and chloroform).

*Anal.* Calcd. for $C_6H_{10}O_4Br_2$: C, 23.55; H, 3.29; Br, 52.2. Found: C, 23.42; H, 3.59; Br, 51.9.

**Amination of Dibromotetrols.**—One gram portions of the tetrols were dissolved in concentrated aqueous ammonia (50 cc.), and the solutions heated in pressure bottles on the steam-bath for fifteen hours. (This ratio of tetrol to ammonia was retained from preliminary experiments, and could probably be decreased considerably.) After cooling the contents of several bottles were combined, and the excess ammonia was removed by repeated distillation *in vacuo* with water. The final aqueous solution was lyophilized, yielding the crude dihydrobromide as an amorphous white hygroscopic mass. Attempts to crystallize these products were unsuccessful.

It might be mentioned that other methods of amination previously explored had proved ineffective. Thus β-

(7) All melting points were taken in the capillary and are corrected for stem exposure.

dibromotetraacetoxycyclohexane was recovered unchanged after treatment with potassium phthalimide at 165° in the bomb tube, or at 100° in the presence of xylene or amyl alcohol, nor would this compound react with sodium amide in boiling xylene. On standing for a week in alcoholic ammonia partial amination occurred, but only a small amount of picrate was obtained.

**Isolation of Diamines as Picrates.**—The crude dihydrobromide (525 mg., 1.54 millimole) from α-dibromocyclohexanetetrol was dissolved in water (3 cc.), and a saturated solution of picric acid in absolute ethanol (7.2 cc., about 3 millimoles) was added. Since only a small amount of precipitate appeared within an hour, the solution was concentrated at room temperature to *ca.* 6 cc. and allowed to stand in the refrigerator overnight. The resulting microcrystalline precipitate was collected by centrifuging, washed with 50% ethanol and dried (600 mg.). The product was suspended in dry methanol (3 cc.), and the mixture was centrifuged after short boiling while still warm. The insoluble part was subjected to the same treatment with 1 cc. of methanol. On addition of benzene (12 cc.) to the combined supernatants and standing clumpy aggregates separated out on the walls of the vessel (322 mg.). Recrystallization from the same solvents yielded **α-diamine I dipicrate** in form of indistinctly crystalline particles. A somewhat better-looking preparation (microscopic rods) could be obtained from warm *t*-amyl alcohol containing a small amount of water and chilling; m. p. 235–236° (dec.) after sintering and darkening from about 210° on (block preheated to 180°). With some preparations a somewhat higher decomposition point (240–242°) was observed. The picrate is fairly readily soluble in water (difference from diamine II dipicrate) and methanol, and sparingly soluble in ethanol and dioxane.

*Anal.* Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 33.93; H, 3.64; N, 17.0.

**A picrolonate,** which is probably that of α-diamine I, was prepared from the same dihydrobromide; hair-like needles from methanol–water, m. p. 265° after sintering and darkening from 235° on.

*Anal.* Calcd. for $C_{26}H_{30}O_{14}N_{10}\cdot H_2O$: C, 43.10; H, 4.45; N, 19.3. Found: C, 43.36; H, 4.51; N, 20.0.

The methanol-insoluble fraction (31 mg.) of the mixed picrate was recrystallized twice from hot water. **Diamine II dipicrate** was obtained as small prisms melting gradually with decomposition at 260–290° after darkening at about 235°.

*Anal.* Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 34.03; H, 3.55; N, 17.4.

Essentially the same procedure was used with the dihydrobromide prepared from β-dibromocyclohexanetetrol. For example, to a solution of the dihydrobromide (4.75 g.) in water (40 cc.) picric acid (6.65 g.) in ethanol (75 cc.) was added. After concentration to about 50 cc. the solution was chilled; and the precipitate (7.2 g., m. p. 155–220°) collected after one hour. For removal of the picric acid present the product was extracted with cold benzene, and the residue leached with methanol (150 cc.). After filtering off of the insoluble portion and concentration of the filtrate to 50 cc. benzene (250 cc.) was added. The solution on standing at 4° deposited 1.9 g. of **β-diamine I dipicrate** in form of indistinctly crystalline aggregates. The recrystallized product was indistinguishable in appearance and melting point from α-diamine I dipicrate (m. p. 240–242° (dec.) after darkening and sintering beginning at 207°). There was no depression of the melting point in mixture.

*Anal.* Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 33.71; H, 3.35; N, 17.8.

The methanol-insoluble fraction (187 mg.) was recrystallized twice from water, yielding 107 mg. of diamine II dipicrate. The product showed the same melting point behavior as the diamine II dipicrate prepared from the α-tetrol.

*Anal.* Calcd. for $C_{18}H_{20}O_{18}N_8$: C, 33.97; H, 3.17; N, 17.6. Found: C, 34.27; H, 3.66; N, 17.8.

**Salts and Acyl Derivatives of α-Diamine I.**—α-Diamine I dipicrate (1.62 g.) was decomposed in the usual way with dilute hydrochloric acid and toluene–benzene. The lyophilized material from the aqueous phase (628 mg.) was dissolved in dry methanol and precipitated with ether. The dihydrochloride was obtained as an amorphous, hygroscopic, white product which started sintering at 90° but showed no definite melting point up to 180°. The analytical sample was dried at 78° *in vacuo*.

*Anal.* Calcd. for $C_6H_{14}O_4N_2\cdot 2HCl$: Cl, 28.2. Found: Cl, 28.2.

The **sulfate** was prepared from the dihydrochloride by double decomposition with one molar equivalent of silver sulfate. It was purified by dissolving it in a small volume of warm water and adding excess methanol; microscopic prisms, which darken from 260° on, and undergo pronounced decomposition from 285° to 340° without melting completely. The salt differs from streptamine sulfate by its crystal shape and its much higher solubility in water.

*Anal.* Calcd. for $C_6H_{14}O_4N_2\cdot H_2SO_4$: N, 10.14; S, 11.6. Found: N, 10.14; S, 11.2.

For the preparation of the **N,N'-diacetate** a mixture of the dihydrochloride (100 mg.), silver acetate (133 mg.), acetic anhydride (1.2 cc.) and dry methanol (0.9 cc.) was shaken for 2.5 hours, allowed to stand overnight and then heated on the steam-bath for five minutes. The silver chloride was filtered off from the warm solution and washed with hot water (10 cc.). A few drops of 1 *N* HCl were added to the filtrate for the removal of dissolved silver and the filtered solution was concentrated *in vacuo* to a small volume. On addition of ethanol (2 cc.) and standing in the refrigerator a precipitate formed, which was recrystallized twice by dissolving it in the minimal volume of hot methanol and adding excess ethanol. The purified product (69 mg.) consisted of small rods melting without decomposition at 210–212°. The analytical sample was dried at 155° *in vacuo* and then melted at 213–215°.

*Anal.* Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.75; H, 7.12; N, 10.42.

The **hexaacetate** was prepared by boiling a mixture of the sulfate (26 mg.), anhydrous sodium acetate (22 mg.), and acetic anhydride (2 cc.) under reflux for one hour. The acetic anhydride was removed by vacuum distillation and the residue was extracted several times with chloroform. The product obtained by evaporating the filtered chloroform extract (40 mg.) was sublimed at 140–150° (0.07 mm.). The sublimate consisted of microscopic rods (23 mg.) melting to a viscous droplet at 142–146° with meniscus formation at 177°. The analysis of this and another preparation was not quite satisfactory.

*Anal.* Calcd. for $C_{18}H_{26}O_{10}N_2$: C, 50.23; H, 6.09; $COCH_3$, 60.0. Found: C, 49.31; H, 5.88; $COCH_3$, 56.5.

For the preparation of the **hexabenzoate** a mixture of the dihydrochloride (199 mg.), pyridine (2.5 cc.) and benzoyl chloride (1 cc.) was heated just to boiling. After cooling the mixture was poured into ice water, acidified with hydrochloric acid, and extracted with chloroform. The extract was washed with bicarbonate solution and water, dried and evaporated. The residue was triturated with warm ether, and the insoluble portion (472 mg.) recrystallized twice from chloroform–ether. Small rods (408 mg.), melting without decomposition at 252–255°. On drying for the analysis at 155° *in vacuo* the melting point remained unchanged.

*Anal.* Calcd. for $C_{48}H_{38}O_{10}N_2$: C, 71.81; H, 4.77. Found: C, 71.86; H, 4.85.

**Salts and Acyl Derivatives of β-Diamine I.**—In general the same procedures were used as in the case of α-diamine I.

The **dihydrochloride** was obtained from the dipicrate in 72% yield, amorphous, gradually decomposed with effervescence after sintering at about 95°. The material was dried for analysis at 78° *in vacuo*.

*Anal.* Calcd. for $C_6H_{14}O_4N_2\cdot 2HCl$: C, 28.70; H, 6.42. Found: C, 28.63; H, 6.51.

**Sulfate**: microscopic prisms, darken above 280°, no m. p. up to 340°.

*Anal.* Calcd. for $C_6H_{14}O_4N_2 \cdot H_2SO_4$: C, 26.12; H, 5.84; N, 10.14. Found: C, 25.80; H, 6.10; N, 9.84.

The **N,N'-diacetate** was prepared from the dihydrochloride (101 mg.) with acetic anhydride (0.12 cc.) and methanol (0.9 cc.) as described for the α-diamine. The crude product was thrice recrystallized from methanol–ethanol, yielding small prisms (42 mg.) which started sintering at 194° and then gradually decomposed over the range 208–245°. This behavior is in marked contrast to that of the α-diamine I N,N'-diacetate (see above). A mixture of the two compounds melted over the same range as the α-isomer. The analytical sample was dried at 150° *in vacuo*.

*Anal.* Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: C, 46.14; H, 6.99; N, 10.57.

The **hexaacetate** was prepared from the dihydrochloride (213 mg.) with sodium acetate (145 mg.) and acetic anhydride (14 cc.) as described for the α-isomer. Like the latter, it could be sublimed in a high vacuum, but the bulk of the material was in this case purified by precipitation from chloroform or dioxane with dry ether. The final product was not distinctly crystalline. The melting point properties were similar to those of the α-isomer (liquefication at 145–149°, meniscus at 170°). A mixture of the isomers showed the same behavior. The compound was dried for analysis at 110° (2 mm.).

*Anal.* Calcd. for $C_{18}H_{26}O_{10}N_2$: C, 50.23; H, 6.09; N, 6.51; 6 $COCH_3$, 60.0. Found: C, 49.83; H, 6.17; N, 6.26; $COCH_3$, 58.6.

The **hexabenzoate** was prepared from 206 mg. of the dihydrochloride and worked up as described for the α-isomer. The residue from the chloroform extract was for the most part soluble in ether (difference from α-isomer). Accordingly the ether-soluble part was recrystallized from chloroform–hexane, and then twice from benzene–hexane, from which it separated in well-defined, short needles, melting without decomposition at 262–263° (block preheated to 230°). The melting point of mixtures with the α-isomer (m. p. 252–255°) was found to be 251–253° in repeated determinations. Admixture of a small amount of streptamine hexabenzoate (m. p. 314–316°) to the β-hexabenzoate depressed the melting point of the latter to 258–260°. The analytical sample was dried at 110° (2 mm.).

*Anal.* Calcd. for $C_{48}H_{38}O_{10}N_2$: C, 71.80; H, 4.77; N, 3.49. Found: C, 71.88; H, 5.04; N, 3.47.

The X-ray diffraction diagram[6] showed the following characteristics (letters in brackets denote intensities, *i. e.*, very strong, strong, medium, faint, very faint): 12.00 (v. s.), 10.10 (m.), 8.70 (f.), 7.45 (v. f.), 6.18 (f.), 5.65 (f.), 5.12 (v. f.), 4.85 (s.), 4.62 (s.), 4.33 (s.), 3.93 (m.), 3.54 (f.), 3.41 (f.), 3.24 (f.), 3.08 (f.), 2.73 (f.), 2.38 (v. v. f.), 2.17 (v. v. f.), 2.05 (v. v. f.), 2.02 (v. v. f.), 1.95 (v. v. f.), 12.70 (s.). On the pattern of the α-diamine I hexabenzoate Dr. G. L. Clark comments as follows:

"The pattern is distinguished by only one sharp crystalline interference which corresponds with the innermost, most intense diffraction line of the preceding sample. In addition, there is a broad outer halo which appears to result from the overlapping of several of the ill-defined lines which appear completely resolved for the β-hexabenzoate. This means, therefore, that this second sample is very imperfectly crystalline and that the molecules in the solid have only one direction in which there is anything like a regular arrangement, this corresponding to the longest interplanar spacing. This very diffuse pattern would not eliminate the possibility of an admixture of more than one compound, and it cannot be interpreted as conclusive evidence either that the compound is the same or different from the well-crystallized β-hexabenzoate even granted that there is an approximate (12.0 and 12.7 å.) correspondence in this longest interplanar spacing. This at least is evidence that one of the molecular dimensions must be common to the two materials."

**Diamine II.**—Diamine II dipicrate (83 mg.) prepared from the β-dibromotetrol was dissolved in hot water (10 cc.). After the addition of 2 *N* hydrochloric acid (0.75 cc.) the solution was extracted with toluene and then with benzene. The residue of the lyophilized phase (165 mg.) was purified by dissolving it in warm methanol and concentrating to a small volume. Repetition of the procedure yielded the **dihydrochloride** (22 mg.) as a well-particulated, possibly microcrystalline precipitate which in the capillary started darkening at about 220° but did not liquefy up to 300°. The analytical sample was dried at 110° (2 mm.).

*Anal.* Calcd. for $C_6H_{14}O_4N_2 \cdot 2HCl$: C, 28.70; H, 6.42. Found: C, 28.84; H, 6.65.

A sample prepared *via* the dipicrate from the α-dibromotetrol behaved similarly.

For the preparation of the **N,N-diacetate** the "α"-dihydrochloride (64 mg.) was acetylated with methanol (2.9 cc.), silver acetate (85 mg.) and acetic anhydride (0.18 cc.). After refluxing for five minutes the mixture was worked up as described for the α-diamine I N,N'-diacetate, except that excess ether was added to the aqueous-ethanolic solution of the crude product to complete the precipitation (63 mg.). Recrystallized twice from methanol–ethanol the diacetate formed long needles melting at 268–269° after some sintering at 265°. The preparation derived from the β-dibromotetrol behaved identically, as did the mixture of the two samples. The desiccator-dry specimens contained one mole of water, which was removed by drying at 150° *in vacuo*.

*Anal.* Calcd. for $C_{10}H_{18}O_6N_2$: C, 45.79; H, 6.92; N, 10.68. Found: (a) from α-tetrol: C, 45.61; H, 6.97; N, 10.80; (b) from β-tetrol: C, 45.60; H, 6.91.

Streptamine N,N'-diacetate was prepared as in the above instances by selective N-acetylation instead of by alkaline hydrolysis of the hexaacetate.[4] Its melting point (282–283°) was depressed to 242–262° by admixture of diamine II N,N'-diacetate.

**Periodate Titration.**—Accurately weighed 4–8 mg. samples of the compounds were dissolved in 10 cc. of potassium periodate solution containing 0.0128 atom of available oxygen per cc. One-cc. aliquots were withdrawn at suitable intervals, and after the addition of sulfuric acid, sodium acetate and potassium iodide, titrated with 0.01 *N* thiosulfate solution. The results are expressed in moles of periodate per mole of substance, the figures in parentheses denoting the reaction time in hours.

α-Diamine I dihydrochloride: 4.21 (0.75), 5.76 (3.25), 6.05 (22).
α-Diamine I N,N'-diacetate: 0.43 (1.0), 1.32 (6), 1.97 (23), 1.95 (30).
β-Diamine I dihydrochloride: 4.39 (0.5), 6.11 (21), 6.05 (26).
β-Diamine I N,N'-diacetate: 0.09 (0.5), 1.97 (21), 1.99 (26).
"α"-Diamine II dihydrochloride: 4.82 (0.5), 6.01 (2.5), 6.09 (24).
"α"-Diamine II N,N'-diacetate: 0.64 (0.5), 1.51 (2.5), 2.93 (24), 2.96 (44).
"β"-Diamine II N,N'-diacetate: 0.36 (0.33), 3.00 (22), 2.99 (70).
α-Dibromotetrol: 1.11 (23), 1.46 (46), 2.79 (69), 3.46 (94), 3.96 (144), 4.01 (192).
β-Dibromotetrol: 1.53 (23), 2.30 (46), 2.76 (70), 2.88 (94), 3.02 (118), 3.02 (192).

The analyses were performed by Mr. J. F. Alicino and his assistants.

## Summary

The two isomeric dibromotetraacetoxycyclohexanes ("α"- and "β") which Griffin and Nelson[1] had obtained by treatment of *meso*-inositol with acetyl bromide were hydrolyzed to the corresponding free tetrols. Amination of the dibromotetrols

with aqueous ammonia afforded a mixture of diaminocyclohexanetetrols which were isolated and separated as the picrates.

The main product from the α-dibromotetrol (α-diamine I) was converted into suitable acyl derivatives and compared with the main product from the β-dibromotetrol (β-diamine I) and its derivatives. Though in many respects similar, the two diamines appear to be different chemical entities. Their N,N′-diacetyl derivatives both consumed two moles of periodate indicating that the parent diamines could be either 1,3- or 1,4-diaminocyclohexanetetrols. Identity with streptamine is excluded in either case by the properties of the acyl derivatives.

In addition both dibromotetrols yielded small amounts of an identical diaminocyclohexanetetrol (diamine II). The N,N′-diacetyl derivative consumed three moles of periodate and hence must carry the acetamido groups in vicinal ring positions.

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[CONTRIBUTION FROM THE NAVAL RESEARCH LABORATORY]

# Ultrasonic Investigation of Molecular Properties of Liquids. V. Inorganic Halides[1]

BY ALFRED WEISSLER

The relation between sound velocity and molecular structure has been studied[2] in several series of organic liquids, but thus far not in inorganic liquids. A group of compounds which seemed especially suitable for this purpose consists of the Group IV tetrahalides. Their molecules may be considered as approximately spherical, so that they are easier to treat theoretically and thus furnish an approach to a better understanding of the liquid state. Because of this, their physical and thermodynamic properties have been studied for many years by Hildebrand[3] and co-workers.

A two-fold aim motivated the present work: (a) comparison of inorganic and organic liquids with respect to sound velocity, and (b) determining further properties of the interesting tetrahalides referred to above. Several thermodynamic quantities may be calculated from the measured velocity of sound in a liquid.

In addition to $CCl_4$, $SiCl_4$, $TiCl_4$, $GeCl_4$ and $SnCl_4$, some of the Group V halides were included here, specifically, $PCl_3$, $PBr_3$, $POCl_3$, $AsCl_3$ and $SbCl_5$.

## Experimental

The ten liquids were procured from commercial sources. Each was purified by fractional distillation (the fraction retained had a boiling-range of 0.5°) shortly before use, and protected as well as possible from deterioration due to moisture. The liquids were handled only under conditions of low atmospheric humidity.

Sound velocities at 30° were measured by means of the three-megacycle ultrasonic interferometer already described,[2] which requires only 10 ml. of sample. In order to minimize contamination of these reactive liquids, all interior surfaces were gold-plated and the usual nickel diaphragm at the floor of the cell was replaced by tantalum.

Densities, heat capacities and coefficients of thermal expansion at 30° were obtained from the "International Critical Tables" and Landolt–Börnstein tables.

## Results and Discussion

The velocity of sound in each of these inorganic halides is given in Table I; the probable accuracy is ±0.1%. These values lie in the range from about 760 to 1000 meters per second, which is somewhat lower than for most other liquids, including the organic halides. Figure 1 shows that no regular change of sound velocity in the tetrachlorides occurs as the atomic number of the central atom increases. In the Group V halides also, there is no consistent trend with molecular weight.

**Molar Sound Velocity.**—Because it is an additive function[4,5] of the chemical bonds in the molecule, the molar sound velocity is useful in correlating molecular structure with sound velocity. It is defined, so as to be empirically almost temperature-independent, as the molar volume times the cube root of sound velocity.[6]

From the values of molar sound velocity listed in Table I, the bond increment characteristic of each bond present in these compounds was obtained by simple arithmetic. For example, the value for $SiCl_4$ was divided by 4 in order to find the Si–Cl increment, while that for $PBr_3$ was divided by 3 to get the P–Br increment. Table II contains the figures so derived, which again fail to vary regularly with atomic number of the central atom, in either Group IV or Group V.

(1) The opinions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Navy service at large. Article not copyrighted.

(2) Weissler, THIS JOURNAL, **71**, 93 (1949); **71**, 419 (1949); and references contained therein.

(3) Hildebrand, *J. Chem. Phys.*, **15**, 727 (1947).

(4) Lagemann and Dunbar, *J. Phys. Chem.*, **49**, 434 (1945).

(5) See, however, Lagemann, Evans and McMillan, THIS JOURNAL, **70**, 2996 (1948), who studied a large number of organic halides and concluded that molar sound velocity is not strictly additive, but rather highly constitutive.

(6) Rao, *J. Chem. Phys.*, **9**, 688 (1941).

TABLE I

PROPERTIES OF INORGANIC HALIDES AT 30°

| Compound | Sound velocity, meters/sec. | Density, g./ml. | Molar sound velocity | Adiabatic compressibility ($10^{-12}$ cm.²/dyne) | Coefficient of thermal expansion | Heat capacity, joule/g. | Isothermal compressibility ($10^{-12}$ cm.²/dyne) | Ratio of specific heats | Thermal pressure coefficient, $10^6$ dyne/cm.² deg. | Energy-volume coefficient, $10^6$ dyne/cm.² |
|---|---|---|---|---|---|---|---|---|---|---|
| $CCl_4$ | 905.8 | 1.5746 | 945.4 | 77.40 | $1.240 \times 10^{-3}$ | 0.866 | 111.6 | 1.44 | 11.11 | 3367 |
| $SiCl_4$ | 766.2 | 1.4622 | 1063.2 | 116.50 | 1.438 | .837 | 167.7 | 1.44 | 8.57 | 2598 |
| $TiCl_4$ | 977.5 | 1.7078 | 1102.6 | 61.28 | 1.045 | .804 | 85.4 | 1.39 | 12.24 | 3708 |
| $GeCl_4$ | 768.6 | 1.8533 | 1059.8 | 91.34 | 1.273 | .699[a] | 129.3 | 1.42 | 9.85 | 2984 |
| $SnCl_4$ | 782.3 | 2.2004 | 1090.9 | 74.26 | 1.178 | .619 | 105.2 | 1.42 | 11.20 | 3394 |
| $PCl_3$ | 944.1 | 1.5567 | 831.3 | 72.07 | 1.207 | .876 | 104.4 | 1.45 | 11.56 | 3504 |
| $PBr_3$ | 916.7 | 2.8513 | 922.4 | 41.74 | 0.858 | | | | | |
| $POCl_3$ | 969.3 | 1.6564 | 916.5 | 64.26 | | | | | | |
| $AsCl_3$ | 1006.7 | 2.1392 | 884.5 | 46.13 | 1.040 | .737 | 66.9 | 1.45 | 15.55 | 4712 |
| $SbCl_5$ | 912.3 | 2.331 | 1244.3 | 51.54 | | | | | | |

[a] Estimated by interpolation.

**Compressibility.**—The adiabatic compressibility $K_{ad}$ is related to the velocity of sound $v$ and the density $d$ by the equation

$$K_{ad} = 1/v^2d \qquad (1)$$

Adiabatic compressibilities computed from (1) are listed in Table I. $SiCl_4$ is by far the most compressible of these liquids, in agreement with its known low boiling point and low internal pressure, while $PBr_3$ is the least compressible.

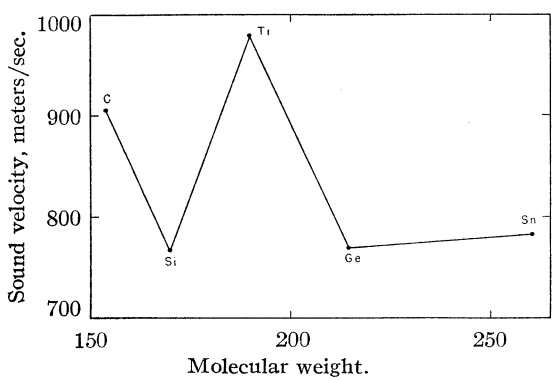



Fig. 1.—Sound velocity in liquid tetrachlorides.

A plot of $K_{ad}$ for the tetrachlorides (solid line, Fig. 2) shows an irregular variation with molecular weight. This is in sharp contrast to the organic halides (for example, methylene chloride, bromide, and iodide) where each increase in molecular weight causes a considerable decrease in compressibility.[5,7]

Freezing points of the tetrachlorides are also plotted in Fig. 2 (broken line) using an inverted temperature scale. The remarkable similarity between the two curves suggests that the same forces which determine compressibility also fix the freezing temperature, for each of these liquids. This may be thought of in the following way. The greater the space between molecules, the greater the compressibility—also, the greater the cooling necessary to bring the molecules sufficiently close together so that their mutual attractive forces become strong enough to freeze the molecules into the solid lattice.

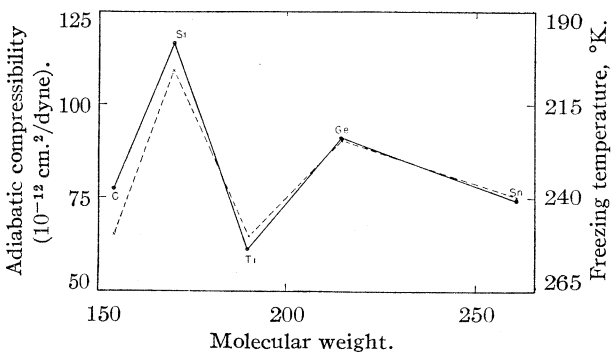



Fig. 2.—Adiabatic compressibility (solid line) and freezing temperature (broken line) of liquid tetrachlorides.

From the adiabatic compressibility plus the heat capacity $c_p$, coefficient of thermal expansion $\alpha$, temperature $T$, and density $d$, the isothermal compressibility may be calculated using the equation

$$K_{is} = K_{ad} + T\,\alpha^2/c_p d \qquad (2)$$

Table I gives the values (where available) for $c_p$, $d$, and $\alpha$, as well as the isothermal compressibilities calculated therefrom for seven of the liquids.

Of thermodynamic interest is the fact that the ratio of isothermal to adiabatic compressibility is equal to the ratio of specific heats $\gamma$. The values for $\gamma$ shown in Table I are as usual considerably higher than those for the same molecules in the gaseous state: thus, 1.44 for liquid $CCl_4$ compared to 1.18 (theoretical) for the gas. For $TiCl_4$, $\gamma$ is appreciably lower than for the other tetrahalides, possibly as a result of the greater ionic character of its bonds.

**Thermal Pressure and Energy–Volume Coefficients.**—The thermal pressure coefficient $(\partial P/\partial T)_V$ is related to the isothermal compressi-

(7) Bergmann, "Der Ultraschall," 3rd ed., Edwards Brothers, Ann Arbor, Mich., 1944, p. 183.

bility in that their product is equal to the coefficient of thermal expansion[8]

$$\left(\frac{\partial P}{\partial T}\right)_V \cdot \frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T = \frac{-1}{V}\left(\frac{\partial V}{\partial T}\right)_P \qquad (3)$$

Values for $(\partial P/\partial T)_V$ computed from this equation are listed in Table I, which shows that $SiCl_4$ has the lowest and $AsCl_3$ the highest. Comparison with the thermal pressure coefficients previously obtained by direct measurement[9] for four of these liquids indicates fairly good agreement; uncertainty in the specific heats probably accounts for much of whatever differences exist.

A thermodynamic equation of state applicable to all substances is

$$(\partial E/\partial V)_T = T(\partial P/\partial T)_V - P \qquad (4)$$

which makes it possible to calculate the important coefficient for the variation of energy with volume, $(\partial E/\partial V)_T$. For a liquid, this quantity is also called the internal pressure (dimensions of energy/volume are equivalent to pressure) because it is a measure of the attractions and repulsions of the molecules. These energy–volume coefficients obtained from equation (4), taking $P$ as atmospheric pressure ($1.013 \times 10^6$ dynes/cm.$^2$), are given in Table I. Again there is no monotonic variation with molecular weight.

(8) Westwater, Frantz and Hildebrand, *Phys. Rev.*, **31**, 135 (1928).

(9) Hildebrand and Carter, THIS JOURNAL, **54**, 3592 (1932).

**Estimation of Heat Capacity.**—The heat capacity $c_P$ may be estimated by means of equation (2), if the other quantities are known. This may be illustrated in the case of $PBr_3$. Assuming as an approximation that $\gamma$ for this compound is 1.45, the same as for $PCl_3$ and $AsCl_3$, we find that the heat capacity at 30° is 0.417 joule/gram, with a presumable accuracy of a few per cent.

TABLE II

BOND INCREMENTS FOR MOLAR SOUND VELOCITY

| Bond | Increment | Bond | Increment |
|---|---|---|---|
| C–Cl | 236 | P–Cl | 277 |
| Si–Cl | 266 | P–Br | 307 |
| Ti–Cl | 276 | P=O | 85 |
| Ge–Cl | 265 | As–Cl | 295 |
| Sn–Cl | 273 | Sb–Cl | 249 |

**Acknowledgment.**—It is a pleasure to acknowledge the many helpful suggestions made by Dr. G. R. Ringo during the course of this work.

## Summary

The velocity of sound at 30° in ten inorganic halides has been determined; on the average, it is lower than in the organic halides. Such properties as compressibility, ratio of specific heats, and the energy–volume coefficient have been computed from the sound velocities. There is no systematic variation with molecular weight in any of these properties.

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[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

# Resolution of the Dissociation Constants of Citric Acid at 0 to 50°, and Determination of Certain Related Thermodynamic Functions[1]

BY ROGER G. BATES AND GLADYS D. PINCHING

The development of exact electromotive-force methods[2,3] has brought about a considerable extension of our knowledge of the thermodynamics of weak electrolytes in recent years. In general, these experimental procedures, based upon electromotive-force measurements of cells without liquid junction, have been applied only to systems the composition of which can be completely expressed in terms of stoichiometric concentrations, the water equilibrium, and a single step in the dissociation of the weak electrolyte. If two or more acids or acidic groups are partially neutralized in the same range of hydrogen-ion concentrations, as is often the case with organic polybasic acids, the composition of the mixture may be quite difficult to establish. For this reason little attention has been directed to the resolution, by thermodynamic methods, of the dissociation constants of dibasic acids for which $K_1/K_2$ is less than 1000.

Separation of the constants for three overlapping equilibria is even more laborious. For citric acid, $K_1/K_2$ and $K_2/K_3$ are both about 44 at 25°. Existing values[4,5,6] of the thermodynamic constants for this acid were derived from electromotive-force measurements of cells with liquid junction. The analysis of the data rests in each instance upon a computation of the hydrogen-ion concentration or activity. Consequently, an assumption regarding the potential at the liquid junction must be introduced.

In spite of the interest that attaches to the thermodynamics of such a three-step dissociation process, no determination of the constants of a tribasic acid, with or without overlapping, has

(1) Presented before the Physical and Inorganic Division at the September, 1947, meeting of the American Chemical Society at New York City.

(2) H. S. Harned and B. B. Owen, THIS JOURNAL, **52**, 5079 (1930).

(3) H. S. Harned and R. W. Ehlers, *ibid.*, **54**, 1350 (1932).

(4) H. S. Simms, *J. Phys. Chem.*, **32**, 1121 (1928).

(5) I. M. Kolthoff and W. Bosch, *Rec. trav. chim.*, **47**, 558 (1928).

(6) N. Bjerrum and A. Unmack, *Kgl. Danske Videnskab. Selskab., Math.-fys. Medd.*, **9**, No. 1 (1929).

heretofore been made by methods free of the uncertainties of a liquid junction. The changes of entropy and of heat capacity accompanying dissociation are computed from the first and second derivatives, respectively, of electromotive force (or log $K$) with temperature. Hence, these functions can be established accurately only from a multifarious series of measurements over a range of temperatures.

The three dissociation constants of citric acid have therefore been determined at intervals of 5° from 0 to 50° by measurement of the electromotive force of hydrogen–silver chloride cells without liquid junction. The changes of free energy, heat content, entropy and heat capacity accompanying the acidic dissociation of one mole of citric acid or one gram ion of primary or secondary citrate ion in the standard state at 0 to 50° have been calculated.

## Method of Resolution

All of the cells are represented by the following scheme

Pt; $H_2$(g), citrate buffer solution, KCl, AgCl(s); Ag

Each value of the electromotive force of this cell for a solution of known chloride concentration furnishes a measure of $-\log (f_H f_{Cl} m_H)$, where $m$ is molality and $f$ is the activity coefficient on the molal scale. For convenience, this experimental quantity has been termed $pw$H.[7] The

$$pw\mathrm{H} \equiv -\log (f_H f_{Cl} m_H) = \frac{(E - E^0)\mathbf{F}}{2.3026\ RT} + \log m_{Cl} \quad (1)$$

value of $E^0$ in int. v. has been determined by Harned and Ehlers,[8] and 2.3026 $RT/\mathbf{F}$ in the same units has been tabulated in an earlier publication from this Bureau.[9]

The buffer solutions in the range of $p$H governed principally by the third dissociation equilibrium were prepared from tertiary potassium citrate and secondary potassium citrate. In order to minimize corrections for the second dissociation step, the salts were combined in the molal ratio 3:1. The advantage of a similar preponderance of free citric acid over primary potassium citrate for the determination of the first constant is offset by the enhanced correction for hydrogen ion, and for this reason a molal ratio of unity was selected. The $K_2$ correction is therefore more important in the determination of $K_1$ than of $K_3$, although only two equilibria need be considered in each instance.

The compositions of mixtures of primary and secondary citrates, on the other hand, can be expressed completely only in terms of all three steps in the dissociation of the acid, namely[10]

$$H_3Ci + H_2O \rightleftharpoons H_2Ci^- + H_3O^+; \quad K_1 \quad (2a)$$
$$H_2Ci^- + H_2O \rightleftharpoons HCi^= + H_3O^+; \quad K_2 \quad (2b)$$
$$HCi^= + H_2O \rightleftharpoons Ci^{\equiv} + H_3O^+; \quad K_3 \quad (2c)$$

Hence, no pair of constants can be evaluated by simple simultaneous solution of two formal equations derived exclusively from data corresponding to the three regions where the buffer capacity is highest. One of the authors has recently shown,[11] however, that the resolution of the constants for overlapping equilibria can be materially simplified with the aid of electromotive-force data for buffer solutions composed simply of a single acid salt (with added chloride). In this way a second equation can be written in terms of $K_1$ and $K_2$ (or $K_2$ and $K_3$) with at most a relatively minor correction for a third equilibrium.

It is therefore possible to obtain the first and second constants from an analysis of only two sets of data and, by a similar procedure, also the second and third constants. In practice, the equations are most conveniently solved by the method of approximations. The concentrations of secondary and tertiary citrates were so chosen that the influence of $K_2$ on the third constant was kept relatively small. It was found by trial that $pK_2$ need be known only within 0.03 to yield a value of $pK_3$ accurate to 0.001 unit. For the same accuracy in $pK_1$, it is necessary to know $pK_2$ to the nearest 0.01 unit. Somewhat larger errors are inherent in the value of $pK_2$ derived in this way, however, for the electromotive force of the cells containing the acid salt depends upon the product of two constants.[11] It follows, then, that the equations for overlapping are of limited usefulness in determining $K_2$ accurately, although they are a material aid in resolving the constants, for they permit the first and third equilibria readily to be freed of the influence of the second. With a knowledge of $K_1$ and $K_3$, however, $K_2$ can be determined by conventional methods.

The buffer solutions studied are conveniently grouped into five series: (1) mixtures of citric acid and potassium dihydrogen citrate, (2) potassium dihydrogen citrate, (3) mixtures of potassium dihydrogen citrate and dipotassium hydrogen citrate, (4) dipotassium hydrogen citrate, and (5) mixtures of dipotassium hydrogen citrate and tripotassium citrate. Potassium chloride was added to each solution. The number of solutions studied in each of these five series was respectively, 19, 25, 10, 5 and 25.

**Series 1.**—For systems governed principally by the first dissociation equilibrium, such as

(7) R. G. Bates, *Chem. Rev.*, **42**, 1 (1948).

(8) H. S. Harned and R. W. Ehlers, THIS JOURNAL, **55**, 2179 (1933). The determination of $E^0$ from these data has also been examined by H. S. Harned and D. D. Wright, *ibid.*, **55**, 4849 (1933), and by W. J. Hamer, J. O. Burton and S. F. Acree, *J. Research Natl. Bur. Standards*, **24**, 269 (1940).

(9) G. G. Manov, R. G. Bates, W. J. Hamer and S. F. Acree, THIS JOURNAL, **65**, 1765 (1943).

(10) In these equations, Ci is written for citrate, and $K$ is the thermodynamic dissociation constant. For simplicity, H will be written for hydronium ion, and the charges will be omitted from the symbols for this ion and for chloride ion. The activity of water does not depart greatly from unity in the dilute solutions, and it will therefore be omitted from the equations. As usual, $pK \equiv -\log K$.

(11) R. G. Bates, THIS JOURNAL, **70**, 1579 (1948).

those of series 1, it is convenient to write the relationship between $pw\mathrm{H}$ and $pK_1$ in the form

$$pK_1 = pw\mathrm{H} + \log \frac{m_{\mathrm{H_3Ci}}}{m_{\mathrm{H_2Ci^-}}} + \log \frac{f_{\mathrm{H_3Ci}} f_{\mathrm{Cl}}}{f_{\mathrm{H_2Ci^-}}} \quad (3)$$

The concentration term, $m_{\mathrm{H_3Ci}}/m_{\mathrm{H_2Ci^-}}$, can be expressed in terms of $m$ (the stoichiometric molality of citric acid and of primary potassium citrate), $m_{\mathrm{H}}$, and $m_{\mathrm{HCi^=}}$ by consideration of the equilibria that fix the compositions of the solutions of series 1. If the Debye–Hückel equation[12] is assumed, the last term of equation (3) disappears at low ionic strengths. Hence, the "apparent" first constant, $K_1'$, which becomes equal to the thermodynamic $K_1$ at zero ionic strength, is given by

$$pK_1' = pw\mathrm{H} + \log \frac{m - m_{\mathrm{H}} + m_{\mathrm{HCi^=}}}{m + m_{\mathrm{H}} - 2m_{\mathrm{HCi^=}}} \quad (4)$$

The apparent hydrogen-ion concentration, $m_{\mathrm{H}}$, which approaches the true hydrogen-ion concentration at low ionic strengths, was obtained from $pw\mathrm{H}$ by substitution of the Debye–Hückel equation for the activity coefficients of hydrogen and chloride ions

$$-\log m_{\mathrm{H}} = pw\mathrm{H} + \log f_{\mathrm{H}} f_{\mathrm{Cl}} = pw\mathrm{H} - \frac{2A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (5)$$

The constants $A$ and $B$ depend upon the temperature[9]; $a^*$ is the ion-size parameter. The ionic strength, $\mu$, of the mixtures of series 1 is

$$\mu = m + m_{\mathrm{H}} + m_{\mathrm{HCi^=}} + m_{\mathrm{KCl}} \quad (6)$$

The necessary correction for the molality of secondary citrate ion, $m_{\mathrm{HCi^-}}$, is made only with an estimate of $K_2$

$$m_{\mathrm{HCi^=}} = m_{\mathrm{H_2Ci^-}} \text{ (antilog } pw\mathrm{H}) \, K_2/f^2 \quad (7)$$

The activity coefficient, $f^{\mathrm{n}}$, was computed here and in other steps of the calculations by the Debye–Hückel equation[12]

$$\log f^{\mathrm{n}} = \frac{-nA\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (8)$$

**Series 2.**—The value of $(K_1K_2)'$, the apparent product of $K_1$ and $K_2$, is related to the electromotive force of the cells containing primary potassium citrate and potassium chloride by the following equation[13]

$$-\tfrac{1}{2}\log (K_1K_2)' = pw\mathrm{H} - \tfrac{1}{2}\log \frac{m_{\mathrm{H_3Ci}} + m_{\mathrm{H}} - m_{\mathrm{Ci^{\equiv}}}}{m_{\mathrm{H_3Ci}}} + \frac{A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (9)$$

The true $K_1K_2$ is obtained by extrapolation of apparent values to zero ionic strength, where the last term of the equation is zero. In writing equation (9), the activity coefficient of the molecular acid has been assumed to be unity, and that of each ionic species has been represented by the Debye–Hückel formula.

The second term on the right of equation (9) changes but slightly with relatively large alterations in the estimated molality of free citric acid. Consequently it can be obtained readily with sufficient accuracy by the approximation[11]

$$\frac{m_{\mathrm{H_3Ci}} + m_{\mathrm{H}} - m_{\mathrm{Ci^{\equiv}}}}{m_{\mathrm{H_3Ci}}} \approx \frac{mx + m_{\mathrm{H}} - 2m_{\mathrm{Ci^{\equiv}}}}{mx - m_{\mathrm{H}}} \quad (10)$$

where $m$ is the molality of potassium dihydrogen citrate and $x$ is a function of the concentration dissociation constants, $k_{\mathrm{n}}$

$$x \equiv \frac{2(k_2/k_1)^{1/2}}{1 + 2(k_2/k_1)^{1/2}} \quad (11)$$

These concentration constants are related to the thermodynamic constants, $K_{\mathrm{n}}$, by the following expression

$$k_{\mathrm{n}} = K_{\mathrm{n}}/f^{2n} \quad (12)$$

The activity coefficient, $f^n$, is obtained by equation (8).

The concentration of hydrogen ion in equation (10) is small compared with $m_{\mathrm{H_3Ci}}$. Its approximate value is derived from $pw\mathrm{H}$ by equation (5). The concentration of citrate ion, $m_{\mathrm{Ci^{\equiv}}}$, in primary citrate solutions of molality, $m$, not exceeding 0.1 is less than 1% of $m_{\mathrm{H_3Ci}}$. Hence, this molality is a correction of secondary importance in equation (10) and can be estimated with sufficient accuracy if the approximate magnitude of $K_3$ is known

$$m_{\mathrm{Ci^{\equiv}}} = \frac{K_3 m_{\mathrm{HCi^=}}}{f^6 m_{\mathrm{H}}} \approx \frac{K_3(mx + m_{\mathrm{H}})}{2f^6 m_{\mathrm{H}}} \quad (13)$$

In order to estimate $m_{\mathrm{H}}$ and $m_{\mathrm{HCi^=}}$, as well as to perform the extrapolation, the ionic strength was calculated by

$$\mu = m(1 + 0.5x) + 1.5m_{\mathrm{H}} + 2.5m_{\mathrm{Ci^{\equiv}}} + m_{\mathrm{KCl}} \quad (14)$$

It has been shown[11] that the choice of $a^*$ in equations (5) and (8) has a negligible influence upon $K_1K_2$ in the limit of zero ionic strength, provided the same value is used in both equations.

**Series 3.**—In a buffer mixture composed of primary and secondary potassium citrates and potassium chloride, each at a molality $m$, the second dissociation constant is given by

$$pK_2 = pw\mathrm{H} + \log \frac{m_{\mathrm{H_2Ci^-}}}{m_{\mathrm{HCi^=}}} + \log \frac{f_{\mathrm{H_2Ci^-}} f_{\mathrm{Cl}}}{f_{\mathrm{HCi^=}}} \quad (15)$$

The second term on the right can be written in terms of $m$ and the actual concentrations of free citric acid and of tertiary ion in the buffer solutions. Likewise, the activity-coefficient term can be expressed by the Debye–Hückel equation, and the second constant can be obtained in the usual manner by extrapolation to zero ionic strength of apparent values, $pK_2'$, defined by

$$pK_2' = pw\mathrm{H} + \log \frac{m - 2m_{\mathrm{H_3Ci}} + m_{\mathrm{Ci^{\equiv}}}}{m + m_{\mathrm{H_3Ci}} - 2m_{\mathrm{Ci^{\equiv}}}} + \frac{2A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (16)$$

The ionic strengths of the buffer solutions of series 3 are given by

$$\mu = 5m + 0.5m_{\mathrm{H}} + m_{\mathrm{H_3Ci}} + m_{\mathrm{Ci^{\equiv}}} \quad (17)$$

The values of $m_{\mathrm{H_3Ci}}$ and of $m_{\mathrm{Ci^{\equiv}}}$ are readily obtained, when $K_1$ and $K_3$ have been determined,

(12) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

(13) Compare Case IV of ref. 11.

with sufficient accuracy by a short series of approximations

$$m_{H_3Ci} = f^2 m_H (m - 2m_{H_3Ci} + m_{Ci^{\equiv}})/K_1 \quad (18)$$

$$m_{Ci^{\equiv}} = K_3(m + m_{H_3Ci} - 2m_{Ci^{\equiv}})/(f^6 m_H) \quad (19)$$

The concentration of hydrogen ion is obtained as before by equation (5).

**Series 4.**—The electromotive force of the cells containing mixtures of secondary potassium citrate and potassium chloride, each at molality $m$, is related to $(K_2K_3)'$, the apparent value of $K_2K_3$, by the equation [14]

$$-{}^1/_2 \log (K_2K_3)' = pwH - {}^1/_2 \log \frac{m_{H_2Ci^-} + m_H + 2m_{H_3Ci}}{m_{H_2Ci^-}} + \frac{3A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (20)$$

The second term on the right of equation (20) is readily obtained by

$$\frac{m_{H_2Ci^-} + m_H + 2m_{H_3Ci}}{m_{H_2Ci^-}} \approx \frac{my + m_H + 2m_{H_3Ci}}{my - m_H - 2m_{H_3Ci}} \quad (21)$$

where

$$y \equiv \frac{2(k_3/k_2)^{1/2}}{1 + 2(k_3/k_2)^{1/2}} \quad (22)$$

The concentration constants, $k_n$, are obtained by equations (8) and (12), and $m_H$ by equation (5). The choice of $a^*$ in equations (5) and (8) has a negligible effect upon the second term on the right of formula (20). The molality of citric acid, $m_{H_3Ci}$, amounts to only 4% of $my$. It is calculated with sufficient accuracy by the approximate formula

$$m_{H_3Ci} \approx \frac{f^2 m_H (my - m_H)}{2K_1} \quad (23)$$

Finally, the ionic strengths of the solutions of series 4 are given by

$$\mu = m(4 + 0.5y) + 2.5m_H + 2m_{H_3Ci} \quad (24)$$

**Series 5.**—The principal equilibrium in mixtures of secondary potassium citrate ($m_1$), tertiary potassium citrate ($m_2$), and potassium chloride is (2c). The third constant is given by

$$pK_3 = pwH - \log \frac{m_{Ci^{\equiv}}}{m_{HCi^{=}}} + \log \frac{f_{Cl} f_{HCi^{=}}}{f_{Ci^{\equiv}}} \quad (25)$$

The concentration of hydrogen ion in these solutions is so small that it can be neglected entirely. Consideration of the second and third dissociation steps, equilibria (2b) and (2c), leads to the equality

$$\frac{m_{Ci^{\equiv}}}{m_{HCi^{=}}} = \frac{m_2 + m_{H_2Ci^-}}{m_1 - 2m_{H_2Ci^-}} \quad (26)$$

Hence, when the activity coefficients are expressed by the Debye–Hückel equation, the following extrapolation formula is obtained.

$$pK_3' = pwH - \log \frac{m_2 + m_{H_2Ci^-}}{m_1 - 2m_{H_2Ci^-}} + \frac{4A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} \quad (27)$$

The molality of the primary anion, $m_{H_2Ci^-}$, is but 1.5% of $m_1$ for mixtures of series 5, in which $= 3m_1$. It was evaluated by equation (7) with substitution of $m_1$ for $m_{iCH^-}$. The ionic strength is given by

$$\mu = 3m_1 + 6m_2 + m_{H_2Ci^-} + m_{KCl} \quad (28)$$

The problem of resolving the three constants was approached in the following manner. Inasmuch as the precise determination of any one of the constants requires a knowledge of at least one of the others, it was first necessary to ascertain the accuracy with which these other constants must necessarily be estimated to allow $pK$ to be established with an accuracy of 0.001. As indicated earlier in this paper, $pK_2$ need be known to 0.01 unit for the accurate determination of $pK_1$ and to 0.03 unit for the calculation of $pK_3$ from the measurements of series 5. As a point of departure, $pK_2$ was taken as 4.76, the value at 25° found by Bjerrum and Unmack.[6] Values for the first and third constants were then obtained by analysis of the data for solutions of series 1 and series 5. With these, values of $K_1K_2$ and of $K_2K_3$, from which a new $K_2$ could be derived, were obtained from the measurements of series 2 and series 4 and the calculation of $pK_1$ and $pK_3$ repeated. A third approximation was usually unnecessary. Finally, with $pK_1$ and $pK_3$ already established, the values of $pK_2$ derived from series 2 and series 4 were supplemented by a calculation of $pK_2$ from the measurements with solutions of series 3. Approximation methods were used in establishing the ionic and molecular concentrations and the ionic strength for each solution.

## Experimental

**Anhydrous Citric Acid.**—Anhydrous citric acid of special purity was obtained through the courtesy of Chas. Pfizer & Co., Inc. Samples of the acid were titrated with a carbonate-free solution of sodium hydroxide to the blue color of thymol blue. The acid was found to have a neutralization value of 100.03 ± 0.05%.

**Tripotassium citrate monohydrate** of reagent grade was crystallized twice from water. Before the first crystallization, the saturated solution of the salt was adjusted to $p$H 8.8 to 9.0 by the addition of small amounts of a solution of potassium hydroxide. The salt was dried at 110°. The weight of ash obtained when three 5-g. samples were heated in a muffle furnace at 800° averaged 100.04% of the theoretical, with a mean deviation of 0.06.

**Potassium dihydrogen citrate** was prepared by mixing aqueous solutions of citric acid and tripotassium citrate monohydrate in the correct proportions and crystallizing. The salt was dried in a vacuum at a temperature below 80°[15] and was analyzed by titration with standard alkali to the thymol blue end-point and by differential electrometric titration. Some difficulty was experienced in obtaining primary salt of the correct composition by repeated crystallization from water or by precipitation from an aqueous solution with ethanol. One sample of salt used appeared to contain about 0.3 mole % of citric acid. Corrections for this amount of free acid were applied to the experimental data.

**Dipotassium hydrogen citrate** could not conveniently be crystallized from water. Solutions of this salt were therefore prepared as required from solutions of citric acid and of the tertiary salt.

**Potassium chloride** was purified and fused in an atmos-

(14) Compare Case V of ref. 11.

(15) I. M. Kolthoff and J. J. Vleeschhouwer, *Biochem. Z.*, **179**, 410 (1926); **183**, 444 (1927).

TABLE I

E.M.F. OF THE CELL Pt; $H_2$, CITRATE BUFFER SOLUTION, KCl, AgCl; Ag FROM 0 TO 50°, IN INTERNATIONAL VOLTS

| $m$ | $E_0$ | $E_5$ | $E_{10}$ | $E_{15}$ | $E_{20}$ | $E_{25}$ | $E_{30}$ | $E_{35}$ | $E_{40}$ | $E_{45}$ | $E_{50}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Series 1. $H_3Ci$ ($m$), $KH_2Ci$ ($m$), KCl ($m$) | | | | | | | | | | | |
| 0.07936 | 0.46670 | 0.46722 | 0.46761 | 0.46794 | 0.46828 | 0.46861 | 0.46854 | 0.46866 | 0.46913 | ..... | 0.46952 |
| .07368[a] | .46884 | ..... | .46976 | ..... | .47058 | .47096 | .47119 | ..... | .47166 | ..... | .47196 |
| .06068 | .47376 | .47435 | .47493 | .47544 | .47593 | .47637 | .47685 | .47717 | .47747 | .47771 | .47794 |
| .05971 | .47410 | .47457 | .47521 | .47558 | .47594 | .47661 | .47694 | .47725 | .47763 | ..... | .47802 |
| .05700 | .47539 | ..... | .47659 | ..... | .47754 | .47807 | .47842 | ... | .47909 | ..... | .47959 |
| .05093[a] | .47835 | ..... | .47969 | ..... | .48074 | .48120 | .48175 | ..... | .48264 | ..... | .48337 |
| .04957 | ..... | ..... | ..... | ..... | ..... | .48210 | ..... | ..... | ..... | ..... | ..... |
| .04145 | .48345 | ..... | .48492 | ..... | .48617 | .48701 | .48743 | ..... | .48852 | ..... | .48938 |
| .04062 | .48386 | .48470 | .48552 | .48626 | .48697 | .48763 | .48814 | .48869 | .48922 | .48969 | .49014 |
| .03978 | ..... | ..... | ..... | ..... | ..... | .48802 | ..... | ..... | ..... | ..... | ..... |
| .03592 | .48700 | ..... | .48884 | ..... | .49032 | .49105 | .49166 | ..... | .49280 | ... | .49359 |
| .03212[a] | .49020 | ..... | .49186 | ..... | .49342 | .49406 | .49482 | ..... | .49610 | ..... | .49720 |
| .02488[a] | .49672 | ..... | .49868 | ..... | .50048 | .50136 | .50216 | ..... | .50370 | ..... | .50500 |
| .02163 | .49997 | .50126 | .50227 | .50332 | .50432 | .50538 | .50609 | .50694 | .50778 | .50854 | .50927 |
| .019524 | .50279 | .50402 | .50507 | .50614 | .50714 | .50811 | .50904 | .50993 | .51076 | ..... | .51235 |
| .014646[a] | ..... | ..... | .51294 | ..... | .51526 | .51640 | .51747 | ..... | .51953 | ..... | .52146 |
| .010042 | ..... | ..... | ..... | ..... | ..... | .52751 | ..... | ..... | ..... | ..... | ..... |
| .009788 | .52108 | .52271 | .52419 | .52564 | .52705 | .52844 | .52958 | .53081 | .53200 | .53316 | .53425 |
| .005074 | .53879 | .54080 | .54263 | .54448 | .54622 | .54793 | .54948 | .55107 | .55259 | .55411 | .55553 |
| Series 3. $KH_2Ci$ ($m$), $K_2HCi$ ($m$), KCl ($m$) | | | | | | | | | | | |
| .08126[a] | .54246 | .54424 | .54602 | .54776 | .54944 | .55122 | .55293 | .55460 | .55636 | .55806 | .55978 |
| .07708 | .54383 | .54562 | .54724 | .54896 | .55067 | .55283 | .55451 | .55625 | .55806 | .55979 | .56142 |
| .06109[a] | .54998 | .55192 | .55386 | .55574 | .55760 | .55964 | .56140 | .56327 | .56525 | .56700 | .56884 |
| .05322 | .55364 | .55561 | .55756 | .55962 | .56160 | .56373 | .56559 | .56757 | .56963 | .57154 | .57352 |
| .04516 | .55804 | .56017 | .56221 | .56438 | .56649 | .56866 | .57058 | .57271 | .57483 | .57684 | .57892 |
| .04039[a] | .56107 | .56319 | .56541 | .56756 | .56964 | .57192 | .57402 | .57610 | .58816 | .58030 | .58217 |
| .02577 | .57314 | .57562 | .57799 | .58040 | .58276 | .58532 | .58759 | .58994 | .59236 | .59469 | .59707 |
| .02085[a] | .57884 | .58139 | .58399 | .58640 | .58886 | .59146 | .59376 | .59614 | .59865 | .60115 | .60362 |
| .017848 | .58301 | .58569 | .58827 | .59083 | .59343 | .59612 | .59857 | .60116 | .60371 | .60620 | .60888 |
| .010551[a] | ..... | .59969 | .60278 | .60572 | .60854 | .61134 | .61413 | .61675 | .61972 | .62268 | .62540 |
| Series 5a. $K_2HCi$ ($m$), $K_3Ci$ ($3m$), KCl ($m$) | | | | | | | | | | | |
| .02087[a] | .66986 | .67448 | .67910 | .68374 | .68842 | .69336 | .69818 | .70320 | .70817 | .71317 | .71834 |
| .017807[a] | .67457 | .67928 | .68400 | .68888 | .69372 | .69871 | .70367 | .70870 | .71374 | .71888 | .72420 |
| .016687[a] | .67648 | .68128 | .68604 | .69092 | .69580 | .70092 | .70558 | .71092 | .71606 | .72117 | .72639 |
| .014133[a] | .68153 | .68639 | .69130 | .69626 | .70128 | .70650 | .71166 | .71677 | .72195 | .72726 | .73260 |
| .012517 | .68518 | .69017 | .69506 | .70018 | .70542 | .71062 | .71579 | .72109 | .72645 | .73180 | .73731 |
| .012489 | .68535 | .69038 | .69519 | .70029 | .70549 | .71074[a] | .71594 | .72132 | .72659 | .73197 | .73750 |
| .010578[a] | .69016 | .69526 | .70048 | .70566 | .71088 | .71615 | .72146 | .72687 | .73236 | .73790 | .74345 |
| .010045 | .69196 | .69715 | .70234 | .70749 | .71282 | .71807 | .72353 | ..... | ..... | ..... | ..... |
| .008453 | .69691 | .70195 | .70720 | .71263 | .71817 | .72373 | .72917 | .73471 | .74023 | .74563 | .75132 |
| .008183[a] | .69804 | .70332 | .70860 | .71398 | .71938 | .72489 | .73023 | .73588 | .74158 | .74729 | .75306 |
| .007056[a] | .70246 | .70784 | .71325 | .71876 | .72426 | .72980 | .73544 | .74109 | .74684 | .75265 | .75847 |
| .005823 | .70797 | .71346 | .71903 | .72454 | .73026 | .73596 | .74169 | ..... | ..... | ..... | ..... |
| .004739[a] | .71447 | .72008 | .72574 | .73147 | .73728 | .74316 | .74905 | .75497 | .76096 | .76702 | .77329 |
| .004117[a] | .71848 | .72426 | .73006 | .73589 | .74178 | .74766 | .75351 | .75960 | .76566 | .77186 | .77809 |
| .003524[a] | .72326 | .72908 | .73494 | .74086 | .74686 | .75288 | .75896 | .76508 | .77133 | .77758 | .78383 |
| .002194[a] | .73739 | .74345 | .74956 | .75574 | .76206 | .76839 | .77476 | .78122 | .78773 | .79428 | .80102 |
| .0013717[a] | .75103 | .75736 | .76374 | .77022 | .77685 | .78342 | .79010 | .79671 | .80357 | .81038 | .81731 |
| Series 5b. $K_2HCi$ ($m$), $K_3Ci$ (2.9795 $m$), KCl (2.7478 $m$) | | | | | | | | | | | |
| .03128[a] | ..... | ..... | ..... | ..... | ..... | .65292 | ..... | ..... | ..... | ..... | ..... |
| .02520 | ..... | ..... | ..... | ..... | ..... | .65992 | ..... | ..... | ..... | ..... | ..... |
| .02241 | ..... | ..... | ..... | ..... | ..... | .66387 | ..... | ..... | ..... | ..... | ..... |
| .02077[a] | ..... | ..... | ..... | ..... | ..... | .66644 | ..... | ..... | ..... | ..... | ..... |
| .017473 | ..... | ..... | ..... | ..... | ..... | .67209 | ..... | ..... | ..... | ..... | ..... |
| .013757 | ..... | ..... | ..... | ..... | ..... | .68026 | ..... | ..... | ..... | ..... | ..... |
| .010626 | ..... | ..... | ..... | ..... | ..... | .68899 | ..... | ..... | ..... | ..... | ..... |
| .005883 | ..... | ..... | ..... | ..... | ..... | .70880 | ..... | ..... | ..... | ..... | ..... |

[a] Each e. m. f. value is the average result of 2 cells (4 pairs of electrodes). Of 193 such measurements, 128 differed by 0.1 mv. or less, 46 by 0.1 to 0.2 mv. and 19 by more than 0.2 mv.

phere of nitrogen as described by the authors in an earlier publication.[16]

Air was removed from each cell solution by bubbling nitrogen through each solution flask for at least two hours. An air-free technique was used in filling the cells. Measurements at the 11 temperatures extended over a period of three days. The cells showed remarkable stability, however, and often resumed their initial values of electromotive force within a few hundredths of a millivolt at the conclusion of the series. The average change during this time was about 0.1 mv.

Two constant-temperature water-baths and two potentiometers were used. Temperatures were measured with a platinum resistance thermometer and with a calibrated mercury thermometer. The standards of electromotive force were two saturated Weston cells maintained in a temperature-controlled box of the type described by Mueller and Stimson.[17] The cells had been calibrated recently by this Bureau. Other details concerning the experimental methods are described elsewhere.[18]

## Results

The electromotive force of the cells containing solutions of series 1, 3 and 5, corrected as usual to 1 atm. partial pressure of hydrogen, is listed in Table I. The electromotive force of cells containing 25 solutions of potassium dihydrogen citrate of molality $m$ in 0.01 $m$ potassium chloride (series 2) was found to be a linear function of log $m$ at each temperature

$$E_t = a + b \log m \qquad (29)$$

The constants of equation (29) are given in Table II, together with the mean difference, $\Delta$, between observed and calculated values of the electromotive force. Five solutions were studied in series 4 to demonstrate, by comparison with the results from series 2, the internal consistency of the equations for overlapping. The data obtained at 25° are listed in Table III.

TABLE II

CONSTANTS OF EQUATION (29) FOR DATA OF SERIES 2

| $t$, °C. | $a$ | $b \times 10^3$ | $\Delta$, mv. |
|---|---|---|---|
| 0 | 0.55279 | −4.15 | 0.08 |
| 5 | .55488 | −4.22 | .07 |
| 10 | .55669 | −4.43 | .07 |
| 15 | .55863 | −4.52 | .09 |
| 20 | .56050 | −4.63 | .10 |
| 25 | .56226 | −4.80 | .07 |
| 30 | .56409 | −4.92 | .08 |
| 35 | .56591 | −5.04 | .12 |
| 40 | .56754 | −5.22 | .11 |
| 45 | .56942 | −5.32 | .12 |
| 50 | .57127 | −5.34 | .12 |

TABLE III

ELECTROMOTIVE FORCE OF THE CELL Pt; $H_2$, $K_2HCi$ ($m$), KCl ($m$), AgCl; Ag AT 25° (SERIES 4)

| $m$ | $E$, int. v. |
|---|---|
| 0.08063 | 0.59149 |
| .06031 | .60053 |
| .04007 | .61352 |
| .02036 | .63490 |
| .01000 | .65700 |

(16) G. D. Pinching and R. G. Bates, *J. Research Natl. Bur. Standards*, **37**, 311 (1946).

(17) E. F. Mueller and H. F. Stimson, *ibid.*, **13**, 699 (1934).

(18) R. G. Bates and S. F. Acree, *ibid.*, **30**, 129 (1943).

The determination of $pK_1$ is portrayed in Fig. 1, where $pK_1'$ at 25° computed from the measurements of series 1 is plotted as a function of the ionic strength. The curve at the bottom represents the value of $pK_1'$ obtained by equation (4) when $m_{HCi^=}$, which embodies the correction for the second dissociation step, is omitted.

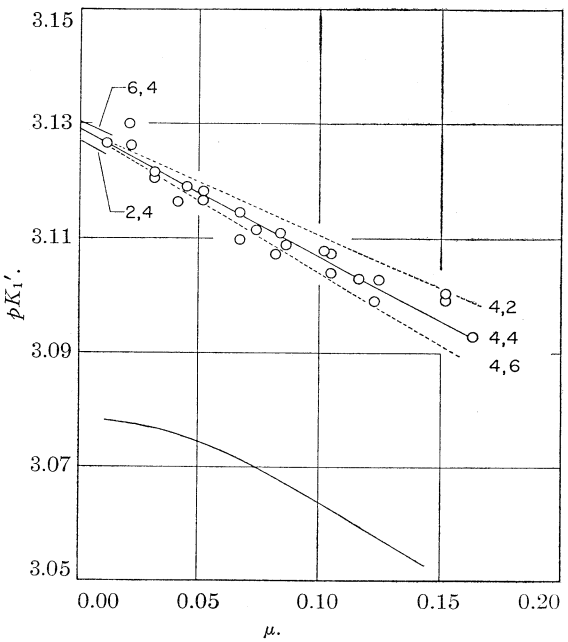



Fig. 1.—Determination of $pK_1$ from data of series 1.

Two numbers appear beside each of the upper curves of Fig. 1. The first of these represents the value of $a^*$ chosen for the computation of $m_H$ by equation (5), and the second is the value used to obtain $m_{HCi^=}$ by equations (7) and (8). Unfortunately, the first acidic dissociation is so strong that some uncertainty is introduced in the final $pK_1$ by the arbitrary choice of $a^*$ for the computation of the hydrogen-ion concentration by equation (5). Nevertheless, the value of $a^*$ used to compute the $K_2$ correction by equations (7) and (8) is of little concern, for the lines converge satisfactorily when the correction for the second dissociation step is made with different values of $a^*$, provided that $a^*$ of equation (5) does not vary. The three different intercepts at zero ionic strength show, however, that the value of $pK_1$ determined by extrapolation is dependent upon the value of $a^*$ chosen to compute the hydrogen-ion correction. When $a^*$ is changed from 4 to 6 or 2, $pK_1$ is, respectively, raised or lowered by 0.001 to 0.002. A value of 4 was used in the calculation at each temperature. It is therefore impossible to consider $pK_1$ more accurate than $\pm 0.003$. Inasmuch as the estimation of $m_H$ or $m_{OH}$ in a buffer solution from the electromotive force necessarily requires an assumption regarding activity coefficients, the accuracy of this electromotive-force method diminishes some-

what when $pK$ is less than 3 or greater than 11.[19]

The extrapolation of data obtained with the solutions in series 2 (mixtures of primary potassium citrate and potassium chloride) is shown in Fig. 2. The choice of $a^*$ in formulas (5) and (8) has, within reasonable limits, a negligible effect on the second term on the right of equation (9). The value of $a^*$ in equation (9) is chosen to yield a straight-line extrapolation. A value of 3 was found best suited to this purpose at each temperature, and, for convenience, this value was also used in equations (5) and (8).

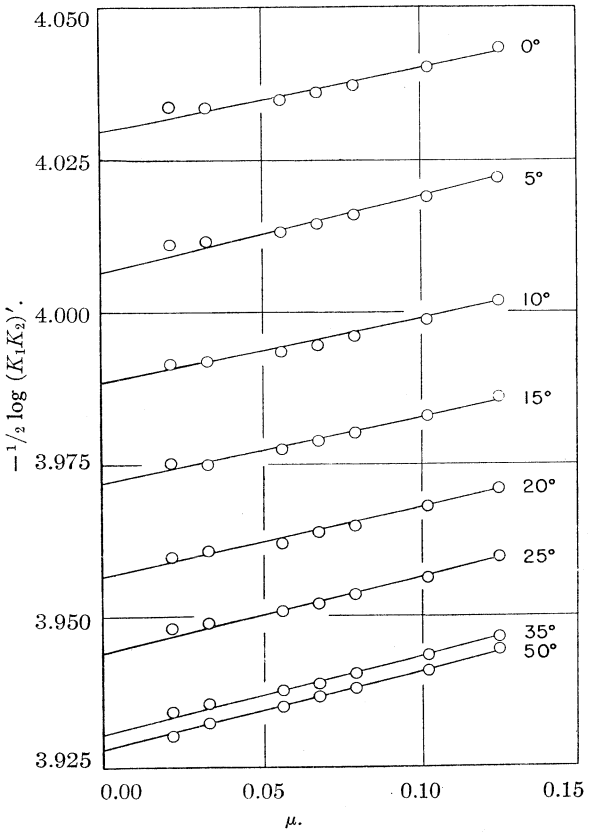



Fig. 2.—Determination of $K_1K_2$ from data of series 2.

Figure 3 is a plot of $pK_2'$, derived from the measurements of series 3 by equation (16), as a function of ionic strength at 25°. The extrapolation was made most conveniently, as the figure shows, with the use of $a^* = 6$ in equation (16). Inasmuch as the curves converged satisfactorily at zero ionic strength when different values of $a^*$ were used in equation (8) to compute the activity coefficients of formulas (18) and (19), $a^*$ was taken as 6 also in equation (8).

(19) In the analysis of some unpublished data, the senior author has found the extrapolated value of $pK$ for the first step in the dissociation of phosphoric acid to be altered by nearly 0.03 when $a^*$ used to compute $m_H$ is changed from 2 to 6. $pK_1$ is 2.12: L. F. Nims, THIS JOURNAL, **56**, 1110 (1934). A similar but much less pronounced effect has been reported by W. J. Hamer, G. D. Pinching, and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 539 (1945), for *o*-phthalic acid, a weaker acid than phosphoric.

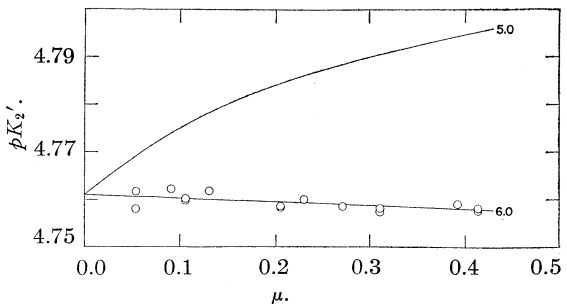



Fig. 3.—Determination of $pK_2$ from data of series 3. Number beside each curve indicates the value of $a^*$ used.

The essential agreement of $pK_2$ values calculated by the equations for overlapping from the measurements of series 8 and of series 4 is demonstrated in Fig. 4. These curves show, as well, the consistency of the results for $pK_1$ and $pK_3$ at this temperature, for the open circles were derived from $-\frac{1}{2}\log(K_1K_2)'$ of equation (9) together with $pK_1$, whereas the dots were obtained from $-\frac{1}{2}\log(K_2K_3)'$ of equation (20), together with $pK_3$. Curves a, b, and c correspond to 4.2, 4.7, and 5.2, respectively, for $a^*$ in formula (20), and d, e, and f were calculated by formula (9) with the use of 2, 3, and 4, respectively, for $a^*$. The value of $a^*$ in equations (5) and (8) is without appreciable effect on the concentration term of formula (20). Hence 4.7, the value yielding the best extrapolation of the data of series 4, was employed.

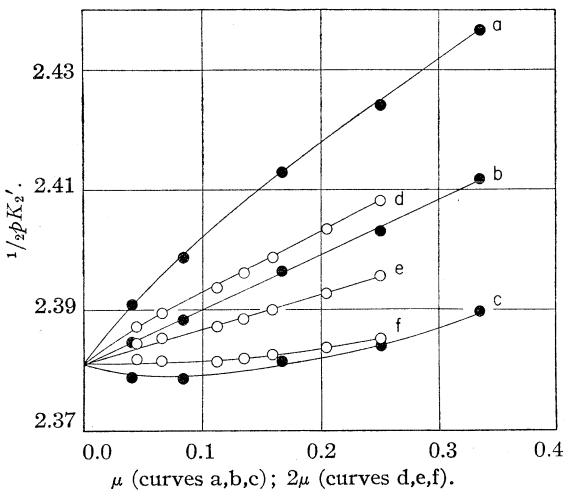



Fig. 4.—Determination of $pK_2$ from data of series 2 (curves d, e, and f) and of series 4 (curves a, b, and c).

The determination of $pK_3$ at 25* from an analysis of the results for buffer solutions of series 5 is illustrated in Fig. 5. The effect of a change of $a^*$ in equation (27) upon the extrapolation is indicated by the positions of the three solid lines labeled 5.6, 6.0 and 6.4. These were calculated from the data of series 5a, whereas series 5b yielded $pK_3'$ values represented by the dots, for

TABLE IV
VALUES OF $pK_1$, $pK_2$ AND $pK_3$

| t, °C. | $pK_1$ | $pK_2$ Series 2 | $pK_2$ Series 3 | $pK_2$ Average | $pK_3$ |
|---|---|---|---|---|---|
| 0 | 3.220 ± 0.0033 | 4.837 | 4.836 ± 0.0012 | 4.837 | 6.393 ± 0.0015 |
| 5 | 3.200 ± .0020 | 4.813 | 4.813 ± .0015 | 4.813 | 6.386 ± .0019 |
| 10 | 3.176 ± .0022 | 4.799 | 4.795 ± .0012 | 4.797 | 6.383 ± .0016 |
| 15 | 3.160 ± .0021 | 4.783 | 4.782 ± .0013 | 4.782 | 6.384 ± .0016 |
| 20 | 3.142 ± .0020 | 4.769 | 4.768 ± .0012 | 4.769 | 6.388 ± .0013 |
| 25 | 3.128 ± .0018 | 4.761 | 4.761 ± .0009 | 4.761[a] | 6.396 ± .0011 |
| 30 | 3.116 ± .0017 | 4.757 | 4.753 ± .0015 | 4.755 | 6.406 ± .0020 |
| 35 | 3.109 ± .0024 | 4.752 | 4.750 ± .0013 | 4.751 | 6.423 ± .0020 |
| 40 | 3.099 ± .0018 | 4.753 | 4.748 ± .0014 | 4.750 | 6.439 ± .0018 |
| 45 | 3.097 ± .0013 | 4.757 | 4.752 ± .0011 | 4.754 | 6.462 ± .0019 |
| 50 | 3.095 ± .0022 | 4.760 | 4.755 ± .0013 | 4.757 | 6.484 ± .0024 |

[a] 4.761 was also obtained from Series 4.

$a^* = 6.0$. The dashed line shows the course of the extrapolation of series 5a solutions when the correction for $K_2$ ($m_{H_2Ci^-}$ in formula (27)) is ignored. It is apparent that employment of a three-fold excess of tertiary salt over secondary salt has effectively reduced the magnitude of the correction. If $a^*$ in equation (8) is changed from 4 to 6, the second term on the right of formula (27) undergoes a change amounting to 0.0023 for an ionic strength of 0.45. Nevertheless, the differences disappear in the extrapolation to zero ionic strength.

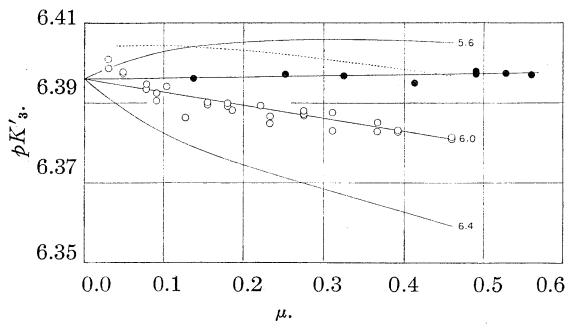



Fig. 5.—Determination of $pK_3$ from data of series 5a (open circles and curved lines) and of series 5b (dots).

The experimental points at the two lowest ionic strengths are seen to lie somewhat above the curves used for extrapolation. The departures correspond to 0.16, 0.20, 0.22, and 0.36 mv. and are, with one exception, only slightly larger than the estimated experimental error. If these data in dilute solutions are correct, the plots of $pK_3'$ with respect to ionic strength would have to depart from the paths predicted by the Hückel equation[20] and followed at the higher concentrations. For $a^*$ less than 5.8, these curves would have points of inflection at ionic strengths near 0.05 that cannot be justified in terms of the Hückel equation alone. The influence of the higher terms of the Debye–Hückel theory[21] upon the last term of equation (25) is large and could cause a rapid change in slope at concentrations below the lowest studied in this investigation. Unfortunately, the effect of higher terms at ionic strengths above 0.1 cannot readily be ascertained, and it is impossible to say whether the linearity of the plot between 0.05 and 0.57$\mu$ is consistent with a pronounced change of slope below $\mu = 0.05$.

The negative logarithms of the constants for the three steps in the dissociation of citric acid at the 11 temperatures are summarized in Table IV and plotted as a function of temperature in Fig. 6. The characteristic minimum in $pK$ is shifted to lower temperatures as the strength of the acidic group decreases. The values of $pK$ at 18, 25 and 37° are compared in Table V with earlier determinations based upon electromotive-force measurements of cells with liquid junction. The agreement among the values of

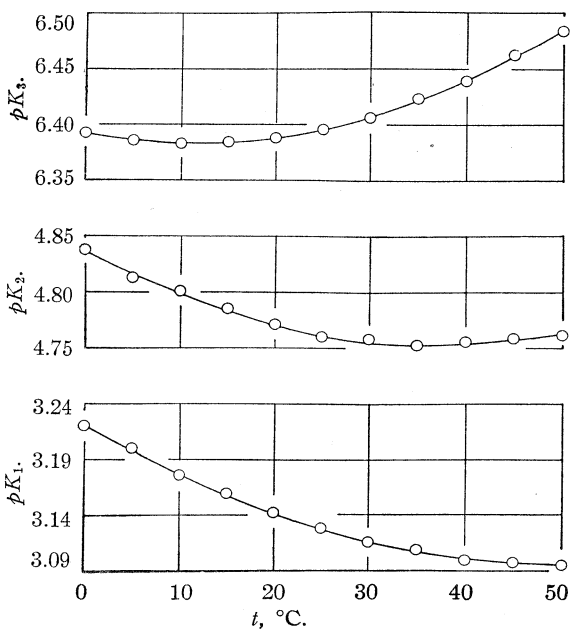



Fig. 6.—$pK_1$, $pK_2$ and $pK_3$ plotted as a function of temperature.

(20) E. Hückel, *Physik. Z.*, **26**, 93 (1925). This equation differs from (8) by inclusion of a term linear in ionic strength.

(21) T. H. Gronwall, V. K. LaMer and K. Sandved, *ibid.*, **29**, 358 (1928); V. K. LaMer, T. H. Gronwall and L. J. Greiff, *J. Phys. Chem.*, **35**, 2245 (1931).

$pK_2$ and among three of the four values of $pK_3$ is satisfactory, but $pK_1$ obtained from cells with liquid junction is lower by 0.05 to 0.07 than that found in this investigation.

TABLE V

COMPARISON OF $pK$ WITH THAT DERIVED FROM THE E. M. F. OF CELLS WITH LIQUID JUNCTION

| | Method | $t$, °C. | $pK_1$ | $pK_2$ | $pK_3$ |
|---|---|---|---|---|---|
| Simms[4] | Cells with l. j. | 25 | 3.08 | 4.74 | 6.26 |
| Kolthoff and Bosch[5] | Cells with l. j. | 18 | 3.075 | 4.752 | 6.407 |
| Bjerrum and Unmack[6] | Cells with l. j. | 18 | 3.087 | 4.769 | 6.398 |
| | | 25 | 3.057 | 4.759 | 6.400 |
| | | 37 | 3.042 | 4.747 | 6.424 |
| This investigation | Cells without l. j. | 18 | 3.149 | 4.774 | 6.386 |
| | | 25 | 3.128 | 4.761 | 6.396 |
| | | 37 | 3.105 | 4.750 | 6.429 |

## Thermodynamic Functions

The values of $pK_1$, $pK_2$ and $pK_3$ listed in Table IV were fitted by the method of least squares to an equation of the form[22]

$$-\log K_n = A/T + B + CT \qquad (30)$$

where $T$ is the temperature on the Kelvin scale (°C. + 273.16). The constants of equation (30) are given in Table VI. The average difference between the "observed" $pK_1$ at the 11 temperatures and the corresponding values calculated by equation (30) is 0.0010. For $pK_2$ and $pK_3$ the differences are, respectively, 0.0009 and 0.0007.[23]

TABLE VI

CONSTANTS OF EQUATION (30)

| Dissociation step | $A$ | $B$ | $C$ |
|---|---|---|---|
| 1 | 1255.6 | −4.5635 | 0.011673 |
| 2 | 1585.2 | −5.4460 | .016399 |
| 3 | 1814.9 | −6.3664 | .022389 |

The molal changes of free energy, $\Delta F^0$, of heat content, $\Delta H^0$, of entropy, $\Delta S^0$, and of heat capacity, $\Delta C_p^0$ that accompany each of the dissociation processes in the standard state are readily derived from the constants of equation (30).

$$\Delta F^0 = 2.3026\,R(A + BT + CT^2) \qquad (31)$$
$$\Delta H^0 = 2.3026\,R(A - CT^2) \qquad (32)$$
$$\Delta S^0 = 2.3026\,R(-B - 2CT) \qquad (33)$$
$$\Delta C_p^0 = 2.3026\,R(-2CT) \qquad (34)$$

where $R$, the gas constant, is 8.3127 int. j. deg.$^{-1}$ mole$^{-1}$. These thermodynamic quantities are summarized in Table VII.

The molal entropy change at 25° for the first step in the dissociation is −11.0 cal. deg.$^{-1}$, −19.8 for the second step, and −32.0 for the third.

(22) H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.*, **36**, 973 (1940).

(23) The first and third constants can be represented by the equation $-\log K_n = A/T + B + C \log T$ with average differences of 0.0018 and 0.0012, respectively, between "observed" and calculated $-\log K_n$. Inasmuch as equation (30) gave a better fit of the dissociation constants, it was used to calculate the thermodynamic functions. The differences between the thermodynamic quantities derived from the two equations are not large at 25° but are considerably greater at the extremes of the temperature range.

TABLE VII

THERMODYNAMIC QUANTITIES FOR THE DISSOCIATION OF CITRIC ACID AND OF THE PRIMARY AND SECONDARY CITRATE IONS

| °C. | $\Delta F^0$, int. j. mole$^{-1}$ | $\Delta H^0$, int. j. mole$^{-1}$ | $\Delta S^0$, int. j. deg.$^{-1}$ mole$^{-1}$ | $\Delta C_p^0$, int. j. deg.$^{-1}$ mole$^{-1}$ |
|---|---|---|---|---|
| Process: $H_3Ci = H^+ + H_2Ci^-$ | | | | |
| 0 | 16,843 | 7,362 | −34.7 | −122 |
| 5 | 17,023 | 6,746 | −37.0 | −124 |
| 10 | 17,214 | 6,118 | −39.2 | −127 |
| 15 | 17,415 | 5,480 | −41.4 | −129 |
| 20 | 17,627 | 4,831 | −43.6 | −131 |
| 25 | 17,852 | 4,170 | −45.9 | −133 |
| 30 | 18,087 | 3,498 | −48.1 | −135 |
| 35 | 18,333 | 2,815 | −50.4 | −138 |
| 40 | 18,590 | 2,121 | −52.6 | −140 |
| 45 | 18,859 | 1,416 | −54.8 | −142 |
| 50 | 19,138 | 700 | −57.1 | −144 |
| Process: $H_2Ci^- = H^+ + HCi^=$ | | | | |
| 0 | 25,284 | 6,921 | −67.2 | −171 |
| 5 | 25,634 | 6,055 | −70.4 | −175 |
| 10 | 25,993 | 5,174 | −73.5 | −178 |
| 15 | 26,368 | 4,278 | −76.7 | −181 |
| 20 | 26,760 | 3,365 | −79.8 | −184 |
| 25 | 27,153 | 2,437 | −82.9 | −187 |
| 30 | 27,589 | 1,494 | −86.1 | −190 |
| 35 | 28,027 | 534 | −89.2 | −193 |
| 40 | 28,481 | −441 | −92.4 | −197 |
| 45 | 28,951 | −1,432 | −95.5 | −200 |
| 50 | 29,437 | −2,438 | −98.6 | −203 |
| Process: $HCi^= = H^+ + Ci^{\equiv}$ | | | | |
| 0 | 33,429 | 2,762 | −112.3 | −234 |
| 5 | 34,000 | 1,581 | −116.6 | −238 |
| 10 | 34,594 | 378 | −120.8 | −243 |
| 15 | 35,209 | −846 | −125.2 | −247 |
| 20 | 35,846 | −2,092 | −129.4 | −251 |
| 25 | 36,503 | −3,359 | −133.7 | −256 |
| 30 | 37,182 | −4,647 | −138.0 | −260 |
| 35 | 37,883 | −5,957 | −142.3 | −264 |
| 40 | 38,604 | −7,288 | −146.6 | −268 |
| 45 | 39,348 | −8,641 | −150.8 | −273 |
| 50 | 40,114 | −10,015 | −155.1 | −277 |

The values for the first two steps are somewhat smaller than those found for other weak acids of the same electric type.[24] These functions have not heretofore been determined for a third dissociation step by methods free of the uncertainties of the liquid junction. However, $\Delta F^0$, $\Delta H^0$ and $\Delta S^0$ for all three steps in the dissociation of phosphoric and citric acids can be derived from the data for hydrogen–calomel cells with liquid junction at 18, 25 and 37° reported by Bjerrum and Unmack.[6] For the third group of phosphoric acid, $\Delta S^0$ is found to be approximately −35 cal. deg.$^{-1}$ mole$^{-1}$ at 27.5°, or about the same as for the third group of citric acid. The thermodynamic functions for the dissociation of citric acid were computed from the data of Bjerrum and Unmack and are compared in Table

(24) H. S. Harned and B. B. Owen, *Chem. Rev.*, **25**, 31 (1939).

VIII with those found in this investigation. The two sets of values are in good agreement. For these purposes, values in calories were obtained by dividing the number of int. j. by the conversion factor 4.1833.

TABLE VIII

COMPARISON OF THERMODYNAMIC FUNCTIONS AT 25°

| | $\Delta F^0$, cal. mole$^{-1}$ | $\Delta H^0$, cal. mole$^{-1}$ | $\Delta S^0$, cal. deg.$^{-1}$ mole$^{-1}$ |
|---|---|---|---|
| Bjerrum and Unmack, Step 1 | 4170 | 940[a] | −11 |
| Step 2 | 6492 | 408[a] | −20 |
| Step 3 | 8731 | −754[a] | −32 |
| This investigation, Step 1 | 4268 | 997 | −11.0 |
| Step 2 | 6491 | 583 | −19.8 |
| Step 3 | 8726 | −803 | −32.0 |

[a] Calculated from values at 27.5° with the use of $\Delta C_p^0$ found in this investigation.

It is possible to compare $\Delta C_p^0$ given in Table VII with that derived from the temperature coefficients of heats of dilution determined by Richards and Mair[25] and from the heat capacity measurements of Richards and Gucker[26] at 18°. From these data, Rossini[27] has evaluated the partial molal heat capacities of citric acid and of the three sodium citrates at infinite dilution. By combination of these with the partial molal heat capacities of hydrochloric acid and sodium chloride, also at infinite dilution,[28] $\Delta C_p^0$ for each dissociation step can be computed. The results are summarized in Table IX. The sum of $\Delta C_p^0$ for the three steps, given in the last line, represents $\Delta C_p^0$ for the process: $H_3Ci = 3H^+ + Ci^{\equiv}$. The agreement can be considered satisfactory, inasmuch as the calorimetric results may be in error by 5 cal.[27] and the E.m.f. determination by an amount at least as large.

TABLE IX

$\Delta C_p^0$ FOR THE DISSOCIATION OF CITRIC ACID AT 18°, IN CAL. DEG.$^{-1}$

| | Calorimetric | E. m. f., mv. |
|---|---|---|
| Step 1 | −41 | −31 |
| Step 2 | −37 | −44 |
| Step 3 | −54 | −60 |
| Process: $H_3Ci = 3H^+ + Ci^{\equiv}$ | −132 | −135 |

Coulombic forces are probably responsible for a considerable part of the change of $\Delta C_p^0$ from step 1 to step 3, for there is no marked change in chemical type. Consequently, the apparent irregularity of the results given in the second column of Table IX seems of doubtful significance. The calorimetric data for citric acid used in computing these results have not been corrected for acidic dissociation, nor have the detailed compositions of the citrate salt solutions been considered in obtaining the heat capacities at infinite dilution. However, these corrections have only a small effect upon the partial molal heat capacities of the salts at infinite dilution. On the other hand, the correction for acidic dissociation alters the value for citric acid itself by 5 to 10 cal., but the magnitude and direction of the change are such as to make more pronounced the irregularity in $\Delta C_p^0$ for the three dissociation steps, although the sum remains in good agreement with the results of the present investigation.

## Summary

The three dissociation constants of citric acid have been determined at intervals of 5° from 0 to 50° from measurements of the electromotive force of hydrogen–silver chloride cells without liquid junction. The resolution was accomplished by analysis of data for 84 buffer solutions grouped into five series, as follows: (1) mixtures of citric acid and primary potassium citrate, (2) primary potassium citrate, (3) mixtures of primary and secondary potassium citrates, (4) secondary potassium citrate, and (5) mixtures of secondary and tertiary potassium citrates. The changes of free energy, heat content, entropy, and heat capacity associated with the dissociation reactions in the standard state have been calculated from the dissociation constants at the eleven temperatures.

WASHINGTON, D. C. RECEIVED SEPTEMBER 24, 1948

(25) T. W. Richards and B. J. Mair, THIS JOURNAL, **51**, 740 (1929).

(26) T. W. Richards and F. T. Gucker, Jr., *ibid.*, **47**, 1876 (1925).

(27) F. D. Rossini, *Bur. Standards J. Research*, **4**, 313 (1930).

(28) F. D. Rossini, *ibid.*, **7**, 47 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

# Rates and Temperature Coefficients in the Hydrolysis of some Aliphatic Esters with a Cation Exchange Resin as the Catalyst[1]

BY VERNON C. HASKELL AND LOUIS P. HAMMETT

It has been noted recently[2] that acidic cation exchangers such as sulfonated coal and resinous exchangers containing sulfonic acid groups are effective as catalysts for various acid-catalyzed reactions. The practical advantages of an acidic catalyst which can be separated quickly and easily from a reactive solution are obvious. From the theoretical point of view this example of heterogeneous catalysis in which the number of active sites on the catalyst can be measured with some certainty possesses considerable interest. A comparison of the kinetics of a reaction catalyzed by a solid acid and by an acid in solution should for instance provide useful information about the mechanism of the heterogeneous process.

The acid-catalyzed hydrolysis of esters in 70% acetone, studied previously by others,[3] was selected for this work; the kinetics of the homogeneous reaction are of the first order in ester concentration, the reaction is easy to follow by titrating the carboxylic acid with standard alkali solution, and the rates are of conveniently measurable magnitude at room temperature. The solid-catalyzed reaction has an advantage that the catalyst acid need not be titrated if the carboxylic acid can be rinsed from the solid rapidly.

## Experimental

The esters used in the rate experiments were fractionated in a thirty-inch column of glass helices, the fractions retained in each case boiling in a range of not more than 0.2°. The following are the esters used with their sources, boiling points (uncor.) at atmospheric pressure, and saponification analyses: methyl acetate, 56.3°, 100.2%; ethyl acetate, Mallinckrodt, 76.6°, 99.5%; ethyl *n*-butyrate, Eimer and Amend, 121.0°, 100.5%; ethyl *n*-caproate, Eastman Kodak, 165.4°, 99.4%. U.S.P. grade acetone was boiled with alkaline permanganate and was fractionated in the above column, the fraction retained boiling over a range of not more than 0.2°.

Sulfonated coal and two synthetic resin cation exchangers were examined as possible catalysts. The resinous exchanger selected[4] was chosen not for its efficiency as a catalyst but because its exchange capacity could be measured within limits of ±0.3% by a simple titration with standard alkali. In contrast the attempts to titrate the other exchangers gave end-points which were neither sharp nor reproducible. Moreover the selected exchanger had a high exchange capacity (3.95 to 4.32 meq. per g. depending on the moisture content) and was available in the form of spherical particles which could be separated into narrow fractions with standard sieves giving samples of easily calculated external area. Fractions taken between 40 and 45 mesh sieves (average diameter 0.38 mm.) and between 80 and 100 mesh sieves (average diameter 0.16 mm.) were used in subsequent rate experiments.

Rate experiments were carried out in thermoregulated water-baths, the temperatures being 12.5, 25.0 and 37.5° with an estimated ±0.02° error. The 25.0 and 37.5° baths were of the conventional type. The 12.5° bath was as described elsewhere.[5]

The solid-catalyzed reactions were done with individual samples of acidic cation exchanger and proportionate volumes of reacting solution in sealed tubes of 12-mm. Pyrex tubing 10 to 15 cm. long. A shaker was designed to provide continuous agitation by tumbling the tubes over at about 30 r. p. m. A study of the effect of agitation showed that with this degree of agitation the rate of hydrolysis of methyl acetate was insensitive to the shaking rate.

Parallel experiments were performed with hydrochloric acid and the acidic cation exchanger respectively as catalysts. In the solid-catalyzed runs, six portions of exchanger weighing between 0.3 and 0.4 g. were delivered into the sample tubes described above. A reaction mixture was prepared from 70 ml. of acetone, 2 ml. of ester (except that 4 ml. of ethyl *n*-caproate was used) added from a volumetric pipet which was calibrated for each ester, and distilled water to make 100 ml. of solution. After agitation the solution was measured from a 10-ml. buret into the sample tubes in the proportion of 10 ml. of liquid per gram of catalyst. The tubes were immersed in ice water, sealed, and introduced into the shaker in the water-bath, the instant of introduction into the bath being taken as zero time. The tubes were broken at appropriate time intervals, the solid was separated by suction filtration through glass wool, and was rinsed with 75 to 100 ml. of distilled water over a period of about five minutes, and the solution with rinsings was analyzed for acid. Tests with acetic acid solutions showed that such rinsing recovered 99.8% of the acid. With the other acids, the reproducibility of the results was taken as evidence of the adequacy of the rinsing process. A 10-ml. buret was used for titration of the acid produced by the reaction and a correction was applied for the amount of base required to achieve a slightly pink shade with phenolphthalein in distilled water.

Measurements of exchange capacity were obtained from samples of catalyst which had been used in the rate experiment. After the rinse with distilled water the sample of exchange resin was transferred to an erlenmeyer flask and was mixed with 25 ml. of water and about 2 g. of solid sodium chloride. The acid was titrated to a phenolphthalein end-point with standard sodium hydroxide. The addition of an excess of sodium hydroxide and back-titration with standard hydrochloric acid gave agreeing results. The exchange capacity of the resin was the same before and after use as catalyst.

The experiments with hydrochloric acid as the catalyst were performed in 50 or 100 ml. volumetric flasks having glass stoppers. The reaction mixture was made up from 70 ml. of purified acetone, 10.00 ml. of 4.405 *N* hydrochloric acid and 2 ml. of ester (or 4 ml. of ethyl *n*-caproate) and distilled water to the 100-ml. mark. These were made up at 25° and were then transferred to the thermostat having the temperature desired. The change in

(1) Dissertation submitted by Vernon Charles Haskell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University, New York City, 1948.

(2) (a) Dierichs Report PB 866, Office of Technical Services, Dept. of Commerce, Washington, 1945; (b) Sussman, *Ind. Eng. Chem.*, **38**, 1228 (1946).

(3) (a) Davies and Evans, *J. Chem. Soc.*, 339 (1940); (b) Smith and Steele, THIS JOURNAL, **63**, 3466 (1941).

(4) Amberlite IR-120, kindly supplied by the Resinous Products and Chemical Co. This is reported (*Chem. Eng. News*, **26**, 1925 (1948)) to be a nuclear sulfonic acid cation exchange resin in bead form of high capacity and chemical stability.

(5) Price and Hammett, THIS JOURNAL, **63**, 2389 (1941).

volume was noted and the correction for change in concentration applied. The instant of addition of ester was taken as zero time but the initial point was not used except in experiments at 25°. In Fig. 1 the result of this technique is shown. The line for the hydrogen chloride-catalyzed hydrolysis of methyl acetate does not go through the origin. This does not affect the value of the specific rate which is obtained from the slope of the line.

## Calculations

The values of $k'$, the specific rate of the hydrolysis, were obtained by least squares methods from the slope of the plot of $\ln a/(a - x)$ against time, using points between zero and half-complete reaction. Here $a$ is the concentration of organic acid which would be obtained if the reaction were complete, calculated from the composition of the original reaction mixture, and $x$ is the concentration at time $t$. In the region used for the calculation these plots were linear within the precision of the measurements for both resin and hydrogen chloride-catalyzed reactions.

The $k'$ values were approximately proportional to the concentration of catalyst acid in the homogeneous reaction; they were found to be very closely proportional to the ratio of quantity of resin to volume of solution in the heterogeneous one. Therefore a rate constant $k$ was calculated in the former case by dividing $k'$ by the concentration of catalyst acid, and in the latter case by dividing $k'$ by the ratio of the number of moles of exchangeable acid in the resin to the volume of the solution. Since the $k$ values thus obtained depended somewhat on the concentration of hydrochloric acid and on the initial concentration of ester the same concentration of a given ester was used in both homogeneous and heterogeneous reactions and a correction was applied for the small difference in acid concentrations between the two systems.

The energies of activation $E$ were calculated using the equation

$$E = 2.303\ R\ \frac{T_1T_2}{T_1 - T_2} \log \frac{k_1}{k_2} \qquad (2)$$

$k_1$ being the rate constant at temperature $T_1$.

Relative entropies of activation were obtained from the expression[6]

$$\Delta\Delta S^{\ddagger} = 2.303\ R\ \frac{\Delta(T \log k_r/k_a)}{\Delta T} \qquad (3)$$

$k_r$ and $k_a$ being rate constants for the same ester with the resinous catalyst and hydrochloric acid respectively at temperature $T$.

## Results

The effect of agitation on the resin-catalyzed hydrolysis of methyl acetate in 70% acetone was studied by subjecting four similar samples of heterogeneous reaction mixture to different degrees of agitation. The results are given in Table I. The time of reaction was five hours. The relatively small difference between the amounts of acid production in the third and fourth samples showed that the limiting rate of reaction was being approached.

(6) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 115–119.

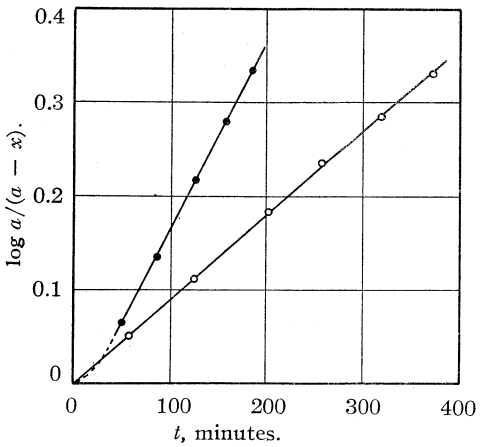



Fig. 1.—Hydrolysis of methyl acetate in 70% acetone at 37.5°: ● catalyst: 0.4350 $N$ HCl (started at 25°, then transferred to 37.5° bath); O catalyst: 1.000 g. resin (4.30 meg. $H_3O^+$/g.) in 10.33 ml. of solution.

TABLE I

THE EFFECT OF AGITATION IN THE HYDROLYSIS OF METHYL ACETATE WITH AN ACIDIC EXCHANGE RESIN AS THE CATALYST

| Sample | $n$ (Half-minute shaking periods per hour) | Vol. of NaOH (per g. catalyst) |
|---|---|---|
| 1 | 0.2 | 9.50 |
| 2 | 1 | 14.72 |
| 3 | 4 | 16.08 |
| 4 | 120 (continuous shaking) | 17.02 |

The effect of varying the ratio of exchange resin to solution was studied in order to determine the order of the reaction with respect to the solid catalyst. Six samples of resin were weighed and were delivered into separate glass tubes. A solution of ethyl acetate in 70% acetone was prepared and was added to the samples of exchange resin in such proportions that the weight of resin per unit volume of solution varied regularly. The sample tubes were sealed, introduced into the 25° bath

TABLE II

THE EFFECT OF WT. RESIN/VOL. SOLUTION ON THE SPECIFIC RATE OF HYDROLYSIS OF ETHYL ACETATE IN 70% ACETONE AT 25°

Exchange capacity of resin: 4.23 meq. $H_3O^+$/g. Calculated titer for complete reaction of 10 ml. solution: $a$ = 34.38 ml. of 0.05877 $N$ NaOH solution. Blank on 100 ml. distilled $H_2O$, 0.06 ml.

| Wt. resin, g. $W$ | Vol. soln., ml. $V$ | Vol. NaOH, ml. | $\log \frac{a}{a - x}$ | $10^5k'V/W$ |
|---|---|---|---|---|
| 0.122 | 3.67 | 2.30 | 0.0850 | 6.48 |
| .196 | 2.94 | 3.36 | .1718 | 6.53 |
| .2885 | 2.88 | 4.48 | .2560 | 6.49 |
| .404 | 3.03 | 5.69 | .3376 | 6.41 |
| .521 | 3.13 | 6.80 | .4274 | 6.50 |
| .597 | 2.985 | 7.20 | .5168 | 6.55 |

and were shaken continuously for 1515 minutes. Titration of the acid formed and substitution of the results into the integrated first order rate equation gave the data of Table II.

These results indicate that the specific rate of the resin-catalyzed reaction is proportional to the "concentration" of resin.

Preliminary experiments were performed to elucidate the effect of surface area of the catalyst resin on the rate of ester hydrolysis. For equal weights of samples the resin passing between 80 and 100 mesh sieves had 2.4 times the geometrical area ($4\pi r^2$) of the 40 to 45 mesh material. The rate constants obtained with the same liquid mixture of a given ester were as shown in Table III.

TABLE III

THE EFFECT OF PARTICLE SIZE ON THE RATE OF THE EXCHANGER-CATALYZED HYDROLYSIS OF ESTERS

| Ester | $10^6k$ 40–45 mesh | $10^6k$ 80–100 mesh | % Difference |
|---|---|---|---|
| Ethyl acetate | 14.8 | 15.4 | +4.1 |
| Ethyl *n*-butyrate | 2.27 | 2.42 | +6.3 |
| Ethyl *n*-caproate | 0.74 | 0.77 | +4.4 |

Subsequent rate experiments were done with 40 to 45 mesh particles only.

Figure 1 is a graph of data from two representative rate experiments. The slopes of the best straight lines obtained by least squares calculation were $1.98 \times 10^{-3}$ and $8.86 \times 10^{-4}$ for the hydrogen chloride- and resin-catalyzed reactions, respectively, and the corresponding rate constants were $1.75 \times 10^{-4}$ l. mol.$^{-1}$ sec.$^{-1}$ and $8.18 \times 10^{-5}$ l. mol.$^{-1}$ sec.$^{-1}$.

The rate data obtained at 25° are summarized in Table IV. The units for the $k$ values of Tables IV and V are l. mol.$^{-1}$ sec.$^{-1}$. Each rate experiment used in calculating catalyst efficiency and heats of activation was performed in duplicate.

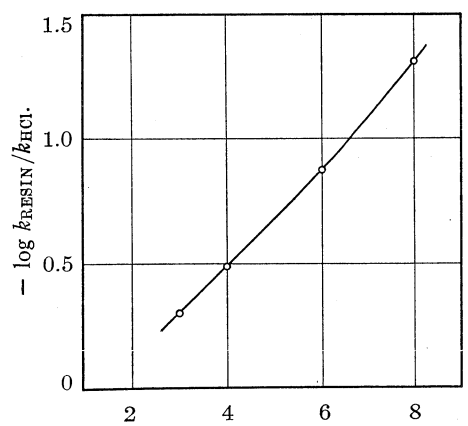



Fig. 2.—Efficiency of exchange resin compared with HCl as a catalyst, as a function of the chain length of the ester hydrolyzed in 70% acetone. Points in increasing order are for methyl acetate, ethyl acetate, ethyl *n*-butyrate and ethyl *n*-caproate.

TABLE IV

RATE CONSTANTS AT 25° FOR HYDROGEN CHLORIDE AND RESIN-CATALYZED HYDROLYSIS OF ESTERS

| Ester | $c_{ester}$, mol./l | $k_{HCl} \times 10^5$ | $k_{HCl} \times 10^5$ (cor.)[a] | $k_{Resin} \times 10^5$ | $k_{Resin}/k_{HCl}$ |
|---|---|---|---|---|---|
| | $c_{HCl}$: 0.4405 mol./l. | | | | |
| Methyl acetate | 0.2483 | 5.45 | 5.41 | 2.70 | |
| | | 5.44 | 5.40 | 2.74 | 0.502 |
| Ethyl acetate | 0.2020 | 4.61 | 4.58 | 1.49 | |
| | | 4.66 | 4.63 | 1.51 | 0.326 |
| Ethyl *n*-butyrate | 0.1504 | 1.92 | 1.91 | 0.255 | |
| | | 1.91 | 1.90 | 0.256 | 0.134 |
| Ethyl *n*-caproate | 0.2401 | 1.53 | 1.52 | 0.0741 | |
| | | 1.53 | 1.52 | 0.0749 | 0.0490 |

[a] The correction was necessary because the acidity of the hydrogen chloride-catalyzed experiments was 6% higher than that of the resin-catalyzed experiments. A 16% decrease in $c_{HCl}$ lowered the rate constant for the hydrolysis of methyl acetate 2.2%. When account is taken of the moisture content of the exchange resin the concentration of water in the reaction mixture containing resin is greater than that in the reaction mixture containing hydrochloric acid by a factor of 1.08. No correction was applied. Because of this and because of possible medium effects associated with the solid catalyst more significance is attached to the variations of the $k$-ratios with the size of the ester molecules than to the actual values of the $k$-ratios.

Figure 2 shows the variation of the efficiency of the solid catalyst with the length of the ester molecule.

Methyl acetate and ethyl *n*-butyrate were hydrolyzed at 37.5° and at 12.5° and the heats and entropies of activation were calculated. The results are shown in Table V.

TABLE V

RATE CONSTANTS, ENERGIES AND ENTROPIES OF ACTIVATION FOR THE HYDROLYSIS OF METHYL ACETATE AND ETHYL *n*-BUTYRATE IN 70% ACETONE

| | Methyl acetate | | Ethyl *n*-butyrate | |
|---|---|---|---|---|
| | Exchange resin | HCl | Exchange resin | HCl |
| $10^5k_{12.5}$ | 0.881 | 1.59 | 0.0866 | 0.577 |
| | 0.881 | 1.57 | 0.0863 | 0.586 |
| $10^5k_{25}$ | 2.70 | 5.45 | 0.255 | 1.92 |
| | 2.74 | 5.44 | 0.256 | 1.91 |
| $10^5k_{37.5}$ | 8.15 | 17.3 | 0.722 | 5.96 |
| | 8.18 | 17.5 | 0.718 | 5.93 |
| $E_{25-12.5}$[a] | 15,300 | 16,800 | 14,700 | 16,100 |
| $E_{37.5-25}$ | 16,200 | 17,100 | 15,200 | 16,700 |
| $\Delta\Delta S^{\ddagger}_{25-12.5}$[b] | −6.5 | | −9.0 | |
| $\Delta\Delta S^{\ddagger}_{37.5-25}$ | −4.5 | | −8.9 | |

[a] Calories. [b] $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}_{Resin} - \Delta S^{\ddagger}_{HCl}$ (cal./deg.).

**An Absorption Experiment.**—When the air-dry exchange resin was mixed with 70% acetone there was 40% increase in the apparent volume of the resin. It was of interest to determine if there was selective absorption of the components of solutions of fatty acids in 70% acetone.

Solutions of caproic acid and of acetic acid in 70% acetone were prepared; these were mixed with the exchange resin in the proportion of 25 ml. of solution to 10 g. of air-dry resin. After agitation and settling of the solid, 1-ml. samples of

the supernatant liquid were removed, added to 50 ml. of distilled water, and titrated with standard alkali in the presence of phenolphthalein. Blanks of 1 ml. from 70% acetone in contact with resin required 0.10 ml. of 0.05185 $N$ alkali for neutralization just after mixing and 0.14 ml. after ten days in contact with the resin. Table VI shows the results.

TABLE VI

CONCENTRATION OF ACID BEFORE ($C_{Acid}$) AND AFTER ($C'_{Acid}$) ABSORPTION OF AQUEOUS ACETONE SOLUTIONS OF CARBOXYLIC ACIDS BY AN EXCHANGE RESIN

"Concentration" of resin: 0.40 g. per ml. of solution

| Acid solution | $C_{Acid}$ | $C'_{Acid}$ | Increase, % |
|---|---|---|---|
| Caproic acid | 0.312 | 0.383 | 22.8 |
| Acetic acid | .353 | .410 | 16.2 |

These results show that the solvent is absorbed in preference to the acid in the case of caproic acid and acetic acid, and that acetic acid is absorbed to a greater degree than caproic acid.

## Errors

At 25° the average deviation of the mean of the $k$ values is ±0.2% for hydrogen chloride-catalyzed experiments and ±0.5% for resin-catalyzed experiments. Residual errors in temperature, concentration of ester, concentration of hydrochloric acid and other factors are expected to increase the precision measure in the $k$ values to ±1% for both hydrogen chloride and resin-catalyzed reactions.

The precision measure for energies of activation is ±200 calories per gram mole, and the precision measure for relative entropies of activation is ±1 calorie per degree.

## Discussion

Whatever the detailed mechanism of the catalysis of hydrolysis by strong aqueous acids, there is every reason to suppose it to be the same for the resin, a strong acid of essentially infinite molecular weight, as for the homogeneous acid. It involves therefore for both a positively charged transition state in which a proton has been transferred to the ester molecule from the oxonium ion of the acid. If, as the present results indicate, diffusion rates are fast enough so that the chemical process is rate determining, the difference in rate between heterogeneous and homogeneous cases depends upon the fact that, in the former, both the oxonium ion and the charged transition state are restricted by electostatic forces to the immediate neighborhood of the negatively charged $RSO_3^-$ groups in the resin. More specifically the ratio $k_{resin}/k_{HCl}$ is determined by the difference

$$F^{\ddagger}_{resin} - F^{\ddagger}_{HCl} - F^{\circ}_{resin} + F^{\circ}_{HCl}$$

in which the $F^{\ddagger}$'s are the standard free energies of the transition states for the resin and hydrogen chloride cases and the $F^{\circ}$'s are the standard free energies of oxonium ion in the resin system and in the hydrochloric acid solution, respectively.

This quantity is observed to be positive in the cases studied and increases rapidly and nearly linearly (Fig. 2) with increasing chain length of the ester molecule. The positive free energy difference results from negative values of the corresponding heat content and entropy differences, the latter being therefore predominant in effect. The heat content difference of about −1.3 kcal. is little if any affected by chain length, the entropy difference changes from −5.5 cal./deg. with methyl acetate to −9.0 with ethyl $n$-butyrate. It appears therefore that the major factor in the effects observed is the loss in internal entropy of the ester molecule accompanying its fixation on the skeleton of the resin catalyst in the formation of the transition state. This conclusion is consistent with the fact that the longer chain ester, having more internal entropy, loses more in the formation of the transition state. Translational entropies, on the other hand, and all effects which depend on the electrical charge of the transition state should to a first approximation cancel out between the transition state and the oxonium ion.

This interpretation of the kinetic results is related to the one given by Barrer[7] for the equilibrium in the absorption of hydrocarbons by zeolites. It is supported by the results reported in Table VI which show that the longer chain molecule caproic acid is less strongly absorbed by the ion exchange resin than the shorter chain molecule acetic acid.

Effects of this sort may very well be important in the general problem of heterogeneous catalysis and in that of enzyme action, although there is no exact correspondence, either qualitative or quantitative, between the net effect observed in these cases and those reported here for the exchange resin catalysis. Thus the energy of activation for the catalysis by yeast saccharase of the inversion of saccharose near the optimum $p$H is 17 kcal. less than for the hydrochloric acid catalyzed reaction,[8] and low temperature coefficients have also been observed[9,10] for other enzyme catalyzed reactions. Further the efficiency of pancreatic lipase in the hydrolysis of esters in water increases with chain length from ethyl acetate to ethyl $n$-butyrate.[10]

It appears however that the balance of conflicting effects may lead to considerable difference in the behavior of the catalysis by an ion exchange resin according to the particular resin used and the medium. Thus Thomas and Davies[11] have reported that the resin Amberlite IR-100 is more efficient than hydrochloric acid for the hydrolysis of aliphatic esters in water and that its efficiency increases with increasing chain length. And Levesque and Craig[12] using Amberlite IR-100 for the

(7) Barrer and Ibbitson, *Trans. Faraday Soc.*, **40**, 195 (1944); Barrer, *ibid.*, p. 374; *Ann. Rep. Chem. Soc.*, **41**, 31 (1944).

(8) Nelson and Bloomfield, THIS JOURNAL, **46**, 1025 (1924).

(9) Sumner and Somers, "Chemistry and Methods of Enzymes," Academic Press, New York, N. Y., 1947, p. 18.

(10) Kastle and Loevenhart, *Am. Chem. J.*, **24**, 491 (1900).

(11) Thomas and Davies, *Nature*, **159**, 372 (1947).

(12) Levesque and Craig, *Ind. Eng. Chem.*, **40**, 96 (1948).

esterification of oleic acid with *n*-butanol obtained specific rates very nearly proportional to the external area of the resin particle employed, indicating that only acid groups near the exterior of the particles are active catalytically. The present results on the effect of particle size of resin, obtained with much smaller molecules, also indicate a superiority of the external acid groups, but one which is of almost negligible total effect. One might attribute this effect to the intrusion of diffusion into the interior of the particle as a significant factor in the control of the over-all rate except that the effect of particle size is unchanged by a change in the size of the reacting molecule which produces a large change in the over-all rate.

## Summary

A method in which reproducible rate constants can be obtained has been developed for following the hydrolysis of esters in 70% acetone with a cation exchange resin as the catalyst. A comparison of the catalytic effect of the exchange resin with that of hydrochloric acid showed that the free energy of activation relative to the hydrogen chloride-catalyzed reaction increased almost linearly with the chain length of the ester in the series methyl acetate, ethyl acetate, ethyl *n*-butyrate, ethyl *n*-caproate at 25°.

Measurements of the temperature coefficients of the rates of hydrolysis of methyl acetate and of ethyl *n*-butyrate showed that the lower rates with the exchange resin were accompanied by lower entropies of activation and lower heats of activation than with hydrochloric acid, the former effect being strongly dependent on the chain length of the ester, the latter relatively independent.

The major factor determining these effects appears to be the loss in internal entropy of the ester molecule which accompanies its fixation on the skeleton of the resin catalyst in the formation of the transition state.

NEW YORK, N. Y. RECEIVED SEPTEMBER 3, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ILLINOIS INSTITUTE OF TECHNOLOGY AND RCA LABORATORIES]

# Absorption Spectra of Some Double Salts Containing Bivalent Cobalt[1]

BY MELVIN L. SCHULTZ[2]

The absorption spectra of crystals of five double salts of cobaltous chloride all containing the tetrahedral $CoCl_4^{--}$ ion have been shown[3] to consist, at room temperature, of a large number of relatively narrow bands. The details of these spectra were found to be almost completely independent of the identity of the cation and therefore it was concluded that the absorption was characteristic of the complex ion.

Prominent among the wave number differences of adjacent bands in these spectra is one of approximately 370 cm.$^{-1}$. This frequency was identified tentatively as one of the characteristic frequencies of the $CoCl_4^{--}$ ion. The validity of this interpretation has, in the present work, been investigated by studying the spectra of two salts, $(PyH)_2CoBr_4$ and $(QuH)_2CoBr_4$,[4] containing the corresponding bromo- complex ion. Substitution of one halogen for another would be expected to lead to changes in frequency differences if the structure of the spectrum is determined by the coupling of vibrations of the complex with electronic transitions.

Such an effect has, in fact, been observed by Brode and Morton[5] for solutions of cobaltous halides in concentrated aqueous solutions of the corresponding hydrogen halides.[6] They found decreasing separations of bands in passing from the chloride to the bromide and to the iodide. Their analysis is subject to some uncertainty, however, since the absorption bands of the solutions are broad and incompletely resolved. The comparison in the case of the crystals is much more clear cut since the bands are considerably sharper and therefore more completely resolved. The expected frequency shifts have been found for many, but not all, of the bands in the spectra of the crystals.

Confirmation of the hypothesis that the detailed structure of the spectra of these complexes of bivalent cobalt is determined essentially by the configuration of the complex ion was obtained by studying the absorption spectrum of crystals of $2(en\ H_2)Cl_2 \cdot CoCl_2$.[7] Although the structure of the complex ion in this compound has not been determined, the coördination number of cobalt is probably six[8] with probably an octahedral arrangement of chloride ions about the central co-

(1) The spectra described here were photographed in 1943 while the author was a member of the staff of Illinois Institute of Technology. The plates obtained were measured and the present paper was written after the author became associated with RCA Laboratories.

(2) Present address: RCA Laboratories Division, Radio Corporation of America, Princeton, N. J.

(3) M. L. Schultz and E. F. Lilek, THIS JOURNAL, **64**, 2748 (1942).

(4) The abbreviations Py, Qu and en represent pyridine, quinoine and ethylenediamine, respectively.

(5) W. R. Brode, *Proc. Roy. Soc.* (*London*), **118A**, 286 (1928); W. R. Brode and R. A. Morton, *ibid.*, **120A**, 21 (1928).

(6) These solutions also contain the $CoX_4^{--}$ ion; see reference 3.

(7) Due to lack of time, this spectrum was only incompletely investigated. Structure in the region of very strong absorption in the red was not resolved since sufficiently thin absorbing layers were not used.

(8) J. Meyer and K. Hoehne, *Z. anorg. allgem. Chem.*, **222**, 161 (1935).

balt ion. Although the spectrum of this salt shows the same general arrangement of groups of bands as do the tetrahalide complexes, the detailed structure of the groups is completely different.

## Experimental

The experimental methods employed were, with some modifications, those previously described.[3] The double salts used were prepared according to published methods.[8,9] In each case, the composition of the preparation was established by the determination of halogen by precipitation and weighing as silver halide.

When large single crystals of the double salts could be obtained these were mounted in Canada balsam between microscope slides and cover glasses. For $(en\ H_2)_2CoCl_6$ which could not be obtained as large crystals or for very thin absorbing layers of the bromides, the micro crystals were suspended in Canada balsam and mounted between slides. In this manner, the transparency of the preparations was increased and, in addition, the crystals were protected from attack by water vapor in the atmosphere. In the case of $(QuH)_2CoBr_4$, crystals obtained from hydrobromic acid solution and material prepared by recrystallization from ethyl alcohol solution gave identical spectra.

The wave lengths of the band maxima were determined from microphotometer tracings, made with a Leeds and Northrup recording microphotometer, of the comparison spectra produced by either a copper arc or a neon discharge tube and of the absorption spectra. Except for the very weak or very diffuse bands, the uncertainties in the wave numbers calculated from the measured wave lengths are about 10 cm.$^{-1}$. In the extreme red where the dispersion of the spectrograph was small, the uncertainty is somewhat greater.

## Results and Discussion

The wave numbers and estimated relative intensities of the observed band maxima for the two bromides are listed in Table I. Except for differences in the region between 18,100 cm.$^{-1}$ and 20,300 cm.$^{-1}$ and for the very weak doublet at 25,300 cm.$^{-1}$, which was observed for $(PyH)_2CoBr_4$ but not for $(QuH)_2CoBr_4$, there is a complete correspondence between the two spectra. The differences in wave lengths of corresponding bands are small and are of the same order of magnitude as the uncertainties in the determination of the band positions. The differences between the two spectra mentioned above represent the only effects of the identity of the cation within the portion of the spectrum studied. A similar situation was observed in the spectra of the chlorides where the specific cation effects appeared between 19,200 cm.$^{-1}$ and 20,600 cm.$^{-1}$.

In order to facilitate comparison of the bromide and chloride spectra, the slight differences among the spectra of the individual salts with a common anion have been neglected and a composite chloride and a composite bromide spectrum have been obtained by averaging wave number values and intensities of corresponding bands. These composite spectra are summarized in Table II and are illustrated in Fig. 1. For convenience, the bands have been numbered consecutively beginning with the one of longest wave length and, in addition, have been classified into groups designated by Roman numerals. In the figure, the band centers are represented by the positions of the vertices of the triangles representing the bands, the relative intensities by the altitudes of the triangles and the approximate band widths by the lengths of their bases. The solid triangles represent bands whose positions are independent of the identity of the cation while the open triangles represent those which are not. For comparison with the tetrahalide spectra, that portion of the spectrum of $(en\ H_2)_2CoCl_6$ which was photographed is also illustrated in the figure. The wave numbers and relative intensities of the bands in this spectrum are listed in Table III.

It is apparent from an examination of Fig. 1, that Groups I and II of the two tetrahalide spectra are essentially identical except for a shift of about 700 cm.$^{-1}$ of the entire bromide spectrum to the red relative to that of the chloride; for small differences in the spacing of the bands and for

TABLE I

ABSORPTION BANDS OF COBALT(II) BROMIDE DOUBLE SALTS

| $(PyH)_2CoBr_4$ | | $(QuH)_2CoBr_4$ | |
|---|---|---|---|
| $\nu$, cm.$^{-1}$ | Intensity | $\nu$, cm.$^{-1}$ | Intensity |
| 13604 | 10 | 13625 | 10 |
| 14193 | 7 | 14217 | 9 |
| 14876 | 7 | 14903 | 7 |
| 15170 | 8 | 15179 | 8 |
| 15538 | 9 | 15506 | 9 |
| 15828 | 7 | 15789 | 7 |
| 16597 | 5 | 16542 | 3 |
| 16985 | 4 | 16974 | 4 |
| 17276 | 6 | 17239 | 5 |
| 17669 | 4 | 17589 | 3 |
| 17866 | 5 | 17793 | 3 |
| 18250 | 3 | | |
| | | 18490 | 2 |
| 18611 | 3 | | |
| | | 19066 | 1 |
| 19197 | 2 | | |
| 19981 | 1 | | |
| 20702 | 4 | 20643 | 4 |
| 21181 | 6 | 21139 | 6 |
| 21482 | 6 | 21450 | 6 |
| 21812 | 4 | 21786 | 4 |
| 22287 | 1 | 22216 | 1 |
| 22993 | 5 | 22972 | 5 |
| 23432 | 4 | 23411 | 4 |
| 23594 | 3 | 23562 | 3 |
| 25205 | 1 | | |
| 25360 | 1 | | |

(9) E. G. V. Percival and W. Wardlaw, *J. Chem. Soc.*, 1505 (1929).

TABLE II

COMPOSITE SPECTRA OF COBALT(II) TETRAHALIDE COMPLEX IONS

| Group | Band | $CoBr_4^{--}$ $\nu$, cm.$^{-1}$ | Int. | $CoCl_4^{--}$ $\nu$, cm.$^{-1}$ | Int. |
|---|---|---|---|---|---|
| I | 1 | 13615 | 10 | 14265 | 10.0 |
| | 2 | 14205 | 8 | 15009 | 10.0 |
| | 3 | 14890 | 7 | 15462 | 8.2 |
| | 4 | 15175 | 8 | 15829 | 9.2 |
| | 5 | 15522 | 9 | 16277 | 8.4 |
| | 6 | 15809 | 7 | 16651 | 7.4 |
| II | 7 | 16570 | 4 | 17248 | 3.6 |
| | 8 | 16980 | 4 | 17684 | 2.4 |
| | 9 | 17258 | 5.5 | 18066 | 3.4 |
| | 10 | 17629 | 3.5 | 18618 | 5.4 |
| | 11 | 17830 | 4 | 18878 | 6.0 |
| III | 12 | 18250[a] | 3 | 19279[c] | 2.3 |
| | 13 | 18490[b] | 2 | | |
| | 14 | 18611[a] | 3 | 19643 | 3.0 |
| | 15 | 19066[b] | 1 | | |
| | 16 | 19197[a] | 2 | 20250[d] | 1.3 |
| | 17 | 19981[a] | 1 | | |
| IV | 18 | 20673 | 4 | | |
| | 19 | 21160 | 6 | 21898 | 2.8 |
| | 20 | 21466 | 6 | 22162 | 3.6 |
| | 21 | 21799 | 4 | 22452 | 3.4 |
| | 22 | 22252 | 1 | 22819 | 0.4 |
| V | 23 | 22983 | 5 | 24025 | 1.0 |
| | 24 | 23422 | 4 | 24480 | 0.8 |
| | 25 | 23578 | 3 | | |
| VI | 26 | 25205[a] | 1 | | |
| | 27 | 25360[a] | 1 | | |

This band observed only for [a] $(PyH)_2CoBr_4$. [b] $(QuH)_2CoBr_4$. [c] $Cs_3CoCl_5$, $(PyH)_2CoCl_4$, and $(QuH)_2CoCl_4 \cdot H_2O$. [d] All of the tetrachloride double salts except $Cs_2CoCl_4$.

some differences in relative intensities. The groups lying at higher frequencies show more pronounced differences but nevertheless, the correspondence between the two spectra is sufficiently close to justify the conclusion that both spectra are due to absorbing groups having the same configuration.

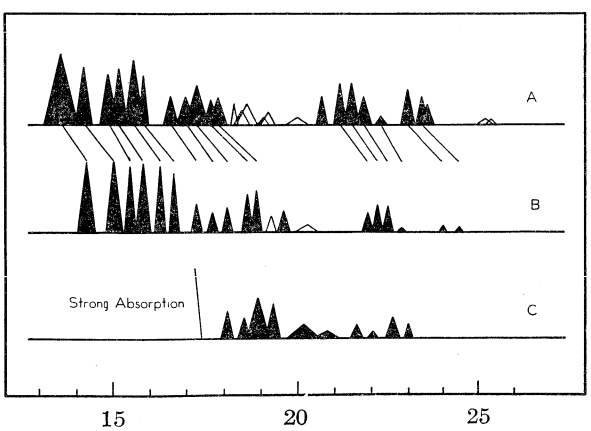



Fig. 1.—Absorption bands of cobalt(II) complex ions: A, $CoBr_4^{--}$; B, $CoCl_4^{--}$; C, $CoCl_6^{4-}$.

TABLE III

ABSORPTION BANDS OF $(en\ H_2)_2CoCl_6$

| Group | $\nu$, cm.$^{-1}$ | Intensity |
|---|---|---|
| I | 17400[a] | |
| II | 18082 | 4 |
| | 18529 | 3 |
| | 18919 | 6 |
| | 19320 | 5 |
| III | 20144 | 2 |
| | 20773 | 1 |
| IV | 21603 | 2 |
| | 22036 | 1 |
| | 22579 | 3 |
| | 23001 | 2 |

[a] Short wave length edge of unresolved group.

On the other hand, the spectrum of $(en\ H_2)_2CoCl_6$ is distinctly different. For it, Groups II and IV are similar in structure (which is not the case for the tetrahalides) and consist of doublets with an average separation of 426 ± 14 cm.$^{-1}$ and with similar relative intensities within each doublet. In each group the less intense doublet occurs displaced to the long wave length side of the more intense one. This displacement is 814 cm.$^{-1}$ in Group II and 970 cm.$^{-1}$ in Group IV.

The comparative sharpness of most of the bands in these spectra suggests that for the transitions responsible for the observed absorption both the initial and final states are rather effectively shielded from perturbing effects of surrounding ions. The absorption is probably due to an unpaired electron in one of the 3d orbitals of the cobalt ion and the shielding is provided by the electron clouds of the coördinated halide ions. The complexity of the spectra may be due to the multiplet nature of the energy levels of the cobalt ion or to the coupling of vibrations characteristic of the complex with the electronic transitions or possibly to both. If vibrational structure is present, then, as has been pointed out above, substitution of one halogen by another should give rise to changes in the characteristic frequencies. The direction and magnitude of such changes will be determined both by the masses of the halide ions and by the force constants of the cobalt–halogen bonds. Examination of Table II and Fig. 1 reveals that a number of intervals between adjacent bands in Groups I and II are smaller in the spectrum of the bromide than in the spectrum of the chloride. This is to be expected if vibrational structure is present and if the force constants of the Co–Br and Co–Cl bonds are not very different in magnitude.

All of the bands, with the exception of number 7, in these two groups can be represented by the energy level diagrams shown in Fig. 2 in which the transitions representing observed bands are indicated by arrows numbered to correspond to Table II. The ground state consists of two levels separated by 263 cm.$^{-1}$ for the bromide and by 346 cm.$^{-1}$ for the chloride. The excited states are also doublets separated by about 600 cm.$^{-1}$ for the

bromide and by about 800 cm.$^{-1}$ for the chloride. The comparison between wave numbers calculated from the term values shown in the figure and the observed wave numbers of these bands is made in Table IV. For the bromide the average difference between calculated and observed values is 12 cm.$^{-1}$ while for the chloride it is 17 cm.$^{-1}$.

TABLE IV

COMPARISON OF CALCULATED AND OBSERVED WAVE NUMBERS

| Band | $\nu$ calcd. | $CoBr_4^{--}$ $\nu$ obs. | Diff. | $\nu$ calcd. | $CoCl_4^{--}$ $\nu$ obs. | Diff. |
|---|---|---|---|---|---|---|
| 1 | 13615 | 13615 | 0 | 14265 | 14265 | 0 |
| 2 | 14205 | 14205 | 0 | 15009 | 15009 | 0 |
| 3 | 14901 | 14890 | +11 | 15472 | 15462 | +10 |
| 4 | 15164 | 15175 | −11 | 15818 | 15829 | −11 |
| 5 | 15534 | 15522 | +12 | 16291 | 16277 | +14 |
| 6 | 15797 | 15809 | −12 | 16637 | 16651 | −14 |
| 8 | 16987 | 16980 | + 7 | 17702 | 17684 | +18 |
| 9 | 17250 | 17258 | − 8 | 18048 | 18066 | −18 |
| 10 | 17598 | 17629 | −31 | 18575 | 18618 | −43 |
| 11 | 17861 | 17830 | +31 | 18921 | 18878 | +43 |

Although no attempt to give a complete interpretation of this energy level diagram will be made, the separation in the ground state will be identified tentatively as the totally symmetric valence vibration of the tetrahedral $CoX_4^{--}$ complex. The magnitude of the observed frequencies is about that to be expected for such an assignment. For example, for several tetrahalides of elements of the fourth group of the Periodic Table, the values of the frequency in question range from 220 cm.$^{-1}$ to 265 cm.$^{-1}$ for the bromides and from 367 cm.$^{-1}$ to 459 cm.$^{-1}$ for the chlorides.[10]

If this assignment is correct and if it be assumed that the vibration may be represented by a simple harmonic force function, the force constants, calculated from the above frequencies, for the Co–X bond in these complexes are $3.25 \times 10^5$ dynes/cm. and $2.50 \times 10^5$ dynes/cm. for the bromide and chloride, respectively. Since the force constant can be taken as being roughly proportional to the dissociation energy of the bond,[11] it may be concluded that in these complexes, the Co–Br bond is stronger than the Co–Cl bond.

From these relative bond strengths, certain conclusions regarding the nature of the binding may be drawn. If ion–ion attractive forces alone were responsible for the binding, the Co–Cl bond would be expected to be stronger than the Co–Br bond since the interionic distance is smaller for the former than for the latter. Clearly, then, other forces must be operative in order to account for the observed relative magnitudes of the bond energies. These are presumably ion-induced dipole forces between the cobalt ion and the dipoles produced by polarization of the halide ions in the field of the cobalt ion. Since the polarizability of the

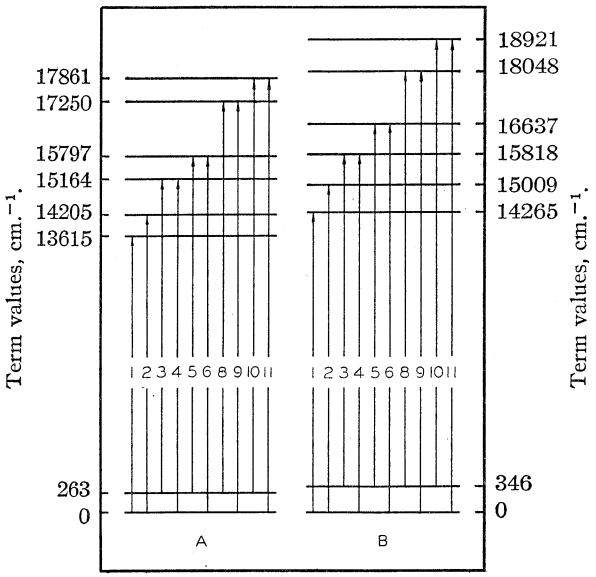



Fig. 2.—Energy level diagram: A, $CoBr_4^{--}$; B, $CoCl_4^{--}$.

bromide ion is larger than that of the chloride ion, this type of force will make a larger contribution in the case of the Co–Br bond than in that of the Co–Cl bond. The ratio of the polarizabilities of the bromide and chloride ions is 1.40[12] while the ratio of the force constants for the complex ions is 1.30. The contribution of the ion–ion forces to the binding is reflected in the smaller value of the latter ratio as compared with the former.

Additional evidence that the binding is not purely of ion–ion type is obtained from a consideration of the interionic distance for the $CoCl_4^{--}$ complex ion. From an analysis of X-ray diffraction measurements upon $Cs_3CoCl_5$,[13] the Co–Cl distance in the complex ion has been found to be 2.34 Å. The sum of the ionic radii[14] for $Co^{++}$ and $Cl^-$ is 2.53 Å. Since the experimental distance is significantly smaller than this sum, a considerable deformation of the electron distribution of the chloride ion is indicated.

The question as to whether the observed relative intensities of the bands agree with those to be expected may now be considered. Since the population of the higher level in the ground state relative to that of the lower is determined by a Boltzmann factor, the intensities of bands originating in the upper level ought to be smaller than that of those from the lower. This condition is satisfied for all of the pairs of bands except numbers 5 and 6 for both the bromide and chloride. Since band 6 occurs at the short wave length edge of Group I where the continuous background absorption is falling very rapidly with decreasing wave length, the estimated relative intensities of bands 5 and 6 may well be in error. It must be emphasized that

(10) J. H. Hibben, "The Raman Effect and its Chemical Applications," Reinhold Publishing Corporation, New York, N. Y., 1939, pp. 138, 348.

(11) A. Eucken, *Ann.*, **440**, 111 (1924).

(12) O. K. Rice, "Electronic Structure and Chemical Binding," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 178.

(13) H. M. Powell and A. F. Wells, *J. Chem. Soc.*, 359 (1935).

(14) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, pp. 326, 330.

the relative intensities reported here are based on visual estimates of blackening of the photographic plate at the band maxima. No account of deviations from linearity of the characteristic curve of the plate or of the effect of the appreciable width and overlapping of the absorption bands has been taken in making the estimates. Therefore the discrepancy in the relative intensities mentioned above cannot be considered to be a serious objection to the suggested interpretation of the spectra; at least not until accurate intensity measurements are made and until the changes of relative intensities with changes of temperature of the absorbing crystals are investigated.

## Summary

1. The room temperature absorption spectra of crystals of pyridinium tetrabromocobaltate(II), quinolinium tetrabromocobaltate(II) and ethylenediaminium hexachlorocobaltate(II) have been photographed.

2. The spectra of pyridinium tetrabromocobaltate(II) and quinolinium tetrabromocobaltate(II) were found to be essentially identical and to bear a very close resemblance to the previously observed spectra of similar double salts containing the tetrahedral tetrachlorocobaltate(II) ion. Therefore the bromides may be assumed to contain the tetrahedral tetrabromocobaltate(II) ion. The spectrum of ethylenediaminium hexachlorocobaltate(II) is distinctly different.

3. A vibration frequency of the tetrahedral complex ions has been identified from an analysis of the tetrahalide spectra. From the magnitude of this frequency, the force constants of the cobalt–bromine and cobalt–chlorine bonds have been determined.

PRINCETON, N. J. RECEIVED SEPTEMBER 28, 1948

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

# The Preparation of the Six *n*-Octynoic Acids[1,2]

BY MELVIN S. NEWMAN AND JOHN H. WOTIZ[3]

In this paper are described the syntheses of the six *n*-octynoic acids and of many intermediates. This work was undertaken with a multiple purpose: (1) to add to our knowledge of the reactivity of the acetylenic function in acids having the triple bond at varying distances from the carboxyl group; (2) to study various methods of synthesis for such acids; (3) to obtain information about the odors of the methyl esters. Inasmuch as the synthetic problems consumed most of our efforts, the first objective must remain for future study. It was deemed of interest to investigate the odors of the methyl esters of these acids because of the commercial use of methyl heptynecarboxylate in perfumery. The odors have been evaluated by men skilled in the art and are described as follows.[4]

$HC{\equiv}C(CH_2)_5COOCH_3$, very green but sharp, chemical, fatty, unpleasant; $CH_3C{\equiv}C(CH_2)_4COOCH_3$, reseda-like, fatty, weak, green seaweed; $CH_3CH_2C{\equiv}C(CH_2)_3COOCH_3$, leafy, cucumber-like, something like talia, sweet, violet; $CH_3(CH_2)_2C{\equiv}C(CH_2)_2COOCH_3$, cucumber-like but sharp, chemical, somewhat fruity; $CH_3(CH_2)_3C{\equiv}CCH_2COOCH_3$, something like fresh cut grass, but crude and fatty.

The synthetic methods used are described below and are summarized in a series of charts. Since many bifunctional acetylenic intermediates of either rare or previously non-existent types were prepared, we prefer to discuss the preparation of these compounds according to the functional group other than the triple bond. In this way the scope and limitations of the methods of synthesis will be emphasized.

## Alkynes and Alkynols

The required 1-alkynes were prepared in high yields by known procedures.[5] 2-Alkyn-1-ols were made in high yield by condensation of 1-alkynylmagnesium bromides with gaseous formadehyde[6] while 3-alkyn-1-ols were prepared in poor yield by the reaction of acetylenic organometallic reagents with ethylene oxide.[7]

## Acetylenic Halides

One useful method for preparation of halogenated acetylenes involved the reaction of alkynylsodium in liquid ammonia with polymethylene chlorobromides.[8] This reaction failed with ethylene

(1) The material herein presented was taken from the Ph.D. thesis of John H. Wotiz, The Ohio State University, June, 1948. Present address of John H. Wotiz, Chemistry Department, University of Pittsburgh.

(2) Presented before the Organic Division of the American Chemical Society at Chicago, Illinois, April, 1948.

(3) The authors wish to express their gratitude to The Ohio State University for a grant from funds donated by The Ohio State University Research Foundation and administered by the Graduate School.

(4) We are indebted to Dr. Ernst T. Theimer of the research department of van Ameringen–Haebler, Inc., Elizabeth, New Jersey, for securing the data on odor.

(5) (a) Vaughn, *et al.*, *J. Org. Chem.*, **2**, 1 (1937); (b) Henne and Greenlee, THIS JOURNAL, **67**, 484 (1945).

(6) Lai, *Bull. soc. chim.*, **53**, 682 1533 (1933); Bartlett and Rosen, THIS JOURNAL, **64**, 545 (1942).

(7) Compare Faucounau, *Compt. rend.*, **199**, 605 (1934); Danehy, Vogt and Nieuwland, THIS JOURNAL, **57**, 2327 (1935); Greenlee, Ph.D. thesis, The Ohio State University, 1942, p. 60.

(8) In a paper which appeared while this manuscript was in preparation, Ahmad and Strong, THIS JOURNAL, **70**, 1699 (1948), mention a 36% yield of 1-chloro-5-decyne from 1-chloro-4-iodobutane and 1-hexynylsodium.

chlorobromide. The condensation of 1-pentynylmagnesium bromide with β-chloroethyl *p*-toluenesulfonate[9] yielded 1-chloro-3-heptyne in 38% yield. This halide was also prepared in 72% yield from the corresponding alcohol, but, because of poor yields in preparation of the required alcohol, this route to 4-octynoic acid was not the best.

Since it was difficult to get a pure sample (required for infrared spectroscopy) of 1-chloro-5-heptyne from the reaction between propynylsodium and 1-chloro-4-bromobutane[10] we attempted to prepare this intermediate by alkylating 1-chloro-5-hexyne with methyl bromide in liquid ammonia. In a similar manner, and for a similar reason, 1-chloro-4-heptyne was prepared by alkylating 1-chloro-4-pentyne with ethyl bromide. It is interesting to note that in each of these alkylations, small quantities of a terminal alkyne, possibly 1-chloro-6-heptyne, were found. This impurity was removed by a treatment with potassium iodomercurate reagent (see experimental). The presence of an acetylenic hydrogen in the distilled reaction products was first suspected when the infrared absorption spectra were examined.[11]

Another method which proved useful for the preparation of acetylenic halides involved replacement of the hydroxyl group of acetylenic alcohols. The behavior of 2-heptyn-1-ol with thionyl chloride and phosphorus tribromide is especially noteworthy. The 1-chloro-2-heptyne thus prepared only reacted with alcoholic silver nitrate on standing and warming whereas the 1-bromo-2-heptyne reacted immediately. The chloro compound could not be brought to react with magnesium even by the "entrainment" method,[12] whereas the bromo compound reacted with such ease that coupling occurred predominantly. However, by using a special high dilution technique recently developed[13] a 98% yield of organomagnesium derivative was obtained from the bromide. A mixture of acids, whose composition is now under investigation, was isolated on carbonation of this derivative.

Examples of an acetylenic–allenic isomerism, $R—C\equiv C–CH_2X \rightleftarrows RCX=C=CH_2$, are described by Johnson.[14] It may be that we were dealing with a similar isomerism. Further work on these halides is being done by one of us (J. H. W.).

## Acetylenic Nitriles

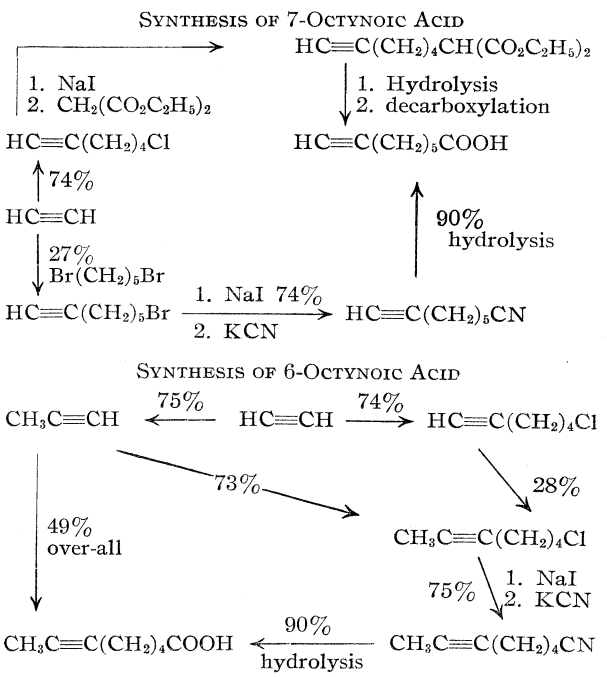
Acetylenic halides having at least three methylene groups between the halogen and the triple bond were best converted into the cyanides *via* the iodides by standard procedures. However, neither 1-chloro-2-heptyne nor 1-bromo-2-heptyne yielded the corresponding iodide or cyanide in this way. Only by heating the bromide in anhydrous medium with cuprous cyanide at 150–160° could the nitrile be obtained. The yield by this method was excellent. It is interesting to note that attempts to prepare $NCCH_2C\equiv CCH_2CN$ from the chloride or bromide were unsuccessful.[15]

Similar difficulties were met in attempting to prepare nitriles from 1-halo-3-heptynes. However, since the corresponding acid could easily be prepared by the malonic ester synthesis from 1-bromo-2-hexyne no intensive study of this reaction was made.

## Acetylenic Acids

Except for 1-cyano-3-heptyne the hydrolysis of acetylenic nitriles proceeded very well by refluxing in aqueous alcoholic alkali until the evolution of ammonia ceased. 1-Cyano-3-heptyne was converted into the corresponding ester by heating with alcoholic hydrogen chloride followed by alkaline hydrolysis of the ester thus produced. Several other methods of hydrolysis were tried without success. 4- and 5-octynoic acids were prepared by decarboxylation of the corresponding malonic acids. 2-Octynoic acid was prepared by carbonation of 1-heptynyl sodium.[16]

The structures of the isomeric *n*-octynoic acids




(9) Compare Johnson, Schwartz and Jacobs, *ibid.*, **60**, 1882 (1938).

(10) Greenlee, Ph.D. thesis, The Ohio State University, 1942, p. 49, points out that $CH_3C\equiv CR$ and RBr usually are difficult to separate by fractionation. Vaughn, *et al.*, ref. 5a, also showed that $RC\equiv CH$ and RCl boil at nearly the same point.

(11) The infrared absorption spectra of many of the intermediates described herein will shortly be published.

(12) Grignard, *Compt. rend.*, **198**, 625 (1934), showed that certain unreactive halides could be made to form Grignard reagents by admixture with ethyl bromide.

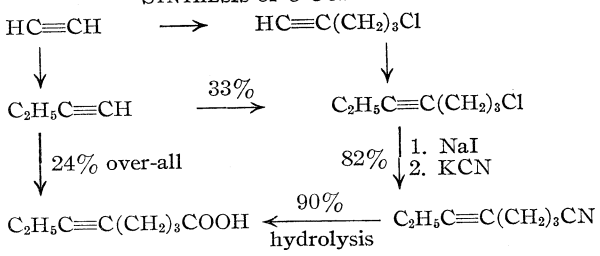
(13) M.S. Thesis of D. Rowlands, The Ohio State University, June, 1948, under supervision of Drs. K. Greenlee and C. E. Boord.

(14) Johnson, "Acetylenic Compounds," Edward Arnold and Company, London, 1946, Vol. I, p. 63.

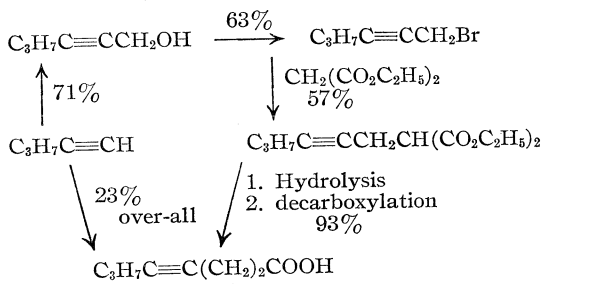
(15) Johnson, *J. Chem. Soc.*, 1009 (1946). In ref. 14, p. 66, Johnson states that no information is available on β,γ-acetylenic nitriles, so that we have evidently prepared the first compound of this type.

(16) Moureu and Delange, *Bull. soc. chim.*, [3] **29**, 648 (1903), Zoss and Hennion, THIS JOURNAL, **63**, 1151 (1941).

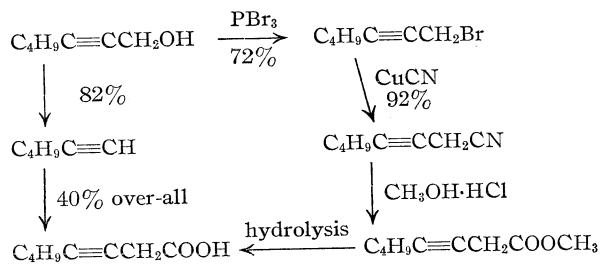
SYNTHESIS OF 5-OCTYNOIC ACID




SYNTHESIS OF 4-OCTYNOIC ACID




SYNTHESIS OF 3-OCTYNOIC ACID




were established by ozonization and by hydrogenation to *n*-octanoic acid. Comparison with the latter of the various samples was effected through the amide.

## Experimental[17]

**Tetramethylene Chlorobromide.**—A fairly rapid stream of hydrogen chloride (cylinder) was passed into a heated mixture of 1 g. of aluminum chloride, 3 cc. of water, and 720 g. (10 moles) of tetrahydrofuran (du Pont). When the temperature levelled off at 105° the heater was removed and hydrogen chloride was introduced until the reaction mixture returned to room temperature. This crude mixture was added slowly to 2 kg. (7.4 moles) of phosphorus tribromide with stirring and ice cooling. After all had been added, the mixture was heated on a steam-bath for one hour and cooled. The upper layer was washed, dried, and rectified to yield 2.13 kg. (62%) of tetramethylene chlorobromide, b. p. 80–82° at 30 mm.

**Pentamethylene Chlorobromide.**—5-Chloroamyl acetate, b. p. 82–84° at 2 mm., was prepared in 93% yield from 430 g. (5 moles) of tetrahydropyran (du Pont), 429 g. (5.5 moles) of acetyl chloride, and 40 g. of freshly fused zinc chloride.[18] A mixture of this ester (329 g., 2 moles), 320 g. of methanol, and 5 g. of *p*-toluenesulfonic acid was rectified until 180 g. of the methanol–methyl acetate azeotrope, b. p. 54°, had been collected. The remaining solvent was removed under reduced pressure at *room temperature*. The residue was reacted with phosphorus tribromide (271 g.) as in the case of tetramethylene chlorohydrin (above) to yield 325 g. (88% over-all) of pentamethylene chlorobromide, b. p. 92–93° at 20 mm., $n^{25}D$ 1.4815.

*Anal.* Calcd. for $C_5H_{10}ClBr$: C, 32.3; H, 5.4. Found: C, 32.8, 32.9; H, 5.4, 5.3.

**2-Heptyn-1-ol.**—A solution of 82 g. (1 mole) of 1-hexyne in 300 cc. of dry ether was added slowly to 1.1 moles of ethylmagnesium bromide in 300 cc. of ether. After refluxing for six hours the mixture was cooled (nitrogen atmosphere). Gaseous formaldehyde was introduced (at a rate to maintain gentle refluxing) by passing dry nitrogen through a flask containing paraformaldehyde (dried over phosphorus pentoxide for at least two weeks) and heated by a bath at 180°. The exothermic reaction ceased when about one equivalent of formaldehyde had been introduced. On working up in the usual manner 92 g. (82%) of 2-heptyn-1-ol, b. p. 113–16° at 56 mm., was obtained.[6] Larger runs gave yields 5 to 10% smaller.

**2-Hexyn-1-ol.**—By a procedure similar to that described above, 2 moles of 1-pentyne yielded 140 g. (71%) of 2-hexyn-1-ol, b. p. 87–89° at 58 mm.

*Anal.* Calcd. for $C_6H_{10}O$: C, 73.4; H, 10.2. Found: C, 73.2, 73.3; H, 10.2, 10.3.

The 3,5-dinitrobenzoate, prepared in high yield, melted at 64–65°.

*Anal.* Calcd. for $C_{13}H_{12}O_6N_2$: C, 53.4; H, 4.1; N, 9.6. Found: C, 53.6, 53.3; H, 4.1, 4.4; N, 9.5, 9.2.

**3-Hexyn-1-ol.**—This compound,[19] prepared in 48% yield from 1-butynylsodium and ethylene oxide in liquid ammonia[5b] boiled at 160–170°. On redistillation almost all of it boiled at 161°. The 3,5-dinitrobenzoate melted at 72–73°, in agreement with Takei.[19]

*Anal.* Calcd. for $C_{13}H_{12}O_6N_2$: C, 53.4; H, 4.1; N, 9.6. Found: C, 53.1, 53.1; H, 4.1, 4.2; N, 9.3, 9.3.

**3-Heptyn-1-ol.**—This compound (Table II) was prepared in 30% yield from 1-pentynylsodium and ethylene oxide in liquid ammonia.[5b] The yield was about the same when prepared from 1-pentynylmagnesium bromide and ethylene oxide. In the latter case, enough 1-pentyne could be recovered to raise the yield to 45% (based on pentyne consumed). No attempt to recover pentyne was made in the liquid ammonia run.

**3-Octyn-1-ol (Table II).**—Using the liquid ammonia procedure[5b] 164 g. of 1-hexyne yielded 53 g. (21%) of 3-octyn-1-ol, b. p. 105–106° at 25 mm. The yield was 37% if based on hexyne consumed (70 g. recovered).

**4-Heptyn-1-ol, 5-Heptyn-1-ol and 6-Heptyn-1-ol (Table II).**—The corresponding chloroalkynes were converted through the iodides to the acetates by heating with potassium acetate in absolute alcohol. After hydrolysis the alcohols were separated from unreacted halide by conversion to the benzoates, distillation, and saponification. No yields for these steps are available because of uncertain purity of starting halides.

**1-Chloroacetylenic Compounds (Table II).**—To a mixture of sodium acetylide (5 moles) in 3 l. of liquid ammonia[5b] was added 858 g. (5 moles) of tetramethylene chlorobromide during four hours and the whole stirred under reflux for seven hours. After most of the ammonia had evaporated (eight hours) 2 l. of water was added slowly. The organic layer was taken into ether, washed with dilute acid and water, and dried. Rectification yielded 430 g. (74%) of 1-chloro-5-hexyne, b. p. 143–144°. In a similar way 1-chloro-6-heptyne (70% yield) and 1-chloro-5-heptyne (73% yield) were prepared from the reaction of sodium acetylide with pentamethylene chlorobromide and of propynyl sodium with tetramethylene chlorobromide. The yield of 1-chloro-4-heptyne by this method was about 30%. Improvement by adding 1-butynylsodium to trimethylene chlorobromide was not achieved.

**1-Chloro-4-heptyne.**—To a solution of 205 g. of 1-chloro-4-pentyne in 2 l. of liquid ammonia was added 78

(17) Microanalyses by Mrs. Klotz and Mr. Polglase, OSU, Arlington Laboratories, and Clarke Microanalytical Laboratories, Urbana, Illinois.

(18) Synerholm, THIS JOURNAL, **69**, 2581 (1947).

(19) Takei, *Ber.*, **73**, 950 (1940).

TABLE I

PHYSICAL PROPERTIES AND ANALYSES OF NEW ACETYLENIC COMPOUNDS[a]

| R | Alcohols, ROH: B. p., °C. | Mm.[b] | $n^{25}D$ | Found, %[p] C (75.0) | H (10.7) | 3,5-Dinitrobenzoates[q]: M. p., °C.[e] | Found, %[p] C (54.9) | H (4.6) | N (9.1) | Acids RCOOH: B. p.,[l] °C. (2 mm.) | M. p. °C.[a] | $n^{25}D$ | Neut. equiv. (140) | Found, %[p] C (68.6) | H (8.6) | Amides, $RCONH_2$: M. p., °C.[a] | Found, %[p] C (69.1) | H (9.3) | N (10.1) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $HC{\equiv}C(CH_2)_5$ | 98 | 20 | 1.4534 | 74.6 | 10.6 | 46 | 55.0 | 4.5 | 9.5 | 123 | 20 | 1.4502 | 140.5 | 68.1 | 8.6 | 86 | 69.9 | 9.5 | 10.5 |
| $CH_3C{\equiv}C(CH_2)_4$ | 96 | 15 | 1.4590 | 74.2 | 10.7 | 53 | 54.8 | 4.4 | 9.2 | 116 | 37 | | 139.5 | 67.9 | 8.6 | 113 | 68.7 | 9.3 | 10.2 |
| $C_2H_5C{\equiv}C(CH_2)_3$ | 91 | 15 | 1.4593 | 75.7 | 10.4 | 52 | 54.8 | 4.6 | 9.2 | 111 | 8 | 1.4540 | 140 | 69.2 | 9.0 | 105 | 69.8 | 9.3 | 10.1 |
| $C_3H_7C{\equiv}C(CH_2)_2$ | 111 | 70 | 1.4530 | 74.8 | 10.5 | 61 | 54.8 | 4.9 | 9.4 | 121 | 49 | | 140.5 | 68.9 | 8.6 | 118 | 69.9 | 9.2 | 10.0 |
| $C_4H_9C{\equiv}CCH_2$— | 98 | 28[d] | 1.4523 | 74.8 | 10.8 | 62 | 55.4 | 4.5 | 9.7 | 110 | 18 | 1.4577 | 140.5 | 68.8 | 8.6 | 52 | 69.1 | 9.1 | 10.1 |
| $C_5H_{11}C{\equiv}C$ | | | | | | | | | | 114 | 5[n] | 1.4588 | | | | 91[n] | | | |
| $C_7H_{15}$[c] | 93 | 30[e] | 1.4218 | | | 47[f] | | | | 99 | 16[m] | 1.4150 | | | | 105[m] | | | |

| R | Chlorides, RCl: B. p., °C., 1 atm. | $n^{25}D$ | Found, %[p] C (64.3) | H (8.4) | Bromides, RBr: B. p., °C. | Mm.[l] | $n^{25}D$ | Found, %[p] C (48.0) | H (6.3) | Nitriles, RCN: B. p., °C. | Mm.[b] | $n^{25}D$ | Found, %[p] C (79.3) | H (9.1) | N (11.5) | Methyl esters, $RCOOCH_3$: B. p., 2 mm.[b] | $n^{25}D$ | Found, %[p] C (70.1) | H (9.1) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $HCC{\equiv}(CH_2)_5$ | 166 | 1.4507 | 64.3 | 8.4 | 92 | 20 | 1.4750 | 48.5 | 6.6 | 80 | 3 | 1.4460 | 79.0 | 9.0 | 11.6 | 64 | 1.4380 | 70.1 | 9.4 |
| $CH_3C{\equiv}C(CH_2)_4$ | 175 | 1.4599 | 64.4 | 8.4 | | | | | | 79 | 2 | 1.4530 | 79.4 | 9.2 | 11.6 | 68 | 1.4433 | 70.1 | 9.2 |
| $C_2H_5C{\equiv}C(CH_2)_3$ | 164 | 1.4540 | 64.8 | 8.5 | | | | | | 111 | 29 | 1.4514 | 80.0 | 9.2 | 11.1 | 64 | 1.4421 | 70.2 | 9.1 |
| $C_3H_7C{\equiv}C(CH_2)_2$ | 162 | 1.4520 | 64.7 | 8.9 | 100 | 65 | 1.4785 | 49.5 | 6.6 | 71 | 3 | 1.4492 | 79.4 | 8.9 | 12.0 | 63 | 1.4414 | 70.0 | 9.4 |
| $C_4H_9C{\equiv}CCH_2$ | 167 | 1.4570 | 64.8 | 8.4 | 84 | 20 | 1.4878 | 49.1 | 6.2 | 124 | 56 | 1.4475 | 79.7 | 9.2 | 11.3 | 64 | 1.4448 | 70.2 | 9.0 |
| $C_5H_{11}C{\equiv}C$ | | | | | 69 | 25[h] | 1.4678 | | | 86 | 17[j] | 1.4551 | | | | 70[n] | 1.4442 | | |
| $C_7H_{15}$[c] | 159[g] | 1.4264 | | | 70 | 15[i] | 1.4476[i] | | | 66 | 4[k] | 1.4178 | | | | 57[m] | 1.4150 | | |

[a] Boiling points represent middle cuts taken for analyses; melting points are usually over a one degree range, the upper limit being that recorded. Duplicate analyses were obtained for almost every sample. To save space, only the best analysis is included in this table. [b] These boiling points were observed with different vacuum systems and flasks and hence are not directly comparable. [c] Known compounds; properties listed for comparison. [d] Reported by Toussaint and Wenzke, THIS JOURNAL, **57**, 668 (1935), without analysis. [e] Ellis and Reid, *ibid.*, **54**, 1678 (1932). [f] Adamson and Kenner, *J. Chem. Soc.*, 287 (1935). [g] Heilbron, "Dictionary of Organic Compounds," Vol. I, p. 473. [h] McCusker and Vogt, THIS JOURNAL, **59**, 1307 (1937). [i] Our values. Heilbron (footnote *g*) p. 296, gives b. p. 70.6° at 19 mm. and $n^{25}D$ 1.4480. [j] Moureu and Lazennec, *Bull. soc. chim.*, [3] **35**, 524 (1906). [k] Footnote *g*, page 393. [l] Boiling points taken in same apparatus, hence comparable. [m] Footnote *g*, p. 393. [n] Moureu and Delange, *Bull. soc. chim.*, [3] **29**, 655 (1903). [o] The 3,5-dinitrobenzoates were prepared in 90% yields by heating with pure 3,5-dinitrobenzoyl chloride until evolution of hydrogen chloride slackened. The products were isolated and recrystallized to constant melting point from petroleum ether (b. p. 30–60°) and benzene. Mixed melting points between the various derivatives all gave large depressions. [p] Values in parentheses are calculated. [q] Of the alcohols, ROH.

g. of sodium amide. After stirring for thirty minutes 218 g. of ethyl bromide was added during three hours. By rectification of this reaction product there was obtained 35 g. (17%) of crude 1-chloro-4-pentyne, b. p. 110–112°, and 45 g. (17%) of crude 1-chloro-4-heptyne, b. p. 163–165°. When the infrared absorption spectrum[11] of this fraction showed the presence of a terminal acetylenic function, 19 g. was treated with a mercuric iodide, reagent[20] until no further precipitate formed. The white solid was collected and recrystallized to a melting point of 66–67°. Analysis showed 48.6% carbon and 4.7% hydrogen, which did not indicate any compound to be expected. The excess mercury reagent was removed by precipitating with 1-hexyne and on rectification 4 g. of a pure sample of 1-chloro-4-heptyne (Table II) was obtained.

**1-Chloro-5-heptyne (Table II).**—By a procedure similar to that used above, there was obtained 50 g. (38%) of crude 1-chloro-5-heptyne, b. p. 173–174°, by treating 116 g. of 1-chloro-5-hexyne with sodium amide and then methyl bromide. Purification of this entire fraction as above yielded 25 g. of pure 1-chloro-5-heptyne. The mercury derivative[20] obtained in this case (4 g.) melted at 76–77° and contained 48.9% of carbon and 4.8% of hydrogen.

**1-Chloro-3-heptyne (Table II).**—1-Chloro-3-heptyne, b. p. 71–75° at 30 mm., b. p. 90–93° at 70 mm., was prepared in 38% yield (calculated on 1-pentyne) essentially as described by Johnson for a similar reaction.[9] This chloride was also prepared in 72% yield from a reaction between thionyl chloride, pyridine, and 3-heptyn-1-ol by the procedure described below, except that a glass stirrer was used.

**1-Chloro-2-heptyne (Table II).**—In the best of several experiments a solution of 112 g. (1 mole) of 2-heptyn-1-ol and 78 g. (1 mole) of dry pyridine in 100 cc. of dry ether was added to a solution of 131 g. (1.1 mole) of thionyl chloride (obtained from the Columbia Chemical Division of the Pittsburgh Plate Glass Company) in 100 cc. of dry ether at such a rate as to maintain refluxing. After the addition was complete ether (about 150 cc.) was distilled until the inside temperature was 80°. Then 13 g. more of thionyl chloride was added and the stirring and heating continued for an hour. The chromel (nickel and chromium alloy) wire stirrer had completely dissolved and the mixture was green. We do not know whether this happening aided or harmed the reaction. The mixture was treated with 500 cc. of cold water and the ether layer was separated, washed with sodium carbonate solution and water, and was dried over calcium chloride. After a rapid vacuum distillation the product was redistilled to yield 100 g. (77%) of 1-chloro-2-heptyne, b. p. 73° at 24 mm. This product gave a precipitate with alcoholic silver nitrate only on warming or long standing.

**1-Bromo-2-heptyne (Table II).**—To a solution of 310 g. (2.75 mole) of 2-heptyn-1-ol and 5 g. of pyridine in 800 cc. of dry ether was added 271 g. (1 mole) of phosphorus tribromide at a rate to maintain refluxing. After heating and stirring for an additional two hours the mixture was cooled and the upper layer poured on ice. The organic matter was taken into ether, washed with sodium carbonate and saturated sodium chloride, and was dried over calcium chloride. The crude mixture remaining after removal of the ether was rapidly vacuum distilled to remove high boiling material and then rectified to yield 340 g. (72%) of 1-bromo-2-heptyne, b. p. 104–105° at 56 mm., and 55 g. (7%) of a hydrogen bromide addition compound presumably 1,3-dibromo-2-heptene, b. p. 112° at 25 mm., 70° at 2 mm., $n^{25}D$ 1.5172.

*Anal.* Calcd. for $C_7H_{12}Br_2$: C, 32.8; H, 4.7. Found: C, 33.3, 33.7; H, 4.8, 4.5.

Repetition of the above reaction under slightly modified conditions gave yields in the range of 60 to 70%. None of the desired product was obtained when one equivalent of pyridine was used.

In a manner similar to the above, 2-hexyn-1-ol was con-

(20) Johnson and McEwen, THIS JOURNAL, **48**, 469 (1926).

verted into 1-bromo-2-hexyne, b. p. 97–98° at 80 mm., $n^{25}D$ 1.4884, in 63% yield.

*Anal.* Calcd. for $C_6H_9Br$: C, 44.7; H, 5.6; Br, 49.7. Found: C, 44.4; H, 5.8; Br, 50.2.

The hydrogen bromide addition product (12% yield) formed here, probably 1,3-dibromo-2-hexene, had a boiling point of 100° at 25 mm., or 62° at 2 mm. and $n^{25}D$ 1.5235.

*Anal.* Calcd. for $C_6H_{10}Br_2$: C, 29.9; H, 4.1. Found: C, 30.4, 30.1; H, 4.3, 4.4.

Both 1-bromo-2-heptyne and 1-bromo-2-hexyne gave immediate precipitates when added to alcoholic silver nitrate.

The yield in the conversion of 3-heptyn-1-ol to 1-bromo-3-heptyne (Table II) by this method was considerably less (crude, 41%).

**1-Bromo-6-heptyne.**—A suspension of 3.2 mole of sodium acetylide in 1.5 l. of liquid ammonia was added during one hour to a stirred mixture of 1050 g. (4.6 mole) of pentamethylene dibromide, 500 cc. of dry ether, and 1 l. of ammonia. The addition was accomplished through a tube dipping into the bottom of the sodium acetylide flask and leading into the other. The rate of addition was controlled by partial release of the ammonia pressure in the acetylide flask as needed. The last amounts of acetylide were transferred by using three 50-cc. portions of ammonia for washing. After stirring for two more hours, the product was isolated as usual as a colorless oil, b. p. 80–100° at 20 min. in 27% yield. On redistillation, pure 1-bromo-6-heptyne of b. p. of 92° at 20 min., $n^{25}D$ 1.4750, was obtained with little loss.

*Anal.* Calcd. for $C_7H_{11}Br$: C, 48.0; H, 6.3. Found: C, 48.8, 48.5; H, 6.5, 6.6.

**1,2,3-Tribromo-2-heptene.**—Because of difficulties met with in the attempted conversion of 1-bromo-2-heptyne to the corresponding cyanide, we thought it might prove useful to add bromine to the triple bond and remove it later. However, we never attempted to do the latter. By adding 80 g. of bromine in 80 cc. of carbon tetrachloride to 56 g. of 2-heptyn-1-ol in 75 cc. of carbon tetrachloride at 0° and waiting until decolorization after adding each drop, there was obtained 110 g. (81%) of 2,3-dibromo-2-hepten-1-ol, b. p. 113–115° at 4 mm.

*Anal.* Calcd for $C_7H_{12}OBr_2$: C, 30.9; H, 4.4. Found: C, 30.8, 30.6; H, 4.5, 4.8.

The 3,5-dinitrobenzoate melted at 84–85°.

*Anal.* Calcd. for $C_{14}H_{14}O_6Br_2N_2$: C, 36.1; H, 3.0; N, 6.0. Found: C, 36.3; H, 3.0; N, 6.1.

By the procedure described above, this alcohol was converted into 1,2,3-tribromo-2-heptene, b. p. 112–114° at 4 mm., 96° at 2 mm., $n^{25}D$ 1.5540, in 87% yield.

*Anal.* Calcd. for $C_7H_{11}Br_3$: C, 25.1; H, 3.2. Found: C, 25.3, 25.4; H, 3.7, 3.6.

**3,4-Dibromo-3-octen-1-ol.**—In a similar way, 3-octyn-1-ol was converted into its dibromide, b. p. 111–113° at 2 mm. *Anal.* Calcd. for $C_8H_{14}OBr_2$: C, 33.5; H, 4.9. Found: C, 33.5, 33.8; H, 5.2, 5.3. The 3,5-dinitrobenzoate melted at 85–86°. *Anal.* Calcd. for $C_{15}H_{16}O_6Br_2N_2$: C, 37.5; H, 3.3; N, 5.8. Found: C, 37.4, 37.2; H, 3.5, 3.7; N, 6.3, 6.2. No further useful experiments with these bromine addition products were performed.

**1-Iodo-5-hexyne.**—Crude 1-chloro-5-hexyne prepared as described above was converted into 1-iodo-5-hexyne, b. p. 94–95° at 35 mm., $n^{25}D$ 1.5286, in 82% yield by refluxing with an excess of sodium iodide in acetone for twenty hours.

*Anal.* Calcd. for $C_6H_9I$: C, 34.4; H, 4.3. Found: C, 35.3; H, 4.4.

**1-Cyano-6-heptyne (Table II).**—A mixture of 120 g. of 1-bromo-6-heptyne, 65 g. of potassium cyanide, 120 cc. of water, and 300 cc. of acetone was stirred and refluxed for forty-eight hours after which 250 cc. of mixed solvent was distilled. After suitable treatment the residue yielded 60 g. (74%) of 1-cyano-6-heptyne as a colorless liquid, b. p. 90–92° at 6 mm.

Similarly, 1-cyano-5-heptyne (Table II) b. p. 88–95° at 5 mm. was prepared from 1-iodo-5-heptyne (prepared from 1-chloro-5-heptyne as above described), the over-all yield from chloro compound being 75%. Likewise, 1-chloro-4-heptyne was converted (Table II) directly into 1-cyano-4-heptyne, b. p. 110–112° at 29 mm., in 82% yield.

**1-Cyano-2-heptyne (Table II).**—In the best of many experiments, a mixture of 70 g. of 1-bromo-2-heptyne, 45 g. of carefully dried cuprous cyanide, and 40 cc. of xylene was stirred and heated by a salt-bath at 160° until the inside temperature reached 157°. The temperature of the bath was lowered to 145° and the reaction proceeded exothermically for about thirty minutes during which time the inside temperature was not allowed to exceed 165°. After cooling the mixture was extracted thoroughly with benzene, all solids being removed by filtration. On distillation there was obtained 44 g. (92%) of nitrile, b. p. 123–126° at 56 mm. In other trials, the yields varied from 0 to 90%. Careful regulation of the temperature of the reaction mixture seems to be most important. Attempts to combine either the chloride or bromide with aqueous solutions of potassium cyanide were always fruitless.

**1-Cyano-3-heptyne (Table II).**—This nitrile was prepared from the corresponding acid via the amide and dehydration of the latter with phosphorus pentoxide. The yield on the last step was 50%.

**5-,6- and 7-Octynoic Acid (Table II).**—The corresponding nitriles were hydrolyzed to the acids in about 90% yields by refluxing with an excess of 10% potassium hydroxide solution until the evolution of ammonia ceased.

**3-Octynoic acid (Table II).**—A stream of hydrogen chloride (tank) was passed into solution of 140 g. of 1-cyano-2-heptyne in 250 cc. of methanol and 25 cc. of water until it refluxed and later fell to 30°. The precipitated ammonium chloride was collected and the filtrate was concentrated. The crude ester was further hydrolyzed with alcoholic alkali to yield 120 g. (74%) of acid, b. p. 120–130° at 6 mm.

One attempt at hydrolysis involving shaking 6 g. of the cyanide with 20 cc. of concentrated hydrochloric acid for four days at room temperature yielded 3 g. (34%) of a product, b. p. 148 at 4 mm., m. p. 54–55° after crystallization from petroleum ether (b. p. 30–60°), which was presumably the amide of 4-chloro-3-octenoic acid.

*Anal.* Calcd. for $C_8H_{14}ONCl$: C, 54.9; H, 7.9; N, 8.0. Found: C, 54.9; H, 7.8; N, 8.1.

When the hydrolysis with concentrated hydrochloric acid was carried out at 80° for twelve hours, 8 g. (46%) of a chloro acid, presumably 4-chloro-3-octenoic acid, b. p. 125–126° at 3 mm., was obtained. The neutral equivalent was 177, 178; calculated for $C_8H_{13}O_2Cl$, 176.5.

When a mixture of 6 g. of 1-cyano-2-heptyne, 5 g. of concentrated sulfuric acid, and 2 cc. of water was heated and stirred at 60° for two days little reaction had occurred. An additional 10 cc. of 6 *N* sulfuric acid was added and the heating and stirring continued for one day. The organic matter was then isolated and heated with aqueous potassium hydroxide until a homogeneous solution was obtained. The acid fraction after vacuum distillation and crystallization from petroleum ether (b. p. 30–60°) amounted to 4 g., m. p. 53–54°, neutral equivalent, 157. Calcd. for $C_8H_{14}O_3$, 156. This acid was thus 4-ketoöctanoic acid.[21]

Because of the difficulty in hydrolyzing 1-cyano-2-heptyne, it was brominated, as described for 1,2,3-tribromo-2-heptene, to yield 50% of the expected 1-cyano-2,3-dibromo-2-heptene, b. p. 118 at 4 mm.

*Anal.* Calcd. for $C_7H_{11}NBr_2$: N, 4.9. Found: N, 4.4.

Hydrolysis of this compound was likewise incomplete as heating 14 g. with 20 cc. of concentrated sulfuric acid to 80° for fifteen minutes, followed by standing at room temperature for three hours yielded only 7 g. (47%) of the amide of 3,4-dibromo-3-octenoic acid, m. p. 130–131°.

*Anal.* Calcd. for $C_8H_{13}ONBr_2$: C, 32.1; H, 4.3; N, 4.7. Found: C, 32.2; H, 4.5; N, 5.0.

(21) Blaise and Koehler, *Compt. rend.*, **148**, 489 (1909).

**4-Octynoic acid (Table II).**—In a typical malonic ester synthesis 280 g. (1.74 mole) of 1-bromo-2-hexyne was added to a solution of 1.5 l. of absolute alcohol, the sodium ethoxide prepared from 41.5 g. (1.8 mole) of sodium, and 320 g. (2 mole) of ethyl malonate. After refluxing for eight hours the product was treated as usual to yield 240 g. (57%) of ethyl 2-hexynylmalonate, b. p. 134–134° at 5 mm., and 75 g. (13%) of ethyl di-(2-hexynyl)-malonate, b. p. 168–170° at 5 mm., $n^{25}D$ 1.4600.

*Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.3. Found: C, 65.3, 65.2; H, 8.2, 8.2. Calcd. for $C_{19}H_{28}O_4$: C, 71.2; H, 8.7. Found: C, 71.2, 71.3; H, 8.8, 8.7.

In another experiment partial saponification occurred during isolation of the products from the reaction mixture and there was isolated a small amount of ethyl di-(2-hexynyl)-acetate, b. p. 135–137° at 3 mm.

*Anal.* Calcd. for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.0, 77.0; H, 9.7, 9.8.

On alkaline hydrolysis 2-hexynylmalonic acid, m. p. 109–110° with dec., and di-(2-hexynyl)-malonic acid, m. p. 138–139° with dec., were obtained. The neutralization equivalents were 92, 91 (theory, 92) and 131, 131 (theory, 132), respectively.

*Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.9; H, 6.5. Found: C, 59.0, 59.0; H, 6.6, 6.7. Calcd. for $C_{15}H_{20}O_4$: C, 68.2; H, 7.6. Found: C, 68.4, 68.5; H, 7.6, 7.6.

Heating at 150 to 170° until the evolution of carbon dioxide ceased afforded 4-octynoic acid in 93% over-all yield from ester. The di-2-hexynylacetic acid was not isolated as such but was converted into the amide, m. p. 63–64°.

*Anal.* Calcd. for $C_{14}H_{21}ON$: C, 76.8; H, 9.6; N, 6.4. Found: C, 76.9, 77.0; H, 10.1, 10.1; N, 6.5, 6.5.

**2-Octynoic Acid.**—In a manner similar to the above, ethyl 2-heptynylmalonate, b. p. 146 at 5 mm., was prepared in 66% yield.

*Anal.* Calcd. for $C_{14}H_{22}O_4$: C, 66.1; H, 8.7. Found: C, 64.9; H, 8.5.[22]

(22) The remaining malonic ester was saponified before the poor analytical result was obtained, hence we were unable to secure a good analysis.

On hydrolysis 2-heptynylmalonic acid, m. p. 93–94°, neutral equivalent 99 (theory, 99), was obtained.

*Anal.* Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 59.9, 59.5; H, 7.1, 7.3.

**Preparation of Methyl Esters.**—The acetylenic acids were obtained in over 90% yields after refluxing for twelve hours in an excess of methanol containing small amounts of *p*-toluenesulfonic acid.

**Ozonization of Octynoic Acids.**—The octynoic acids were oxidized in acetic acid in an ozonizer of the Henne–Perilstein type[23] using a flow rate of 23 l. of oxygen, containing 1 g. of ozone, per hour. Only the dibasic acid fractions were isolated. The acids were checked by melting point and neutralization equivalent. The yields from solutions of about 4 g. of acids in 50 cc. of acetic acid (ozonized for four hours at room temperature) were as follows: 7-octynoic acid, 46% pimelic acid; 6-octynoic acid, 52% adipic acid; 5-octynoic acid, 71% glutaric acid; 4-octynoic acid, 67% succinic acid; and 3-octynoic acid, 80% malonic acid. No attempt to isolate maximum amounts of these dibasic acids was made.

**Hydrogenation of Octynoic Acids.**—The octynoic acids, 0.8 to 1.4 g., were dissolved in 20 cc. of pure ethyl alcohol and reduced over 0.20 g. of Adams platinum catalyst in a quantitative manner using an apparatus similar to that described by Joshel.[24] In each case almost exactly the theoretical amount of hydrogen was absorbed in times which varied from 150 to 300 minutes. 5-Octynoic acid was hydrogenated on a larger scale in a shaking device (Parr Instrument Company). In each case the saturated acid, obtained in almost theoretical yield, proved to be *n*-octanoic acid. Comparison was always effected by means of the amide, m. p. and mixed m. p., 103–104°.

## Summary

The synthesis of 7-, 6-, 5-, 4- and 3-octynoic acids and the preparation and chemical behavior of many of the new acetylenic intermediates are described.

(23) Henne and Perilstein, THIS JOURNAL, **65**, 2183 (1943).

(24) Joshel, *Ind. Eng. Chem., Anal. Ed.*, **15**, 590 (1943).

COLUMBUS, OHIO RECEIVED SEPTEMBER 13, 1948

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# Native Lignin. II. Native Aspen Lignin[1,2]

BY M. A. BUCHANAN, F. E. BRAUNS AND R. L. LEAF, JR.

The isolation of native lignin fractions from black spruce and western hemlock has been described by Brauns.[3] These two preparations represent softwood (gymnosperm) lignin and are similar in nature. It is well known that hardwood (angiosperm) lignin differs from softwood lignin in that the former contains a greater amount of methoxyl and is built up of both syringyl and guaiacyl nuclei, whereas only the latter are found in softwood lignins. In recent years, the hardwoods have become increasingly important as a source of wood pulp. Consequently, it was of interest to isolate and investigate the native lignin fraction from a typical hardwood.

Native aspen lignin was isolated by means of neutral ethanol under conditions designed to prevent any change in the lignin during its isolation and purification. The crude lignin contained 17.6% methoxyl, which agrees with the value of 17.5% reported by Lovell and Hibbert[4] for a lignin preparation extracted from aspen with neutral alcohol. These investigators separated their product into three fractions by a fractional distribution between water, methanol, chloroform and carbon tetrachloride. They obtained one fraction having a methoxyl content of 18.4%, but apparently did not investigate their lignin further.

(1) For paper I of this series see F. E. Brauns, THIS JOURNAL, **61**, 2120–2127 (1939).

(2) Presented before the Division of Cellulose Chemistry at the 114th meeting of The American Chemical Society, Portland, Oregon, September 13–16, 1948.

(3) F. E. Brauns, *J. Org. Chem.*, **10**, 211–215 (1945).

(4) E. L. Lovell and H. Hibbert, THIS JOURNAL, **63**, 2070–2073 (1941).

Purification of the crude native aspen lignin by repeated precipitations into water and into ether increased the methoxyl content to a constant value of 19.5%. The purified lignin on treatment with 72% sulfuric acid under the conditions of the lignin determination gave approximately 90% of a "Klason lignin." The composition corresponds very well with those normally obtained from Klason lignin isolated directly from hardwoods.[5] The isolated native aspen lignin, therefore, undergoes changes similar to those produced in native spruce lignin on treatment with 72% sulfuric acid. The exact nature of these changes is not known, but they may involve loss of some fragment of the lignin molecule, in addition to loss of water as a result of condensation.

Treatment of the purified native aspen lignin with methanol containing hydrogen chloride resulted in a product having a methoxyl content slightly higher than the value (25.6%) reported by Harris[6] for methanol lignin prepared directly from aspenwood.

Methylation of the purified native aspen lignin with diazomethane indicates the introduction of 1.5 methoxyl groups per six methoxyl groups originally present. On the other hand, diazomethylation of the methanol native aspen lignin introduced one additional methoxyl group. Under these conditions, diazomethane methylates only acidic hydroxyl groups. Methanol in the presence of hydrogen chloride methylates carboxyl groups and forms acetals with aldehydic or ketonic carbonyl groups and, therefore, the above results indicate the presence of one phenolic group per six methoxyl groups in the original aspen lignin. The additional 0.5 methoxyl group introduced by diazomethane may represent the methylation of one enolic group per 12 original methoxyl groups. However, the methoxyl content of the methanol derivative suggests that there may be as many as 2.5 carbonyl groups per 12 original methoxyl groups.

Complete methylation of the diazomethane-methylated native aspen lignin and acetylation of the original lignin suggests that it contains six hydroxyl groups. However, *p*-toluenesulfonyl chloride reacts with one or two less groups than does acetic anhydride under similar conditions.

A spruce lignin building unit containing four methoxyl groups has been postulated which agrees very well with the analytical results of a number of derivatives.[1] Attempts to postulate a similar unit for aspen lignin have not been entirely satisfactory. If one assumes a unit of aspen lignin containing six methoxyl groups, the unit weight is calculated to be approximately 950 on the basis of the methoxyl content of the native aspen lignin. The carbon and hydrogen data suggest that a unit of this size contains 50 carbon, 56 hydrogen, and 18 oxygen atoms. This combination corresponds to a unit weight of 945. Calculated values for a unit of this size are compared with the observed values in Table I. The data for the original native aspen lignin, as well as those for the completely methylated and acetylated products, agree rather well with the calculated values. However, the diazomethane-methylated material, the methanol lignin, and the phenylhydrazine reaction product do not correspond to the introduction of an integral number of groups. This suggests that either the true unit is a multiple of 945 or that the native aspen lignin is not homogeneous. If the lignin is non-homogeneous, any attempts to derive a unit weight can represent only an average composition of the material. Hence, the 945 unit is only tentative in nature and may require revision when more data are available.

**Absorption Spectra.**—Methylation of the native aspen lignin reduces the absorption in the visible range by a factor of about four (Fig. 1). Ultraviolet absorption spectra were determined by means of a Beckman Model DU spectrophotometer. The results, expressed as specific extinction (optical density/concentration in grams per liter), are shown in Fig. 2. Methylation has but little effect on the absorption in the ultraviolet region. The native aspen lignin differs from spruce lignin in that it does not have a well-defined maximum at about 280 mmu. It does show a slight inflection at 275 mmu but does not have the minimum at approximately 260 mmu. The aspen lignin curve may be composed of the same general absorption bands which are responsible for the spruce lignin curve. If this is true, the bands are broadened sufficiently to remove the characteristic maximum and minimum.

Patterson and Hibbert[7] likewise found a broadening of the absorption bands in the case of certain hardwood lignin products obtained by the ethanolysis of maplewood.

The infrared spectrum of native aspen lignin has been determined and will be reported later. Its general nature is similar to that reported for native spruce lignin.[8]

## Experimental

**Isolation of Native Aspen Lignin.**—A 17-year old aspen (*Populus tremuloides*) tree having a butt diameter of 5.25 inches was felled shortly after leafing. The wood was immediately converted into sawdust. A 59-pound portion of sawdust (containing 50.6% moisture and 2.4% ethanol-soluble material) was extracted with 95% ethanol at room temperature. One to two gallons of the alcoholic extract was removed from the bottom of the percolator per day, which was then replenished with fresh ethanol. After three weeks, approximately half of the original

(5) Wise, "Wood Chemistry," Reinhold Publishing Corp., New York, N. Y., 1944, p. 297.

(6) E. E. Harris, THIS JOURNAL, **58**, 894–896 (1936).

(7) R. F. Patterson and H. Hibbert, *ibid.* **65**, 1869–1873 (1943).

(8) E. J. Jones, *ibid.*, **70**, 1984–1985 (1948).

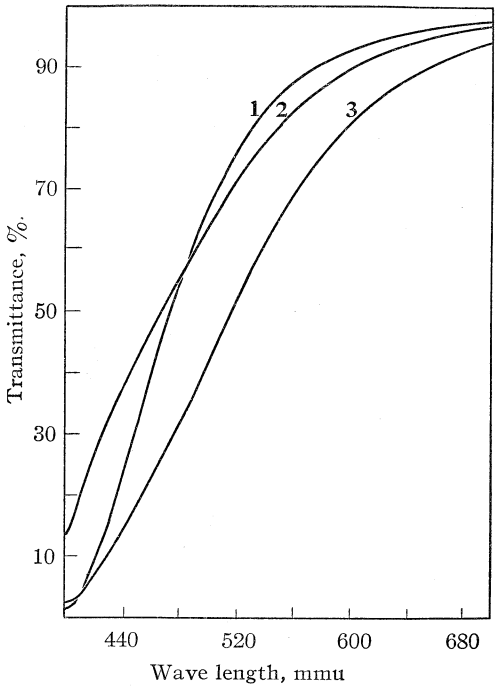



Fig. 1.—Spectral transmittance curves for a dioxane solution: 1, diazomethane-methylated product (concn. 25.0 g./l.); 2, aspen native lignin (concn. 6.3 g./l.); 3, aspen native lignin (concn. 12.5 g./l.).

ethanol-soluble material had been removed from the sawdust and the extraction was discontinued. The alcoholic solutions were concentrated under reduced pressure to a volume of 3 liters. This removed the alcohol and caused precipitation of considerable water-insoluble material.

TABLE I

ANALYTICAL RESULTS

| | Number of groups introduced | Calculated for 945 unit ($C_{50}H_{56}O_{18}$), % MeO | Other | Found, % MeO | Other |
|---|---|---|---|---|---|
| Native aspen lignin (N. A. L.) | ... | 19.7 | C, 63.5 H, 6.0 | 19.5 | 63.2 5.9 |
| N. A. L. methylated with $CH_2N_2$[a] | 1.5 | 24.1 | .. | 24.1 | .. |
| Completely methylated N. A. L.[b,c] | 6 | 36.2 | .. | 36.1 | .. |
| Methanol N. A. L.[c] | 2.5 | 26.2 | .. | 26.1 | .. |
| Methanol N. A. L. methylated with diazomethane[a] | 1[d] | 28.8 | .. | 28.8 | .. |
| Acetylated N. A. L.[e] | 6 | 15.5 | .. | 15.4 | .. |
| Tosylated N. A. L.[e] | 4 | 11.9 | S, 8.2 | 11.8 | 9.0 |
| | 5 | 10.8 | S, 9.3 | | |
| "Phenylhydrazone" of N. A. L.[c] | 0.5 | 18.8 | N, 1.4 | 18.5 | 1.5 |
| "Klason" N. A. L.[f] | ... | .. | .. | 20.5 | C, 63.9 H, 5.5 |

[a] Methylated in dioxane solution to constant methoxyl content. [b] N. A. L. methylated with dimethyl sulfate. [c] Prepared according to Brauns.[1] [d] Number of groups introduced by diazomethane. [e] N. A. L. treated with 2.5 parts *p*-toluenesulfonyl chloride and 15 parts pyridine for 24 hours at room temperature. [f] N. A. L. treated with 72% sulfuric acid under conditions of the lignin determination; yield 90%.

The aqueous mixture was extracted directly with ether, which removed 179.1 g. of ether-soluble material.

The extracted mixture was filtered and the moist precipitate dissolved in dioxane.[9] The resulting solution was dehydrated by distilling under reduced pressure with fresh dioxane. The dry dioxane solution was adjusted to approximately 10% solids and was added dropwise (in small portions) with vigorous stirring to 30 volumes of anhydrous ether. The precipitated product was washed thoroughly with low boiling petroleum ether to remove all traces of ethyl ether. This crude product contained 17.6% methoxyl. It was purified by reprecipitating from a 10% solution in 1:1 methanol–acetone into 10 volumes of water. Eighty per cent. of the material was recovered as a water-insoluble product which, after an additional precipitation into ether, contained 19.2% methoxyl. The yield at this stage was 87.7 g. or 0.7% of the original wood (oven-dry basis). After three additional precipitations into ether, the product contained 19.5% methoxyl (ash-free basis) and 0.12% ash. Additional precipitations into water or into ether did not change the methoxyl content. The analysis of this and other derivatives is given in Table I.

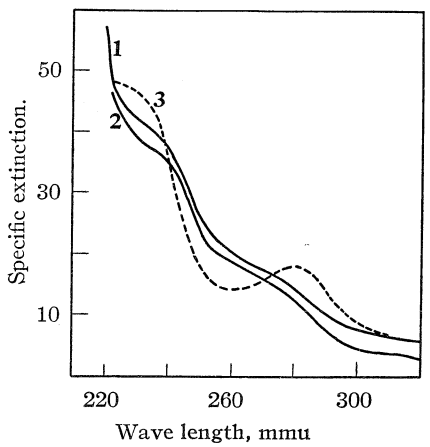



Fig. 2.—Ultraviolet absorption spectra of dioxane solutions: 1, aspen native lignin (concn. 0.021 g./l.); 2, diazomethane-methylated aspen, native lignin (concn. 0.021, g./l.); 3, spruce native lignin[10] (concn. 0.03 g./l.).

**Acknowledgment.**—The authors are indebted to the Analytical Department of The Institute of Paper Chemistry for some of the analyses reported in this paper.

## Summary

A native hardwood lignin has been isolated from aspenwood. After purification, the product contains 19.5% methoxyl. On treatment with 72% sulfuric acid, using the Klason procedure, the methoxyl content is increased to 20.4%. A unit of native aspen lignin containing six methoxyl groups also contains six hydroxyl groups, one of which is phenolic in nature. The ultraviolet absorption spectrum of the aspen lignin differs from that of softwood lignins in that no well-defined maximum is present.

APPLETON, WISCONSIN RECEIVED OCTOBER 16, 1948

(9) All dioxane used in this investigation was purified by refluxing and distilling over sodium.

(10) J. S. Barton, Ph.D. dissertation, The Institute of Paper Chemistry, 1947.

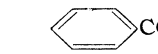
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Sulfur-Containing Amines. VII.[1] Local Anesthetics. II

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

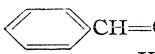
A logical extension of local anesthetic type compounds derived from the 4-aminobenzoyl nucleus and sulfur-containing amines[2] is to analogous types containing other parent nuclei. Gilman, *et al.*,[3] have shown, in a correlation of therapeutic activity with aromaticity, that the dialkylaminoalkyl esters of cinnamic acid are more effective than the corresponding benzoate esters; this observation has been extended by McElvain[4] to a series of methylpiperidinoalkyl benzoates and cinnamates. In the latter series it was shown that activity was highest with the cinnamates; however, in general, toxicity was found to increase proportionally. It is also interesting to note in this connection that Gardner, *et al.*,[5] have succeeded in lowering toxicity with retention of activity in the cinnamate series, through the use of esters containing the terminal morpholine group.

The present report describes a representative series of benzoates (I), benzamides (II–III), cinnamates (IV), cinnamamides (V, VI) and 2-butyloxycinchonyl derivatives (VII, VIII) derived from



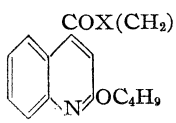
$COX(CH_2)_nS(CH_2)_mNR_2$

I, X = O
II, X = NH
III, X = $NC_2H_5$



$CH{=}CHCOX(CH_2)_nS(CH_2)_mNR_2$

IV, X = O
V, X = NH
VI, X = $NC_2H_5$



$COX(CH_2)_nS(CH_2)_mNR_2$

VII, X = O
VIII, X = NH

certain of the sulfur-containing amines previously reported,[6] with the purpose of ascertaining whether the high therapeutic index associated with the related 4-aminobenzoyl types[2] could be extended to non-aminated nuclei. Compounds of types VII and VIII were of especial interest, since they contain the parent nucleus of the very active but very toxic substance, Dibucaine.

All of the above compounds were prepared by standard procedures with little difficulty. The pharmacological results will be reported upon by Dr. T. J. Becker and Dr. F. P. Luduena of these Laboratories at a later date. In general, it may be stated here that most of the compounds were of a low order of activity.

## Experimental[7]

**Esters and Amides, I–VI.**—The esters were prepared from a slight excess of acid chloride and the appropriate alcohol[6] in cold dry benzene, and the amides from an excess of acid chloride and the amine[6] in chloroform–water mixture in the presence of sodium bicarbonate, with due precautions to avoid decomposition of the amines.[2] In general the bases were isolated in the usual manner and purified by washing with dilute sodium hydroxide solution. In certain cases distillation was necessary to provide bases suitable for conversion to salts. The yields varied from 80–95%.

**1-(2-Dimethylaminoethylmercapto)-propyl-2 benzoate hydriodide, I,** cottony white needles from isopropyl alcohol, m. p. 119.5–120.8°.

*Anal.* Calcd. for $C_{14}H_{22}INO_2S$: S, 8.11; HI, 32.36. Found: S, 8.25; HI, 32.70.

**2-(3-(Piperidyl-1)-propylmercapto)-ethyl benzoate hydriodide, I,** white needles from absolute alcohol, m. p. 116.0–117.5°.

*Anal.* Calcd. for $C_{17}H_{26}INO_2S$: S, 7.36; HI, 29.38. Found: S, 7.42; HI, 29.24.

**3-(3-(Piperidyl-1)-propylmercapto)-propyl benzoate, I,** pale yellow viscous oil, b. p. 147–148° at 0.05 mm.

*Anal.* Calcd. for $C_{18}H_{27}NO_2S$: N, 4.35; S, 9.97. Found: N, 4.35; S, 9.74.

The **citrate** formed rosettes of small white needles from absolute alcohol–acetone, m. p. 68.3–70.5°.

*Anal.* Calcd. for $C_{24}H_{35}NO_9S$: S, 6.24; N, 2.72. Found: S, 6.08; N, 2.85.

**2-(3-(Piperidyl-1)-propylmercapto)-ethyl cinnamate hydrochloride, IV,** small white needles from isopropyl alcohol, m. p. 131–134°.

*Anal.* Calcd. for $C_{19}H_{28}ClNO_2S$: S, 8.66; Cl, 9.58. Found: S, 8.68; Cl, 9.57.

**N-(2-(2-Diethylaminoethylmercapto)-ethyl)-benzamide citrate, II,** small white needles from absolute alcohol–ethyl acetate, m. p. 118–121°.

*Anal.* Calcd. for $C_{21}H_{32}N_2O_8S$: N, 5.93; S, 6.78. Found: N, 5.75; S, 6.80.

**N-(2-(2-(Piperidyl-1)-ethylmercapto)-ethyl)-benzamide hydrochloride, II,** needles from absolute alcohol–acetone, m. p. 118–120°.

*Anal.* Calcd. for $C_{16}H_{25}ClN_2OS$: S, 9.74; Cl, 10.78. Found: S, 9.78; Cl, 10.85.

**N-(2-(2-Diethylaminoethylmercapto)-ethyl)-cinnamamide citrate, V,** rosettes of white prisms from absolute alcohol–ethyl acetate, m. p. 82.5–85.0°.

*Anal.* Calcd. for $C_{23}H_{34}N_2O_8S$: N, 5.62; S, 6.43. Found: N, 5.45; S, 6.36.

**N-Ethyl-N-(2-(2-Diethylaminoethylmercapto)-ethyl)-benzamide hydrochloride, III,** white needles from ethyl acetate–Skellysolve B, m. p. 101.6–102.6°.

*Anal.* Calcd. for $C_{17}H_{29}ClN_2OS$: N, 8.07; S, 9.24. Found: N, 8.12; S, 9.40.

**N-Ethyl-N-(2-(2-Diethylaminoethylmercapto)-ethyl)-cinnamide hydrochloride, VI,** prisms from acetone–Skellysolve A, m. p. 105.2–107.6°.

(1) Paper VI: Fohlen, Huber, Laskowski and Clinton, THIS JOURNAL, **71**, 642 (1949).

(2) Clinton, Salvador, Laskowski and Suter, *ibid.*, **70**, 950 (1948).

(3) Gilman, *et al.*, *ibid.*, **47**, 245 (1925); **50**, 437 (1928).

(4) (a) McElvain, *ibid.*, **49**, 2835 (1927); (b) Bailey and McElvain, *ibid.*, **52**, 2007 (1930).

(5) Gardner, Clarke and Semb, *ibid.*, **55**, 2999 (1933).

(6) (a) Clinton, *et al.*, *ibid.*, **67**, 594 (1945); (b) Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

(7) All melting points and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

*Anal.* Calcd. for $C_{19}H_{31}ClN_2OS$: N, 7.51; Cl, 9.50. Found: N, 7.38; Cl, 9.64.

**2-Butyloxyquinoline-4-carboxylic Acid Derivatives.**—These compounds were readily prepared from 2-butyloxyquinoline-4-carbonyl chloride[8] and the amine or alcohol in dry benzene.

**2-(2-Diethylaminoethylmercapto)-ethyl 2-butyloxyquinoline-4-carboxylate hydrochloride, VII,** white leaflets from ethyl acetate, m. p. 125.8–127.0°.

*Anal.* Calcd. for $C_{22}H_{33}ClN_2O_3S$: N, 6.35; Cl, 8.04. Found: N, 6.20; Cl, 8.03.

**2-(3-(Piperidyl-1)-propylmercapto)-ethyl 2-butyloxyquinoline-4-carboxylate hydrochloride, VII,** waxy white needles from isopropyl alcohol, m. p. 118.4–120.4°.

*Anal.* Calcd. for $C_{24}H_{35}ClN_2O_3S$: N, 6.01; Cl, 7.61. Found: N, 6.01; Cl, 7.56.

**N-(2-(2-Diethylaminoethylmercapto)-ethyl 2-butyloxyquinoline-4-carboxamide, VIII,** long slender white needles from Skellysolve B, m. p. 63.5–64.5°.

*Anal.* Calcd. for $C_{22}H_{33}N_3O_2S$: N, 10.41; S, 7.94. Found: N, 10.31; S, 8.08.

The **citrate** formed tiny white prisms from absolute alcohol–ethyl acetate, m. p. 87.5–90.5° (dec.).

*Anal.* Calcd. for $C_{28}H_{41}N_3O_9S$: N, 7.05; S, 5.38. Found: N, 6.83; S, 5.22.

(8) Gardner and Hammel, THIS JOURNAL, **58**, 1360 (1936), report 37–51% yields of 2-alkoxycinchonyl chlorides, with accompanying by-products of the 2-alkoxycinchoninic acid hydrochloride. Modification of their procedure, by inclusion of a one hour reflux period of the acid–thionyl chloride–benzene mixture, increased the yields of acid chlorides to 95–97%, with no formation of 2-alkoxycinchoninic acid hydrochloride.

## Summary

There has been described the preparation of a series of esters and amides derived from sulfur-containing amines.

RENSSELAER, NEW YORK RECEIVED NOVEMBER 9, 1948

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# A Family of Long-Acting Depressors[1,2]

BY RICHARD BALTZLY, JOHANNES S. BUCK,[3] EDWIN J. DE BEER AND FREDERICK J. WEBB[4]

Some years ago Ide and Buck[5] prepared a number of N-methyltetrahydro*iso*quinolines by the cyclization of the appropriate N-methylphenethylamines with formalin and hydrochloric acid. A pharmacological study was performed by Fassett and Hjort,[6] who found all but one member of this group to be weak pressors or depressors with transient action, while 6-ethoxy-N-methyltetrahydro*iso*quinoline was an extremely potent depressor with a long period of action. While correlation of physiological action with chemical structure is on essentially an empirical basis at present, such correlation within classes of related compounds usually is fairly good. It was therefore felt that the physiological results cast grave doubt on the purity and identity of this sample of 6-ethoxy-N-methyltetrahydro*iso*quinoilne.

An authentic specimen of 6-ethoxy-2-methyltetrahydro*iso*quinoline hydrochloride was prepared by an alternative route.[7] The new sample had none of the remarkable physiological activity of the older specimen. Further fractionation of material prepared according to the formalin procedure afforded a sample more nearly resembling the authentic (new) specimen. De-ethylation of the original material also yielded a sample of 6-hydroxy-N-methyl tetrahydro*iso*quinoline hydrochloride identical with an authentic specimen of this substance. It was thus evident that the Ide and Buck material was preponderantly 6-ethoxy-N-methyl tetrahydro*iso*quinoline hydrochloride contaminated by a small amount of a highly potent depressor substance whose physical properties and composition were not markedly different from those of the major component.

A number of formalin cyclizations of 3-ethoxyphenethylmethylamine followed by attempts to fractionate the reaction products gave rather irregular results. Usually such preparations, like the original one, produced strong, lasting depression of blood pressure when administered intravenously to anesthetized dogs in doses of 1 mg./kg. body weight. One specimen, a chloroform-insoluble hydrochloride obtained by successive precipitations from chloroform solution by ethyl acetate, was about four times as active.

Serious progress in elucidating the nature of the unknown depressor was not made until a change in the amine under study was effected. Cyclization of a phenethylamine to a tetrahydroisoquinoline by the formalin–hydrochloric acid procedure is effective only when there is an activating group para to the cyclization-point. Ortho and para methoxyphenethylmethylamines are not cyclized by this method. When these amines were treated by the usual procedure, however, the products were by far the most active depressors so far obtained. It was now possible to secure a fall in the blood-pressure of 100 mm. of mercury lasting for an hour or more with doses of the

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Washington Meeting, August, 1948.

(2) The work here reported is part of a project carried out in collaboration with a pharmacological group in these laboratories headed successively by A. M. Hjort and E. J. de Beer. The detailed pharmacological study will be published separately.

(3) Present address: Sterling-Winthrop Research Institute, Rensselaer, N. Y.

(4) Present address: Firestone Rubber Co., Akron, Ohio.

(5) Ide and Buck, THIS JOURNAL, **59**, 726 (1937).

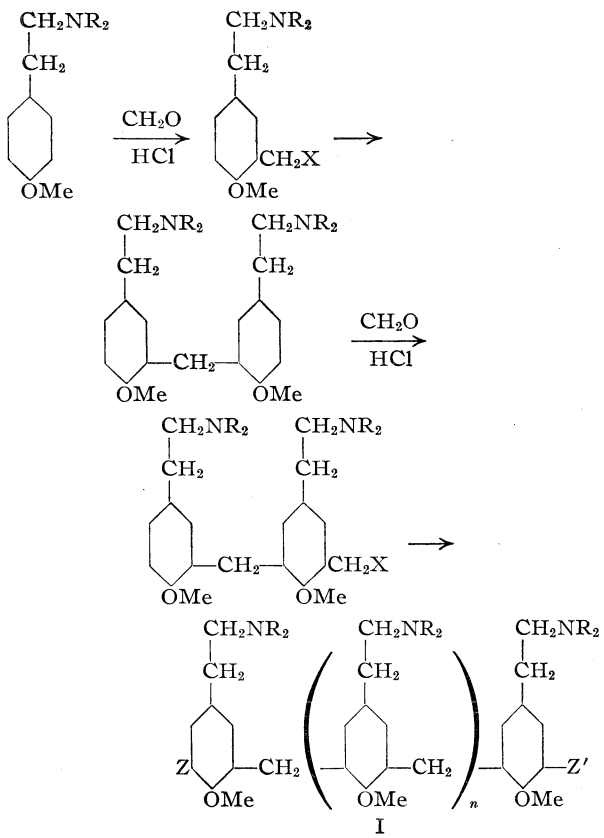
(6) Fassett and Hjort, *J. Pharmacol. Exptl. Therap.*, **63**, 253 (1938).

(7) Hjort, de Beer, Buck and Randall, *ibid.*, **76**, 64, 252 (1942).

order of 0.1 mg./kg. body weight.[8] This indicated that the depressor type was not a tetrahydro*iso*quinoline.

Two main possibilities remained: cross-linking between nitrogen atoms by formaldehyde, and formation of methylene links between aromatic nuclei. The first possibility was eliminated when it was found that hordenine methyl ether and its metho-chloride both yielded preparations of maximum potency. It was therefore probable that the depressor type was formed by the sort of reaction shown in Chart I.

CHART I




I

wherein X might be Cl or OH and Z and Z′ could be H or $CH_2OH$ or $CH_2Cl$. The conditions of the reaction are essentially those of a mild chloromethylation and formation of a condensation polymer as indicated in Chart I is not at all surprising.

The optimum conditions for the condensation were found to be when the formalin was approximately equimolecular with the amine, when the hydrochloric acid was about 6*N*, and when heating was continued for about four hours on the steam-bath. The products so obtained were light colored glasses when dried thoroughly. They exhibited the usual amine-hydrochloride solubilities and could be ground to powders under ether. Precipitation from absolute ethanolic solution by ethyl acetate and ether under controlled conditions gave filterable powders that appeared granular to gross inspection and which were not clearly crystalline or non-crystalline under the microscope. Such powders, however, were incapable of seeding out more material from solutions in alcohol brought to the point of turbidity by addition of ether, and undoubtedly were not truly crystalline. Further fractionation revealed a variety of components.

When a "Standard Preparation" from *p*-methoxyphenethylmethylamine was dissolved in water, perchloric acid and ammonium perchlorate were added and the solution was refrigerated, a solid perchlorate separated. This material, doubtfully crystalline to start with, became definitely crystalline on recrystallization from water and could be transformed to a crystalline hydrochloride. This hydrochloride had a composition consistent with that of a "dimer" (I, $n = 0$, $Z = Z' = H$). The base corresponding gave a molecular weight in agreement with this formulation. The "dimer" base distils at about 120° at 0.5 $\mu$ pressure. On the basis of the amounts of perchlorate isolable about a third of the "standard preparation" is "dimer." This material is nearly inactive physiologically giving a weak depression of short duration.

After removal of the "dimer" as its perchlorate, partial basifications followed by extraction with ether and later ether–ethyl acetate mixtures produced a series of base fractions. All were oils and were increasingly viscous and diminishingly soluble in ether as the basification proceeded. The more ether-soluble fractions gave "molecular weights" about right for a "trimer," the less ether-soluble fractions were probably more highly polymerized; their Rast values were about right for the "tetramer." In high vacuum the "trimer fraction" was partially distillable, perhaps with some decomposition. The distillate (boiling around 200° at 0.3 $\mu$ pressure) was highly active; it left a residue on redistillation. It is not clear whether this residue consists of higher molecular material initially present or produced by further condensation during the distillation. Some of these residues proved to be reactive on testing, but some were too insoluble for investigation.

The above experiments indicated that the physiological activity was associated with trimeric and tetrameric condensation products. Attempts at crystallizing such fractions were not successful and further fractionation appeared required. The most fruitful results were obtained by the use of Craig's method of counter-current distribution[9] on the product from the condensation

(8) We have not been able to improve on this potency. Some fractions obtained subsequently were undoubtedly more homogeneous and probably more potent. Unfortunately, the physiological assay will not differentiate clearly between preparations whose activity is in the ratio of 3:2. As will be seen this is about the greatest ratio of potencies that could be expected between a pure component and a total reaction mixture of this type.

(9) Craig, *J. Biol. Chem.*, **155**, 519 (1944); Craig, Golumbic, Mighton and Titus, *ibid.*, **161**, 321 (1945); Williamson and Craig, *ibid.*, **168**, 687 (1947).

of *p*-methoxyphenethyldimethylamine with formaldehyde. This polymer is perhaps less active than that from the corresponding secondary amine but appeared more suitable for investigation. An eight-plate fractionation between 50% benzene–hexane and 75% methanol–water yielded two fractions. The more hydrophobic of these, which contained about two-thirds of the active material, was presumably free of hydroxymethyl groups since it gave no gas in a Zerewitinoff machine. The more hydrophilic fraction could be separated further by a repeated distribution using 55% methanol as the lower phase. The separation was only approximate but indicates the presence of low polymers having one hydroxymethyl group and of another type having two. All of these fractions were highly potent, and equally potent within the limits of accuracy of the physiological assay. So far, however, no active fraction has yielded crystalline salts. It is to be expected that molecules of this type would not crystallize readily and failure to crystallize them is not in itself proof of non-homogeneity but their physical properties taken together with the analytical data seem to indicate that separation had been made only between types, not between species.[10]

Condensations between formaldehyde and amines with shorter side chains resulted in qualitatively similar products. Those from *p*-methoxybenzylmethylamine and *p*-methoxybenzyldimethylamine were somewhat less potent and more toxic. The proportion of dimer was higher and the general state of polymerization appeared to be lower. This would be anticipated on the general principles of aromatic substitution since a cationic group only one stage removed from a benzene ring is well known to interfere appreciably with substitution.[11]

Condensation products of the same general type were also obtained from *o*-anisidine. The polymeric aromatic bases had no depressor action but the derived methiodides were fairly potent. This would seem to show that activity is dependent on the presence of groups that would be cationic under physiological conditions and suggests that a molecule of the approximate dimensions of a "trimer" and possessing two or three properly spaced cationic groups should exhibit strong depressor action. Experiments in this direction have been in progress and will be reported separately.

## Experimental

**Physiological Testing.**—Since evaluation of the chemical work was at all times dependent on physiological assay a few remarks about the methods used and their interpretation are desirable even though the pharmacology of these depressors is to be reported elsewhere. In Table I are shown typical results selected from the very large number available. The preparations tested are identified by code numbers referring to the section "Chemical Manipulations."

TABLE I

POTENCIES OF TYPICAL DEPRESSOR PREPARATIONS

| Specimen (Code number) | Potency | Specimen (Code number) | Potency |
|---|---|---|---|
| IV-132 | ++ | GC-60 | + |
| Q-190C | +++ | GC-55 | + |
| M-25 | ++ | GC-125 I | ++++ |
| M-27 | ++ | GC-125 II | ++++ |
| GD-6 | + | GC-69A | ++++ |
| GC-142-1 | + | GC-69B | ++++ |
| GC-142-2 | ++ | GC-131-2 | ++++ |
| GC-142-3 | +++ | GC-131-3 | ++++ |
| GC-142-4 | ++++ | GC-132-8 | ++++ |
| GC-142-5 | +++ | M-124 res. | ++++ |
| M-96 | +++ | GC-114 | ++++ |
| GC-81 II | ++++ | GC-114 II | ++++ |
| M-118 | ++++ | GC-104 II | + |
| M-114 | ++++ | GC-110 | +++ |

Assay was carried out by injecting aqueous solutions intravenously into anesthetized dogs in the usual set-up for observation of blood pressure. In the earlier period of this work chief attention was given to discovering the minimum effective dose for the preparation used. This led to irregularities since relatively few animals could be tested and individual variations in sensitivity were considerable. It was later decided to administer standard doses (usually 0.4 mg./kg.) of the more potent preparations and to evaluate the response by the magnitude and duration of depression. Such methods might distinguish one preparation from another of twice the potency but smaller differences are not detected with certainty.

Potency is indicated in Table I by the notations ++++, +++, etc. The maximum potency is ascribed to preparations that in doses of 0.02–0.05 mg./kg. body weight lowered the blood pressure by about 30 mm. (of mercury) and whose effect lasted at least fifteen minutes *or*, by the later method of testing, gave depressions of 90 mm. or more lasting at least one hour in doses of 0.1–0.4 mg./kg. Preparations giving only short depressions (five to ten minutes) of small amplitude in doses of 1 mg./kg. are indicated with +. The notations +++ and ++ show samples of intermediate activity.

**Chemical Preparations.**—Sample IV-132 was the original specimen of "6-ethoxy-2-methyltetrahydroisoquinoline hydrochloride."[5]

Q-190-C was prepared from a repeat preparation of IV-132 by repeated solution in chloroform and precipitation with ether. Q-190-C represented a final, chloroform-insoluble fraction.

**Standard Preparations.**—For these preparations the base was suspended in water and the whole chilled in ice. An exact equivalent of formalin solution was added followed by sufficient concentrated hydrochloric acid to make the final concentration 6 *N*. (As an example, 12.4 g. of N-methylhomoanisylamine was suspended in 15 cc. of water and 5.85 cc. of formalin solution added slowly, followed by 30 cc. of cold concentrated hydrochloric acid.) The flask was then covered with a watch-glass and heated on the steam-bath for four hours. All preparations subsequently identified as "standard preparation" were subjected to this treatment. GC-142-1 received one hour of heating, GC-142-2 two hours and the other GC-142 samples the number of hours indicated by the last digits. It will be observed that GC-142-4 was the most potent. A minor variation was to extract the amine-formaldehyde reaction mixture with ether before adding acid, to evapo-

(10) The occurrence of methylene substitution in positions other than those ortho to the methoxyl groups, while doubtless of minor quantitative importance, is to be expected and would add to the complexity of the polymer mixture, while presumably having little influence on the physiological properties.

(11) *Cf.* Goss, Houbart and Ingold, *J. Chem. Soc.*, 250 (1927); Ingold and Wilson, *ibid.*, 810 (1927).

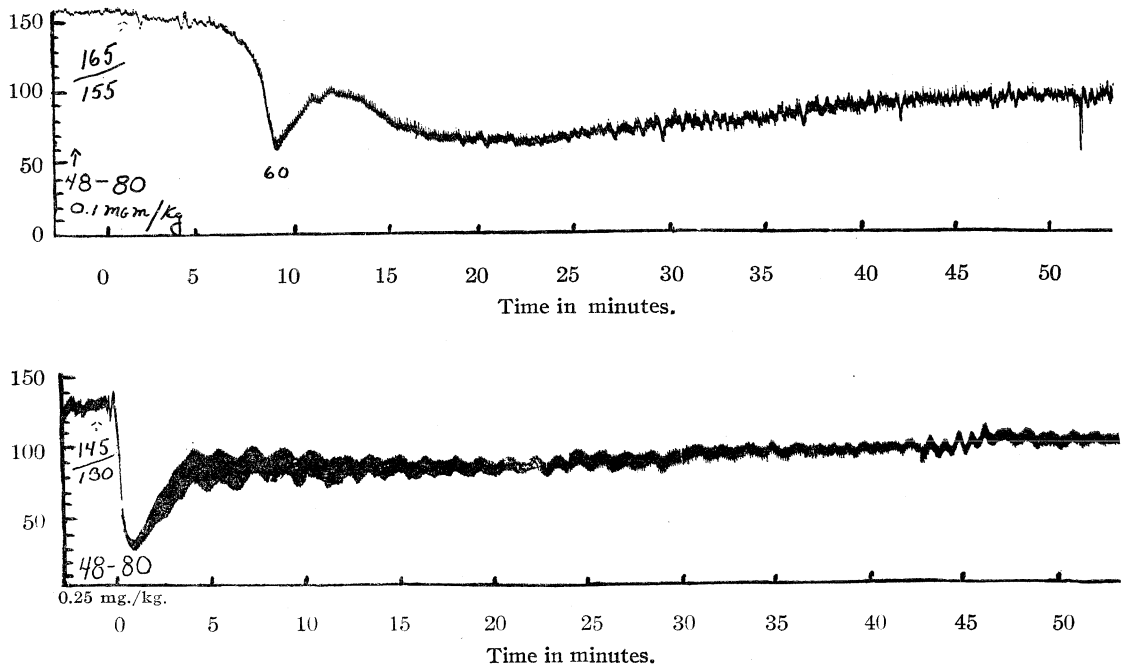



Fig. 1.—Blood pressure tracings for "Standard Preparations." The vertical scale indicates pressure in mm.

rate the ether and heat with acid as before. The products so obtained were not distinguishable from those previously described and the term "standard preparation" is intended to cover both. After completion of the heating period, the solution was evaporated *in vacuo* on the steam-bath and the residue was dissolved in a minimum of absolute ethanol (about 40 cc. for the quantity previously quoted). To the hot ethanolic solution was added an equal volume of ethyl acetate and the solution, which set to a jelly on cooling, was refrigerated overnight. About two volumes of anhydrous ether were then stirred in whereby the jelly was broken up to a colorless suspension of granular appearance. This was filtered rapidly, washed with anhydrous ether and dried *in vacuo*. Figure 1 shows typical blood pressure tracings with a "standard preparation" from *p*-methoxyphenethylmethylamine administered in two dose levels as indicated.

M-25 was a "standard preparation" from 3,4-dimethoxyphenethylmethylamine, M-27 from 2,3-dimethoxyphenethylmethylamine, GD-6 from hordenine. M-96 was a "standard preparation" from hordenine methyl ether and M-118 from hordenine methyl ether methochloride. The five samples GC-142-1 through GC-142-5 were obtained from *p*-methoxyphenethylmethylamine as previously indicated. M-114 was prepared from *o*-methoxyphenethyldimethylamine, GC-114 from *p*-methoxybenzylmethylamine, and GC-104 II from *o*-anisidine. GC-110 was the quaternary salt formed by the methylation of GC-104 II with methyl iodide in methanol (in the presence of sodium carbonate).

### Isolation of "Dimers"

**GC-60 from *p*-Methoxyphenethylmethylamine.**—This was prepared by a variation of the "standard preparation" using perchloric acid instead of hydrochloric. To 6.4 g. of base was added 3.0 cc. of formalin and 20 cc. of 20% perchloric acid in the cold. The mixture was heated two hours on the steam-bath and placed in the refrigerator. The gummy solid that separated was crystallized twice from water giving 3.7 g. of a colorless micro crystalline powder. The perchlorate was converted to the base and transformed to the hydrochloride which melted at 261–262° (m. p. not raised by four recrystallizations from ethanol-ether mixtures).

*Anal.* Calcd. for $C_{21}H_{32}Cl_2N_2O_2$: C, 60.69; H, 7.77 Calcd. for $C_{32}H_{49}Cl_3N_3O_3$: C, 60.9; H, 7.84. Found: C, 60.91; H, 7.30.

The base was again liberated from its salt and was distilled at 0.4 $\mu$ pressure, bath temperature, 125–130°. By the Rast method the base showed a molecular weight of 329 (calcd. for $C_{21}H_{30}N_2O_2$, 342). On reconversion to the hydrochloride the m. p. was 264–265°.

**GC-55 from 4-Methoxy-3-methylphenethyldimethylamine.**—This amine was condensed with formalin and hydrochloric acid in the expectation that the "dimer" would be obtained to the virtual exclusion of other material. Actually, considerable amounts of more highly polymerized bases were formed (as shown by distillation of the base in high vacuum). The presumed "dimer" was isolated in poor yield from the reaction mixture by repeated crystallizations from ethanol–ether mixtures, m. p. 221–222°.

*Anal.* Calcd. for $C_{25}H_{40}Cl_2N_2O_2$: C, 63.66; H, 8.56. Calcd. for $C_{36}H_{57}Cl_3N_3O_3$: C, 63.88; H, 8.61. Found: C, 63.47; H, 8.51.

The analysis fits either a "dimer" or a "trimer," but in view of the failure to obtain any "trimer" crystalline that possibility appears remote. Some of the starting amine was recovered from the reaction mixture but since its hydrochloride melts at 181–182°, the 221–222° material is clearly a condensation product.

**GC-125-I and GC-125-II.**—These were products from an attempt to conduct a condensation so as to favor formation of a "trimer." Four grams of formalin solution, 9.65 g. of 4-methoxy-3-methylphenethyldimethylamine and 48 g. of concentrated hydrochloric acid were held at 30–40° for two hours during which time a current of hydrogen chloride was passed through the solution. The reaction mixture was then evaporated *in vacuo*. It was hoped that at this stage the main constituent would be a mono-chloromethyl derivative. To the residue from evaporation was then added 5.4 g. of *p*-methoxyphenethyldimethylamine hydrochloride and 10 cc. of concentrated hydrochloric acid and the solution was heated on the steam-bath for seven hours. The reaction mixture was again taken down *in vacuo*, redissolved in water and basified. GC-125-I was the fraction of base soluble in ether while GC-125-II was insoluble in ether but soluble in

ethyl acetate. The former fraction, as a base, had a "molecular weight" of 520 (Rast method). Both fractions were tested as hydrochlorides.

**GC-114-II.**—A portion (275 mg.) of base from the "standard preparation" with *p*-methoxyphenethylmethylamine (GC-114) was subjected to distillation up to 130° at 0.3 μ pressure. There distilled 115 mg. of oil giving a "molecular weight" of 244 (calcd. for "dimer," 314). The residue (GC-114-II), weighed 140 mg. and showed a "molecular weight" of 496 (calcd. for "trimer," 477).

**Counter-current Distribution.**—A "standard preparation" from hordenine methyl ether was largely freed of "dimer" by partial basification of its aqueous solution and solvent extraction. Fraction GC-81-II represented about 70% of the original preparation, about 25% being in the "dimer" fraction first removed. Two 1-g. portions of GC-81-II were separately subjected to distributions by the Craig method (using separatory funnels) between 50-50 benzene-hexane and 75% aqueous methanol (120 cc. of each solvent mixture in each funnel). On completion of an "eight-plate" distribution (with Tube 0 containing the initial upper layer and Tube 8 the final lower layer) the contents of each funnel was evaporated separately. The evaporation residues from the tubes in Run 2 were as follows: Tube 0, 50 mg.; Tube 1, 155 mg.; Tube 2, 205 mg.; Tube 3, 170 mg.; Tube 4, 110 mg.; Tube 5, 60 mg.; Tube 6, 65 mg.; Tube 7, 100 mg.; Tube 8, 110 mg. It was evident that about two-thirds of the material was contained in Tubes 0–4, inclusive, and that a separate hydrophilic component was concentrated in Tubes 7–8. Run 1 was an almost exact duplicate, but Tube 8 was lost by an accident.

The combined contents of Tubes 1–3 of the two runs amounting to 1.08 g. was redistributed and now gave a curve indicating homogeneity (Tubes 6, 7 and 8 contained 30, 15 and 20 mg., respectively). The contents of Tubes 2 and 3, transformed into hydrochlorides, were tested as GC-131-2 and GC-131-3. GC-131-2 gave no gas in the Zerewitinoff machine.

The combined contents of Tube 7 of Run 1, Tubes 7 and 8 of Run 2 and Tubes 7 and 8 of a third similar run, totaling 490 mg. was redistributed in the same fashion. The contents of Tubes 0–8 were as follows: Tube 0, 15 mg.; Tube 1, 5 mg.; Tube 2, 5 mg.; Tube 3, 10 mg.; Tube 4, 10 mg.; Tube 5, 35 mg.; Tube 7, 80 mg.; Tube 7, 155 mg.; Tube 8, 185 mg. The contents of Tube 8 was analyzed (as the base).

*Anal.* Calcd. for $C_{37}H_{55}N_3O_5$ (trimer with two hydroxy methyl groups): C, 71.40; H, 8.84; m. wt., 621. Found: C, 72.18; H, 8.72; m. wt., 630.

In a Zerewitinoff machine 14.77 mg. gave 1.20 cc. of gas at 25° and 771 mm. = 1.12 cc. at 0° and 760 mm. Calcd. for m. wt. 621 and two active hydrogen atoms: 1.07 cc. The remainder of this sample was dissolved in dilute hydrochloric acid and tested as GC-132-8.

One-tenth g. of fraction GC-131-2 was distilled as base, three fractions being taken. The first, boiling up to 175° at 0.2 μ weighed 40 mg. and gave a "molecular weight" of 296. Distillation was continued on the residue but nothing came over below 195°. A total of 25 mg. distilled, mainly at 208°. This showed a "molecular weight" of 572. (Calcd. for "trimer" with no hydroxy methyl groups, 561.) The residue weighed 25 mg. and showed a "molecular weight" of 557. It seems likely that the material suffered some decomposition.

Several larger distributions having been made, several terminal fractions amounting to 655 mg. were united and redistributed between 50-50 benzene–hexane and 55% aqueous methanol. The contents of Tubes 0–8 were as follows: Tube 0, 135 mg.; Tube 1, 95 mg.; Tube 2, 70 mg.; Tube 3, 75 mg.; Tube 4, 55 mg.; Tube 5, 40 mg.; Tube 6, 50 mg.; Tube 7, 45 mg.; Tube 8, 90 mg. The contents of Tube 0 gave a "molecular weight" of 746 (in camphor). The "tetramer" with one hydroxy methyl group would have mol. wt., 782. 27.8 mg. in the Zerewitinoff machine gave 0.61 cc. of gas (reduced to 0° and 760 mm.). Calcd. for mol. wt. of 782 with one active hydrogen, gas = 0.80 cc.

The contents of Tube 8 was not sufficiently soluble in camphor for a molecular weight determination. In borneol (observed mol. m. p. depression 33°; lit. value, 35.6°) the "molecular weight" was 567 (or 612 using the literature m. p. depression). A "trimer" with two hydroxy methyl groups would have mol. wt. = 621. In the Zerewitinoff machine 25.6 mg. gave 1.57 cc. of gas (reduced to 0° and 760 mm.). Calcd. for "trimer" with two active hydrogens, 1.85 cc.

**Acknowledgment.**—The authors wish to express their gratitude to Mr. Samuel Blackman, who performed the microanalyses, and to Mr. Lloyd Wnuck for assistance in preparing the blood pressure tracings.

## Summary

1. The condensation of formaldehyde with alkoxyphenalkylamines in the presence of acid results in mixtures of low-polymeric bases that have been only partially separated into their constituents.

2. Those polymers having three or four residues of the parent amine joined by methylene groups between the rings have a pronounced and enduring effect in lowering the blood pressure.

3. Evidence is presented that some of these polymers have one or two hydroxy methyl groups attached (presumably to the terminal rings). Presence or absence of these groups is not critical to the effect on the blood pressure.

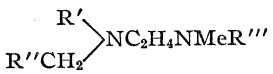
TUCKAHOE 7, NEW YORK RECEIVED OCTOBER 15, 1948

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF LAKESIDE LABORATORIES, INC.]

# Antihistaminics. I. Some Ethylene Diamines and an Aminoether

BY JOHN H. BIEL

In the course of a search for new antihistaminic agents we have investigated the effect of substituting chloro and methoxy as well as various heterocyclic groups into different moieties of compounds possessing antihistaminic activity. With one exception the compounds prepared conformed to the general formula



where R′ was a substituted or unsubstituted phenyl, 2-pyridyl or 2-pyrimidyl radical, R″ was a phenyl, substituted phenyl, 2-thienyl or 2-furyl radical and R‴ was a methyl or isopropyl group. In addition we prepared a furan analog of "Benadryl"

$C_4H_3OCH(Ph)OC_2H_4NMe_2$, $(Ph)_2CHOC_2H_4NMe_2$ (Benadryl)

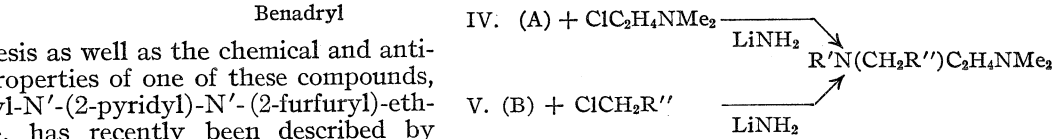
The synthesis as well as the chemical and antihistaminic properties of one of these compounds, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-furfuryl)-ethylenediamine, has recently been described by Vaughan and Anderson.[1] The authors reported a 15% yield of the purified base which was described to be quite unstable even at temperatures of −80° and to polymerize in the presence of mineral acids. We prepared the pure tertiary amine in 54% yield by condensing N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine[2] with freshly distilled 2-furfuryl chloride[3] in the presence of lithium amide (procedure V). The light yellow oil could be stored in the refrigerator for a long period of time without decomposition. Its dihydrochloride salt proved to be non-hygroscopic and stable on storage at room temperature. Its 1% aqueous solution has not shown any loss in antihistaminic activity in the guinea pig ileum test after being stored in the refrigerator for a considerable length of time.

The intermediate secondary amines of the pyridine and pyrimidine series (R″ = phenyl or substituted phenyl) were prepared by condensing 2-aminopyridine, 2-aminopyrimidine or their substituted derivatives with either the appropriate araldehyde in the presence of formic acid[4] (method I) or with the corresponding chloromethyl compound in toluene using lithium amide as the condensing agent (method II).

The intermediate secondary ethylenediamines $R'NHC_2H_4NMe_2$ (R′ = 2-pyridyl, 2-pyrimidyl, phenyl or substituted phenyl) were obtained by treating the primary amine with β-dimethylaminoethyl chloride in the presence of either anhydrous potassium carbonate[5,6] or lithium amide[6] according to general methods described in the literature (method III).

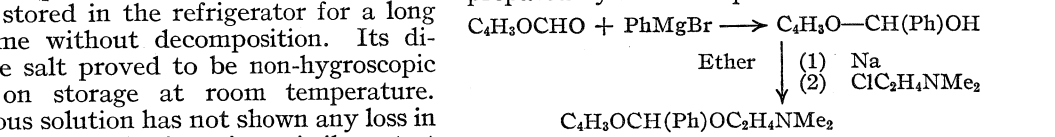


The tertiary amines were obtained by the alkylation of (A) by method IV or the aralkylation of (B) by method V using lithium amide in dry toluene as the condensing agent



They were then converted to water soluble salts in which form they were evaluated pharmacologically. The N-isopropyl analog of "Pyribenzamine" did not form a solid derivative. For the purpose of pharmacological testing the base was dissolved in dilute acetic acid and the *p*H of the aqueous solution adjusted to 6.8.

The furan analog of "Benadryl" was readily prepared by standard procedures.



The tertiary amino ether proved to be quite unstable in the presence of mineral acids, but in dilute acetic acid solution it was stable long enough to be tested pharmacologically.

The physical properties and analytical data of the secondary and tertiary amines are summarized in Tables I and II, respectively. The data on the antihistaminic activities are to be found in Table II. For the synthesis of the tertiary amines procedure IV was used except where it is otherwise indicated.

Preliminary *in vitro* studies on the isolated guinea pig ileum strip indicate the furyl isosteres of "Pyribenzamine" (PBZ), N,N-Dimethyl-N′-(2-pyridyl)-N′-benzylethylenediamine, and "Antergan," N,N-dimethyl-N′-phenyl-N′-benzyl-

(1) Vaughan and Anderson, THIS JOURNAL, **70**, 2607 (1948).

(2) Whitmore, Mosher, Goldsmith and Rytina, *ibid.*, **67**, 393 (1945).

(3) Kirner, *ibid.*, **50**, 1955 (1928).

(4) Tchitchibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

(5) Leonard and Solmssen, THIS JOURNAL, **70**, 2065 (1948).

(6) Huttrer, Djerassi, Beears, Mayer and Scholz, *ibid.*, **68**, 1999 (1946).

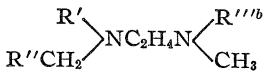
TABLE I

SECONDARY AMINES $R_1$—$NHR_2$

| $R_1$ | $R_2$ | Procedure | B. p., °C. | B. p., Mm. | M. p., °C. | Yield, % | Formula | N Analyses, % Calcd. | N Analyses, % Found |
|---|---|---|---|---|---|---|---|---|---|
| 2-(4-Methoxy)-pyrimidyl | $-CH_2C_6H_5$ | II | | | 85–87 | 23 | $C_{12}H_{13}N_3O$ | 19.55 | 19.50 |
| 2-(5-Chloro)-pyridyl | $-CH_2C_6H_5$ | I | | | 119–119.5 | 54 | $C_{12}H_{11}ClN_2$ | 12.81 | 12.70 |
| 2-(5-Chloro)-pyridyl | $-CH_2C_6H_4OMe$ | I | | | 158–159 | 36 | $C_{13}H_{13}ClN_2O$ | 11.27 | 11.05 |
| *p*-Isopropyl-phenyl | $-C_2H_4NMe$ | III | 113–115 | 0.2 | ..... | 74 | $C_{13}H_{22}N_2$ | 13.60 | 13.55 |
| *p*-Methoxy-phenyl | $-C_2H_4NMe_2$ | III | 141–146 | 0.9–1.0 | ..... | 79 | $C_{11}H_{18}N_2O$ | 14.44 | 14.30 |
| 2-Pyridyl | $-CH_2C_6H_4OCH(CH_3)_2$ | II | 170–177 | 0.15–0.20 | 101–103 | 28 | $C_{15}H_{18}N_2O$ | 11.57 | 11.41 |

TABLE II

TERTIARY AMINES AND THEIR HYDROCHLORIDES



| | | Bases | | | | | | | Hydrochlorides | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | B. p. | | | Nitrogen, % | | Chlorine, % | | M. p., | Activity[h] | $LD_{50}$[i] |
| R′ | R″ | °C. | Mm. | Formula | Calcd. | Found | Calcd. | Found | °C. | | mg./kg. |
| $2\text{-}C_4H_3N_2$ | $2\text{-}C_4H_3S$[a] | 131–133 | 0.05 | $C_{18}H_{19}N_4S$ | 21.40 | 21.32 | 11.90 | 12.01 | 176–177 | 10 | 19.0 |
| $2\text{-}C_5H_4N$ | $2\text{-}C_4H_3O$[a,c,e] | 106–108 | .02 | $C_{14}H_{19}N_3O$ | 17.15 | 17.09 | 22.30 | 22.08[k] | 163–164 | 76 | 19.0 |
| $4\text{-}CH_3O\text{-}2\text{-}C_4H_2N_2$ | $C_6H_5$ | 141–143 | .04 | $C_{16}H_{22}N_4O$ | 19.57 | 19.40 | 11.00 | 10.99 | 164–166 | 36 | 12.5–15.0 |
| $5\text{-Cl-}2\text{-}C_5H_3N$ | $C_6H_5$ | 145–146 | .02 | $C_{16}H_{20}ClN_3$ | 14.51 | 14.42 | 10.90 | 10.73 | 179–180 | 58 | 12.5–15.0 |
| $C_6H_5$ | $2\text{-}C_4H_3O$[a,d] | 127–129 | .05 | $C_{15}H_{20}N_2O$ | 11.49 | 11.45 | 12.65 | 12.56 | 147–148 | 70 | 30.0 |
| $5\text{-Cl-}2\text{-}C_5H_3N$ | $p\text{-}CH_3OC_6H_4$ | 180–185 | .05 | $C_{17}H_{22}ClN_3O$ | 13.12 | 13.04 | 9.97 | 10.07 | 141–142 | 34 | 26.0 |
| $4\text{-}(CH_3)_2CHC_6H_4$ | $2\text{-}C_4H_3O$[a] | 130–131 | .04 | $C_{18}H_{26}N_2O$ | 9.79 | 9.72 | 11.00 | 10.84 | 137–139 | 29 | 9.4 |
| $4\text{-}CH_3OC_6H_4$ | $2\text{-}C_4H_3O$[a] | 155–156 | .075 | $C_{16}H_{22}N_2O_2$ | 10.22 | 10.25 | 11.43 | 11.56 | 125–126 | 3 | 35.0 |
| | | | | | 6.99 | 7.17[g] | | | 96–97[g] | | |
| $2\text{-}C_5H_4N$ | $C_6H_5$[f,j] | 155–156 | .075 | $C_{18}H_{25}N_3$ | 14.84 | 14.86 | ... | ... | ..... | 21 | 10.4 |
| $2\text{-}C_5H_4N$ | $p\text{-}(CH_3)_2CHOC_6H_4$ | 194–195 | .20 | $C_{19}H_{27}N_3O$ | 13.42 | 13.40 | 10.16 | 10.23 | 151–152 | 60 | 18.5 |
| $2\text{-}C_5H_4N$ | $C_6H_5$[l] | ..... | ... | ..... | ... | ... | ... | ... | ..... | 37 | 12.5–15.0 |
| $(C_6H_5)(2\text{-}C_4H_3O)CHOC_2H_4NMe_2$[j] | | 100–101 | .035 | $C_{15}H_{19}NO_2$ | 5.71 | 5.70 | ... | ... | ..... | 30 | 24.0 |
| $(C_6H_5)_2CHOC_2H_4NMe_2$ (Benadryl) | | | | | ... | ... | ... | ... | ..... | 17 | 19.5 |

[a] Prepared according to procedure V. [b] R‴ = methyl, except where otherwise indicated. [c] Vaughan and Anderson, THIS JOURNAL, **70**, 2607 (1948). [d] Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947). [e] $n^{30}D$ 1.5485. [f] R‴ = isopropyl. [g] Bisuccinate. [h] Average per cent. by which a bath concentration of 0.00009375 micrograms/cc. of antihistaminic reduced guinea pig ileum response to a histamine base concentration of 0.024 microgram/cc. [i] Acute toxicity, intravenous to rats. [j] For the purpose of pharmacological testing the base was dissolved in dilute acetic acid and the *p*H of the aqueous solution adjusted to 6.8. [k] Dihydrochloride. [l] Pyribenzamine.

ethylenediamine, to be the most potent histamine antagonists of this series. They proved to be approximately twice as active as PBZ. The acute toxicities were comparable to those of the parent compounds.[7] The antihistaminic activity of these two compounds has been described previously by other authors. Viaud[8] reported the furyl analog (2803 R.P.) of PBZ (2750 R.P.) to be less active than "Antergan" (2339 R.P.) or less than one-half as active as PBZ in the ileum test, but equal in activity to PBZ in the histamine aerosol test. Vaughan and Anderson[1] found its activity to be "comparable to PBZ when tested in guinea pigs by the histamine aerosol technique or the intravenous injection of histamine." Viaud[8] described the antihistaminic activity of the furyl analog (2349 R.P.) of "Antergan" to be equal to that of the parent compound in the ileum test.

Methoxyl or isopropyl substitution in the para-position of the phenyl ring of the furyl isostere of "Antergan" resulted in an appreciable lowering of activity, coupled with an increase of acute toxicity in the case of the isopropyl derivative.

The furyl isostere of "Benadryl," β-dimethylaminoethyl benzhydryl ether, proved to be about 80% as active as PBZ, and less than twice as "Benadryl," however, the true evaluation of this drug was hampered by deterioration in aqueous solution.

Winter[9] reported the antihistaminic activity of "Benadryl" to be about sixty per cent. that of PBZ in the ileum test. Other investigators[10] described it to be only 20% that of PBZ in the same test.

The introduction of chlorine in the pyridine ring almost doubled the activity of the unsubstituted analog (PBZ), while the toxicity was only slightly elevated. A similar observation was made by Clapp and associates[11] who reported that the introduction of chlorine in the thiophene ring (Chlorothen) of "Thenylene," N,N-dimethyl-N′-(2-pyridyl-N′-(2-thienylmethyl)-ethylenediamine, doubled the activity of that compound and decreased its acute toxicity by one-half.

A simultaneous introduction of chlorine and methoxyl in the pyridine and phenyl ring, respectively, resulted in decreased activity, but also

(7) Loew, *Physiol. Rev.*, **27**, 542 (1947).

(8) Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947). We are indebted to Dr. C. P. Huttrer of the Warner Institute for Therapeutic Research, New York City, for a copy of this article.

(9) Winter, *J. Pharmacol.*, **90**, 224 (1947).

(10) Lee, Dinwiddie and Chen, *ibid.*, **90**, 83 (1947).

(11) Clapp, Clark, Vaughan, English and Anderson, THIS JOURNAL, **69**, 1548 (1948).

an appreciable lowering of acute toxicity. A *p*-isopropoxy substituent in the benzyl moiety of PBZ markedly enhanced the antihistaminic activity and lowered the acute toxicity of the parent compound. A similar effect was obtained following the introduction of a para-methoxy group in the same position (Neo-Antergan) as reported by Viaud[8] (2786 R.P.) and Winter.[9] An ethoxy group[8] (2843 R.P.), however, did not seem to bring about any change in activity.

The thienyl isostere of "Hetramine," N,N-dimethyl-N′-(2-pyrimidyl)-N′-benzylethylenediamine, produced a compound of very low activity. Thienyl isosteres of PBZ[10,12] and "Antergan[8,13,14] were reported to be less potent antihistaminics than their corresponding parent compounds.

Introduction of a methoxyl group in the pyrimidine ring of "Hetramine" afforded a compound with an activity and acute toxicity comparable to PBZ. Substitution of N-methyl by N-isopropyl in PBZ resulted in a decrease in activity and increase in acute toxicity. A similar observation was made by Viaud[8] concerning the activity of the N,N-diethyl analog (2323 R.P.) of PBZ.

Of the compounds tested the furyl analogs of "Pyribenzamine" and "Antergan" deserve particular attention: the first, because of its high activity and fair toxicity, the second, because of its high activity and particularly low toxicity.

## Experimental

2-Thienyl chloride,[15] 2-(β-dimethylaminoethyl)-aminopyrimidine,[16] 2-(β-dimethylaminoethyl)-aminopyridine,[2] 2-furfuryl chloride,[3] 2-amino-4-methoxypyrimidine,[16] 2-amino-5-chloropyridine,[17], *p*-nitrocumene,[18] β-dimethylaminoethyl chloride hydrochloride[19] and phenyl isopropyl ether[20] were obtained by methods described in the literature.

**Substituted Aniline Derivatives.**—These compounds were readily prepared by the catalytic reduction of their respective nitro compounds. In a typical experiment 36.0 g. (0.22 mole) of *p*-nitrocumene was dissolved in 75 cc. of absolute alcohol and hydrogenated over 0.15 g. of Adams platinum oxide catalyst at four atmospheres of hydrogen. The catalyst was filtered off, the filtrate concentrated *in vacuo* and 26.8 g. (91%) of primary amine collected, b. p. 60–61° (0.3 mm.).[21]

**β-Isopropylaminoethanol.**—To a mixture of 307 g. (5.20 mole) of isopropylamine,[22] 18.0 g. (1.0 mole) of water and 8.6 g. (approximately 0.1 mole) of concentrated hydrochloric acid there was added with stirring from a Dry Ice–acetone jacketed dropping funnel 76.8 g. (1.74 mole) of ethylene oxide over a period of three and a half hours. The temperature of the reaction mixture gradually rose to 51° during the course of the addition. After all the ethylene oxide had been added the mixture was refluxed for another twelve hours, fractionated and 137 g. (76%) of product collected, b. p. 169–171°.[23]

**β-(N-Methyl-N-isopropyl)-aminoethanol.—Method A:** To a mixture of 113 g. (1.10 mole) of isopropylaminoethanol, 152 g. (1.10 mole) of anhydrous potassium carbonate and 200 cc. of benzene was added 156 g. (1.10 mole) of methyl iodide with vigorous mechanical stirring over a period of six hours. Stirring and refluxing was continued for another three hours, the reaction mixture filtered and the precipitate dissolved in water. The aqueous solution was then made strongly alkaline with solid sodium hydroxide, extracted with benzene and the benzene extracts combined with the filtrate. The benzene was removed and the residual liquid distilled at 67–70° (13–14 mm.); yield, 46.0 g. (36%).

*Anal.* Calcd. for $C_6H_{15}NO$: N, 11.97. Found: N, 12.19.

**Method B:** A solution of 10.0 g. (0.10 mole) of β-isopropylaminoethanol, 13.1 g. (0.25 mole) of 88% formic acid and 8.9 g. (0.11 mole) of 37% formaldehyde was refluxed for twenty-four hours. The reaction mixture was cooled, 5.0 g. of concentrated hydrochloric acid added to it and the resulting solution distilled until the temperature of the distillation had reached 110°. To the residual liquid was added 10 cc. of water, the aqueous solution made strongly alkaline with potassium hydroxide pellets and subjected to vacuum distillation. After saturation of the distillate with solid sodium hydroxide it was extracted repeatedly with ether, the ether extracts dried over potassium carbonate and distilled. The product was collected at 161–162°; yield, 8.0 g. (68%).

*Anal.* Calcd. for $C_6H_{15}NO$: N, 11.97. Found: N, 11.70.

**β-(N-Methyl-N-isopropyl)-aminoethyl Chloride.**—To a solution of 46.1 g. (0.40 mole) of methylisopropylaminoethanol in 225 cc. of chloroform at 0° was added 47.0 g. (0.40 mole) of thionyl chloride with stirring at room temperature for thirty minutes and it was then allowed to reflux for three hours. Chloroform was removed, the residue taken up in 100 cc. of water, the aqueous solution made strongly alkaline with 40% sodium hydroxide and then quickly extracted with ether. The ether extract was dried over potassium carbonate, the ether distilled and 34.0 g. (63%) of the chloro-amine collected at 72–74° (40 mm.). On standing at room temperature the free base quickly changed to a white, crystalline solid—presumably its dimerized quaternary salt—and, therefore, had to be used immediately for any subsequent reaction.

***p*-Chloromethylphenyl Isopropyl Ether.**—The compound was prepared according to the directions described by Sommelet and Marszak[24] for the chloromethylation of anisole. From 50.0 g. (0.37 mole) of phenyl isopropyl ether there was obtained 35.0 g. (51%) of the desired product, b. p. 85–87° (0.3–0.4 mm.) and 16.0 g. of unreacted starting material. The yield based on the amount of starting material reacted was 76%.

*Anal.* Calcd. for $C_{10}H_{13}ClO$: Cl, 19.24. Found: Cl, 18.80.

**Procedure I. N-(*p*-Methoxybenzyl)-2-amino-5-chloropyridine.**—From 24.0 g. (0.19 mole) of 2-amino-5-chloropyridine, 25.4 g. (0.19 mole) of *p*-anisaldehyde (Eastman Kodak Co.) and 47 cc. of 90% formic acid there was obtained 17.0 g. (36%) of the desired product, m. p. 154–156°. This material was pure enough to be used in any subsequent reactions. A small amount recrystallized from isopropyl alcohol melted at 158–159°.

**Procedure II. N-(*p*-Isopropoxybenzyl)-2-aminopyridine.**—To 20.0 g. (0.19 mole) of 2-aminopyridine in 100 cc. of dry toluene was added 4.4 g (0.19 mole) of lithium amide and the resulting mixture slowly heated to reflux with stirring. Refluxing and stirring was continued for three hours. The reaction mixture was then allowed to

(12) Feinberg and Bernstein, *J. Lab. Clin. Med.*, **32**, 1370 (1947).

(13) Kyrides, Meyer and Zienty, THIS JOURNAL, **69**, 2240 (1947).

(14) Ercoli, Schachter, Hueper and Lewis, *J. Pharmacol.*, **93**, 216 (1948).

(15) Blicke and Leonard, *ibid.*, **63**, 1936 (1946).

(16) Adams and Whitmore, *ibid.*, **67**, 736 (1945).

(17) Tchitchibabin and Jegorow, *Chem. Zentr.*, **99**, II, 1670 (1928).

(18) Sterling and Bogert, *J. Org. Chem.*, **4**, 20 (1939).

(19) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(20) Waser, *Helv. Chim. Acta*, **12**, 435 (1929).

(21a) Constam and Goldschmidt, *Ber.*, **21**, 1157 (1888), reduced the nitro compound with zinc and hydrochloric acid; b. p. 217–220°.

(21b) Sterling and Bogert, *J. Org. Chem.*, **4**, 20 (1939), reduced the nitro compound with tin and hydrochloric acid; b. p. 222.5°.

(22) Generously supplied by Sharples and Company.

(23) Mathes, *Ann.*, **315**, 117 (1901); b. p. 171°.

(24) Sommelet and Marszak, *Compt. rend.*, **198**, 2256 (1934).

cool to 60° and 35.0 g. (0.19 mole) of *p*-chloromethylphenyl isopropyl ether in 50 cc. of toluene added dropwise. The temperature of the reaction mixture rose to 87° during the addition. Stirring and heating at 80–90° was continued for three hours. The cooled reaction mixture was then shaken repeatedly with 100-cc. portions of a dilute hydrochloric acid solution (60 cc. of concd. acid and 250 cc. of water). Three layers appeared; the two lower layers were separated and made alkaline with solid potassium hydroxide. The water insoluble oil was extracted with ether and the ether dried over potassium carbonate. After removal of the ether the residue was distilled *in vacuo* through a modified, vacuum-jacketed Claisen head. The product was collected at 194–202° (0.3–0.4 mm.) and 26.0 g. of a viscous, yellow oil obtained which soon solidified to a white semisolid mass. This was recrystallized from 80 cc. of Skelly B and 6 cc. of isopropyl alcohol and 13.1 g. (28.5%) of a white, crystalline precipitate obtained; m. p. 101–102°. A small amount was again recrystallized from a mixture of Skelly B and isopropyl alcohol; m. p. 101–102°.

**Procedure III. N-β-Dimethylaminoethyl-*p*-isopropylaniline.**—A mixture of 53.0 g. (0.39 mole) of *p*-isopropylaniline, 29.0 g. (0.21 mole) of β-dimethylaminoethyl chloride hydrochloride, 54.0 g. (0.39 mole) of anhydrous potassium carbonate and 200 cc. of dry toluene was refluxed with stirring for twenty-one hours, and worked up in the usual manner. The residual liquid was fractionated through a 10″ vacuum-jacketed Vigreux column and two fractions were collected, one at 96–97° (6 mm.), 23.0 g. of recovered *p*-isopropylaniline and the other at 113–115° (0.2 mm.); 32.5 g. (a 74% yield, based on recovered material, of the desired product).

**Procedure IV. N,N-Dimethyl-N′-(2-pyridyl)-N′-(*p*-isopropoxybenzyl)-ethylenediamine Monohydrochloride.**—To 2.1 g. (0.09 mole) of lithium amide in 100 cc. of dry toluene was added 22.0 g. (0.09 mole) of N-(*p*-isopropoxybenzyl)-2-aminopyridine. The mixture was stirred and refluxed for three hours, cooled and 10.8 g. (0.10 mole) of β-dimethylaminoethyl chloride in 50 cc. of dry toluene added. Stirring and refluxing were continued for eighteen hours. The mixture was allowed to cool and was then extracted several times with dilute hydrochloric acid solution. The *p*H of the aqueous phase was adjusted to 6.8 with concentrated ammonium hydroxide solution and a small amount of unreacted starting material filtered off. The filtrate was made strongly alkaline with solid potassium hydroxide and extracted several times with ether. The combined ether extracts were dried over potassium carbonate, the ether removed, the residual oil distilled through a modified, vacuum jacketed Claisen head and 18.0 g. (64%) of desired product collected, b. p. 192–193° (0.190 mm.). The yield based on actual starting material reacted was 77%.

The **monohydrochloride** was obtained by adding an equivalent amount of 3.3 *N* ethereal hydrochloric acid to the base in dry isopropyl alcohol. The white, crystalline solid melted at 151–152°.

**Procedure V. N,N-Dimethyl-N′-(*p*-methoxyphenyl)-N′-(2-furfuryl)-ethylenediamine Monohydrochloride.**—A mixture of 33.0 g. (0.17 mole) N,N-dimethyl-N′-(*p*-methoxyphenyl)-ethylenediamine, 3.9 g. (0.17 mole) of lithium amide and 100 cc. of dry toluene was stirred and refluxed for two hours, cooled to room temperature and 19.8 g. (0.17 mole) freshly distilled furfuryl chloride in an equal weight of dry toluene added with stirring at such a rate as to keep the temperature of the reaction mixture at 60–70°. Stirring was then continued for three hours at 50–60°, the reaction mixture cooled, washed with water and the toluene removed by distillation *in vacuo*. The residue was fractionated through a 2″ Vigreux column and 24.0 g. (63%) of product collected, b. p. 137–139° (0.030 mm.).

The **monohydrochloride** was prepared in the manner described under procedure IV, m. p. 125–126°.

The **bisuccinate** was prepared by the addition of 1.18 g. (0.01 mole) of succinic acid dissolved in 10 cc. of hot isopropyl alcohol to 2.75 g. (0.01 mole) of the base in 10 cc. of anhydrous ether. After scratching and cooling for several minutes crystallization finally started. The white, crystalline material was filtered, washed with 1:1 dry ether:dry isopropyl alcohol; yield, 3.6 g. (92%), m. p. 96–97°.

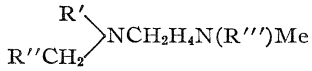
**Phenyl-2-furylmethyl β-Dimethylaminoethyl Ether.**—To a suspension of phenylmagnesium bromide freshly prepared from 2.5 g. (0.10 mole) of magnesium and 20.0 g. (0.10 mole) of bromobenzene in 50 cc. of anhydrous ether was added 9.1 g. (0.10 mole) of freshly distilled furfural[25] in 50 cc. of anhydrous ether with cooling and stirring over a period of fifteen minutes. Refluxing and stirring were continued for another two hours. A saturated solution of ammonium chloride (17 g.) was then added slowly with stirring. At the completion of the addition the finely divided solid had set to a stiff mass. The ethereal solution was readily decanted, the precipitate washed twice with fresh ether and the combined ether layers were dried over Drierite. The ethereal solution was then concentrated to a volume of 50 cc. and added to 2.0 g. (0.087 mole) of bird-shot sodium suspended in 100 cc. of dry toluene. The mixture was stirred at 60° for three hours, when no more hydrogen was evolved. A solution of 10.8 g. (0.10 mole) of β-dimethylaminoethyl chloride in 100 cc. of dry toluene was then added and the resulting mixture stirred and refluxed for sixteen hours in such a manner as to allow the ether to distil off, in order to raise the temperature of the reaction mixture. The reaction mixture was cooled, washed with water and the toluene distilled *in vacuo*. The oily residue was poured into 50 cc. of water and the *p*H of the aqueous solution adjusted to 6.0 by the addition of 22 cc. of 2.4 *N* hydrochloric acid. The aqueous mixture was extracted with ether to remove any water insoluble material and was then made strongly alkaline with potassium hydroxide solution, extracted with ether and the ether layer dried over potassium carbonate. After removal of the ether 9.5 g. (39%) of a clear, yellow oil were obtained, b. p. 100–102° (0.035 mm.). The oil could be stored in the refrigerator over many months, but was quite unstable in the presence of mineral acids. Any attempts to form a solid salt with either organic or inorganic acids failed. For the purpose of testing the compound pharmacologically it was dissolved in dilute acetic acid solution and the *p*H adjusted to 6.8. However, this solution deteriorated on standing.

*Anal.* Calcd. for $C_{15}H_{19}NO_2$: C, 73.40; H, 7.75. Found: C, 73.52; H, 7.58.

**Acknowledgment.**—We are indebted to Messrs. P. Nuhfer and O. Torstveit of the Biology Division for supplying the pharmacological data, to Mr. E. Schwarz for preparing some of the intermediates, and to Mr. E. Curschmann for the analytical data. We wish to thank Dr. H. L. Daiell for his continued interest throughout the course of this project.

## Summary

Eight new and two previously reported ethylenediamine derivatives have been synthesized in



which R′ is a substituted or unsubstituted phenyl, 2-pyridyl or 2-pyrimidyl radical, R″ is a phenyl, substituted phenyl, 2-thienyl or 2-furyl radical, and R‴ is a methyl or isopropyl group. A furan analog of "Benadryl" also has been prepared. Some of these compounds were found to be potent antihistaminic agents. The relationship between chemical structure and antihistaminic activity has been discussed briefly.

MILWAUKEE 1, WISCONSIN

RECEIVED SEPTEMBER 30, 1948

(25) Generously supplied by the Quaker Oats Company.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# The Reaction of Amides with Isocyanates

BY PAUL F. WILEY

The reaction of amides with isocyanates was discovered in 1884 by Kühn,[1,2] who found that amides reacted as shown

$$RCONH_2 + R'NCO \longrightarrow RCONHCONHR'$$

Although experiments were limited it appeared that R and R' could be either aliphatic or aromatic. It was observed that some N-substituted amides, such as acetanilide, gave a reaction of the above type, but others reacted in a much more complex manner. The reaction has never been investigated extensively and has been reported infrequently until its recent use in the preparation and curing of polymers.[3,4] Some employment of the reaction has been made occasionally in the preparation of aroylarylureas,[5,6,7,8,9,10] and a very similar reaction, the reaction of urea derivatives with isocyanates, has been studied.[11,12,13]

The purpose of the present study was to investigate optimum conditions for the reaction of amides with isocyanates and to extend the reaction to other amides and isocyanates. The isocyanates used were ethyl, phenyl and α-naphthyl, and of these only phenyl isocyanate was studied extensively. The amides used and optimum conditions are shown in Table I and the Experimental. The most generally useful solvent was found to be toluene, and it was used in all experiments listed in Table I except where indicated that no solvent was used.

It was found that inclusion of aluminum chloride and stannic chloride in the reaction mixtures caused a marked decrease in yields. Triethylamine had no discernible effect on yields when included.

A totally unexpected result appeared when phenyl isothiocyanate was allowed to react with acetamide or benzamide. The reactions in both cases required prolonged heating without solvents, and the resultant products were acetanilide and benzanilide. Low yields of about 10% were obtained in both cases. This result can be readily explained only by the operation of a different mechanism than prevails in the case of isocyanates. Apparently the nitrogen atom of the isothiocyanate molecule reacts with the carbonyl carbon atom of the amide followed by the expulsion of the elements of thiocyanic acid.

This reaction of amides with isocyanates would be a very convenient one to use in the preparation of derivatives of unsubstituted amides for identification purposes.

TABLE I

| Amide | Isocyanate | Time in hours | Yield, % |
|---|---|---|---|
| Benzamide | Phenyl | 18 | 86 |
| Acetamide | Phenyl | 18 | 89 |
| Nicotinamide | Phenyl | 12 | 94 |
| *p*-Nitrobenzamide | Phenyl | 24 | 95 |
| β,β-Diphenylbutyramide | Phenyl | 18 | .. |
| Butyramide | Phenyl | 18 | 60 |
| Diethylaminoacetamide | Phenyl | 24 | 35 |
| Nicotinamide | α-Naphthyl | 24 | 96 |
| *p*-Nitrobenzamide[a] | α-Naphthyl | *ca.* 1 | 87 |
| Benzamide | Ethyl | 18 | 38 |
| Nicotinamide | Ethyl | 24 | 34 |
| Butyramide | Ethyl | 24 | 24 |
| Diethylaminoacetamide | Ethyl | 24 | 27 |

[a] This experiment was run using no solvent.

TABLE II

| Compound | Formula | Nitrogen, % Calcd. | Found | M. p., °C.[a] |
|---|---|---|---|---|
| 1-Nicotinoyl-3-(α-naphthyl)-urea | $C_{17}H_{13}N_3O_2$ | 14.42 | 14.14 | 222–223 |
| 1-(*p*-Nitrobenzoyl)-3-(α-naphthyl)-urea | $C_{18}H_{13}N_3O_4$ | 12.52 | 12.53 | 244–247 |
| 1-(*p*-Nitrobenzoyl)-3-phenylurea | $C_{14}H_{11}N_3O_4$ | 14.74 | 14.90 | 241–243 |
| 1-(β,β-Diphenylbutyryl)-3-phenylurea | $C_{23}H_{22}N_2O_2$ | 7.81 | 7.83 | 184.5–186 |
| 1-Diethylaminoacetyl-3-phenylurea | $C_{13}H_{19}N_3O_2$ | 16.85 | 17.11 | 155 at 0.2 mm. |
| 1-Nicotinoyl-3-ethylurea | $C_9H_{11}N_3O_2$ | 21.74 | 21.77 | 120.5–122.5 |
| 1-Diethylaminoacetyl-3-ethylurea | $C_9H_{19}N_3O_2$ | 20.87 | 20.65 | 108–110 at 0.8 mm. |

[a] Where pressure is indicated the figure represents boiling point.

## Experimental[14]

The experiments recorded here are representative of those used throughout this study. At least one of the methods recorded is illustrative of and applicable to all the pairs of reactants studied. New compounds not discussed in connection with their preparation are listed in Table II with analytical data. The isocyanates and amides used with the exception of diethylaminoacetamide and β,β-diphenylbutyramide were commercial products. Diethylaminoacetamide was prepared by the method of Einhorn and Hamburger.[15]

**β,β-Diphenylbutyramide.**—A solution of 17.9 g. (0.075 mole) of β,β-diphenylbutyric acid in 44.6 g. (0.375 mole) of thionyl chloride was refluxed for one hour. The excess thionyl chloride was removed by evaporation under re-

(1) Kühn, *Ber.*, **17**, 2880 (1884).
(2) Kühn, *ibid.*, **18**, 1476 (1885).
(3) Berchet, U. S. Patent 2,333,914 (November 9, 1943), *C. A.*, **38**, 2421 (1944).
(4) Belgian Patent 448,187 (December 31, 1942), *C. A.*, **39**, 1572 (1945).
(5) Swartz, *Am. Chem. J.*, **19**, 295 (1897).
(6) Folin, *ibid.*, **19**, 339 (1897).
(7) Stieglitz and Earle, *ibid.*, **30**, 412 (1903).
(8) French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).
(9) Hahn, Stiehl and Schulz, *Ber.*, **72**, 1291 (1939).
(10) Huber, Boehme and Laskowski, THIS JOURNAL, **68**, 188 (1946).
(11) Kühn and Henschel, *Ber.*, **21**, 504 (1888).
(12) Biltz and Beck, *ibid.*, **58**, 2187 (1925).
(13) Lakra and Dains, THIS JOURNAL, **51**, 2220 (1929).
(14) Melting points are uncorrected.
(15) Einhorn and Hamburger, *Ann.*, **361**, 127 (1908).

duced pressure. A cold solution of the residue in 200 cc. of dry benzene was stirred while ammonia was bubbled in until reaction appeared to be complete. The reaction mixture was filtered, and the filter cake was triturated with water and again isolated by filtration. The dried solid obtained was dissolved in 500 cc. of benzene, and the benzene solution was filtered. The filtrate was concentrated until crystals appeared. Cooling gave 11.7 g. (65%) of amide, m. p. 103–105°. Three recrystallizations from benzene gave a sample with no higher melting point.

*Anal.* Calcd. for $C_{16}H_{17}NO$: N, 5.85. Found: N, 5.25.

**1-Benzoyl-3-phenylurea.**—(a) With Solvent: A solution of 12.1 g. (0.1 mole) of benzamide and 11.9 g. (0.1 mole) of phenyl isocyanate in 200 cc. of dry toluene was refluxed for twenty-four hours. The cooled reaction mixture deposited a crystalline product which was removed by filtration and dried. The crude product weighed 24.0 g. and melted at 193–198°. Recrystallization from 135 cc. of dioxane gave 21.5 g. (89%) of 1-benzoyl-3-phenylurea, m. p. 203–204° (lit. 204°). (b) Without Solvent:—A mixture of 12.1 g. (0.1 mole) of benzamide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated slowly to about 115°. At this temperature a vigorous reaction began, and the temperature mounted rapidly to 185°. External heating was stopped when the reaction began to occur vigorously. The mixture became almost completely liquid while the temperature was climbing rapidly, but at about 185° solidification began. The cooled reaction mixture was crystallized from dioxane to give 19.8 g. (82%) of 1-benzoyl-3-phenylurea, m. p. 203–204°.

**1-Benzoyl-3-ethylurea.**—A solution of 7.1 g. (0.1 mole) of ethyl isocyanate and 12.1 g. (0.1 mole) of benzamide in 150 cc. of dry toluene was refluxed for eighteen hours. When the reaction mixture was refrigerated, a crystalline precipitate formed. This precipitate proved to be 4.5 g. of benzamide, m. p. 120–124° and no depression in melting point upon admixture with benzamide. Evaporation of the toluene solution under reduced pressure left a white residue. This residue was recrystallized three times from alcohol. The final product was 7.3 g. of white needle-like crystals, m. p. 112–114° (lit. 114–115°); yield 38%.

**1-Butyryl-3-ethylurea.**—A mixture of 8.7 g. (0.1 mole) of butyramide and 7.1 g. (0.1 mole) of ethyl isocyanate was dissolved in 100 cc. of dry toluene. The solution was refluxed for twenty-four hours, cooled and filtered. The solvent was removed from the filtrate by evaporation under reduced pressure. Two recrystallizations of the residue from alcohol gave 4.0 g. (25%) of 1-butyryl-3-ethylurea, m. p. 98.5–100°, crystallizing in irregular oblong plates.

*Anal.* Calcd. for $C_7H_{14}N_2O_2$: N, 17.72. Found: N, 17.79.

**Phenyl Isothiocyanate and Benzamide.**—A mixture of 12.1 g. (0.1 mole) of benzamide and 13.5 g. (0.1 mole) of phenyl isothiocyanate was heated at a temperature of 180–190° for four hours. The reaction mixture was recrystallized four times from alcohol. The only product isolated was 2.9 g. of a light tan solid melting at 149–153°. Several more recrystallizations from alcohol gave a cream colored product melting at 157–159°. The melting point of a mixture with benzanilide (m. p. 160°) was 158–160°.

*Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.56. Found: C, 78.18; H, 5.74; N, 7.34.

**Phenyl Isothiocyanate and Acetamide.**—A mixture of 13.5 g. (0.1 mole) of phenyl isothiocyanate and 5.9 g. (0.1 mole) of acetamide was heated at 180–190° for four hours. Cooling gave a dark brown liquid which had no isothiocyanate odor or lachrymatory properties but did smell strongly of hydrogen sulfide. The residue was dissolved in an equal volume of absolute alcohol and cooled. The precipitate which formed was removed and recrystallized from alcohol. There was obtained 2.3 g. of acetanilide melting at 110–112°. The mixed melting point with authentic acetanilide (m. p. 113–115°) was 112–114°.

## Summary

1. The reaction of isocyanates with unsubstituted amides to give acylaryl- or alkylureas has been found to be quite general. The effects on the reaction of temperature, solvent, time, catalysts, and different types of amides and isocyanates have been studied.

2. Phenyl isothiocyanate has been found to react with amides only under severe conditions giving anilides.

INDIANAPOLIS, INDIANA RECEIVED AUGUST 19, 1948

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[CONTRIBUTION FROM THE DEPARTMENTS OF AGRICULTURAL CHEMISTRY AND OF CHEMISTRY, UNIVERSITY OF MISSOURI]

# Hydrogen Bonding in Some 4-Substituted Cyclohexanols

BY E. E. PICKETT AND H. E. UNGNADE

The spectroscopic evidence for hydrogen bonding in liquid alcohols has been studied extensively. In pure liquid alcohols there is a broad intense absorption band peaked between 2.95 and 3.00$\mu$ attributed to associated molecules, which decreases in intensity with dilution in an inert solvent, and a sharper band appears at 2.75$\mu$, arising from single molecules.

Fox and Martin[1] resolved the association band of certain alcohols into two components. They suggested that the shorter wave length component is due to dimers and the longer wave length component is due to higher polymers. In the dimer form no single molecule serves as both donor and acceptor of hydrogen and the OH stretching force constant thus differs from that of the higher polymer.

In a study of several of the isomeric hexanols[2] it was found that the formation of polymers higher than dimers was inhibited in all of those isomers which contained the structures —C(R)—C—OH or —C(R)—OH.

With the *cis* and *trans* 4-phenyl and cyclohexylcyclohexanols at hand,[3] the question arose as to whether differences in steric inhibition of hydrogen bonding could be detected spectroscopically in such compounds. On the basis of viscosity and molecular weight determinations, the *cis* alcohols are thought to be less associated than the *trans* alcohols, but the 4-substituents are less effective than the 2-substituents in preventing association.[4]

(1) Fox and Martin, *Proc. Roy. Soc.* (*London*), **A162**, 419 (1937).

(2) Stanford and Gordy, THIS JOURNAL, **62**, 1247 (1940).

(3) Ungnade, *J. Org. Chem.*, **13**, 361 (1948).

(4) Hückel, Kumetat and Preuss, *Ann.*, **517**, 229 (1935); Gough, Hunter and Kenyon, *J. Chem. Soc.*, 2052 (1926).

## Experimental

The samples were prepared and purified in an earlier investigation by one of us.[3] Optical properties, melting point diagrams, and other properties have been determined for these compounds and they are believed to be of high purity. Solutions of them were made up to the desired molarities in purified carbon tetrachloride. A single 1.00 mm. absorption cell, refillable without dismantling, was used for all samples. The concentration range employed was imposed by the solubility of the samples or by the cell thickness. Point-by-point per cent. transmission measurements were made against air, at constant slit width, in the range 2.68 to 3.20$\mu$ at every 0.02$\mu$ interval by means of a Beckman IR-2 spectrophotometer. Recorder tracings indicated that this measurement interval was acceptable. The spectra are presented in Fig. 1. The curve marked $CCl_4$ shows the transmission of the cell filled with pure carbon tetrachloride.

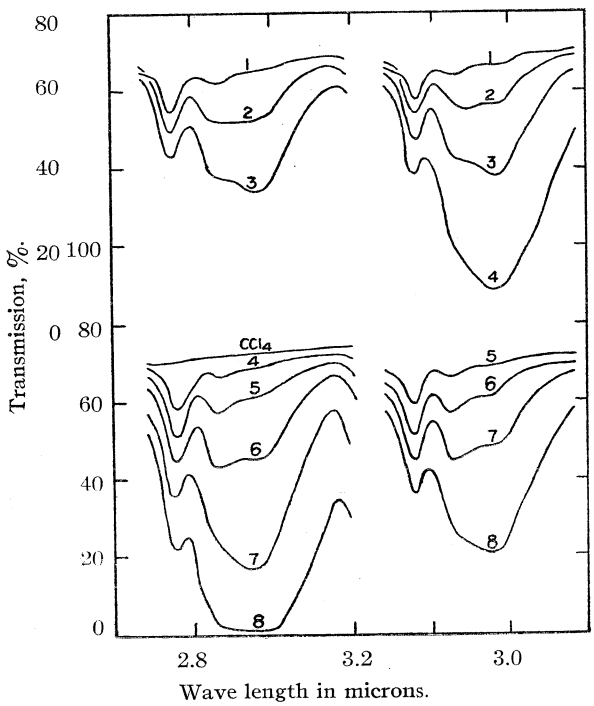



Fig. 1.—Upper left curves: *trans*-4-phenylcyclohexanol in $CCl_4$ soln.; 1, 0.051 *M*; 2, 0.103 *M*; 3, 0.159 *M*. Lower left curves: *cis*-4-phenylcyclohexanol in $CCl_4$ soln.; 4, 0.051 *M*; 5, 0.102 *M*; 6, 0.159 *M*; 7, 0.256 *M*; 8, 0.517 *M*. Upper right curves: *trans*-4-cyclohexylcyclohexanol in $CCl_4$ soln.; 1, 0.050 *M*; 2, 0.100 *M*; 3, 0.154 *M*; 4, 0.247 *M*. Lower right curves: *cis*-4-cyclohexylcyclohexanol in $CCl_4$ soln.; 5, 0.050 *M*; 6, 0.099 *M*; 7, 0.154 *M*; 8, 0.247 *M*.

## Discussion

All of the four compounds exhibit hydrogen bonded absorption regions, 2.8–3.2$\mu$, which increase in intensity with increasing concentration more rapidly than the free OH bands, at 2.75$\mu$. Beer's law "fails" for both types of bands, the deviations being negative for the free OH band and positive for the association band. However, the extinction *versus* concentration curves of both band types are nearly straight above 0.10 molar concentration.

The associated OH absorption regions quite obviously consist of two chief components in each case, centered at about 2.87 and 2.97$\mu$. The former of these may be taken as the dimer component and the latter as the polymer component. At low concentrations the dimer component is more intense than the polymer, the latter being almost absent at the concentration 0.05 molar. The intensity of the polymer component then increases more rapidly than that of the dimer. This behavior seems consistent with the interpretation of these components as being due to dimer and polymer aggregates in solution.

It is apparent that the *trans* forms show somewhat greater hydrogen bonded OH absorption than the corresponding *cis* isomers at similar concentration, as was anticipated, indicating some steric inhibition to intermolecular association in the latter. At a given concentration, the intensity of the dimer component of each *trans* isomer is only slightly greater than that of the corresponding *cis* isomer, while the intensity of the polymer component is considerably greater in the former than in the latter. This suggests that the formation of the polymers is more sensitive to steric interference than is the formation of the dimers.

Moreover, in the spectra of the two *cis* isomers, the intensity of the association band relative to that of the free OH band is somewhat greater for the 4-phenyl than for the 4-cyclohexyl derivative, at each similar concentration, to an extent larger than can be accounted for entirely by the slightly higher molar concentrations of the former, perhaps indicating that the 4-cyclohexyl group is a bit more effective in preventing association than the 4-phenyl group. This effect is of course not observed in the *trans* isomers: the intensities of both the association and the free OH bands are greater for the *trans*-phenyl than for the *trans*-cyclohexyl derivative of similar concentration, and to about the same extent in each band.

## Summary

The infrared spectra between 2.7 and 3.2$\mu$ of carbon tetrachloride solutions of *cis*- and *trans*-4-phenyl and 4-cyclohexylcyclohexanols were measured in the concentration range 0.05 to 0.5 molar. The *trans* isomers exhibit greater intermolecular association than the *cis* isomers. The 4-cyclohexyl group produces slightly greater interference with association than the 4-phenyl group. Certain other conclusions are obtained from the data.

RECEIVED OCTOBER 25, 1948

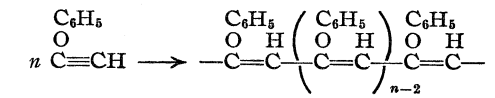
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

# Acetylenic Ethers. V.[1] The Polymerization of Phenoxyacetylene

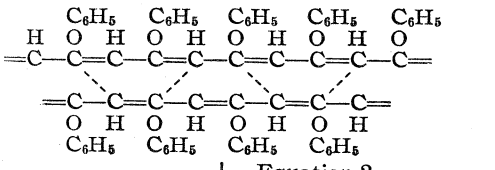
BY THOMAS L. JACOBS AND WILLIAM PENN TUTTLE, JR.[2]

The polymerization of acetylenic compounds other than acetylene itself has been investigated in only a few instances[3] although the literature occasionally contains a reference to the changes which these compounds undergo when heated, and a few substituted acetylenes are known to polymerize readily at room temperature or below.[4,5,6,7] Among the latter, acetylenic ethers of the type ROC≡CH appear to offer several advantages for a more careful study of the process.

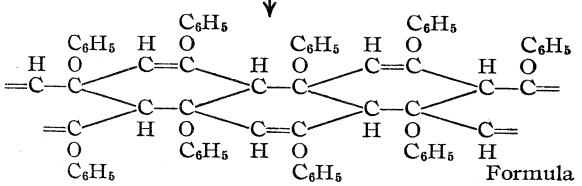
Phenoxyacetylene polymerizes spontaneously at a moderate rate at room temperature to give first a deep red liquid and finally a hard, shiny, brittle, black solid. The change was shown to be a true polymerization by powdering this solid and extracting it with benzene in which it is partially soluble. The insoluble residue had the same composition as the monomer. The reaction appears to occur in two stages, involving first a chain reaction to give a linear, conjugated polyene and next a cross-linking step in which the conjugation is broken. The second reaction probably begins soon after the first linear chains are formed and insolubility occurs well before all of the monomer is consumed. It is suggested that the cross-linking may occur by a Diels–Alder reaction and that the polymerization may be represented by the equations shown.



Equation 1 Formula I

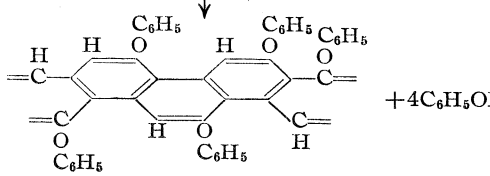


Equation 2



Formula II

Equation 3



The first stage in the polymerization may be followed by observing the rate of disappearance of monomer. Methods of analysis involving the acetylenic hydrogen of phenoxyacetylene or other properties such as ultraviolet absorption were not readily adapted to the problem, and the determination finally was made by finding the molecular weights cryoscopically of samples polymerized under various conditions. This method was used by Taylor and Vernon[8] to follow the photopolymerization of styrene and vinyl acetate in benzene solution. It was found that the polymers themselves as precipitated from benzene by petroleum ether had molecular weights of 3000 to 8000 so that, within the experimental error, the lowering of the freezing point of benzene by a small sample of partly polymerized phenoxyacetylene was due entirely to monomer. Tables I and II record the data obtained at 25 and 40°. The percentage of polymerization of each sample was readily calculated, and also the rate constants for the gross reaction. A first order rate equation fits the data slightly better than a second order one, but the reaction could not be followed much beyond 50% completion due to insolubility of the polymer and no choice between first and second order kinetics could be made (see Fig. 1). The values of the rate constants are

| | $k$ at 25° | $k$ at 40° |
|---|---|---|
| First order | $0.34 \times 10^{-6}$ sec.$^{-1}$ | $2.2 \times 10^{-6}$ sec.$^{-1}$ |
| Second order | $0.41 \times 10^{-6}$ sec.$^{-1}$ wt. fraction$^{-1}$ | $2.6 \times 10^{-6}$ sec.$^{-1}$ wt. fraction$^{-1}$ |

From the first order values, the temperature coefficient for the over-all reaction of producing the linear polymer is found to be 4.3 per 10° between 25 and 40° and the total energy of activation is 23 kcal. per mole of monomer. It is interesting that styrene gives a value of 23.5 kcal. from specific rates determined at 100.5° and 132°.[9,10] The

(1) For the fourth paper of this series see Jacobs and Searles, THIS JOURNAL, **66**, 686 (1944).

(2) Much of this paper is based upon the Ph.D. thesis of William Penn Tuttle, Jr., September, 1943. A preliminary report of the work was given before the Organic Division of the American Chemical Society at the New York Meeting, September, 1942. Dr. Tuttle was killed while hiking in the Sierra Nevada in August, 1946.

(3) The literature to 1941 is summarized by Mark and Raff, "High Polymeric Reactions," Interscience Publishers, Inc., New York, N. Y., 1941, pp. 298–316.

(4) Butadiyne: Mueller, *Helv. Chim. Acta*, **8**, 826 (1925); Straus and Kollek, *Ber.*, **59**, 1664 (1926).

(5) Haloacetylenes: Nef, *Ann.*, **298**, 356 (1897); Lawrie, *Am. Chem. J.*, **36**, 487 (1906); Hofmann and Kirmreuther, *Ber.*, **41**, 314 (1908); **42**, 4232 (1909); Wallach, *Ann.*, **203**, 88 (1880); Ingold, *J. Chem. Soc.*, **125**, 1528 (1924).

(6) Cyanoacetylene: Moureu and Bongrand, *Ann. chim.*, [9] **14**, 47 (1920).

(7) Propargyl aldehyde: Hüttel, *Ber.*, **74**, 1680 (1941).

(8) Taylor and Vernon, THIS JOURNAL, **53**, 2527 (1931).

(9) Schulz and Husemann, *Z. physik. Chem.*, **36B**, 184 (1937).

(10) Walling, Briggs and Mayo, THIS JOURNAL, **68**, 1145 (1946).

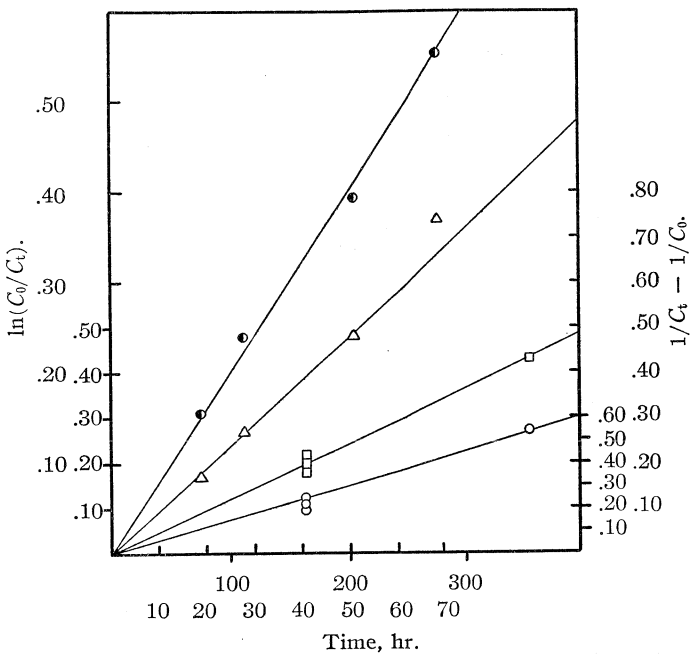



Fig. 1.—Thermal polymerization of phenoxyacetylene at 25.0 and 40.0°: □, first order equation, 25°, inner left-hand scale and inner time scale; O, second order equation, 25°, inner right-hand scale and inner time scale; ◐, first order equation, 40°, outer left-hand scale and outer time scale; △, second order equation, 40°, outer right-hand scale and outer time scale; $C_t$ is wt. fract. of monomer, $C_0$ is original wt. fract. of monomer = 1.

cross-linking reaction made it difficult to get information about the constancy of chain length.

Although no attempts were made to determine the heat of polymerization of phenoxyacetylene, a considerable amount of heat is evolved in the reaction. Samples of monomer in an air-bath produced heat faster than it was conducted away at temperatures of 55° or above, and sealed samples could seldom be polymerized above 80° without exploding violently. Larger samples exploded as low as 65°.

Tables I and II also contain the results of a preliminary study on the influence on the polymerization of typical catalysts and inhibitors for vinyl monomers. Most of these were ineffective in the concentrations used. Among substances expected to promote ionic polymerization only cadmium iodide produced a change, and even with it the catalysis was erratic in a series of qualitative experiments. The polymer obtained appeared to be different from that formed in the absence of the catalyst. Stannic chloride and aluminum chloride gave no qualitative evidence of catalytic action, but were not tested quantitatively. *p*-Toluenesulfonic acid may have been without effect because it added to the triple bond.

Iodine was tried because it is a powerful catalyst for the polymerization of vinyl ethers.[11] Since it is known to add to phenoxyacetylene,[12] the failure to observe catalysis is not surprising. The experiment with metallic sodium was noteworthy because when care was taken to bring the phenoxyacetylene into contact with the bright metallic surface under an inert atmosphere and with care-

TABLE I

THE RATE OF POLYMERIZATION OF PHENOXYACETYLENE AT 25.0° AND THE EFFECT OF CATALYSTS

| Time, hr. | Substance added | Amount added, mole % | Number average mol. wt. | % polymerized $\left(1 - \frac{118}{\text{M. W.}}\right)100$ |
|---|---|---|---|---|
| 0 | ..... | ..... | 117.2 (theoret. 118) | 0 |
| 164 | ..... | ..... | 142 | 16.6 |
| 164 | Iodine | 1.4 (as $I_2$) | 141 | |
| 164 | ..... | ..... | 146 | 19.0 |
| 164 | Cadmium chloride | 2.8 | 145 | |
| 164 | ..... | ..... | 144 | 17.9 |
| 164 | Metallic sodium | 11.8 | 147 | |
| 164 | Cadmium chloride | 2.2 | 144 | |
| 164 | Cadmium iodide | 2.3 | 665 | |
| 356 | ..... | ..... | 182 | 35.1 |
| 356 | Benzoyl peroxide | 0.20 | 181 | |
| 288[a] | ..... | ..... | 165[a] | 28.5[a] |

[a] This experiment was run at 23–24°.

TABLE II

RATE OF POLYMERIZATION OF PHENOXYACETYLENE AT 40.0° AND THE EFFECT OF CATALYSTS AND INHIBITORS

| Time, hr. | Substance added | Amount added, mole % | Number average mol. wt. | % polymerized $\left(1 - \frac{118}{\text{M. W.}}\right)100$ |
|---|---|---|---|---|
| 19 | ..... | ... | 138 | 14.6 |
| 19 | Phenylazotriphenylmethane | 0.29 | 141 | |
| 28 | ..... | ... | 150 | 21.4 |
| 33[a] | ..... | ... | 163[a] | 27.3[a] |
| 33[a] | Powdered cupric acetate | Trace | 162[a] | |
| 51 | ..... | ... | 175.0 | 32.5 |
| 51 | Phenyl α-naphthyl amine | Trace | 175.6 | |
| 69 | ..... | ... | 205 | 42.2 |
| 69 | *p*-Toluenesulfonic acid | 0.05 | 203 | |
| 114 | ..... | ... | (283)[b] | (58.3)[b] |

[a] The thermostat was raised to 45° during the last hour.
[b] This sample dissolved extremely slowly in benzene; the freezing point lowering was determined after standing two months.

(11) Chalmers, *Can. J. Research*, **7**, 472 (1932).
(12) Jacobs, Cramer and Weiss, THIS JOURNAL, **62**, 1849 (1940).

ful exclusion of moisture, even the expected reaction of the acetylenic hydrogen with the metal failed to occur and the surface remained clean and bright throughout the experiment. In other experiments when a piece of sodium was mashed under phenoxyacetylene, the metal dissolved but there was no evidence that the polymerization was catalyzed.

The experiments with benzoyl peroxide and phenylazotriphenylmethane give very little evidence about the influence of free radicals on the polymerization because, at the temperature used, the rate of production of radicals was probably so small that it was negligible. If one assumes that the rate of decomposition of benzoyl peroxide in phenoxyacetylene is about the same as in benzene, styrene, phenetole, and diphenyl ether, and calculates the rate of formation of radicals by the first order process,[13] it is found that at 25° with the concentration used, no more than one or two chains in a thousand could be started by radicals resulting from the decomposition of benzoyl peroxide even if these were 100% effective. The rate of radical formation in phenylazotriphenylmethane is not known, but the compound is an effective catalyst for styrene polymerization at 50°[14] although the evolution of nitrogen is not observed below 55°.[15] Since the rate of thermal chain initiation appears to be about 10,000 times greater for phenoxyacetylene than for styrene at 25 or 40°, it is not surprising that most of the catalysts which are commonly used with the latter are ineffective with the former. Phenyl α-naphthylamine which merely destroys peroxides should be without action on the polymerization as was observed. Cupric acetate, commonly used to inhibit the polymerization of vinyl acetate, is quite insoluble in phenoxyacetylene which may account for its lack of inhibiting action. Further experiments are planned on the effect of more powerful inhibitors and of compounds that decompose to give radicals at lower temperatures.

Absorption spectra give considerable information on the structure of the polymer and the course of the polymerization. Studies were made on samples polymerized for various periods and on polymers isolated by precipitation Typical curves are shown in Figs. 2 and 3. Phenoxyacetylene does not absorb above 3000 Å. (Fig. 4) and the absorption by the polymers at longer wave lengths is believed to be due to a conjugated system of double bonds as suggested above. It is somewhat surprising to find a maximum in the absorption curve of a polymer only once reprecipitated (A, Fig. 2). A number of reprecipitations produced only slight sharpening of this maximum (A, Fig. 3). This may indicate that the conjugated chains are somewhat uniform in length, but

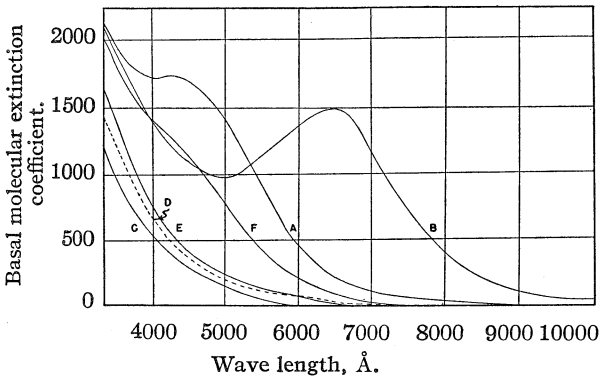



Fig. 2.—Absorption spectra of polyphenoxyacetylene in benzene: A, polymer 2, 0.029 g./l.; B, solution used for A plus 40.0 g. trichloroacetic acid/l.; C, solution used for A after standing 62 days at 25°; D, solution used for C plus 40.0 g. trichloroacetic acid/l.; E, solution used for B after standing 62 days at 25°; F, polymer 4.

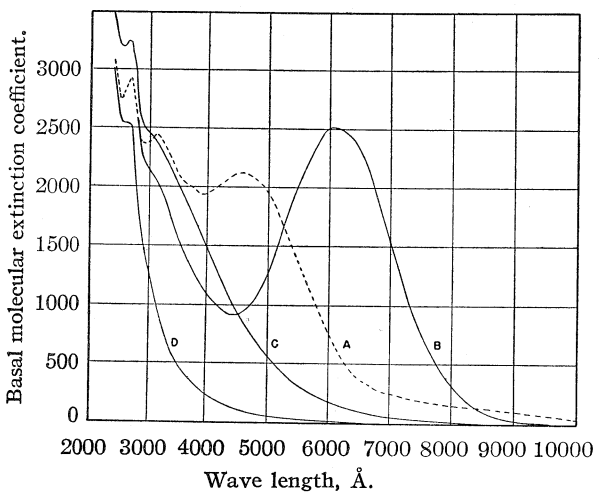



Fig. 3.—Absorption spectra of polyphenoxyacetylene in chloroform: A, polymer 3, 0.0166 g./l.; B, solution used for A plus 1.76 g. antimony trichloride/l.; C, polymer 5, 0.0166 g./l.; D, polymer 6.

in the absence of suitable model systems the evidence is uncertain. If one assumes that a straight line represents the plot of the squares of the wave lengths of the absorption maxima of a series of compounds indicated by Formula I against the number of double bonds ($n$), that the slope is the same as for the corresponding plot for the α,ω-diphenylpolyenes,[16] and that the value of the 2250 Å. band of phenyl vinyl ether (B, Fig. 4) may be taken for $n = 1$, then the 4600 Å. maximum in Curve A, Fig. 3 corresponds to about 10 conjugated double bonds. The effect of phenoxyl groups placed either alternately along the chain as shown in Formula I, or at random, cannot be predicted quantitatively, but such groups would be expected to increase the wave length ab-

(13) Bartlett and Nozaki, THIS JOURNAL, **68**, 1686 (1946); **69**, 2299 (1947).

(14) Schulz, *Z. Elektrochem.*, **47**, 265 (1941).

(15) Wieland, *Ann.*, **514**, 145 (1934).

(16) Lewis and Calvin, *Chem. Rev.*, **25**, 290 (1939).

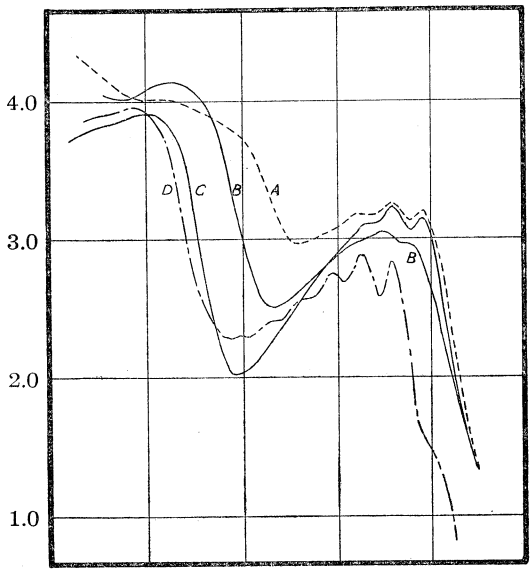
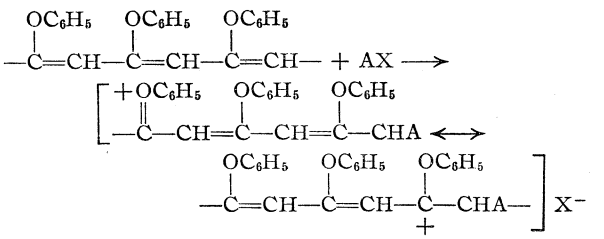



Fig. 4.—Absorption spectra in 96% ethanol: A, diphenyl ether; B, phenyl vinyl ether; C, phenetole; D, phenoxyacetylene.

sorbed.[17] Further uncertainty arises from lack of knowledge of the steric arrangement of the chain.[18] However, the value of 10 is not unreasonable. If the degree of polymerization were 40 corresponding to a molecular weight of 4700, it would take only one cross link per molecule to reduce the conjugation on the average to 10 double bonds, since each cross link that breaks the conjugation effects the absorbing system by a factor 4. Lack of material prevented determination of the molecular weight of the five-hour polymer, but a six-day polymer gave a cryoscopic molecular weight of 8100 and it is probable that considerable cross linking had already occurred in this sample. The polymers show some absorption out to 9000 Å. and beyond, which corresponds to 46 or more conjugated double bonds on the assumptions indicated.

It was found that polymers isolated after brief polymerization absorbed at longer wave lengths than later polymers and that the absorption in the visible of the early polymers decreased greatly when their solutions were allowed to stand for long periods. This change is represented by the difference between Curves A and C in Fig. 2 and indicates clearly that a secondary reaction involving decrease in conjugation has occurred. In ether solution the decrease was even more marked. The absorption at 4300 and 3850 Å. of an ether solution containing $1.49 \times 10^{-4}$ basal moles of polymer 4 per liter changed from basal molecular extinction coefficients of 2060 and 1900 to 30 and 152, respectively, on standing at room temperature in the dark for 202 days. At the end of this experiment the solution appeared visually to be completely colorless.

The early polymers behaved like linear, conjugated systems, giving a deep blue color with antimony trichloride in chloroform (Curve B, Fig. 3), bromine (violet) and stannic chloride (violet). This behavior is similar to that of positive ethylenes[19,20] such as 1,1-di-(*p*-dimethylaminophenyl)-ethylene, and can be interpreted similarly as due to the formation of a resonating positive ion in which the positive charge is distributed among the oxygens of the phenoxyl groups and the alternate carbons along the chain.



and other resonance forms.

These formulas are drawn with the monomer units arranged head-to-tail, which permits the maximum participation of the oxygen atoms in the resonance, but there is as yet no evidence for such arrangement in these polymers and the participation of part of the oxygens, which could occur in random or other arrangements, might account for the colors produced. As with the positive ethylenes, highly colored solids could be obtained in certain instances (bromine or stannic chloride) by adding the reagent to the polymer in a non-polar solvent such as carbon tetrachloride. The solid could be redissolved by adding ethanol to the reaction mixture, although this solvent would not dissolve the original polymer. This behavior would be expected of a polar salt of the type suggested.

The color produced by acids was readily discharged by even such weakly basic compounds as diethyl ether. Relatively large amounts of less basic compounds like phenyl vinyl ether or phenetole were required to discharge the color and diphenyl ether had no influence on the phenomenon. Pyridine discharged the color instantly and an insoluble pyridinium salt soon precipitated. Further evidence that the color produced by acids was due to transfer of a proton to the polymer, was obtained by studying the color change with a number of acids. The intensity of the color produced (as determined visually) was greater, the greater the dissociation of the acid, as indicated in Table III. Acetic acid not only failed to alter the color of the polymer solution, but in large amounts discharged the color produced by stronger acids.

(17) Bowden, Braude and Jones, *J. Chem. Soc.*, 948 (1946). In this paper it is shown that the effect of alkoxyl and similar groups is less when placed in cross-conjugation, but that it is in the same direction. Additional unpublished results from the same group on alkoxy and aryloxy dienoic and trienoic acids support this generalization. We wish to thank Dr. Ernest A. Braude for his assistance and suggestions in the interpretation of the absorption spectra of the polymers.

(18) Zechmeister, Le Rosen, Schroeder, Polgar and Pauling, THIS JOURNAL, **65**, 1940 (1943).

(19) Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928).

(20) Wizinger and Fontaine, *Ber.*, **60**, 1377 (1927).

TABLE III

| Acid | Dissociation constant in water at 25° | Color produced on polymer in chloroform or benzene |
|---|---|---|
| Trichloracetic | Strong acid | Bright blue |
| Maleic | $1.5 \times 10^{-2}$ | Bluish green |
| Malonic | $1.61 \times 10^{-3}$ | Olive |
| Chloroacetic | $1.55 \times 10^{-3}$ | Olive |
| *dl*-Malic | $4 \times 10^{-4}$ | Slight darkening (in chloroform) |
| α-Naphthoic | $2 \times 10^{-4}$ | Reddish color |
| Benzoic | $6.6 \times 10^{-5}$ | of polymer |
| Acetic | $1.86 \times 10^{-5}$ | unchanged |

The maximum in the absorption spectrum of the colored solution produced with antimony trichloride (Curve B, Fig. 3) is at nearly the same wave length as that produced similarly with Vitamin A (617 mm.).[21] This corresponds to five double bonds in the absorbing ion,[22] but since the carotenoids with larger conjugated chains absorb at lower wave lengths,[21] possibly due to coördination with more than one molecule of antimony trichloride,[22] and since no information on the effect of phenoxyl groups is available, it is not possible to correlate the maximum with chain length in our system. The maximum is surprisingly distinct for a polymer system, however, and again suggests some uniformity in the chain length of the absorbing system.

The secondary reaction of cross-linking must involve the double bonds of the polyene polymer, and results in loss of the conjugation. The cross-linked material no longer gives colors with acids, antimony trichloride, etc., as is shown in Curve D, Fig. 2. The colors produced by these reagents on the early polymers fade fairly quickly and cannot be restored by more reagent. This fading occurs much more rapidly than the simple solutions of polymer lose their power to give the colors, which suggests that these reagents catalyze the cross-linking reaction.

Further evidence for the cross-linking reaction is obtained by chromatography. A sample of phenoxyacetylene polymerized for six days at 25° could be separated by adsorption from benzene solution onto magnesium oxide into a strongly held, dark red material and a weakly held, yellow substance. Complete separation of these bands was attained by elution of the yellow material with benzene and of the red with alcohol–benzene. Absorption curves showed that the latter absorbed more strongly, but insufficient material was at hand for isolation of the polymers and the value of the extinction coefficients were therefore not known. It was found that the precipitated, early polymer was absorbed strongly like the dark red material and could be eluted similarly. Its absorption spectrum (Curve A, Fig. 2) was only slightly changed by the adsorption.

(21) "The Application of Absorption Spectra to the Study of Vitamins, Hormones and Coenzymes," by R. A. Morton, Adam Hilger Ltd., 1942, p. 95.

(22) Meunier, *Compt. rend.*, **221**, 64 (1945); *Bull. soc. chim.*, **13**, 73 (1946).

The physical properties of the polymers gave evidence that the secondary reaction was a true cross-linking. Early, precipitated polymers had sintering points as low as 90° while late polymers obtained by bulk polymerization at 65–75° did not sinter at 400°. Intermediate polymers sintered at intermediate temperatures. These polymers were thermosetting, and could not be remelted after heating. Under controlled conditions the thermosetting did not involve decomposition, and the products were very brittle. The thermosetting polymers were poor cements, having low adhesive and cohesive strengths. Attempts to draw threads from the "melts" led only to exceedingly brittle fibers. All of these properties are consistent with a structure made up of cross-linked relatively short chains.

It was found that the cross-linked polymers lost phenol when heated under reduced pressure to 200°. The amount of phenol liberated corresponded to 46% of the phenoxyl groups present, and no more was obtained by heating to above 400°. The polymerization probably did not involve substitution in the ring of the remaining phenoxyl groups, since fusion of the dephenolated polymer with alkali gave a moderate yield of phenol based on phenoxyls still remaining. It was found that the soluble polymers also lost phenol when heated in benzene solution. The ready loss of phenol is easily interpreted if the cross-linking is assumed to occur by a Diels–Alder reaction (Equation 2). The product of such a cross-linking would be a hydroaromatic compound that could aromatize by losing phenol (Equation 3). In bulk or precipitated polymers the cross-linking would be expected to occur at random, leaving considerable portions of the linear, conjugated system unchanged. In solution the cross-linking might occur in a more regular fashion to produce a polycyclic hydroaromatic compound such as is shown in Formula II. Such a change requires the loss of just 50% of the phenoxyl groups. These polymers would absorb much less at the longer wave lengths than would a cross-linked polymer produced by bulk polymerization. The absorption spectra are in agreement with this interpretation.

The primary polymerization to form the linear, conjugated polyene appears on the basis of absorption spectra to be a chain reaction, and this may involve a free radical mechanism. The failure of the usual free radical catalysts to influence the polymerization is explained by the high rate of thermal initiation relative to the rates of production of free radicals by the catalysts. Solvents slow down the polymerization very markedly, and long exposure of an ether solution of phenoxyacetylene to sunlight gave a polymer that appeared to contain fragments of the ether molecule. This is most readily interpreted on the basis of a free radical mechanism. It seems clear that an ionic mechanism is also possible for the polymerization since cadmium iodide acts as a catalyst.

The investigation is being extended to establish the course of the reaction more exactly.

The polymerization of acetylenic compounds in general is relatively complex, and on the basis of the extensive work on acetylene itself probably takes place in several ways.[3] It has been suggested[23] that conversion of acetylene to cuprene occurs by primary formation of a conjugated linear polyene which cross links at once. Cuprene is believed to have an aromatic or partially aromatic structure,[24,25] and analyses indicate that some hydrogen has been lost during the reaction. This suggests that under these special conditions acetylene may behave like phenoxyacetylene. Other readily polymerized acetylenes are now being investigated to determine how general this mode of reaction may be.

## Experimental Part

**Phenoxyacetylene** was prepared as described earlier[12] and was redistilled at least twice before use. Care was taken to exclude moisture at all times; the distillate was collected in a receiver cooled in solid carbon dioxide, and the samples sealed off under reduced pressure and stored without allowing them to warm up. The following physical constants are more accurate than those reported earlier[12]: b. p. 61.5–61.8° (25 mm.); $d^{20}_4$ 1.0114; $n^{20}D$ 1.5171 $MR_D$ obsd. 35.34, calcd. 35.12; $d^{25}_4$ 1.0088; $n^{25}D$ 1.5143. The density and refractive index did not change perceptibly in the course of an hour although the samples darkened markedly.

**The rate of polymerization and the effect of catalysts** were found by polymerizing 0.3-g. samples in thin-walled bulbs of 0.5 to 1 ml. capacity. Carefully cleaned, dry Pyrex glass tubing which had been rinsed with ammonia and repeatedly with distilled water was used in making the bulbs and care was taken to exclude moisture. However, soft glass bulbs or less carefully cleaned Pyrex gave the same results. The purified phenoxyacetylene sample was allowed to warm up to room temperature before opening, and the liquid transferred to the bulbs with a micropipet. The bulbs were then cooled in solid carbon dioxide and sealed. Catalysts were added to the bulb before the acetylene was introduced. The sealed bulbs were weighed to determine the exact amount of phenoxyacetylene and the samples polymerized by immersion in a thermostatted bath at 25 or 40°.

The depression of the freezing point of pure benzene by the samples was determined in the usual Beckmann apparatus modified to exclude moisture and using a carefully standardized rate of cooling which gave reproducible values. In each case the freezing point of the pure benzene was determined, the bulb carefully dried and broken in the benzene and the freezing point depression determined at once. The results are summarized in Tables I and II.

**Cross-linked Polyphenoxyacetylene Polymer 1.**—Phenoxyacetylene (8 g.) was sealed in glass under 20 mm. pressure and polymerized at 40° for forty-eight hours to a thick red fluid. The temperature was then increased to 60° for twenty-one hours, slowly raised to 75° during five hours and maintained at 75° for nineteen hours longer. After cooling, the glass was broken away leaving a hard, brittle, shiny, ebony-black solid which had a faint odor of phenoxyacetylene. The mass was homogeneous and contained no bubbles. It broke with conchoidal fracture. Pieces barely floated in carbon disulfide, indicating a density of about 1.26. Chips of the material colored chloroform and carbon disulfide, but otherwise were unaltered even on prolonged standing, remaining hard and brittle. Carbon tetrachloride, alcohol, 15% aqueous sodium hydroxide and 10% sulfuric acid exerted no visible effect over a long period of time. Concd. sulfuric acid attacked the solid only slowly. The polymer was ground in a mortar, giving a dark brown powder.

*Anal.* Calcd. for $(C_8H_6O)_x$: C, 81.35; H, 5.08. Found: C, 81.61; H, 4.83.

The powder was exhaustively extracted with benzene in a Soxhlet extractor. The soluble portion, 39%, was almost entirely polymer; a trace of phenoxyacetylene (odor) was recovered by heating under reduced pressure, and as the temperature was raised to 370° at 1 mm. a crystalline material (35% of the weight of the soluble portion) was collected in a receiver cooled in Dry Ice. Phenol was separated from this distillate by extraction with 5% sodium hydroxide, and determined as usual.[26] It made up 85% of the weight of the distillate, and was identified by conversion to tribromophenol, m. p. and mixed m. p. 93.0–93.5° The neutral material (50 mg.) in the distillate was a dark oil with a faint odor of phenoxyacetylene. It was not identified.

The insoluble portion from the benzene extraction of the original polymer had the composition of phenoxyacetylene.

*Anal.* Found: C, 81.31; H, 5.38.

It was heated at 1 mm. in an all-glass apparatus with a U-tube receiver cooled in solid carbon dioxide; at 200° a distillate collected, and no further change was observed as the temperature was raised to 400° and maintained there for some time. The total distillate amounted to 44% of the initial weight of polymer (1 g.) and 84% of the distillate was phenol (by titration[26]) which corresponds to 46.4% of the phenoxyls present in the polymer. The rest of the distillate was an oil with a pleasant, fruity (almost cinnamon-like) odor which was a mixture and could not be identified.

The powder remaining in the flask was dark brown and inert to reheating to 400°. It absorbed air readily and was burned with difficulty.

To show that the phenoxyl groups remaining in the polymer were unsubstituted, 0.21 g. of the dephenolated powder was added to 14 g. of molten potassium hydroxide (C. P. 85% alkali plus 0.6 ml. of water) at 250°. The fusion was continued for fifteen minutes at 300–350° which gave a homogeneous melt. It was poured onto ice and phenol isolated and determined as usual. The yield was 0.04 g. which corresponds to 25% of the phenoxyls which should still remain on the dephenolated polymer. The rest of the fusion product was an alkali soluble, dark brown resin which may have resulted in part from phenol. Although the yield of phenol was not high, it is as good as could be expected under the conditions of the experiment and furnishes some evidence that the original polymerization did not involve substitution of the phenoxyl groups.

**Early Polyphenoxyacetylene.**—Quantitative precipitation of the polymers could not be achieved due to their solubility in phenoxyacetylene or in the large amounts of solvent required to remove the monomer, and to their tarry nature while even traces of the monomer remained. Petroleum ether (b. p. 30–60°) was the most effective precipitating solvent and in reprecipitations and fractionation the polymer was dissolved in a little benzene and 4 to 8 volumes of petroleum ether added. Due to the tendency of the powders to acquire an electric charge, it was necessary to avoid rubbing or scratching of vessel walls, and a centrifuge technique proved far superior to filtration, which was used at first.

**Polymer 2.**—Only 20 mg. of a reddish brown powder was obtained after a single precipitation from 25.6 g. of phenoxyacetylene allowed to polymerize for five hours at 25°. The first order rate constant shows that 160 mg. should have been obtained. Losses were due to solubility and to mechanical difficulties in the filtration technique used. The polymer had sintering point 90° m. p. 110–115°.

**Polymer 3** was obtained from 45.3 g. of phenoxyacetylene which was allowed to polymerize for five hours at 25°

(23) Staudinger, *Z. angew. Chem.*, **42**, 37, 67 (1929).

(24) Herzog, *Kunststoffe*, **21**, 49 (1931).

(25) Kaufmann and Schneider, *Ber.*, **55**, 267 (1922).

(26) Redman, Weith and Brock, *Ind. Eng. Chem.*, **5**, 389 (1913).

and reprecipitated eight times using a centrifuge technique. The yield was 80 mg. or 30% of the weight calculated to have been formed (from the first order rate constant, the polymerization should be 0.61% complete); sintering point, 86–87°, m. p. 103–107°. No molecular weight determinations were carried out because of the small amounts of material available.

**Polymer 4** was prepared from 19.2 g. of phenoxyacetylene by polymerization at 25° for six days and reprecipitated once (filtration technique); yield, 2.05 g.; sintering point, 113°; mol. wt. 8100 (cryoscopic determination in benzene).

*Anal.*[27] Calcd. for $(C_8H_6O)_x$: C, 81.35; H, 5.08; C/H ratio, 16.0. Found: C, 78.30, 78.07; H, 4.83, 4.95; C/H ratio 16.0.

The low values are believed to be due to adsorption of air by the powder. The combustion left no residue, and the polymer contained no halogen. When the polymer was placed under dibutyl ether, in which it was insoluble, or dissolved in benzene, a continuous stream of bubbles was produced. No bubbles could be obtained similarly from polymer 1.

A micro Zerewitinoff determination[27] on the polymer gave 1 active H for 17 phenoxyacetylene units and 1 mole of methylmagnesium iodide adding for 2.5 moles of phenoxyacetylene. The presence of adsorbed air accounts for much of the Grignard reagent addition and may have vitiated the active hydrogen determination as well.

**Polymer 5** was obtained from 12.3 g. of phenoxyacetylene by polymerization at 40° for seventy-four hours. After 1 reprecipitation the yield was 3.75 g.; sintering point, 125°, mol. wt. 2900 (cryoscopic determination in benzene).

**Absorption Spectra.**—An older Beckmann Photoelectric Spectrophotometer, Model D, was used to determine the curves given in Fig. 2 while the newer model DV equipped with fused silica cells was employed for all other curves given. The polymers were insoluble in ethanol or hexane; benzene was used when working with the older instrument and chloroform or ether with the new. All solvents were redistilled through a 2-ft. column packed with helices. When carefully purified chloroform free from alcohol was stored, it decomposed even when under nitrogen in the dark and soon produced a slight acid color reaction with the early polymers. This purified chloroform was therefore used only to make up a standard antimony trichloride solution. For other spectra a redistilled chloroform containing a little alcohol was employed; it did not give an acid reaction with the early polymers even after standing for some time in the dark. Chloroform is opaque to ultraviolet light below 2420 Å., but was used because it is the most suitable solvent for the antimony trichloride color reaction.

The antimony trichloride solution was made up with freshly purified chloroform and kept under nitrogen in the dark. Its concentration was 17.6 g./l. and exactly 1 ml. was added to the dilute polymer solution in chloroform in making up the final 10 ml. dilution for the spectrophotometer. This amount of antimony trichloride was approximately twice that needed to give a strong blue color with polymer 4. The intense blue color (Curve B, Fig. 3) did not fade perceptibly in one or two hours, but the solution was nearly colorless in one or two days. The stock solution did not absorb in the range 3350–12000 Å., but below 3300 Å. absorption increased and the solution was opaque at 2810 Å. In the curves with antimony trichloride present, the stock solution was used in the reference cell of the spectrophotometer.

$\epsilon$, the basal molecular extinction coefficient, is obtained as usual except that concentration is expressed in basal moles (weight of polymer per liter divided by the molecular weight of the monomer, 118).

It was shown with polymer 3 in benzene that Beer's law is closely obeyed over a three-fold change in concentrations. Thus with concentrations of $0.720 \times 10^{-4}$, $1.44 \times 10^{-4}$ and $2.16 \times 10^{-4}$ basal moles/l. $\epsilon$ at 4400 Å. was 2180, 2190 and 2170, respectively, and at 3850 Å. $\epsilon$ was 2010, 2040, and 2010, respectively.

The absorption spectra of phenoxyacetylene and phenyl vinyl ether were of interest for study of the polymer absorptions. Phenetole and diphenyl ether were also measured for comparison. Ethanol (96%) was used as the solvent because in general it is more satisfactory than chloroform. The curve for phenetole in methanol or hexane is very similar[28] but was not extended to show the maximum at 2205 Å. Our curve for diphenyl ether agrees with spectra in the literature.[29,30,31]

The phenoxyacetylene used for the measurement was a carefully purified sample which was dissolved very quickly in the solvent and contained so little polymer that there was no measurable absorption at 4000 Å. The phenetole, phenyl vinyl ether and diphenyl ether were purified by distillation under reduced pressure through a 30-cm. Podbielniak-type column and had the following physical properties.

Diphenyl ether: b. p. 114° (8 mm.), m. p. 27–27.4°. Values from 26 to 29° are recorded in the literature.

Phenyl vinyl ether: b. p. 112° (200 mm.), $n^{15}D$ 1.5255, $n^{20}D$ 1.5226, $n^{25}D$ 1.5198. Chalmers[32] found $n^{20}D$ 1.5226.

Phenetole: b. p. 105° (100 mm.), $n^{18.8}D$ 1.5087. The literature[33] records $n^{18.8}D$ 1.5084.

**Polymerization in Solution: Polymer 6.**—Eight grams of phenoxyacetylene in 75 ml. of anhydrous ether was sealed in Pyrex glass under reduced pressure and allowed to polymerize for seven months in the open air exposed to sunlight. The resulting solution was reddish yellow and contained a small amount of a light colored, flocculent precipitate. A control sample kept in the dark was similar in color but homogeneous. The main sample contained 0.0072 g. of phenol per g. of phenoxyacetylene, the control only 0.002 g. Ether was removed under reduced pressure and phenoxyacetylene recovered from the main sample by distillation in a molecular still at room temperature with pressures finally as low as $5 \times 10^{-4}$ mm. The recovery of phenoxyacetylene was 61%; after extraction of phenol and redistillation, this phenoxyacetylene polymerized at the usual rate. The dark red sirup in the molecular still was dissolved in benzene and precipitated with petroleum ether as a very light, buff-colored powder. Two reprecipitations left 0.22 g. of polymer, sintering point 115–120°, m. p. 145–210° with thermosetting at 210°.

*Anal.* Calcd. for $(C_8H_6O)_x$: C, 81.35; H, 5.08. Found: C, 77.24, 77.06; H, 6.33, 6.36; ethoxyl, 5.11, 5.20.

The material was not hygroscopic and burned smoothly. Its absorption in chloroform was lower than any of the cross-linked polymers (Curve D, Fig. 3, in which it was assumed to have the composition of polyphenoxyacetylene for the purposes of calculating the extinction coefficients). It gave no color reactions with antimony trichloride, bromine or trichloroacetic acid.

The mother liquors from the precipitation contained more distillable by-products than could be obtained from the products of ordinary polymerization. These were oils that could not be purified or identified.

## Summary

Phenoxyacetylene polymerizes spontaneously at room temperature and above by a two stage process. The first step is a chain reaction believed to yield a linear, conjugated polyene which then undergoes cross-linking. The rate of disappearance of monomer could not be followed beyond

(27) Microchemical Laboratories, California Institute of Technology

(28) Wolf and Herold, *Z. physik. Chem.*, **13B**, 201 (1931).

(29) Ley and Specker, *Z. wiss. Phot.*, **38**, 13 (1939).

(30) Ramart-Lucas and Hoch, *Compt. rend.*, **194**, 96 (1932).

(31) Marenzi and Vilallonga, *Rev. soc. Argentina biol.*, **17**, 262 (1941).

(32) Chalmers, *Can. J. Research*, **7**, 464 (1932).

(33) Cotton and Mouton, *Ann. chim.*, [8] **28**, 214 (1913).

50% reaction and no choice between first and second order kinetics could be made. A preliminary study of the effect on the reaction, of several of the common catalysts and inhibitors for vinyl polymerization showed that only cadmium iodide was effective. Thermal initiation appears to be so rapid that the usual free radical catalysts have negligible effect, and the question of free radical initiations can be answered only by examining more active radical-producing substances. Early polymers isolated by precipitation have absorption spectra indicating a conjugated, polyene structure, and give color reactions with strong acids, metallic salts and bromine easily explained on this basis. Cross-linking involves breaking of the conjugation of the chain as indicated by decreased absorption, and the cross-linked polymers readily lose up to 46% of their phenoxyl content on heating. This suggests that the cross-linking may occur by a Diels–Alder reaction and that the hydroaromatic structure so produced is aromatized by loss of phenol. The early polymers are thermosetting and can be separated from later, cross-linked polymers chromatographically. Solvents greatly retard the polymerization and some indication that the primary reaction may involve free radicals was obtained by carrying out the reaction in ether which produced a polymer containing fragments of the ether molecule.

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[CHEMICAL INSTITUTE, FACULTY OF SCIENCE, TOKYO UNIVERSITY]

# Raman Frequencies of *n*-Paraffin Molecules

BY SAN-ICHIRO MIZUSHIMA AND TAKEHIKO SIMANOUTI

## I. Intramolecular Rotation

The experimental results of Raman effect, infrared absorption, dipole moment and electron diffraction made for ethylene dihalides by Mizushima, Morino, Watanabe, Simanouti, and others in our Laboratory[1] has shown that there are three potential minima in one complete rotation about a carbon single bond as axis (Fig. 1). These three potential minima correspond to one *trans* form (T) in which two halogen atoms are at the farthest distance apart and two *gauche* forms (G and G′) obtainable from the *trans* form by internal rotation of $\pm 120°$ (see Fig. 2). The energy difference between the *trans* and the *gauche* minima amounts to 1 kcal./mole (1.2 kcal. for ethylene dichloride and 1.3 kcal. for ethylene dibromide), from which the equilibrium isomeric ratio in the gaseous state can readily be calculated, but this ratio becomes naturally different in the liquid state owing to the intermolecular effect. In the solid state the intermolecular force (*i. e.*, crystal force) plays such a predominant role as to make only the *trans* form stable, which is most clearly seen from the disappearance of Raman lines assigned to *gauche* form on solidification.[2]

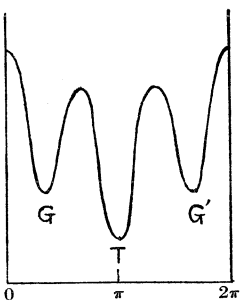



Fig. 1.—Intramolecular potential curve of ethylene dihalides $XH_2C–CH_2X$.

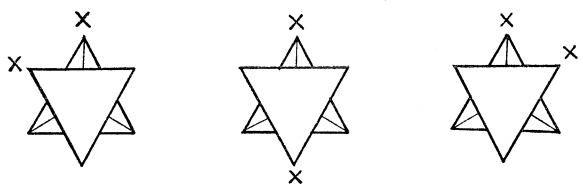


Fig. 2.—Molecular forms corresponding to the three potential minima.

## II. Raman Spectra of *n*-Paraffins in the Liquid and Solid States

The change of Raman spectra of *n*-paraffins on solidification observed by Mizushima, Okazaki, Morino, Takeda and Nakamura in our Laboratory (see Table I) can readily be explained, if we assume quite similarly the existence of only one molecular form in the solid state and of several forms in the liquid state. It is seen from the calculation of normal frequency similar to that made for ethylene dihalide that the only one molecular form realized in solid butane is the *trans* form.[3] It is, therefore, quite reasonable to assume that the molecular form of *n*-paraffin in general is the extended zigzag configuration in which four consecutive $CH_2$-groups form the *trans* configuration. This is also compatible with the results of X-ray investigation made by Müller[4] and Bunn[5] for long chain paraffins. Let us explain in the following the Raman frequencies observed for solid paraffins on the basis of this molecular model.

In Table I we see that in the lower frequency region there was observed only one Raman line for each solid paraffin and its frequency is inversely

(1) Mizushima, Morino and others, *Physik. Z.*, **35**, 905 (1934); **38**, 459 (1937); *J. Chem. Phys.*, **9**, 826 (1941); Mizushima, Morino, Watanabe, Simanouti and others, *Sci. Pap. I. P. C. R. (Tokyo)*, **39**, 396, 401 (1942); **40**, 87, 100, 417, 425 (1942); **42**, *Chem.* 1, 5, 27, 51 (1944).

(2) Mizushima and Morino, *Physik. Z.*, **38**, 459 (1937); Mizushima, Morino and Takeda, *J. Chem. Phys.*, **9**, 826 (1941).

(3) Mizushima, Morino and Simanouti, *Sci. Pap. I. P. C. R. (Tokyo)*, **40**, 87 (1942).

(4) Müller, *Proc. Roy. Soc. (London)*, **A120**, 437 (1928); **124**, 317 (1929); **127**, 417 (1930).

(5) Bunn, *Trans. Farad. Soc.*, **35**, 482 (1939).

TABLE I

RAMAN SPECTRA OF *n*-PARAFFINS IN THE LIQUID AND SOLID STATES[a]

| *n*-Butane | | *n*-Pentane | | *n*-Hexane | | *n*-Heptane | |
|---|---|---|---|---|---|---|---|
| Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid |
| 207 (00) | | | | | | 198 (0) | |
| 223 (0) | | | | | | 222 (0) | |
| 259 (0) | | | | | | | |
| 287 (0) | | | | | | 285 (1) | |
| | | | | 315 (1b) | | 310 (6) | 311 (5) |
| 320 (1) | | 333 (1) | | 335 (1) | | | |
| | | | | | | 358 (2) | |
| | | | | 370 (4) | 373 (3) | | |
| | | | | | | 394 (3) | |
| | | 400 (7) | 406 (3) | 401 (2) | | 404 (0) | |
| 429 (5) | 425 (4) | | | | | | |
| | | 467 (2) | | 450 (1) | | 455 (1) | |
| | | | | | | 506 (2) | |
| | | | | | | 695 (0) | |
| | | | | | | 721 (1) | |
| | | | | 746 (0) | | 742 (1) | |
| | | 764 (3) | | 760 (0) | | 775 (2b) | |
| 789 (2) | | | | 794 (0) | | | |
| 809 (0) | | | | 810 (1) | | 807 (0) | |
| 827 (6) | | | | 826 (3) | | 829 (2) | |
| 837 (7) | 837 (6) | 838 (5) | | | | 838 (6) | |
| | | | | | | 851 (3) | |
| | | 864 (4) | 869 (3) | 868 (3) | | 866 (0) | |
| | | | | 890 (4) | | 888 (2) | |
| | | 904 (1b) | | 900 (2) | 898 (3) | 901 (5) | |
| | | | | | | 909 (3) | 905 (5) |
| | | | | | | 930 (½) | |
| 955 (1b) | | 953 (0) | | 952 (0) | | 950 (0) | |
| | | | | 976 (00) | | 960 (1) | |
| 980 (2) | | 990 (1) | | | | 988 (0) | |
| | | | | 1005 (1) | 1005 (0) | | |
| | | 1025 (3) | | | | 1023 (1b) | 1028 (1) |
| | | 1035 (3) | 1031 (0) | 1040 (3) | | 1044 (3) | |
| 1057 (4) | 1059 (5) | | | 1065 (1) | 1064 (3) | 1057 (2) | 1056 (3) |
| 1077 (1) | | 1072 (3b) | 1069 (3) | | | 1071 (2) | 1072 (2) |
| | | | | 1080 (4) | | 1086 (4b) | |
| 1150 (2) | 1151 (4) | 1142 (3) | 1145 (3) | 1140 (3) | 1143 (3) | 1139 (4) | 1139 (4) |
| 1168 (0) | | 1165 (0) | | 1165 (0) | | 1163 (2) | |
| | | | | | | 1206 (0) | |
| | | | | 1220 (00) | | 1237 (1) | |
| | | 1264 (1) | | 1250 (0) | | 1264 (0) | |
| 1281 (0) | | | | | | 1281 (0) | |
| 1301 (1b) | 1300 (4) | 1302 (4b) | 1303 (3) | 1302 (5b) | 1300 (4) | 1298 (6b) | 1296 (4) |
| | | | | | | 1312 (2) | |
| | | | | 1343 (00) | | 1342 (1) | |
| | | | | 1366 (0) | | 1364 (0) | |
| 1444 (5b) | 1442 (3) | 1437 (5b) | 1445 (4) | 1436 (5b) | 1450 (5) | 1432 (7b) | 1446 (4b) |
| | 1460 (2) | 1458 (6b) | 1466 (5) | 1459 (7b) | 1462 (4) | 1460 (7b) | 1473 (3) |
| 2666 (1) | | 2666 (1) | 2666 (1) | 2672 (1) | | 2670 (1) | |
| 2702 (1) | 2703 (1) | 2713 (1) | | 2703 (0) | 2696 (1) | 2708 (1) | |
| 2733 (3) | 2725 (1) | 2733 (2) | 2720 (2) | 2735 (2) | 2723 (2) | 2730 (3) | 2725 (1) |
| | 2853 (8) | 2847 (5) | 2848 (2) | 2849 (8) | 2851 (5) | 2848 (10b) | 2852 (3) |
| 2860 (8) | | 2861 (5) | 2859 (2) | 2862 (5) | | | 2866 (2b) |
| 2877 (10) | 2872 (8) | 2875 (10) | | 2875 (10) | 2871 (5) | 2873 (8) | 2878 (7) |
| | | | 2885 (8) | | 2885 (8) | | |
| 2901 (2) | 2896 (10) | | | | | 2901 (5b) | 2904 (2) |

[a] These data have been partly published. See Mizushima, Morino and Nakamura, *Sci. Pap. I. P. C. R.* (*Tokyo*), **37**, 205; Mizushima, Morino and Takeda, *ibid.*, **38**, 437 (1941); Okazaki, *J. Chem. Soc.* (*Japan*), **63**, 1500, 1255 (1942). Many of them have, however, been remeasured.

TABLE I (*Continued*)

| *n*-Butane | | *n*-Pentane | | *n*-Hexane | | *n*-Heptane | |
|---|---|---|---|---|---|---|---|
| Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid |
| 2914 (5) | 2912 (4) | 2908 (5b) | 2909 (4) | 2916 (5) | 2907 (5) | | |
| 2938 (8b) | 2931 (1) | 2936 (8b) | 2934 (5) | 2939 (10) | 2934 (5) | 2937 (8) | 2930 (3) |
| | 2950 (4) | | 2956 (2) | | 2953 (3) | | 2950 (2) |
| 2962 (6b) | 2965 (9) | 2964 (8b) | 2966 (6) | 2964 (10b) | 2965 (6) | 2963 (10b) | 2964 (7) |

| *n*-Octane | | *n*-Nonane | | *n*-Decane | | *n*-Dodecane | | *n*-Cetane | |
|---|---|---|---|---|---|---|---|---|---|
| Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid |
| 196 (0) | | 196 (0) | | | | 195 (1) | 194 (2) | 199 (1) | 150 (3) |
| 218 (00) | | 221 (0) | | 200 (0) | | 218 (1) | | 215 (2) | |
| 241 (00) | | 248 (3) | 249 (2) | 230 (3) | 231 (3) | 239 (2b) | | 231 (1) | |
| 279 (5) | 283 (3) | 264 (4) | | 250 (4) | | | | 278 (0b) | |
| 295 (1) | | 283 (1) | | | | 308 (0) | | 330 (0) | |
| 347 (0) | | 340 (1) | | 339 (0) | | 349 (0) | | 356 (0) | |
| 374 (1/2) | | 375 (1/2) | | 359 (1/2)′ | | | | | |
| 399 (0) | | 404 (1) | | 404 (2b) | | 397 (1) | | 404 (1) | |
| 427 (1) | | 417 (1/2) | | | | 421 (1/2) | | | |
| 454 (0) | | 453 (1/2b) | | 441 (1/2) | | 453 (00) | | 450 (00) | |
| | | 489 (0) | | 465 (1/2) | | 487 (00) | | | |
| 505 (0b) | | 510 (0) | | | | | | | |
| | | 523 (0) | | 521 (1) | | | | | |
| | | 548 (0) | | 661 (0b) | | | | | |
| 696 (00) | | 697 (0) | | 697 (1/2) | | | | | |
| 723 (1/2) | | 721 (1/2) | | 723 (1) | | 724 (1) | | 724 (1) | |
| 735 (1/2) | | 751 (1/2) | | 744 (1) | | 749 (0) | | 742 (00) | |
| 765 (1) | | | | 772 (2b) | | 772 (1b) | | 762 (00) | |
| | | 781 (1) | | | | | | 784 (00) | |
| | | | | 810 (2b) | | 805 (1) | | 808 (0) | |
| 815 (2b) | | 820 (3) | | | | 817 (1) | | | |
| 843 (2) | | 843 (3) | | 844 (3b) | | 845 (2b) | | 839 (2b) | |
| 861 (3) | | 871 (3) | | 870 (1) | | 872 (1) | | 871 (2) | |
| 878 (3) | | | | 886 (3) | 886 (2) | | | | |
| 896 (4) | 899 (2) | 892 (4) | 888 (2) | 898 (3) | | 893 (3) | 892 (1) | 894 (3) | 888 (1) |
| | | | | 921 (1) | | 917 (00) | | | |
| | | 926 (0) | | | | 931 (00) | | | |
| 953 (1) | | | | 952 (1) | | 955 (1) | | | |
| 970 (2) | | 970 (1b) | | 971 (1) | | 964 (1) | | 962 (1) | |
| 999 (00) | | | | 991 (1) | | | | 997 (00) | |
| | | | | 1008 (1) | | 1002 (00) | | | |
| 1026 (2) | | 1019 (1) | | 1023 (1) | | 1032 (1b) | | 1015 (0) | |
| 1045 (2) | 1045 (1/2) | 1046 (0) | | 1047 (2) | | | | | |
| 1060 (4) | 1062 (2) | 1062 (3) | 1060 (1) | 1062 (4) | 1060 (3) | 1061 (3) | 1061 (2) | 1063 (4) | 1058 (2) |
| 1083 (4b) | | 1082 (3b) | | 1080 (4) | | 1078 (3) | | 1082 (5b) | |
| | | | | 1092 (3) | | 1100 (0) | | 1108 (0) | |
| 1137 (4) | 1138 (2) | 1134 (3) | 1136 (2) | 1133 (4) | 1136 (3) | 1129 (3) | 1136 (3) | 1132 (4) | 1135 (2) |
| 1162 (1) | 1176 (0) | 1159 (1) | | 1161 (2) | | 1159 (1) | | 1165 (0) | |
| 1199 (0) | | 1192 (0) | | 1189 (0) | | | | | |
| 1226 (0) | | 1217 (0) | | 1211 (0) | | | | | |
| | | | | 1250 (0) | | | | | |
| | | | | 1271 (0) | | | | | |
| 1299 (5b) | 1297 (3) | 1299 (4b) | 1297 (3) | 1301 (6b) | 1295 (3) | 1300 (6b) | 1297 (3) | 1304 (7b) | 1295 (2) |
| | | | | | | | | 1314 (2) | |
| 1342 (0) | | 1340 (0) | | 1340 (1/2) | | 1341 (1/2) | | 1344 (0) | |
| 1366 (0b) | 1384 (1) | 1365 (0) | | 1366 (1) | | 1369 (1) | | 1368 (1) | |
| 1434 (7b) | 1449 (3b) | 1433 (8) | 1444 (2) | 1433 (8b) | 1447 (2b) | 1433 (7b) | 1441 (3b) | 1435 (8b) | 1442 (2b) |
| 1459 (5b) | 1469 (3b) | 1460 (8) | 1465 (3) | 1460 (6b) | 1475 (1) | 1461 (5b) | 1462 (2b) | 1460 (6b) | 1471 (2b) |
| | | | 1486 (0) | | | | | | |
| 2668 (1) | | 2666 (1) | 2660 (1) | 2673 (1) | 2660 (1) | 2670 (0b) | | 2673 (0b) | |
| 2714 (0) | 2699 (0) | 2706 (1) | | | | 2718 (0) | | 2713 (2) | |
| 2732 (3) | 2727 (0) | 2731 (2) | 2720 (0) | 2732 (3) | 2724 (1) | 2730 (3b) | 2723 (0b) | 2730 (3) | |
| | 2765 (0) | | | | | | | | |
| 2849 (10) | 2853 (3b) | 2846 (10) | 2847 (2) | 2850 (10) | 2843 (2) | 2849 (10) | 2845 (4b) | 2847 (10b) | 2846 (3) |

TABLE I (*Continued*)

| *n*-Octane | | *n*-Nonane | | *n*-Decane | | *n*-Dodecane | | *n*-Cetane | |
|---|---|---|---|---|---|---|---|---|---|
| Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid | Liquid | Solid |
| 2873 (6) | 2882 (10) | 2873 (2) | 2877 (5) | | 2877 (6) | | 2879 (10) | 2885 (8b) | 2878 (5) |
| 2904 (6) | | 2896 (3) | | 2897 (6b) | | 2896 (8b) | | | |
| 2937 (8) | 2937 (2) | 2933 (7) | 2934 (2) | 2936 (7) | 2935 (1) | 2936 (8) | 2933 (1) | 2937 (8b) | 2934 (1) |
| 2965 (8b) | 2965 (5) | 2964 (8) | 2964 (4) | 2966 (8) | 2964 (3) | 2964 (9b) | 2964 (3) | 2965 (6b) | 2963 (2) |

proportional to the number of carbon atoms when it is greater than five. This would be explained simply, if we approximate the extended carbon chain by a continuous rod and assign the said Raman line to its longitudinal motion whose frequency is given by

$$\nu = \frac{1}{2l}\sqrt{\frac{E}{\rho}} \qquad (1)$$

where $E$ is Young's modulus, $\rho$ the density, $l$ the length of the rod. This relation means that the frequency is inversely proportional to the length of the chain or to the number of carbon atoms. Putting the observed frequencies into $\nu$ of Eq. (1), we obtain a value of $E$ ($34 \times 10^{11}$ dynes/sq. cm.) comparable to that of diamond ($55 \times 10^{11}$ dynes/sq. cm.). This is quite reasonable, since this value of $E$ refers to the carbon chain connected by covalency just as in the case of diamond, but not to the solid paraffins whose molecules are connected by van der Waals forces.

The calculation of skeletal modes of vibration was made by Kirkwood,[6] and by somewhat different method by Thomas, Whitcomb and Nielsen[7] and by Barriol.[8] Kirkwood's formulation will be used here with, however, a modification in the potential function, since the simple valence force formula used by Kirkwood cannot explain the quantitative feature of our problem.

As in the case of our previous calculation[3] for ethylene dihalide we assume the potential function of the form

$$V = K'r_0 \sum_n (\Delta r_n) + \frac{1}{2}K \sum_n (\Delta r_n)^2 + H'r_0 \sum_n (r_0 \Delta\alpha_n) + \frac{1}{2}H \sum_n (r_0\,\Delta\alpha_n)^2 + F' \sum_n q_0\,(\Delta q_n) + \frac{1}{2}F \sum_n (\Delta q_n)^2 \qquad (2)$$

where the significance of the force constants $K$, $H$, $F$, etc., and of the increments in atomic distances $\Delta r_n$ and $\Delta q_n$ and in bond angles $\Delta\alpha_n$ is clear from Fig. 3. Eliminating $q$'s through the relation $q_n^2 = r_n^2 + r_{n+1}^2 - 2r_n r_{n+1}\cos\alpha_n$, we can set up the equations of motion as

$$\ddot{\xi}_n + \frac{K+2F'(1+\cos\alpha_0)}{m}\left[\sin^2\left(\frac{\alpha_0}{2}\right)(2\xi_n - \xi_{n+1} - \xi_{n-1}) + (-1)^n \sin\frac{\alpha_0}{2}\cos\frac{\alpha_0}{2}(\eta_{n+1} - \eta_{n-1})\right] + \frac{H}{m}\left[\cos^2\left(\frac{\alpha_0}{2}\right)(2\xi_n - \xi_{n+2} - \xi_{n-2}) + (-1)^n \sin\frac{\alpha_0}{2}\cos\frac{\alpha_0}{2}(2\eta_{-1} - 2\eta_{n+1} + \eta_{n+2} - \eta_{n-2})\right] + \frac{F}{m}[2\xi_n - \xi_{n+2} - \xi_{n-2}] = 0$$

$$\ddot{\eta}_n + \frac{K+2F'(1+\cos\alpha_0)}{m}\left[\cos^2\left(\frac{\alpha_0}{2}\right)(2\eta_n - \eta_{n+1} - \eta_{n-1}) + (-1)^n \sin\frac{\alpha_0}{2}\cos\frac{\alpha_0}{2}(\xi_{n+1} - \xi_{n-1})\right] + \frac{H}{m}\left[\sin^2\left(\frac{\alpha_0}{2}\right)(6\eta_n - 4\eta_{n+1} - 4\eta_{n-1} + \eta_{n+2} + \eta_{n-2}) - (-1)^n \sin\frac{\alpha_0}{2}\cos\frac{\alpha_0}{2}(2\xi_{n+1} - 2\xi_{n-1} + \xi_{n+2} - \xi_{n-2})\right] - \frac{F'}{m}[6\eta_n - 4\eta_{n+1} - 4\eta_{n-1} + \eta_{n+2} + \eta_{n-2}] = 0$$

where $\xi$ is the displacement from equilibrium along the length of the chain, $\eta$ the displacement perpendicular to the chain (see Fig. 3), and $m$ the mass of $CH_2$-group.

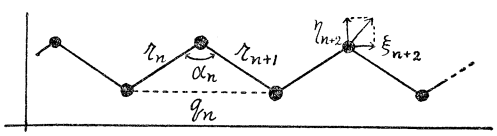



Fig. 3.—Coördinates of the extended chain.

Let $N$ be the number of carbon atoms in the chain. We have then $2N$ such equations of motion, the particular solutions of which are of the form

$$\xi_n = Ae^{i(\omega t + n\lambda)},\ \eta_n = (-1)^n Be^{i(\omega t + n\lambda)}$$

where the amplitudes $A$ and $B$ satisfy the equations.

$$\left.\begin{aligned}(\kappa_{11} - \omega^2)A + i\kappa_{12}B &= 0\\ -i\kappa_{12}A + (\kappa_{22} - \omega^2)B &= 0\end{aligned}\right\} \qquad (3)$$

$$m\kappa_{11} = (1-\cos\lambda)[\{K + 2F'(1+\cos\alpha_0)\}(1-\cos\alpha_0) + 2H(1+\cos\alpha_0)(1+\cos\lambda) + 4F(1+\cos\lambda)]$$

$$m\kappa_{22} = (1+\cos\lambda)[\{K + 2F'(1+\cos\alpha_0)\}(1+\cos\alpha_0) + 2H(1-\cos\alpha_0)(1+\cos\lambda) - 4F'(1+\cos\lambda)]$$

$$m\kappa_{12} = \sin\lambda\,[-\{K + 2F'(1+\cos\alpha_0)\}\sin\alpha_0 + 2H\sin\alpha_0(1+\cos\lambda)]$$

The values of $\omega^2$ corresponding to non-trivial solutions of Eq. (3) satisfy the secular equation

$$\begin{vmatrix}\kappa_{11} - \omega^2 & i\kappa_{12}\\ -i\kappa_{12} & \kappa_{22} - \omega^2\end{vmatrix} = 0 \qquad (4)$$

Since an integral number of half wave length must be completed within the molecule,[9] we have

$$\left.\begin{aligned}\lambda &= \pi l/N\\ l &= 0, 1, 2, \ldots, N-1\end{aligned}\right\} \qquad (5)$$

(6) Kirkwood, *J. Chem. Phys.*, **7**, 506 (1939).

(7) Thomas and Whitcomb, *Phys. Rev.*, **56**, 383 (1939); Whitcomb, Nielsen, and Thomas, *J. Chem. Phys.*, **8**, 143 (1940).

(8) Barriol, *J. phys. rad.*, **10**, 215 (1939).

(9) Instead of Eq. (5) Kirkwood put $\lambda = 2\pi l/N$, which is not correct as pointed out by Pitzer, *J. Chem. Phys.*, **8**, 711 (1940).

By the examination of the character of motion associated with each mode of vibration we see that the two vibrations of $l = 1$ appear in the Raman spectrum as strong lines.[10] One of them corresponds to the symmetric deformation vibration and the other to the symmetric valency vibration. It is evident that the former is assigned to the said Raman line of the lowest frequency and the latter to the line observed at about 900 cm.$^{-1}$. As the values of force constants and equilibrium angle we shall use the following reasonable ones:

$$\left.\begin{aligned} K &= 4.0 \times 10^5 \text{ dynes/cm.} \\ H &= 0.11 \times 10^5 \text{ dynes/cm.} \\ F &= 0.96 \times 10^5 \text{ dynes/cm.} \\ F' &= 0 \\ \alpha_0 &= \text{tetrahedral angle} \end{aligned}\right\} \quad (6)$$

With these molecular constants we can calculate the two frequencies stated above as shown in Table II. The agreement with the observed and the calculated frequencies is satisfactory.[11]

TABLE II

THE CALCULATED AND OBSERVED SKELETAL FREQUENCIES (IN CM.$^{-1}$) OF *n*-PARAFFIN MOLECULES IN THE EXTENDED FORM[a]

| Number of carbon atoms in a molecule | Deformation frequency Calcd. | Obs. | Valency frequency Calcd. | Obs. |
|---|---|---|---|---|
| 4 | 432 | 425 | 835 | 837 |
| 5 | 402 | 406 | 851 | 869 |
| 6 | 369 | 373 | 893 | 898 |
| 7 | 325 | 311 | 890 | 905 |
| 8 | 289 | 283 | 888 | 899 |
| 9 | 259 | 249 | 888 | 888 |
| 10 | 235 | 231 | 887 | 886 |
| 12 | 198 | 194 | 887 | 892 |
| 16 | 150 | 150 | 887 | 888 |

[a] The frequencies of *n*-butane and *n*-pentane have been calculated similarly to those of dichloroethane.[3] The values of force constants was put equal to those of the long chain paraffins except that of the end group $CH_3$–$CH_2$ for which $K$ was put equal to $3.2 \times 10^5$ dynes/cm.

We want to add a few words about the spectra in the liquid state. As already stated they have many more lines than the spectra observed in the solid state (see Table I), which is due to the fact that several rotational isomers co-exist with one another in the liquid state. It is very interesting that the lines observed in the solid state remain very strong in the liquid state for low homologs, while the strong line at 150 cm.$^{-1}$ of solid cetane, $C_{16}H_{34}$, escaped detection in the liquid state. This means that for lower homologs the extended molecular form is abundant in the liquid state, while for cetane this is almost absent in that state. This would have something to do with the idea proposed by Eyring[12] that the long chain molecules act in segments in the liquid state.

(10) This is consistent with Pitzer's assignment (*J. Chem. Phys.*, **8**, 711 (1940)), but our calculated frequencies are different from those of Pitzer who used the same potential function as Kirkwood.

(11) In Eq. (6) we put $F' = 0$. This means that only the quadratic terms were taken into account in our numerical calculation. Hence the difference of the present calculation from the previous ones results from the last term in potential function (2).

## III. Intramolecular Rotation of Highly Elastic Substances

We shall take this opportunity to make a short discussion on high elasticity. This property of rubber-like polymers has been considered to be due to the chain structure of their molecules, but all the substances with chain molecules do not show high elasticity. For instance polyisobutylene, $-C(CH_3)_2-CH_2-C(CH_3)_2-CH_2-$, shows highly elastic properties even at considerably lower temperature, while a simpler hydrocarbon polyethylene does not show this property at ordinary temperature.

We consider that such a difference can be explained readily from the result of our study stated in I. A unit structure of these two polymers corresponds, respectively, to 2,2-dimethylbutane, $CH-C(CH_3)_2-CH-CH_3$, (polyisobutylene) and to *n*-butane, $CH_3-CH_2-CH_2-CH_3$, (polyethylene). In the former case the three stable molecular forms are identical and, therefore, have the same energy, while in the latter case the *trans* form has a lower energy than the *gauche* forms. From this fact it immediately follows that the molecular chain of polyisobutylene can be folded more easily than that of polyethylene and hence the former substance shows high elasticity at a lower temperature than the latter.

It seems that high elasticity at lower temperature is observed for a substance whose molecule has at least two potential minima of practically the same energy. In the case of carbon chain such an intramolecular potential will be realized by the existence of side chain, which is quite consistent with our experience. If, however, we consider that the energy difference between the *trans* and the *gauche* forms of *n*-butane amounts only to about 1 kcal./mole, the straight carbon chain will have considerable probability to be folded at a slightly higher temperature. This would be the reason why polyethylene shows elastic property at a temperature higher than about 120°.

## Summary

The disappearance of many Raman lines of *n*-paraffins on solidification has been explained by considering only one molecular form in the solid state and several ones in the liquid state. The molecular form in the solid state has been shown to be the extended form for which the calculation of normal vibrations has been made. A short discussion on high elasticity has been added.

BUNKYOKU, TOKYO RECEIVED SEPTEMBER 7, 1948

(12) Powell, Clark and Eyring, *J. Chem. Phys.*, **9**, 268 (1941).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

# Studies of Sulfonates. X.[1] Sodium Triisopropylbenzenesulfonate as a Colloidal Electrolyte[2,3]

BY GORDON R. SHUCK[4,5] AND E. C. LINGAFELTER

The colloidal electrolyte behavior of several sodium *n*-alkylbenzene-*p*-sulfonates has been previously reported.[6] It seemed of interest to compare the behavior of a polyalkylbenzene sulfonate, since the effective length of the molecule could be considerably decreased while maintaining a hydrocarbon residue of considerable molecular weight. The compounds which we have prepared and studied are triisopropylbenzenesulfonic acid and its sodium salt. These may be compared with the sodium *n*-octylbenzene-*p*-sulfonate,[6] which differs in molecular weight by that of one methylene group only.

The critical concentration for micelle formation has been determined from solubility and electrical conductance measurements and by the use of the dye, pinacyanol chloride.[7]

## Experimental

**Preparation of Compounds.**—Triisopropylbenzene and tetraisopropylbenzene were prepared by the repeated alkylation of cumene (Eastman Kodak Co. white label) with isopropyl alcohol and sulfuric acid under reflux conditions. The alkylation procedure consisted of the slow addition of the sulfuric acid to a boiling solution of hydrocarbon and isopropyl alcohol. Using this method, the mole ratio and acid concentration found to give the greatest yield of alkylated product with minimum loss due to sulfonation was 1 mole hydrocarbon:1 mole isopropyl alcohol:1.2 moles 98% sulfuric acid. After each alkylation, the hydrocarbons were separated from the acid in a separatory funnel, washed with water and finally with 10% aqueous sodium hydroxide to remove sulfonic acids, and dried with calcium chloride. The final alkylated product was fractionated in an 18-inch helices-packed column at about 15 mm. pressure to separate the mono-, di- and triisopropylbenzenes, and the tetraisopropylbenzene was distilled from the residue in a special distillation apparatus. The tetraisopropylbenzene was further purified by three recrystallizations from isopropyl alcohol. From 1 liter of cumene there was obtained 650 ml. of triisopropylbenzene (boiling range 230–240° at 760 mm.) and 260 g. of tetraisopropylbenzene (m. p. 117.5°). Francis[8] gives the following data: 1,2,4-triisopropylbenzene, b. p. 244°; 1,3,5-triisopropylbenzene, b. p. 238°; 1,2,4,5-tetraisopropylbenzene, m. p. 118.4° Newton[9] reports that the triisopropylbenzene prepared by sulfuric acid alkylation consists of 84% 1,2,4-triisopropylbenzene and 16% 1,3,5-triisopropylbenzene. No serious attempt was made to separate these isomers, although our triisopropylbenzene fraction was fractionated at a slow rate several times, the first portion being discarded each time. Therefore our final product was probably quite largely 1,2,4-triisopropylbenzene, but almost certainly contained some 1,3,5-triisopropylbenzene.

100 ml. of triisopropylbenzene was dissolved in 300 ml. of carbon tetrachloride and agitated with 100 ml. of fuming sulfuric acid (15% free $SO_3$) for fifteen minutes. The layers were then separated, the carbon tetrachloride was evaporated off and the residue taken up in water. The aqueous solution was neutralized with sodium hydroxide and upon cooling yielded crystals of sodium triisopropylbenzenesulfonate.

Tetraisopropylbenzene was also sulfonated by the same method, yielding a product identical with that obtained from the triisopropylbenzene. The identity of the two substances is shown by a comparison of powder patterns of the sodium salts (see Table I). The product of the sulfonation of tetraisopropylbenzene was further shown to be triisopropylbenzenesulfonic acid by three additional experiments: (1) hydrolysis of the compound in boiling dilute sulfuric acid yielded a hydrocarbon boiling at 235–240°; (2) the equivalent weight of the solid hydrate, determined by titration with 0.1 *N* NaOH, was found to be 299.5 (calculated for triisopropylbenzenesulfonic acid monohydrate, 302.5); (3) the barium salt was prepared and analyzed for barium by precipitation of barium sulfate (found 19.50% Ba, calculated for barium triisopropylbenzenesulfonate 19.51% Ba). Newton[10] also found that the sulfonic acids formed from 1,2,4-triisopropylbenzene and 1,2,4,5-tetraisopropylbenzene by the action of chlorosulfonic acid were identical. Thus our product consists of a mixture of the isomeric triisopropylbenzenesulfonic acids.

TABLE I

POWDER PATTERN DATA FOR SODIUM TRIISOPROPYLBENZENESULFONATE

| Compound prepared from triisopropylbenzene | | Compound prepared from tetraisopropylbenzene | |
|---|---|---|---|
| Intensity[b] | Ring diameter, mm.[a] | Intensity[b] | Ring diameter, mm.[a] |
| w | 6.5 | w | 6.7 |
| m | 8.0 | m | 8.1 |
| s | 8.9 | s | 9.0 |
| m | 12.2 | m | 12.1 |
| w | 13.5 | w | 13.6 |
| w | 15.8 | w | 16.0 |
| m | 17.9 | m | 17.9 |
| w(b) | 20.0 | w(b) | 20.0 |
| w | 24.1 | w | 24.2 |
| w+ | 26.9 | m− | 27.0 |
| | | w− | 28.5 |
| w | 29.7 | w | 29.8 |
| m | 32.2 | m | 32.3 |
| m− | 34.3 | m− | 34.4 |
| w+ | 35.6 | mw | 35.6 |
| about 5 weak unmeasurable rings | | about 5 weak unmeasurable rings | |
| m | 47.7 | m | 47.6 |

[a] Diffraction patterns taken with unfiltered CuK$\alpha$ radiation in a cylindrical camera with radius = 5.00 cm. [b] S = strong, m = medium, w = weak, (b) = broad.

(1) Paper IX of this series, Neff, Wheeler, Tartar and Lingafelter, THIS JOURNAL, **70**, 1989 (1948).

(2) Taken from a thesis submitted by Gordon R. Shuck in partial fulfillment of the requirements for the Ph.D. degree at the University of Washington.

(3) Presented at the Research Conference of the Puget Sound Section of the American Chemical Society, November, 1947.

(4) Standard Oil Company Research Fellow, 1946–1947.

(5) Present address: Procter and Gamble Co., Ivorydale, Ohio.

(6) Paquette, Lingafelter and Tartar, THIS JOURNAL, **65**, 686 (1943).

(7) Corrin, Klevens and Harkins, *J. Chem. Phys.*, **14**, 480 (1946).

(8) Francis, *Chem. Rev.*, **42**, 144 (1948).

(9) Newton, THIS JOURNAL, **65**, 320 (1943).

(10) Newton, THIS JOURNAL, **65**, 2439 (1943).

The solubility of sodium triisopropylbenzenesulfonate in water was determined at intervals over the range 10 to 49°. Two large test-tubes, each containing 30 ml. of water and excess solid were placed in a water thermostat regulated to ±0.05° and stirred mechanically for two hours. One of the solutions had been heated above the bath temperature to obtain complete solution, while the other had been made up below the bath temperature. Thus, agreement between the results from the two solutions indicated that equilibrium had been established. After the excess solid had settled, samples were pipetted from the solutions by means of a pipet whose tip was covered with filter paper. The samples were discharged into weighing bottles, evaporated to dryness, and weighed again. The results of the solubility determination are given in Fig. 1.

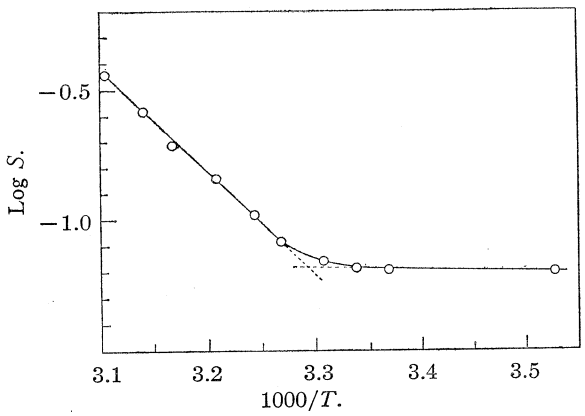



Fig. 1.—Solubility of sodium triisopropylbenzene-sulfonate in water (moles per 1000 g. of water).

The electrolytic conductance of aqueous solutions of sodium triisopropylbenzenesulfonate and of triisopropylbenzenesulfonic acid were measured using the bridge and cells previously described.[11] The cells were replatinized and their constants redetermined before use. The results are given in Figs. 2 and 3.

The critical concentration of the sodium salt was determined to be 0.061 *M* at 50° by the use of the dye pinacyanol chloride.[7]

## Discussion of Results

The solubility and pinacyanol chloride results with sodium triisopropylbenzenesulfonate and the conductance of the acid clearly indicate that these substances behave as colloidal electrolytes. The absence of any marked discontinuity in the conductance curve of the sodium salt illustrates the danger of basing conclusions on one property alone.

The values obtained for the critical concentration from the several properties seem to agree as well as corresponding results for other colloidal electrolytes. The values for the sodium salt are 0.065 *M* (from solubility) and 0.061 *M* (from the pinacyanol chloride method), while the value for the acid is 0.055 *M* (from the equivalent conductance). In particular, it may be pointed out that a comparison of the data of Wright, Abbott, Sivertz and Tartar[11] with those of McBain, Dye and Johnston[12] show the critical concentrations of the alkane-sulfonic acids to be slightly less than those of the sodium alkane-sulfonates.

(11) Wright, Abbott, Sivertz and Tartar, THIS JOURNAL, **61**, 549 (1939).

(12) McBain, Dye and Johnston, *ibid.*, **61**, 3210 (1939).

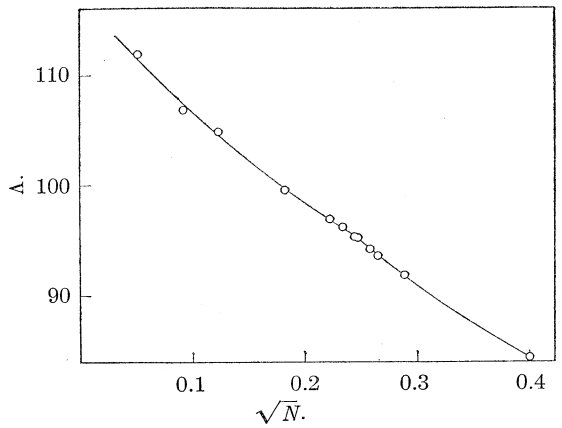



Fig. 2.—Equivalent conductance of aqueous solutions of sodium triisopropylbenzenesulfonate at 50°.

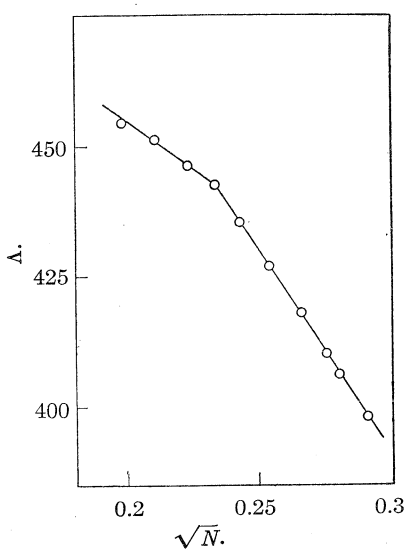



Fig. 3.—Equivalent conductance of aqueous solutions of triisopropylbenzenesulfonic acid at 50°.

The average value for the sodium salt, 0.063 *M*, may be compared with the value for sodium *n*-octylbenzene-*p*-sulfonate, 0.013 *M*.[6] Thus, although the triisopropylbenzenesulfonate ion contains one more carbon atom, it does not aggregate until a higher concentration is reached. This indicates the importance of the shape of the molecule in determining the tendency toward micelle formation, agreeing with the observation of Hartley[13] that branching of the hydrocarbon portion increases the critical concentration. It does not seem possible at present to decide whether this effect is a consequence of the efficiency of packing in the micelle, the size of the micelle, or the interfacial free energy of the unassociated ion.

Furthermore, the observation that the conductance of the sodium salt does not decrease at the critical concentration indicates that the fraction of gegenions attached to the micelles is smaller

(13) Hartley, *Trans. Far. Soc.*, **37**, 130 (1941).

than is the case for the long-chain compounds. This may be due to the greater distance between charges on the surface of the micelle, or to a smaller aggregation number.


## Summary

1. Triisopropylbenzenesulfonic acid has been prepared by the sulfonation of triisopropylbenzene and of tetraisopropylbenzene.

2. Triisopropylbenzenesulfonic acid and its sodium salt have been shown to be colloidal electrolytes, with critical concentrations of 0.055 and 0.063 *M*, respectively.

3. The comparison of these compounds with sodium *n*-octylbenzene-*p*-sulfonate illustrates the importance of molecular shape as well as size in determining the tendency toward aggregation.

4. The conductance of the sodium salt shows no discontinuity at the critical concentration, indicating a relatively small fraction of attached gegenions.


SEATTLE, WASHINGTON RECEIVED MAY 5, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

# Transference Numbers of Dodecylammonium Chloride in Water–Organic Solvent Systems

BY A. W. RALSTON AND A. E. BRAKE

Dodecylammonium chloride is a typical cationic colloidal electrolyte and the equivalent conductivity of its aqueous solutions shows an abrupt drop at $1.44 \times 10^{-2}$ molar[1] at which concentration it undergoes a transition from an ordinary to a colloidal electrolyte. It has been shown recently[2] that the addition of organic solvents such as acetone, methyl or ethyl alcohol or acetonitrile to aqueous solutions of dodecylammonium chloride increases the concentration of colloidal electrolyte at the critical point. As the concentration of organic addend is increased the conductivity curves of dodecylammonium chloride are no longer characteristic of those of a colloidal electrolyte and resemble those of an ordinary electrolyte. This decreased tendency toward association has been attributed to the decreased ionizing powers and dielectric properties of the mixed solvent, the latter factor increasing the effectiveness of the repulsion of similarly charged ions. When the equivalent conductivities of various concentrations of dodecylammonium chloride are plotted against the mole per cent. of organic addend the effect of the organic addend is seen to vary greatly depending upon whether the concentration of colloidal electrolyte is more or less than the critical concentration. At concentrations lower than critical the conductivity falls to a minimum and then rises smoothly as the composition of the solvent approaches that of the pure organic addend. On the other hand, the conductivity curves for concentrations higher than the critical concentration rise quite sharply to a maximum and then gradually decrease as the mole percentage of organic addend is increased. It has been postulated that these maxima occur at those points which represent a transition of the dodecylammonium chloride from a colloidal to an ordinary electrolyte. Since it is well established that at concentrations beyond the critical point the transference number of the associated ion exhibits a characteristic, sharp rise, it is apparent that transference data would be of great assistance in the interpretation of the effect of organic addends upon the colloidal behavior of dodecylammonium chloride. This present paper presents transference data upon dodecylammonium chloride in two of the water–organic solvent systems studied; namely, water–methanol and water–acetonitrile, and correlates these data with the conductometric behavior of these systems.

(1) Ralston and Eggenberger, THIS JOURNAL, **70**, 436 (1948).

(2) Ralston and Eggenberger, *J. Phys. and Colloid Chem.*, **52**, 1494 (1948).

## Experimental

**Apparatus.**—The Washburn cell[3] employed in earlier transference experiments in these laboratories[4] was again employed for a portion of the work herein reported.

Comparable results were obtained in a smaller apparatus designed to economize amine salt and to avoid complications of changing solution density. This cell consisted of three U-tubes sealed together, having a uniform internal diameter of 15 mm. and a mean total length of 80 cm., and required only 150 ml. of solution. The cell was provided with glass stopcocks at the bottom of each U-tube and with vent tubes at the top. The electrodes were helices of 18 gage, pure silver wire (15 turns of 1 cm. diameter). A silver surface for the anode and a silver chloride surface for the cathode were produced electrolytically. Two silver coulometers of the Kohlrausch type were employed. Observations and initial adjustment of current were made with the usual resistances and meters. Constant temperature of 30° was obtained by the use of a large air bath having temperature control to ±0.05°.

**Materials.**—The dodecylammonium chloride employed in these studies has been previously described.[1] The solutions were made with freshly prepared conductivity water, dried and redistilled acetonitrile and C. P. absolute methanol.

**Procedure.**—Experiments in the Washburn cell were conducted in the manner previously described.[4]

In the smaller cell the silver anode was washed repeatedly in distilled water and dried by burning off methanol before use. The silver-chloride cathode, also washed, was suspended in the solution to be electrolyzed with occasional stirring for a day prior to its use. This permitted the establishment of the initial concentration of dodecylammonium chloride in the pores of the cathode surface.

(3) Washburn, THIS JOURNAL, **31**, 322 (1909).

(4) Hoerr and Ralston, *ibid.*, **65**, 976 (1943).

After the completion of the electrolysis the stopcocks at the bottom of each U-tube were carefully opened, thus dividing the solution into three portions, namely, anode, cathode and middle.

**Electrode Reactions.**—The usual electrode reactions, the formation of silver chloride at the anode and the reduction of silver chloride to free silver at the cathode were observed.

The formation of a complex salt between silver chloride and dodecylammonium chloride at the anode resulted in a poorly adhering deposit which clouded the solution in this compartment. It is necessary to include the dodecylammonium chloride contained both in the electrode itself and in the detached material in the analytical results in order to obtain check results for the content of amine salt in the anode and cathode compartments. This procedure is much preferable to employing a correction such as that recently discussed by Hale and De Vries.[5] At the cathode the reduction of silver chloride to free silver in the presence of the colloidal electrolyte resulted in the production of a colloidal silver sol as evidenced by the development of a yellow color in these solutions. Both these effects were greatly reduced as the amount of organic solvent increased and they were not observed in those mixtures which were rich in organic solvent.

**Analyses.**—The concentration of dodecylammonium ion was determined by steam distillation of the amine and its titration with standard acid.[6] As stated previously, it was necessary to decompose the silver chloride–dodecylammonium chloride in order to obtain satisfactory analytical values. The chloride ion was determined gravimetrically as silver chloride after removal of the dodecylammonium ion. In the experiments with acetonitrile it was necessary to remove the acetonitrile by distillation of its azeotrope from the amine salt solution before satisfactory analytical results could be obtained.

Agreement between the analyses of the original solution and the middle portion was better than 1% for all results reported. The transference numbers in aqueous solution were reproducible within ±0.02 unit. In mixtures rich in organic solvent the analyses were in better agreement (±0.2%) and the transference numbers in methanol were reproducible within ±0.003 unit.

## Results and Discussion

The cationic transference numbers at 30° of dodecylammonium chloride plotted against the mole percentage of methanol in the solvent are shown in Fig. 1. Two concentrations of dodecylammonium chloride were studied, 0.1 molar which is materially greater than the critical concentration and 0.01 molar which is less. At the concentration greater than the critical concentration increase in the percentage of methanol is attended by a very rapid decrease in $T_c$, the value reaching a minimum at approximately thirty mole per cent. of methanol and then slowing rising. The conductometric work, to which reference has previously been made,[2] showed that a maximum value in the equivalent conductivity of dodecylammonium chloride in methanol–water mixtures occurs at about thirty mole per cent. methanol. The rapid drop to a minimum in the transference number of the dodecylammonium ion and its subsequent rise presents further evidence of the transition of dodecylammonium chloride from a colloidal to an ordinary electrolyte as the composition of the solvent goes from pure water to pure methanol. This transition is apparently completed in the neighborhood of the minimum in the $T_c$ curve. The rise in the transference numbers after the minimum can be attributed to the reduction in the viscosity of the solvent as its composition approaches pure methanol. Decrease in the viscosity of the solvent should have a greater relative effect upon the large dodecylammonium ion than upon the smaller chloride ion.

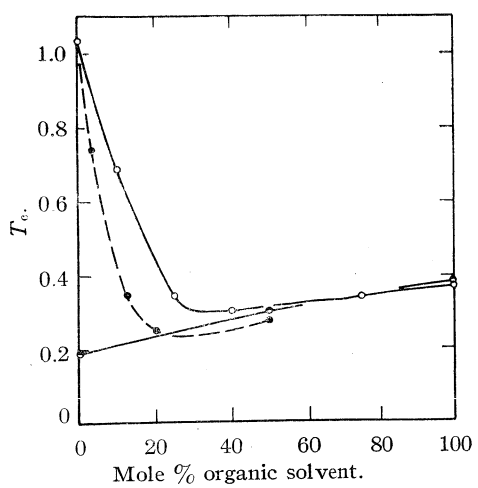



Fig. 1.—Transference numbers of dodecylammonium chloride in methanol–water and acetonitrile–water at 30°: ○, 0.1 *M* in methanol–water; ●, 0.1 *M* in acetonitrile–water; ◒, 0.01 *M* in methanol–water.

The transference numbers for the dodecylammonium ion in 0.01 molar dodecylammonium chloride show a gradual rise as the composition of the solvent goes from pure water to pure methanol. The values in the water-rich mixtures do not exhibit the abnormal behavior shown by the higher concentration of amine salt when the dodecylammonium chloride functions as a colloidal electrolyte. The increase in the value $T_c$ is explainable on the basis of decreased solvation of the dodecylammonium ion coupled with viscosity changes in the solvent. It is of interest to note that in the methanol-rich solvents the values of $T_c$ for 0.1 and 0.01 molar dodecylammonium chloride are similar and are in marked contrast with the rise to abnormally high values obtained in aqueous solutions in this concentration range.

Figure 1 also shows the transference numbers of the dodecylammonium ion in several acetonitrile–water mixtures. The decrease in the values of $T_c$ is somewhat more abrupt than in the methanol–water solvents and the minimum occurs at a lower value of $T_c$ and at a somewhat lower concentration of organic addend. It has been previously observed[2] that the addition of acetonitrile brings about a more rapid transition of this amine salt from a colloidal to an ordinary electrolyte than does the addition of methanol. A maximum in the equivalent conductivity curve was observed in the neighborhood of fifteen per cent. acetonitrile a value in approximate agreement with the minimum in the $T_c$ values.

(5) Hale and De Vries, THIS JOURNAL, **70**, 2473 (1948).

(6) Ralston and Hoerr, *Ind. Eng. Chem., Anal. Ed.*, **16**, 459 (1944).

The values of $\Lambda_c$ plotted against the solvent composition are shown in Fig. 2. It is significant that the values for 0.1 molar dodecylammonium chloride in those solvent compositions in which it functions as a colloidal electrolyte are identical for similar molar concentrations of methanol and acetonitrile. This suggests that the results described in this paper for methanol–water and acetonitrile–water systems may constitute examples of a general effect which may be encountered with other organic solvent–water systems. The values of $\Lambda_c$, unlike those of $T_c$, are of course greater for the lower concentration of amine salt in methanol–water mixtures under those conditions where the amine salt functions as an ordinary electrolyte.

The numerical values of $T_c$, $\Lambda_c$, $T_a$ and $\Lambda_a$ at 30° are shown in Table I.

TABLE I

| Mole % $CH_3OH$ | $T_c$ | $\Lambda_c$[a] | $T_a$ | $\Lambda_a$[a] |
|---|---|---|---|---|
| | $C_{12}H_{25}NH_3Cl$, 0.10 *M* | | | |
| 0 | 1.033 | 40.3 | −0.027 | .. |
| 10.0 | 0.689 | 27.6 | +0.325 | 13.0 |
| 25.0 | .343 | 15.1 | .663 | 29.2 |
| 40.0 | .302 | 13.0 | .723 | 28.9 |
| 75.0 | .345 | 15.2 | .673 | 29.6 |
| 100.0 | .369 | 18.5 | .665 | 30.9 |
| | $C_{12}H_{25}NH_3Cl$, 0.01 *M* | | | |
| 0 | 0.189 | 19.3 | 0.814 | 83.0 |
| 50 | .301 | 15.9 | .725 | 38.4 |
| 100 | .378 | 27.6 | .658 | 48.0 |
| | $C_{12}H_{25}NH_3Cl$, 0.10 *M* | | | |
| $CH_3CN$ | | | | |
| 3.66 | 0.738 | 36.9 | 0.316 | 15.8 |
| 12.5 | .346 | 25.3 | .656 | 47.8 |
| 20.0 | .250 | 17.5 | .719 | 50.3 |
| 50.0 | .275 | 15.1 | .725 | 39.8 |

[a] The ionic conductances were computed from data of reference.[2]

The negative value of $T_a$ for dodecylammonium chloride in pure water is noteworthy. A value of 0.13 for $T_a$ at 30° has previously been reported.[4] The low value is explainable on the basis of solubilization of the undissociated amine salt by the micelles.

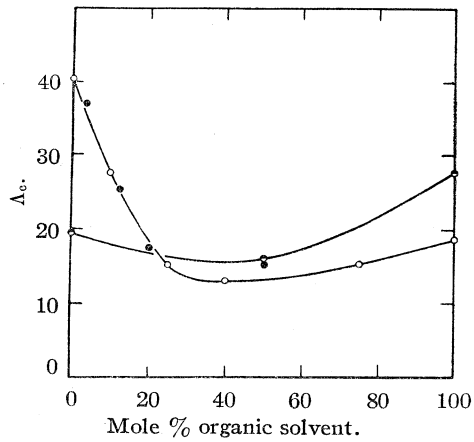



Fig. 2.—Cationic conductances of dodecylammonium chloride in methanol–water and acetonitrile–water at 30°: ○, 0.1 *M* in methanol–water; ●, 0.1 *M* in acetonitrile–water; ◓, 0.01 *M* in methanol–water.

Above forty mole per cent. methanol the values of $\Lambda_a$ for 0.1 molar dodecylammonium chloride are in close agreement with those of Longsworth and MacInnes[7] for 0.05 molar lithium chloride and sodium chloride in similar methanol–water mixtures. This is further evidence of the normal behavior of dodecylammonium chloride in methanol-rich solvents. Below forty mole per cent. methanol the values are widely divergent owing to association of the colloidal electrolyte.

## Summary

The values of $T_c$, $T_a$, $\Lambda_c$ and $\Lambda_a$ for dodecylammonium chloride in methanol–water and acetonitrile–water mixtures at 30° have been determined or derived.

At 0.10 *M* the transference numbers indicate a transition of dodecylammonium chloride from a colloidal to an ordinary electrolyte as the percentage of organic addend is increased.

CHICAGO, ILLINOIS RECEIVED OCTOBER 15, 1948

(7) Longsworth and MacInnes, *J. Phys. Chem.*, **43**, 239 (1939).

[CONTRIBUTION FROM THE UNIVERSITY OF COLORADO]

# Reaction Heats of Organic Fluorine Compounds. I. Apparatus and the Heat of Chlorination of Tetrafluoroethylene[1]

BY J. R. LACHER, J. J. MCKINLEY, C. M. SNOW, L. MICHEL, G. NELSON AND J. D. PARK

Since the pioneering work of Swarts[2] very few thermochemical data on organic fluorine compounds have been obtained. Wartenberg and Schütte,[3] using elemental fluorine, measured the heat of formation of carbon tetrafluoride. However, since higher fluorides of carbon were probably formed in the reaction, the actual value for the heat may be greater than that reported. In the case of organic chlorine and bromine compounds the situation is not much better. Kistiakowsky and co-workers[4] have measured the heat of chlorination of ethylene and the heats of bromination of several simple olefins. The heats of combustion of some chloro derivatives of benzene have been measured recently by Hubbard, Knowlton and Huffman,[5] and by L. Smith.[5a]

Thermochemical data are necessary for the thermodynamic and statistical calculations of equilibrium constants. They give valuable information concerning the nature of a chemical bond and are useful in the design of process equipment. Accordingly a long range program is being undertaken to measure directly the heats of vapor phase reactions of organic halogen compounds. The calorimeter constructed for this purpose possesses the flow characteristics of the one described by Kistiakowsky and co-workers[6] but it operates at constant temperature in a manner similar to those described by Kraus,[7] Tong and Kenyon[8] and Coon and Daniels.[9]

The operation of the calorimeter is simple in principle and is essentially one of substitution. The gaseous reactants are led into a catalyst chamber where the reaction takes place, and the products pass through a heat exchanger out to a collecting system. A volatile liquid surrounding the heat exchanger absorbs the heat of reaction. At the same time nitrogen is bubbled through this liquid thereby removing heat by vaporization at such a rate as to maintain the temperature constant. When equilibrium has been established on the catalyst, the flow of reactants is stopped and direct electrical heating substituted for that due to the reaction, the nitrogen flow remaining constant. The electrical energy required is then equal to that produced by the reaction. From the rate of energy input and the rate of formation of product, the heat of reaction can be calculated.

**Apparatus.**—The essential parts of the calorimeter are shown in Fig. 1. The reaction chamber was machined from a cylinder of monel metal 1″ × 10″. The chamber is charged with catalyst through a cap at the bottom which is soldered in place. The reactants are led into the catalyst chamber through two concentric tubes and mix at the top of the catalyst bed. The products are taken from the bottom and led through a heat exchanger made of six feet of $^1/_4$″ copper tubing and thence to the collecting system. This chamber and accessories were suspended from a circular brass plate so that they could be immersed in a 960-ml. wide-mouth dewar flask. This dewar contained chlorobenzene and the heat of reaction was transferred to it. In order to remove heat from the system, dry nitrogen was bubbled through the chlorobenzene and was dispersed by means of a size B fritted glass distributor. The metal-to-glass joint was below the liquid level in the dewar. The waste nitrogen and chlorobenzene were led out through a $^1/_2$″ thin-walled brass tube. The upper part served as a condenser to return most of the chlorobenzene.

A bare nichrome heater, made of number 32 wire and having a resistance of 42 ohms, was fastened to the glass distributor tube. The potential and current leads were led out through the nitrogen line. The heating current was supplied by four lead storage batteries in series. During a run the batteries were charged at a slightly lower rate than the power requirement.[10] In this way very constant currents were obtained. The electrical energy input was obtained by measuring the e. m. f. across a standard resistance in series with the heater and also the potential drop across the heater. A Rubicon type B potentiometer and high sensitivity galvanometer were used for these measurements. In case of the potential drop across the heater, a voltage divider was necessary.

A 12-junction copper–constantan thermel was used to measure the temperature differential between the chlorobenzene and the oil-bath in which the whole assembly was immersed. One end of the thermel was located in a well made of telescopic iron tubing and extending about midway into the

(1) Presented before the Division of Inorganic and Physical Chemistry, 114th meeting of the American Chemical Society, Portland, Oregon, Sept. 13–17, 1948.

(2) F. Swarts, *J. chim. phys.*, **17**, 3 (1919); W. Swietoslawski and J. Bobinska, *ibid.*, **24**, 545 (1927).

(3) H. Wartenberg and R. Schütte, *Z. anorg. Chem.*, **211**, 222 (1933).

(4) J. B. Conn, G. B. Kistiakowsky and E. Smith, THIS JOURNAL, **60**, 2764 (1938).

(5) W. N. Hubbard, J. W. Knowlton and H. M. Huffman, to be published.

(5a) L. Smith, "The Svedberg" (Mem. Vol.), 352 (1944).

(6) G. B. Kistiakowsky, Romeyn, Ruhoff, Smith and Vaughan, THIS JOURNAL, **57**, 65 (1935).

(7) C. A. Kraus and J. A. Riddenhoff, *ibid.*, **56**, 79 (1934).

(8) L. K. J. Tong and W. O. Kenyon, *ibid.*, **67**, 1278 (1945).

(9) E. D. Coon and F. Daniels, *J. Phys. Chem.*, **37**, 1 (1933).

(10) We wish to thank Dr. D. M. Stull, of the Dow Chemical Co., Midland, Michigan for suggesting this to us.

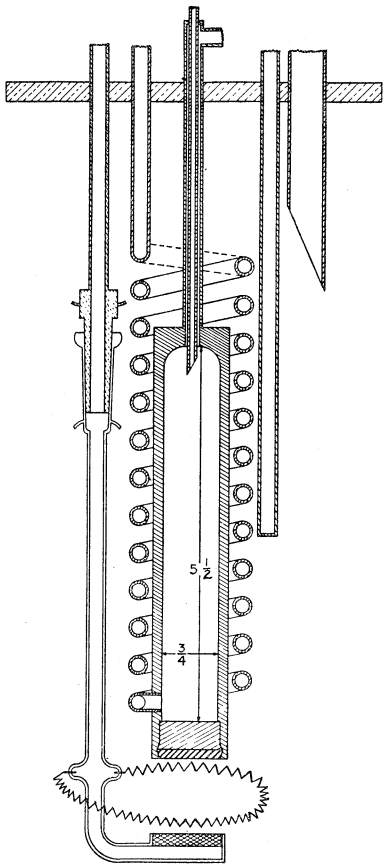



Fig. 1.

chlorobenzene (shown in Fig. 1). The other end was located in the surrounding oil-bath. By means of a suitable switching arrangement, the e. m. f. of the thermel could be read on a potentiometer or placed directly on the high sensitivity galvanometer or on a Rubicon photoelectric galvanometer depending on the sensitivity required. When the reacting system had reached a steady state during a run, the e. m. f. of the thermel would fluctuate about zero.

The 960 ml. wide-mouth dewar containing the chlorobenzene was tightly contained in a brass cylinder as shown diagrammatically in Fig. 2. The dewar rested on a platform supported by three stiff metal springs. The bottom plate of the brass cylinder was fitted with a $^3/_4$" pipe flange and a pipe extension in order that the assembly could be supported from the bottom of the thermostat. The top plate held the catalyst chamber and auxiliary equipment. It was tightly bolted on using sheet gaskets. The gases entering the calorimeter were brought to temperature by passing them through heat exchangers made of $^1/_4$" copper tubing immersed in the oil thermostat.

The thermostat consisted of a cubical iron tank containing 110 gallons of lubricating oil. It was thoroughly insulated with "Sil-o-cell" brick and is designed for operation up to 200°. Continuous

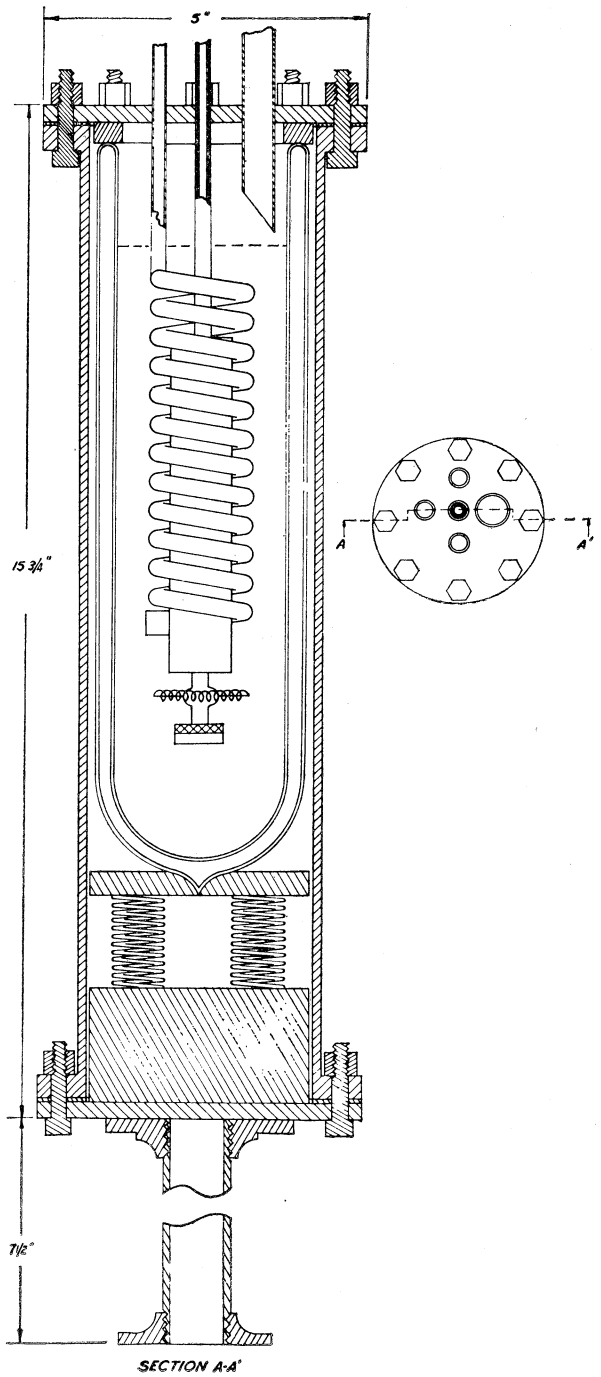



Fig. 2.

heating was supplied by nichrome elements evenly spaced in the top, bottom and sides of the thermostat. Intermediate heating was obtained by four nichrome immersion heaters. These surround the propeller shafts located in each of the four corner "wells" in the tank. The temperature was controlled by a d. c. bridge-photoelectric cell system. The temperature sensing element was a thermister (type D 169,604), developed by the Bell Telephone

Laboratories and formed one arm of the bridge. When the heating current was on, a reversible "Telechron" increased the voltage of the "Variac" controlling the heaters. On the other hand, when this current was off, this voltage was slowly decreased. The system sought a condition where the current was on half the time. A 25-ohm platinum resistance thermometer and Mueller bridge were used to measure temperatures. No gradients could be measured in the bath while operating at 80° and temperature fluctuations were less than 0.001° over a period of several hours.

The flow rate of the nitrogen used to cool the chlorobenzene was carefully controlled. Nitrogen from a commercial cylinder was supplied to a Moore[11] "Nullmatic" pressure regulator at a pressure of six pounds by means of a standard reducing valve. It then passed to an adjustable head overflow tower, buffer tank and through an ordinary capillary flow meter. Several manometers were included in the line for observation of back pressures. It was necessary only to maintain a constant nitrogen flow once the catalyst had reached a steady state and while the electrical energy balance was being made. A differential of more than 100 mm. across the flow meter could be held constant to 0.2 mm. during the course of a run.

## Experimental

**Hydrogenation of Cyclohexene.**—The cyclohexene was prepared from commercial cyclohexanol after the methods of Kistiakowsky, *et al.*,[12] and Coleman and Johnstone.[13] The crude cyclohexene obtained was distilled twice in a vacuum-jacketed column packed with glass helices, having a total condensation head and a variable magnetic takeoff. The middle fraction consisting of 60% of the crude material was used. The refractive index, $n^{20}D$ 1.4466, of this product was in close agreement with that of Kistiakowsky.[11] The catalyst used for hydrogenation was platinum black on asbestos found satisfactory by Kistiakowsky[11] and prepared by the method of Shiels.[14]

The hydrogen, from a commercial cylinder, was led through heated copper and a "Drierite" and "Ascarite" tower. It then passed through a Moore pressure regulator, Moore constant flow regulator, precatalyst chamber and to a valve system whereby it could be sent either directly to the calorimeter or to a gas-saturating device containing cyclohexene. In this cyclohexene bubbler, the hydrogen becomes partially saturated. The temperature was so controlled that hydrogen was in excess when the mixture was led to the calorimeter. The amount of cyclohexane formed was determined by condensing it from the excess hydrogen and weighing the product. In order to test the effectiveness of the collecting system used, the hydrogen stream was saturated with cyclohexane in auxiliary experiments. The amount of cyclohexane recovered was compared with that removed by the hydrogen from a weighed sample. The results, shown in Table I, indicate that the per cent. loss decreases with increasing size of the sample. We were not able to recover quantitatively all of the cyclohexane, due apparently to a small initial loss by entrainment which was stopped when the glass wool in the trap became matted with crystals of cyclohexane.

(11) Manufactured by Moore Products Co., Philadelphia, Pa.

(12) G. B. Kistiakowsky, *et al.*, THIS JOURNAL, **58**, 137 (1936).

(13) Coleman and Johnstone, "Organic Synthesis," Coll. Vol. I, p. 183.

(14) D. O. Shiels, *J. Phys. Chem.*, **33**, 1167 (1929).

TABLE I

RECOVERY OF CYCLOHEXANE FROM A HYDROGEN STREAM

| Grams of cyclohexane | | |
|---|---|---|
| Lost from saturator | Condensed in collector | Loss, % |
| 2.998 | 2.930 | 2.3 |
| 3.352 | 3.290 | 1.8 |
| 5.144 | 5.134 | 0.2 |
| 6.334 | 6.296 | 0.6 |

In making a calorimetric run, hydrogen was first passed through the calorimeter and collecting system to flush out air. An arbitrary flow of nitrogen through the chlorobenzene was chosen and sufficient electrical energy supplied to establish isothermal conditions. The amount of energy required was independent of the flow rate of hydrogen through the system. After a balance was obtained, the electrical heating was discontinued and the hydrogen was sent to the cyclohexene bubbler. The rate of reaction on the catalyst was adjusted to again give isothermal conditions. After collecting a sample, the flow of reactants was stopped and the electrical energy required for the same nitrogen flow was again measured. The final results obtained are shown in Table II. The second column gives the time during which the product was collected. The weight was increased steadily from 2.8 g. in sample 1 to 6.6 g. in sample 5. The amount of cyclohexane formed in moles per minute was obtained from the weight of the sample collected and the time. Owing to the fact that complete conversion of the cyclohexene did not occur on the catalyst, a correction was applied. The amount of cyclohexene present in the product was determined by measurement of refractive index. The catalyst slowly lost activity during these runs and the conversion which was initially 99% fell to 93%. The heat of hydrogenation in calories per mole was obtained by dividing the heat input in calories per minute by the rate of formation of cyclohexane in moles per minute. The per cent. deviations in the values so obtained from that found by Kistiakowsky[12] are shown in the last column. It is apparent that, if a sufficiently large sample is collected, the results agree to within a per cent. Since this is the accuracy desired, it was not thought worthwhile to improve the collecting system further.

TABLE II

HYDROGENATION OF CYCLOHEXENE AT 78°

| Run | Sampling time, min. | Cyclohexane formed[a] moles/min. $\times 10^{+4}$ | Energy input cal./min. | $-\Delta H_{351°}$, cal./mole | % Deviation from 28,592 |
|---|---|---|---|---|---|
| 1 | 59.0 | 5.713 | 16.829 | 29,457 | +3.0 |
| 2 | 60.0 | 9.384 | 28.179 | 30,029 | +5.0 |
| 3 | 63.0 | 9.635 | 28.141 | 29,207 | +2.1 |
| 4 | 60.04 | 10.267 | 29.728 | 28,955 | +1.3 |
| 5 | 72.0 | 10.130 | 29.247 | 28,872 | +0.97 |

[a] Corrected for unreacted cyclohexene.

**Heat of Formation of Hydrogen Chloride.**—Commercial hydrogen was purified by passing it over calcium chloride, hot copper gauze, and phosphorus pentoxide before entering the "Nullmatic" pressure regulating valve. This resulted in water-free hydrogen at the exit of the valve. The gas then went through a flow meter, a pre-catalyst chamber (palladium-on-carbon) and directly to the calorimeter. It was found, on treating this hydrogen with chlorine, that considerable amounts of water were discharged from the calorimeter indicating that either the hydrogen or chlorine contained oxygen which reacted in the palladium–carbon catalyst chamber. When two precatalyst chambers were installed in the hydrogen line and followed by three phosphorus pentoxide-drying tubes, very little, if any, water was formed in the main catalyst chamber.

Earlier work in this Laboratory showed that commercial

chlorine must be purified by a low temperature distillation before it could be used in calorimetric studies. Chlorine[15] from Matheson gave satisfactory results without further purification and was used in all experiments reported here. The cylinder was maintained at 0° to minimize pressure fluctuations. The chlorine was dried over phosphorus pentoxide and run through a suitable series of needle valves, constant pressure overflow tower to a capillary glass tube flow-meter. Several manometers were in the line to indicate back pressures. From the flow-meter, the chlorine could be sent either directly to the calorimeter or to a potassium hydroxide absorption tower.

The catalyst was prepared on "Columbia" activated carbon sized to pass a no. 6 and be retained on no. 20 screens. A suspension of $PdCl_2 \cdot 2H_2O$ in carbon tetrachloride was poured over the carbon (10% by weight of the chloride based on carbon was used). The solvent was removed by heating at 120° and hydrogen was used to reduce palladium chloride to palladium at the same temperature. The catalyst was then heated to 200° *in vacuo* for three hours. Upon cooling, nitrogen was admitted and the catalyst transferred to the calorimeter.

In making a run the flow rates of hydrogen and chlorine were arbitrarily chosen with hydrogen being in excess. The heat of reaction was removed by adjusting the nitrogen flow. One and one-half to two hours were required for an isothermal balance. After the balance had been obtained, the exit flow was sent through a collecting tower of 6 *N* potassium iodide to determine the amount of unreacted chlorine. The flow of chlorine was then directed from the calorimeter to a waste line and the hydrogen flow continued through the catalyst chamber for ten to fifteen minutes, electrical energy being substituted for that produced by the reaction. The hydrogen flow was then shut off and the nitrogen flow balanced with electrical energy. The chlorine was then sent through a collecting tower of 3 *N* potassium hydroxide for a definite time to determine the input of chlorine to the calorimeter. The same chlorine flow was used throughout. The amount of chlorine in the sample was determined, after reduction with hydrogen peroxide, by adding an excess of silver nitrate and back-titrating with potassium thiocyanate in the usual way. The analytical procedure was shown to average 0.2% low by analyzing weighed samples of chlorine dissolved in potassium hydroxide.

The results obtained are shown in Table III. Only those runs are included which were carried out after the installation of two pre-catalyst chambers and phosphorus pentoxide drying towers in the hydrogen line. Rossini[16] burned hydrogen and chlorine at constant pressure in a flame calorimeter and obtained heats of formation of HCl(g) to be 22,063 and 22,060 calories per mole at 25 and 18°, respectively. From heat capacity data, the heat of reaction is estimated to be −22,120 calories at 90°. The per cent. deviation of the values listed in Table III from this are given in the last column. The agreement is better than one per cent.

TABLE III

HEAT OF FORMATION OF HYDROGEN CHLORIDE AT 90°

| $H_2$ flow, moles/min. $\times 10^{+4}$ | $Cl_2$ flow, moles/min. $\times 10^{+4}$ | % $Cl_2$ reacted | Energy rate, cal./min. | $-\Delta H$, cal./mole of HCl | % Deviation from −22,120 |
|---|---|---|---|---|---|
| 6.514 | 3.333 | 98.92 | 14.5574 | 22,077 | −0.2 |
| 6.481 | 3.8477 | 98.42 | 16.7869 | 22,164 | + .2 |
| 6.481 | 3.770 | 97.99 | 16.4164 | 22,246 | + .6 |

**Chlorination of Tetrafluoroethylene.**—Matheson chlorine was used in all experiments. The tetrafluoroethylene,[17] taken from a cylinder, was passed through a purification train consisting of concentrated sulfuric acid, 10% sodium hydroxide, water, and a calcium chloride drying tower followed by phosphorus pentoxide. An ordinary capillary glass flow meter indicated the flow and the gas was then sent directly to the calorimeter.

The catalyst used was 10% by weight of ferric chloride on "Columbia" activated carbon. The carbon was sized to go through no. 6 and retained on no. 20 screens. It was then activated by heating under vacuum at 250°, cooled and mixed with iron powder obtained by reduction. After charging it in the calorimeter, the iron was converted to the chloride by passing chlorine through the chamber for several hours. When no further reaction took place, as indicated by the heat generated, the conversion was assumed to be complete. Antimony chloride catalyst, prepared in the same way, will quantitatively chlorinate the tetrafluorethylene at room temperature.

In making a run, the olefin was used in excess and the amount of reaction was taken as being equal to the amount of chlorine consumed. If the catalyst was active and if the reactants were sufficiently pure, neither chlorine nor hydrogen chloride could be detected in the product gases with fresh starch–potassium iodide and moist litmus paper. Since the carbon catalyst adsorbs considerable amounts of the gases in reaching a steady state, the flows of both reactants were carefully controlled. In starting a run, the flow of olefin and chlorine were arbitrarily set and the ni-

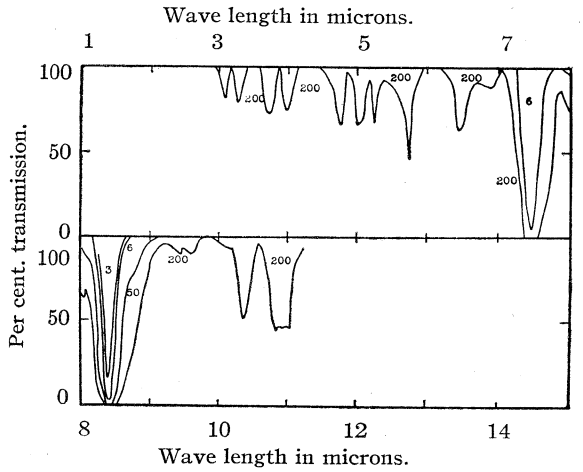



Fig. 3a.—Infrared absorption spectrogram of $CF_2{=}CF_2$ gas at room temperature in 10-cm. cell and ind. mm. pressure.

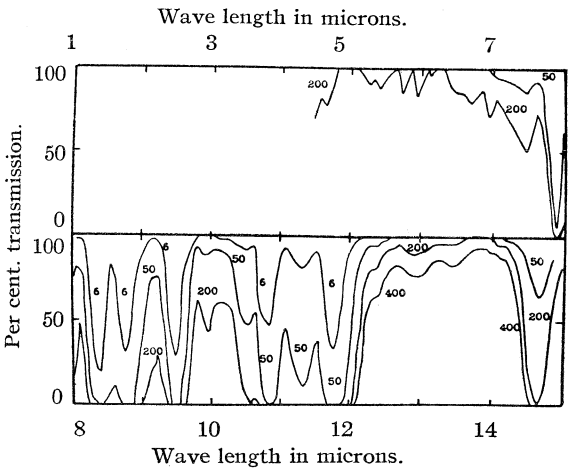



Fig. 3b.—Infrared absorption spectrogram of $CF_2Cl$–$CF_2Cl$ gas at room temperature in 10-cm. cell at ind. mm. pressure.

(15) Matheson Co., Inc., Purity 99.5%.

(16) F. D. Rossini, *Bur. Stand. J. Research*, **8**, 119 (1932).

(17) The tetrafluoroethylene was furnished us through the kindness of the Jackson Laboratory, du Pont Co., Wilmington, Del.

trogen flow adjusted to give isothermal conditions at a steady state. This meant that the energy balance was obtained only at the end of the run. While this energy balance was being taken, the chlorine was directed to the potassium hydroxide tower and a sample collected at the same flow rate as used in the reaction. The amount of chlorine in the sample was determined as described previously.

The products resulting while the calorimeter was at a steady state were condensed in a trap at −80°. Infrared absorption spectra[18] were taken on the first, middle and last fraction of the sample. By comparing the curves so obtained with those given by the pure olefin and dichloride, it was shown that no appreciable amounts of disproportionation or degradation reactions took place on the catalyst. The curves for the pure materials are given in Figs. 3a and 3b.

The data obtained on the chlorination of tetrafluoroethylene are summarized in Table IV. The results are quite reproducible and show that the heat of chlorination of this olefin is considerably greater than that of ethylene which is 43,600 calories.[3]

TABLE IV

HEAT OF CHLORINATION OF TETRAFLUOROETHYLENE AT 90°

| Run no. | Olefin flow, moles/min. × $10^{+4}$ | Chlorine flow, moles/min. × $10^{4}$ | Energy rate, cal./min. | $-\Delta H$, cal./mole |
|---|---|---|---|---|
| 29 | 7.60 | 5.101 | 29.22 | 57,283 |
| 30[a] | 8.25 | 5.77 | 33.04 | 57,262 |
| 31 | 9.04 | 6.071 | 34.86 | 57,420 |
| 32 | 6.93 | 6.109 | 35.02 | 57,325 |

[a] The chlorine flow was read off the flow meter in this case rather than being determined by direct analysis.

(18) The instrument is a model 12B manufactured by the Perkin-Elmer Corporation of Glennbrook, Conn.

**Acknowledgment.**—This work was made possible by a grant from the Research Corporation of New York. A special grant from the Regents of the University of Colorado made possible the purchasing of the infrared spectrometer. We wish to thank Mr. C. Walden and K. Lea for assistance in operating the calorimeter and infrared spectrometer. Mr. D. K. Vail assisted in the preparation of some of the compounds used and Mrs. C. M. Snow carried out the analysis for chlorine. Mr. E. Holderby constructed the calorimeter proper and most of the accessories in the shops of the University of Colorado.

## Summary

An isothermal constant-flow calorimeter is described which is suitable for measuring heats of vapor phase reactions at temperatures up to 90°. By measuring the heat of hydrogenation of cyclohexene and the heat of formation of hydrogen chloride and comparing the results obtained with data existing in the literature, the calorimeter was shown to give heats of reactions to an accuracy of one per cent. The vapor phase heat of chlorination of tetrafluoroethylene was measured to be $\Delta H = -57{,}322 \pm 200$ calories per mole at 90°.

BOULDER, COLORADO RECEIVED OCTOBER 25, 1948

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[CONTRIBUTION FROM THE UNIVERSITY OF COLORADO]

# Reaction Heats of Organic Fluorine Compounds. II. The Vapor Phase Heats of Chlorination of Some Simple Fluoroölefins[1,2]

BY J. R. LACHER, J. J. MCKINLEY, C. WALDEN, K. LEA AND J. D. PARK

In the first paper of this series[2] an isothermal constant flow calorimeter was described. The performance of the equipment was determined by measuring the heat of hydrogenation of cyclohexene and the heat of formation of gaseous hydrogen chloride. New data on the vapor phase chlorination of tetrafluoroethylene were also presented. The present paper deals with the vapor phase heats of chlorination of trifluorochloroethylene, 1,1-dichloro-2,2-difluoroethylene, perfluoropropene and perfluorocyclobutene.

**Preparation of Compounds.**—The trifluorochloroethylene[3] was purified by a low temperature distillation in a vacuum-jacketed column packed with glass helices using a magnetic take-off head and a reflux ratio greater than 5 to 1. The still head was cooled by circulating a carbon tetrachloride–chloroform–Dry Ice mixture from a reservoir at such a rate as to maintain about a 20° differential between the still head and the boiling point of the olefin. A forecut was discarded and the center fraction having a boiling point variation of less than 0.1° was collected and stored in a steel cylinder for subsequent use. The infrared absorption spectrum is shown in Fig. 1a. Using auxiliary equipment, a sample of the chlorine adduct of trifluorochloroethylene was prepared. A flow system identical with that used in the calorimeter was employed and the chlorination was carried out in the presence of ferric chloride–impregnated carbon catalyst previously described. After distillation, the product, 1,1,2-trifluoro-1,2,2-trichloroethane, gave an absorption spectrum as shown in Fig. 1b. The isomer of this compound,[3] 1,1,1-trifluoro-2,2,2-trichloroethane, gives an absorption spectrum as shown in Fig. 1c. By studying the spectrum of the product formed in an actual calorimetric run, it was concluded that little or no disproportionation occurred on the catalyst. However, if the olefin was not pure, the absorption spectrum of the calorimeter product was not a combination of those shown in Figs. 1a and 1b. Instead, anomalous absorption peaks appeared at 6.50 and 11.77 $\mu$, hydrochloric acid was in the effluent gases and the heat of reaction was low. The trouble was overcome by scrubbing the olefin in the purification train described in Paper I of this series.[2] The 1,1-dichloro-2,2-difluoroethylene and perfluoropropene[3] were passed through the purification train and then sent directly to the calorimeter. The infrared absorption spectra of 1,1-dichloro-2,2-difluoroethylene and its chlorine adduct, 1,1,1,2-tetrachloro-2,2-

(1) Presented before the Division of Inorganic and Physical Chemistry, 114th Meeting of the American Chemical Society, Portland, Oregon, September 13–17, 1948.

(2) J. R. Lacher, J. J. McKinley, C. M. Snow, L. Michel, G. Nelson and J. D. Park, THIS JOURNAL, **71**, 1330 (1949).

(3) A generous sample was supplied us through the couretsy of the Jackson Laboratory, du Pont Co., Wilmington, Delaware.

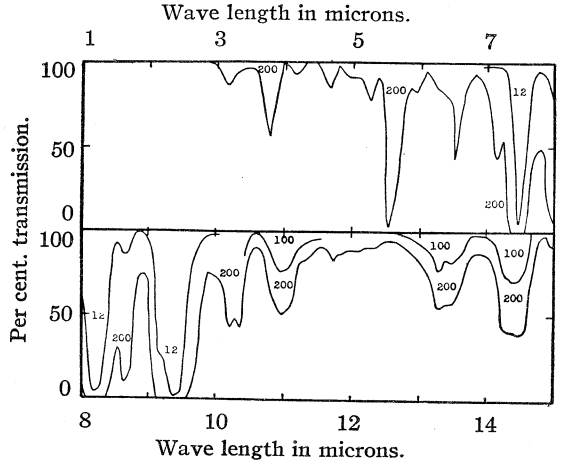



Fig. 1A.—Infrared absorption spectrogram of $CF_2$=CFCl gas at room temperature in 10-cm. cell at ind. mm. pressure.

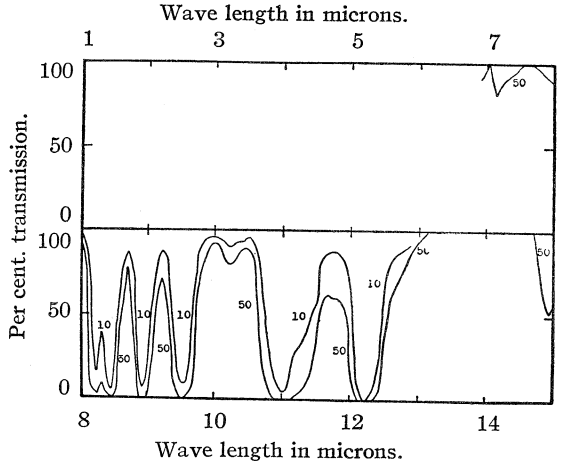



Fig. 1B.—Infrared absorption spectrogram of $CF_2Cl$—$CFCl_2$ gas at room temperature in 10-cm. cell at ind. mm. pressure.

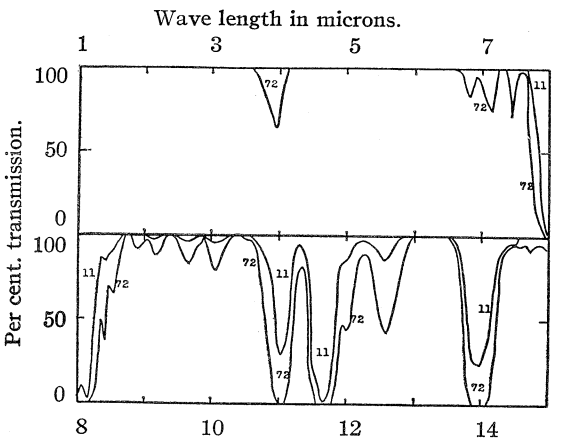



Fig. 1C.—Infrared absorption spectrogram of $CF_3$—$CCl_3$ gas at room temperature in 10-cm. cell and ind. mm. pressure.

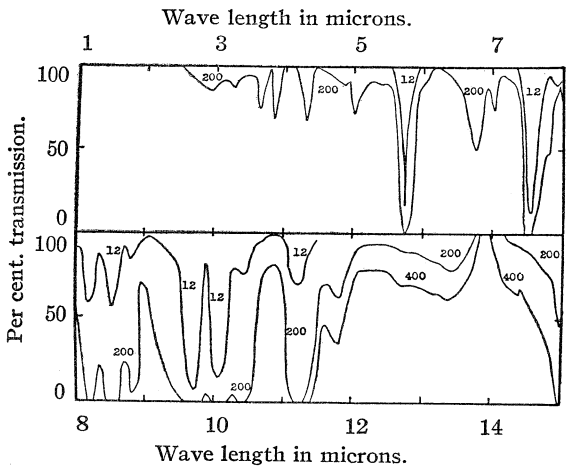
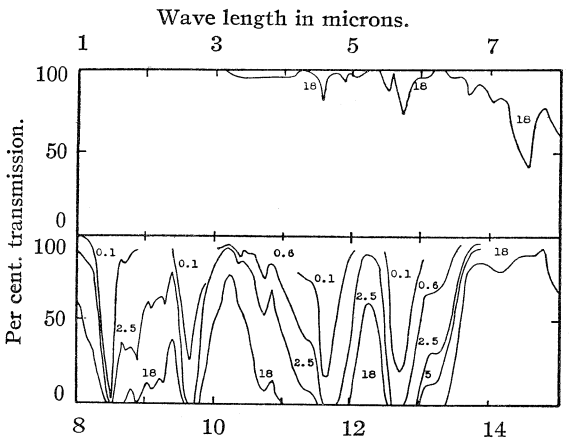



Fig. 2A.—Infrared absorption spectrogram of $CF_2$=$CCl_2$ gas at room temperature in 10-cm. cell and ind. mm. pressure.




Fib. 2B.—Infrared absorption spectrogram of $CF_2Cl$—$CCl_3$ gas at room temperature in 1-meter cell and ind. mm. pressure.

difluoroethane, are given in Figs. 2a and 2b, respectively. The absorption spectra of perfluoropropene and its chlorine adduct are given in Figs. 3a and 3b, respectively.

The perfluorocyclobutene was prepared[4] by dimerization of trifluorochloroethylene followed by subsequent removal of two chlorine atoms by alcoholic zinc.[5] The olefin was purified by distillation in a modified Podbielniak column packed with glass helices using a reflux ratio of about 15 to 1. The forecut was discarded and the center cut, having a boiling point constant to 0.1°, was collected and stored in a steel cylinder for subsequent use. The olefin was also sent through the scrubbing train before entering the calorimeter. The infrared absorption spectrum is shown in Fig. 4a. The absorption spectrum and freezing point of the chlorine adduct depend on how the material is prepared.[6] The absorption spectrum of the compound produced by catalytic chlorination at 90° is shown in Fig. 4b and is probably a mixture of *cis–trans* isomers.

(4) We wish to thank Dr. M. L. Sharrah of this Laboratory for the preparation of this compound.

(5) A. L. Henne and W. J. Zimmerschied, THIS JOURNAL, **69**, 281 (1947).

(6) Unpublished work of this Laboratory.

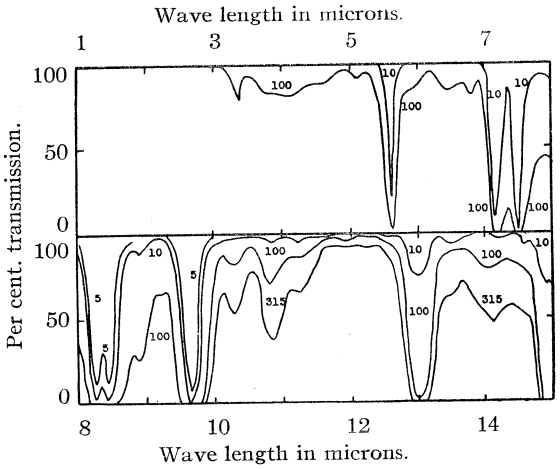



Fig. 3A.—Infrared absorption spectrogram of $CF_3$—$CF{=}CF_2$ gas at room temperature in 10-cm. cell and ind. mm. pressure.

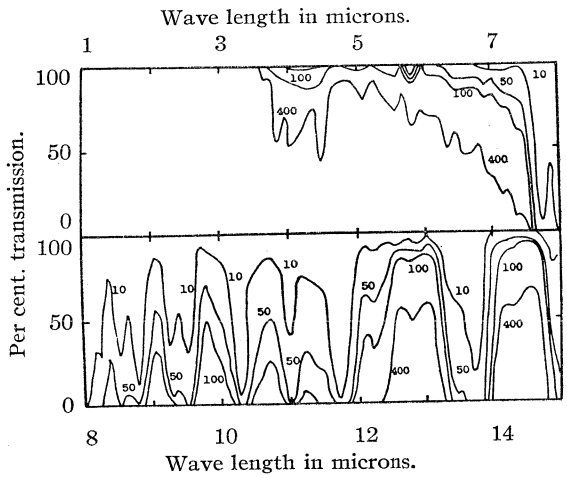



Fig. 3B.—Infrared absorption spectrogram of $CF_3$—$CFCl$—$CF_2Cl$ gas in 10-cm. cell and ind. mm. pressure.

**Experimental Results.**—The procedure used in making a run was similar to that described in Paper I[2] for the chlorination of tetrafluoroethylene. The chlorine was mixed in the catalyst chamber with an excess of olefin. The product gases were tested for unreacted chlorine and the presence of hydrogen chloride. They were found to be absent. In the case of trifluorochloroethylene some difficulty was experienced in obtaining products free of hydrogen chloride and with perfluorocyclobutene a high olefin to chlorine ratio was necessary to ensure complete reaction.

New reagents were used in the scrubbing train whenever the olefin was changed; a new catalyst, however, was not always used. The products of a previous run were thoroughly removed by displacement with dry nitrogen until no organic fluorine compounds could be detected in the effluent. The catalyst chamber was then evacuated for several hours and the system then filled with nitrogen.

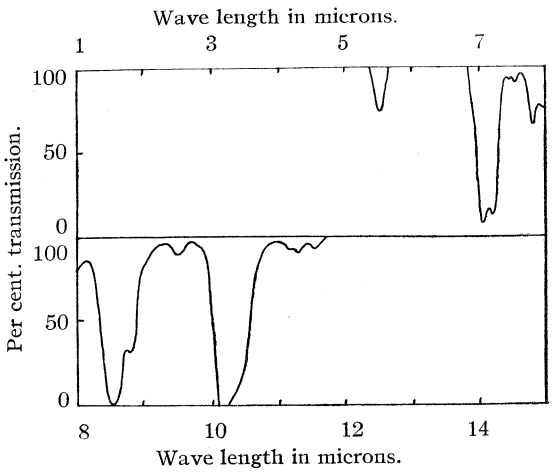



Fig. 4A.—Infrared absorption spectrogram of $CF_2{=}CF{-}CF{=}CF_2$ gas at 10 mm. pressure, room temperature and in 10-cm. cell.

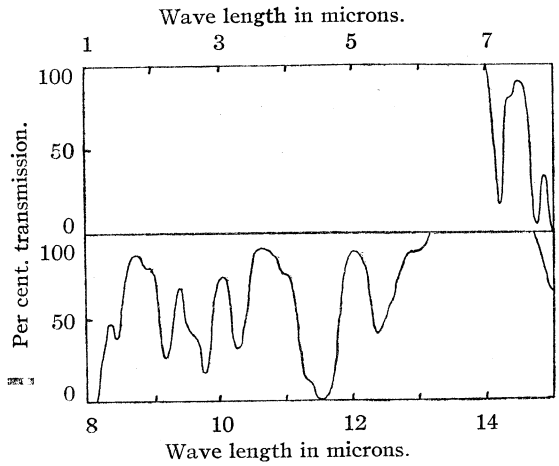



Fig. 4B.—Infrared absorption spectrogram of $CF_2{=}CFCl{-}CFCl{-}CF_2$ gas at 11 mm. pressure, in 10-cm. cell at room temperature, thermal chlorination.

After the catalyst had reached a steady state, the products were collected for thirty minutes or more in a Dry Ice-trap and reserved for infrared analysis. Two separate series of infrared spectra were obtained from each of the runs. The first was obtained by drawing off at $-80°$ a vapor sample into the absorption cell. This sample was run at several pressures necessary to obtain absorption peaks. This foreshot was rich in olefin and should have contained the low boiling impurities, if present. The second series of spectra were run after distilling off most of the olefin and then taking a sample. This tail fraction consisted mainly of the chlorine adduct and should have any high boiling impurities, if present. The analysis was again carried out at several pressures. Slight amounts of impurities would be detected at the higher pressure runs and the low pressure anal-

ysis served to identify the olefin and chlorine adduct. A comparison of the spectra so obtained with those shown by the purified olefin and chlorine adduct showed the presence of no new bands. Since some of the bands given by fluorocarbons are very intense, we believe that any undesirable side reactions, if they took place at all, were less than 0.2%.

The results obtained on chlorinating the four olefins at 90° are summarized in Table I. All of the experiments are reported except in the case of trifluorochloroethylene. Many experiments using this compound served merely in developing the technique of handling the calorimeter, purification method for the olefin and the method of analysis for the chlorine sample. In this case only the last three runs are included. It is believed that the average values for the vapor phase heats of chlorination are reliable to about 1%.

TABLE I

VAPOR PHASE HEATS OF CHLORINATION AT 90°

| Run | Olefin flow, moles/min. × $10^4$ | $Cl_2$ flow, moles/min. × $10^4$ | Energy input, cal./min. | $-\Delta H_{363}$ °K. cal./mole |
|---|---|---|---|---|
| | | Trifluorochloroethylene | | |
| 43 | 8.6 | 5.8616 | 28.759 | 49,063 |
| 44 | 8.9 | 6.3200 | 30.993 | 49,040 |
| 45 | 8.9 | 6.4346 | 31.106 | 48,342 |
| | | | Average 48,815 ± 475 cal./mole | |
| | | 1,1-Dichloro-2,2-difluoroethylene | | |
| 39 | 6.2 | 5.2633 | 21.628 | 41,092 |
| 40 | 6.2 | 5.4325 | 22.725 | 41,832 |
| 41 | 6.2 | 5.9512 | 24.114 | 40,520 |
| 42 | 6.5 | 6.1930 | 25.306 | 40,862 |
| | | | Average 41,076 ± 556 cal./mole | |
| | | Perfluoropropene | | |
| 46 | 6.7 | 4.8014 | 22.635 | 47,142 |
| 47 | 6.4 | 5.0244 | 23.636 | 47,042 |
| 48 | 8.0 | 5.9983 | 23.624 | 47,264 |
| | | | Average 47,149 ± 115 cal./mole | |
| | | Perfluorocyclobutene | | |
| 50 | 6.8 | 2.2709 | 8.6209 | 37,962 |
| 51 | 9.6 | 2.9701 | 11.134 | 37,487 |
| 52 | 5.7 | 2.6600 | 10.020 | 37,669 |
| 53 | 5.7 | 3.4052 | 12.390 | 36,386 |
| | | | Average 37,376 ± 990 cal./mole | |

## Discussion of Results

The vapor phase heats of chlorination obtained to date are summarized in Table II. Also included in the table is the heat of chlorination of ethylene as determined by Kistiakowsky and coworkers.[7] It is apparent that for this series of reactions there are strong deviations from the additivity rule. The heat of chlorination of tetrafluoroethylene is 20 kcal. greater than that of perfluorocyclobutene. When one fluorine in tetrafluoroethylene is replaced by chlorine, the reaction heat drops 8.5 kcal. When two are replaced on the same carbon, the heat drops by 16.2 kcal. or just twice. If the fluorine in tetrafluoroethylene is replaced by a $CF_3$–group, the heat drops by 10.1 kcal. and the $CF_3$– group has a greater effect than a chlorine atom. In this case, one of the added chlorine atoms is on a carbon containing a $CF_3$– group and a fluorine atom and is, therefore, "secondary." When chlorine adds to perfluorocyclobutene, both the chlorine atoms go into secondary positions. The lowering of the heat is 19.9 kcal. or just twice that shown by perfluoropropene. Systematic generalizations concerning the deviations from the additivity rule will, of course, have to wait upon further experimentation.

TABLE II

VAPOR PHASE HEATS OF CHLORINATION

| Compound | $-\Delta H_{363}$, cal./mole |
|---|---|
| $CF_2{=}CF_2$ | 57,323 |
| $CF_2{=}CFCl$ | 48,815 |
| $CF_2{=}CCl_2$ | 41,076 |
| $CF_2{=}CF{-}CF_3$ | 47,149 |
| $\begin{matrix} CF_2{-}CF \\ \vert \quad \Vert \\ CF_2{-}CF \end{matrix}$ | 37,376 |
| $CH_2{=}CH_2$[a] | 43,600 |

[a] Reference 7.

The calorimetric studies of Swarts[8] show that rather large deviations from the additivity rule are to be expected. For the series ethyl alcohol, monofluoroethanol and difluoroethanol, his data show that 9 kcal. more heat is liberated when a second hydrogen is replaced by fluorine than obtains for the first one. The difference in stability of the –CHF– and $-CF_2-$ groups is accounted for by thermochemical data. The same is true for the reactions studied here.

**Acknowledgment.**—This work was made possible by a grant from the Research Corporation of New York.

## Summary

The vapor phase heats of chlorination of trifluorochloroethylene, 1,1-dichloro-2,2-difluoroethylene, perfluoropropene and perfluorocyclobutene have been measured at 90°. The heats of these reactions deviate strongly from the additivity rule.

BOULDER, COLORADO RECEIVED OCTOBER 25, 1948

(7) J. D. Conn., G. B. Kistiakowsky and E. Smith, THIS JOURNAL, **60**, 2764 (1938).

(8) E. Swarts, *J. chim. phys.*, **17**, 3 (1919).

[CONTRIBUTION FROM ARGONNE NATIONAL LABORATORY, CHICAGO, ILLINOIS]

# The Volatilization of Beryllium Oxide in the Presence of Water

BY CLYDE A. HUTCHISON, JR.,[1a] AND JOHN G. MALM

## Introduction

It has been noted by many observers[1b] in connection with the use of beryllium oxide as a refractory that: (a) under certain conditions it is quite volatile at temperatures as low as 1800° as evidenced by weight losses; (b) that firing of beryllium oxide produces relatively rapid vapor phase transfer at temperatures as low as 1500° as shown by changes in individual crystals; (c) that beryllium oxide condenses in the cooler portion of furnaces with maximum temperatures not in excess of 1800°. Similar phenomena were noted in this Laboratory[2] under conditions involving the presence of water in the vapor phase. The data of Erway and Seifert,[3] however, showed equilibrium vapor pressures of beryllium oxide too low to account for the observed rates of volatilization ($3.2 \times 10^{-8}$ mm. at 1500° and $1.5 \times 10^{-4}$ mm. at 1800°). Their vapor pressure data are also inconsistent with the phenomena mentioned in (a), (b) and (c). We have performed experiments showing that the volatilization is due to the presence of water in the gas in contact with the beryllium oxide. A reaction with the water results in the formation of a volatile compound which condenses at lower temperatures with decomposition to beryllium oxide. Previous studies on the BeO–$H_2O$ system in a lower temperature range have been made by HaldunTerem[4] and Hackspill and Kieffer.[5]

## Experimental Description

Pure beryllium oxide half cylinders weighing ~2 g. and ~19 mm. in diameter and ~8 mm. in altitude, of density 2.38 g. cc.$^{-1}$ were prepared by bisecting fired pellets made from a pressed dry paste by adding 0.5 cc. of 6 *M* nitric acid to 5 g. of 200-mesh Brush high fired beryllium oxide powder. This beryllium oxide powder was of high purity. Spectrographic analyses on the samples taken gave these results in p.p.m.

| Fe | Mg | Mn | Si |
|---|---|---|---|
| 50 | 50 | <2 | <500 |

More extensive spectrographic analyses on a similar sample of beryllium powder gave the results shown, in p.p.m.

| Ag | Ba | Ca | Cd | Co | Cr | Cu |
|---|---|---|---|---|---|---|
| <10 | <100 | 100 | 0.5 | <10 | <10 | 50 |
| Fe | Li | Mg | Mn | Na | Ni | |
| 400 | <20 | 100 | 5 | 300 | <100 | |
| Pb | Si | Sn | Ti | V | Sb | |
| 10 | 100 | <10 | 100 | <500 | <200 | |

The pellets were fired at 1650° for one hour. When such samples were placed in a platinum boat in a mullite tube and water at ~1 atm. passed through the tube, the per cent. weight losses listed in Table I were observed in the temperature range 1483–1528°.

TABLE I

| Time, hours | 4.13 | 6.80 | 10.80 | 15.05 |
|---|---|---|---|---|
| Weight loss, % | 1.7 | 5.6 | 10.3 | 13.3 |

Condensation of beryllium oxide crystals in the form of a white cotton-like mass in the cooler portion of the tube and on the downstream side of the sample was observed. This material was shown to be nearly pure beryllium oxide by X-ray examination by W. H. Zachariasen.

Similar experiments were then performed with nitrogen–hydrogen mixtures passing over the sample at ~1 atm. and in stagnant air with no measurable volatilization of the beryllium oxide.

In a series of similar experiments[6] with water at 1 atm. the effect of temperature (shown in Table II) was observed when the water was passed over the samples at a rate of 0.11 mole min.$^{-1}$ in a tube of 3.6 cm. inside diameter.

TABLE II

| Temperature, °C. | 1000 | 1250 | 1400 | 1500 | 1550 |
|---|---|---|---|---|---|
| BeO lost in 2.5 hr., % | 0.01 | 0.19 | 0.66 | 1.58 | 2.24 |

Similar experiments performed with samples of magnesia and beryl resulted in no measurable volatilization.

## Conclusions

1. The presence of water vapor in contact with beryllium oxide results in its relatively rapid volatilization at temperatures at which the vapor pressure of beryllium oxide is too low to account for the observed rates.

2. Reaction of water with beryllium oxide results in the formation of a volatile compound at temperatures of 1250° or greater. This volatile substance condenses with decomposition to beryllium oxide.

The reported observations (a, b and c) may be

(1a) Present address: Institute for Nuclear Studies, University of Chicago, Chicago, Illinois.

(1b) For a review of such observations reference may be made to F. H. Norton, "Pure Beryllium Oxide as a Refractory," United States Atomic Energy Commission, MDDC-126, 4/30/46.

(2) J. G. Malm and J. E. Willard, unpublished results, approximately January, 1946.

(3) N. D. Erway and R. L. Seifert, "Vapor Pressure of Beryllium Oxide," United States Atomic Energy Commission, MDDC-1030, September, 1946.

(4) HaldunTerem, *Rev. Faculté sci. univ. Istanbul*, **8A**, 99 (1943).

(5) Hackspill and Kieffer, *Ann. chim.*, **14**, 227 (1930).

(6) These measurements were carried out by M. G. Berkman.

accounted for by assuming the presence of moisture in the gases in contact with the beryllium oxide (flame gases, etc.).

3. The volatilization rate increases with increasing temperature.

4. The volatilization does not occur in the cases of beryl or magnesia.

CHICAGO, ILLINOIS RECEIVED NOVEMBER 1, 1948

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[CONTRIBUTION FROM THE GENERAL ELECTRIC CO. RESEARCH LABORATORY]

# The Distillation of Mixtures Containing Diborane and the Identification of Two Azeotropes

BY LEWIS V. MCCARTY[1]

Depending upon the method of manufacture diborane may be contaminated with hydrogen halides, boron halides and ethane. Thus in Schlesinger's[2] and Stock's[3] methods of preparation hydrogen chloride and boron trichloride, and hydrogen bromide and boron tribromide are possible contaminants. In Schlesinger's later preparation[4] ethane might also contaminate the diborane. In other reactions described by Hurd[5] boron trifluoride as well as boron trichloride and hydrogen chloride may be impurities. A knowledge of the various possible mixtures of diborane with these materials becomes important both for the purification of diborane and the analytical distillation of the products of the reactions.

## Experimental

**Apparatus.**—The apparatus used to perform the distillations was the Automatic Recording Low Temperature Fractional Distillation Apparatus, Hyd Robot Model, Serial No. H 576, manufactured by the Podbielniak Centrifugal Super Contactor Company. The entering stopcock of the "Super Cool" column was attached to a vacuum line that was equipped with bulbs of known volume. This part of the system was not thermostated, and all measurements of the gases entered into the column were made at room temperature. All values reported in the tables, however, have been reduced to 0° and 760 mm. Samples were mixed in the column by entering each gas separately. No van der Waals corrections were applied to any of the gases. The time under total reflux was ordinarily about thirty minutes to one hour long.

**Chemical Analysis.**—In Expt. 1 of Table I a chemical analysis was made for hydrogen chloride. This was accomplished by freezing a known volume of the gases into a sample bulb and then expanding through two bubblers of distilled water. A slow stream of dry nitrogen was used to prevent water from sucking back into the sampling bulb. The water was analyzed for hydrogen chloride by titration with a sodium hydroxide solution to a methyl orange end-point.

**Materials.**—The hydrogen chloride and diborane used in Expt. I, Table I, were distilled and only the middle cuts were saved. All boron trichloride was distilled prior to use. The diborane, ethane and boron trifluoride of Tables III and IV were distilled before use. All other hydrogen chloride and diborane as well as the hydrogen bromide came from tanks in which the impurities were known to be mainly gases not condensable in liquid nitrogen. Accordingly, the purification procedure for these samples was to freeze some gas into a bulb in liquid nitrogen, and then pump on the bulb.

## Results

**The System Hydrogen Chloride–Diborane.**—A few preliminary runs (not reported here) with rather impure materials served to indicate that an azeotrope was formed having the approximate composition 26–30% hydrogen chloride and 70–74% diborane. This material boiled at about −94° at 760 mm., 1.5° lower than the value for diborane, −92.5°.

In order to get an accurate value for the composition of the azeotrope at 760 mm., samples of distilled hydrogen chloride and diborane were used in Expt. 1 of Table I. It will be noticed that in this experiment the difference between the total volume of gas used and that found is only 2 cc. in 4,934. This is fortuitous as will be found by an inspection of other data in this and subsequent tables. Sometimes less and sometimes more gas was found than was originally used. This is attributed to solution and possibly reaction in some cases with the stopcock grease of the Podbielniak apparatus. Apiezon L was the lubricant used. In making calculations on azeotrope composition, it is convenient to have the total volumes found agree with the total volumes used. If there is a discrepancy, it is assumed to be due to the causes mentioned, and the volumes found are pro-rated with an appropriate factor to bring them into agreement with the volumes used. It is then a simple matter to make the azeotrope composition calculations. The value for the azeotrope at 755 mm. was found to be 29.9% hydrogen chloride on a molar basis. When 1984 cc. of the azeotrope at S.T.P. was analyzed for hydrogen chloride in water solution,[6] 0.957 g. of hydrogen chloride was found. This corresponds to 29.6 mole per cent. in the azeotrope.

Experiments 2, 3 and 4 of Table I are determinations of the azeotrope composition at a lower pressure (205–208 mm.). The average of the three determinations of the composition is 26.2% hydrogen chloride and 73.8% diborane. The boiling point of the azeotrope at 207 mm. is about −114.5°, whereas for pure diborane at 207 mm. the boiling point is −113°.

(1) This work was done on Army Ordnance Contract TU1-2000.

(2) Schlesinger and Burg, THIS JOURNAL, **53**, 4321 (1931).

(3) Stock and Sütterlein, *Ber.*, **67B**, 407 (1934).

(4) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947).

(5) Hurd, *ibid.*, **71**, 20 (1949).

(6) Analysis courtesy of L. B. Bronk.

TABLE I

THE SYSTEM HCl–$B_2H_6$

| Expt. | HCl used, cc. | $B_2H_6$ used, cc. | Azeotrope found, cc. | B. p. of azeotrope, °C. | HCl found, cc. | B. p. of HCl, °C. | Dist. pres., mm. | % in azeotrope HCl | % in azeotrope $B_2H_6$ |
|---|---|---|---|---|---|---|---|---|---|
| 1[b] | 2470 | 2464 | 3513 | − 94 | 1419 | − 85 | 755 | 29.9[a] | 70.1 |
| 2[c] | 939 | 1142 | 1523 | −115.5 | 512 | −106 | 205 | 26.7 | 73.3 |
| 3[b] | 1106 | 1242 | 1646 | −114.5 | 674 | −105.5 | 207 | 25.5 | 74.5 |
| 4[b] | 1004 | 1244 | 1666 | −114.5 | 554 | −105.5 | 208 | 26.3 | 73.7 |

[a] 1984 cc. of azeotrope analyzed for hydrochloric acid by solution in water and titration, 29.6% of hydrochloric acid on a molar basis. [b] HCl entered into column first. [c] $B_2H_6$ entered into column first.

**The System Boron Trichloride–Diborane.**—Data for the single experiments on this system are: cc. $B_2H_6$ used, 1262; cc. $B_2H_6$ found, 1280 b. p. −93.5°, 750 mm.; cc. $BCl_3$ used, 1173; cc. $BCl_3$ found, 1183, b. p. +11.5°, 750 mm. The data on the gas found as compared to that put into the distillation column checks sufficiently closely so that an azeotrope probably does not exist.

**The System Hydrogen Chloride–Boron Chloride.**—Although this system does not include diborane, it was considered important because of the ternary system which follows: cc. HCl used, 1274; cc. HCl found, 1271, b. p. −85.5° 754 mm.; cc. $BCl_3$ used, 934; cc. $BCl_3$ found, 945, b. p. +11.5°, 754 mm. Somewhat more $BCl_3$ was found than used to make up the sample, but the amount is within the experimental error.

**The System Hydrogen Chloride–Diborane–Boron Trichloride.**—The data for this ternary system are: cc. $BCl_3$ used, 1208; cc. $BCl_3$ found, 1228, b.p. +12.5°, 752 mm.; cc. $B_2H_6$ used, 1249; cc.* azeotrope found, 1782, b.p. −95.5°, 752 mm.; cc. HCl used, 1246; cc. HCl found, 713, b.p. −85.5°, 752 mm. (*Composition from these data, 29.9% HCl, 70.1% $B_2H_6$.) There was slightly more boron trichloride found than used, but again this is most likely to be experimental error. It does not apparently form a ternary azeotrope with the other components, nor does it influence the composition of the hydrogen chloride–diborane azeotrope.

TABLE II

THE SYSTEM $B_2H_6$–HBr

| Expt. | HBr used, cc. | $B_2H_6$ used, cc. | HBr found, cc. | B. p. of HBr, °C. | $B_2H_6$ found, cc. | B. p. of $B_2H_6$, °C. | Dist press. mm. |
|---|---|---|---|---|---|---|---|
| 1 | 1194 | 932 | 1188 | −84 | 941 | −108 | 298 |
| 2 | 1058 | 1040 | 1062 | −83.5 | 1012 | −108 | 309 |
| 3 | 1199 | 528 | 1219 | −67.5 | 496 | − 93.5 | 753 |
| 4 | 2315 | 2060 | 2280 | −67.5 | 2013 | − 94 | 756 |

TABLE III

THE SYSTEM $B_2H_6$–$C_2H_6$

| Expt. | $B_2H_6$ used, cc. | $B_2H_6$ found, cc. | $C_2H_6$ use cc. | $C_2H_6$ found, cc. | B. p. of $B_2H_6$, °C. | B. p. of $C_2H_6$, °C. | Dist. press., mm. |
|---|---|---|---|---|---|---|---|
| 1[a] | 1121 | 1179 | 975 | 902 | − 92 | − 88 | 753 |
| 2[b] | 772 | 776 | 130 | 135 | − 92 | − 88 | 753 |
| 3[a] | 1287 | 1270 | 133 | 147 | − 92 | − 88 | 753 |
| 4[a] | 1260 | 1258 | 131 | 121 | −121 | −118 | 102 |
| 5[b] | 618 | 590 | 127 | 116 | −120.5 | −117.5 | 99 |
| 6[b] | 740 | 744 | 132 | 114 | −121.5 | 118.5 | 100 |

[a] $C_2H_6$ entered into column first. [b] $B_2H_6$ entered into column first.

**The System Hydrogen Bromide–Diborane.**—The conclusion drawn from the data presented in Table II is that no azeotrope exists at the pressures studied. The system is somewhat difficult to study because of the relatively high melting point of the hydrogen bromide, −86°.

**The System Diborane–Ethane.**—Table III presents the data for the distillation of known samples of diborane–ethane. Experiment 1 does not show very good agreement between the amount of materials used and found in the analysis. This was blamed on insufficient reflux time rather than on the formation of an azeotrope. Accordingly, two hours of reflux time was allowed before taking off any gas from the top of the distillation column in all other experiments. There does not seem to be any general trend dependent upon which liquid, ethane or diborane, wets the packing of the column first. There does not seem to be any trend dependent upon the size of the sample or the ratio of diborane to ethane. The conclusion drawn is that there is no azeotrope in the system.

**The System Diborane–Boron Trifluoride.**—For the experiments of Table IV a total reflux time of two hours was allowed before any gas was taken off the top of the distillation column. As can be seen from the data the composition of the azeotrope formed is reasonably constant regardless of which material is in excess or entered into the column first. The average of the three

TABLE IV

THE SYSTEM $B_2H_6$–$BF_3$

| Expt. | $B_2H_6$ used, cc. | $BF_3$ used, cc. | Azeotrope found, cc. | $B_2H_6$ found, cc. | $BF_3$ found, cc. | B. p. of azeotrope, °C. | B. p., °C. of $B_2H_6$ | B. p., °C. of $BF_3$ | Dist. press., mm. | % in azeotrope $B_2H_6$ | % in azeotrope $BF_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 1295 | 1279 | 2193 | 357 | .. | −105.5 | −92 | ... | 755 | 42.2 | 57.8 |
| 2[b] | 1261 | 1092 | 1841 | 500 | .. | −106 | −92.5 | ... | 745 | 41.0 | 59.0 |
| 3[a] | 1036 | 2573 | 2476 | ... | 1108 | −106 | .... | −100 | 760 | 41.6 | 58.4 |

[a] $B_2H_6$ entered into column first. [b] $BF_3$ entered into column first.

values determined is 41.6% diborane and 58.4% boron trifluoride, and the boiling point at atmospheric pressure is about −106°.


## Summary

The systems $HCl-B_2H_6$, $B_2H_6-BCl_3$, $HCl-BCl_3$, $HCl-B_2H_6-BCl_3$, $HBr-B_2H_6$, $B_2H_6-C_2H_6-C_2H_6$ and $B_2H_6-BF_3$ have been studied.

An azeotrope containing 70.1% $B_2H_6$ and 29.9% HCl and boiling at −94° at atmospheric pressure has been identified. The presence of $BCl_3$ does not affect the $HCl-B_2H_6$ azeotrope.

An azeotrope containing 41.6% $B_2H_6$ and 58.4% $BF_3$ and boiling at −106° at atmospheric pressure has been identified.

None of the other systems studied show azeotrope formation.


SCHENECTADY, N. Y. RECEIVED NOVEMBER 18, 1948

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA 18, PENNSYLVANIA]

# Ultraviolet Absorption Spectra of Nicotine, Nornicotine and Some of Their Derivatives

BY MARGARET L. SWAIN, ABNER EISNER, C. F. WOODWARD AND B. A. BRICE

Nicotine and its analog, nornicotine, and the myosmines and nicotyrines derived from them as dehydrogenation products, represent interesting examples of series of compounds possessing progressively increasing conjugated unsaturation of the cyclic type. Characteristic and similar ultraviolet absorption spectra for the two parent compounds and for the pairs of analogs obtained at each successive dehydrogenation step may therefore be expected. Such spectra determined on preparations of high purity should be useful as a means of further characterizing the compounds, provide a test of the correctness of assigned structures, and furnish a possible method of assay and analysis. Although the increasing practical importance of nicotine has prompted an intensive study of the chemistry of the alkaloid and its derivatives during recent years, no spectroscopic studies using modern photoelectric instruments have been reported. The only available absorption curves are those for nicotine published by Purvis[2] and Dobbie and Fox[3] and others during the early years of the century. A systematic determination of the ultraviolet spectra of pure preparations of nicotine, nornicotine, their dehydrogenated derivatives, and a few related compounds has therefore been carried out.

The wave length positions of the clearly defined maxima and minima occurring in the spectra of the compounds in a number of solvents and the specific extinction coefficients at these maxima and minima are listed in Table I. Molecular extinction coefficients at the maxima are also listed to permit comparison on a molar basis. Absorption curves for all the compounds in 95% ethanol solution and for representative compounds in acidified 95% ethanol are shown in Figs. 1 to 9.

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(2) Purvis, *J. Chem. Soc.*, **97**, 1035 (1910).

(3) Dobbie and Fox, *ibid.*, **103**, 1193 (1913).

As might be expected, the absorption curves of nicotine (A, Fig. 1) and nornicotine (A, Fig. 5) are almost identical in shape and in position of maxima and minima. The observed difference in specific extinction coefficients is apparently entirely due to the diluent effect of the methyl group occurring on the pyrrolidine ring of nicotine; on a molecular basis the extinction coefficients are nearly identical. The spectra of nicotine and nornicotine show the close relationship to the ultraviolet spectrum of pyridine (A, Fig. 2) that was to be expected. Differences between the curves of the alkaloids and that of pyridine, namely, a bathochromic shift of about 5 mμ in the position of the chief maximum, an elevation in molecular extinction coefficient, and a loss in fine structure, are of the kind to be anticipated as a result of substitution of the pyrrolidine ring on the pyridine nucleus. Addition of acid produces similar exaltations of the absorption maxima, depressions of the minima, and loss of fine structure in nicotine (B, Fig. 1) and nornicotine (A, Fig. 7) as it does in pyridine (B, Fig. 2).

Introduction of an additional double bond in conjugation with the pyridine ring as in myosmine (B, Fig. 5) results in a further shift of the pyridine absorption to longer wave lengths, accompanied by the appearance of a new strong, structureless band at 234 mμ. Presumably this latter band represents the bathochromic shifting through conjugation of the pyridine absorption normally lying below 200 mμ. An ever greater shift toward the red is exhibited in the spectrum of metanicotine (A, Fig. 4), in which the pyrrolidine ring has been opened and the introduced unsaturation conjugated with the pyridine nucleus occurs in an open chain. As is generally the case, the conjugation of ring and open chain unsaturation possessed by metanicotine also produces a substantially higher intensity of absorption than does the equivalent ring to ring conjugated unsaturation of myosmine. The spectrum of the comparison compound, 3-vinylpyridine (A, Fig. 6),

TABLE I

LOCATION AND INTENSITY OF ABSORPTION MAXIMA AND MINIMA OF NICOTINE AND RELATED COMPOUNDS

| Compound | Solvent | 1st maximum λ, mμ | 1st maximum $k^a$ | 1st maximum $\epsilon^b$ | 2nd maximum λ, mμ | 2nd maximum $k$ | 2nd maximum $\epsilon$ | 3rd maximum λ, mμ | 3rd maximum $k$ | 3rd maximum $\epsilon$ | 1st minimum λ, mμ | 1st minimum $k$ | 2nd minimum λ, mμ | 2nd minimum $k$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nicotine | 95% Ethanol | 262 | 17.9 | 2900 | | | | | | | 232 | 6.48 | | |
| | Acidified EtOH[c] | 260 | 29.7 | 4820 | | | | | | | 231 | 5.72 | | |
| | Neohexane | 261 | 14.0 | 2270 | | | | | | | 236 | 8.15 | | |
| | Water | 260 | 18.6 | 3020 | | | | | | | 230 | 5.67 | | |
| | Acidified $H_2O$[d] | 259 | 34.1 | 5530 | | | | | | | 226 | 1.04 | | |
| Nornicotine | 95% Ethanol | 262 | 19.7 | 2920 | | | | | | | 233 | 7.13 | | |
| | Acidified EtOH | 260 | 33.7 | 4990 | | | | | | | 231 | 6.19 | | |
| "N-Methylmyosmine" (Dihydronicotyrine) | 95% Ethanol | 261 | 18.2 | 2920 | | | | | | | 237 | 10.2 | | |
| | Acidified EtOH | 260 | 27.9 | 4470 | | | | | | | 234 | 7.49 | | |
| | Neohexane | 261 | 14.5 | 2320 | | | | | | | 241 | 12.7 | | |
| | Water | 260 | 19.1 | 3060 | | | | | | | 234 | 7.60 | | |
| Myosmine | 95% Ethanol | 266 | 26.6 | 3890 | 234 | 77.7 | 11360 | | | | 261 | 26.2 | 214 | 42.2 |
| | Acidified EtOH | 262 | 36.1 | 5280 | 226 | 42.7 | 6240 | | | | 244 | 32.6 | | |
| | Neohexane | 267 | 23.2 | 3390 | 234 | 83.6 | 12220 | | | | 259 | 21.8 | 212 | 34.4 |
| | Water | 264 | 29.6 | 4330 | 234 | 69.2 | 10120 | | | | 261 | 29.6 | 214 | 38.1 |
| Nicotyrine | 95% Ethanol | 288 | 62.1 | 9820 | | | | | | | 251 | 26.6 | | |
| | Acidified EtOH | 310 | 69.1 | 10930 | 244 | 54.5 | 8620 | | | | 264 | 12.9 | 226 | 18.1 |
| Nornicotyrine | 95% Ethanol | 294 | 109.4 | 15770 | 229 | 42.4 | 6110 | | | | 251 | 16.4 | 221 | 38.9 |
| | Acidified EtOH | 316 | 112.8 | 16260 | 241 | 64.8 | 9340 | | | | 259 | 14.7 | 221 | 19.1 |
| | Neohexane | 286 | 99.3 | 14320 | 226 | 41.2 | 5940 | | | | 242 | 17.7 | 219 | 38.7 |
| Metanicotine | 95% Ethanol | 282 | 25.0 | 4060 | 246 | 99.8 | 16190 | | | | 275 | 24.0 | 221 | 38.4 |
| | Acidified EtOH | 292 | 27.1 | 4400 | 253 | 74.6 | 12100 | 223 | 90.4 | 14670 | 277 | 21.1 | 237 | 47.8 |
| | Neohexane | 281 | 26.7 | 4330 | 245 | 103.8 | 16840 | | | | 278 | 26.5 | 217 | 31.9 |
| Benzoylmyosmine | 95% Ethanol | 271 | 41.6 | 10410 | 224 | 53.6 | 13420 | | | | 249 | 37.1 | 216 | 52.4 |
| | Acidified EtOH | 252 | 54.9 | 13740 | | | | | | | 236 | 43.9 | | |
| 3-Pyridyl-ω-benzamido ketone | 95% Ethanol | 228 | 73.5 | 19720 | | | | | | | 212 | 47.9 | | |
| | Acidified EtOH | 225 | 63.2 | 16960 | | | | | | | 212 | 45.4 | | |
| Pyridine | 95% Ethanol | 257[e] | 34.0 | 2690 | | | | | | | 216[e] | 5.3 | | |
| | Acidified EtOH | 256 | 67.7 | 5360 | | | | | | | 225 | 5.1 | | |
| 3-Vinylpyridine | 95% Ethanol | 278 | 26.2 | 2760 | 238 | 108.2 | 11380 | | | | 266 | 21.9 | 217 | 47.3 |
| | Acidified EtOH | 287 | 31.9 | 3350 | 246 | 75.2 | 7910 | 218 | 115.5 | 12140 | 267 | 19.8 | 233 | 56.1 |
| | Neohexane | 277 | 25.5 | 2680 | 237 | 110.3 | 11600 | | | | 265 | 22.9 | 214 | 39.7 |
| 3-Pyridyl methyl ketone | 95% Ethanol | 267 | 23.8 | 2880 | 228 | 70.0 | 8480 | | | | 250 | 16.9 | | |
| | Acidified EtOH | 264 | 32.3 | 3910 | 224 | 47.8 | 5790 | | | | 245 | 16.6 | | |
| | Neohexane | 267 | 20.4 | 2470 | 227 | 76.3 | 9240 | | | | 246 | 13.5 | | |

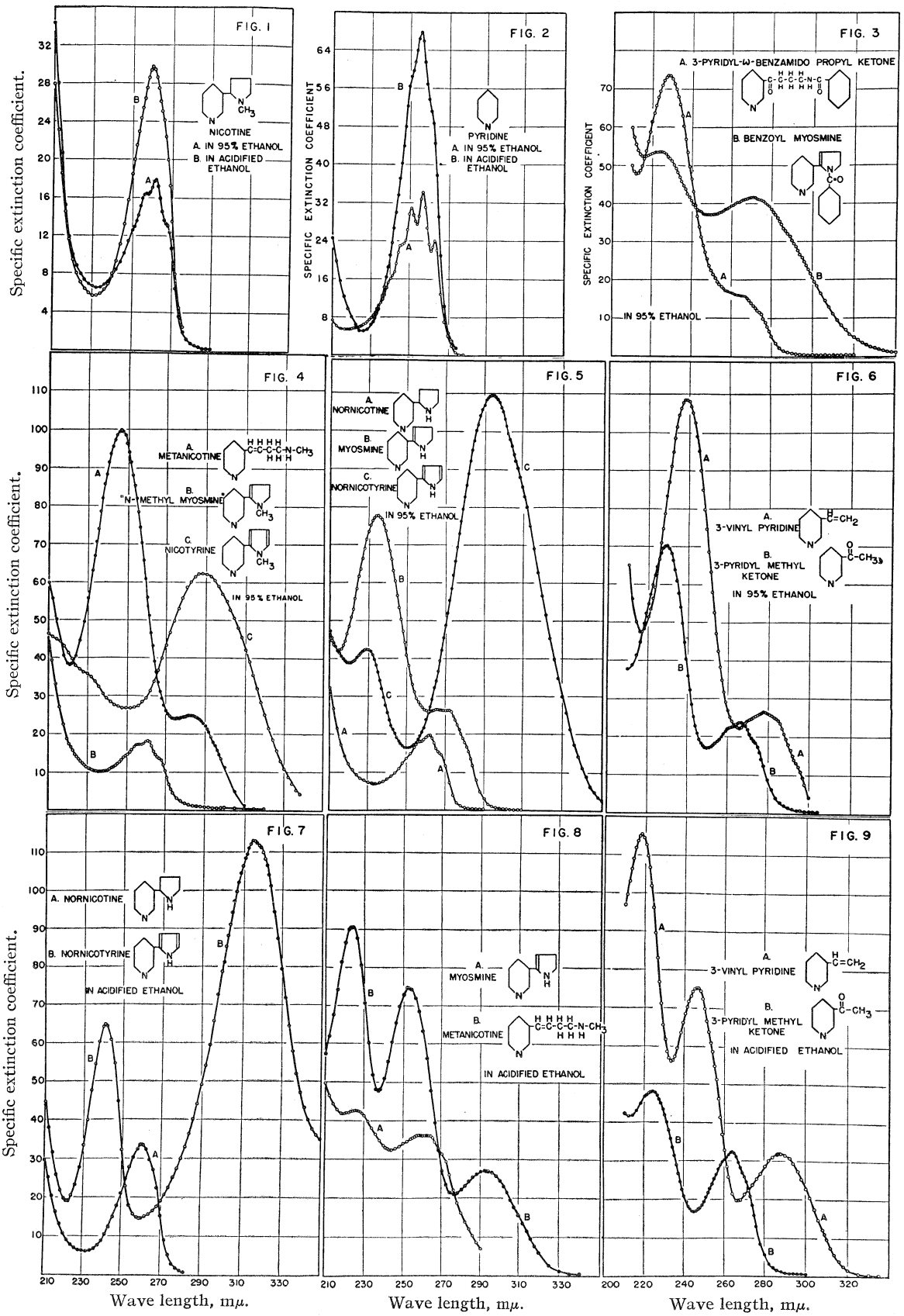
[a] Specific extinction coefficient, $k$, is the spectral density of a solution of thickness 1 cm. and concentration 1 g. per liter compared with 1 cm. of solvent. [b] Molecular extinction coefficient, $\epsilon$, is equal to $kM$, where $M$ is the molecular weight. [c] 95% ethanol containing 0.045 mole of hydrochloric acid per liter. [d] 0.045 molar hydrochloric acid. [e] Chief maximum and minimum, respectively.

which possesses the ring to open chain type of conjugation, therefore resembles that of metanicotine in location and intensity of absorption maxima more closely than it does that of myosmine.

The spectrum obtained on introduction of a >C=O group in conjugation with the pyridine nucleus, as exemplified by the comparison compound 3-pyridyl methyl ketone (B, Fig. 6), is similar to that obtained on introduction of >C=C< conjugation. No gross differences are found, therefore, between the spectrum of myosmine in neohexane and that in water, in which it exists at least in part in a hydrolyzed ketonic form. The changes produced in the spectra of compounds containing the pyridine nucleus conjugated with >C=C< and those containing the pyridine nucleus conjugated with >C=O on acidification are, however, markedly different. Thus the spectra of metanicotine (B, Fig. 8) and vinylpyridine (A, Fig. 9) on acidification undergo bathochromic shifts resulting in each case in a displacement of the two original bands by 7 to 10 mμ and the appearance of a new strong band at about 220 mμ. Acidification of pyridyl methyl ketone (B, Fig. 9) and myosmine (A, Fig. 8) on the contrary leads to hypsochromic shifting of the two original maxima, with an increase in intensity of the longer wave length band and a decrease in the intensity of the other.

A spectral curve similar to that of myosmine was expected from its methylated analog, "N-methylmyosmine," whose structure had been chemically established by Späth, Wibaut and Kesztler[4] as 1-methyl-2-(3-pyridyl)-2,3-pyrroline.

(4) Spath, Wibaut and Kesztler, *Ber.*, **71**, 100 (1938).


FIG. 1
NICOTINE
A. IN 95% ETHANOL
B. IN ACIDIFIED ETHANOL
FIG. 2
PYRIDINE
A. IN 95% ETHANOL
B. IN ACIDIFIED ETHANOL
FIG. 3
A. 3-PYRIDYL-W-BENZAMIDO PROPYL KETONE
B. BENZOYL MYOSMINE
IN 95% ETHANOL
FIG. 4
A. METANICOTINE
B. "N-1 METHYL MYOSMINE
C. NICOTYRINE
IN 95% ETHANOL
FIG. 5
A. NORNICOTINE
B. MYOSMINE
C. NORNICOTYRINE
IN 95% ETHANOL
FIG. 6
A. 3-VINYL PYRIDINE
B. 3-PYRIDYL METHYL KETONE
IN 95% ETHANOL
FIG. 7
A. NORNICOTINE
B. NORNICOTYRINE
IN ACIDIFIED ETHANOL
FIG. 8
A. MYOSMINE
B. METANICOTINE
IN ACIDIFIED ETHANOL
FIG. 9
A. 3-VINYL PYRIDINE
B. 3-PYRIDYL METHYL KETONE
IN ACIDIFIED ETHANOL
Specific extinction coefficient.
SPECIFIC EXTINCTION COEFFICIENT
Wave length, mμ.

"N-Methylmyosmine" (B, Fig. 4) as prepared by the accepted method of partially hydrogenating nicotyrine, however, had an absorption curve essentially identical with that of nicotine rather than with that of myosmine. Apparently in this compound no conjugation of the pyridine nucleus with a double bond in the dehydrogenated pyrrolidine ring exists. Some evidence for the existence of a greater degree of non-conjugated unsaturation than that occurring in nicotine is indicated by the heightened end absorption encountered in the neighborhood of 210 mμ. The observed results can be explained if it is assumed that in the preparation of "N-methylmyosmine" by the partial hydrogenation of nicotyrine, the hydrogen is added 1,4 rather than 1,2. The product of 1,4 addition would be a compound having a double bond in the 3,4 position of the methylpyrroline ring and possessing the observed absorption characteristics. The spectroscopic results suggest that further chemical studies should be made.

The absorption curves of nicotyrine (C, Fig. 4) and nornicotyrine (C, Fig. 5), both of which contain a pyrrole ring in conjugation with the pyridine nucleus, are similar in shape and in the wave length positions of maxima and minima. Conjugation of the pyridine nucleus with a doubly conjugated system results in further shifting of the absorption toward the red and complete loss of the fine structure associated with the pyridine ring. The large differences in the extinction coefficients at the maxima observed between nicotyrine and nornicotyrine are probably to be expected, since in these compounds the methyl substituent differentiating nicotine and nornicotine is intimately associated with the chromophore. Acidification of these compounds, for example (B, Fig. 7), leads to further bathochromic shifts in absorption, accompanied by an increase in intensity, particularly of the low wave length band.

In benzoylmyosmine the hydrogen of the secondary amine group of myosmine has been replaced by the benzoyl group, but the added aromatic unsaturation is not in conjugation with the myosmine chromophore. The observed spectrum (B, Fig. 3) is related to that of myosmine but is modified by the additive and interacting effects of the two absorbing groups. A similar effect is encountered in the spectrum of 3-pyridyl-ω-benzamido ketone (A, Fig. 3), which contains isolated pyridyl ketone and benzoyl chromophores.

The observed ultraviolet absorption spectra of nicotine, nornicotine and those of their derivatives which possess additional conjugated unsaturation are characteristic and intense enough to afford a means of identification and characterization of these compounds and to provide a rapid method for the assay of crude preparations. Detection and determination of the more highly unsaturated compounds in nicotine or nornicotine preparations are possible, although not extremely sensitive. Satisfactory analysis of partially purified fractions such as those obtained in the pyrolysis of nicotine should, however, be possible. Ultraviolet spectrophotometry cannot be used to distinguish between nicotine and nornicotine or between the various dehydrogenated derivatives possessing equivalent degrees of conjugated unsaturation.

The impossibility of distinguishing between nicotine and nornicotine is a drawback common to both ultraviolet spectrophotometry and the chemical precipitation method generally used for the determination of nicotine. Determination of nicotine by ultraviolet spectrophotometry in solutions or concentrates derived from natural products which contain both alkaloids but are essentially free of other interfering absorbers may therefore be expected to yield results in agreement with those obtained by the chemical method. Preliminary tests have shown that this expectation is realized and that generally good agreement exists between the percentages of nicotine found by the two methods. The results of a study now in progress to determine the applicability of the spectrophotometric method to the estimation of nicotine in a variety of sample types will be published shortly.

## Experimental

The spectra were obtained with a Beckman Model DU Spectrophotometer with slit widths corresponding to approximately 1.5 mμ in the 260 mμ region and to 2 mμ in the 230 mμ region for all solvents and for all compounds with the exception of pyridine. Narrowing of the slit was without measureable effect on the location or intensity of the absorption maxima and minima except in the case of pyridine. For determinations on this compound, the narrowest possible slit, corresponding to about 0.6 mμ at 256 mμ, was used. The undenatured 95% ethanol possessed sufficient transparency for use without further purification; the neohexane was purified to suitable transparency by percolation through silica gel. Ethanol was generally acidified by the addition of 3.75 ml. of concentrated hydrochloric acid per liter of solution; higher concentrations exerted no further effect on the spectra of any of the compounds with the exception of pyridine. For the determination of pyridine, the acid concentration used to provide an excess over that required to exert the maximum effect on the spectrum was about 0.2 *M*.

In general, commercial nicotine and some of the fractions derived from it on pyrolysis served as starting materials for the preparation of the pure compounds. Whenever possible, the bases were purified by recrystallizing the picric acid derivatives until further recrystallization did not raise the melting point. The recrystallized base picrates were decomposed by addition of 10% hydrochloric acid, the precipitated picric acid was filtered off, and any small residual amounts of picric acid were removed by extraction of the filtrate with ether. The filtrates were then made strongly alkaline with sodium hydroxide, and the free bases were recovered from them by successive extractions with ether. The ether extracts were dried over anhydrous sodium carbonate, the ether was evaporated off, and the free bases which were left at residues were distilled under reduced pressure in a nitrogen atmosphere. Departures from this scheme of purification were necessary for bases like nicotyrine, whose monopicrates are not readily decomposed by 10% hydrochloric acid. The procedures used in these cases are described in the notes on the preparation of the individual bases which follow.

**Nicotine.**—The commercially available material, rated as 99% alkaloid, was steam distilled through a fractionat-

ing column to separate it from nornicotine. The steam volatile product was purified by the general method described above. The recrystallized picrate had a melting point of 224–225°, and the boiling point of the free base recovered from it was 93.2° (2 mm.) and $n^{25}D$ 1.5278.

*dl*-**Nornicotine.**—A sample of myosmine obtained from the pyrolysis of nicotine[5] was hydrogenated to nornicotine, with palladous oxide as catalyst.[6] The *dl*-nornicotine was recovered from the mixture as picrate and purified by the general procedure. The recrystallized picrate had a melting point of 193° and yielded a free base boiling at 91.5° (0.4 mm.) and having $n^{25}D$ 1.5469.

**"N-Methylmyosmine" (Dihydronicotyrine).**—Nicotyrine (see below) was subjected to the zinc–hydrochloric acid reduction procedure of Wibaut and Hackman.[7] The resulting dihydronicotyrine was recovered as the dipicrate and purified in the usual manner. The recrystallized dipicrate had a melting point of 162–163° and yielded a free base boiling at 99° (2.3 mm.) and having $n^{25.5}D$ 1.5358.

**Myosmine.**—This base was prepared from a freshly distilled myosmine fraction obtained on pyrolysis of nicotine. The general scheme of purification was employed to secure the pure base. The recrystallized dipicrate had a melting point of 184–185° and the free base recovered from it boiled at 118° (3.2 mm.).

**Nicotyrine.**—A distilled fraction of nicotyrine obtained by the catalytic dehydrogenation of nicotine over nickel-impregnated bauxite served as a source of the crude base. Nicotyrine monopicrate is not readily decomposed by cold 10% hydrochloric acid. A new compound, nicotyrine tartrate dihydrate, which is more easily decomposable was used in the purification of the base. After recrystallizing from water and drying in a vacuum desiccator, a sample of nicotyrine tartrate[8] melted at 105–106° and had the analysis: C, 48.61; H, 5.88; N, 8.10; calcd. for $C_{10}H_{10}N_2 \cdot H_2C_4H_4O_6 \cdot 2H_2O$: C, 48.84; H, 5.81; N, 8.14.

Nicotyrine tartrate was prepared by treating nicotyrine with an equal weight of tartaric acid dissolved in the least amount of hot 95% ethanol. The precipitated product after five recrystallizations from 95% ethanol, had a melting point of 105–106°. The purified nicotyrine tartrate was dissolved in water and the solution made strongly alkaline with sodium hydroxide to liberate the base, which was then extracted with ether; b. p. 117° (1.2 mm.), $n^{24.5}D$ 1.6138.

**Nornicotyrine.**—The base was prepared from pure myosmine by catalytic dehydrogenation with palladium black.[9] Since nornicotyrine picrate is not readily decomposed by the usual method, an alternative procedure suggested by Burger[10] for obtaining the free base from its picrate was tried. In this modification, lithium hydroxide is used as the alkali, so that any remaining picric acid is supposedly present in the aqueous phase as the soluble lithium salt during extraction of the liberated base with ether. However, poor results were obtained on application of this procedure to the recovery of nornicotyrine from its picrate. Nornicotyrine was therefore purified by recrystallization of the base itself from a benzene–petroleum ether mixture. The purified base so obtained had a melting point of 99–101°.

**Metanicotine.**—Metanicotine was prepared by Löffler and Kober's[11] modification of Pinner's[12] original method with one change, namely, the unreacted nicotine was removed by fractional vacuum distillation from the final product rather than from the N-methylbenzoyl-3-pyridylchlorobutylamine in the early stages of the preparation. The product so obtained gave a picrate which, after several recrystallizations, had a melting point of 170–171° instead of 163°, as reported by Pinner. The metanicotine was further characterized by catalytic reduction to dihydrometanicotine, as described by LaForge.[13] The base recovered from the recrystallized picrate had a boiling point of 141° (3.7 mm.) and $n^{25}D$ 1.5540.

**N-Benzoylmyosmine and 3-Pyridyl-ω-benzamidopropyl Ketone.**—These compounds were prepared by the same methods and possessed the same constants as those described in an earlier paper.[6]

**3-Vinylpyridine.**—The starting material for this base was a crude vinylpyridine obtained as one of the low-boiling pyridine-base fractions from the pyrolysis of nicotine. The base was purified as the picrate by the general method. The recrystallized picrate had a melting point of 144° and yielded a base having a boiling point of 162° and $n^{25}D$ 1.5370.

**3-Pyridyl Methyl Ketone.**—This ketone was prepared by the method described by LaForge[13]; b. p. 217–221°, $n^{25}D$ 1.5250.

## Summary

The ultraviolet absorption spectra of nicotine, nornicotine, and some of their derivatives have been determined in a number of solvents and found to bear the expected relationship to the spectrum of pyridine. Progressive hyperchromic and bathochromic effects were exhibited by the increasingly unsaturated members of the series derived from each of the parent compounds by dehydrogenation, with the exception of "N-methylmyosmine," which had a spectrum incompatible with the structure assigned to it. A few potential applications of the spectra to problems of analysis and assay are suggested.

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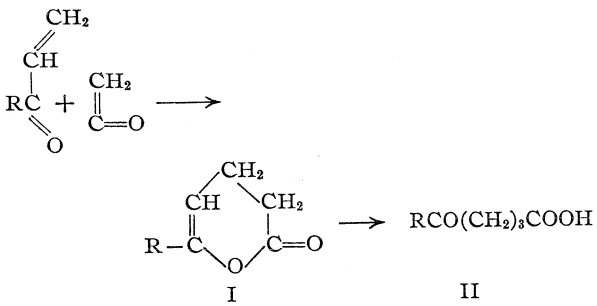
(5) Woodward, Eisner and Haines, THIS JOURNAL, **66**, 911 (1944).
(6) Haines, Eisner and Woodward, *ibid.*, **67**, 1160 (1945).
(7) Wibaut and Hackman, *Rec. trav. chim.*, **51**, 1157 (1932).
(8) Originally prepared by P. G. Haines of this Laboratory.
(9) Späth, Wenusch and Zajic, *Ber.*, **69**, 393 (1936).
(10) Burger, THIS JOURNAL, **67**, 1615 (1945).
(11) Löffler and Kober, *Ber.*, **42**, 3431 (1909).
(12) Pinner, *ibid.*, **27**, 1058, 2863 (1894).
(13) LaForge, THIS JOURNAL, **50**, 2477 (1928).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT OF THE CARBIDE AND CARBON CHEMICALS CORPORATION]

# The Reaction of Ketene with Unsaturated Ketones

BY FRANK G. YOUNG

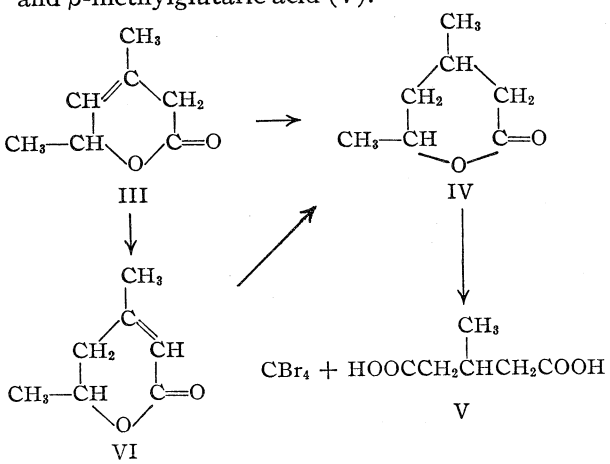
Recent patents have described the reaction of ketene with saturated aldehydes and ketones giving $\beta$-lactones[1] and $\alpha,\beta$-unsaturated acids.[2] The reaction of vinyl methyl ketone with ketene was described in patents[3,4] by Hopff and Rapp. This reaction was carried out in absence of catalyst and the product was described as a $\gamma,\delta$-unsaturated lactone (I) which was easily hydrolyzed, by water or aqueous alkali, to a $\delta$-keto acid (II). The over-all equation



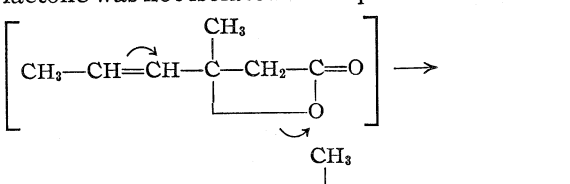

I II

proposed[3] presumably involves a 1,4-addition of ketene to the unsaturated system.

Because of the widespread physiological activity of unsaturated lactones,[5] it was of interest to determine if $\beta$-alkyl vinyl methyl ketones would undergo similar condensation with ketene. In contrast to its reaction with vinyl methyl ketone, no reaction between ketene and $\beta$-alkyl vinyl methyl ketones could be produced in the absence of a catalyst, but a trace of boron trifluoride or other acidic agent afforded rapid reaction and good yields of unsaturated lactones. The lactone isolated, after neutralization of catalyst, from the condensation of ketene and ethylidene acetone was not of type I, since it remained unchanged on treatment with boiling water, and saponification with aqueous alkalies followed by acidification of the cold solution, produced the same substance as that originally isolated. Presumably the intermediate product of the acidification was an unsaturated acid, which under the experimental conditions rapidly isomerized to the lactone. This eliminated the possibility of a $\beta$-lactone and indicated that the unsaturation was not in the $\gamma,\delta$-position, an observation which was supported by its mode of hydrogenation,[6] and confirmed by reaction with iodine bromide.[7,8,9,10] Distinction among $\Delta^{\alpha,\beta}$, unconjugated, and enol-lactones can be made using this reagent.[7] Since the lactone required approximately one mole of halogen per mole, the $\beta,\gamma$-position of the double bond was indicated. The $\delta$-lactone structure of the molecule (III) was proved by hydrogenation to a saturated lactone (IV), which upon oxidation with alkaline hypobromite solution gave carbon tetrabromide and $\beta$-methylglutaric acid (V).



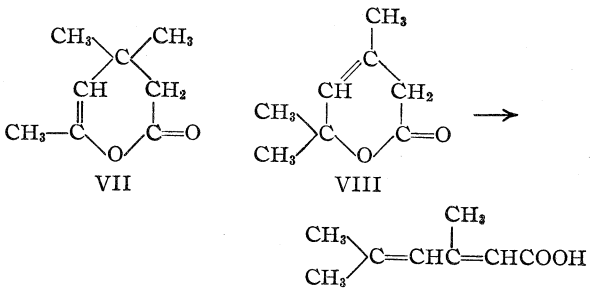

The production of a $\Delta^{\beta,\gamma}$ rather than a $\Delta^{\gamma,\delta}$ enol-lactone indicated that 1,4-addition of ketene to the ene-one system, $-C=C-C=O$ could not represent the true reaction mechanism. An alternative mechanism involving 1,2-addition of ketene to the carbonyl group of the ketone, producing an intermediate unsatured $\beta$-lactone, analogous to the mechanism proposed for the reaction of ketene with saturated aldehydes,[1] is postulated. The $\beta$-lactone was not isolated in the present work.




The electron-donating effect of the $\gamma$-double bond would be expected to enhance the instability of the $\beta$-lactone ring, and the formation of a doubly unsaturated acid by $\beta$-displacement. The methylsorbic acid would then rapidly equilibrate with its isomeric $\delta$-lactone (III).

(1) Küng, U. S. Patent 2,356,459 (August 22, 1944).
(2) Boese, U. S. Patent 2,387,464 (August 14, 1945).
(3) U. S. Patent 2,265,165 (December 9, 1941).
(4) German Patent 723,277 (August 8, 1942).
(5) Haynes, *Quarterly Reviews*, **II**, 46 (1948), The Chemical Society, London.
(6) Jacobs and Scott, *J. Biol. Chem.*, **87**, 601 (1930); **93**, 139 (1931).
(7) Cavallito and Haskell, THIS JOURNAL, **68**, 2332 (1946).
(8) Thiele and Straus, *Ann.*, **319**, 155 (1901).
(9) Jacobs, Hoffman and Gustus, *J. Biol. Chem.*, **70**, 1 (1926).
(10) Caldwell and Piontowski, THIS JOURNAL, **56**, 2086 (1934).

Addition of ketene to ethylidene acetone by either of these mechanisms would produce an unsaturated δ-lactone, differing only in the location of the double bond. Support for the latter mechanism was found in the reaction of mesityl oxide and ketene. In this case reaction by 1,4-addition should yield VII, but VIII was formed as proved by its conversion to β,δ-dimethylsorbic acid.



VII VIII

Lactone III may be converted quantitatively to the $\Delta^{\alpha,\beta}$-isomer (VI) by heating it with a trace of an alkaline catalyst. This lactone is unreactive toward the iodine monobromide reagent, and on hydrogenation yields a saturated lactone identical with IV.

Spectrographic examination of the lactones III and VI in *n*-heptane shows a much more intense ultraviolet absorption below 220 mμ for VI, but the distinct maximum at 265 mμ, characteristic of the carbonyl group, is much weakened. Longer wave lengths are about equally absorbed by the two lactones. Molecular extinction values are 115 at 240 mμ, 130 at 265 mμ, 68 at 280 mμ, and 5 at 300 mμ for III; and $\epsilon$ = 267, 108, 60, and 10 at corresponding values for VI. The lactone III is readily soluble to the extent of 5% by volume in *n*-heptane, but VI is less than 2% soluble in the same solvent.

## Experimental[11]

**β-Methyl-$\Delta^{\beta,\gamma}$-δ-hexenolactone (III).**—Into a solution of 800 g. (10.0 moles) of dry ethylidene acetone in 715 g. of anhydrous ether maintained at 0° by external cooling, there was diffused simultaneously 240 g. (5.7 moles) of ketene at the rate of 168 g. per hour and 10 g. of boron trifluoride at the rate of 6.6 g. per hour. Enough 0.5 *N* sodium hydroxide solution to destroy the catalyst was then added. The lower aqueous layer was separated and discarded. After removal of the ether, the residue from the upper layer was distilled. There was obtained 404 g. of unreacted ethylidene acetone and 467 g. (95% based on the ketone consumed) of the unsaturated lactone (III), b. p. 85° (5 mm.); sp. gr. $^{20}_{15.6}$ 1.043; $n^{30}D$ 1.4640. *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0; sapn. equiv., 126.2. Found: C, 66.4; H, 8.0; sapn. equiv., 126.0.

**Saponification of β-Methyl-$\Delta^{\beta,\gamma}$-δ-hexenolactone (III).**—Eighty-seven grams of the lactone was stirred with 350 ml. of 10% aq. sodium hydroxide at 20° until solution was complete. The clear solution was acidified with 75 ml. of concentrated hydrochloric acid, and the oil which separated was distilled, b. p. 85° (5 mm.); sp. gr. $^{20}_{15.6}$ 1.042; $n^{30}D$ 1.4640, identical in all respects with the original lactone (III).

**Reaction of β-Methyl-$\Delta^{\beta,\gamma}$-δ-hexenolactone (III) with Iodine Bromide Reagent.**—The iodine number was determined by the usual Hanus procedure[12] using the modifications suggested by Cavallito and Haskell.[7]

*Anal.* 0.1103 g. (III) required 9.40 ml. of 0.1001 *N* IBr = 1.07 moles of halogen per mole.

**β-Methyl-δ-hexanolactone (IV).**—Fifteen hundred grams of the unsaturated lactone (III) was hydrogenated at 50° and 1000 p. s. i. hydrogen in the presence of 15 g. of Raney nickel. The catalyst was filtered off and the filtrate was washed several times with 10% sodium bicarbonate solution to remove the small amount of β-methylcaproic acid formed by hydrogenolysis of the lactone ring. The neutral material was dried and distilled, b. p. 83–86° (3 mm.); sp. gr. $^{30}_{15.6}$ 1.020; $n^{30}D$ 1.4437. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4; sapn. equiv., 128.2. Found: C, 65.4; H, 9.4; sapn. equiv., 128.1. Iodoform test positive. The yield was 1250 g. (82%).

**Oxidation of β-Methyl-δ-hexanolactone (IV).**—Six and one-half grams of the saturated lactone (IV) was added to a solution of 40 g. of bromine and 20 g. of sodium hydroxide in 400 ml. water. During twelve hours standing at room temperature a heavy liquid separated which was soon converted to a white crystalline solid. The material (9.0 g., 70% of the theoretical) was filtered off and identified as carbon tetrabromide by its m. p. of 90.1°. The filtrate was extracted with ether, acidified with hydrochloric acid and re-extracted with ether. After removal of the solvent, the residue of 5 g. was distilled at 0.5 mm., 140° bath temperature. The distillate crystallized, m. p. 87–89°, undepressed by admixture with an authentic sample of β-methylglutaric acid (V).

**β-Methyl-$\Delta^{\alpha,\beta}$-δ-hexenolactone (VI).**—Seven hundred eighty-two grams of III and 3.7 g. (0.5%) of anhydrous potassium carbonate were heated together by means of an oil-bath to a temperature of 118°. A mild exothermic reaction set in and the temperature rose to 130° with the bath removed. The mixture was allowed to cool to 115°, and maintained at that temperature for fifteen minutes by replacing the oil-bath. Distillation gave a fraction of 743 g. (94%), b. p. 105° (5 mm.); sp. gr. $^{20}_{15.6}$ 1.045; $n^{30}D$ 1.4746. *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0; sapn. equiv., 126.2. Found: C, 66.6; H, 8.0; sapn. equiv., 126.2. 1.9094 g. required 1.02 ml. of 0.1001 *N* IBr = 0.0067 mole of halogen per mole.

**Hydrogenation of β-Methyl-$\Delta^{\alpha,\beta}$-δ-hexenolactone (VI).**—Two hundred fifty-two grams (2 moles) of the lactone (VI) and 6.5 g. of Raney nickel in 400 ml. of dioxane were shaken at 80–100° and 800 p. s. i. of hydrogen until the uptake was completed. Distillation of the filtered material gave 250 g. of a liquid b. p. 84–85° (3 mm.); sp. gr. $^{30}_{15.6}$ 1.020; $n^{30}D$ 1.4437; *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4; sapn. equiv., 128.2. Found: C, 65.5; H, 9.3; sapn. equiv., 128.2, identical in all respects with IV previously prepared.

A sample of each of the two saturated lactones from the different sources, III and VI, dissolved in cold aqueous sodium hydroxide and treated with *p*-bromophenacyl bromide, gave identical *p*-bromophenacyl esters m. p. 139–140°, undepressed when mixed.

Thirteen grams of the saturated lactone prepared from VI was oxidized with excess aqueous sodium hypobromite solution. Twelve grams of carbon tetrabromide m. p. 90.1° was collected after standing for twenty-four hours. The filtrate was acidified with hydrochloric acid and freed from bromine with a little sodium bisulfite. Extraction with ether and evaporation gave 10 g. of an acid m. p. 87°; undepressed when mixed with authentic β-methylglutaric acid or the acid from the oxidation of the saturated lactone derived from (III). *Anal.* Calcd.: neut. equiv., 73.1. Found: neut. equiv., 73.7.

**Reaction of Mesityl Oxide with Ketene.**—Into a well-agitated solution of 1 g. of boron trifluoride diethyl etherate in 479 g. of mesityl oxide, 185 g. of ketene was introduced over a period of two hours at 0–10°. The catalyst was destroyed by stirring with an excess of dilute (2%) sodium hydroxide solution at this temperature. Distilla-

(11) All m. p. are corrected and b. p. uncorrected.

(12) Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Co., New York, N. Y., 1922, p. 1166.

tion of the organic layer gave 133 g. of unreacted mesityl oxide, and 396 g. (80%) of β,δ-dimethyl-Δβ,γ-δ-hexenolactone (VIII) b. p. 92–93° (2 mm.); sp. gr. $^{20}_{15.6}$ 1.012; $n^{30}D$ 1.4600. *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.6; H, 8.6; sapn. equiv., 140.3. Found: C, 68.5; H, 8.5; sapn. equiv., 140.0.

**β,δ-Dimethylsorbic Acid.**—Fifty grams of VIII was refluxed eight hours with 100 ml. of 50% sodium hydroxide solution. The clear solution was cooled to 10° and strongly acidified. β,δ-Dimethylsorbic acid crystallized and was filtered off (24 g., 48%), m. p. 94–95°, undepressed by admixture with authentic material. By extraction of the filtrate with ether 25 g. of reformed VIII was isolated.

**β-Methyl-Δβ,γ-δ-octenolactone (IX).**—One hundred and nine grams of ketene was introduced at 10° into a solution of 291 g. of butylidene acetone dissolved in 800 ml. of ether containing 4 g. of boron trifluoride. The catalyst was destroyed with sodium hydroxide as previously described. Distillation gave 73 g. unreacted ketone and 298 g. (99%) of IX, b. p. 111° (3.5 mm.); sp. gr. $^{20}_{15.6}$ 1.002; $n^{30}D$ 1.4660. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.0; H, 9.2; sapn. equiv., 154.2. Found: C, 70.1; H, 9.2; sapn. equiv., 154.2.

## Summary

β,γ-Unsaturated δ-lactones were readily obtained by the reaction of ketene with β-alkyl vinyl methyl ketones in the presence of boron trifluoride.

The β,γ-unsaturated lactones were transformed quantitatively to α,β-unsaturated lactones by heating with potassium carbonate.

The mechanism for the condensation reaction is discussed.

SOUTH CHARLESTON, WEST VIRGINIA
RECEIVED OCTOBER 20, 1948

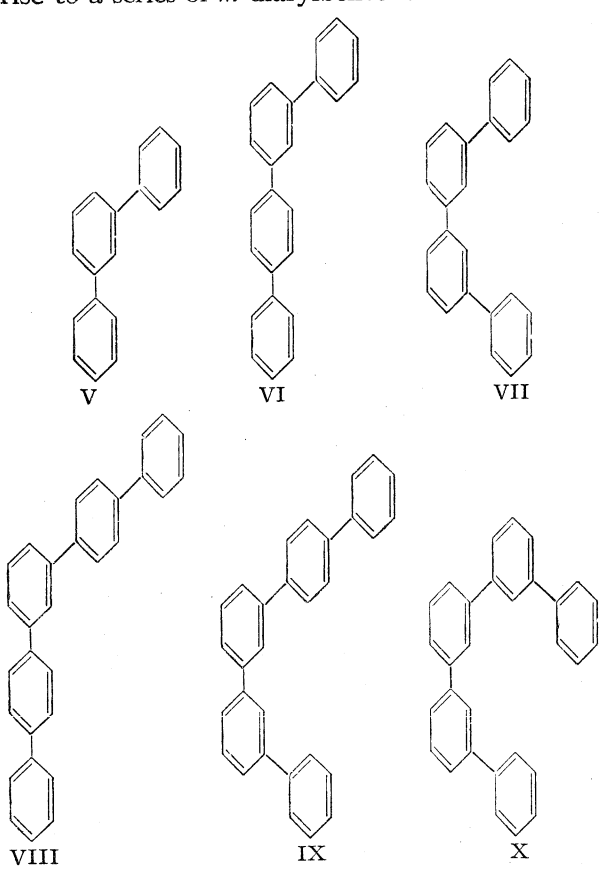
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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF MARYLAND]

# *m*-Diarylbenzenes

BY G. FORREST WOODS AND FRED T. REED

The reaction of the monoethyl ether of dihydroresorcinol with organo-metallic reagents[1] gives rise to a series of *m*-diarylbenzenes.




An earlier communication[2] described the preparation of V, VI and VIII. The present study describes the preparation of VII, IX and X, these syntheses being summarized in the flow sheet.

The intermediate dienes were not isolated and identified in all cases, since they undergo oxidation very readily, presumably to the aromatic compounds. In practice, the dienes were treated directly without purification with palladium–charcoal to effect aromatization. 1-Phenyl-3-(3-xenyl)-benzene, VII, was best prepared by the reaction of IV with 3-xenylmagnesium bromide rather than by the alternate route since a Wurtz type of reaction in the preparation of 3-xenylmagnesium bromide gives VII as a product. Substance VII, obtained by either procedure, corresponds in properties with those reported by Bowden[3] for 1-phenyl-3-(3-xenyl)-benzene prepared by the treatment of 3-xenyl iodide with copper powder. Substance IX was best prepared by treating II with 3-xenylmagnesium bromide rather than by the alternate method. Substance X could be prepared only by the one series of reactions indicated.

The authors wish to acknowledge that this work was supported in part by a contract from the Office of Naval Research.

## Experimental

**Preparation of 3-Xenyl Bromide.**—The synthesis of 3-xenyl bromide, first attempted without success by the Gomberg–Bachmann[4] reaction, was realized by the method of Huber, *et al.*,[5] modified by extracting the deamination reaction mixture with ether and obtaining crude 3-xenyl bromide by distillation of this extract. A solution prepared by adding an approximately equal volume of 30–60° petroleum ether to the crude 3-xenyl bromide was passed through a chromatographic column packed with activated alumina, resulting in an effective removal of colored impurities. The resulting solution was distilled, yielding

(1) Woods and Tucker, THIS JOURNAL, **70**, 2174 (1948).
(2) Woods and Tucker, *ibid.*, **70**, 3340 (1948).
(3) Bowden, *J. Chem. Soc.*, **139**, 111 (1931).
(4) Gomberg and Bachmann, THIS JOURNAL, **46**, 2339 (1924).
(5) Huber, *et al.*, *ibid.*, **68**, 1111 (1946).

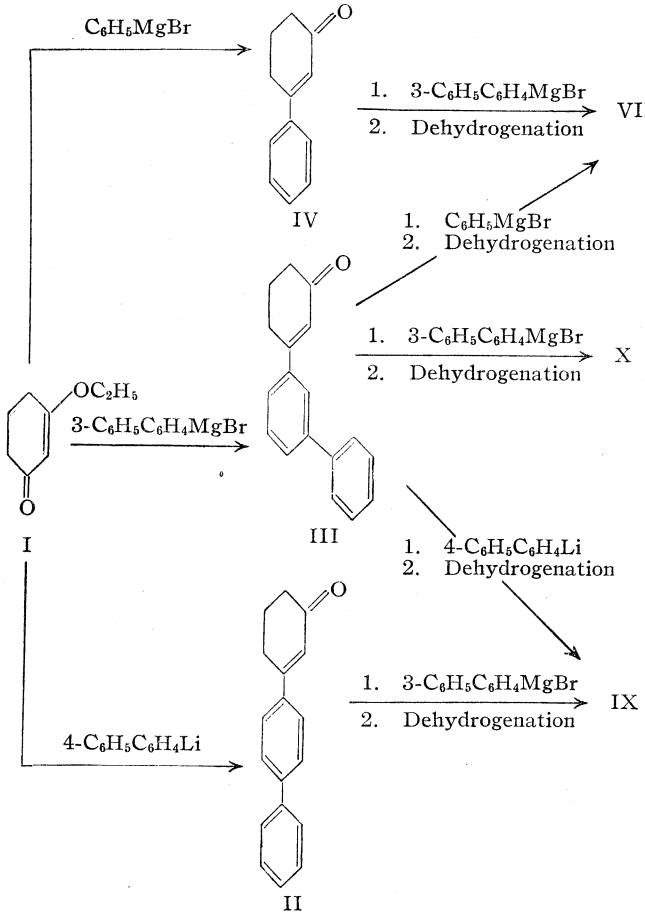



CHART I

water white 3-xenyl bromide boiling at 113–115° at 0.1 mm. Physical constants agreed with those reported by Huber, *et al.*, and yields were about the same.

Since this work dealt in part with positional isomerism, the identity of the above product was determined as follows: Fifteen grams of the 3-xenyl bromide was converted to the Grignard reagent by reaction with 1.6 g. of magnesium in 35 ml. of dry ether. This was poured into a mixture of dry ice and ether and then acidified with 150 ml. of 10% sulfuric acid. After washing the ether layer with 20% sulfuric acid, it was extracted with a 25% solution of potassium hydroxide. Acidification of the alkaline extract gave 9 g. of crude 3-xenylcarboxylic acid, melting at 150–3°, a 70% yield.

**Preparation of 1-Phenyl-3-(3-xenyl)-benzene (VII).**—(A) A solution of 92 g. of monoethyl ether of dihydroresorcinol[1] (I) in dry ether (100 ml.) was added to a solution of 3-xenylmagnesium bromide prepared from 3-xenyl bromide (142.6 g.) and magnesium (14.8 g.) in dry ether (250 ml.) in the usual manner. The resulting mixture was hydrolyzed with 10% sulfuric acid (about 100 ml.) and steam-distilled until no organic material was observed in the distillate. The residue was extracted with ether, washed with sodium bicarbonate solution and with water, and dried over magnesium sulfate. After removal of solvent the residue was distilled in a Hickman apparatus using a high vacuum diffusion pump. An extremely viscous, slightly colored distillate (70 g.) of 3-(3-xenyl)-$\Delta^2$-cyclohexenone (III) was obtained. Attempts to crystallize this compound were without success.

The red 2,4-dinitrophenylhydrazone of this compound was prepared, m. p. 210–211°. *Anal.* Calcd. for $C_{24}H_{20}O_4N_4$: C, 67.28; H, 4.71. Found: C, 67.81; H, 4.68.

The intermediate compound 1-(3-xenyl)-3-phenylcyclohexediene-1,3 was prepared by the addition of 3-(3-xenyl)-$\Delta^2$-cyclohexenone (III) (25 g.) in dry ether (20 ml.) to a solution (40 ml.) of phenylmagnesium bromide prepared from bromobenzene (25 g.) and magnesium (3.3 g.) in the usual manner. The resulting mixture was hydrolyzed with 10% sulfuric acid (about 50 ml.) and the impurities removed in part by steam-distillation. The gummy residue, washed several times by water using decantation, was extracted with ether, and dried over magnesium sulfate. After removal of the solvent, the residue was distilled in the Hickman apparatus as before. 1-(3-Xenyl)-3-phenylcyclohexediene-1,3 (22.7 g.), a highly viscous substance was obtained, which did not crystallize.

This substance (7.7 g.) was dehydrogenated[1] by treatment with 5% palladinized charcoal (4 g.) in refluxing *p*-cymene (25 ml.) for three hours. Most of the cymene was removed by distillation and to the residue was added 100 ml. of ethyl alcohol. The catalyst was removed by filtration of the hot solution. Cooling of the filtrate yielded 3.43 g. of 1-phenyl-3-(3-xenyl)-benzene (VII) which melted at 85.5–86.0°[6] after recrystallization from ethyl alcohol. *Anal.* Calcd. for $C_{24}H_{18}$: C, 94.07; H, 5.91. Found: C, 93.63; H, 6.05.

(B) Employing the method of Woods and Tucker,[1] 3-phenyl-$\Delta^2$-cyclohexenone (IV) was prepared.

A solution of this substance (9.7 g.) in dry ether (30 ml.) was added to 40 ml. of dry ether solution of 3-xenylmagnesium bromide prepared from 3-xenyl bromide (16.3 g.) and magnesium (1.58 g.). The Grignard complex thus formed was isolated by rapid filtration and then hydrolyzed with 10% sulfuric acid. The mixture obtained was extracted with ether and the extract washed with sodium bicarbonate solution and with water and dried over magnesium sulfate. After filtration, the ether was permitted to evaporate and there remained a viscous residue composed principally of 1-phenyl-3-(3-xenyl)-cyclohexadiene-1,3. No further attempt at isolation or purification was made.

A portion of this material (about 2 g.) was aromatized and the product (about 1 g.) isolated exactly as described in (A). The 1-phenyl-3-(3-xenyl)-benzene (VII) thus obtained melted at 84.5–85.0° and showed no depression in melting point when mixed with an equal portion of the product obtained by procedure (A).

**Preparation of 1-(4-xenyl)-3-(3-xenyl)-benzene (IX).**—(A) 3-(4-Xenyl)-$\Delta^2$-cyclohexenone (II) was prepared as described by Woods and Tucker.[2]

To a solution of 3-xenylmagnesium bromide, prepared from 3-xenyl bromide (25 g.) and magnesium (2 g.) in dry ether (40 ml.), was added 3-(4-xenyl)-$\Delta^2$-cyclohexenone (II) (15.0 g.) as finely divided solid. After the reaction was complete, the reaction vessel was chilled in a salt–ice bath to precipitate the Grignard complex. The complex was isolated by filtration and hydrolyzed with cold 10% sulfuric acid (about 50 ml.). The hydrolysis mixture was extracted with benzene and the solution washed with water and sodium bicarbonate solution and finally dried over magnesium sulfate. After removal of a portion of the benzene, a precipitate was obtained upon chilling. Recrystallization of this solid from ethyl alcohol yielded 1-(4-xenyl)-3-(3-xenyl)-cyclohexadiene-1,3 (9.6 g.), melting at 148–149°. *Anal.* Calcd. for $C_{30}H_{24}$: C, 93.70; H, 6.29. Found: C, 93.35; H, 6.48.

This compound (2.4 g.) was dehydrogenated by the same procedure as before using *p*-cymene (25 ml.) and 5% palladinized charcoal (0.5 g.). Benzene was added to the dehydrogenation mixture and the catalyst removed by filtration. Upon addition of an equal volume of ethyl alcohol crystals of 1-(4-xenyl)-3-(3-xenyl)-benzene (IX)

(6) Bowden reports a melting point of 86° for this compound (*cf.* ref. 3).

(1.89 g.) were obtained. These were recrystallized from an equal mixture of benzene and alcohol, m. p. 155.0–155.5°. *Anal.* Calcd. for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 94.57; H, 5.67.

(B) 3-(3-Xenyl)-$\Delta^2$-cyclohexenone (III) was prepared as described above.

A 40-ml. dry ether solution of the substance (17.6 g.) was added to a 40-ml. dry ether solution of 4-xenyllithium, prepared from 4-xenyl bromide (35.0 g.) and lithium (0.76 g.). Hydrolysis of the complex formed was effected as before with 10% sulfuric acid (50 ml.) and the resulting mixture was steam-distilled until there was no further appearance of organic material in the distillate. The residue was extracted with benzene, the extract being then washed successively with sodium bicarbonate solution and with water and finally dried over magnesium sulfate. This was filtered and the solvent allowed to evaporate. The resulting residue of 1-(3-xenyl)-3-(4-xenyl)-cyclohexediene-1,3 was not purified further.

This crude product (3.60 g.) was aromatized as described in procedure A, and the residue taken up in benzene. After filtration and addition of about four times the volume of ethyl alcohol, crystals of 1-(4-xenyl)-3-(3-xenyl)-benzene (IX) were obtained which upon recrystallization from an equal mixture of benzene and ethyl alcohol melted at 153–154°. Mixed melting point with the product obtained by procedure A showed no depression.

**Preparation of 1,3-Di-(3-xenyl)-benzene (X).**—A Grignard solution prepared in dry ether (40 ml.) from 3-xenyl bromide (30.3 g.) and magnesium (3.2 g.) was treated with a dry ether solution (20 ml.) of 3-(3-xenyl)-$\Delta^2$-cyclohexenone (III). The Grignard complex was isolated as before by rapid filtration of the chilled ether reaction mixture. The precipitate obtained was hydrolyzed with cold 10% sulfuric acid and then extracted with ether. The extract was washed with water and sodium bicarbonate solution and dried over magnesium sulfate. After removal of the solvent, distillation of the residue in the Hickmann apparatus yielded a very viscous yellow liquid (11.36 g.). Attempts to crystallize this material were unsuccessful.

Dehydrogenation of this substance was accomplished as before, by adding dropwise the 1,3-di-(3-xenyl)-cyclohexediene-1,3 (7.55 g.) to a refluxing mixture of 5% palladinized charcoal (4 g.) in *p*-cymene (25 ml.). The reaction mixture was worked up as before using ethyl alcohol, but crystallization from this solution yielded an oil. A portion of this oil was dissolved in benzene–petroleum ether (30–60°) and, upon cooling, crystalline material precipitated, which upon recrystallization from benzene and petroleum ether, yielded 1,3-di-(3-xenyl)-benzene, melting at 97–98°. *Anal.* Calcd. for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 94.60; H, 5.89.

## Summary

The reaction of the monoethyl ether of dihydroresorcinol with organo-metallic reagents has been extended to include the preparation of 1-phenyl-3-(3-xenyl)-benzene, 1-(4-xenyl)-3-(3-xenyl)-benzene and 1,3-di-(3-xenyl)-benzene.

COLLEGE PARK, MD. RECEIVED SEPTEMBER 23, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

# Condensations of Esters by Diisopropylaminomagnesium Bromide and Certain Related Reagents[1]

BY FREDERICK C. FROSTICK, JR., AND CHARLES R. HAUSER

Dialkylaminomagnesium bromides may react with esters either at the $\alpha$-hydrogen, effecting their condensations, or at the carbonyl carbon to form the corresponding N,N-dialkylamide, thus

$$RCH_2CO_2C_2H_5 + R'_2NMgBr \begin{cases} \longrightarrow (RCHCO_2C_2H_5)MgBr \xrightarrow{RCH_2CO_2C_2H_5} RCH_2COCHRCO_2C_2H_5 \\ \longrightarrow RCH_2CONR'_2 \end{cases}$$

Diethylaminomagnesium bromide has recently been shown[2] to effect the self-condensation of ethyl phenylacetate, *t*-butyl acetate and certain other esters but not ethyl *i*-valerate and ethyl *i*-butyrate with which the amide is presumably formed. This reagent self-condensed ethyl *n*-butyrate, but the condensation product was contaminated with the amide. The condensation product from ethyl propionate was reported free of the amide, but later work has shown that this condensation product also is generally contaminated with the amide.[3]

In the present investigation, diisopropylaminomagnesium bromide has been found to be a more suitable condensing agent than diethylaminomagnesium bromide. The diisopropyl reagent effects in good yield the self-condensation not only of the straight chain esters, ethyl propionate, ethyl *n*-butyrate and methyl laurate, but also that of the branched chain esters, ethyl *i*-valerate and ethyl *i*-butyrate, which are known to be more difficult to condense. The results are summarized in Table I. The yields have been based on the diisopropylaminomagnesium bromide since a 10% excess of the ester was employed; however, the yields would be approximately the same if they were based on the ester used minus that recovered. The condensation products were shown by the sodium fusion test for nitrogen to be free from the amide with the exception of that from ethyl *i*-valerate when the reaction time was twenty hours; in this case, secondary reactions appeared to have occurred. The products obtained when the reac-

(1) Paper XLII on "Condensations"; paper XLIII, THIS JOURNAL, **71**, 770 (1949).

(2) Hauser and Walker, *ibid.*, **69**, 295 (1947).

(3) In a private communication, Dr. Robert W. Holley of the State College of Washington, Pullman, Washington, has stated that the condensation product he obtained from ethyl propionate using diethylaminomagnesium bromide was contaminated with the amide. We have similarly found that this condensation product is contaminated with the amide (as detected by the sodium fusion test) when the reaction is carried out for either one-half hour or for four hours.

tion time was four hours were converted by ketonic cleavage to the corresponding ketones which were obtained in good yields. With ethyl diethylacetate, diisopropylaminomagnesium bromide gave, after a reaction time of two and one-half hours, a mixture containing nitrogen. An attempt to self-condense ethyl diphenylacetate with this reagent failed even after twenty hours, 55% of the original ester being recovered. However, the magnesium enolate of ethyl diphenylacetate was evidently formed since, on treatment of the reaction mixture with benzoyl chloride after one-half hour, ethyl benzoyldiphenylacetate was obtained in 38% yield.

$$(C_6H_5)_2CHCO_2C_2H_5 \xrightarrow{[(CH_3)_2CH]_2NMgBr} [(C_6H_5)_2CCO_2C_2H_5]MgBr \xrightarrow{C_6H_5COCl} C_6H_5COC(C_6H_5)_2CO_2C_2H_5$$

The present method for self-condensing esters is conveniently carried out and the condensing agent, diisopropylaminomagnesium bromide, is readily prepared from standardized ethylmagnesium bromide and diisopropylamine which is available commercially. Diisopropylaminomagnesium bromide is particularly suitable for the self-condensations of ethyl *i*-valerate and ethyl *i*-butyrate which are not condensed by sodium alkoxides. Although sodium hydride[4] self-condenses ethyl *i*-valerate, and sodium[5] and potassium triphenylmethide[6] and mesitylmagnesium bromide[7] self-condense both ethyl *i*-valerate and ethyl *i*-butyrate, diisopropylaminomagnesium bromide is probably more convenient to use.

Certain esters have also been condensed by means of dicyclohexylaminomagnesium bromide and di-*n*-butylaminomagnesium bromide. With the dicyclohexyl reagent, both ethyl *n*-butyrate and ethyl *i*-valerate were self-condensed to form β-keto esters which were free from the amide. However, the yields were somewhat lower than those obtained with the diisopropyl reagent. Moreover, working up the reaction mixture is more convenient with the diisopropyl reagent than with the dicyclohexyl reagent. With the di-*n*-butyl reagent, some amide formation appeared to occur along with the self-condensation of ethyl *i*-valerate since the condensation product gave a positive test for nitrogen.

These results indicate that, as the complexity of the basic reagent is increased, the α-hydrogen reaction of an ester is favored over the reaction at the carbonyl carbon. Similarly, the relatively complex mesitylmagnesium bromide[7] and sodium[5] and potassium triphenylmethides[6] react with the α-hydrogen of ethyl *i*-valerate or ethyl *i*-butyrate effecting self-condensation whereas simpler basic reagents such as methyl or ethyl magnesium bromide[8] and sodium amide[9] appear to react mainly at the carbonyl carbon of the ester.

In these Claisen condensations by dialkylaminomagnesium bromides, the magnesium cation as well as the dialkylamino anion (both of which are present at least potentially) appears to be involved in the mechanism.[2] However, the magnesium appears to influence mainly the rate of the reaction[2] whereas the basic anion may influence both the rate and the equilibrium. Actually, the condensation has been possible only when a sufficiently weaker base is formed.[10] A study of these factors is in progress.

## Experimental

**Self-condensations of Esters by Diisopropylaminomagnesium Bromide.**—In a 500-ml., three-necked flask equipped with a mercury-sealed stirrer, dropping funnel and reflux condenser (having a drying tube), was placed the appropriate quantity (0.2–0.4 mole) of standardized[11] ethylmagnesium bromide in ether solution. To the stirred mixture was added an equivalent number of moles of dry diisopropylamine in 50 ml. of dry ether at such a rate that the ether refluxed and stirring was continued for fifteen to thirty minutes to complete the formation of the diisopropylaminomagnesium bromide.[12] The ester (molar equivalent plus 10% excess) in 100 ml. of dry ether was added at such a rate that the ether refluxed gently. This addition required about one-half hour. In most cases, stirring was continued at room temperature (25–30°) for a longer period.

The reaction mixture was poured with stirring onto 300 g. of crushed ice mixed with 40–70 ml. of concentrated hydrochloric acid and the flask rinsed with some of the solution. After acidification, the ether phase was separated and the aqueous layer extracted twice with ether. The combined ether solution was washed with water, 10% sodium bicarbonate solution, and again with water, dried over Drierite, and the solvent distilled from a steam-bath. The residue was distilled *in vacuo* or recrystallized. Approximately 10–15% of the original ester was recovered in a low-boiling fraction obtained before the product distilled. The products were tested qualitatively for nitrogen by the sodium fusion method,[13] and certain of them were subjected to ketonic cleavage in the presence of acid.[14] The results are summarized in Table I.

With ethyl diethylacetate (b. p. 148.7–150°, 26.9 g., 0.187 mole), there was obtained, after a total reaction time of two and one-half hours, 9.5 g. (35% recovery) of the ester, b. p. 147–151°, and 13.8 g. of material boiling at 110–132° at 11 mm. which gave a positive test for nitrogen.

With ethyl diphenylacetate (m. p. 59.0–59.5°),[15] after refluxing on a steam cone for five hours and standing at room temperature for fifteen hours, 55% of the ester (m. p. 57–58°, mixed m. p. 57–59°) was recovered.

(4) Swamer and Hauser, THIS JOURNAL, **68**, 2647 (1946).

(5) (a) Hauser and Renfrow, *ibid.*, **59**, 1823 (1937); (b) Hudson and Hauser, *ibid.*, **63**, 3156 (1941).

(6) Levine, Baumgarten and Hauser, *ibid.*, **66**, 1230 (1944).

(7) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

(8) Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft m. b. H., Stuttgart, 1944, p. 377.

(9) Hauser, Levine and Kibler, THIS JOURNAL, **68**, 26 (1946).

(10) Renfrow and Hauser, *ibid.*, **60**, 463 (1938).

(11) One liter of two to four moles of ethylmagnesium bromide was prepared in the usual manner. The solution was standardized as described by Gilman, Wilkinson and Meyers, *ibid.*, **45**, 150 (1923).

(12) The complete formation of this reagent is indicated when ethane ceases to be evolved or when a test for the Grignard reagent with Michler's ketone is negative (see ref. 2).

(13) (a) McElvain, "The Characterization of Organic Compounds," The Macmillan Company, New York, N. Y., 1946, p. 40. (b) Shriner and fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(14) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).

(15) The ester was prepared by the carbonation of diphenylmethane using potassium amide and esterifying the resulting acid; Yost and Hauser, *ibid.*, **69**, 2325 (1947).

TABLE I

SELF-CONDENSATIONS OF ESTERS BY DIISOPROPYLAMINOMAGNESIUM BROMIDE

| Ester, ethyl | Reaction time, hr.[a] | β-Keto ester | B. p., °C., uncor. | Mm. | Yield, % |
|---|---|---|---|---|---|
| Propionate | 4 | Ethyl α-*n*-propionylpropionate[b] | 92.5–94 | 19[j] | 73[c] |
| *n*-Butyrate | 1 | Ethyl α-*n*-butyryl-*n*-butyrate[b] | 101.5–104.5 | 11.5 | 65 |
| *n*-Butyrate | 4 | Ethyl α-*n*-butyryl-*n*-butyrate[b] | 102–104.5 | 12[k] | 66[d] |
| *i*-Butyrate | 1.3 | Ethyl α-*i*-butyryl-*i*-butyrate[b] | 88–92.5 | 15 | 48 |
| *i*-Butyrate | 2 | Ethyl α-*i*-butyryl-*i*-butyrate[b] | 90.5–93.5 | 15 | 55 |
| *i*-Butyrate | 4 | Ethyl α-*i*-butyryl-*i*-butyrate[b] | 91.5–94.5 | 15[l] | 55[e] |
| *i*-Valerate | 1 | Ethyl α-*i*-valeryl-*i*-valerate[b] | 117–118.5 | 15 | 61 |
| *i*-Valerate | 4 | Ethyl α-*i*-valeryl-*i*-valerate[b] | 116–118 | 14[m] | 71[f] |
| *i*-Valerate | 20 | Ethyl α-*i*-valeryl-*i*-valerate | 110–118 | 15 | (55)[h] |
| Laurate (methyl) | 4 | Methyl α-lauryl-laurate[b,i] | 37–39[n] | M. p. | 92[g] |

[a] Reaction time includes one-half hour for adding the ester and one-half hour on a steam-bath; additional time was at room temperature (25–30°). [b] Product gave a negative test for nitrogen. [c] Ketonic cleavage gave a 41% yield of diethyl ketone, b. p. 98–102°; m. p. of semicarbazone, 138–139° (ref. 13a, p. 240). [d] Ketonic cleavage gave an 84% yield of di-*n*-propyl ketone, b. p. 135–143°; m. p. of semicarbazone, 131–132° (ref. 13a, p. 240). [e] Ketonic cleavage gave a 68% yield of diisopropyl ketone, b. p. 120–125°; m. p. of 2,4-dinitrophenylhydrazone, 94–95° (ref. 13b, p. 262). [f] Ketonic cleavage gave a 69% yield of diisobutyl ketone, b. p. 163–166; m. p. of 2,4-dinitrophenylhydrazone, 91–92° (ref. 13a, p. 240). [g] Ketonic cleavage gave an 88% yield of laurone, m. p. 68–69° (ref. 13b, p. 264). [h] Product gave a positive test for nitrogen. [i] Product recrystallized from methanol at −5° after all traces of ether had been removed under vacuum. [j] Reported b. p. 92–93° at 20 mm. [Dieckmann and Kron, *Ber.*, **41**, 1269 (1908)]. [k] See ref. 17. [l] Hudson and Hauser, THIS JOURNAL, **63**, 3159 (1941). [m] Reported b. p. 118–119° at 15 mm. (see ref. 6). [n] Reported m. p. 38–40° [Hansley, U. S. Patent 2,158,071 (1939)].

**Benzoylation of Ethyl Diphenylacetate.**—To a solution of 0.227 mole of diisopropylaminomagnesium bromide in ether was added slowly 43.0 g. (0.179 mole) of ethyl diphenylacetate (m. p. 57–59°)[15] dissolved in 150 ml. of dry ether. The reaction mixture was refluxed on a steam cone for ten minutes during which time a thick cream-colored precipitate was formed. After stirring an additional thirty minutes, 35.0 g. (0.250 mole) of benzoyl chloride was added and the resulting mixture stirred for thirty minutes. The reaction mixture was poured with stirring onto 50 ml. of concentrated hydrochloric acid and 500 ml. crushed ice. The ether phase was separated and the white solid left with the aqueous phase was dissolved in ether after several extractions with this solvent. The combined ether solution was washed with water, dried with Drierite and the solvent distilled. The residue was treated with hydriodic acid and glacial acetic acid according to the procedure described previously.[16] There was obtained 23.1 g. (38% yield) of ethyl benzoyldiphenylacetate, m. p. 146–147.5°; a mixed melting point with a known sample, m. p. 147–148°,[16] was 146–148°.

**Self-condensations of Esters by Other Dialkylaminomagnesium Bromides.**—Dicyclohexylaminomagnesium bromide and di-*n*-butylaminomagnesium bromide were prepared by the action of ethylmagnesium bromide on equivalent amounts of dicyclohexylamine and di-*n*-butylamine, respectively. With the latter amine, the reaction mixture was refluxed for about one hour.

In the usual manner, ethyl *n*-butyrate was self-condensed by the dicyclohexyl reagent for one hour (total time) to form ethyl α-*n*-butyryl-*n*-butyrate, b. p. 103–106° at 12 mm. (reported b. p. 102–103° at 12 mm.)[17] in 46% yield. Ethyl *i*-valerate was self-condensed by this reagent for four hours to form ethyl α-*i*-valeryl-*i*-valerate, b. p. 116–118° at 14 mm. (reported b. p. 118–119° at 15 mm.)[6] in 55% yield. In these cases, approximately six liters of water was required to dissolve the aminomagnesium halide complex formed on pouring the reaction mixture onto the acid. Tests for nitrogen on these condensation products were negative.

Ethyl *i*-valerate was treated with di-*n*-butylaminomagnesium bromide for three hours to form a product boiling at 126–144° at 14 mm. which gave a positive test for nitrogen.

(16) Hauser, Saperstein and Shivers, THIS JOURNAL, **70**, 608 (1948).

(17) Roberts and McElvain, *ibid.*, **59**, 2007 (1931).

**Acknowledgment.**—The authors wish to thank the Shell Chemical Corporation, New York, N. Y., for the diisopropylamine, Monsanto Chemical Company, Charlotte, N. C., for the dicyclohexylamine, and Sharples Chemicals, Inc., New York, N. Y., for the di-*n*-butylamine.

## Summary

1. Diisopropylaminomagnesium bromide effects satisfactorily the self-condensation of various esters including ethyl *i*-butyrate and ethyl *i*-valerate.

2. This reagent converts ethyl diphenylacetate to its magnesium enolate which has been benzoylated.

3. Certain esters have been condensed by dicyclohexylaminomagnesium bromide and by di-*n*-butylaminomagnesium bromide.

4. Comparisons have been made between various basic reagents in their reactions with esters where attack may occur at the α-hydrogen or at the carbonyl carbon atom.

DURHAM, N. C. RECEIVED SEPTEMBER 27, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AMHERST COLLEGE]

# The Wolff–Kishner Reduction. I. The Preparation and Properties of N-Alkyl- and N,N-Dialkylhydrazones

BY DAVID TODD

The Wolff–Kishner reduction of a carbonyl group to a methylene group by decomposition of a hydrazone, azine or semicarbazone in the presence of an alkaline catalyst or platinum has recently been shown to be practicable for large-scale operations[1] and, in the absence of solvent, not to require the fairly high temperatures commonly employed.[2] It seems of interest to investigate the mechanism of the reaction with a view to widening its scope. As a first step, the effect of alkali on N-alkyl- and N,N-dialkylhydrazones was investigated.[3] In this paper the preparation of these substituted hydrazones is described.

Very few N-alkylated hydrazones are known. Of the compounds of this class reported in this paper only the methylhydrazone and diethylhydrazone of benzaldehyde, and the methylhydrazone of *p*-nitrobenzaldehyde are in the literature. A preparation of benzaldehyde methylhydrazone was claimed by Harries and Haga,[4] but their product was a high-melting solid whereas one would expect that the compound should be an oil of lower boiling point (because of less hydrogen bonding) than the liquid benzaldehyde hydrazone. In this paper the isolation of the methylhydrazone of the expected physical properties is described. The diethylhydrazones of benzaldehyde and *p*-nitrobenzaldehyde were prepared by Brady and McHugh.[5] Hurd and Spence[6] have reported the preparation of several oily diethylhydrazones without giving details or properties.

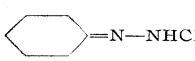
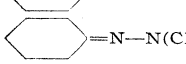
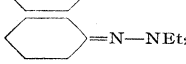
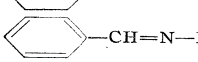
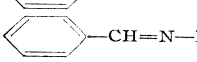
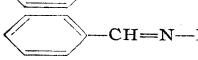
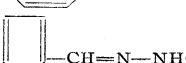
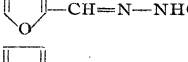
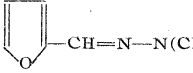
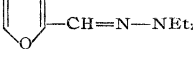
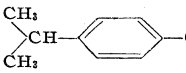
It was found that the hydrazones could be readily prepared by refluxing the appropriate carbonyl compound with an aqueous-alcoholic solution of the free alkylhydrazine. The latter was prepared by distilling to dryness an alkaline solution of a salt of the hydrazine. The hydrazones could also be prepared by refluxing an ether or benzene solution of the hydrazine with the carbonyl compound. In this case the hydrazine solution was prepared by solvent extraction of a cold basic solution of the hydrazine salt. The hydrazones were generally liquids, and almost all could be characterized as the picrate, styphnate, or N-nitroso derivative (in the case of monoalkylhydrazones). Furfural methylhydrazone was rapidly decomposed by picric acid in dry benzene, but the N-nitroso derivative was easily prepared. Cyclohexanone diethylhydrazone gave only a small yield of the styphnate in dry benzene while the picrate would not come out at all.

The ultraviolet absorption spectra of the hydrazone, methylhydrazone, dimethylhydrazone and diethylhydrazone of benzaldehyde are given in Fig. 1.

The molecular refractions of these materials were determined and found to show some remarkably high exaltations when the literature values for hydrazone nitrogen atomic refractivities were employed to calculate the molecular refractions.

It has been found[7] that for a series of four monoalkylhydrazones of aliphatic carbonyl compounds the calculated molecular refractions could be made to fit the observed values by assigning (1) to the C=N link the normal C=C bond refractivity of 1.733 units, (2) to the double-bonded nitrogen the normal secondary amine nitrogen value of 2.65 units, and (3) to the other nitrogen the normal primary amine nitrogen value of 2.45 units. These values were used to calculate the molecular refractions in Table I.

TABLE I

| | $MR_{obs.}$ | $MR_{calcd.}$ | Exaltation |
|---|---|---|---|
|  | 39.12 | 39.16 | −0.04 |
|  | 43.70 | 43.78 | − .08 |
|  | 52.97 | 53.01 | − .04 |
|  | 44.86 | 42.38 | 2.48 |
|  | 50.97 | 46.99 | 3.98 |
|  | 60.68 | 56.23 | 4.45 |
|  | 37.88 | 35.25 | 2.63 |
|  | 43.67 | 39.87 | 3.80 |
|  | 53.49 | 49.10 | 4.39 |
|  | 59.86 | 56.23 | 3.63 |
|  | 64.43 | 60.85 | 3.58 |
|  | 73.70 | 70.08 | 3.62 |

(1) Soffer, Soffer and Sherk, THIS JOURNAL, **67**, 1435 (1945); Herr, Whitmore and Schiessler, *ibid.*, **67**, 2061 (1945); Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(2) Lock and Stach, *Ber.*, **76**, 1252 (1943); **77**, 293 (1944).

(3) See paper II of this series, THIS JOURNAL, **71**, 1356 (1949).

(4) Harries and Haga, *Ber.*, **31**, 62 (1898)

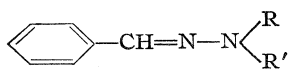
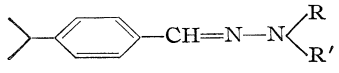
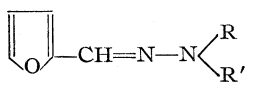
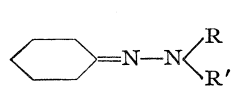
(5) Brady and McHugh, *J. Chem. Soc.*, 1648 (1922).

(6) Hurd and Spence, THIS JOURNAL, **49**, 266 (1927).

(7) Barrick, Drake and Lochte, *ibid.*, **58**, 160 (1936).

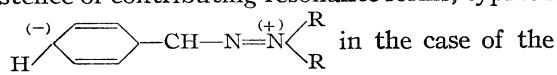
TABLE II

N-ALKYL- AND N,N-DIALKYLHYDRAZONES

| | | R | R′ | Method | Yield | B. p., °C. | Mm. | $N_D^{20}$ | $d_4^{20}$ | t |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  | $CH_3$ | H | a and b | 69 and 75 | 130–131 | 18 | 1.6053 | 1.0305 | 21.5 |
| 2 | | $CH_3$ | $CH_3$ | a and b | 83 and 60 | 127–128 | 20 | 1.5920 | 0.9840 | 29 |
| 3 |  | $C_2H_5$ | $C_2H_5$ | a | 22 | 140–141 | 14 | 1.5754 | .9604 | 24 |
| 4 | | $CH_3$ | H[a] | a | 58 | 148–152 | 7 | 1.5779 | .9769 | 25 |
| 5 | | $CH_3$ | $CH_3$[b] | a | 59 | 147 | 10 | 1.5649 | .9593 | 24 |
| 6 | | $C_2H_5$ | $C_2H_5$ | b | 47 | 156–158.5 | 8 | 1.5548 | .9506 | 23 |
| 7 |  | $CH_3$ | H[c] | a | 80 | 113–116 | 15 | 1.5846 | 1.0978 | 25 |
| 8 | | $CH_3$ | $CH_3$ | a | 73 | 98 | 9.5 | 1.5748 | 1.0423 | 24 |
| 9 | | $C_2H_5$ | $C_2H_5$ | b | 50 | 113 | 7 | 1.5569 | 1.0003 | 25 |
| 10 |  | $CH_3$ | H | a | 59 | 92–93 | 11 | 1.4990 | 0.9474 | 24 |
| 11 | | $CH_3$ | $CH_3$ | a | 73 | 177–180 | 760 | 1.4697 | 0.9031 | 27 |
| 12 | | $C_2H_5$ | $C_2H_5$ | b | 57 | 81–83 | 7 | 1.4646 | 0.8776 | 26 |

[a] M. p. (by immersion) is 10–12°. This compound is completely hydrolyzed by fifteen minutes contact with cold 5% HCl. [b] This material was not hydrolyzed after fifteen minutes contact with cold 5% HCl. [c] It is necessary to work up the reaction mixture immediately to avoid polymerization of the product. The compound is very sensitive to air oxidation. [d] Turns green on storage. [e] In ethanol this picrate is rapidly converted to the picrate of dimethylhydrazine, m. p. 140–142.5° dec. *Anal.* Calcd. for $C_8H_{11}N_5O_7$: C, 33.22; H, 3.83. Found: C, 33.06; H, 3.96.

It will be observed that in the cyclohexanone series no appreciable exaltation is found. In the benzaldehyde and furfural series the exaltations are not only unusually high but increase sharply with increased molecular weight.

The abnormalities in both the spectroscopic and refraction data are probably best explained by the existence of contributing resonance forms, typified by  in the case of the aromatic and furfural hydrazones. It would be expected that an increase in the number of alkyl groups on the terminal nitrogen of the hydrazones of aromatic carbonyl compounds would favor the increased participation of these resonance forms because of the electron-donating nature of the alkyl groups. It will be observed in Fig. 1 that the bathochromic shift of the maximum amounts to about 10 millimicrons as one passes from benzaldehyde methylhydrazone to the dimethylhydrazone. This is large in comparison with the almost negligible shift that occurs when such a change in structure does not alter the resonating character of the molecule.

Similarly it is well known that the stabilization of resonance forms leads to abnormal exaltations of molecular refractivities.[8] It is not at all clear why the *p*-isopropylbenzaldehyde hydrazones should show identical exaltations; they would be expected to show the same changes as the benzaldehyde series, though the exaltations should be of a lower order of magnitude because of the resonance-damping effect of the isopropyl group.

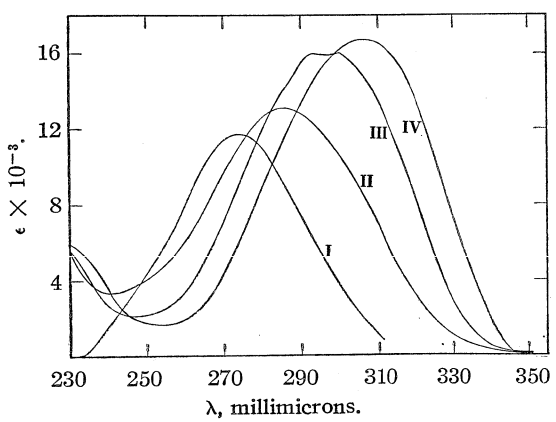



Fig. 1.—I, Benzaldehyde hydrazone; II, benzaldehyde methylhydrazone; III, benzaldehyde dimethylhydrazone; IV, benzaldehyde diethylhydrazone.

## Experimental

The two general methods for preparing the alkylhydrazones are described in detail for the preparation of benzaldehyde methylhydrazone. In Table II will be found the data on the preparation and properties of all the hydrazones prepared in this work.

**Benzaldehyde Methylhydrazone: Method (a).**—Twenty-one and six-tenths grams (0.15 mole) of methylhydrazine sulfate was dissolved in 25 ml. of warm water and dropped slowly from a separatory funnel into excess aqueous sodium hydroxide. The free hydrazine was distilled off, and several more portions of water added to the damp salt cake and distilled off. To the distillate was added about 25 ml. of ethanol and 15.9 g. (0.15 mole) of benzaldehyde, and the mixture heated on the steam-bath for three hours. The ethanol was removed *in vacuo*, the residual solution extracted with ether, the ether solution washed and dried, and the ether removed. The residual oil was distilled at 20 mm. After a small forerun had been removed the product came over at 129–133° as a pale yellow oil of characteristic camphoraceous-basic odor.

(8) Palermiti and Curran, THIS JOURNAL, 70, 3526 (1948).

TABLE II (*Continued*)

| Derivative | M. p., °C. | Neut. eq. Calcd. | Neut. eq. Found | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|
| Picrate | 133.0–133.5 | 363 | 358 | 46.28 | 46.46 | 3.61 | 3.60 | | |
| N-nitroso cpd. | 73.0–73.5 | | | | | | | 25.75 | 25.36 |
| Picrate | 142.5–143.5 | 377 | 377 | 47.74 | 47.90 | 4.01 | 3.94 | | |
| Chloroplatinate | 180–188 dec. | 353 | 357 | | | | | | |
| Picrate | 166–168 dec. | 405 | 400 | 50.37 | 49.98 | 4.72 | 4.95 | | |
| Picrate | 138–140 dec. | 405 | 412 | 50.37 | 50.63 | 4.72 | 4.55 | | |
| Picrate | 157–166 dec. | 419 | 425 | 51.55 | 51.21 | 5.04 | 4.63 | | |
| Picrate | 122–123 dec. | 447 | 455 | 53.68 | 53.69 | 5.63 | 5.39 | | |
| Styphnate | 117.5–120 dec. | 231.6 | 236 | | | | | | |
| N-nitroso cpd. | 108–109.5 | | | | | | | 27.44 | 26.72 |
| Picrate[d] | 124–125 dec. | 367 | 367 | 42.51 | 42.15 | 3.57 | 3.65 | | |
| Picrate[d] | 140–145 dec. | 395 | 402 | | | | | | |
| Styphnate | 135–136 dec. | 205.6 | 207.5 | 43.80 | 43.63 | 4.17 | 3.74 | | |
| Picrate[e] | 124–125 dec. | | | 45.53 | 45.21 | 5.19 | 5.06 | | |
| Styphnate | 137–140 dec. | 192.5 | 193 | | | | | | |
| Styphnate | 135–138 dec. | 206.5 | 211.5 | 46.48 | 46.78 | 5.62 | 5.10 | | |

The yield was 13.85 g. (69%). (If the alcohol–water solution of the product is allowed to stand at room temperature for several days the yield is far lower and a large amount of non-distillable polymer is formed.)

**Method (b).**—To 20 ml. of cold 50% sodium hydroxide in an ice-bath was added 14.4 g. (0.10 mole) of finely powdered methylhydrazine sulfate. The mixture was well stirred until the pale yellow hydrazine salt had dissolved; a heavy white precipitate of sodium sulfate came down during this period. The suspension was extracted twice with 50-ml. portions of ether, and the ether solution dried over potassium hydroxide pellets for an hour. To the filtered ether solution was added 10.6 g. (0.10 mole) of benzaldehyde; a mildly exothermic reaction set in immediately. The solution was refluxed one half hour, washed twice with 40% sodium bisulfite, with water, and dried over sodium hydroxide. After removal of the ether the product was distilled at 18 mm.; b. p. is 130–131°: yield is 10.03 g. (75%). The material was redistilled *in vacuo* for purification. The boiling point is 133° at 20 mm. (130–131° at 18 mm., 118–119° at 8 mm.); $n^{21.5}D$ 1.6053; $d^{21.5}_4$ 1.0305; $MR_{obs}$ 44.86; $MR_{calcd.}$ 42.38. (This material was found to be quite stable to cold 5% hydrochloric acid for half an hour or so at least. This fact was made use of several times to separate the hydrazone from unchanged benzaldehyde.)

**Picrate.**—To a solution of 2.29 g. of picric acid in warm benzene was added a benzene solution of 1.34 g. of benzaldehyde methylhydrazone. The yellow precipitate that formed was filtered and recrystallized from benzene; m. p. 133–133.5° (dec.).

Harries and Haga reported that benzaldehyde methylhydrazone was a colorless crystalline solid, m. p. 179°.

**The N-nitroso derivative** was prepared by refluxing a mixture of 5.36 g. of freshly-distilled benzaldehyde methylhydrazone with 9.36 g. of isoamyl nitrite in 50 ml. of hexane for two hours. The solution was cooled to −20° and two crops of pale yellow crystals totalling 2.25 g. (35% yield) were obtained. Two recrystallizations of this material from ethanol–water gave massive pale yellow prisms, m. p. 73.0–73.5°. This material gives a strong Liebermann nitroso test.

An attempt was made to prepare the N-acetate by the method employed by Brady and McHugh[4] to prepare the N-acetate of *p*-nitrobenzaldehyde methylhydrazone. Only unreacted starting material was recovered from the reaction mixture.

## Summary

The preparation and physical properties of the methyl-, dimethyl- and diethylhydrazones of benzaldehyde, *p*-isopropylbenzaldehyde, furfural and cyclohexanone are reported.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AMHERST COLLEGE]

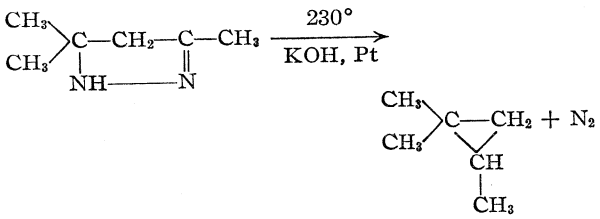
# The Wolff–Kishner Reduction. II. The Effect of Alkali on N-Substituted Hydrazones

BY DAVID TODD

The net change in the Wolff–Kishner reduction is a shift of two hydrogen atoms from nitrogen to carbon and simultaneous loss of a molecule of nitrogen

$$R_2C{=}N{-}NH_2 \longrightarrow R_2CH_2 + N_2$$

That monoalkylhydrazones might undergo the same reaction with loss of $N_2$ and formation of a new carbon–carbon bond would seem not unlikely in view of the fact that alkylpyrazolines, when heated to 230° in the presence of potassium hydroxide and platinum, have been found to lose nitrogen with the formation of a cyclopropane ring



A glance at the formula of the above pyrazoline will show that such compounds are cyclic N-alkylhydrazones. By the same analogy, since N-substituted pyrazolines are stable to hot alkali, it would be expected that dialkylhydrazones would also be stable.

The observed facts are in good accord with expectations. Three methylhydrazones have been found to lose close to the theoretical amount of nitrogen under the influence of hot alkali. Benzaldehyde methylhydrazone lost nitrogen in the presence of potassium hydroxide and platinum at 220–230°. Among the products of the reaction there were identified ethylbenzene (about 10% yield), benzoic acid and stilbene. When *p*-isopropylbenzaldehyde methylhydrazone was treated in a similar fashion, a 25% yield of *p*-ethylisopropylbenzene was obtained, as well as a small amount of *p*-isopropylbenzoic acid. No diisopropylstilbene could be detected. The *p*-ethylisopropylbenzene was identified by conversion to 2-ethyl-5-isopropylbenzenesulfonamide. The structure of the latter was proved by oxidation to the known 3-sulfonamido-4-ethylbenzoic acid.

Furfural methylhydrazone lost nitrogen at 170–190° in the presence of alkali and platinum but no products could be isolated from the reaction mixture.

Cyclohexanone methylhydrazone distilled unchanged from alkali and platinum at about 200°, but when the mixture of reagents was heated in a sealed tube at 250° there was obtained a colorless crystalline product of unknown structure. It is apparently a tertiary amine of the empirical formula $C_9H_{15}N$. There was no methylcyclohexane detected.

The dimethyl and diethylhydrazones of benzaldehyde, *p*-isopropylbenzaldehyde and furfural were all stable to alkali at 250°. The dialkylhydrazones of cyclohexanone, however, were largely decomposed to tarry products under these conditions.

## Discussion of Results

The fact that some N-monoalkylhydrazones, but not N,N-dialkylhydrazones, can be made to lose nitrogen in the presence of hot alkali with the formation of a product analogous to that formed in the Wolff–Kishner reduction of simple hydrazones makes it appear plausible that these processes go by a similar mechanism at least in the absence of solvent. It has been suggested[1] that the Wolff–Kishner reduction proceeds by a preliminary shift of the double bond to form a diimine, which then loses nitrogen in the manner characteristic of compounds containing the N=N linkage

$$R{-}CH{=}N{-}NH_2 \xrightarrow{OH^-} RCH_2{-}N{=}N{-}H \longrightarrow RCH_3 + N_2$$

Balandin and Vaskevitch[2] have reported kinetic data on the decomposition of cyclohexanone hydrazone that indicate an intermediate is formed in the process, and suggest that the only reasonable intermediate is the diimine.

If this mechanism is applied to the decomposition of benzaldehyde methylhydrazone it is difficult to avoid the conclusion that the diimine decomposes into two free radicals and a molecule of nitrogen. The free radicals then combine with each other to form ethylbenzene. The three steps in the reaction are then

$$C_6H_5CH{=}N{-}N(H)CH_3 \rightleftharpoons C_6H_5CH_2{-}N{=}N{-}CH_3 \quad (1)$$

$$C_6H_5CH_2{-}N{=}N{-}CH_3 \longrightarrow C_6H_5CH_2\cdot + CH_3\cdot + N_2 \quad (2)$$

$$C_6H_5CH_2\cdot + CH_3\cdot \longrightarrow C_6H_5CH_2CH_3 \quad (3)$$

There is a considerable amount of evidence that points to the existence of the reversible reaction (1).[3] The hydrazone is evidently always favored in this equilibrium though there are cases known in which the diimine form exhibits considerable stability. Phenyl ethyl diimine can be distilled at

(1) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," New York, N. Y., 1938, p. 384.

(2) Balandin and Vaskevitch, *J. Gen. Chem. U.S.S.R.*, **6**, 1878 (1936); [*C. A.*, **31**, 4575 (1938)].

(3) Sidgwick, "Organic Chemistry of Nitrogen," Oxford University Press, New York, N. Y., 1937, p. 432.

180° without isomerizing to acetaldehyde phenylhydrazone, and is stable to dilute alkali.[4] Phenyl benzyl diimine and dibenzyl diimine have been prepared, and are converted to the corresponding hydrazones by the action of either acid or base.[5] Surprisingly enough, diisopropyl diimine is so stable that the action of alkali at 180° for three to five hours converts it only partially into the hydrazone form.[6] It is evident that not only are the diimine forms characterized by considerable stability, but that alkali is a catalyst for the diimine-hydrazone equilibrium.

The evidence for step (2) is equally impressive. The thermal decomposition of dimethyl diimine in the gas phase into nitrogen and ethane at 275 to 320° has been carefully studied,[7] and shown to proceed almost certainly by a free radical mechanism.[8] Substitution of the hydrogens of one or both methyls in dimethyl diimine by alkyl groups leads to a slight decrease in thermal stability of the compound, whereas substitution by aromatic groups leads to a far more pronounced decrease in thermal stability. Thus, the temperatures of roughly comparable rates of decomposition are: dimethyl diimine, 320°; methyl isopropyl diimine, 300°[9]; diisopropyl diimine, 280°[10]; dibenzyl diimine,[5] 160–170°. It would then be expected that methyl benzyl diimine formed by isomerization of benzaldehyde methylhydrazone, would decompose at a temperature between 170° and 280°. The observed temperature is 220–230°.

If the reaction proceeds by a free radical mechanism, it could be expected that the particles might recombine partly with themselves and partly with each other. Therefore a search was made for dibenzyl among the reaction products of the benzaldehyde methylhydrazone decomposition but none could be detected. It was thought likely that the small amount of stilbene formed in the reaction might have arisen by platinum dehydrogenation of dibenzyl produced. But dibenzyl was found to be completely stable under the reaction conditions, and the formation of stilbene remains unexplained. However Wolff[3] found some symmetrical tetraphenylethane among the reaction products when benzophenone phenylhydrazone was heated with sodium ethoxide at 190° or slowly distilled in the absence of alkali. In this case the relatively high stability of the diphenylmethyl radical can explain the formation of this product though it is difficult to see why triphenylmethane was not also formed.

Similarly, it seems highly likely that the thermal decomposition of pyrazolines proceeds by initial isomerization to the $\Delta'$-form, which loses nitrogen to form a di-free radical. This becomes stabilized by forming a cyclopropane derivative. Further work on appropriately substituted pyrazolines is now in progress.

(4) Fischer, *Ann.*, **199**, 328 (1879); *Ber.*, **29**, 793 (1896).
(5) Thiele, *ibid.*, **376**, 267 (1910).
(6) Lochte, Bailey and Noyes, THIS JOURNAL, **44**, 2556 (1922).
(7) Ramsperger, *ibid.*, **49**, 912 (1927).
(8) Leermakers, *ibid.*, **55**, 3499 (1933); Rice and Evering, *ibid.*, **55**, 3898 (1933).
(9) Ramsperger, *ibid.*, **51**, 2134 (1929).
(10) Ramsperger, *ibid.*, **50**, 714 (1928).

## Experimental

**Attempted Alkaline Decomposition of the Dialkylhydrazones.**—The procedure used involved simply heating the compound in question, with a pellet of sodium or potassium hydroxide and a small platinum spiral, in a Woods metal bath to 250° for about half an hour. The apparatus was connected with a gas buret.

The dimethyl- and diethylhydrazones of benzaldehyde, *p*-isopropylbenzaldehyde and furfural were all found to be stable under the above conditions. There was little or no net evolution of gas and the hydrazones could be recovered virtually quantitatively, as shown by the boiling points, indices of refraction, and preparation of solid derivatives.

Because of their low boiling point, the dimethyl- and diethylhydrazones of cyclohexanone had to be heated in sealed tubes. Considerable pressure had developed when the tubes were cooled and opened, and a strong amine odor was evident. In both cases very little dialkylhydrazone could be recovered from the dark tarry mass, and it was evident that almost complete decomposition had occurred.

**Alkaline Decomposition of Benzaldehyde Methylhydrazone.**—In a 50-ml. modified Claisen flask equipped with a receiver and connected to a gas buret were placed 5.0 g. of the hydrazone, a pellet of sodium hydroxide and several pieces of platinized porous plate. The flask was heated in a Woods metal-bath. Gas began to evolve rapidly at 235° (bath temp.). The bath was heated to 254° and maintained there for one-half hour, when gas evolution had virtually ceased. The gas evolved corresponded to 83% of the theoretical amount of nitrogen expected.

In the receiver there was found a mixture of two liquids. This turned out to consist of a few drops of methylhydrazine and 0.5 g. of ethylbenzene. The former was identified by its rapid positive Fehling test and conversion to the picrate. The ethylbenzene was removed with a pipet, washed with 1 ml. of water, dried over potassium carbonate. The material has b. p. (micro) 137°, $n^{20}D$ 1.4943 (ethylbenzene has b. p. 136.2, $n^{20}D$ 1.4959). Several hundred milligrams of this material was converted to 2,4-diacetaminoethylbenzene,[11] m. p. 223–225° (no depression with an authentic specimen of m. p. 224–227°).

The residue in the flask was taken up in ether, washed with water and 5% hydrochloric acid and dried. (From the aqueous washings there was recovered a little benzoic acid.) The ether residue was distilled at 16 mm. to give 0.3 g. of material coming over below 100° (odor of benzaldehyde, positive DNP test), 0.73 g. of a fraction boiling at 160–180° (A), and 0.60 g. of a fraction of b. p. 213° (B). The residue weighed 0.88 g.

Fraction A was partially crystalline. After seven crystallizations from ethanol–water there was isolated about 20 mg. of slightly impure stilbene, m. p. 116–121°, mixed m. p. with stilbene (m. p. 120–124°) showed no depression.

*Anal.* Calcd. for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.17; H, 7.27.

Fraction B was almost entirely crystalline, but was evidently a mixture since it could not be obtained crystalline from ethanol–water. The ethanol solution on treatment with trinitrobenzene gave a yellow precipitate that after two more crystallizations gave yellow needles, m. p. 110.0–111.5°. The analysis indicates this compound is still impure.

*Anal.* Found: C, 38.04; H, 2.11.

**Alkaline Decomposition of *p*-Isopropylbenzaldehyde Methylhydrazone.**—The decomposition was carried out as described in the previous case. From 13.4 g. of the hydrazone there was obtained 119% of the theoretical amount of gas. A sample of this gas was cooled to −193°

(11) Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937).

and pumped off with a mercury pump. No significant portion of the gas remained after this treatment. Evidently no detectable amount of ethane is formed in the reaction.

The distillate produced during the reaction was combined with the few drops of material that could be distilled *in vacuo* (bath to 180°), worked up in ether as usual and finally distilled from sodium. There was obtained 2.8 g. (25%) of *p*-ethylisopropylbenzene. Micro b. p. is 194°, $n^{23}D$ 1.4858, $d^{23}_4$ 0.8530 (the literature values are: b. p. 196°, $n^{16}D$ 1.4928, $d^{16}_4$ 0.8606); $MR_{obs}$ 49.90; $MR_{calcd.}$ 49.40.

**2-Ethyl-5-isopropylbenzenesulfonanilide.**—One gram of the hydrocarbon was dissolved in 5 ml. of chloroform, cooled to 0°, and while stirred in an ice-bath was treated dropwise with 5 ml. of chlorosulfonic acid. The solution was held at 0° for ten minutes, allowed to warm to room temperature and poured on ice. The chloroform solution was separated, washed and dried. One-half of the chloroform solution of sulfonyl chloride was evaporated to dryness and to the oil was added 2 ml. of aniline. The solution was boiled for two minutes, and the product was worked up by extraction from ether with 1% of sodium hydroxide. There was obtained 0.74 g. (72%) of the crude anilide of m. p. 104–107°. Crystallization from ethanol–water gave the pure material as tiny serrated needles melting constantly at 108.0–109.0°.

The same material was prepared from authentic hydrocarbon. It had the same melting point and a mixture of the two showed no melting point depression.

This material is probably identical with the compound (position of sulfonanilide group unknown), prepared by Klages and Keil,[12] reported to melt at 110°.

The position of the entering sulfonyl chloride group was demonstrated as follows:

Authentic *p*-ethylisopropylbenzene was treated as described above, and the chloroform solution of the acid chloride was divided into two parts. One of these was converted to the anilide as described. The other was evaporated, heated with ammonium carbonate on the steam-bath for one-half hour, the solid washed well with cold water, and the residue crystallized from ethanol to give 64% of crude 2-ethyl-5-isopropylbenzenesulfonamide. Two crystallizations from ethanol gave a product melting at 69.0–70.5°.

*Anal.* Calcd. for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54. Found: C, 58.11; H, 6.92.

**3-Sulfonamido-4-ethylbenzoic acid.**—Two-tenths of a gram of the above sulfonamide was refluxed with 1.2 g. of potassium dichromate, 1 ml. of concentrated sulfuric acid, and 3 ml. of water for four hours. The acid fraction was crystallized from ethanol–water several times to give the pure acid which has a constant, though wide, melting range. It begins to soften at 235°, and melts at 248–257°, mostly at 253–257°. Widman[13] reported that this compound melted at 259–260°.

An authentic specimen of this material was prepared by the same series of reactions applied to *p*-diethylbenzene. The acid so formed was obtained as colorless needles that begin to soften at about 235°, and melts at 248–259°, mostly at 253–259°. A mixture of the two materials shows exactly the same melting characteristics.

**Alkaline Decomposition of Furfural Methylhydrazone.**—This material was decomposed in the usual way. It was found that the decomposition temperature was considerably lower than in the other cases. At about 140° the compound begins a very rapid evolution of gas. The temperature was carried up to 200° to ensure complete reaction. There was collected 91% of the theoretical volume of gas.

On working up the reaction mixture nothing but tar could be obtained. Evidently little or no ethylfuran was formed.

**Alkaline Decomposition of Cyclohexanone Methylhydrazone.**—This material was found to distill unchanged at about 200° from potassium hydroxide and platinum. The hydrazone (3.45 g.) one pellet of potassium hydroxide and a platinum spiral were heated in a sealed tube at 250° for two hours. On being cooled the tube's contents were found to be a solid mass of crystals. On being worked up this material was found to contain no trace of methylcyclohexane. The solid material was crystallized from ethanol to give 0.40 g. of colorless plates, m. p. 88.0–89.5°. A second crop of 0.39 g. of less pure material was obtained. Recrystallization of the first crop from ethanol gives platelets of m. p. 90.5–91.0°.

*Anal.* Found: C, 81.90, 81.57; H, 9.63, 9.51; N, 7.95, 8.32. Calcd. for $C_{11}H_{15}N$: C, 81.9; H, 9.3; N, 8.8.

This material is a very weak base (soluble in 6 *N* HCl, insoluble in 1.3 *N* HCl), and is probably a tertiary amine (forms no derivative in the Hinsberg process). It does not form a picrate or a chloroplatinate.

## Summary

The stability of some N-alkyl and N,N-dialkylhydrazones to alkali has been investigated. The results indicate that the decomposition of monoalkylhydrazones, of unsubstituted hydrazones, and of pyrazolines may all proceed by the same mechanism in the absence of solvent: *i. e.*, preliminary isomerization of the hydrazone to the diimine, and loss of nitrogen from the diimine to give two free radicals (a di-free radical in the case of pyrazolines) that rapidly combine to give the observed products.

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(12) Klages and Keil, *Ber.*, **36**, 1641 (1903).

(13) Widman, *ibid.*, **23**, 3086 (1890).

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

# Morphine Studies. The Synthesis of a Tetralin–Piperidine Fused-Ring System[1]

BY E. C. HORNING AND R. U. SCHOCK, JR.[2]

One of the chief problems connected with the synthesis of morphine derivatives and morphine analogs lies in the synthesis of bridged-ring piperidine systems similar to that in morphine. This problem has been studied in a number of laboratories, and several methods have been found suitable for the preparation of certain types of analogs. A bicyclic system, containing a piperidine ring bridged at appropriate points, has been described recently by Cronyn.[3] Another bicyclic system involving a bridged-piperidine structure, in which the nitrogen was present in a quaternary salt group, was obtained by Barltrop,[4] and the method of synthesis was extended to the preparation of a tetralin analog. The synthesis of a compound (morphan) containing the carbon skeleton of morphine was recently announced by Grewe,[5] although experimental details of this work are lacking.

We have been interested in the preparation of certain tetralin analogs of morphine,[6] and in the course of the work it was necessary to investigate the problem of obtaining a tetralin–piperidine fused-ring system. At the same time, it was hoped that the investigation might result in a method sufficiently general to allow further application to the preparation of a synthetic tetrahydrodesoxycodeine. The work described here includes a study of two methods aimed at a ring system of the required sort.

The starting compound, 2,3-dimethoxyphenylacetonitrile, was alkylated with β-ethoxyethyl methanesulfonate to provide α-(2,3-dimethoxyphenyl)-γ-ethoxybutyronitrile (I). Addition of acrylonitrile led to the dinitrile II; this was converted into methyl γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III) by means of hydrogen chloride in methanol. Formylation of the ester III with ethyl formate and sodium methoxide, followed by cyclization of the formyl derivative (IV) with sulfuric–phosphoric acids, gave the dihydronaphthalene derivative (V). Hydrolysis of the ester group, followed by hydrogenation with palladium–carbon catalyst in acetic acid, resulted in the tetralin derivative VI. The acid group was then transformed into the urethan group of compound VII through a method somewhat similar to that employed earlier,[6] except that ethanol was used during the Curtius rearrangement. Through the action of 48% hydrobromic acid under reflux, the crude urethan was converted into an amine hydrobromide (VIII). The structure of this intermediate was evident from the results of cyclization experiments; preliminary trials aimed at isolating a pure sample of this salt were not successful, and in later experiments solutions of the salt were used directly for cyclization after clarification with decolorizing carbon. There are six functional group reactions, including cleavage of three ether groups, hydrolysis of the cyano group, and hydrolysis-decarboxylation of the ester group, which occur at this point.

Cyclization of the intermediate was best carried out in aqueous solution in the presence of sodium acetate at *p*H 5. The resulting product was isolated as a crystalline acetyl derivative by acetylation in a solution maintained at *p*H 7–8 with sodium bicarbonate. The crystalline product was obtained in pure form without difficulty, and analytical data indicated that the empirical formula corresponded to a diacetyl derivative (IXb). The acetylation of only one phenol group in the parent compound, IXa, under acetylation conditions, is not without analogy in the morphine series. At the same time, the possibility that cyclization might have occurred to yield a chroman, with subsequent acetylation to provide the diacetyl derivative X, was also present. Freshly prepared solutions of the product gave an azo dye when treated with diazotized aniline or diazotized sulfanilic acid; this indicates the presence of a free phenolic group. The alternate assumption, that the compound is a chroman in which the acetyl group is hydrolyzed on contact with aqueous alkali, followed by *o*-coupling, appears far less probable.

A second method of synthesis was carried to the point indicated in the accompanying figure. It was hoped that the nitrosoketone could be reduced by the methods of Rosenmund[7] and Kindler.[7] Unfortunately, the nitrosation gave as a product an unstable oil from which very little crystalline material could be isolated.

The application of reaction methods leading to the formation of a tetralin–piperidine system are of particular interest in connection with a synthesis of tetrahydrodesoxycodeine. A useful precursor, 2-(2′,3′,-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone, has been prepared,[8] and work in this direction is under way.

(1) Abstracted from the dissertation of R. U. Schock, Jr., presented to the faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy, April, 1948.

(2) Bristol Laboratories Fellow, 1946–1947. National Institute of Health Predoctorate Fellow, U. S. Public Health Service, 1947–1948. Present address: The Abbott Research Laboratories, North Chicago, Illinois.

(3) Cronyn, Paper 87 of the Division of Organic Chemistry, American Chemical Society Meeting, April, 1948.

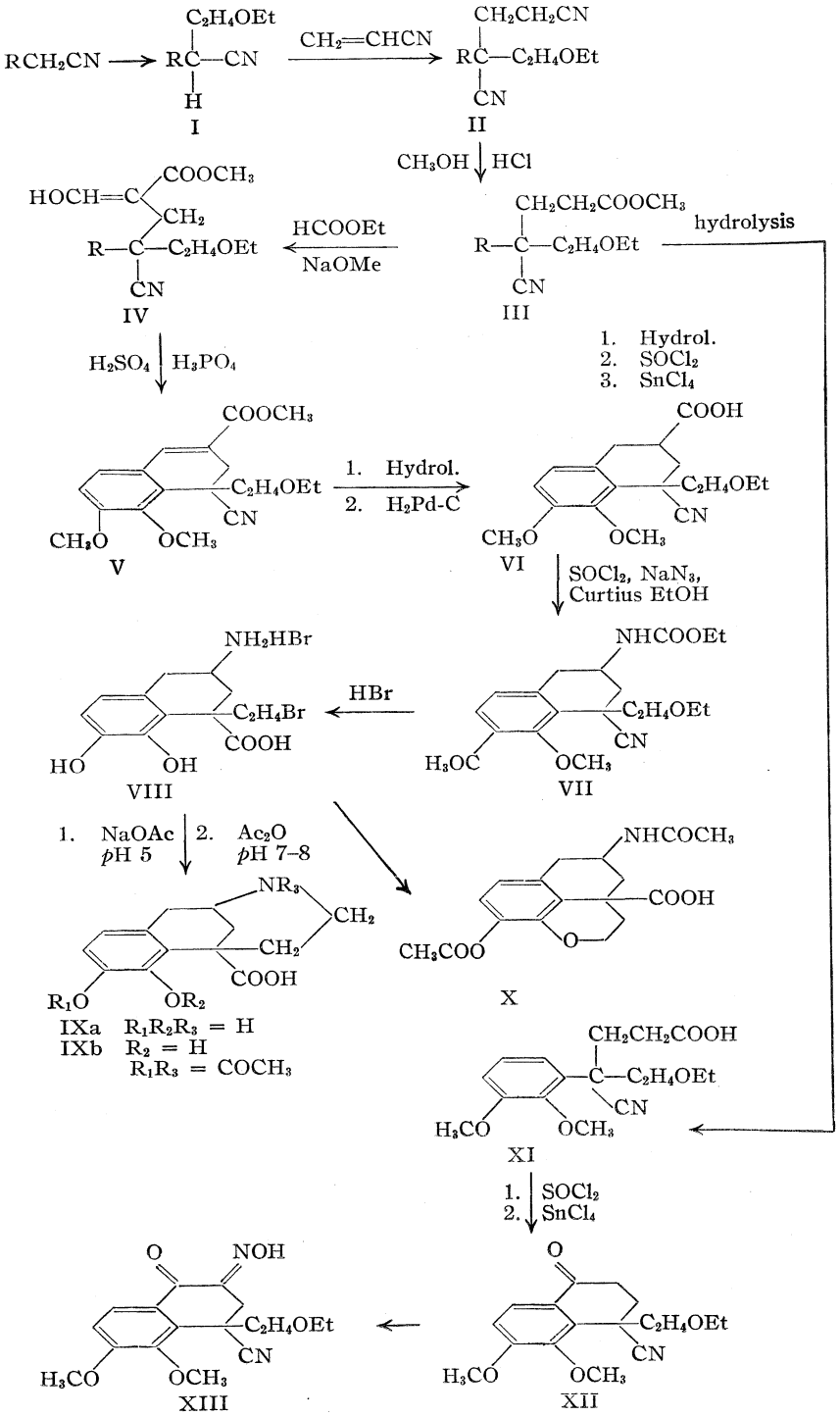
(4) Barltrop, *J. Chem. Soc.*, 399 (1947).

(5) Grewe, *Naturwiss.*, **11**, 333 (1946).

(6) Horning and Schock, THIS JOURNAL, **70**, 2941, 2945 (1948).

(7) Rosenmund and Karg, *Ber.*, **75**, 1850 (1943); Kindler and Dschi-yin Kwok, *Ann.*, **554**, 9 (1943).

(8) Horning, Horning and Platt, THIS JOURNAL, **70**, 2072 (1948).




**Acknowledgment.**—We are indebted to Mrs. Sarah Miles Woods for the analytical data.

## Experimental

All melting points are corrected.

**α-(2,3-Dimethoxyphenyl)-γ-ethoxybutyronitrile (I).**—Sodamide was prepared from the reaction of 12.7 g. of sodium (0.55 mole) and 400 ml. of liquid ammonia in the presence of a trace of ferric nitrate.[9] A solution of 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile in 100 ml. of dry benzene and 100 ml. of dry ether was added to the suspension of sodamide in liquid ammonia. The suspension was stirred for one hour or until the ammonia evaporated. Then, with vigorous stirring, a mixture of 92.4 g. (0.55 mole) of β-ethoxyethyl methanesulfonate[10] and 100 ml. of dry ether was added at such a rate that the heat of reaction maintained the mixture at gentle reflux. After heating under reflux for one hour, the mixture was cooled and diluted with 500 ml. of water. The layers were separated and the aqueous phase extracted once with 100 ml. of ether. The combined organic solutions were washed successively with 5% sodium hydroxide solution, 5% hydrochloric acid and with water. The extract was dried over magnesium sulfate, the solvents removed by distillation and the residue fractionated through a short Vigreux column. The fraction boiling at 131–140° (0.4 mm.) was collected. The yield of nearly colorless product was 105.2 g. (84%).

*Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.48; H, 7.63.

**α-(β-Ethoxyethyl)-α-(2,3-dimethoxyphenyl)-glutaronitrile (II).**—The procedure followed was essentially that described by Bruson[11] for the cyanoethylation of phenylacetonitrile. A solution of 105.2 g. of the nitrile I in 90 ml. of *t*-butyl alcohol was heated to 40° and then, with stirring, the dropwise addition of a solution of 24 g. of acrylonitrile in 30 ml. of *t*-butyl alcohol was started. After the addition of a few drops, 2 ml. of a 30% aqueous solution of benzyltrimethylammonium hydroxide was added, and the temperature maintained at 40–45° by occasional external cooling. Another 2-ml. portion of catalyst was introduced after half the acrylonitrile was added. When the temperature no longer rose spontaneously, the solution was heated for one hour at 40–45° and allowed to stand overnight. The dark solution was acidified with dilute hydrochloric acid and diluted with 250 ml. of cold water. The layers were separated with the aid of ether and the aqueous layer extracted once with 50 ml. of ether. The combined extracts were washed with water and dried over magnesium sulfate. Distillation of the residue remaining after evaporation of

(9) "Organic Syntheses," **25**, 25 (1945).

(10) Newman and Magerlein, THIS JOURNAL, **68**, 942 (1947).

(11) Bruson and Riener, *ibid.*, **65**, 25 (1943).

the solvent yielded 108.5 g. (85%) of a colorless viscous oil boiling at 171–178° (0.3 mm.).

*Anal.* Calcd. for $C_{17}H_{22}O_3N_2$: C, 67.53; H, 7.33. Found: C, 67.68; H, 7.24.

**Methyl γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III).**—A solution of 108.5 g. of the dinitrile II in 400 ml. of absolute methanol was treated with a stream of dry hydrogen chloride for thirty minutes. The mixture was heated gently under reflux for one hour, and then approximately one-half the alcohol was removed in a current of air. Dilution of the cooled residue with water produced an oil which was separated by three 100-ml. portions of ether. The extract was washed with water, once with 50 ml. of saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent left a colorless residue which was distilled at reduced pressure. The fraction boiling at 176–180° (0.5 mm.) was collected; the yield was 104.7 g. (87%).

*Anal.* Calcd. for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51. Found: C, 64.51; H, 7.37.

**γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic Acid (XI).**—The ester-nitrile was hydrolyzed with aqueous alkali. It was found that greater yields were obtained if the intermediate ester was not distilled, but was saponified immediately after distillation of the solvent ether. Thus, the methyl ester obtained from 70.0 g. of the dinitrile II was boiled under reflux for two and one-half hours with a solution of 18 g. of sodium hydroxide in a mixture of 400 ml. of water and 10 ml. of ethanol. Upon acidification of the cooled alkaline solution with dilute hydrochloric acid, a colorless oil precipitated which was separated with two 75-ml. portions of ether. The extract was dried over magnesium sulfate and the ether distilled, leaving 72.7 g. (97%) of an oily residue. The product, γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid XI, did not crystallize on standing and was not purified further. Derivatives prepared for characterization could not be crystallized.

**1-Cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic Acid (VI). A. Formylation.**—Sodium methoxide was prepared from 4.6 g. of sodium (0.2 mole) and absolute methanol. Then, at room temperature, a solution of 33.5 g. of the nitrile-ester III (0.1 mole) and 14.8 g. of ethyl formate (0.2 mole) in 100 ml. of dry ether was added to a vigorously stirred suspension of the sodium methoxide in 100 ml. of dry ether. After one and one-half hours, an additional 0.2 mole of ethyl formate was added and the stirring continued for another hour, at which time all suspended material was in solution. The solution was allowed to stand for fifteen hours; then 200 ml. of cold water was added and the layers separated. The aqueous layer was washed once with 50 ml. of ether and this extract combined with the original organic layer. From this ether solution there was obtained 5.6 g. of unchanged III which was pure enough for further use. The aqueous layer was acidified with dilute acetic acid and extracted with two 75-ml. portions of ether. The extract was washed once with 50 ml. of saturated sodium bicarbonate solution, dried, and the solvent evaporated. There was obtained 29.2 g. of the formyl derivative, as a pale yellow oil. The yield was 80% or 97% based on unrecovered nitrile-ester.

**B. Cyclization.**—A solution of 64.7 g. of the formyl derivative in 60 ml. of glacial acetic acid was added to a mixture of 175 ml. of 85% phosphoric acid and 45 ml. of concentrated sulfuric acid, keeping the temperature below 0°. The solution was allowed to stand at −5° for thirty minutes and 1.5 hours at room temperature. Pouring upon ice produced a viscous gum which was separated with three 100-ml. portions of ether. The extract was washed once with 75 ml. of 5% sodium hydroxide solution and then concentrated. The residue was heated under reflux for one and one-half hours with a solution of 16 g. of sodium hydroxide in 600 ml. of water and 20 ml. of ethanol. Acidification of the hot solution produced a gum which crystallized after standing twenty-four hours in an ice-chest. The dried crystalline **1-cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-3,4-dihydro-3-naphthoic acid** melted at 165–166° and weighed 55.2 g. (93%). Recrystallization from dilute acetic acid raised the melting point to 167–168°.

*Anal.* Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39. Found: C, 65.31; H, 6.35.

**C. Reduction.**—A solution of 17.0 g. of the acid in 150 ml. of glacial acetic acid was hydrogenated in a low-pressure apparatus in the presence of 5% palladium–carbon catalyst at 65°. The catalyst was removed by filtration and the filtrate concentrated in a current of air on a steam cone. The crystalline residue was fractionally crystallized from dilute acetic acid in an effort to isolate each of two possible diastereoisomers. The melting points of three crops (*ca.* 129–131°) were almost the same, and the filtrates yielded a compound which was apparently identical with that obtained in the first three crops but less pure. It is believed that one isomer is formed exclusively. Recrystallization raised the melting point to 131–132°. The yield of VI was 17.0 g.

*Anal.* Calcd. for $C_{18}H_{23}O_5N$: C, 64.84; H, 6.95. Found: C, 64.75; H, 6.76.

**Conversion of VI to 1-Carboxy-3,1-acetyliminoethano-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (IXb).**—A mixture of 2 ml. of thionyl chloride and 1.65 g. of VI was allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump and the residual acid chloride taken up in 25 ml. of dry reagent-grade acetone. The solution was chilled in an ice-bath, and a solution of 0.73 g. of sodium azide in 2 ml. of water was added with vigorous stirring. After fifteen minutes the mixture was diluted with 75 ml. of cold water and the crude azide separated with three 25-ml. portions of ether. The extracts were washed once with saturated sodium bicarbonate solution and dried for fifteen minutes over magnesium sulfate. To the ether extract was added 25 ml. of absolute ethanol and the solution slowly distilled on a steam cone through a short column. The residue of the **ethyl urethan** weighed 1.8 g. (95%). The residue was then boiled vigorously under reflux with 20 ml. of 48% hydrobromic acid for four hours, allowing the initial volatile products of reaction to escape from the reflux condenser. The dark solution was diluted with 50 ml. of hot water, treated with carbon and the colorless filtrate made slightly alkaline with solid sodium bicarbonate. Dilute hydrochloric acid was then added until the filtrate was acid. The acidified filtrate was boiled under reflux with 5.0 g. of sodium acetate trihydrate for 1.5 hours; the addition of sodium acetate brought the *p*H to approximately 5. The cooled solution was then treated with 2 ml. of acetic anhydride and solid sodium bicarbonate was added with stirring to keep the mixture alkaline (*p*H 7–8). After fifteen minutes, a further 2-ml. portion of acetic anhydride was added. After an additional fifteen minutes, the solution was acidified with dilute hydrochloric acid and extracted with four 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and evaporated, leaving a crystalline residue weighing 1.50 g. This material was purified by recrystallization from dilute acetic acid. The melting point of the pure compound varied from 258 to 262° (dec.) depending upon the rate of heating of the bath.

*Anal.* Calcd. for $C_{17}H_{19}O_6N$: C, 61.25; H, 5.74; N, 4.22. Found: C, 61.21; H, 5.68; N, 4.26.

Structure IXb, with the phenolic hydroxyl group acetylated (*viz.*, $C_{19}H_{21}O_7N$) requires: C, 60.79; H, 5.64; N, 3.73.

The presence of a phenolic group in this product was indicated by the addition of either diazotized sulfanilic acid or diazotized aniline to a freshly prepared alkaline solution of the compound; a deep orange color resulted. A small amount of the azo dye from diazotized *p*-nitroaniline was isolated in solid form, but it proved difficult to purify and was not characterized further.

**4-Cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XII).**—A solution of 63.0 g. of crude γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid (XI) in 50 ml. of

absolute ether was treated with 30 ml. of thionyl chloride and three drops of pyridine. After standing for fifteen hours, the volatile constituents were removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 600 ml. of dry thiophene-free benzene and chilled until the solvent began to crystallize. Then a solution of 40 ml. of stannic chloride in 40 ml. of benzene was added rapidly with shaking and the mixture allowed to stand in the ice-bath for fifteen minutes. The yellow complex was destroyed by pouring upon a mixture of 50 ml. of ether, 100 ml. of concentrated hydrochloric acid, and ice. The organic layer was then separated and washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. Drying, followed by evaporation of the solvent, left an oil which was distilled at reduced pressure. The fraction boiling at 192–198° (0.4 mm.) was collected as product; the yield was 42.2 g. (71%). The pale yellow oil solidified on standing and melted at 67–68° after recrystallization from cyclohexane–petroleum ether.

*Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.30; H, 6.98. Found: C, 67.14; H, 6.89.

**Nitrosation of the Tetralone XII.**—Various conditions and methods were tried without good results. Nitrosation with an ester of nitrous acid in the presence of dry hydrogen chloride produced only resinous products. In the presence of sodium alkoxides with either freshly prepared butyl or isopropyl nitrite, small amounts of the desired oximinoketone XIII were obtained. The yields in all cases were too low to warrant continuance of the synthesis along this path. The following procedure is an example of a successful experiment. A solution of 1.5 g. (0.005 mole) of XII and 0.23 g. of sodium in 50 ml. of absolute ethanol was prepared. Then, 1.5 g. (0.0075 mole) of freshly prepared *n*-butyl nitrite was added, and the mixture was allowed to stand at 5° for two days. The alcohol solution was diluted with an equal volume of cold water and extracted twice with 30-ml. portions of ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted three times with 30-ml. portions of ether. Drying, followed by evaporation of the solvent, left 1.5 g. of a red oil which partially solidified on standing. Trituration with ether provided 0.15 g. of pale yellow **2-nitroso-4-cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XIII)** which melted with darkening at 154–155° after three recrystallizations from ethyl acetate–petroleum ether.

*Anal.* Calcd. for $C_{17}H_{20}O_5N_2$: C, 61.43; H, 6.07. Found: C, 61.33; H, 5.81.

## Summary

A method leading to a compound containing a fused-ring tetralin–piperidine system, similar to part of the morphine ring system, has been developed.

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# The Preparation of the $C_{10}$ Monocyclic Aromatic Hydrocarbons

BY S. F. BIRCH, R. A. DEAN, F. A. FIDLER AND R. A. LOWRY

## Introduction

A comparatively elaborate program has been carried out over a number of years to produce a supply of hydrocarbons in a high degree of purity required in connection with spectroscopic analysis and other analytical problems. Although interest in the aromatic series at first centered primarily round the hydrocarbons in the $C_6$ to $C_9$ range, it was later found desirable to include the $C_{10}$ compounds. At the time this work was commenced, no source of these hydrocarbons was available, and the physical data reported in the literature were extremely scanty and contradictory.

The present paper describes in general the methods and techniques employed in these laboratories for their preparation. Possibly its chief interest is on account of the steps taken at each stage to ensure that the intermediate compounds were satisfactorily purified before proceeding to the next step in the synthesis. Particular emphasis was placed on the determinations of the physical constants and purities of the intermediates at all stages of their purification and as a result the densities, refractive indices and freezing points of many compounds of known purity are recorded for the first time. At any point at which an intermediate proved relatively impure, it was possible to continue purification until a satisfactory product had been obtained. Only when a following stage permitted the easier separation of impurities was the synthesis continued without satisfactory purification being attained. Thus in some cases it was more satisfactory to purify the carboxylic acid than the nitrile from which it was obtained.

The scale of the preparation was based upon a quantity of 1500 to 2000 ml. of final hydrocarbon in a satisfactory state for purification. This quantity is appreciably smaller than that generally made available to Rossini and his co-workers for purification at the National Bureau of Standards and it would have been desirable to increase this quantity two- or three-fold. Unfortunately, the effort necessary for preparations on this scale was not available. It was felt, however, that taking considerable care in the purification of the intermediates would in great measure offset the smaller quantity of hydrocarbon available for final treatment.

The methods chosen as being most satisfactory were made as general as possible so that they would be applicable to the preparation of more than one hydrocarbon. By so doing, not only was the working out of new techniques largely avoided but the same apparatus could frequently be employed for a number of preparations. Routes were selected which enabled readily avail-

able and easily purified starting materials to be employed for the synthesis. Thus it will be observed that amines formed the most common class of starting materials, since these can readily be purified in bulk by crystallization of their salts or acyl derivatives.

Care was taken to avoid reactions in which the possibility of isomerization was likely to occur at any stage or in which impurities separated only with difficulty from the final products, would be formed. Thus, the Friedel–Crafts method for preparing substituted ketones, *e.g.*, *p*-ethylacetophenone from acetyl chloride and ethylbenzene with aluminium chloride, was avoided, since previous experience had shown that this reaction tends to produce a mixture of isomers. Also, an early batch of *n*-butylbenzene was prepared by the Wurtz–Fittig reaction using bromobenzene and *n*-butyl bromide. The purification of the hydrocarbon obtained by this method proved so difficult, owing to the presence of halogen compounds in the product, and the yield was so poor, that this reaction was avoided in further syntheses. The low yield obtained in this reaction is in agreement with the findings of Karabinos, Serijan and Gibbons[1]. Still another reaction which was avoided was that exemplified by the Grignard condensation of benzylmagnesium chloride and diethyl sulfate for the production of *n*-propylbenzene. This preparation had been carried out several years ago in these laboratories but the purification of the hydrocarbon proved extremely difficult with the columns then available. At the time, this was assumed to be due to halogen substitution in the benzene ring but a recent publication[2] has shown that in this reaction, a certain amount of rearrangement occurs giving *p*-ethyltoluene as well as *n*-propylbenzene.

A further point which influenced the choice of route was that, as far as possible, the stages involved should be adaptable to relatively large-scale laboratory operation. Thus the reactions which were found to be most applicable and were repeatedly used included the diazo reaction, Grignard condensations, ketonization by passage of mixed acids over a thoria catalyst and Clemmensen reductions.

## Experimental

For simplicity, since more than one hydrocarbon was often prepared by the same route, the general method adopted is described once only and details of physical properties and yields of intermediates are quoted for each individual hydrocarbon. Thus the route

Amine ⟶ Nitrile ⟶ Acid ⟶ Ketone ⟶ Hydrocarbon

was used for *p*-diethylbenzene, 1,2-dimethyl-3-ethylbenzene, 1,2-dimethyl-4-ethylbenzene, and 1,4-dimethyl-2-ethylbenzene while the route

Amine ⟶ Nitrile ⟶ Ketone ⟶ Hydrocarbon

was employed for *o*-diethylbenzene, 1,3-dimethyl-4-ethylbenzene, 1,3-dimethyl-5-ethylbenzene and the three methyl-*n*-propylbenzenes.

**Conversion of Amines to Ketones via Nitriles and Acids.**—The procedures used for the conversion of the various toluidines, xylidines and ethylanilines to their corresponding ketones through the nitriles and carboxylic acids followed very closely on those described in Organic Syntheses.[3] The hydrolysis of the nitriles to carboxylic acids by 75% sulfuric acid worked perfectly satisfactorily in all the cases tried except for *m*-2-xylonitrile. When this nitrile was heated with the acid, the only recoverable product was *m*-xylene.

Since pumice was unobtainable when much of the work was carried out (1942), the thoria catalyst used for the conversion of the carboxylic acids into substituted acetophenones was supported on unglazed porcelain (approximately 0.25 inch). Furthermore, owing to the low solubility of many of the acids in glacial acetic acid, it was necessary to increase the mole ratio of acetic acid to carboxylic acid to 8 to 1. Even so, in certain instances it was essential to provide the dropping funnel with a heating jacket in order to prevent crystallization and subsequent blockage. A reaction tube 48 inches long and 1.5 inches in diameter, and holding approximately 500 ml. of the impregnated unglazed porcelain, was employed. With a new batch of catalyst it was found that no more than about 500 to 600 ml. of the mixed acids could be put through the reactor tube in eight hours, otherwise a considerable portion passed through unchanged. However, when the catalyst had been in use for several days, the rate could be almost doubled. The most satisfactory method of arranging the processing and regeneration was to carry out the ketonization during the day and regenerate the catalyst each night by drawing through air at a temperature of between 500 and 550°.

**Reaction of Nitriles with Alkylmagnesium Halides.**—In the production of an arylalkyl ketone from a nitrile and a Grignard reagent, it has been observed that the best yield is obtained by the use of an aryl nitrile and aliphatic Grignard rather than an aromatic Grignard and alkyl nitrile.[4] The procedure adopted for the Grignard condensations described here was based on a private communication received from Dr. G. Baddeley.

A quantity of methylmagnesium (or ethylmagnesium) chloride was prepared in the usual manner by passing methyl (or ethyl) chloride into a stirred suspension of magnesium turnings in absolute ether. The nitrile (1 mole to each 1.2 moles of Grignard) was then added with stirring over a period of one hour. During the addition, the reaction product became yellow but no temperature rise was observed.

After stirring for seventeen to twenty hours, the magnesium complex was decomposed to the ketimine by pouring on to crushed ice and the precipitated magnesium compounds were dissolved by the subsequent addition of dilute sulfuric acid. During this process, the ethereal layer changed in color giving a green solution. The combined aqueous and ethereal layers were heated on a steam-bath for one and a quarter hours during which time the ether distilled off and the ketimine was hydrolyzed to give an upper layer of ketone.[5]

The ketone was separated off, the aqueous layer extracted with ether and the combined ketone and extract dried. After removal of the solvent the residue was distilled under reduced pressure.

**Clemmensen Reduction of the Ketones to Hydrocarbons.**—The method which was found most satisfactory and which gave good yields of hydrocarbons from the ketones was the modification of the Clemmensen reduction described by Brady and Day.[6]

(1) Karabinos, Serijan and Gibbons, THIS JOURNAL, **68**, 2107 (1946).

(2) Burtle and Shriner, *ibid.*, **69**, 2059 (1947).

(3) "Organic Syntheses," Coll. Vol. I, 1943, p. 500; Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 389 and 588.

(4) Baddeley, *J. Chem. Soc.*, **147**, 232 (1944).

(5) An evolution of ammonia at this stage indicated that an insufficient quantity of acid had been used and that more should be added.

(6) Brady and Day, *J. Chem. Soc.*, **137**, 114 (1934).

**Purification.**—In almost all cases the purification of the hydrocarbons obtained in the last stages of the syntheses comprised refluxing over sodium for several hours, distilling to as small a residue as possible and fractionating in 50- or 100-plate columns. Recently, the 100-plate columns have been modified to operate at reduced pressures and, as a result, some of the higher boiling aromatic hydrocarbons have been fractionated at 50 mm. or 100 mm. instead of at 760 mm. From these distillations, the final "best" samples were obtained by bulking fractions of constant boiling point and constant refractive index. In a number of cases, freezing points of individual fractions were used as an additional check.

### Tetramethylbenzenes

**1,2,4,5-Tetramethylbenzene (Durene).**—The alkylation of a mixed coal-tar *meta/para*-xylene cut was carried out as described by Smith.[7] The yield of tetramethylbenzenes obtained from a number of runs varied from 8.3% to 43% based on the xylene taken while the yield of crude durene varied from 2% up to 15.3%. The average yield of tetramethylbenzene cut from nine thirty mole runs was 17% theoretical.

Cooling the mixture to −10° brought about the crystallization of the durene, which was filtered off and crystallized three times from ethanol and finally from benzene. The mother liquors were used for the preparation of prehnitene and isodurene (see below). The yield of pure durene (no. 1129) from 28.6 kilograms of xylene was 1470 g.

**1,2,3,4-Tetramethylbenzene (Prehnitene).**—The experimental procedure for the conversion of durene and isodurene sulfonic acids by the Jacobsen reaction into prehnitene sulfonic acid varied slightly from that given in "Organic Reactions."[8] It was found that the reaction between the acid and hydrocarbon was too violent to allow shaking in a separating funnel, and consequently the sulfonation was carried out in a wide-mouthed bottle with efficient stirring. The starting material for this preparation was the mother liquors from the tetramethylbenzenes, obtained by the alkylation of xylenes, after filtration of the durene.

The prehnitene sulfonic acid from 750 g. of hydrocarbon was hydrolyzed by dissolving in 2 liters of water and allowing this aqueous solution to drip into sulfuric acid (600 ml. of 96% acid and 400 ml. of water) which was maintained at 140–150°. During the hydrolysis, a stream of super-heated steam was blown through the reaction mixture, the prehnitene thus being steam distilled over as rapidly as formed. The yield of crude prehnitene thus obtained was 1564 g. from 2350 g. of mixed durene–isodurene. Final purification was effected by distillation in a 100-plate column at 48 mm. pressure.

**1,2,3,5-Tetramethylbenzene (Isodurene): First Method, via Bromomesitylene.**[9]—The bromination of mesitylene proceeded satisfactorily and the crude bromocompound, which was obtained in 75 to 80% yields, was fractionated in a 20-plate column under reduced pressure. The fractions, which were bulked together, boiled at 135.5° at 50 mm. pressure and had a constant refractive index $n^{20}D$ of 1.5520.

Reaction of the Grignard compound of the bromomesitylene with dimethyl sulfate[9] gave a 55% yield of crude isodurene (600 g.) which on fractionation in a 50-plate column at 36 mm. pressure gave 308 g. of hydrocarbon. The purity of this hydrocarbon as indicated by its freezing point was 99.8% by weight.

**Second Method, by Alkylation of Xylene.**—The mother liquors, after filtration of crude durene from the tetramethylbenzene fractions, were twice fractionated in a 100-plate column at 100 mm. pressure.

TABLE I

PHYSICAL CONSTANTS OF DURENE, PREHNITENE AND ISODURENE

| | | Durene no. 1129 | Prehnitene no. 1130 | Isodurene: From bromomesitylene no. 1131 | Isodurene: By fractionation no. 1134 |
|---|---|---|---|---|---|
| B. p. | °C. | 196.85 | 205.10 | 198.15 | 198.15 |
| | Mm. | 760 | 760 | 760 | 760 |
| | °C. | .... | 115.3 | 104.5 | 120.0 |
| | Mm. | .... | 49 | 36 | 73 |
| $n^{20}D$ | | .... | 1.5203 | 1.5130 | 1.5130 |
| $d^{20}$ | | .... | 0.9046 | 0.8905 | 0.8904 |
| F. p., °C. | | 79.09 | −6.33 | −23.81 | −23.77 |
| Estimated purity, wt. % | | 99.6 | 99.8 | 99.8 | 99.88 |

(7) "Organic Syntheses," Coll. Vol. II, p. 248.

(8) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 382.

(9) "Organic Syntheses," Coll. Vol. II, pp. 95 and 360.

### Ethylxylenes

#### 1,3-Dimethyl-4-ethylbenzene

***m*-4-Xylidine (1,3-Dimethyl-4-aminobenzene): 2,4-Dimethylbenzonitrile.**—Approximately 15 kilograms of technical *m*-4-xylidine acetate was crystallized once from petroleum ether which served to remove most of the attached oil. The amine was then regenerated from the acetate, distilled at 30 mm. pressure and converted to the hydrochloride. Crystallization of this salt from 5% hydrochloric acid gave a final material (7,931 g.) of melting point 161–162°. The yield of nitrile from the hydrochloride *via* the Sandmeyer reaction was 52.4%.

**2,4-Dimethylacetophenone.**—The product from the Grignard reaction contained a mixture of the ketone and unchanged nitrile and these proved very difficult to separate by distillation. However, trial Clemmensen reductions on the mixture indicated that although the ketone was reduced to hydrocarbon, the nitrile remained unaffected. Consequently the whole of the mixture (2,473 g.) was reduced and the reaction product distilled at a pressure of 140 mm. The hydrocarbon boiled at 130° at this pressure and the residue which remained consisted almost entirely of unreacted nitrile.

#### 1,2-Dimethyl-4-ethylbenzene

**4-Nitro-*o*-xylene. (1,2-Dimethyl-4-nitrobenzene).**—*o*-Xylene (19,150 g., purity 99.92%) was nitrated according to the method of Emerson and Smith.[10] The crude nitroxylenes (21,622 g.) were fractionated in a 7-ft. all-glass helix-packed column under reduced pressure when the 3-nitro compound (11,020 g.) was taken overhead and the 4-nitro-*o*-xylene left as a residue. The latter was distilled from a Claisen flask at 12 mm. pressure, the distillate solidifying on cooling. Final purification was effected by crystallization from ethanol, the recrystallized 4-nitro-compound weighing 8,122 g.

***o*-4-Xylidine (1,2-Dimethyl-4-aminobenzene).**—Reduction of the nitro compound was carried out with hydrogen in a stirred autoclave using a Raney nickel catalyst, the pressure employed being 1500 lb. per sq. in. As soon as the reaction commenced, usually at 90 to 100°, the temperature rose very rapidly due to the strongly exothermic nature of the reaction, and the external heating was stopped. By regulation of the hydrogen pressure and the rate of stirring, the temperature was maintained at 150 ± 2°.[11] Before the amine solidified, the product was removed from the autoclave, steam distilled and then distilled under reduced pressure. Crystallization of the crude amine from 60–80° petroleum ether gave 4,930 g. of purified *o*-4-xylidine.

**3,4-Dimethylbenzonitrile: 3,4-Dimethylbenzoic Acid.**—The Sandmeyer reaction on *o*-4-xylidine gave a 43.5% yield of nitrile (2,015 g.) and hydrolysis of this material gave a 70% yield of acid melting at 164°.

(10) Emerson and Smith, THIS JOURNAL, **62**, 141 (1940).

(11) It is important that the temperature is not allowed to fall below 145° whilst the hydrogenation is proceeding otherwise the reaction rate slows down considerably and can only be raised again with difficulty.

**3,4-Dimethylacetophenone.**—The acetic acid solution of the 3,4-dimethylbenzoic acid (150 g. in 500 ml. of acetic acid) was maintained at a temperature of approximately 60° to avoid crystallization of the xylic acid. The pure ketone (906 g.), obtained from 1,560 g. of acid, had the physical properties given in Table II.

### 1,3-Dimethyl-5-ethylbenzene

***m*-5-Xylidine (1,3-Dimethyl-5-aminobenzene).**—The most satisfactory method for the preparation of this amine was by the direct amination of 1,3,5-xylenol. Amination of this xylenol, with ammonia and ammonium chloride under pressure, had previously been studied by Morgan and Pratt[12] who found that treatment with ammonia alone at 350° for eight hours gave a 20% yield of the required xylidine.

Various catalysts have been recommended to increase the production of *m*-5-xylidine, chiefly chlorides of such metals as zinc, iron, etc., but a preliminary experiment using ferric chloride (5% by weight) yielded mostly the secondary base and very little xylidine. To avoid formation of the secondary amine, it was therefore decided to use no catalyst at all but merely to heat the xylenol with ammonia, recover the unchanged starting material from the base and reaminate.

The aminations were kindly carried out by Dr. Hardy at the Chemical Research Laboratory, Teddington, England, in an 18-liter autoclave equipped with a stirrer. Commercially "pure" 1,3,5-xylenol (6,530 g.) and liquid ammonia (2,025 g.) were weighed into an autoclave and stirring was commenced whilst cold and continued throughout the warming up period. The time taken to reach the reaction temperature of 350° was approximately six hours and at this temperature the pressure was of the order of 200 to 250 atmospheres. The autoclave was maintained at 350 to 360° for eight hours and was then allowed to cool. At the end of each run, the excess of ammonia was blown to waste and the autoclave flushed out with a current of air.

The crude product was dissolved in 60–80° petroleum ether at 35 to 40°, and washed several times with dilute hydrochloric acid until all the amine had been extracted. The acid extracts were neutralized with caustic soda and the amine, which was recovered by steam distillation, was distilled under reduced pressure. Approximately 25% of the amination product was recovered as crude xylidine. The unchanged xylenol crystallized out from the petroleum ether solution on cooling and was filtered off.

A further batch of xylidine was prepared employing only xylenol recovered from the earlier runs. On working up the product, it was discovered that the yield of xylidine had increased to 70 to 75%, the weight of crude xylidine obtained from 7,138 g. of xylenol being 4,900 g. This increased yield of amine obtained indicated that the recovered xylenol must have contained some material which was capable of catalyzing the amination reaction.[13]

The crude *sym*-xylidine (11,400 g.) was converted to the formyl-derivative, which was crystallized from methanol to constant melting point (76%). The final amine (9,274 g.) was obtained by steam distilling the pure formxylidide (11,680 g.) from caustic soda solution.

**3,5-Dimethylbenzonitrile.**—The yield of nitrile based on amine was 45% of the theoretical.

**3,5-Dimethylacetophenone.**—A preliminary experiment was carried out using the conditions employed for the *m*-4-xylonitrile, but the yield of ketone was only of the order of 50%. In addition to the expected ketone, a small amount of yellow solid separated during the decomposition of the ketimine. Analysis showed this material to be trixylyldiazine produced from two molecules of nitrile and one of ketimine. It was found that the best method of carrying out the Grignard reaction on symmetrical xylonitrile was to use a considerable excess of methylmagnesium iodide over that theoretically required. Using a 2.5 to 1 mole ratio of Grignard to nitrile, the yield of ketone was 63%. The yield of ethylxylene from the ketone was 82%. A high-boiling residue, obtained from the fractionation of the crude hydrocarbon, was shown to contain a solid hydrocarbon (m. p. 277.5°) believed to be trixylylbenzene.

### 1,4-Dimethyl-2-ethylbenzene

***p*-Xylidine (1,4-Dimethyl-2-aminobenzene): 2,5-Dimethylbenzonitrile.**—The hydrochloride of this base was obtained by crystallization of a batch of commercial *p*-xylidine hydrochloride (as obtained by treatment of coal-tar xylidines with hydrochloric acid) from dilute hydrochloric acid. The free base regenerated from the hydrochloride (m. p. 223°) had the physical properties shown in Table II. The yield of nitrile from amine in this case was only 38%.

Although the purity of this nitrile was only 96.0%, no further purification was attempted since it was considered that this could be most satisfactorily carried out at the next stage.

**2,5-Dimethylbenzoic Acid.**—Hydrolysis of the nitrile (2,600 g.) by the standard procedure gave 2,5-dimethylbenzoic acid, which was crystallized to a constant melting point of 132°.

**2,5-Dimethylacetophenone.**—Ketonization of the above acid with acetic acid over thoria produced 2,5-dimethylacetophenone in 69% yield

### 1,2-Dimethyl-3-ethylbenzene

***o*-3-Xylidine (1,2-Dimethyl-3-aminobenzene): 2,3-Dimethylbenzonitrile.**—This was obtained by reduction of 3-nitro-*o*-xylene, the preparation of which has already been described, with hydrogen in the presence of Raney nickel under conditions similar to those used for *o*-4-xylidine. Purification of the amine was effected through its sulfate, the *o*-3-xylidine sulfate being much less soluble in water than the *o*-4-salt.[14] The amine was regenerated from the purified sulfate for the diazotization and Sandmeyer reaction. The yield of nitrile from amine was 27%.

Again, further purification was considered easier at the next stage of the synthesis.

**2,3-Dimethylbenzoic Acid.**—The yield of xylic acid, which was purified to a constant melting point of 143.5°, was 68% based on the nitrile.

**2,3-Dimethylacetophenone.**—The ketone was prepared in the usual way by passage of *o*-3-xylic acid with acetic acid over thoria.

### 1,3-Dimethyl-2-ethylbenzene

***m*-2-Xylidine (1,3-Dimethyl-2-aminobenzene).**—When the preparation of this amine was commenced, it was realized that the most satisfactory method would have been by the nitration of pure *m*-xylene, separation of the 2-nitro-*m*-xylene and 4-nitro-*m*-xylene by fractionation, followed by reduction of the former in a manner similar to that employed for the *o*-xylidines.[15] Unfortunately, at the time, an insufficient supply of pure *m*-xylene was available and the raw material used was a commercially available xylidine mixture even though it was known that the desired amine was present only to a small extent in this product and was contaminated with isomeric amines derived from ethylbenzene, *o*-xylene and *p*-xylene. The separation of *m*-2-xylidine from this mixture was however, relatively easily if tediously effected.

A quantity (80 gallons) of "Xylidine residues," which is the material obtained from coal-tar xylidines after removal of the bulk of the *m*-4- and *p*-xylidines as acetate and hydrochloride respectively, was made available through the kindness of Imperial Chemical Industries, Ltd. (Dyestuffs Division). The method of separation adopted was also suggested by I. C. I. and depended on the isolation of

(12) Morgan and Pratt, *J. Soc. Chem. Ind.*, **51**, 283(T) (1932).

(13) Further work on this process has since been carried out and is covered in British Patent Application No. 17,719/46.

(14) The solubility of *o*-3-xylidine sulfate was approximately 200 g. in 3-liters of water at the boiling point.

(15) A report describing German work on the nitration of *m*-xylene and the separation of the nitro-*m*-xylenes at Leverkusen has recently been issued (British Intelligence Objectives Subcommittee Final Report 1146, Published by H. M. Stationery Office, London, 1947).

TABLE II

PHYSICAL CONSTANTS OF THE SIX ISOMERIC ETHYLXYLENES TOGETHER WITH THOSE OF THEIR INTERMEDIATES

| Ethylxylene | 1,3-Dimethyl-4-ethyl | 1,2-Dimethyl-4-ethyl | 1,3-Dimethyl-5-ethyl | 1,4-Dimethyl-2-ethyl | 1,2-Dimethyl-3-ethyl | 1,3-Dimethyl-2-ethyl |
|---|---|---|---|---|---|---|
| Nitro-compound | | | | | | |
| B. p., °C. (mm.) | .... | 130(12) | .... | .... | 116(10)<br>106(5) | .... |
| M. p., °C. | .... | +28.5 | .... | .... | +14.2 | .... |
| $n^{20}D$ | .... | .... | .... | .... | 1.5441 | .... |
| $d^{20}$ | .... | .... | .... | .... | 1.1402 | .... |
| Estimated purity, wt. % | .... | 99.5 | .... | .... | 99.6 | .... |
| Amine | | | | | | |
| F. p., °C. | −14.3 | +48.9 | +9.8 | +14.2 | +3.5[a] | +11.2 |
| $n^{20}D$ | 1.5576 | .... | 1.5581 | 1.5596 | 1.5684 | 1.5610 |
| $d^{20}$ | 0.9763 | .... | 0.9706 | 0.9755 | 0.9931 | 0.9842 |
| Estimated purity, wt. % | 99.0 | 99.4 | 99.6 | 99.0 | 99.3 | 98.9 |
| Nitrile | | | | | | |
| B. p., °C. (mm.) | 112(21) | .... | .... | 104–105(18) | 112(25) | .... |
| F. p., °C. | +23.9 | +65.7 | +42.9 | +11.0 | +16.4 | .... |
| Estimated purity, wt. % | 99.1 | 99.5 | 99.6 | 96.0 | 92.7 | .... |
| Ketone | | | 129(22) | | | |
| B. p., °C. (mm.) | .... | 132(19) | 122(17) | 127(31) | 108(13) | .... |
| F. p., °C. | .... | −5.1 | +22.9 | −18.1 | −14.3 | .... |
| $n^{20}D$ | .... | 1.5400 | ($n^{25}D$) 1.5276 | 1.5306 | 1.5334 | .... |
| $d^{20}$ | .... | 1.0042 | ($d^{25}$) 0.9879 | 0.9955 | 1.0079 | .... |
| Estimated purity, wt. % | .... | 99.1 | 99.6 | 99.4 | 99.65 | .... |
| Hydrocarbon, no. | 1085 | 1087 | 1088 | 1098 | 1102 | 1103 |
| Sunbury determinations | | | | | | |
| B. p., °C. at 760 mm. | 188.45 | 189.55 | 183.65 | 186.45 | 193.80 | 189.95 |
| M. p., °C. | −63.01 | −67.09 | −84.43 | −53.74 | −49.54 | −16.34 |
| $n^{20}D$ | 1.5039 | 1.5032 | 1.4981 | 1.5043 | 1.5117 | 1.5107 |
| $d^{20}$ | 0.8759 | 0.8741 | 0.8644 | 0.8777 | 0.8920 | 0.8905 |
| Estimated purity, wt. % | >99.6 | >99.6 | >99.7 | >99.8 | >99.6 | 99.84 |
| N. B. S. determinations[b] | | | | | | |
| B. p., °C. at 760 mm. | 188.41 | 189.75 | 183.75 | 186.91 | 193.91 | 190.01 |
| $dt/dP$ at 760 mm., °C./mm. | 0.055 | 0.0563 | 0.0542 | 0.0533 | 0.0554 | 0.0561 |
| $n^{20}D$ | 1.50383 | 1.50311 | 1.49810 | 1.50435 | 1.51172 | 1.51072 |
| $n^{25}D$ | 1.50156 | 1.50086 | 1.49583 | 1.50199 | 1.50950 | 1.50850 |
| $d^{20}$ | 0.87627 | 0.87452 | 0.86479 | 0.87717 | 0.89209 | 0.89043 |
| $d^{25}$ | 0.87230 | 0.87058 | 0.86078 | 0.87317 | 0.88814 | 0.88642 |

[a] M. p. of formyl derivative 102°. [b] Determinations of the physical constants on the six ethylxylenes, whose preparations are described here, were kindly carried out by Dr. Rossini at the National Bureau of Standards and these are included together with the values obtained at Sunbury.

the *m*-2-xylidine as the nitrate after a preliminary treatment of the residues with sulfuric acid.

The crude amine was purified through its formyl derivative. The total amount of xylidine residues treated was 311 kg. from which 9,510 g. of *m*-2-formxylidide of melting point 164° was obtained. The amine was regenerated in the usual manner by steam distillation in the presence of caustic soda whereby 6,990 g. of *m*-2-xylidine was obtained from 8,750 g. of formyl compound.

While the above work on the isolation of *m*-2-xylidine from the residues was proceeding, it was decided to investigate whether any individual xylidines could be separated from this material by means of fractionation alone. It was found that it was possible by distillation of the residues at a pressure of 10 mm. in a 20-plate column to obtain a low boiling fraction rich in *m*-2-xylidine and a high boiling fraction rich in *o*-4-xylidine. Further work along these lines is given in British Patent Application 15,840/46.

It was found that neither of the schemes already described for going from the amine to the hydrocarbon could be applied to the 1,3-dimethyl-2-ethylbenzene. Using the Grignard technique, no reaction occurred with *m*-2-xylonitrile and the latter was recovered completely unchanged. An attempt was also made to prepare the carboxylic acid from the nitrile but it was found, rather surprisingly, that on hydrolysis the —CN group was eliminated and the only product recoverable was *m*-xylene. The method finally adopted was the conversion of the amine to the iodo compound which in turn was treated with magnesium, the Grignard compound thus formed being then treated with diethyl sulfate.

**2,6-Dimethyliodobenzene.**—The method adopted for the conversion of the amine to the iodo compound was based on that of Hickinbottom.[16] Diazotization of the amine was carried out in the presence of sulfuric acid and the diazo solution reacted with potassium iodide solution at 0°. After allowing to stand overnight, the product was worked up in the usual manner. Fractionation of the crude iodoxylene gave a final material (5857 g. from 6137 g. of *m*-2-xylidine) which was used for the Grignard reaction. Physical properties of 2,6-dimethyliodobenzene; b. p. 102.3° (14 mm.); f. p. + 11.2°; $n^{20}D$ 1.6035; $d^{20}$ 1.6518; estimated purity 99.6% by wt.

**1,3-Dimethyl-2-ethylbenzene.**—The iodoxylene was converted to the magnesium compound which in turn was treated with diethyl sulfate. The crude hydrocarbon obtained from this reaction was given a purification by reflux-

(16) Hickinbottom, "Reaction of Organic Compounds," Longmans-Green, London, 1936, p. 341.

ing for one hour with alcoholic soda followed by steam distillation. Fractionation in a 40-plate column gave a material boiling at 188° and having a refractive index of 1.5110. Further purification of the hydrocarbon, which was yellow in color, was effected by stirring with 20% caustic potash for two hours followed by sodium treatment and fractionation.

### Diethylbenzenes

#### *o*-Diethylbenzene

***o*-Nitroethylbenzene.**—Ethylbenzene was nitrated according to the method of Cline and Reid.[17] The crude nitration product was distilled under reduced pressure from an oil-bath, care being taken that the temperature of the liquid did not exceed 150°. The isomeric nitro compounds were then fractionated in a 7-ft. glass helix-packed column under reduced pressure. Fractions containing the *o*-nitroethylbenzene from several distillations boiling at 119° at 19 mm. were bulked and refractionated, fractions of the distillate of constant refractive index being bulked prior to reduction. Nitration of 12 kg. of ethylbenzene produced 12,104 g. of crude nitroethylbenzenes from which was isolated 4,650 g. of the pure *ortho* isomer.

***o*-Ethylaniline.**—The reduction of the nitroethylbenzene was carried out under conditions similar to those employed for the reduction of the nitro-*o*-xylenes.

***o*-Ethylacetophenone.**—Trial runs indicated that reaction of *o*-ethylbenzonitrile with an excess of methylmagnesium iodide gave a product which was a mixture of ketone and unchanged nitrile in approximately equal proportions and these two compounds proved to be separable by vacuum fractionation. The procedure therefore adopted was to treat the whole of the nitrile with methylmagnesium iodide and separate the unchanged nitrile by fractionation. The latter then reacted further until the final yield of ketone based on reacted nitrile was 62% of the theoretical.

#### *m*-Diethylbenzene

**Fractionation of Commercial Diethylbenzene.**—A commercial diethylbenzene cut, which was kindly given by the Distillers Co., Ltd., was fractionated in a 100-plate column and the fractions boiling between 180.6 and 181.5° and having refractive indices of 1.4954 or 1.4955 were bulked, refluxed with sodium and refractionated. Separation of the *o*- and *p*-isomers from this material could not be effected by fractionation owing to the similarity in their boiling points.

#### *p*-Diethylbenzene

***p*-Nitroethylbenzene.**—The *p*-nitroethylbenzene was obtained with the *ortho* derivative in the product from the nitration of ethylbenzene, this isomer distilling at 125° at 12 mm. Attempts to isolate the *meta* isomer from the intermediate boiling fractions failed. From the 12 kg. of ethylbenzene which was nitrated, the final yield of *p*-nitroethylbenzene was 4,750 g.

***p*-Ethylaniline.**—The amine obtained by the catalytic reduction of the above nitro compound appeared from its freezing point to be relatively impure (92.5%) and further purification was effected through its acetyl derivative (m. p. 89.5° to 90.5°).

***p*-Ethylbenzoic Acid.**—The *p*-ethylbenzoic acid, which was obtained on hydrolysis of the nitrile, was crystallized to a constant melting point of 112°. The yield of pure acid based on nitrile was 85% theoretical.

***p*-Ethylacetophenone.**—*p*-Ethylbenzoic acid and glacial acetic acid (300 g. per liter of acetic acid) were passed over a thoria catalyst at 450° and the resulting product was fractionated in a 25-plate column at a pressure of 20 mm.

### Methyl-*n*-Propylbenzenes

**Methylpropiophenones.**—The three ketones were prepared from the corresponding nitriles and ethylmagnesium chloride using the procedure already described. The reaction was usually carried out in 12-liter flasks, 350 g. of the nitrile being added to the Grignard reagent from 168 g. of magnesium in 3-liters of ether. The crude ketones were fractionated at reduced pressures from which fractions of constant refractive index and constant boiling point were bulked.

(17) Cline and Reid, THIS JOURNAL, **49**, 3150 (1927).

TABLE III

PHYSICAL CONSTANTS OF *o*- AND *p*-DIETHYLBENZENES TOGETHER WITH THOSE OF THEIR INTERMEDIATES

| Diethylbenzene | *Ortho* | *Para* |
|---|---|---|
| Nitro-compound | | |
| B. p., °C. (mm.) | 119(19) | 125(12) |
| $n^{20}D$ | 1.5354 | 1.5455 |
| F. p., °C. | ..... | −12.3 |
| $d^{20}$ | ..... | 1.1183 |
| Estimated purity, wt. % | ..... | 98.4 |
| Amine | | |
| B. p., °C. (mm.) | 108(30) | 111(22) |
| F. p., °C. | −46.6 | −5.85 |
| $n^{20}D$ | 1.5588 | 1.5550 |
| $d^{20}$ | 0.9810 | 0.9690 |
| Estimated purity, wt. % | 99.3 | 97.8 |
| Nitrile | | |
| B. p., °C. (mm.) | 115(29) | *ca.* 121(24) |
| F. p., °C. | −23.6 | −24.2 |
| $n^{20}D$ | 1.5232 | 1.5274 |
| $d^{20}$ | 0.9781 | 0.9716 |
| Estimated purity, wt. % | 96.5 | 97.0 |
| Yield, % theoretical on amine | 50 | 38 |
| Ketone | | |
| B. p., °C. (mm.) | 118(29) | 125(20) |
| F. p., °C. | −19.0 | −20.6 |
| $n^{20}D$ | 1.5249 | 1.5298 |
| $d^{20}$ | 0.9918 | 0.9985 |
| Estimated purity, wt. % | 96.0 | 99.3 |
| Hydrocarbon, no. | 1099 | 1100 |
| B. p., °C. at 760 mm. | 183.30 | 183.60 |
| F. p., °C. | −31.44 | −43.25 |
| $n^{20}D$ | 1.5034 | 1.4947 |
| $d^{20}$ | 0.8805 | 0.8619 |
| Estimated purity, wt. % | 99.85 | 99.65 |

TABLE IV

PHYSICAL CONSTANTS OF *m*-DIETHYLBENZENE

| | |
|---|---|
| B. p., °C. at 760 mm. | 181.25 |
| F. p., °C. | −83.82 |
| $n^{20}D$ | 1.4956 |
| $d^{20}$ | 0.8641 |
| Estimated purity, wt. % | 99.98 |

### Methylisopropylbenzenes (Cymenes)

***o*- and *m*-Cymenes.**—These two isomers were synthesized by identical routes. The toluic acids, obtained from the toluidines *via* the nitriles, were converted to the acid chlorides which in turn were converted to the tertiary alcohols by reaction with methylmagnesium chloride. These reactions were carried out in 10-liter cylindrical copper pots. The products, after working up in the usual way, were mixtures of the olefins and alcohols. Dehydration was completed by distillation at atmospheric pressure through a column packed with short lengths of glass tubing.

***m*-Isopropenyltoluene.**—B. p. 184°; $n^{20}D$ 1.5321, yield 81%.

***o*-Isopropenyltoluene.**—B. p. 170–171°; yield, 79.5%.

The olefins were hydrogenated in an autoclave using a Raney nickel catalyst. Reaction commenced at room

TABLE V

PHYSICAL PROPERTIES OF *o*-, *m*- AND *p*-METHYL-*n*-PROPYLBENZENES AND *o*-, *m*- AND *p*-METHYLPROPIOPHENONES

| | *Ortho* | *Meta* | *Para* |
|---|---|---|---|
| Ketone | | | |
| B. p., °C. (mm.) | 127.5(38) | 134(32) | 135(30) |
| F. p., °C. | −27.6 | − 4.4 | + 7.2 |
| $n^{20}D$ | 1.5250 | 1.5249 | 1.5278 |
| Estimated purity, wt. % | 99.3 | 99.0 | 97.3 |
| Yield, % based on nitrile | 65 | 82 | 97 |
| Hydrocarbon, no. | 1120 | 1124[a] | 1119 |
| B. p., °C. at 760 mm. | 184.75 | 181.75 | 183.10 |
| F. p., °C. | −60.44 | ..... | −63.77 |
| $n^{20}D$ | 1.4998 | 1.4936 | 1.4918 |
| $d^{20}$ | 0.8744 | 0.8610 | 0.8585 |
| Estimated purity, wt. % | 99.4 | ..... | 99.6 |

[a] This hydrocarbon set to a glass on cooling and consequently an estimate of its purity was not possible.

temperature with a hydrogen pressure of 1700 lb./sq. in. and the temperature then rose rapidly to 90° at which it was maintained until hydrogenation was complete. Under these conditions no hydrogenation of the aromatic ring

TABLE VI

PHYSICAL PROPERTIES OF *o*-, *m*- AND *p*-CYMENES

| | *Ortho*, 1073 | *Meta*, 1076 | *Para* From technical cymene, 1044 | *Para* From camphor, 1054 |
|---|---|---|---|---|
| B. p., °C. at 760 mm. | 178.35 | 175.20 | 177.25 | 177.10 |
| F. p., °C. | −71.71 | −63.89 | −68.21 | −70.13 |
| $n^{20}D$ | 1.5006 | 1.4930 | 1.4909 | 1.4910 |
| $d^{20}$ | 0.8766 | 0.8610 | 0.8573 | .08575 |
| Estimated purity, wt. % | 99.96 | 99.96 | 99.8 | 95.8 |

fluxing with 10% by weight of powdered sulfur; (2) treatment with small amounts of sulfuric acid followed by chlorosulfonic acid and an alkali wash; (3) shaking for three hours with potassium permanganate solution; (4) refluxing for five hours over sodium.

Fractions of constant refractive index ($n^{20}D$) were bulked to give 1,013 g. of "best" *p*-cymene.

**Second Method, from Camphor.**—A quantity of *p*-cymene was prepared from camphor and phosphorus pentoxide.[19] The yield of purified material was poor (30%) and the product rather impure.

### Butylbenzenes

***n*-Butylbenzene: First Method, *n*-Butyrophenone.**—*n*-Butyrophenone was prepared in the usual manner by the reaction of *n*-butyryl chloride and benzene in the presence of aluminium chloride. Properties of ketone: b. p. 142° at 50 mm., 128° at 27 mm., $n^{20}D$ 1.5198–1.5199.

The hydrocarbon obtained by reduction of the ketone was extremely sensitive to oxidation by air and had to be freshly distilled before the physical constants were determined.

**Second Method, Bromobenzene.**—The product from the reaction of bromobenzene and *n*-butyl bromide[20] was obtained in poor yield and was of low purity.[21]

**Isobutylbenzene.**—Isobutyrophenone was prepared from isobutyryl chloride and benzene as for *n*-butyrophenone. The pure ketone, which was obtained by fractionation of the product at 50 mm. pressure, amounted to 1,653 g. Properties of ketone; b. p. 131.0° at 50 mm.; $n^{20}D$ 1.5176.

***s*-Butylbenzene: First Method, by Alkylation.**—The conditions used for the alkylation of benzene with 2-butanol were those given by Meyer and Bernhauer.[22] The yield of crude *s*-butylbenzene (1,710 g.) on benzene taken was 52% of the theoretical.

Purification was effected by vigorous stirring with concentrated sulfuric acid (1% by volume of 96% acid) followed by removal of the acid, neutralization with sodium hydroxide solution, refluxing with sodium and finally fractionation.

The purity of the hydrocarbon could not be estimated accurately owing to the peculiar shape of the freezing curve but it was not less than 99.75%. The fact that only one isomer is formed by this method of alkylation confirms the findings of both Meyer and Bernhauer and of Nightingale and Smith.[23]

**Second Method, Methylethylphenylcarbinol.**—This carbinol was obtained in 85% yield from acetophenone and

TABLE VII

PHYSICAL PROPERTIES OF THE BUTYLBENZENES

| | B. p., °C. at 760 mm. | F. p., °C. | $n^{20}D$ | $d^{20}$ | Estimated purity, wt. % |
|---|---|---|---|---|---|
| *n*-Butylbenzene | | | | | |
| (a) From butyrophenone, no. 1094 | 183.35 | −87.54 | 1.4897 | 0.8603 | Not less than 99.9 |
| (b) From bromobenzene, no. 1070 | 183.10 | −87.82 | 1.4897 | .8603 | Not less than 98.9 |
| Isobutylbenzene | | | | | |
| From isobutyrophenone, 1092 | 172.85 | −51.59 | 1.4865 | .8535 | 99.98 |
| *s*-Butylbenzene | | | | | |
| (a) By alkylation, no. 1093 | 173.30 | −75.39 | 1.4898 | .8619 | Not less than 99.75 |
| (b) From acetophenone, no. 1082 | 173.30 | −75.30 | 1.4902 | .8622 | Not less than 99.75 |
| *t*-Butylbenzene | | | | | |
| (a) By alkylation, no. 1002 | 169.5 | −58.09 | 1.4926 | .8666 | 99.92 |
| (b) By disproportionation, no. 1001 | 169.45 | −58.34 | 1.4927 | .8667 | 99.66 |

occurred. Yields based on toluic acids; *m*-cymene, 67%; *o*-cymene, 65%.

***p*-Cymene: First Method, from Technical Cymene.**—The commercial material, a by-product from the wood-pulp industry, was fractionated after the following series of refining treatments:[18] (1) steam distillation after re-

(18) Le Fèvre, Le Fèvre and Robertson, *J. Chem. Soc.*, **138**, 480 (1935).

(19) Fittig, *Ann.*, **172**, 307 (1874).

(20) Read and Foster, THIS JOURNAL, **48**, 1606 (1926).

(21) Since this work was completed, it has been observed that 1-phenylbutadiene-1,3 can be obtained in satisfactory yields from cinnamaldehyde. This diene would probably be an excellent starting material for preparing further quantities of *n*-butylbenzene in a high state of purity.

(22) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721 (1929).

(23) Nightingale and Smith, THIS JOURNAL, **61**, 101 (1939).

ethylmagnesium chloride. Properties of carbinol: b. p. 140° at 25 mm.; $n^{20}D$ 1.5198.

The carbinol was dehydrated over activated alumina at 300–350°, and the olefin hydrogenated as for *o*- and *m*-cymenes.

***t*-Butylbenzene: First Method, by Alkylation.**—*t*-Butyl chloride (1.108 g.) was added to a stirred mixture of benzene (5.320 g.) and powdered anhydrous aluminum chloride over a period of two hours. Stirring was continued for a further thirty minutes after which the hydrocarbon was decanted from the catalyst and worked up in the usual manner. The residue in the flask was used as catalyst for eleven similar runs with addition of 20 g. of fresh aluminium chloride in between each batch.

A total quantity of 11 gallons of fractionated hydrocarbon was prepared.

**Second Method. By Disproportionation of *p*-Di-*t*-Butylbenzene and Benzene.**—The conditions used for this reaction were those described by Ipatieff and Corson,[24] approximately 2 kg. of *t*-butylbenzene being prepared by this method. The yield of final hydrocarbon was 85% based on *p*-di-*t*-butylbenzene initially taken.

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(24) Ipatieff and Corson, THIS JOURNAL, **59**, 1417 (1937).

## Summary

Selected methods for the preparation of the twenty-two monocyclic $C_{10}$ aromatic hydrocarbons are described. Selection was based upon readily available starting materials, which could be conveniently purified, and upon reactions easy to carry out on a relatively large scale. Excepting where a required hydrocarbon could be readily separated from a commercially available material by fractionation, *e.g.*, *m*-diethylbenzene, syntheses have been chosen to avoid the presence of impurities in the final hydrocarbon which would prove difficult to separate.

Physical constants have been determined on the hydrocarbons and on most of the amines, nitriles, ketones and nitro compounds which were obtained as intermediates in the syntheses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE]

# Interaction of Homologous Alkyl Sulfates with Bovine Serum Albumin

BY FRED KARUSH[1] AND MARTIN SONENBERG

The study of the structure of the protein molecule as it exists in aqueous solution meets formidable difficulties not only because of the complexity of the structure but also because of the absence of any really direct and general experimental method. It is true, of course, that important structural information has come and more will undoubtedly follow from X-ray diffraction investigations with protein crystals and that much of this knowledge can be carried over to the dissolved molecule. However, it is still an open question whether the diffraction method can disclose the fine details of protein structure, particularly those associated with the configuration of side chains. These elements of structure are undoubtedly of crucial significance in the determination of specificity. In any case, it would appear that the environment of the protein molecule in the crystal is sufficiently different from that in solution that significant limits on the extrapolation from solid to solution must be imposed. It seems very likely that distinctive structural properties would accrue to the protein molecule in the transition from the crystalline to the dissolved state.

One experimental approach which offers promise of obtaining information which can be interpreted in terms of protein configuration is the study of complex formation of protein with small organic ions or molecules of known structure. In the specialized field of immunochemistry this method has been intensively employed[2] and has led to considerable clarification with regard to the problem of serological specificity. It is particularly applicable to the study of serum albumins since these proteins are able to combine reversibly with a great variety of compounds of known structure, in particular, organic anions.[3–7]

In the investigation described here we have studied the reversible binding by bovine serum albumin of an homologous series of straight chain alkyl sulfates. These compounds offer the possibility of distinguishing between polar and nonpolar contributions to the binding. The work was conducted with a view to obtaining the maximum amount of thermodynamic information about the binding process. Earlier studies[8] of the interaction of serum albumin and alkyl sulfates, as well as other synthetic detergents, have involved much higher concentrations of detergent

(1) Investigation conducted during tenure of a Fellowship in Cancer Research of the American Cancer Society, recommended by the Committee on Growth of the National Research Council; present address: Sloan-Kettering Institute for Cancer Research, New York.

(2) K. Landsteiner, "The Specificity of Serological Reactions," Harvard University Press, Cambridge, Mass., 1945.

(3) B. D. Davis, *J. Clin. Invest.*, **22**, 753 (1943).

(4) B. D. Davis, *Am. Scientist*, **34**, 611 (1946).

(5) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946).

(6) I. M. Klotz and J. M. Urquhart, *J. Biol. Chem.*, **173**, 21 (1948).

(7) J. D. Teresi and J. M. Luck, *ibid.*, **174**, 653 (1948).

(8) F. W. Putnam, *Adv. Prot. Chem.*, **4**, 79 (1948).

than employed here. As a result the interpretation of the data in terms of the binding properties of the native protein has been complicated by micelle formation and, in many cases, denaturation.

## Experimental

**Materials.**—The serum albumin used was crystallized bovine serum albumin obtained from Armour & Co. The actual protein content of the powdered material was determined by Kjeldahl analysis using a value of 16.07%[9] for nitrogen. The particular lot of albumin used in these experiments contained 94.5% protein.

The alkyl sulfates ($C_nH_{2n+1}SO_4Na$) employed, sodium dodecyl, sodium decyl and sodium octyl sulfates, were specially purified samples generously supplied by the Fine Chemicals Division of E. I. du Pont de Nemours and Co. The purity of the dodecyl sulfate was checked by determining the additional acidity developed after acid hydrolysis. Accurately weighed samples of about 0.3 g. were placed in Pyrex test-tubes with 5 ml. of 0.1 *N* HCl and 2 ml. of water. The tubes were sealed and kept at 110° for forty-eight hours. After cooling and solidification of the dodecyl alcohol, the aqueous phase was quantitatively transferred and titrated. A value of 99.7% for the purity of the dodecyl sulfate was thus obtained. Other samples of these three materials from the same source have also been analyzed[10] for sodium and on this basis calculated to be practically 100% alkyl sulfate.

**Dialysis Method.**—The binding of alkyl sulfates by albumin was determined by equilibrium dialysis. All the experiments were conducted at *p*H 6.1 with a final buffer concentration of 0.025 *M* phosphate. This concentration was selected so as to be just large enough to render the Donnan correction negligible within the range of protein concentration employed, namely, 0.05 to 0.5%, and permit a maximum free alkyl sulfate concentration. The latter is limited by the salting-out effect of the buffer salt.

The dialysis was carried out with 20 ml. of protein solution in 0.05 *M* phosphate contained in a bag of Visking sausage casing. This bag was placed in a large test-tube with 20 ml. of a solution of alkyl sulfate free of buffer and the tube stoppered with a serum cap. All the phosphate was placed in the protein solution to allow larger initial concentrations of the alkyl sulfate to be used than would be possible if the original sulfate solution were made up in 0.025 *M* phosphate. The tubes were placed on a rocker, with a capacity of 24 tubes, in a horizontal position and gently rocked at a frequency of 1 or 2 cycles per minute. If the bag is prepared so that it is taut and an air bubble is enclosed and if an air space is provided inside the tube, very efficient mixing, both inside and outside the bag, takes place. With this arrangement at room temperature, equilibrium is attained in four hours or less and at low temperature (2°) overnight rocking is more than adequate.

To ensure maximum accuracy protein concentrations were selected so that the concentration of bound anion, wherever feasible, would be two to three times that anticipated for the free anion at equilibrium. This precaution avoids the situation in which the calculation of the amount of bound anion depends on a small difference between two large numbers. The initial outside concentrations of alkyl sulfate were chosen in such a way that the resulting equilibrium values of free anion when plotted as described below would be fairly evenly distributed over the range encompassed by the plot.

Equilibrium controls consisting of alkyl sulfate outside and buffer inside the bag were frequently included in the experiments. In addition the possibility that loss of alkyl sulfate might occur, either by adsorption or chemical reaction, was investigated. It was found that no significant adsorption took place in the range of anion concentration of interest, namely, $10^{-3}$ to $10^{-5}$ *M*. Fortunately also, chemical losses were negligible for these dilute solutions when subjected to room temperature for not more than several hours and to low temperature for not more than two days. It is worth noting, however, that longer exposure at room temperature, say, twenty-four to forty-eight hours, usually led to detectable loss of alkyl sulfate, particularly with the very dilute solutions.

In order to calculate the values of the thermodynamic functions $\Delta H$ and $\Delta S$ for the binding process, experiments were conducted at room temperature (25–28°) and at low temperature (1–2°). For each experiment fresh solutions of protein and alkyl sulfate were prepared and all determinations were done in duplicate. The concentration of free anion in equilibrium with bound anion was obtained by the determination of the concentration of alkyl sulfate anion outside the dialysis bag.

**Analytical Method.**—The investigation reported here required the quantitative measurement of long chain alkyl sulfate concentrations as low as $10^{-5}$ *M*. A search of the literature revealed that no adequate method was available. We therefore undertook the development of a suitable colorimetric method following along lines initiated by Brodie and Udenfriend.[11] The method is based upon the fact that octyl and higher alkyl sulfates form complexes with rosaniline hydrochloride which can be extracted into organic solvents. A detailed description of the method will be published elsewhere. It is sufficient to mention here that the procedure involves the addition of 4 ml. or less of alkyl sulfate solution to 1 ml. of $4 \times 10^{-4}$ M rosaniline hydrochloride in 0.025 *M* phosphate, *p*H 6.1, in a total volume of 5 ml., and the extraction of the colored complex with 5 ml. of a mixed solvent consisting of 50% chloroform and 50% ethyl acetate. The two-phase system is centrifuged and the light absorption of the lower phase, which contains the complex, is measured with a Klett colorimeter using a green filter. The method is suitable for concentrations as low as $10^{-5}$ *M* and has an accuracy of about 2%.

## Results

The protocol with attendant calculations for a typical dialysis experiment is shown in Table I. The values in the first column are simply one-half the initial outside concentrations of alkyl sulfate. The molar concentration of protein is based upon a value of 69,000[12] for the molecular weight of bovine serum albumin. The last two columns give the reciprocal of the average number of anions bound per molecule of protein ($1/r$) and the reciprocal of the free equilibrium anion concentration ($1/c$). These quantities are most convenient for graphical representation of the data. It may be noted that although the concentrations of protein and bound anion shown in columns 3 and 4 may be somewhat in error due to volume changes inside the dialysis bags, the values of $1/r$ and $1/c$ are independent of such variations.

It has been found by Klotz[13] that the value of $r$ depends on the protein concentration as well as on $c$, for the range 0.2 to 1%, in the binding of methyl orange by bovine serum albumin. A few observations with our systems on the effect of protein concentration in the range 0.5 to 0.05% have not revealed any significant dependence of $r$ on protein content, though we have not investigated this question in any great detail.

In Figs. 1 and 2 we present a summary of the

(9) E. Brand, *Ann. N. Y. Acad. Sci.*, **47**, 187 (1946).

(10) F. D. Hoffner, G. A. Piccione and C. Rosenblum, *J. Phys. Chem.*, **46**, 662 (1942).

(11) B. B. Brodie and S. Udenfriend, personal communication.

(12) E. J. Cohn, W. L. Hughes, Jr., and J. H. Weare, THIS JOURNAL, **69**, 1753 (1947).

(13) I. M. Klotz, personal communication.

binding data for sodium octyl, decyl and dodecyl sulfates at room and low temperatures. The experimental results are the points in the plot of $1/r$ *vs.* $1/c$. The reason for this mode of representation will be indicated below.

TABLE I

BINDING OF DECYL SULFATE ANION BY BOVINE ALBUMIN AT ROOM TEMPERATURE IN 0.025 *M* PHOSPHATE BUFFER, *p*H 6.1

| Equil. concn. without protein m./l. $\times 10^5$ | Equil. concn. with protein m./l. $\times 10^5$ | Concn. of bound anion m./l. $\times 10^5$ | Concn. of protein m./l. $\times 10^5$ | Moles anion bound per mole protein, $r$ | $1/r$ | $1/c \times 10^{-4}$ |
|---|---|---|---|---|---|---|
| 80.0 | 43.0 | 74.0 | 6.84 | 10.8 | 0.0925 | 0.232 |
| 50.0 | 17.6 | 64.8 | 6.84 | 9.46 | .1057 | .568 |
| 25.00 | 13.2 | 23.6 | 2.74 | 8.61 | .1161 | .758 |
| 17.50 | 6.84 | 21.3 | 2.74 | 7.77 | .1287 | 1.46 |
| 8.75 | 4.01 | 9.48 | 1.37 | 6.93 | .1444 | 2.49 |
| 7.00 | 2.64 | 8.72 | 1.37 | 6.37 | .1570 | 3.79 |
| 6.25 | 2.10 | 8.30 | 1.37 | 6.06 | .1650 | 4.76 |
| 3.375 | 1.44 | 3.88 | 0.684 | 5.66 | .1765 | 6.95 |
| 3.125 | 1.24 | 3.76 | 0.684 | 5.49 | .1822 | 8.07 |
| 2.875 | 1.06 | 3.64 | 0.684 | 5.32 | .1881 | 9.43 |

Because of the importance of a knowledge of the binding capacity of the protein, several experiments were done at room temperature using 2% protein and as high concentration of decyl and dodecyl sulfates as feasible. For the decyl sulfate salt the maximum equilibrium concentration of the free anion was $1.7 \times 10^{-3}$ *M* and that for the dodecyl sulfate was $3.25 \times 10^{-4}$. Under these conditions values of $r$ very close to 14 but not exceeding it were obtained. It must be emphasized, however, that this figure is not necessarily a maximum one since the data when plotted, for example, in the form of $r$ against log $c$ do not indicate 14 to be a limiting value. The significance of this fact will be explored in the following section.

## Discussion

**General Considerations.**—In order to justify a thermodynamic analysis of our data, it is necessary to show that the binding process is a reversible one. This can be done experimentally by immersing dialysis bags containing protein which have previously been equilibrated against an alkyl sulfate solution into 20 ml. of 0.025 *M* $PO_4$ buffer, *p*H 6.1 and determining the new equilibrium values of $r$ and $c$. The results of such an experiment with dodecyl sulfate at low temperature are shown by the two points in Fig. 2 indicated by arrows. This second equilibration, in contrast to the usual binding experiment, involves a net removal of anion from combination with the protein.

A complication which must be avoided with long-chain anions to permit a thermodynamic treatment is the formation of micelles. This has been achieved in the present study by working well below the critical concentrations[10] for micelle formation, taking into account the effect of salts on these values.[14]

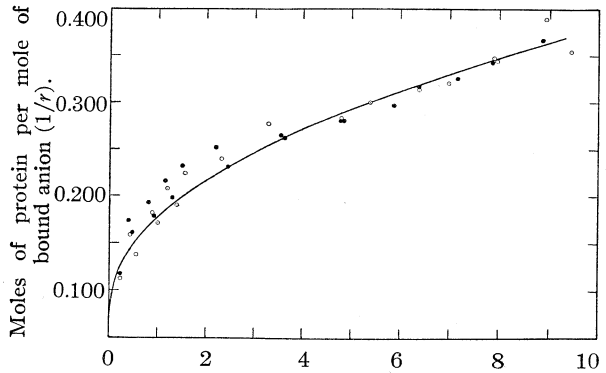



Fig. 1.—Binding data for octyl sulfate: O, low temp.; ●, room temp.

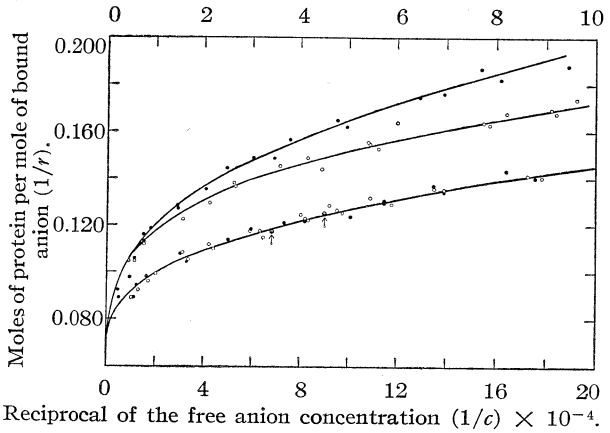



Fig. 2.—Binding data for decyl and dodecyl sulfates; upper two curves and top scale refer to decyl sulfate and lower curve and bottom scale to dodecyl sulfate; reversibility points (see text) indicated by arrows; O, low temp.; ●, room temp.

**Simple Theory.**—The application of the law of mass action to the case of multiple binding leads to the following simple relation between $r$ and $c$ under the conditions that all the binding sites have the same intrinsic association constant $K$ and that, aside from the statistical factor, the free energy of binding to any particular site is independent of binding to other sites.[15,16] The value

$$\frac{1}{r} = \frac{1}{Kn}\,\frac{1}{c} + \frac{1}{n} \qquad (1)$$

of $K$ depends, of course, on the particular system under consideration and $n$ represents the average maximum number of sites per molecule, *i. e.*, the binding capacity. According to equation (1) a plot of $1/r$ *vs.* $1/c$ will give a straight line. From the slope of this line and its intercept with the $1/r$ axis the values of $K$ and $n$ can be obtained. Such

(14) M. L. Corrin and W. D. Harkins, THIS JOURNAL, **69**, 683 (1947).

(15) A. L. von Muralt, *ibid.*, **52**, 3518 (1930).

(16) I. M. Klotz, *Arch. Biochem.*, **9**, 109 (1946).

a procedure has been used by Klotz, Walker and Pivan[5] in their study of the binding of anionic dyes by bovine serum albumin and by Teresi and Luck[7] in an investigation of the binding of other organic anions by the same protein.

As is evident from Figs. 1 and 2 the binding of alkyl sulfates by bovine albumin does not satisfy the conditions noted above since the experimental points deviate significantly from linearity and increasingly so with decrease of $1/c$. This deviation is more striking with decyl sulfate than with dodecyl sulfate because the data for the former cover a wider range of $1/r$. From the shape of the curves it appears that, ignoring the statistical contribution, the binding of each additional anion on an albumin molecule involves a smaller decrease in free energy than the binding of the previous one. There are a number of possible factors which would lead to such an effect and we now proceed to consider them.

**Electrostatic Interaction.**—Studies of the acid–base titration curves of soluble proteins and the effect of ionic strength on these curves have shown that it is necessary to introduce an electrostatic correction to account adequately for the shapes of these curves.[17,18] This correction is associated with the variation of charge on the protein during the titration and is based on the Debye–Huckel theory of interionic attraction.

The contribution of the electrostatic interaction to the free energy of binding has been calculated by Klotz, *et al.*,[5] for the binding to bovine serum albumin of the monovalent anion methyl orange, and the divalent anion azosulfathiazole. More recently Scatchard[19] has developed an explicit relation between $r$ and $c$ containing an electrostatic interaction term which is applicable with high accuracy for values of $n > 4$. This relation can be put in a form analogous to (1) as follows

$$\frac{1}{r} = \frac{1}{Kn}\frac{e^{2w'r}}{e^{w}}\frac{1}{c} + \frac{1}{n} \qquad (2)$$

where $w' = (1 + 1/n)w$ and $w$ is given by

$$w = \frac{\epsilon^2 Z^2}{2DkT}\left(\frac{1}{b} - \frac{\kappa}{1 + \kappa a}\right) \qquad (3)$$

in which $\epsilon$ is the electron charge, $Z$, the charge on the small anion, $D$, the dielectric constant of the medium, $k$, Boltzmann's constant, $T$ the absolute temperature, $b$, the radius of the protein molecule, $a$, the distance of closest approach, and

$$\kappa = \left(\frac{4\pi N\epsilon^2}{1000\ DkT}\right)^{1/2}\Gamma^{1/2} \qquad (4)$$

Here, $N$ is Avogadro's number and $\Gamma$ is twice the ionic strength of the medium. To calculate $w$ we have assumed, following Klotz, *et al.*,[5] a value of 30 Å. for $b$ and 31.5 Å. for $a$. Since $\Gamma$ for 0.025 $M$ $PO_4$ buffer at $p$H 6.1 is 0.0644, we have calculated a value of 0.0451 for $w$ at 27°. This represents an electrostatic free energy contribution of 54 cal./mole for the binding of each additional anion to the protein.

To test the adequacy of the electrostatic interpretation of our results by the application of equation (2), we have plotted our experimental data in the form of $1/r$ *vs.* $e^{2w'r}/c$. For this purpose a value of 10 was assigned to $n$ to obtain $w'$. An examination of such a plot reveals no reduction in the deviation of the data from a straight line. It appears that the electrostatic free energy correction is too small by almost an order of magnitude. Even if $w'$ is treated as a parameter it is impossible to adjust its value so that the experimental points fall on a linear curve. It is clear, therefore, that not only is the electrostatic effect unable to explain our results but that any interaction or correction which takes the mathematical form represented in equation (2) will be unsatisfactory.

There is some question whether any electrostatic correction should be made in our case since Klotz, *et al.*,[5] found, in the presence of phosphate buffer, that the binding of the monovalent anion methyl orange obeyed a linear relation between $1/r$ and $1/c$ without such a correction. We have therefore chosen in the following discussion and calculations to omit further consideration of the electrostatic effect.

**Heterogeneity Theory.**—On *a priori* grounds there is no reason to believe that the intrinsic association constants of all the binding sites are identical. We must therefore consider the possibility that a variation of these constants would account for the shape of our binding curves. Indeed, qualitatively, it is clear that if the binding constants are not the same, the slope of the curve of $1/r$ *vs.* $1/c$ should decrease with increasing $1/c$, as is experimentally the case. Before we attempt a quantitative formulation, we want to consider two other possible effects associated with the paraffin chain character of the anions.

It is well known that due to the large organic groups in these anions, they tend to interact with one another in aqueous systems as evidenced by the formation of micelles. One may ask therefore if the association of one anion on a particular site may not lead with increase in concentration of free anion to the adsorption of at least a second one in the same neighborhood of the protein due to interaction between the paraffin chains. This phenomenon would be similar to micelle formation but might be expected to occur at a somewhat lower concentration due to the immobilization of half of the dimer by the protein. However, it can be inferred from an inspection of our curves that if such were the case significant dimerization should have already occurred at concentrations of $5 \times 10^{-6}$ $M$ for dodecyl sulfate, $3 \times 10^{-5}$ $M$ for decyl sulfate and $1 \times 10^{-4}$ $M$ for octyl sulfate. These values are approximately 1000-fold less than the critical concentrations for micelle formation[9]

(17) R. K. Cannan, *Chem. Rev.*, **30**, 395 (1942).

(18) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943, Chap. 20.

(19) G. Scatchard, *Ann. N. Y. Acad. Sci.*, in press.

and for this reason it appears unlikely to us that such an effect is significant for the interpretation of our results.

Due to the relatively great length of the alkyl sulfate it is imaginable that steric interference may lead to a continuous reduction of binding energy with increase in $r$. That this is probably not important here is indicated by a comparison of the data for decyl and dodecyl sulfates. If one considers a specified range of $1/r$, say 0.100 to 0.140, and compares the curvature exhibited by the experimental points in this range for the two anions, there is no indication of a greater curvature for the dodecyl sulfate. Such a difference would be expected as a consequence of the greater length of the dodecyl anion resulting in more extensive steric interference. The probable absence of steric effects also is suggested by the fact that the value of $\sigma$ (see below) is not greater for dodecyl than for decyl sulfate. The quantity $\sigma$ is a measure of the spread of $K$ values which must be assumed to account for our data in accordance with the heterogeneity theory which we will now discuss.

We take as our model a protein molecule with a large number of binding sites which combine with small ions or molecules independently of each other. We then assume that the number and distribution of the intrinsic binding constants are such as to be adequately described in terms of the free energy of binding by a Gauss error function which when normalized is

$$(1/\sqrt{\pi}\sigma)e^{-[\ln(K/K_0)]^2/\sigma^2} \qquad (5)$$

where $K_0$ is an average binding constant and $\sigma$ measures the range of values of $K$. This formulation is similar to that used by Pauling, Pressman and Grossberg[20] to describe the heterogeneity of binding of hapten by antibody in competition with antigen. In their case the heterogeneity was associated with differences among the antibody molecules whereas we are concerned with differences among the sites on the same molecule. The shape of this distribution function for $\sigma = 1$ to 4 is shown in Fig. 1 of their paper. The fraction of the total number of sites on the molecule which have a particular value of $K$ in an infinitesimal region is given by

$$\frac{dn}{n} = \frac{1}{\sqrt{\pi}} e^{-[\ln(K/K_0)]^2/\sigma^2} d\,[\ln (K/K_0)] \qquad (6)$$

With the aid of this relation and the condition that the sites act independently it is easily shown that the average fraction of sites occupied as a function of $c$ is expressed by

$$\frac{r}{n} = 1 - \frac{1}{\sqrt{\pi}} \int_{-\infty}^{\infty} \frac{e^{-\alpha^2}}{1 + K_0 c e^{\alpha\sigma}}\, d\alpha \qquad (7)$$

in which $\alpha$ has been substituted for $\ln(K/K_0)/\sigma$. For purposes of calculation and plotting it is convenient to put equation (7) in the form

$$\frac{n}{r} = \frac{1}{1 - f(c)} \qquad (8)$$

where

$$f(c) = \frac{1}{\sqrt{\pi}} \int_{-\infty}^{\infty} \frac{e^{-\alpha^2}}{1 + K_0 c e^{\alpha\sigma}}\, d\alpha \qquad (9)$$

Unfortunately, the integral in (9) cannot be evaluated analytically and recourse must be had to numerical or graphical integration for the computation of $f(c)$. Prior to such integration the values of the parameters $K_0$ and $\sigma$ must be fixed. It turns out, however, that $f(c) = 1/2$ for all values of $\sigma$ when $K_0 c = 1$. This means that $K_0$ is equal to the reciprocal of the free anion concentration at which the protein is half-saturated and its value can be obtained directly from the experimental data if the value of $n$ has been previously ascertained. The value of $\sigma$ is taken to be that which gives the best agreement between experimental and calculated binding curves. It is of interest to note that for $\sigma = 0$, $f(c) = 1/(1+K_0c)$ and equation (8) reduces to (1). That is, the simple theory is a limiting case of the more general heterogeneity theory.

The application of equation (8) to experimental binding data is most readily and generally done by preparing theoretical curves of $n/r$ *vs.* $1/K_0c$ for various values of $\sigma$. For this purpose numerical integration was carried out using Weddle's rule[21] with integration limits $-2.4$ to 1.2 or $-2.4$ to 2.4 depending largely on the value of $\sigma$. The theoretical curves are shown in Figs. 3 and 4 for two different ranges of $1/K_0c$. It is important to note that beyond $1/K_0c = 1$, the curves do not deviate much from linearity. In fact, if binding data of not high accuracy were to fall on such a curve, the temptation would be to draw a straight line through the points and conclude that the binding obeys the simple theory. This situation has important implications for the interpretation of data in the literature which we shall discuss below.

On the basis of the curves in Figs. 3 and 4 we have calculated the theoretical curves shown as solid lines in Figs. 1 and 2 using $n = 14$. The values of $K_0$ and $\sigma$ employed are listed in Table II. It is clear that a satisfactory fit of the curves with the data is obtained except possibly for very

TABLE II

CONSTANTS AND THERMODYNAMIC DATA FOR BINDING OF ALKYL SULFATES BY BOVINE SERUM ALBUMIN. THE DATA REFER TO THE BINDING OF ONE MOLE OF ALKYL SULFATE

| Compound | Temperature | $\sigma$ | $K_0 \times 10^{-4}$ | $-\Delta F^0$, kcal. | $\Delta S^0$, E. U. |
|---|---|---|---|---|---|
| Octyl sulfate | Room and low | 4.5 | 0.4 | 5.01[a] | 16.7 |
| Decyl sulfate[c] | Room | 5 | 2.5 | 6.03[a] | 13.3 |
| Decyl sulfate[c] | Low | 6 | 3.4 | 5.70[b] | 13.3 |
| Dodecyl sulfate | Room and low | 5 | 18.2 | 7.22[a] | 24.0 |

[a] Calculated for 27°. [b] Calculated for 2°. [c] $\Delta H^\circ = -2.0$ kcal.

(20) L. Pauling, D. Pressman and A. L. Grossberg, THIS JOURNAL, **66**, 784 (1944).

(21) H. Margenau and G. M. Murphy, "The Mathematics of Physics and Chemistry," D. Van Nostrand Co., New York, N. Y., 1943, Chap. 13.

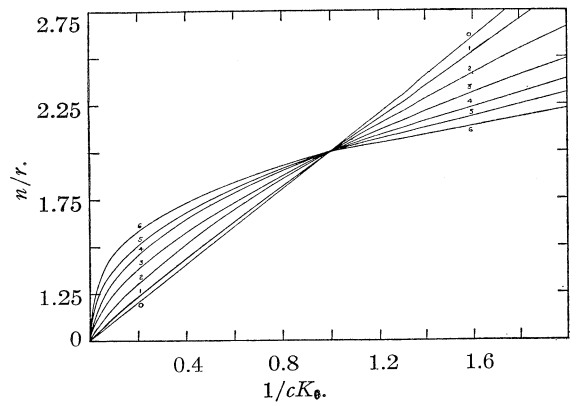



Fig. 3.—Theoretical binding curves for $\sigma = 0$ to 6 for range of high binding.

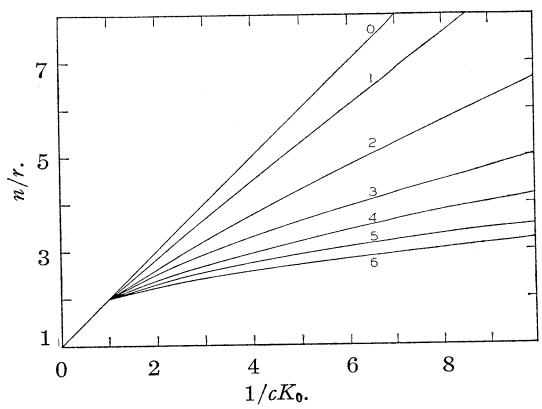



Fig. 4.—Theoretical binding curves for $\sigma = 0$ to 6 for range of low binding.

low values of $1/c$ where the curves tend to be slightly higher than the points. It may be noted that our procedure involves the approximation of substituting a continuous spectrum of $K$ values for what must be a discontinuous set for any particular molecular species of albumin. There is, however, the possibility that crystallized albumin is not molecularly homogeneous with respect to its binding properties. Our analysis would not reveal such a condition because it does not really distinguish between variation of binding energy among the sites on a single molecule as compared to differences among different molecules. However, because of the large range of values of $K$ indicated by values of $\sigma$ of 4 or 5, which in turn would imply considerable differences among the albumin molecules, we are inclined to attribute most of the effect to variation among the sites within the individual molecules. A rough calculation shows that for $\sigma = 5$ and a value of $K_0$ corresponding to $-\Delta F^\circ = 6$ kcal, the range of $K$ values would correspond to a range of $-\Delta F^\circ$ from approximately 2 kcal. to 10 kcal.

It will be noted in Table II that there is some variation in the values of $\sigma$. It would be premature to attempt at this point to assign any physical significance to this variation both because of the relatively small differences involved and because of the limited range of $r$ for which $\sigma$ is employed in the theoretical calculation.

The question may be raised as to whether our choice of distribution function is uniquely suitable to account for our data. It appears to us that it is very likely not so and that other distribution functions may be equally adequate. This view is based on the fact that our data cover a rather narrow range of $1/r$ so that the suitability of the distribution function is not put to a severe test. Further, this distribution does not fit in with the kind of physical picture of the interaction which we favor though, of course, no definite judgment on this point can be made at the present time.

**Thermodynamic Considerations.**—Although the values of $K_0$ listed in Table II are average values, their comparison with one another is nevertheless of significance. It is clear that the binding becomes greater with increase in the length of the paraffin chain. This is, of course, obvious from the data of Figs. 1 and 2. Its importance follows from the fact that it shows that probably the whole alkyl group is involved in the interaction with the protein in addition to the electrostatic interaction between charged groups.

The study of the temperature dependence of the binding of alkyl sulfates has also led to interesting conclusions. Although the data for octyl sulfate are not as good as that for the other homologs, it appears that the binding of the octyl anion is practically independent of temperature as with dodecyl sulfate. On the other hand, decyl sulfate binding is dependent on temperature and an average value for $\Delta H^\circ$ of $-2.0$ kcal. is obtained. This is a rather unexpected difference among the homologs and, though it may have important implications for the structure of albumin, confirmation and extension of this kind of data is required before theoretical interpretation is justified.

The binding of the alkyl sulfates is largely or wholly an entropy effect. The standard entropy changes for the process are listed in the last column of Table II. To what extent these changes are associated with the release of water molecules bound to protein and anion and/or structural changes of the protein, it is not possible to decide at this time. The predominance of the entropy contribution to the free energy of complex formation between copper (cupric) and bovine albumin has been demonstrated by Klotz and Curme.[22]

Another important point which emerges from the thermodynamic data is that there is danger in the tendency, which is found in the literature, to interpret an increased binding as due to larger van der Waals forces because of increase in size of the non-polar portion of the bound molecule.

(22) I. M. Klotz and H. G. Curme, THIS JOURNAL, **70**, 939 (1948).

The comparison of dodecyl with decyl sulfate shows that the binding of the smaller anion yields a larger reduction in the energy of the system and serves to emphasize the desirability of measuring the temperature dependence of binding whenever possible.

**Significance of $n$.**—Previous work[5,7] on the binding of organic anions by albumin has proceeded on the assumption that it is possible to define a value of $n$ for the anions studied by the extrapolation of the $1/r$ *vs.* $1/c$ plot, corrected where necessary for electrostatic effects. We have already indicated that though we have taken $n = 14$ for the alkyl sulfates, we do not regard this value as necessarily the binding capacity of albumin. In the binding of methyl orange Klotz, *et al.*,[5] obtained a value of 22 for $n$ by extrapolation. However, the maximum value of $r$ obtained experimentally was apparently about 15 and the curve of $r$ *vs.* log $c$ gave no indication of tending toward a limiting value. It is therefore quite possible that the correct value of $n$ is larger than 22 and that all the binding sites do not have the same value of $K$ as the apparent linearity of the $1/r$ *vs.* $1/c$ plot would suggest.

The interpretation of Teresi and Luck's data[7] according to the simple theory is even more questionable because the range of $1/r$ and especially $1/c$ is more restricted.[23] Furthermore the data are not of high accuracy due to the fact that the amount of bound anion was only about one tenth of free anion. According to their results *o*-nitrophenolate is bound more strongly than *p*-nitrophenolate though $n = 6$ for the former and 25 for the latter compound. This appears rather unlikely to us on physical grounds and is especially open to question because the calculation of the intrinsic constants depends on the prior determination of $n$. In fact, if $n$ is assumed to be the same for the two compounds the fact that the binding curve of *p*-nitrophenolate lies below that of *o*-nitrophenolate would indicate that contrary to the conclusion of Teresi and Luck, the former compound is bound more strongly.

Such a reversal could arise if the portions of the binding curves of the two anions being compared corresponded to different ranges of $1/K_0c$ as shown in Figs. 3 and 4. The possible danger of being misled because of such a situation is readily seen by a comparison of our octyl and decyl sulfate data. If one considers the octyl sulfate data for the range of $1/c = 2 \times 10^4$ to $10 \times 10^4$, one could draw the best straight line through the points and conclude that $n = 5$ and that the intrinsic association constant $K$ is $10 \times 10^4$. On the other hand, if the data for decyl sulfate were limited to the range $1/c = 1 \times 10^4$ to $3 \times 10^4$, the conclusion would be reached that $n = 10$ and $K = 5 \times 10^4$. Thus a comparison of the two limited sets of data would lead to the inference that the binding capacity of the protein for octyl sulfate is less than for decyl but that the former is more strongly bound, though both conclusions are contrary to fact.

It appears, therefore, that the interpretation of the extrapolated value of $1/r$ as measuring the binding capacity of the protein for a particular anion is of dubious validity. Such a value may be quite adventitious depending on the concentration range studied and the magnitude of $\sigma$ or any other parameter which reflects the variation of $K$ values. A possibility that deserves serious consideration is that the binding capacity is the same for all organic anions, within a certain size range, and is equal to the number of positively charged sites on the surface of the protein molecule. If this were actually the case it would mean that for any particular organic anion the values of $K$ for the various sites would cover a very wide range.

**Structural Implications.**—The binding of organic anions to serum albumin very probably involves the electrostatic interaction between a positively charged group on the protein and the negative group of the anion.[24,25] However, not all of the positive groups of the protein are equally available for binding. This is clear from the analytical data for bovine serum albumin[8] which shows that there are 84 such groups at *p*H 6.1 from the arginine and lysine residues alone. Yet according to our results only 14 groups are involved in binding.

It appears useful to make a division of the cationic groups into two sets, one which is practically completely excluded from the association reaction in the native protein possibly because of inaccessibility, and the second set the members of which can bind organic anions but may do so with varying affinity. Some justification for such a distinction is to be found in the results of a study of the interaction between sodium dodecyl sulfate and horse serum albumin by Neurath and Putnam.[26] They observed that this protein could form a stoichiometric complex with about 55 detergent anions per albumin molecule without detectable changes in molecular shape. At higher detergent–protein ratios a second complex was formed involving the combination of about 110 anions per protein molecule. As shown by diffusion and viscosity measurements the formation of the second complex was accompanied by an increase in the molecular asymmetry of the protein. It may be remarked that the study with horse serum albumin was carried out with much higher concentrations of detergent, above the critical concentration for micelle formation, than was the case in our experiments.

(23) The values of $K$ and $\Delta F$ listed in their paper require correction due to an oversight in calculation (see *J. Biol. Chem.*, **177**, 383 (1949)).

(24) I. M. Klotz and F. M. Walker, THIS JOURNAL, **69**, 1609 (1947).

(25) F. W. Putnam and H. Neurath, *J. Biol. Chem.*, **159**, 195 (1945).

(26) H. Neurath and F. W. Putnam, *ibid.*, **160**, 397 (1945).

Perhaps the most interesting question of structural significance raised by our results has to do with the variation of $K$ values among the 14 sites which bind alkyl sulfate. Though, obviously no detailed answer is possible now, it does appear that the configuration of the protein in the interacting area around each positive charge is not the same for all the sites. It would be of considerable interest to determine the degree of such heterogeneity for the binding of organic anions of different sizes and shapes.

**Acknowledgment.**—We are indebted to Professor R. Keith Cannan for the generous hospitality afforded us in his laboratory during the conduct of this investigation. We are also grateful to Dr. I. M. Klotz of Northwestern University for many enlightening discussions.

## Summary

The reversible binding of homologous alkyl sulfates by bovine serum albumin has been studied at two temperatures by the method of equilibrium dialysis. This has required the development of a colorimetric method for determining low concentrations ($10^{-5}$ $M$) of these compounds. Deviations of the binding curves from the simple theory based on the mass action law have been shown to be inexplicable on the basis of electrostatic effects. A new heterogeneity theory based on a particular distribution of the intrinsic binding constants has been proposed and has been found to account quantitatively for our results. The values of the thermodynamic functions $\Delta F°$, $\Delta H°$ and $\Delta S°$, for the binding process have been calculated and the importance of the entropy contribution emphasized. The validity of the determination of binding capacity ($n$) by linear extrapolation has been subject to question and interpretations of binding data in the literature reconsidered. Finally, some structural implications of our results have been noted.

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[CONTRIBUTION FROM THE LABORATORIES OF PHYSICAL CHEMISTRY AND PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF WISCONSIN]

# Biophysical Studies of Blood Plasma Proteins. IX. Separation and Properties of the Immune Globulins of the Sera of Hyperimmunized Cows[1]

BY E. L. HESS[2,3] AND H. F. DEUTSCH

## Introduction

The antibody fraction of normal bovine serum has been previously separated in high yield by means of ethanol fractionation.[4] Our attention has now been directed to the application of these procedures for the recovery of the antibody enriched fractions of the sera of cows immunized to *Brucella abortus* organisms and Newcastle virus. The various globulin fractions separated have been subjected to solubility, molecular kinetic and immunological study.

## Experimental

The hyperimmune sera were prepared by inoculating two Holstein cows with Newcastle virus in whole egg embryo and with the viable *Brucella abortus* organisms at four-day intervals over a three-month period. In addition, a low titer serum pool of two calves immunized to diphtheria and tetanus toxin was studied briefly. The increase of the serum $\gamma$-globulins was followed by electrophoretic analysis and the extent of antibody production was determined by immunological assays.

*Brucella abortus* antibodies of two types, agglutinins and bactericidins, were assayed according to the methods published by Huddleson[5] and Irwin and Beach,[6] respectively. Newcastle virus hemagglutination inhibiting and neutralizing antibodies were assayed according to the method of Brandly, Jungherr, Moses and Jones.[7] The titers reported are based upon the assay of fractions reconstituted in phosphate buffer to their original serum concentration.

Except in certain subfractionations as indicated below, the fractionation steps follow the procedure outlined in Fig. 5 of the prior article.[4] The course of the fractionation of the hyperimmune bovine serum is shown by the electrophoretic diagrams in Fig. 1. The designation of the fractions is consistent with that adopted in the earlier report. Precipitates A from various sera were pooled for subsequent subfractionation or rework operations.

Standard electrophoretic and sedimentation procedures were followed in the physical chemical characterizations of the fractions. Solubility studies utilized the customary phase rule solubility procedures as reviewed by Herriott[8] and the successive extraction of the solid phase with

(1) A portion of this material was presented before the Division of Biological Chemistry of the American Chemical Society at the 113th Meeting, Chicago, April 19–22, 1948. This work was supported in part by grants from the Wisconsin Alumni Research Foundation and from the U. S. Public Health Service.

(2) du Pont Fellow in Chemistry in 1947.

(3) Post-doctorate Fellow in Chemistry 1948.

(4) Hess and Deutsch, THIS JOURNAL, **70**, 84 (1948).

(5) Huddleson, "Brucellosis in Man and Animals," Oxford Press, New York, N. Y., 1943.

(6) Irwin and Beach, *J. of Agr. Res.*, **72**, 83 (1946).

(7) Brandly, Jungherr, Moses and Jones, *Am. Jour. Vet. Research*, **7**, 289 (1946).

(8) Herriott, *Chem. Rev.*, **30**, 413 (1942).

TABLE I

FRACTIONATION, YIELD AND IMMUNOLOGICAL ASSAY DATA

| | Brucella abortus[a] agg. | Brucella abortus[a] bact. | Newcastle virus[b] h. i. V. dil.[e] | Newcastle virus[b] neutralizing MLD | Total[c] protein g./l. | % γ-(d)-globulins | Wt. γ-globulins g./l. | % Yield γ-globulins g./l. | β[d] globulins |
|---|---|---|---|---|---|---|---|---|---|
| Pre-immunization | 0 | 1:160 | 0 | 0 | 76 | 28 | 21 | | |
| Hyperimmune serum | 1:2560 | 1:81,920 | 1:5 | $10^6$ | 76 | 41 | 31 | | |
| Precipitate A (pooled) | 1:2560 | 1:81,920 | 1:5 | $10^5$ | 34 | 85 | 29 | 93 | 5 |
| Supernatant (pooled) | 1:40 | 1:20,480 | 0 | $10^1$ | 42 | 7 | 2 | | |
| Precipitate B | 1:100 | 0 | 0 | 0 | 6 | 17 | 1 | | 5 |
| Precipitate C | 1:2560 | 1:81,920 | 1:5 | $10^5$ | 25.6 | 95 | 25.6 | 83 | |
| Precipitate C-1 | 1:4096 | 1:81,920 | 1:5 | $10^5$ | 11.4 | 97 | 11.4 | 37 | |
| Precipitate C-2 | 1:1024 | 1:7680 | 0 | $10^2$ | 10.6 | 100 | 10.6 | 34 | |

[a] These assays were performed by Dr. D. Berman. [b] These assays were performed by Mr. R. Hanson. [c] $N_2$ detn. or lyophilized dry weight of precipitates. [d] Electrophoretic analysis. [e] Zero in this column indicates no detectable antibody.

aliquots of buffer. The usual precautions of equilibration and approach of equilibrium from both under and supersaturated solution were observed. Veronal, cacodylate and acetate buffers of $\mu = 0.01$ and 0.1 were used in the solubility and electrophoretic studies.

## Results

Analytical and antibody data for the serum and the various fractions are shown in Table I. The assays clearly show that the major portion of the antibodies is precipitated from the diluted serum at *p*H 7.6 and 18% ethanol. This precipitate (A) which amounted to 24 g./liter of serum in the case of normal cows and 34 g./liter of serum with the hyperimmune serum, represents more than 90% of the γ-globulins present in the original serum (electrophoretic analysis). Further fractionation of precipitate C gives products richer in the antibodies. It is apparent from Table I that the major portions of the antibodies separate with the $\gamma_1$-globulin fraction (Ppt. C-1).

In an effort further to concentrate the antibodies, certain subfractionations, exploratory in nature, were tried. For example, precipitate C-1 was separated into three fractions at $\mu = 0.003$ by varying *p*H and the ethanol concentrations. Brucella abortus agglutinins and Newcastle virus neutralizing antibody concentrations were doubled (as indicated by serial dilution assays) in the fraction that was soluble in the aqueous phase at $\mu = 0.003$, *p*H = 5.8, protein concentration = 0.5%, but which precipitated upon addition of ethanol to 25% concentration. In another instance, when the *p*H of an aqueous solution of precipitate C (protein = 0.5%, $\mu = 0.013$) was varied over the range 5.5 to 6.3 there occurred a precipitation of from 7.5 to 11.4% of the total protein in solution. The precipitate in each case gave negligible antibody titers.

Both the $\gamma_1$- and $\gamma_2$-globulins have sedimentation constants of $s_{20w} = 7.4S$ at a protein concentration of approximately 1% in 0.15 *M* NaCl. The sedimentation constants are substantially independent of concentration from 0.25 to 1% protein, and are in exact agreement with those previously reported[4] for the $\gamma_1$- and $\gamma_2$-globulins from normal bovine serum. The criterion of molecular mass homogeneity previously applied[4] revealed an essentially monodisperse system. Evidence of traces of a heavier component, $s_{20w} = 18S$, was found in the case of the $\gamma_1$-globulins, in contrast to its absence in the corresponding precipitate from normal bovine serum.

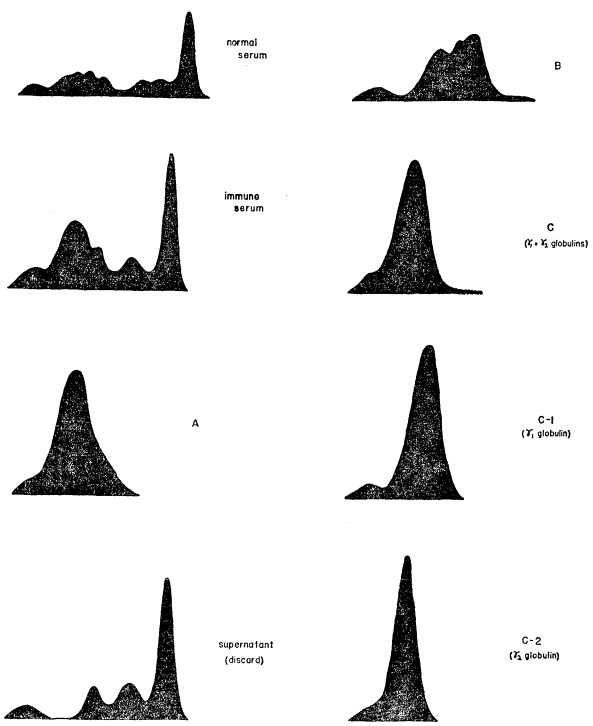



Fig. 1.—Electrophoretic patterns of hyperimmune bovine serum fractions in veronal buffer *p*H 8.6, $\mu = 0.10$ after 7200 seconds at 6.0 volts/cm. Concentration of protein is 3% in all cases; normal serum in barbiturate–citrate buffer at *p*H 8.60, $\mu = 0.088$, $E = 8.5$ volts/cm. Detailed statements of conditions for these separations appear in Fig. 5 of ref. (4).

Isoelectric points ($pI_e$) determined from the customary plot of mobilities ($U$) against *p*H are

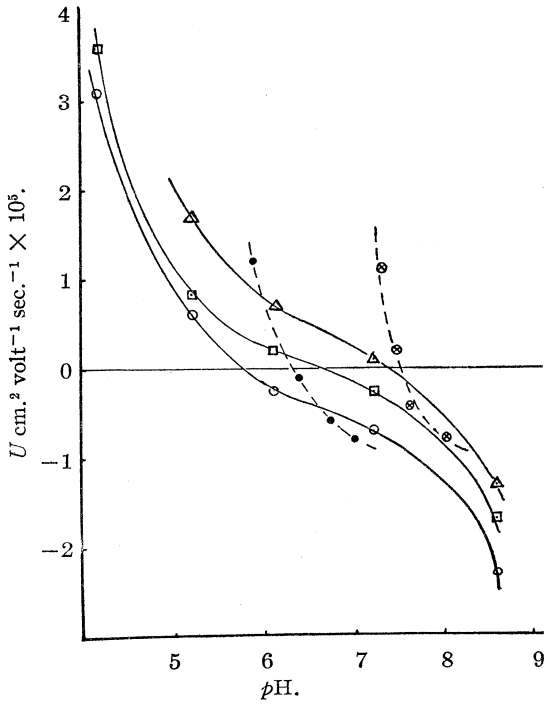



Fig. 2.—*p*H–mobility relationships:

| | | | | |
|---|---|---|---|---|
| □ | γ-globulins | $\mu$ = 0.10 | $pI_e$ 6.60 |
| ○ | $\gamma_1$-globulins | $\mu$ = .10 | $pI_e$ 5.85 |
| △ | $\gamma_2$-globulins | $\mu$ = .10 | $pI_e$ 7.35 |
| ● | $\gamma_1$-globulins | $\mu$ = .01 | $pI_e$ 6.35 |
| ⊗ | $\gamma_2$-globulins | $\mu$ = .01 | $pI_e$ 7.50 |

shown in Fig. 2. The $pI_e$ are sensitive to $\mu$ and increase with decreasing $\mu$. The isoionic points ($pI_i$) as determined by extrapolating the $pI_e$ obtained in $\mu$ = 0.1 and $\mu$ = 0.01 buffers to $\mu$ = 0 gives *p*H values of 6.4 for the $\gamma_1$-globulins and 7.5 for the $\gamma_2$-globulins. In Table II are assembled data obtained from electrophoretic studies at $\mu$ = 0.10. The heterogeneity constants ($H$) are calculated according to the method of Sharp, Taylor, Beard and Beard.[9]

The apparent diffusion constants are calculated from the relation $D^* = (Xi)^2/2t$.[10,11] The time ($t$) is in seconds, $X_i$ is the half width of the gradient curve of the electrophoretic pattern at the point of inflection ($h_i$), where $h_i$ is equal to $1/\sqrt{e}$ times the height of the maximum ordinate. The ascending and descending boundaries are virtually enantiographs at $\mu$ = 0.10. The values of the heterogeneity and the apparent diffusion constants listed in columns 3 and 4 of Table II are averages for the ascending and descending boundaries.

TABLE II

ASSEMBLED MOBILITY AND HETEROGENEITY DATA

| Sample | *p*H | $U \times 10$ cm.² volt⁻¹ sec.⁻¹ | $D^a \times 10^7$ cm.² sec.⁻¹ | $H \times 10^5$ cm.² volt⁻¹ sec.⁻¹ | Buffer[b] $\mu$ = 0.1 |
|---|---|---|---|---|---|
| C1 | 4.20 ± 0.05 | +3.1 | 67 | 0.92 | Acetate |
| | 5.20 | +0.6 | 80 | .98 | Acetate |
| | 6.10 | −0.3 | 69 | .93 | Cacodylate |
| | 7.20 | −0.7 | 65 | .90 | Cacodylate |
| | 8.60 | −2.3 | 53 | .80 | Veronal |
| C2 | 4.20 ± 0.05 | +4.7 | 63 | .87 | Acetate |
| | 5.20 | +1.6 | 71 | .95 | Acetate |
| | 6.10 | +0.7 | 93 | 1.05 | Cacodylate |
| | 7.20 | +0.1 | 73 | 0.95 | Cacodylate |
| | 8.60 | −1.3 | 62 | 0.87 | Veronal |

[a] Values are calculated from Schlieren patterns after 120 minutes at $E$ = 5.0 volts cm.$^{-1}$ $\mu$ = 0.10 in all cases at ≦ 1° C. [b] All acetate and cacodylate buffers, $\mu$ = 0.02 with the sodium salt of the acid and $\mu$ = 0.08 with NaCl.

Resolution of the schlieren pattern into more than a single peak was not observed at any of the *p*H values listed in Table II although the γ-globulins showed reversible electrical spreading to a marked degree. At $\mu$ = 0.01, the electrophoretic boundaries for both the $\gamma_1$- and $\gamma_2$-globulins are very asymmetric and actually resolve into several peaks. In Fig. 3 the resolution of these two globulin fractions at $\mu$ = 0.01 and 0.1 are compared, while Fig. 4 shows the reversible spreading phenomenon and the resolution at a *p*H close to the "average" $pI_e$ of the $\gamma_1$-globulins. The asymmetry and the separation of more or less distinct components precludes the calculation of heterogeneity constants at $\mu$ = 0.01 for either $\gamma_1$- or $\gamma_2$-globulins.

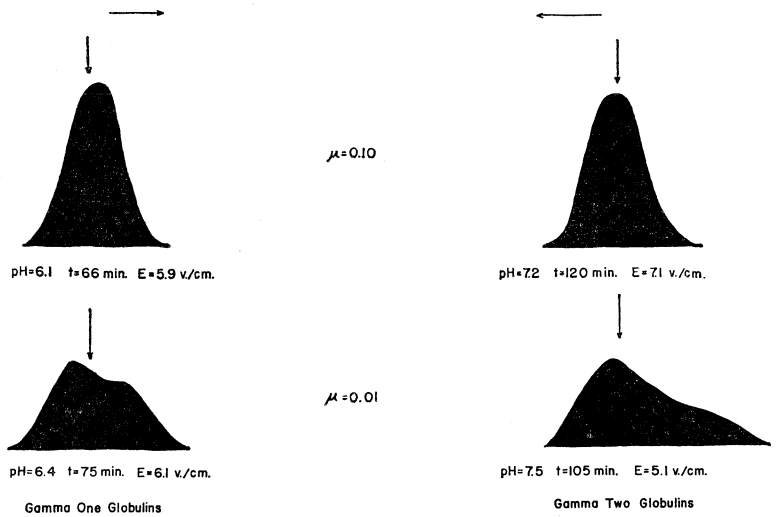



Fig. 3.—The effect of ionic strength on electrophoretic resolution.

The successive extraction of 6.7 g. of $\gamma_1$-

(9) Sharp, Taylor, Beard and Beard, *J. Biol. Chem.*, **142**, 193 (1942).

(10) Lamm, Dissertation, Upsala, 1937.

(11) Neurath, *Chem. Rev.*, **30**, 372 (1942).

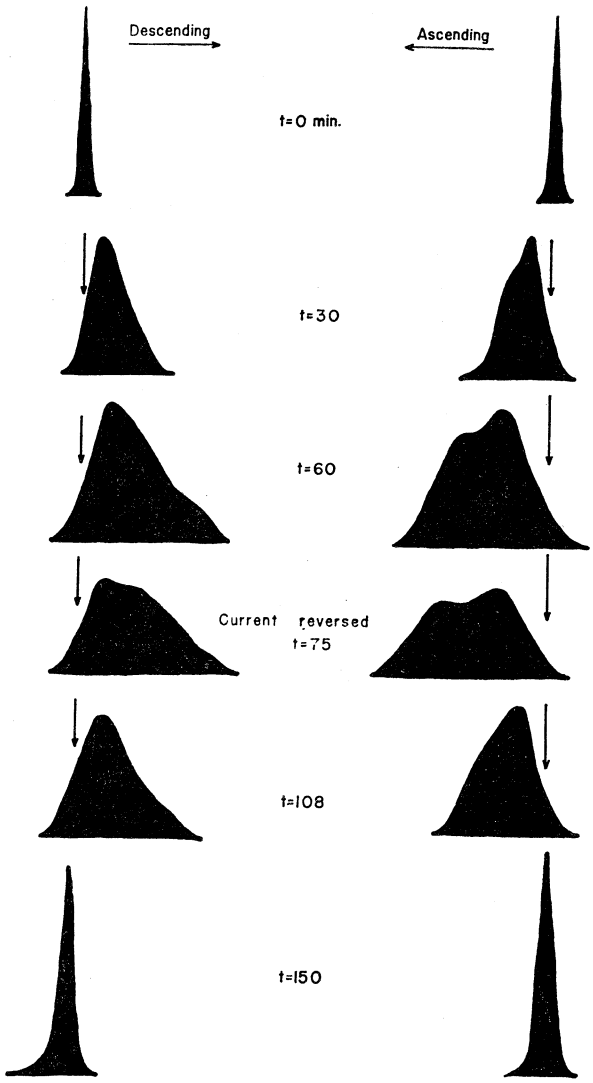



Fig. 4.—Electrophoretic reversible spreading of $\gamma_1$-globulins: $p$H, 5.95, $\mu$ = 0.01, $E$ = 6.1 v./cm.

globulins (Ppt. C-1) with 25-ml. portions of sodium cacodylate buffer at $p$H = 5.95±0.05, $\mu$ = 0.01, yielded the data plotted in Fig. 5. It is apparent that the solid phase remaining after ten extractions represents within the limit of error of the nitrogen determination a protein of constant solubility. Electrophoretic patterns of the supernatants from the first, fourth, seventh and tenth extractions are shown in Fig. 6. Progressive increase in symmetry is evident. However, even the residue possessing a relatively constant solubility clearly shows spreading far greater than can be attributed to normal diffusion. Phase rule solubility curves for the $\gamma_1$- and $\gamma_2$-globulins in $\mu$ = 0.01 buffers at their "average isoelectric points" give no evidence of a major component of relatively constant solubility and corroborated the heterogeneous nature of the fractions as revealed by electrophoretic spreading and solu-

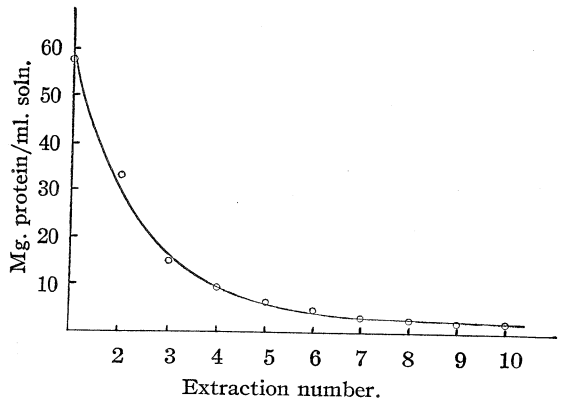



Fig. 5.—Successive extraction of $\gamma_1$-globulins at $p$H 5.95 ± 0.05, $\mu$ = 0.01 sodium cacodylate buffer, $T$ = 0°.

bility extraction procedures. Under the above conditions the $\gamma_1$-globulin fraction is far less soluble than the $\gamma_2$-globulin fraction and even in the most dilute solutions it fails to dissolve completely. The phase rule solubility behavior of the $\gamma_2$-globulins is similar to that observed by Englehardt[12] with myosin solutions. In low ionic strength aqueous solutions at higher protein concentrations the $\gamma_2$-globulins do not separate into the customary solid and liquid phases but separate into a liquid phase and a gel.

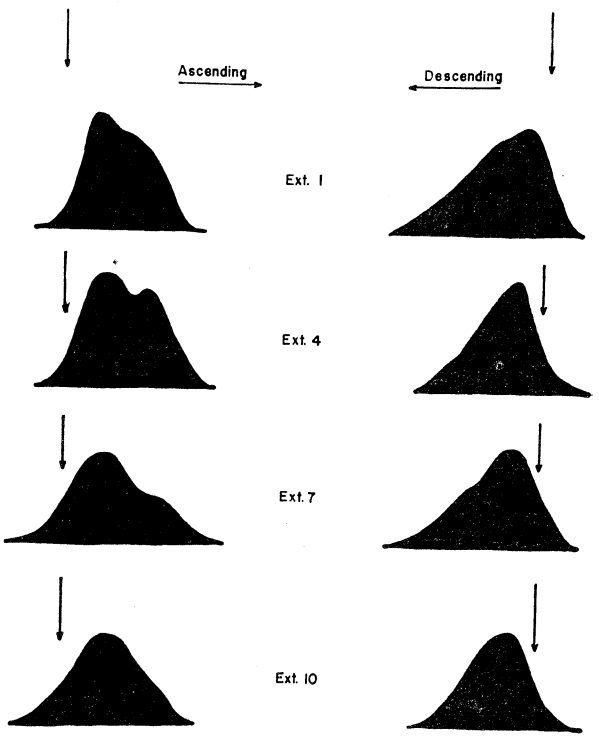



Fig. 6.—Electrophoretic patterns of $\gamma_1$-globulin extracts: $\mu$ = 0.01; $p$H 5.95; $t$ = 60 minutes; $E$ = 6.0 volts/cm.

(12) Englehardt, *Adv. in Enzymol.*, **VI**, 147 (1947).

That the procedures used on adult animals apply to calf serum is substantiated both by yield and antibody recovery data. Actual yields are somewhat low, however, due to the lower $\gamma$-globulin levels in the younger animals. Percentage yields of each fraction are essentially the same as reported in Table I.

## Discussion

The fractionation methods developed for removal of the $\gamma$-globulins from normal bovine sera[4] have been found to be applicable to immune bovine sera with the resultant separation of the major portion of the serum antibodies. Larger amounts of antibody fractions are obtained per unit of serum as a consequence of a higher concentration of $\gamma$-globulins in the starting serum.

Differences in solubility of the antibodies studied are shown by the greater solubility of the *Brucella abortus* bactericidins as compared with the agglutinins. Thus, a significant portion of the bactericidins remain in the supernatant from the first precipitate (Ppt. A, Fig. 1) although the agglutinating antibodies seem to be almost quantitatively removed. More quantitative antibody assay methods are needed to determine the exact solubility differences.

Subfractionation of the $\gamma$-globulins reveals that further separation of individual antibodies by chemical methods is feasible. Thus, while the neutralizing antibodies for Newcastle virus are found in both the $\gamma_1$- and $\gamma_2$-globulin fractions, the hemagglutination inhibiting antibody appears to reside largely in the $\gamma_1$-globulin fraction. However, the concentration of the former antibody as well as those to Brucella organisms are distinctly lower in the $\gamma_2$-globulin fraction. The result for the Brucella antibodies may be in contrast to the response of the horse to bacterial antigens where immunization to bacterial cells causes a marked increase in the normal $\gamma$-globulins ($\gamma_2$) levels[13] as compared to the $\gamma_1$-globulin (T-component) area. The actual distribution of the horse antibodies to bacterial antigens is however unknown.

Further aqueous subfractionations at $\mu = 0.013$, however, reveal that both of the Newcastle virus antibodies are concentrated largely in the pseudoglobulin fraction of precipitate C-1. Thus while as much as 15% of this portion may be removed as aqueous insoluble material no significant amounts of the Newcastle antibodies are removed. Such findings indicate that as regards the antibodies studied in this work a larger amount of protein ($\gamma_1$-englobulin) can be removed with Ppt. B, Fig. 1 without significant loss of the antibodies if this precipitation is carried out at *p*H 6.1 rather than at *p*H 4.9.

A rework of a $\gamma_1$-globulin fraction involving the variables *p*H, ionic strength and ethanol concentration to give three subfractions resulted in the Newcastle virus neutralizing antibody being concentrated entirely in the more soluble (pseudoglobulin) fraction of C-1. No hemagglutination inhibiting antibody was detectable in any of the above three subfractions although recombination of two of the fractions resulted in a low but significant titer. Further studies of this apparent antibody complex are being carried out.[14]

Electrophoretic spreading experiments in $\mu = 0.1$ and 0.01 buffers reveal that the $\gamma$-globulin fractions are electrically inhomogeneous. The inhomogeneity (spreading greater than can be attributed to diffusion and which is electrically reversible) is more evident at low ionic strengths ($\mu = 0.01$). Such data indicating the presence of electrokinetically inhomogeneous *molecular* species have been previously noted.[4,10,15,16,17,18,19]

Solubility studies corroborate the heterogeneous nature of antibody fractions that give a single electrophoretic peak at $\mu = 0.10$. Successive extraction procedures utilizing a buffer solution of relatively low ionic strength tend to leave a residue of more uniform electrophoretic composition than the starting fraction, but one that still shows marked reversible electrophoretic spreading. In this respect the reversible spreading type of experiment provides a delicate criterion of homogeneity.

The $\gamma_1$- and $\gamma_2$-globulins reveal the same degree of mass molecular homogeneity exhibited by the corresponding fractions from normal bovine serum. The sedimentation constants, however, are somewhat higher than one reported by Cohn and his associates[20] but are essentially in agreement with the values obtained by Pedersen[21] for salt fractionated material.

**Acknowledgments.**—We wish to thank the following individuals who aided us in this work: Dr. David Berman of the Department of Veterinary Science provided us with the *Brucella abortus* antigen, immunized and helped bleed the animals, and performed the agglutination and bactericidal assays. His coöperation, advice and assistance were invaluable. Mr. R. M. Hansen, also of the Department of Veterinary Science, performed the Newcastle virus hemagglutination inhibition and neutralizing assays. Mr. Edwin M. Hanson made the sedimentation velocity runs and designed and constructed much of the multiple stirring apparatus for the solubility studies. We are grateful to Professor J. W. Williams for his continued interest in this research.

(13) Van der Scheer, Wyckoff and Clark, *J. Immunol.*, **39**, 65 (1940).

(14) Hansen, Brandly and Winslow, Abst. Proc. Soc. Am. Bacty., 48th Meeting, May 10–14 (1948), Minneapolis, Minnesota.

(15) Tiselius and Horsfall, *Ark. Kem. Min. Geol.*, **13A**, 18 (1939).

(16) Horsfall, *Ann. N. Y. Acad. Sci.*, **39**, 203 (1939).

(17) Longsworh, Cannan and MacInnes, THIS JOURNAL, **62**, 2580 (1940).

(18) Lauffer and Ross, *ibid.*, **62**, 3296 (1940).

(19) Alberty, Anderson and Williams, *J. Phys. Colloid Chem.*, **52**, 217 (1948).

(20) Cohn, Luetscher, Oncley, Armstrong and Davis, THIS JOURNAL, **62**, 3396 (1940).

(21) Pedersen, Dissertation, Upsala, 1945.

## Summary

Two γ-globulin fractions, isoelectric at *p*H 5.85 and 7.35 in $\mu = 0.1$ buffers, were prepared by methods previously described, from sera of cows immunized to Brucella abortus and Newcastle virus. These fractions are inhomogeneous as indicated by electrophoretic spreading experiments and solubility studies, but are essentially monodisperse as regards sedimentation behavior. The antibodies studied are largely concentrated in the fraction of lower isoelectric point ($\gamma_1$-globulins). Concentration and separation of certain antibodies were obtained, indicating the feasibility of chemical separation of individual antibodies from polyvalent systems.


RECEIVED APRIL 30, 1948

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

# Hydrodiethylstilbestrol Compounds. IV. The Unsaturated Ketones[1,2]

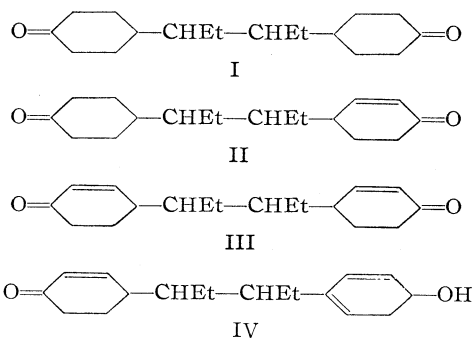
BY HERBERT E. UNGNADE AND PAUL W. TUCKER[3]

Unsaturated ketones derived from perhydrostilbestrol have been described by Schoeller and coworkers.[4] The di-unsaturated diketones are said to be colorless oils, the mono-unsaturated compounds have not been characterized nor is any criterion of purity disclosed in the pertinent examples. Since the compounds are claimed to possess androgenic activity up to one capon unit per mg., it appeared possible that purified preparations might possess considerable biological activity.

The substances have been prepared essentially as described by the previous investigators. The two known perhydrodiketones (I)[4,5] can be brominated rapidly in chloroform[4] or in glacial acetic acid[6] with the introduction of one or more atoms of bromine. In view of the possibility of replacing the tertiary hydrogens of the hexane chain in the diketones (I) the bromination has now been effected by means of N-bromosuccinimide which supposedly does not react with tertiary hydrogens in the absence of peroxides.[7]

Bromination of the diketones (I) with N-bromosuccinimide in carbon tetrachloride proceeds rapidly with the introduction of one atom of bromine. The second and third bromines are introduced more slowly, the second bromine entering preferentially the unbrominated nucleus. On the basis of recovered succinimide (98–100%) the reaction is nearly quantitative. The glassy bromodiketones are best dehydrobrominated by refluxing with collidine. Chromatographic adsorption of the crude glassy substances on alumina from benzene solution yields homogeneous products containing benzene of solvation which can be removed only by vacuum sublimation.

Ultraviolet absorption spectra of the analytically pure sublimates (II) and (III)[8] show relatively low extinction values at 225 mμ and only a weak secondary maximum at 280–285 mμ. Both phenolic ketones (IV) give the expected phenolic band of 280 mμ. Traces of a phenolic by-product (V) have been isolated from the dehydrobromination of the *meso*-tribromodiketone regardless whether it is prepared by direct bromination or with N-bromosuccinimide. This substance has a strong maximum at 300 mμ which may be taken as evidence for the presence of a double bond conjugated with the phenolic ring.[9] A red ketonic by-product is obtained in the same reaction which must possess a multiple conjugated system in view of its color. The formation of these by-products and the small extinction values for the compounds (II) and (III) lend support to the assumption that N-bromosuccinimide may also attack tertiary hydrogens even in the absence of peroxides and that the substances (II), (III) and (IV) probably consist of mixtures of conjugated and non-conjugated unsaturated ketones.




The *meso* compounds (II) and (III) have been tested biologically. Both show little or no androgenic activity in the seminal vesicle test with three daily doses of 1.0 and 0.75 mg. of substance, respectively.[10]

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society, Chicago, April, 1948.

(2) From the Ph.D. thesis of Paul W. Tucker, 1948.

(3) George Breon Fellow, 1946–1948. Present address: Research Dept., Phillips Petroleum Company, Bartlesville, Okla.

(4) Schoeller, Inhoffen, Steinruck and Höss, U. S. Patent 2,392,-864.

(5) Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945).

(6) Ludutsky, Ph.D. thesis, University of Missouri, 1946.

(7) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(8) Absorption spectra by Dr. E. E. Pickett, University of Missouri.

(9) Jones, *Chem. Rev.*, **32**, 36 (1943); Kaiser and Koenig, THIS JOURNAL, **68**, 740 (1946).

(10) Androgenic tests by Mr. K. D. Sprague, Control Department, Winthrop-Stearns, Inc., Rensselaer, N. Y.

## Experimental[11]

**Bromination of the Diketones.**—The calculated amount of N-bromosuccinimide was added to a solution of the diketone dissolved in carbon tetrachloride. The mixtures were refluxed for four and one-half, five and one-half and nine hours, respectively, for introducing one, two or three atoms of bromine. Part of the solvent was removed by distillation and the reaction mixtures were allowed to cool. The succinimide was filtered off and washed with carbon tetrachloride. Evaporation of the solvents from the filtrates gave the crude bromo compounds which were used without further purification. The experimental values are listed in Table I.

TABLE I

BROMINATION OF THE DIKETONES

| Diketone, g. | $CCl_4$, cc. | N-Bromosuccinimide, g. | Yield of bromodiketone, % |
|---|---|---|---|
| *meso* 4.0000 | 50 | 2.5632 | 98.2 |
| *meso* 8.0000 | 100 | 10.2172 | 91.7 |
| *meso* 12.0000 | 150 | 23.0688 | 98.9 |
| *dl* 5.0000 | 50 | 3.2040 | 98.0 |
| *dl* 10.0000 | 100 | 12.8160 | 98.0 |
| *dl* 15.0000 | 150 | 19.2240 | 90.0 |

**Dehydrobromination of the Bromodiketones.**—The bromodiketones, dissolved in 4 to 6 parts by weight of collidine, were refluxed for one and one-half hours in an oil-bath. The collidine hydrobromide was filtered off and washed with benzene. The filtrates were extracted with benzene and the combined benzene solutions were washed with 10% aqueous hydrochloric acid and water, dried by distillation and evaporated. The dark colored glassy substances were dissolved in benzene and extracted with Claisen alkali. The remaining benzene solutions were washed, dried and adsorbed on alumina. The ketonic fractions were eluted with benzene and distilled to remove the solvent. The identity of the fractions was checked by means of their ultraviolet absorption spectra. Traces of starting material showed very low extinction values over the range of 215–335 mμ.

Phenolic substances were obtained only in minute quantities from mono- and dibromodiketones, but formed in fairly good yield from the tribromodiketones. They were regenerated by acidification of the Claisen alkali solutions with 1:1 aqueous hydrochloric acid, extracted with benzene, washed, dried and distilled. The residual material was adsorbed on alumina from benzene solution and eluted with the same solvent. The fraction with appropriate ultraviolet spectrum was sublimed under reduced pressure.

Vacuum sublimation of both phenolic and non-phenolic ketones was carried out in a molecular pot still with a path length of 1 cm. at 160–180° ($1 \times 10^{-4}$ mm.). Yields and constants of the unsaturated ketones are given in Table II.

**Ultraviolet Absorption Spectra.**—The unsaturated ketones were run in 95% alcohol in concentrations of 0.000185 mole per liter in a Beckman spectrophotometer.[8] The saturated *meso*-diketone (I) was run in a 0.005 molar solution. The extinction values are given in Table III.

(11) All temperatures uncorrected.

TABLE II

DEHYDROBROMINATION OF THE BROMODIKETONES

| Bromodiketone, g. | Crude unsaturated ketone, yield, % | | Phenolic material, yield, % | Analyses C, % | Analyses H, % | M. p. °C. |
|---|---|---|---|---|---|---|
| 5.00 | *meso* (II) | 71 | Traces | 78.09 | 10.21[a] | Glass |
| 11.01 | *meso* (III) | 66.3 | Traces | 78.63 | 9.32[b] | Glass |
| 22.00 | *meso* (IV) | 70.8 | 46.4 | 79.79 | 8.74[c] | Glass |
| 7.00 | *dl* (II) | 74.4 | Traces | 78.00 | 10.02[a] | Glass |
| 15.00 | *dl* (III) | 84 | Traces | 79.00 | 9.75[b] | Glass |
| 25.57 | *dl* (IV) | 62.4 | 11.5 | 78.84 | 8.70[c] | 52–53 |

[a] Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. [b] Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. [c] Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

| Compound | Maxima | $\epsilon_{max}$[c] | Minima | $\epsilon_{min}$. |
|---|---|---|---|---|
| *meso* (I) | 280 | 39 | 240 | 18 |
| *meso* (II) | 225 | 2890 | 220 | 2840 |
| | 280 | 1130 | 270 | 1080 |
| *dl* (II) | 230[a] | 2290 | 225[b] | 2460 |
| | 285 | 1180 | 270 | 1100 |
| *meso* (III) | 225 | 4580 | 220 | 4470 |
| | 285 | 2400 | 265 | 2040 |
| *dl* (III) | 235[a] | 2790 | 225[b] | 6030 |
| | 285 | 3240 | 270 | 2890 |
| *meso* (IV) | 225 | 12900 | 215 | 11500 |
| | 280 | 5250 | 255 | 3900 |
| *dl* (IV) | 225[a] | 11300 | 220[b] | 11500 |
| | 280 | 4900 | 255 | 3810 |
| *meso* (V) | 220 | 8300 | 265 | 3600 |
| | 300 | 6300 | | |

[a] Shoulder. [b] Inflection point. [c] $\epsilon$ = molecular extinction coefficient.

## Summary

Analytically pure unsaturated diketones and unsaturated phenolic ketones derived from perhydrostilbestrol have been prepared by bromination and dehydrobromination of the saturated diketones.

On the basis of the absorption spectra of the products and the by-products in the reaction it is proposed that N-bromosuccinimide may attack tertiary hydrogens even in the absence of peroxides and that the products may consist of mixtures of conjugated and non-conjugated unsaturated ketones.

The mono- and di-unsaturated *meso*-diketones fail to show any appreciable androgenic activity.

COLUMBIA, MO. RECEIVED NOVEMBER 12, 1948

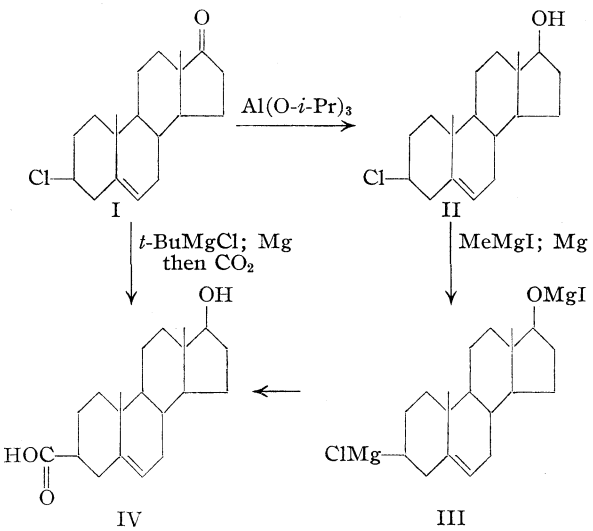
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Derived Steroids. III. 5-Androsten-17-ol-3-carboxylic Acid[1]

BY ROBERT H. BAKER AND EDWARD N. SQUIRE[2]

Marker[3] prepared 17-androstanone-3-carboxylic acid and found that it had estrogenic properties. We now report the synthesis of a similar compound (IV) with the additional feature of a double bond in the 5,6-position.

Two methods were used to prepare IV. Since the steroid halides form Grignard reagents only in the presence of preformed Grignards, it appeared that *t*-butylmagnesium chloride would serve both this role and as reducing agent for the 17-keto group.[4] This route produced only an 8% yield of the acid and it proved better to reduce the ketone by standard procedures and proceed by the longer route.




The ketone (I) is reduced only slowly and crystallization of the product gives what appears to be a molecular compound of I and II. This substance, m. p. 134°, resists separation by chromatography on alumina, but after acetylation the ester and ketone may be separated by either crystallization or chromatography. So prepared, II and its acetate agree in m. p. with the products prepared by Kuwada[5] by the action of thionyl chloride on 17-acetoxy-5-androsten-3-ol.

Because of the low solubility of II in ether, and the still lower solubility of III, the treatment with methyl Grignard was best carried out on the more soluble acetate of II. This produced a fine suspension of III which even then required a prolonged contact with carbon dioxide. Maximum yields of the acid (IV) were not obtained with less than eighteen hours for Grignard formation and eight hours for carbonation.

## Experimental[6]

**3-Chloro-5-androsten-17-one** (I).—This was prepared essentially by the method of Wallis and Fernholz[7] except that the phosphorus pentachloride was added slowly and the product was purified by absorption from chloroform solution on alumina, m. p. 154–154.4°.

**3-Chloro-5-androsten-17-ol** (II).—A solution made from 60 ml. of isopropyl alcohol containing 0.037 mole of aluminum isopropoxide and 1.15 g. (0.0037 mole) of I was refluxed for fourteen hours, and then slowly distilled to a residue of 15 ml. This was hydrolyzed with hydrochloric acid, extracted with ether and crystallized from methanol, m. p. 128–138°. The solid was dissolved in 10 ml. of benzene, diluted with 40 ml. of petroleum ether (b. p. 60–70°) and passed through a column containing 15 g. of alumina. Elution with the same solvent, 50 ml., produced 390 mg., m. p. 120–135°. The next four fractions, eluted with benzene, gave 650 mg. of the chloro alcohol, m. p. 162.5–165.5°, lit.[5] 163°.

**3-Chloro-17-acetoxy-5-androstene.**—This could be prepared by heating (95°) the 120–135°-melting product with acetic anhydride and pyridine for two hours. Repeated crystallization from methanol gave m. p. 182–184°, lit.,[5] 183°. For preparative purposes the pure chloro alcohol was used.

**5-Androsten-17-ol-3-carboxylic Acid** (IV).—To a mixture of methylmagnesium iodide and magnesium, made from 2.28 g. ($1.6 \times 10^{-2}$ mole) of the iodide and 1.0 g. ($4.1 \times 10^{-2}$ mole) of metal, in 5 ml. of ether there was added a solution of 0.702 g. ($2 \times 10^{-3}$ mole) of 3-chloro-17-acetoxy-5-androstene in 35 ml. of ether. This mixture was refluxed under nitrogen and stirred for twenty-four hours. The mixture was then cooled by a dry ice-acetone bath and subjected to 790 mm. pressure of dry carbon dioxide during sixteen hours, then for two more hours at room temperature. The reaction mixture was decomposed with 10% hydrochloric acid and extracted with 50 ml. of ether. The carboxylic acid was extracted from the ether with four 25-ml. portions of 5% potassium hydroxide. The alkaline solution, after extraction with ether, was acidified to precipitate the acid which was then crystallized from ether to give four fractions, 0.540 g., m. p. 220–243° (top fraction 240–243°). Crystallization from benzene gave m. p. 239–242°. The analytical sample was dried four days at 100° *in vacuo* over phosphorus pentoxide.

*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.96, 75.45; H, 9.92, 9.74.

The ether washes contained suspended solid which was removed by filtration, 20 mg., m. p. *ca.* 300°. This is probably 3,3′-bis-5-androsten-17-ol formed similarly to the bicholesteryl.[1]

Evaporation of the neutral ether washes left a product which did not crystallize well from methanol, 0.2 g., m. p. 138–154°. In this was identified **5-androsten-17-ol** by conversion into the acetate, 0.1 g., m. p. 135–136°, lit.,[8] 133–135°.

The acid (IV) was also prepared directly from 3-chloro-5-androsten-17-one. To 1.0 g. ($3.2 \times 10^{-3}$ mole) of the

(1) Preceding papers Baker and Squire, THIS JOURNAL, **70**, 1487 (1948); **70**, 4134 (1948).

(2) Junior Fellow of the National Institute of Health. Present address Franklin and Marshall College, Lancaster, Pa.

(3) Marker, Kamm, Oakwood and Laucius, THIS JOURNAL, **58**, 1948 (1936).

(4) Ruzicka and Rosenberg, *Helv. Chim. Acta*, **19**, 357 (1936), used propylmagnesium iodide for the reduction of 17-ketosteroids.

(5) Kuwada and Miyasaka, *J. Pharm. Soc. Japan*, **57**, 232 (1937).

(6) Microanalyses by Margaret Hines and Jean Gibbs.

(7) Wallis and Fernholz, THIS JOURNAL, **59**, 764 (1937).

(8) Marker and Wittle, U. S. Patent 2,397,424–5–6; *Chem. Abs.*, **40**, 3570 (1946).

chloroketone in 50 ml. of ether there was added 0.243 g. ($1 \times 10^{-2}$ mole) of magnesium powder and 10 ml. of 2 *N* *t*-butylmagnesium chloride. The mixture was refluxed for four hours, and carbonated as previously described to give 83 mg. of the acid, m. p. 243°.

**3-Carbomethoxy-5-androsten-17-ol.**—A solution of 10 ml. of absolute methanol, 110 mg. ($3.4 \times 10^{-4}$ mole) of IV and 6 drops of concd. sulfuric acid was refluxed for twenty-four hours. The mixture was poured into water, extracted with ether and washed free of acid by alkali. Crystallization from methanol–petroleum ether followed by chromatography over alumina from benzene–petroleum ether gave 80 mg., m. p. 141–142°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.73. Found: C, 75.20; H, 9.79.

**17-Acetoxy-5-androsten-3-carboxylic Acid.**—A crude sample, 250 mg., of the acid (IV) was heated at 100° for two hours with excess acetic anhydride in pyridine. The product obtained by pouring into water was dissolved in acetone and filtered to remove some insoluble material. Slow crystallization from acetone gave 110 mg., m. p. 211–213°, $[\alpha]^{23}D$ −40.6 (*C*, 4.90 in chloroform).[9]

*Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.00; H, 8.99.

**Acknowledgment.**—We wish to thank Dr. Wayne Cole of the Soya Products Division of the Glidden Co. for supplying the dehydroisoandrosterone.

## Summary

5-Androsten-17-ol-3-carboxylic acid has been prepared by carbonation of a Grignard reagent. Its acetate and methyl ester are described.

(9) The specific rotations of the intermediates and other compounds in this series will appear in a future publication by Dr. Squire.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 10, 1948

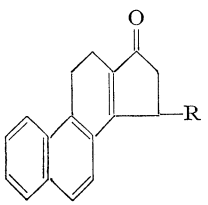
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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

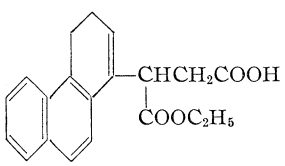
# The Stobbe Condensation with 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene. A New Approach to β-17-Equilenone[1]

BY WILLIAM S. JOHNSON, VERNER L. STROMBERG AND JACK W. PETERSEN[2]

A few years ago we described a convenient synthesis of the ketone I (R = H) by the cyclization of the half-ester II produced by a Stobbe condensation with III (R = H), followed by hydrolysis and decarboxylation of the resulting keto ester I (R = $COOC_2H_5$).[3] Since then this scheme has been applied successfully by Riegel, Siegel and Kritchevsky[4] to the synthesis of a number of derivatives of I (R = H) containing alkyl substituents at the 3-position of the phenanthrene nucleus.

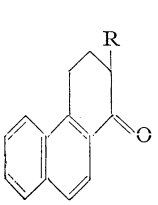



I

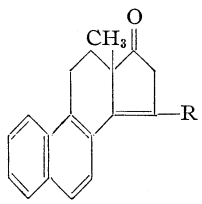



II

It seemed of particular interest to extend the synthesis to the homologous ketone III (R = $CH_3$) containing the methyl substituent at the 2-position, since if the cyclization proceeded into the alicyclic ring, a substance IV (R = $COOC_2H_5$) would be produced which is known to be convertible by hydrolysis, decarboxylation and hydrogenation into the 17-equilenones (3-desoxyequilenins).[5] The results of such an investigation are reported in this communication.

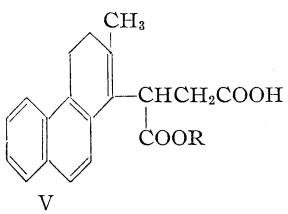



III

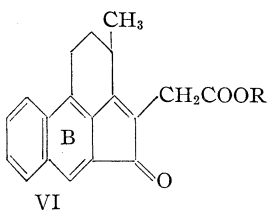



IV

The Stobbe condensation with III (R = $CH_3$) proceeded less readily than with the unsubstituted ketone III (R = H), but by altering conditions a non-homogeneous half-ester V (R = $CH_3$)[6] was obtained in excellent yield, from which a pure crystalline isomer was isolated in 61% yield.




V




VI

Cyclization of the crude half-ester V (R = $CH_3$ or $C_2H_5$) with a mixture of zinc chloride, acetic acid and acetic anhydride gave a neutral crystalline product of the expected composition. Because of its bright yellow color, however, it was presumed to be the indenone derivative VI produced by cyclization accompanied by ester exchange as observed in other studies.[7] That the ring had indeed closed into the aromatic nucleus was proved by oxidative degradation to benzenepentacarboxylic acid evidently arising from ring B (formula VI).

(1) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) W. A. R. F. Research Assistant, 1943–1945. Deceased, January 29, 1948.

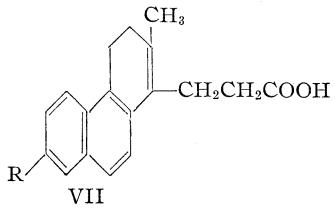
(3) Johnson and Petersen, THIS JOURNAL, **67**, 1366 (1945).

(4) Riegel, Siegel and Kritchevsky, *ibid.*, **70**, 2950 (1948).

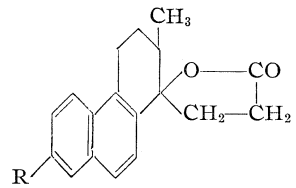
(5) Johnson, Petersen and Gutsche, *ibid.*, **69**, 2942 (1947).

(6) The formulation of the ethylenic bond in the endocyclic position is tentative. *Cf.* the structure of the lower homolog, ref. 3.

(7) Johnson and Goldman, THIS JOURNAL, **67**, 430 (1945).

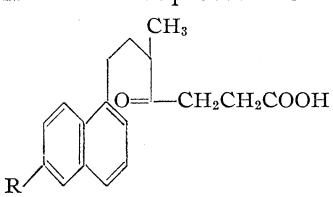



VII

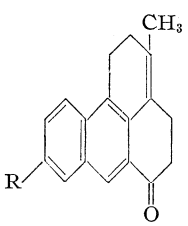



VIII

To circumvent ring closure to VI the carbomethoxy group was removed before cyclization as in previous studies with the lower homolog.[3] Saponification with barium hydroxide gave the crystalline dibasic acid V (R = H)[6] which lost carbon dioxide readily on warming in the presence of an acid catalyst. The product consisted of oily lactonic material and a mixture of unsaturated acids from which a pure isomer VII (R = H)[6] was isolated in 41% yield. This product and the crystalline lactone VIII (R = H) produced by treatment of VII (R = H)[6] with cold hydrogen fluoride[8] proved to be identical (by mixed melting point determinations) with samples prepared from IX (R = H) according to a scheme employed by Haberland[9] for the synthesis of VII (R = $OCH_3$) and VIII (R = $OCH_3$) by the cyclization of the keto acid IX (R = $OCH_3$). For the cyclization of IX (R = H) hydrogen fluoride proved to be much better than sulfuric acid, the lactone VIII (R = H) being obtained in 93% yield. In spite of this improvement the method involving the Stobbe condensation proved to be easier for preparing the unsaturated acid VII (R = H),[6] particularly since the conversion of the lactone into this acid did not proceed well.




IX




X

Even though Haberland's[9] attempts to cyclize the unsaturated acid VII (R = $OCH_3$) have been shown[5] to give what is most likely the ketone X (R = $OCH_3$) arising from cyclization into the aromatic nucleus, nevertheless it seemed worth investigating other methods of ring closure of VII (R = H), particularly since in the tetralone series[8] it was discovered that cyclization could take place into either the alicyclic or the aromatic nucleus depending on the conditions. Accordingly VII (R = H) was treated with zinc chloride, acetic acid and acetic anhydride as described for the cyclization of II,[3] but only dark intractable oils were produced. By reducing the amount of zinc chloride to trace quantity, however, a neutral nonsaponifiable oil was obtained from which a ketone crystallized in 21% yield (m. p. 152° after purification). Analysis was compatible with the formula $C_{18}H_{16}O$, and since both 14,15- and 15,16-dehydro-17-equilenone have considerably lower melting points,[5] this substance was presumed to be the product X (R = H) of cyclization into the aromatic nucleus. From the mother liquor a second ketone crystallized in 20% yield. This substance proved to be 14,15-dehydro-17-equilenone, IV (R = H) melting at 135° as shown by comparison of the ketone and semicarbazone with authentic samples. Since reduction of IV (R = H) is known to give β-17-equilenone,[5] the present scheme represents a new synthesis of desoxyequilenin. From previous experience it seems probable that some of the tautomeric 15,16-dehydro-17-equilenone remained in the oily residue.[5] An investigation in the methoxy series which is now in progress is expected to afford a new synthesis of 14,15-dehydroequilenin methyl ether, and hence of equilenin.[9a]

## Experimental[10]

**The Stobbe Condensation with 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene.**—A cold solution of 3.02 g. of potassium in 63 ml. of dry *t*-butyl alcohol was mixed with 12.9 g. of dimethyl succinate and 15 ml. of this mixture was added from a dropping funnel to 2.50 g. of the ketone (m. p. 72–73°) contained in the flask of a special apparatus,[11] the whole operation being conducted under an atmosphere of nitrogen. The flask was immersed in an oil-bath at 50° and the remainder of the solution added slowly with stirring over a period of four hours. After an additional hour at 50° the mixture was cooled, acidified with hydrochloric acid, and the alcohol removed under reduced pressure. The semi-solid residue was taken up in ether, washed with water, then extracted with 1 *N* ammonium hydroxide. Acidification of the alkaline solutions gave 3.57 g. (93% yield) of crude yellow oily half-ester which solidified on standing, m. p. 119–143°. Crystallization from benzene–petroleum ether (b. p. 60–68°) followed by recrystallization from dilute methanol gave 2.37 g. (61% yield) of colorless needles, m. p. 156–159°. Repeated recrystallization from this solvent raised the melting point of this substance, **β-carbomethoxy-β-(2-methyl-3,4-dihydro-1-phenanthryl)-propionic acid,**[6] to 159–160.5°.

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.78; H, 6.42.

**β-Carboxy-β-(2-methyl-3,4-dihydro-1-phenanthryl)-propionic Acid.**[6]—To a solution of 10.0 g. of the half-ester, m. p. 156–159°, in 860 ml. of alcohol was added a solution of 126 g. of barium hydroxide octahydrate in 720 ml. of water. The mixture was boiled under reflux for one hour, and most of the alcohol was removed under reduced pressure. The cooled (ice–salt-bath) semi-solid residue was acidified with 1 to 1 hydrochloric acid, the temperature

(8) *Cf.* W. S. Johnson, H. C. E. Johnson and Petersen, THIS JOURNAL, **67**, 1360 (1945).

(9) Haberland, *Ber.*, **72**, 1215 (1939); **76**, 621 (1943).

(9a) This expectation has now been realized, the acid VII (R = $OCH_3$),[6] m. p. 184–185°, giving 14,15-dehydroequilenin methyl ether in low yield. (Added in proof, March 22, 1949.)

(10) Unless otherwise specified, all melting points are corrected.

(11) See the apparatus used in "Step 4" of the synthesis of equilenin, ref. 5.

always being kept below 10° to prevent decarboxylation. The precipitated dibasic acid amounted to 9.51 g. (99% yield), m. p. 190–194° dec. A single recrystallization from acetone-benzene gave colorless prisms melting at 209–211° dec. After repeated recrystallization the m. p. was 209.5–210° dec.

*Anal.* Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.61, 73.52; H, 5.92, 5.77.

The **anhydride** was produced by the action of boiling acetyl chloride on the dibasic acid. Crystallization from benzene-petroleum ether (b. p. 60–68°) gave colorless prisms, m. p. 147.5–148°.

*Anal.* Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.97, 78.21; H, 5.38, 5.61.

**β-(2-Methyl-3,4-dihydro-1-phenanthryl)-propionic Acid, VII** (R = H).[6]—Decarboxylation of the dibasic acid (1.000 g.) (m. p. 209–210°) was effected by heating with 18 ml. of pyridine, 30 ml. of concentrated hydrochloric acid and 10 g. of oxalic acid. After twenty-five minutes under reflux the calculated volume of gas was evolved. The mixture was diluted with water and the organic material taken up in ether, washed with water and extracted with 1 *N* ammonium hydroxide. Acidification of the alkaline extracts gave 0.652 g. (76% yield) of colorless acid, m. p. 95–110°. Recrystallization from dilute methanol gave 0.352 g. (41% yield) of fairly pure material, m. p. 125–128°. Further recrystallization gave colorless plates, m. p. 131–132° undepressed on admixture with the sample of VII (R = H) prepared by the Haberland scheme (see below); calcd.: neut. equiv., 266.3. Found: neut. equiv., 265.0.

A sample of the unsaturated acid was lactonized by treatment with cold anhydrous hydrogen fluoride.[8] Recrystallization of the neutral fraction from methanol gave the lactone VIII (R = H), m. p. 155–157°, undepressed on admixture with the sample prepared by the Haberland synthesis (see below).

**Cyclization of the Unsaturated Acid VII** (R = H).[6]—A solution of 0.400 g. of the above unsaturated acid in 20 ml. of acetic anhydride to which 2 drops of a solution of zinc chloride in acetic acid (20 mg./ml.) had been added was boiled under reflux for eight hours in an atmosphere of nitrogen. The acetic anhydride was decomposed with methanol, and the volatile materials removed on the steam-bath. The red solution was diluted with water, and extracted with ether. The ether solution was washed with 5% sodium hydroxide to remove acidic material, concentrated, and the residue heated on the steam-bath with 20 ml. of 10% potassium hydroxide solution for ten minutes in an atmosphere of nitrogen. The unsaponified material was taken up in ether, washed with 5% sodium hydroxide, 5% hydrochloric acid, and saturated sodium chloride solution. The red glass remaining on evaporation of the ether was evaporatively distilled at 155° (0.1 mm.) giving 0.328 g. of yellow semi-solid distillate. Crystallization from ether gave 0.078 g. (21% yield) of pale yellow needles, m. p. 145.5–150°, probably X (R = H). Repeated recrystallization from alcohol gave yellow needles, m. p. 152.1–152.7°.

*Anal.* Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.14; H, 6.15.

The **semicarbazone** crystallized from pyridine in the form of pale yellow needles, m. p. (in an evacuated tube) 245.2–246.2° dec. (introduced at 235°).

*Anal.* Calcd. for $C_{19}H_{19}ON_3$: C, 74.73; H, 6.27. Found: C, 74.82; H, 5.94.

The filtrate from which the 152° ketone separated was evaporated to dryness and crystallized from alcohol to give 0.074 g. (20% yield) of colorless needles, m. p. 118–123°. Recrystallization gave material melting at 134.5–135.5° alone or when mixed with an authentic specimen of 14,15-dehydro-17-equilenone, m. p. 135.5–136°.[5]

The **semicarbazone** crystallized from pyridine in the form of colorless needles, m. p. 248–250° dec., undepressed on admixture with a sample of the derivative (m. p. 248.5–250° dec.) prepared from authentic ketone.[5]

*Anal.* Calcd. for $C_{19}H_{19}ON_3$: C, 74.73; H, 6.27. Found: C, 74.64; H, 5.97.

**Cyclization of the Half-Ester V** (R = $CH_3$).[6]—A mixture of 1.2 g. of the crude half-ester, 6 ml. of acetic acid containing fused zinc chloride (20 mg./ml.), 6 ml. of acetic acid and 12 ml. of acetic anhydride was boiled under reflux for ninety minutes, cooled, treated with water to hydrolyze the acetic anhydride and evaporated under reduced pressure. The residual red oil was taken up in ether, washed with 5% potassium hydroxide solution and, after evaporation of the solvent, crystallized from benzene–ligroin. **Methyl 3-methyl-1,2,3,5-tetrahydroacephenanthryl-3a,4-ene-5-one-4-acetate, VI** (R = $CH_3$), was thus obtained as bright yellow prisms, m. p. 134–137°; yield 0.340 g. (30%). A sample prepared for analysis melted at 136.5–138°.

*Anal.* Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.10; H, 5.98.

Ultraviolet absorption in ethanol: $\lambda_{max.}$ 235 mμ (log *E* 4.30), 279 (4.73), 412 (3.41).

A cyclization with 0.150 g. of pure half-ester, m. p. 156–158°, gave 0.070 g. (49% yield) of crude product, m. p. 124–128°.

The same substance was produced when the cyclization was conducted with phosphorus pentoxide in boiling benzene.

**Cyclization of the Half-Ester V** (R = $C_2H_5$)[6] was carried out with the crude acidic material produced by the condensation of 2.10 g. of the ketone III (R = $CH_3$) with 1.74 g. of diethyl succinate in the presence of potassium *t*-butoxide according to procedures already described.[3] The oily half-ester could not be crystallized and was cyclized directly with 13.5 ml. of acetic acid containing fused zinc chloride (20 mg./ml.), 18.5 ml. of acetic acid and 27 ml. of acetic anhydride as described above for the methyl ester. The crude product, 0.150 g., crystallized from benzene–ligroin in the form of yellow prisms, m. p. 113–118°. Recrystallization raised the m. p. to 115–116.5°.

*Anal.* Calcd. for $C_{21}H_{20}O_3$: C, 78.72; H, 6.29. Found: C, 78.48; H, 5.98.

Ultraviolet absorption in ethanol: $\lambda_{max.}$ 235 mμ (log *E* 4.30), 279 (4.72), 412 (3.40).

**Oxidation of Keto Ester VI** (R = $CH_3$) **to Benzenepentacarboxylic Acid.**—A mixture of 0.340 g. of the keto ester, 2 ml. of concentrated nitric acid and 1.5 ml. of water was heated in a sealed tube at 180–200° for eighteen hours. The residue obtained after evaporation was crystallized once from concentrated nitric acid; yield 0.058 g. of crude colorless acid, m. p. 222–227°, dec. (reported,[12] 232–233°, dec.). The pentamethyl ester prepared with diazomethane melted at 146.5–148.8° (reported,[13] 147–148°).

**1-Bromo-3-methyl-5-(1-naphthyl)-2-pentanone.**—A solution of 11.40 g. of α-methyl-γ-(1-naphthyl)-butyric acid in 25 ml. of chloroform was treated with 18 ml. of purified thionyl chloride. After refluxing for one hour the mixture was evaporated at 40° under reduced pressure, the thionyl chloride being completely removed by adding small portions of chloroform to the residue and repeating the evaporation. The acid chloride was dissolved in 25 ml. of dry ether and added slowly to a dry ether solution of diazomethane prepared from 20.8 g. of nitrosomethylurea. After one and one-half hours at room temperature 25 ml. of 48% hydrobromic acid was added with shaking. The organic layer was separated, washed with water, then with a saturated solution of sodium bicarbonate, and dried over anhydrous sodium sulfate. Crystallization of the oily residue obtained on evaporation from ether-petroleum ether gave 8.80 g. of brownish product, m. p. 57–60°. An additional 1.65 g. of material, m. p. 52–58° was crystallized from the mother liquor making the total yield 68%. This product was satisfactory for the next step of the synthesis which gave homogeneous material in 86% yield, thus establishing the nature of the bromo ketone which could not be purified satisfactorily for analysis.

(12) Fleischer and Retze, *Ber.*, **56**, 228 (1923).

(13) Ruzicka and Rudolph, *Helv. Chim. Acta*, **10**, 915 (1927).

**4-Keto-4-methyl-7-(1-naphthyl)-heptanoic Acid, IX** (R = H).—The bromo ketone (5.16 g.) in 20 ml. of dry toluene was added to a solution of sodiomalonic ester prepared from 4.08 g. of diethyl malonate and 0.38 g. of sodium shot in 20 ml. of toluene, whereupon a precipitate formed immediately. After refluxing for four hours, the mixture was evaporated under reduced pressure and the residue saponified by heating for four hours on the steam-bath with 11.5 g. of potassium hydroxide in 15 ml. of water and 5 ml. of alcohol. The substituted malonic acid which was separated by acidification, followed by ether extraction, was decarboxylated by heating at 150–160° for twenty minutes. The brown residue was dissolved in benzene, treated with Norit, and crystallized from benzene–petroleum ether; yield 4.14 g. of slightly brownish needles, m. p. 82–84°. A sample purified for analysis by repeated recrystallization from benzene–petroleum ether was colorless and melted at 89–90°.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.80; H, 7.20.

**Lactone, VIII** (R = H) **of β-(1-Hydroxy-2-methyl-1,2,-3,4-tetrahydro-1-phenanthryl)-propionic Acid.**—Anhydrous hydrogen fluoride (about 40 g.) was added to 1.15 g. of the keto acid contained in a platinum vessel chilled in an ice–salt mixture. After five minutes the reagent was evaporated in a current of air, and the solid residue taken up in ether and washed with sodium bicarbonate solution. The residue obtained on evaporation of the ether was triturated with 5 ml. of cold ether leaving 1.00 g. (93% yield) of tan crystals of the lactone, m. p. 152–155°. Recrystallization from methanol gave colorless prisms, m. p. 155–156°.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.16; H, 6.81. Found: C, 81.38; H, 6.92.

The lactone was also produced in high yield when the methyl ester of IX (R = H) was treated with hydrogen fluoride.

**β-(1-Hydroxy-2-methyl-1,2,3,4-tetrahydro-1-phenanthryl)-propionic acid** was prepared from 0.150 g. of the above lactone by hydrolysis with 0.250 g. of sodium hydroxide in 10 ml. of water. After heating for three hours on the steam-bath the clear solution was chilled and acidified slowly with cold dilute acetic acid. The crystalline hydroxy acid which precipitated (0.145 g.) was recrystallized from methanol giving colorless needles, m. p. 187–188° with dec. (lactonization). Further recrystallization did not raise the melting point.

*Anal.* Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.97; H, 7.12.

In contrast to the 7-methoxy derivative[9] this hydroxy acid showed no tendency to undergo dehydration to the unsaturated acid, but reverted to the lactone. In order to prepare the unsaturated acid VII (R = H) the procedure of Bachmann, Cole and Wilds[14] for the dehydration of β-hydroxy esters was applied. Thus the hydroxy ester produced from 0.100 g. of the lactone and 2 ml. of methanolic hydrogen chloride, was treated with pyridine (2 drops) and thionyl chloride (3 drops) in 0.5 ml. of benzene for thirty minutes at room temperature, then for ten minutes at 40°. The product was worked up *via* saponification with 45% potassium hydroxide; yield 0.035 g. (35%) of colorless crystals, m. p. 122–126°, soft at 118°. Two recrystallizations from benzene–petroleum ether gave colorless plates, m. p. 131.5–132°.

*Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.16; H, 6.81. Found: C, 81.10; H, 7.16.

## Summary

A synthetic scheme involving the Stobbe condensation, previously developed for the production of steroid-like structures from 1-keto-1,2,3,4-tetrahydrophenanthrene, has now been applied with some modifications to the 2-methyl derivative to give a homolog containing the 13-angular methyl group. The product, 14,15-dehydro-17-equilenone, is the precursor of β-17-equilenone (3-desoxyequilenin).

(14) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

MADISON, WISCONSIN RECEIVED NOVEMBER 13, 1948

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Decarboxylation and Cyclization Reactions of Some Pimelic Acid Derivatives

BY ROBERT L. FRANK AND JAMES B. MCPHERSON, JR.

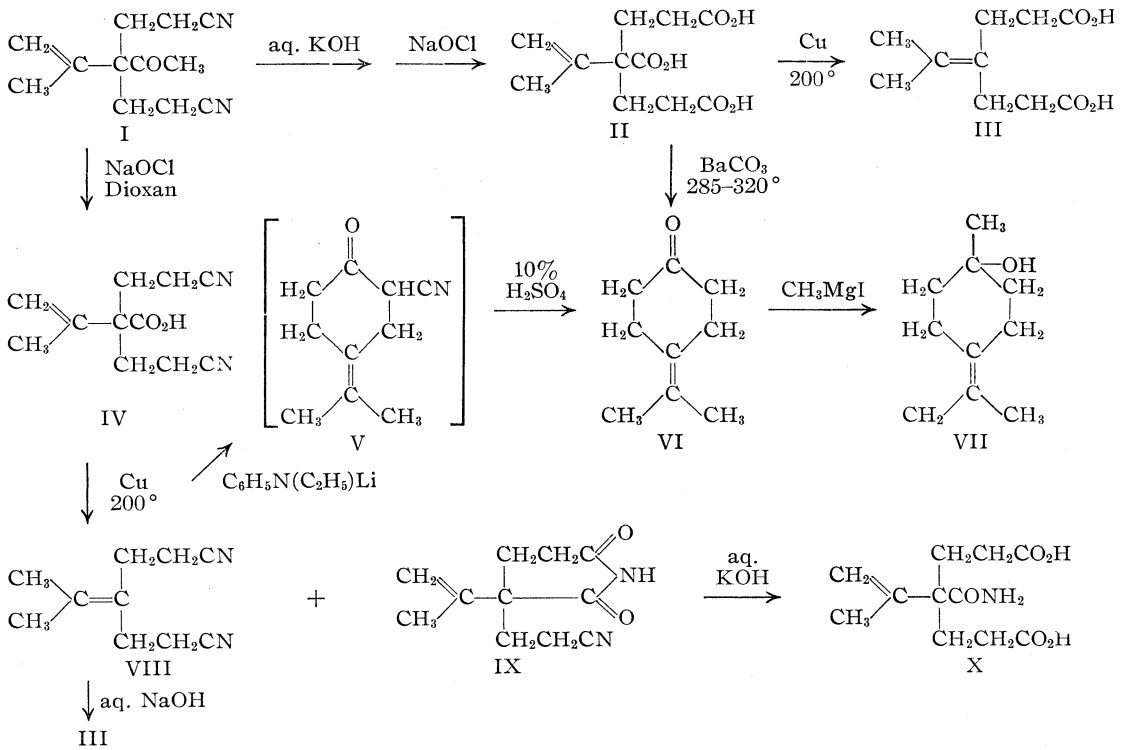
The cyanoethylation reaction described by Bruson and Riener[1] affords a convenient method for the preparation of pimelic acid derivatives, certain of which suggest themselves as possible intermediates in the syntheses of cyclohexanones related to some of the monocyclic terpenes. In this paper are reported the decarboxylations and ring closures of a group of compounds derived from γ-acetyl-γ-isopropenylpimelonitrile (I), the cyanoethylation product of mesityl oxide. We have been particularly interested in the lability of the unsaturation of the isopropenyl group during these reactions.

Pyrolysis of γ-carboxy-γ-isopropenylpimelic acid (II), a derivative reported by Bruson and Riener,[1] at 285–320° in the presence of barium carbonate resulted in simultaneous decarboxylation and ring closure to give a substituted cyclohexanone. Ozonolysis showed this material to be almost entirely 4-isopropylidenecyclohexanone (VI), since the products isolated were acetone and 1,4-cyclohexanedione. Derivatives of formaldehyde or formic acid were not obtained, although these were detected by faint color tests. Thus this pyrolysis was accompanied by nearly complete isomerization of the double bond of the isopropenyl group. Further evidence for the isopropylidene structure for the cyclohexanone was obtained by reaction with methylmagnesium iodide to give γ-terpineol (VII) rather than β-terpineol. Incidentally, this constitutes a total synthesis for this naturally-occurring terpene.[2]

During the heating of γ-carboxy-γ-isopropenylpimelic acid (II) it was noted that carbon dioxide was evolved at temperatures considerably below 300°. This indicated that simple decarboxylation might be occurring before the cyclization reaction,

(1) Bruson, THIS JOURNAL, **64**, 2457 (1942); Bruson and Riener, *ibid.*, **65**, 18 (1943).

(2) Simonsen, *Ind. For. Rec.*, **10**, 1 (1923).




a conclusion confirmed by heating the triacid (II) with copper-bronze at 200° to give 32% of a dicarboxylic acid. Further work as described below showed the latter to be γ-isopropylidenepimelic acid (III). Thus even under these milder conditions there was isomerization of the isopropenyl group.

Similar decarboxylation of γ-carboxy-γ-isopropenylpimelonitrile (IV), obtained in 81% yield by the haloform reaction on γ-acetyl-γ-isopropenylpimelonitrile (I), also resulted in shifting of the double bond. The product (VIII), obtained in 34% yield, gave acetone on ozonolysis; no formaldehyde was detected. Hydrolysis of the dinitrile gave the same dicarboxylic acid obtained from γ-carboxy-γ-isopropenylpimelic acid (II). We therefore believe the dibasic acid to have the isopropylidene structure represented by III.

As a by-product in the decarboxylation of the dinitrile (IV) there was also obtained an equal amount of a crystalline solid. This was shown by analysis and molecular weight determination to be isomeric with the starting material (IV), although not subject to similar decarboxylation. Further pyrolysis gave only tar. A neutral equivalent showed the presence of no free carboxyl group, although the compound was soluble in aqueous sodium hydroxide. It was insoluble in sodium bicarbonate solution. A saponification equivalent indicated two saponifiable groups; the product of this determination was isolated as a crystalline dicarboxylic acid having the composition $C_{11}H_{17}NO_5$. To this has been assigned the structure γ-formamido-γ-isopropenylpimelic acid (X) and to the by-product itself the structure α-cyanoethyl-α-isopropenylglutarimide (IX). Supporting evidence is the infrared absorption spectrum of the latter and its comparison with the spectrum of glutarimide in the CO (1705 cm.$^{-1}$) and NH (3000–3200 cm.$^{-1}$) regions (Fig. 1). The failure of complete saponification of α-cyanoethyl-α-isopropenylglutarimide (IX) to a tricarboxylic acid is to be expected because of the tertiary nature of the γ-formamido grouping (X).

The formation of an imide by interaction of a cyano and a carboxyl group has been known since 1869[3] and has recently been studied by Wiley and Guerrant.[4]

A further reaction of 4-isopropylidenepimelonitrile (VIII) has been its ring closure by the Thorpe reaction to 2-cyano-4-isopropylidenecyclohexanone (V). Hydrolysis of the latter with 10% aqueous sulfuric acid gave a low yield of a ketone, the 2,4-dinitrophenylhydrazone of which gave no depression in mixed m. p. with that of 4-isopropylidenecyclohexanone (VI). A semicarbazone was also obtained; this was different from but isomeric with that formed by the 4-isopropylidenecyclohexanone (VI) derived from γ-carboxy-γ-isopropenylpimelic acid (II). Its formation indicates the possible presence of the isopropenyl analog of the ketone (VI).

Infrared absorption spectra have also been studied because it was hoped they might provide a method for differentiating isopropenyl and isopropylidene groups in this series. As indicated by

(3) Gautier, *Z. Chem.*, **5**, 127 (1869).
(4) Wiley and Guerrant, THIS JOURNAL, **71**, 981 (1949).

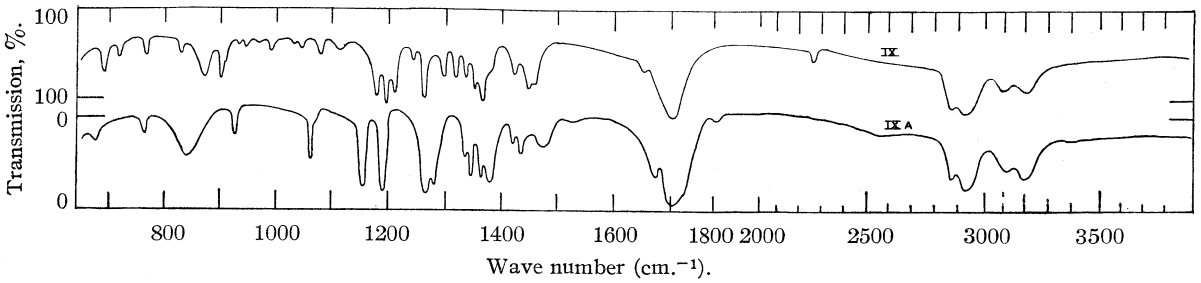



Fig. 1.—Infrared spectra of glutarimides: IX is α-cyanoethyl-α-isopropenylglutarimide; IXA is glutarimide.

Thompson and Torkington,[5] however, both terminal and non-terminal double bonds produce absorption maxima in the region 890–970 cm.$^{-1}$. In this region particularly the absorption depends not only on the position of the double bond, but also on the complete molecular structure. As shown in Fig. 2, all of our compounds, isopropenyl and isopropylidene, exhibit maxima between 890 and 918 cm.$^{-1}$.

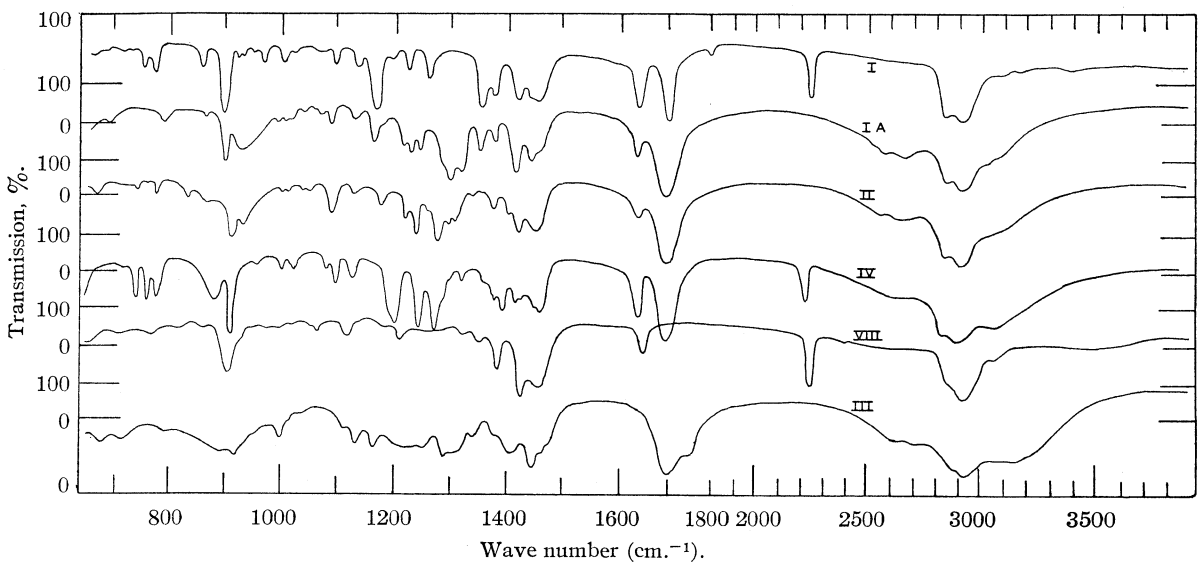



Fig. 2.—Infrared spectra: the Roman numerals correspond to those of the manuscript; IA is γ-acetyl-γ-isopropenylpimelic acid.

## Experimental

**γ-Acetyl-γ-isopropenylpimelonitrile (I).**—The method of Bruson and Riener[1] was employed using 98.0 g. (1.00 mole) of purified mesityl oxide, 106.0 g. (2.00 moles) of acrylonitrile, 100 ml. of *t*-butyl alcohol and 5 g. of Triton B (40% aqueous benzyltrimethylammonium hydroxide). The yield of product was 72 g. (35%), m. p. 115–117°; saponification equiv. calcd.: 102.1; found: 98.0. The purity of the mesityl oxide is critical, and the commercial product generally results in low yields. Purification is accomplished by washing with aqueous sodium carbonate and with water, drying over calcium chloride, and distilling.

**γ-Acetyl-γ-isopropenylpimelic Acid and γ-Carboxy-γ-isopropenylpimelic Acid (II).**—The procedures of Bruson and Riener[1] were used. Saponification of 28.6 g. (0.14 mole) of γ-acetyl-γ-isopropenylpimelonitrile by means of 20.8 g. (0.37 mole) of potassium hydroxide in 230 ml. of water gave 24.4 g. (72%) of γ-acetyl-γ-isopropenylpimelic acid, m. p. 137.5–138.5°; neutral equiv. calcd., 121.1; found, 120.1. The haloform reaction with 38.6 g. (0.159 mole) of this acid dissolved in 84 ml. of 20% aqueous sodium hydroxide and 512 ml. of 9.5% sodium hypochlorite solution, prepared by the method of Newman and Holmes,[6] yielded 26.0 g. (67%) of colorless crystalline tricarboxylic acid, m. p. 158–160°; neutral equiv. calcd., 81.4; found, 81.5.

**4-Isopropylidenecyclohexanone (VI).**[7]—An intimate mixture of 46.7 g. (0.191 mole) of γ-carboxy-γ-isopropenylpimelic acid and 1.51 g. (0.0076 mole) of barium carbonate was heated in three separate batches in a 50-ml. distilling flask fitted with a thermometer which extended to the bottom of the flask. Strong effervescence began at 285°, causing the temperature to drop to 275°. The temperature was ultimately increased to 320° as a mixture of water and yellow oil distilled. The distillates from the three batches were combined, the water separated, the oil dissolved in ether, washed with aqueous sodium bicarbonate and with water, and dried over calcium sulfate. Distillation gave 12.0 g. (45%) of colorless liquid product having a cedar-like odor, which on redistillation had the constants: b. p. 54° (1 mm.); $n^{20}$D 1.4817; sp. gr.$^{20}_{20}$ 0.959; *MR* calcd. 41.1; *MR* found 41.2.

(5) Thompson and Torkington, *Proc. Roy. Soc.* (*London*), **184A**, 3 (1945).

(6) Newman and Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 428.

(7) Preliminary work on this reaction was performed by Mrs. Blossom Katz.

*Anal.*[8] Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.07, 77.36; H, 10.10, 10.10.

The semicarbazone, prepared by the directions of Shriner and Fuson,[9a] melted at 196–198° after six crystallizations from ethanol.

*Anal.* Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78. Found: C, 61.63; H, 8.67.

The 2,4-dinitrophenylhydrazone, prepared by the method of Shriner and Fuson,[9b] recrystallized three times from ethanol and seven from methanol to form orange platelets, melted at 130.5–132°.

*Anal.* Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70. Found: C, 56.78; H, 5.75.

**Ozonolysis of 4-Isopropylidenecyclohexanone (VI).**—A stream of 4% ozone was passed at a rate of 88 ml. per minute through a solution of 1.01 g. (0.0072 mole) of 4-isopropylidenecyclohexanone in 15 ml. of methylene chloride in a Dry Ice-bath for two and one-half hours. The ozonide solution was then added dropwise at room temperature with stirring to a mixture of 1.7 g. of 30% hydrogen peroxide, 0.1 ml. of concentrated sulfuric acid, and 35 ml. of water. The mixture was stirred at room temperature for forty-five minutes and then gradually heated to boiling and refluxed for one hour. The methylene chloride escaping through the condenser was collected in a Dry-Ice trap and tested for formaldehyde by means of methone.[10] No formaldehyde was detected. The condenser was set downward for distillation and 24 ml. of aqueous distillate collected. Testing of this distillate with methone[10] failed to detect formaldehyde, but aqueous resorcinol and concentrated sulfuric acid gave an orange-red ring, indicating a trace of formaldehyde.[11a] Heating with mercuric oxide gave a faint gray precipitate of mercury, a weak indication of formic acid.[11b] The haloform reaction[9c] gave a copious precipitate of iodoform, and acetone was further identified by the formation of its 2,4-dinitrophenylhydrazone,[9b] m. p. 120–123°, and mixed m. p., 121–125°, with an authentic sample.

The aqueous pot residue from the above distillation was neutralized with sodium carbonate, extracted with ether, acidified with sulfuric acid, and saturated with ammonium sulfate. A brown oil separated and was removed. The aqueous solution was extracted with chloroform, the chloroform solution washed with water, dried over magnesium sulfate, and evaporated to dryness. The residual oil was dissolved in 95% ethanol and the solution evaporated to yield white crystalline 1,4-cyclohexanedione, m. p. 68–73°. This was sublimed at 60° and 28 mm. pressure to give about 50 mg. of colorless needles, m. p. 77–78°. A mixed m. p. with an authentic sample, prepared by the method of Baeyer,[12] melted at 77–78°.

**γ-Terpineol (VII).**—The method was based on that of Perkin[13] for β-terpineol. A solution of 3.98 g. (0.029 mole) of 4-isopropylidenecyclohexanone in 10 ml. of anhydrous ether was added slowly with stirring to the Grignard reagent from 15.6 g. (6.84 ml., 0.118 mole) of methyl iodide, 2.64 g. (0.109 gram-atom) of magnesium, and 70 ml. of anhydrous ether. The reaction mixture, after standing overnight, was decomposed by pouring into a mixture of 8 g. of ammonium chloride in 125 g. of ice and water. The solution was barely acidified with hydrochloric acid, the ether layer removed, and the aqueous layer extracted with three 25-ml. portions of ether. The combined ether solutions were washed with dilute aqueous sodium bicarbonate and with water, dried over magnesium sulfate, evaporated, and the oily residue steam distilled. The crude yellow liquid product, separated from the distillate, weighed 1.76 g. Distillation (65° ( 1 mm.)) gave 0.77 g. of oil which crystallized on chilling, m. p. 57–66°. Sublimation at 45–50° (15 mm.) yielded 0.16 g. (3.6%) of white tabular crystals, m. p. 63–67° (lit.[14] 69–70°), having an odor reminiscent of lilacs.

*Anal.* Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 76.85; H, 11.97.

**γ-Isopropylidenepimelic Acid (III).**—Five grams (0.0205 mole) of γ-carboxy-γ-isopropenylpimelic acid mixed with 0.5 g. of copper–bronze powder was heated under a stream of nitrogen to 195–205°. Formation of carbon dioxide was evidenced by a white precipitate when the evolved gases were passed through aqueous calcium hydroxide. The mixture was cooled, dissolved in acetone, filtered and the filtrate evaporated to a brown oil. This, after solution in 10% aqueous sodium hydroxide and acidification with concentrated hydrochloric acid, yielded 1.3 g. (32%) of crystalline product, m. p. 102–105°. An additional 0.3 g. (7%) was obtained by extraction of the acidified solution. Recrystallization of the combined product gave shiny white platelets, m. p. 104.5–106° (lit.[15] 97°); neutral equiv. calcd., 100.1; found, 101.1.

*Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.05; H, 8.29.

**γ-Carboxy-γ-isopropenylpimelonitrile (IV).**—To a stirred solution of 2.68 moles of sodium hypochlorite in *ca.* 2300 ml. of water in a 5-l., three-necked flask was added 850 ml. of peroxide-free dioxane and the mixture was cooled to 0–10°. A solution of 121.6 g. (0.596 mole) of γ-acetyl-γ-isopropenylpimelonitrile in 810 ml. of dioxane was then added dropwise, and the cold reaction mixture stirred for four additional hours. The excess hypochlorite was decomposed by the addition of aqueous sodium bisulfite, the reaction mixture filtered, and the filtrate washed with two 200-ml. portions of ether. The aqueous filtrate was acidified with concentrated hydrochloric acid and allowed to stand for twelve hours at 0°. The white solid then present was collected on a filter, washed with cold water, and dried at 90°. It was digested in 900 ml. of hot water to dissolve inorganic salts, precipitated by chilling, collected on a filter, and dried at 100° to yield 99.9 g. (81%) of white powder, m. p. 164–166°. An analytical sample was prepared by recrystallization as shiny platelets from ethylene chloride, m. p. 166–167.5°; neutral equiv. calcd., 206.2; found, 210.3.

*Anal.* Calcd. for $C_{11}H_{14}N_2O_2$: N, 13.59. Found: N, 13.44.

**γ-Isopropylidenepimelonitrile (VIII) and α-Cyanoethyl-α-isopropenylglutarimide (IX).**—Forty-five grams (0.184 mole) of γ-carboxy-γ-isopropenylpimelonitrile was mixed with 4.5 g. of copper–bronze and 4.5 g. of powdered soft glass and heated in a small flask to 200–230° under a stream of nitrogen until evolution of carbon dioxide had ceased. The mixture was cooled and 50 ml. of benzene added, and the solid residue removed by filtration. The filtrate was washed with dilute sulfuric acid, aqueous sodium bicarbonate and water, dried over magnesium sulfate, and some of the benzene removed by distillation. At this point crystals formed in the solution; addition of ether increased this formation. These were removed by filtration and combined with the original solid residue. Fractional distillation of the benzene solution then gave 12.3 g. (41%) of colorless liquid γ-isopropylidenepimelonitrile, b. p. 135–137° (1 mm.); $n^{20}D$ 1.4733.

*Anal.* Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70. Found: C, 73.81; H, 8.59.

The combined solid residue, containing copper and glass, was warmed with 50 ml. of acetone and filtered. Evaporation of the filtrate gave a greenish-brown solid which after two recrystallizations, from dilute hydro-

(8) Microanalyses were performed by Misses Emily Davis, Betty Alice Snyder, Theta Spoor, Jane Wood, Mr. Maurice Dare and Mr. Howard Clark.

(9) (a) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, rev. ed., 1940, p. 142; (b) p. 143; (c) p. 53.

(10) Ionescu and Bodea, *Bull. soc. chim.*, **47**, 1408 (1930).

(11) (a) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, 1941, p. 49; b) p. 179.

(12) Baeyer, *Ann.*, **278**, 91 (1893).

(13) Perkin, *J. Chem. Soc.*, **85**, 654 (1904).

(14) Baeyer, *Ber.*, **27**, 444, 745 (1894).

(15) Perkin and Simonsen, *J. Chem. Soc.*, **91**, 1736 (1907).

chloric acid and from ethanol, yielded 9.8 g. (26%) of white tabular $\alpha$-cyanoethyl-$\alpha$-isopropenylglutarimide, m. p. 119–121°: mol. wt. calcd., 206; found (Rast), 221, 198; saponification equiv. calcd. for two saponifiable groups, 103.1; found, 100.2, 99.1. The product was soluble in 5% aqueous sodium hydroxide and insoluble in 5% aqueous sodium bicarbonate.

*Anal.* Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 63.84; H, 6.93; N, 13.53.

When mixed with 0.7 g. of copper–bronze, 7.0 g. of product heated to 350° showed no apparent decarboxylation; only a black tar was formed.

**Hydrolysis of $\gamma$-Isopropylidenepimelonitrile (VIII).**—A mixture of 0.7 g. (0.0043 mole) of the dinitrile, 0.4 g. (0.01 mole) of sodium hydroxide and 5 ml. of water was refluxed for six hours. Acidification with concentrated hydrochloric acid and recrystallization of the precipitate from petroleum ether and from water gave 0.1 g. of shiny white platelets, m. p. 104.5–106°; mixed m. p. with $\gamma$-isopropylidenepimelic acid (III) 104.5–106°.

**Ozonolysis of $\gamma$-Isopropylidenepimelonitrile (VIII).**—Two grams (0.0123 mole) of the dinitrile dissolved in 25 ml. of purified carbon tetrachloride was cooled in an ice–salt-bath and a stream of *ca.* 200 ml. per minute of 2.6% ozone passed through it for one hour. The ozonide formed a separate layer during this time. The solvent was evaporated (30° at 30 mm.), and 70 ml. of water and 2.85 g. of zinc dust added to the liquid ozonide. The mixture was heated gradually to boiling and 50 ml. distilled into an ice-cooled receiver containing 10 ml. of water. Both the distillate and the residue, tested by means of methone,[10] showed no indication of formaldehyde; nor was formic acid detected.[11b] From the aliquot of the distillate was prepared a 17% yield (based on the dinitrile) of the 2,4-dinitrophenylhydrazone of acetone,[9b] m. p. 125–126°; mixed m. p. with an authentic sample 125–126°.

**$\gamma$-Formamido-$\gamma$-isopropenylpimelic Acid (X).**—One gram (0.0048 mole) of $\alpha$-cyanoethyl-$\alpha$-isopropenylglutarimide (IX) was heated just below the b. p. for one hour with 1.1 g. (0.019 mole) of potassium hydroxide in 20 ml. of water. The solution was cooled, acidified with concentrated hydrochloric acid, evaporated to dryness at room temperature; the solid was dissolved in acetone, the solution filtered, and the filtrate allowed to evaporate to give 0.9 g. (77%) of colorless tablets, m. p. 154–160°. Two crystallizations from water raised the m. p. to 164.5–166°; neutral equiv. calcd., 121.6; found, 121.1.

*Anal.* Calcd. for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.05; N, 5.76. Found: C, 54.53; H, 7.15; N, 5.88.

Boiling of $\gamma$-formamido-$\gamma$-isopropenylpimelic acid with 3% aqueous potassium hydroxide for sixteen hours and with sulfuric–nitrous acid mixture[16] for one hour failed to hydrolyze the amide to a tricarboxylic acid.

**Ring Closure of $\gamma$-Isopropylidenepimelonitrile (VIII).**—A solution of lithium N-ethylaniline was prepared by the procedure of Ziegler and co-workers[17] from 47.6 g. (0.392 mole) of N-ethylaniline in 200 ml. of ether and *n*-butyllithium solution made by the directions of Gilman, Zoellner and Selby[18] from 4.1 g. (0.59 gram-atom) of lithium and 25.3 g. (0.274 mole) of *n*-butyl chloride in 50 ml. of ether. This was stirred and heated to gentle refluxing in a 1-l., three-necked flask, and a solution of 16.3 g. (0.10 mole) of $\gamma$-isopropylidenepimelonitrile in 100 ml. of anhydrous ether was added dropwise over a period of five hours. A white precipitate formed as soon as the addition was begun. The reaction mixture was then poured quickly into 360 ml. of 2 *N* hydrochloric acid. The layers were separated; the aqueous layer extracted with three 100-ml. portions of ether, and all the ether solutions combined and washed twice with 20% hydrochloric acid and with water, then dried over magnesium sulfate. Evaporation of the solution gave 13.8 g. of a brown oil, crude 2-cyano-4-isopropylidenecyclohexanone. Attempts to hydrolyze this oil were unsuccessful using 10% aqueous sodium hydroxide and 37 and 50% sulfuric acid solutions. Hydrolysis was accomplished in low yield by means of 10% aqueous sulfuric acid. To 718 ml. of 10% acid was added 8.4 g. of the oil, and the mixture was refluxed for six hours, then steam-distilled. The residue was refluxed for an additional twelve hours and steam distilled. The combined distillates were extracted with ether, the extracts dried over magnesium sulfate, and evaporated to leave 1.0 g. of residual oil from which a 2,4-dinitrophenylhydrazone[9b] and a semicarbazone[9a] were prepared. The 2,4-dinitrophenylhydrazone, orange platelets from ethanol, m. p. 130–132°, showed no depression in mixed m. p. with that of 4-isopropylidenecyclohexanone (VI) prepared by pyrolysis of the triacid (II).

*Anal.* Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70. Found: C, 56.39; H, 5.93.

The semicarbazone, colorless crystals from ethanol, m. p. 193–195°, when mixed with that of 4-isopropylidenecyclohexanone (VI), m. p. 196–198°, gave a depressed m. p. 176–185°.

*Anal.* Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78. Found: C, 61.60; H, 8.91.

**Infrared Absorption Spectra.**—Determinations were kindly carried out by Mrs. J. L. Johnson, using a Perkin–Elmer Model 12B infrared spectrometer with rock salt optics. The solids were suspended in Nujol for the measurements; the liquid was used pure in a 0.025-mm. cell.

## Summary

1. $\gamma$-Acetyl-$\gamma$-isopropenylpimelonitrile, the cyanoethylation product of mesityl oxide, has been studied as a starting material for substituted cyclohexanones related to monocyclic terpenes.

2. Decarboxylations of $\gamma$-carboxy-$\gamma$-isopropenylpimelonitrile and $\gamma$-carboxy-$\gamma$-isopropenylpimelic acid, with and without ring closure of the latter, result in rearrangement of the isopropenyl to isopropylidene groups.

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(16) Bouvealt, *Bull. soc. chim.*, **9**, 368 (1893); Haller and Bauer, *Compt. rend.*, **152**, 1638 (1911).

(17) Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 116 (1933); Ziegler and Aurnhammer, *ibid.*, **513**, 55 (1934).

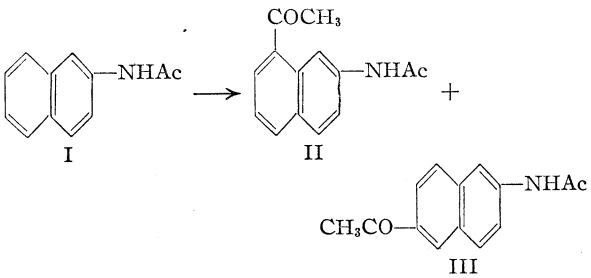
(18) Gilman, Zoellner and Selby, THIS JOURNAL, **54**, 1957 (1932).

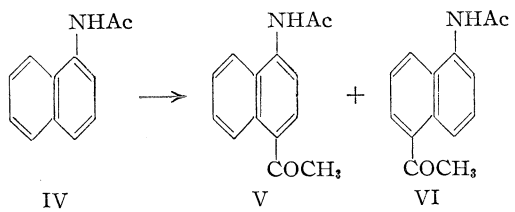
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Directive Influence of the Acetylamino Group in the Friedel–Crafts Acylation of the Acetylaminonaphthalenes

BY NELSON J. LEONARD AND ARCHIBALD M. HYSON[1]

The structure of the main product of Friedel–Crafts acetylation of acet-2-naphthalide (I) was recently established[2] as 7-acetylamino-1-acetonaphthone (II). The structure of the secondary product obtained in the same reaction[3] has now been established as 6-acetylamino-2-acetonaphthone (III). The primary and secondary products of Friedel–Crafts acetylation of acet-1-naphthalide (IV) have been proved to be 4-acetylamino-1-acetonaphthone (V) and 5-acetylamino-1-acetonaphthone (VI).




The isolation of an isomeric acetylaminoacetonaphthone, along with the main product (II)[2] of the Friedel–Crafts acetylation of I, was previously realized by Brown, Jacobs, Winstein, Levy, Moss and Ott.[3] They suggested that the isomer was probably the 6-substituted product, and this assumption has now been proved correct. The minor product (III) was converted to 6-hydroxy-2-acetonaphthone, which was methylated to give 6-methoxy-2-acetonaphthone, and this was oxidized to 6-methoxy-2-naphthoic acid. All three compounds were known previously, and direct comparison with an authentic sample of the acid was also possible. The ratio of the products II and III of ring-acetylation was approximately 12:1 (on the basis of amounts isolated after hydrolysis). The reaction proceeded in an identical manner when 2-naphthylamine was used and acet-2-naphthalide was formed *in situ*.

Since the β-acetylamino group was found to direct substitution entirely in the unsubstituted ring, it was of interest to determine the directive influence of the acetylamino group in the α-position. The products of Friedel–Crafts acetylation of acet-1-naphthalide (IV) were V and VI, isolated as 4-amino-1-acetonaphthone and 5-amino-1-acetonaphthone in a ratio of approximately 4:1. The reaction proceeded in an identical manner when 1-naphthylamine was used and acet-1-naphthalide was formed *in situ*. The structure of 4-amino-1-acetonaphthone was proved by conversion to a hydroxyacetonaphthone and a methoxyacetonaphthone identical with compounds prepared by the Friedel–Crafts acetylation of 1-methoxynaphthalene,[4] the structures of which had been established unequivocally as 4-hydroxy-1-acetonaphthone and 4-methoxy-1-acetonaphthone. The structure of the 5-isomer was proved by replacement of the amino group by chlorine, followed by hypochlorite oxidation to the known 5-chloro-1-naphthoic acid.

When the results of the Friedel–Crafts acetylation of the acetylaminonaphthalenes are compared with those of other electrophilic substitution reactions (*e. g.*, nitration) of the acetylaminonaphthalenes, it is apparent that an additional factor must be considered in the reaction involving aluminum chloride—probably the steric effect of the amino group or its large complex with aluminum chloride. The β-acetylamino group usually directs electrophilic substitution at the 1-, 6- and 8-positions, with the 1-position favored, but in the Friedel–Crafts acetylation substitution occurs only at the unhindered 6- and 8-positions. The α-acetylamino group usually directs electrophilic substitution at the 2-, 4- and 5-positions, but in the Friedel–Crafts acetylation substitution occurs only at the unhindered 4- and 5-positions.

## Experimental[5]

**Friedel–Crafts Acetylation of Acet-2-naphthalide. 6-Amino-2-acetonaphthone.**—The Friedel–Crafts acetylation of acet-2-naphthalide was carried out according to the method of Brown and his co-workers.[3] After hydrolysis two aminoacetonaphthones were isolated: 7-amino-1-acetonaphthone, m. p. 108.5–110°,[2] and a position isomer. It was found necessary to purify the isomer through its hydrochloride. The contaminating hydrochloride of 7-amino-1-acetonaphthone was less soluble in water and the major portion was removed by fractional crystallization. Precipitation of the more soluble hydrochloride with ammonia gave the free base, which was recrystallized from ethanol as pale yellow prisms, m. p. 166.5–168° (reported, 163–164°).[3]

*Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 78.00; H, 6.15; N, 7.70.

(1) Present address: Ammonia Department, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

(2) Leonard and Hyson, *J. Org. Chem.*, **13**, 164 (1948).

(3) Brown, Jacobs, Winstein, Levy, Moss and Ott, *ibid.*, **11**, 163 (1946).

(4) Witt and Braun, *Ber.*, **47**, 3219 (1914).

(5) All melting points are corrected.

### Proof of Structure of 6-Amino-2-acetonaphthone

**Conversion to 6-Hydroxy-2-acetonaphthone.**—Four-tenths of a gram of the amine was precipitated as the hydrochloride in finely divided form and was diazotized by the addition of sodium nitrite in the usual manner. The diazonium salt solution was allowed to stand overnight at room temperature, after which the diazonium reaction was completely destroyed by heating the solution for one hour on the steam-bath. Two volumes of ethanol were added, and the solution was decolorized, filtered, and cooled. The precipitate was recrystallized from aqueous ethanol, then from benzene; m. p. 170–171° (reported, 171°).[4]

**6-Methoxy-2-acetonaphthone.**—This compound was prepared from 6-hydroxy-2-acetonaphthone by alternate additions of 2.5 *N* sodium hydroxide solution and dimethyl sulfate at steam-bath temperature until the addition of base no longer produced any yellow color. When the reaction was complete, sufficient hot methanol was added to dissolve all oily material, and the solution was cooled. The colorless, flaky crystals which separated melted at 104.5–105.5° (reported, 105°).[6]

**6-Methoxy-2-naphthoic Acid.**—The 6-methoxy-2-acetonaphthone in methanol solution was oxidized in the usual manner with a solution of sodium hypochlorite (commercial Clorox). The acid was recrystallized from ethanol; m. p. 209–210.5°, after sintering (reported, 209°,[6] 205°).[7] It was identical with an authentic sample of 6-methoxy-2-naphthoic acid.

**Friedel–Crafts Acetylation of 2-Naphthylamine.**—To a cooled mixture of 14.3 g. (0.1 mole) of 2-naphthylamine, 67 g. (0.5 mole) of anhydrous aluminum chloride and 400 ml. of carbon disulfide under anhydrous conditions was added 15 g. (0.24 mole) of redistilled acetyl chloride over a period of thirty minutes. The reaction was allowed to proceed at room temperature for three hours and then at reflux temperature for three hours. The cooled solvent was decanted and the residue was decomposed by the addition of 500 g. of cracked ice followed by 200 ml. of 10 *N* hydrochloric acid. The mixture was heated on the steam-bath until all the solid dissolved. The hot solution was decolorized, filtered, and cooled. The precipitated hydrochloride was separated, suspended in water, and neutralized by the addition of ammonia to give 8.5 g. of crude aminoacetonaphthone. After one recrystallization from benzene, the compound melted at 109–110° and was identical with an authentic sample of **7-amino-1-acetonaphthone.** The acetyl derivative was also identical with authentic 7-acetylamino-1-acetonaphthone. The acidic filtrate from the precipitated hydrochloride was treated with excess aqueous potassium hydroxide, and the solid which separated was extracted with acetone. The acetone extract was evaporated, and the residue was treated with hot 2 *N* hydrochloric acid. The acid extract was decolorized and cooled, with deposition of 1.8 g. of hydrochloride, identified as **6-amino-2-acetonaphthone** hydrochloride by conversion to 6-methoxy-2-naphthoic acid as previously described.

**Friedel–Crafts Acetylation of Acet-1-naphthalide. 4-Amino-1-acetonaphthone and 5-Amino-1-acetonaphthone.**—The same molar proportions and the same conditions were used as in the Friedel–Crafts acetylation of 2-naphthylamine. The reaction mixture was cooled, the carbon disulfide was decanted, and the complex was decomposed by the addition of ice. The insoluble material was collected and 19 g. of this crude product was subjected to hydrolysis by refluxing forty-five minutes with 500 ml. of 1.5 *N* hydrochloric acid. The solution was refluxed an additional twenty minutes with 8 g. of decolorizing carbon and was filtered hot. The solid hydrochloride (A) which separated on cooling was removed by filtration, and the acidic filtrate (B) was retained. The solid (A) was suspended in water and the mixture was made basic with ammonia to precipitate the free amine. Recrystallization from benzene–ligroin gave 7 g. of **4-amino-1-acetonaphthone** (31% yield based on acet-1-naphthalide) as yellow prisms, m. p. 135.5–136.5°.

*Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 77.69; H, 5.81; N, 7.43.

The filtrate (B) from the separation of the 4-amino-1-acetonaphthone hydrochloride was rendered basic with ammonia and the yellow precipitate (3.5 g.) was removed by filtration. The ammoniacal filtrate was extracted with ether and the ethereal solution was evaporated to give a greenish oil. More such oil was obtained from the mother liquor remaining after the recrystallization of the yellow precipitate. The combined oil was dissolved in hot 1.5 *N* hydrochloric acid, from which 1.8 g. of colorless crystalline hydrochloride separated on cooling (9% yield based on acet-1-naphthalide). This **5-amino-1-acetonaphthone hydrochloride** was recrystallized from ethanol–ether; m. p. 248–251°, with decomposition.

*Anal.* Calcd. for $C_{12}H_{12}ClNO$: C, 65.00; H, 5.46; N, 6.32. Found: C, 64.92; H, 5.65; N, 6.59.

**5-Amino-1-acetonaphthone** was liberated from its hydrochloride by treatment with aqueous ammonia, followed by cooling. The yellowish plates which separated were recrystallized from benzene–ligroin; m. p. 96.5–97.5°.

*Anal.* Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 77.68; H, 6.02; N, 7.62.

### Proof of Structure of 4-Amino-1-acetonaphthone

**Conversion to 4-Hydroxy-1-acetonaphthone.**—Two grams of 4-amino-1-acetonaphthone, m. p. 135.5–136.5°, was precipitated as the hydrochloride in finely divided form and was diazotized by the addition of sodium nitrite in the usual manner. The solution of the diazonium salt was added dropwise, with stirring, to 50 ml. of 4 *N* sulfuric acid heated to the boiling point. After the addition was complete, the mixture was heated for an additional five minutes and was then cooled. The solid which separated was dissolved in hot 2 *N* sodium hydroxide and was reprecipitated by acidification of the decolorized solution. Recrystallization from benzene–ligroin gave 1.0 g. of long, silky, colorless needles, m. p. 197.5–199°. The compound gave no melting point depression when mixed with an authentic sample of 4-hydroxy-1-acetonaphthone prepared by the method of Witt and Braun.[4]

**4-Methoxy-1-acetonaphthone.**—The compound was made from 4-hydroxy-1-acetonaphthone by the same method which was employed for the methylation of 6-hydroxy-2-acetonaphthone, and was purified by recrystallization from ligroin; m. p. 69–71°. The compound gave no melting point depression when mixed with an authentic sample of 4-methoxy-1-acetonaphthone prepared by the method of Witt and Braun.[4]

### Proof of Structure of 5-Amino-1-acetonaphthone

**Conversion to 5-Chloro-1-naphthoic Acid.**—One-half gram of the amine hydrochloride, m. p. 248–251°, was suspended in 10 *N* hydrochloric acid and solid sodium nitrite was added in small portions until diazotization was complete. The excess nitrous acid was destroyed by the addition of urea. One-half gram of copper bronze powder was added to the solution of the diazonium salt, and the mixture was warmed on the steam-bath until the evolution of nitrogen ceased. The cooled reaction mixture was extracted with two 25-ml. portions of carbon tetrachloride. The combined extracts were washed with 2 *N* sodium hydroxide and finally with water. The carbon tetrachloride solution was evaporated, leaving a small amount of reddish oil which was oxidized in methanol solution by sodium hypochlorite in the usual manner. When the reaction was complete, the excess hypochlorite was destroyed by the addition of bisulfite and the solution was acidified with mineral acid. The precipitated organic acid, after recrystallization from aqueous ethanol, then from benzene, melted at 251–252°. The melting point of the compound was not depressed on admixture with an authentic sample of 5-chloro-1-naphthoic acid. The authentic sample was prepared in an unequivocal manner starting with 1,5-dinitronaphthalene. 5-Nitro-1-naphthylamine was prepared from the dinitro compound by the

(6) Fries and Schimmelschmidt, *Ber.*, **58**, 2835 (1925).

(7) Short, Stromberg and Wiles, *J. Chem. Soc.*, 319 (1936).

method of Hodgson and Walker.[8] The preparation of 5-chloro-1-nitronaphthalene was carried out by replacing the amino group of 5-nitro-1-naphthylamine by chlorine,[9] followed by reduction of the nitro group to form 5-chloro-1-naphthylamine.[10] 5 - Chloro - 1 - naphthonitrile[11] was formed by replacement of the amino group by nitrile through the diazonium salt and was finally hydrolyzed to 5-chloro-1-naphthoic acid by the method of Gomberg and Blicke.[12]

**Friedel–Crafts Acetylation of 1-Naphthylamine.**—The same molar proportions of reactants, conditions of reaction, and methods of hydrolysis and isolation were employed as in the Friedel–Crafts acetylation of the acet-1-naphthalide. The products, in somewhat lower yields, were identified as 4-amino-1-acetonaphthone and 5-amino-1-acetonaphthone by comparison with the samples isolated previously.

**7-Bromo-1-nitronaphthalene.**—This compound was prepared from 8-nitro-2-naphthylamine[13] by the method which Hodgson and Walker[14] applied to the preparation of 2-bromo-1-nitronaphthalene.

**7-Bromoacet-1-naphthalide.**—A mixture of 1 g. of 7-bromo-1-nitronaphthalene 20 ml. of glacial acetic acid, 4 ml. of acetic anhydride and 2 g. of iron powder was heated at reflux temperature for one hour. Additional iron powder (3 g.) was added and refluxing was continued an additional hour. The mixture was poured into 150 ml. of water and the whole was cooled in an ice-bath. The precipitate (0.8 g.) was recrystallized from ethanol as colorless needles, m. p. 195.5–196.5°.

*Anal.* Calcd. for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.24; H, 3.60; N, 5.13.

**7-Bromo-1-naphthylamine.**—The acetyl derivative in aqueous ethanol was heated under reflux with 10 *N* hydrochloric acid for five hours. The clear solution, upon cooling, deposited the amine hydrochloride as glistening plates, m. p. 260°, with decomposition. The free base was precipitated by treatment of the hydrochloride in aqueous solution with aqueous sodium carbonate. Recrystallization from aqueous ethanol gave colorless needles, m. p. 65–66°.

*Anal.* Calcd. for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 53.78; H, 3.33; N, 6.31.

The **benzoyl** derivative was obtained in the usual manner and was recrystallized from ethanol and benzene; m. p. 211–212°.[15]

*Anal.* Calcd. for $C_{17}H_{12}BrNO$: C, 62.59; H, 3.71; N, 4.29. Found: C, 62.85; H, 3.80; N, 4.56.

**Attempted Preparation of 2-Amino-1-acetonaphthone by a Bucherer Type Reaction.**—Two grams of 2-hydroxy-1-acetonaphthone[16,17] was placed in a mortar and was finely ground with 8 g. of calcium chloride ammonia complex which had been prepared by the addition of pulverized anhydrous calcium chloride to liquid ammonia.[18] The mixture was placed in a bomb of 37 ml. capacity and was heated at 200° for seven hours. After cooling, the solid was removed and was pulverized in a mortar. This powder was extracted with two 100-ml. portions of moist ether and the ether was removed. The residue after ether evaporation was extracted with 300 ml. of hot 3 *N* hydrochloric acid. The hot acid extract was filtered and the filtrate was cooled and neutralized with ammonia. The precipitate was recrystallized three times from benzene–ligroin to give 1.0 g. of colorless plates, m. p. 126–127.5°.

*Anal.* Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.18; H, 6.17; N, 5.02.

The analysis indicated that the material could be an equimolar mixture of 2-naphthol and 2-naphthylamine. Equivalent quantities of pure 2-naphthol and pure 2-naphthylamine were mixed and the mixture was recrystallized from benzene–ligroin. The melting point of the colorless plates which separated was 126–128°, and the melting point of a mixture of this product with the material described above was identical.

The Bucherer reaction was repeated using seven and one-half times the previous quantities of reactants in a 250-ml. bomb. From this reaction there was isolated 6.4 g. of 2-naphthylamine, as determined by mixed melting point.[19]

## Summary

1. The structure of the product formed in lesser amount, along with 7-acetylamino-1-acetonaphthone, in the Friedel–Crafts acetylation of acet-2-naphthalide in carbon disulfide solution has been established as 6-acetylamino-2-acetonaphthone.

2. The products of the Friedel–Crafts acetylation of acet-1-naphthalide have been proved to be 4-acetylamino-1-acetonaphthone and 5-acetylamino-1-acetonaphthone, with the former in preponderance.

3. The results indicate that the acetyl group does not enter a position *ortho* to the acetylamino group.

URBANA, ILLINOIS RECEIVED DECEMBER 6, 1948

(8) Hodgson and Walker, *J. Chem. Soc.*, 1346 (1933).

(9) Ferraro and Caflisch, *Helv. Chim. Acta*, **11**, 803 (1928).

(10) Friedländer, Karamessinis and Schenk, *Ber.*, **55**, 45 (1922).

(11) Eckstrand, *J. prakt. Chem.*, [2] **38**, 139 (1888).

(12) Gomberg and Blicke, THIS JOURNAL, **45**, 1765 (1923).

(13) Saunders and Hamilton, *ibid.*, **54**, 636 (1932).

(14) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(15) 2-Bromo-1-benzoylaminonaphthalene melts at 179° (Dziewonski and Sternbach, *Bull. intern. acad. polonaise*, **1931A**, 59). Melting point comparison of the N-benzoyl derivatives of 7-bromo-1-naphthylamine and 2-bromo-1-naphthylamine thus provides a means of distinguishing between these compounds which was previously lacking, since the 7-bromo- and 2-bromo-1-naphthylamines melt at 65–66° (see above) and 65–67° (Hodgson and Hathway, *J. Chem. Soc.*, 538 (1944)), and the corresponding acetyl derivatives melt at 195.5–196.5° and 196.5–197°.

(16) Chattaway, *J. Chem. Soc.*, 2495 (1931).

(17) Fries, *Ber.*, **54**, 709 (1921).

(18) Fries and Hübner, *ibid.*, **39**, 444 (1906).

(19) The intermediate in the modified Bucherer reaction is probably the 1,3-diketonic form of 2-hydroxy-1-acetonaphthone, which should be quite susceptible to cleavage by ammonia. The β-naphthol thus formed could undergo normal conversion (partial or total) to β-naphthylamine.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 1-Cyano-1,3-butadiene. III. The Dimer of 1-Cyano-1,3-butadiene

BY H. R. SNYDER AND GEORGE I. POOS

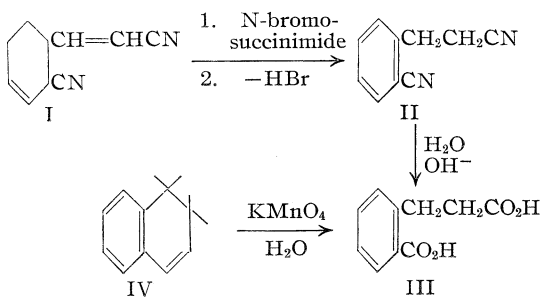
In the course of further studies of the chemistry of 1-cyano-1,3-butadiene,[1,2] a dimer[2a] of the substance has been isolated and characterized. In common with many butadienes, 1-cyano-1,3-butadiene condenses with itself in the Diels–Alder fashion to yield a cyclic dimer,[3] which in this instance proved to be 1-(β-cyanovinyl)-2-cyano-3-cyclohexene (I).

Separation of the *cis* and *trans* forms of the diene by fractional distillation[2] was always accompanied by a considerable loss due to the formation of higher-boiling material in the still-pot. The dimeric compound was isolated by high vacuum distillation of the gummy still residues. After redistillation, the thick oil could be induced to crystallize to a low-melting solid. There was no indication of the presence of more than one dimer. Microanalysis and molecular weight determinations were correct for a dimeric structure.

Attempts to hydrolyze the dimer with alkaline hydrogen peroxide and with acid resulted in the production of intractable materials. Hydrolysis with base of varying strength, with and without a solvent, produced an acidic substance which appeared to be polymeric. It was not possible to effect dehydrogenation of the dimer by heating to 320° with 10% palladium on carbon.

Proof of the dimer structure was obtained by aromatization followed by hydrolysis to a known aromatic acid according to the following scheme (equation A). The dimer (I) was brominated with one equivalent of N-bromosuccinimide and the

Equation A




product was dehydrobrominated by heating with isoquinoline to yield *o*-cyanohydrocinnamonitrile (II). Basic hydrolysis of II yielded *o*-carboxyhydrocinnamic acid (III) which was identified by comparison with an authentic specimen. The preparation of III for comparison was accomplished by oxidizing 1,2-dihydronaphthalene (IV) with cold aqueous permanganate according to the method of Straus and Lemmel.[4]

It was of interest to investigate the relative contributions of the *cis* and *trans* isomers in the dimerization of 1-cyano-1,3-butadiene. When the higher-boiling isomer ($n^{20}$D 1.4960, presumably *trans*) was maintained at 100° for sixteen hours in the presence of a polymerization inhibitor (picric acid), 66% of the material was converted into the dimer, and the remainder could be accounted for as monomer and polymer. On the other hand, in two similar experiments with the lower-boiling isomer ($n^{20}$D 1.4852, presumably *cis*), heating nine and eighteen hours produced only 13% dimer, the major portion of the diene having been converted into polymer.

The dimer itself is a rather stable compound and shows little tendency to polymerize. Since it might be considered possible that polymerization of the monomer proceeds through the dimer under the conditions described in the experiments above, a sample of the dimer was maintained at 100° in the presence of picric acid for twenty-five hours. When the material was distilled, no polymeric residue remained.

These experiments indicate that I is formed chiefly by the dimerization of the higher-boiling 1-cyano-1,3-butadiene.

## Experimental[5,6]

**Isolation of the Dimer.**—In a short-path distillation apparatus 30 g. of the brown gummy residue from the fractionation of 1-cyano-1,3-butadiene was distilled, yielding 22 g. of a heavy yellow oil, b. p. 122–123° (0.2 mm.), $n^{20}$D 1.5170, and leaving a hard, polymeric residue in the pot. Redistillation of the oil did not alter its boiling point or index of refraction. However, after standing a portion of the redistilled material solidified.

A solution of several grams of the twice-distilled liquid dimer in hot 95% ethanol was treated with Darco, filtered and cooled to about 50°. Water was then added dropwise to cloudiness and the solution was cooled slowly with scratching of the walls of the flask until crystals formed. After drying *in vacuo* the colorless crystals melted at 53–54°. This product was recrystallized twice from absolute ether–petroleum ether (30–60°) and submitted for microanalysis; m. p. 53–54°.

*Anal.* Calcd. for $C_{10}H_{10}O_2$: C, 75.91; H, 6.37; mol. wt., 158.2. Found: C, 76.09; H, 6.59; mol. wt., 136, 142 (ebulloscopic in benzene).

**Aromatization of the Dimer. A. Bromination.**—To a mixture of 2.00 g. of the crystalline dimer (m. p. 53–54°) and 45 ml. of benzene was added 2.40 g. of N-bromosuccinimide. The mixture was heated with stirring until it became homogenous and then was refluxed until a negative test for active bromine was obtained with acidified potassium iodide solution (three hours). The hot solu-

(1) For the preceding paper in this series, see Snyder and Poos, THIS JOURNAL, **71**, 1057 (1949).

(2) Snyder, Stewart and Myers, *ibid.*, **71**, 1055 (1949).

(2a) The same dimer apparently has been isolated in an impure state by Coffman (*ibid.*, **57**, 1981 (1935)).

(3) For the dimer of 2-cyano-1,3-butadiene, see Marvel and Brace, *ibid.*, **71**, 79 (1949).

(4) Straus and Lemmel, *Ber.*, **46**, 239 (1913).

(5) All melting points are uncorrected.

(6) Microanalyses by Miss Emily Davis.

tion was cooled to 0° and the precipitated succinimide was collected on a filter and washed with several portions of cold benzene (wt. 1.19 g., m. p. 123–124.5°).

B. **Dehydrobromination.**—The benzene solution from above was concentrated, transferred to a small flask, and the remainder of the benzene was removed. To the residual yellow oil 8 ml. of isoquinoline was added portionwise with agitation. The flask was then set in an oil-bath and the bath was heated to 180° for twenty-five minutes, then to 190° for five minutes, after which the flask was removed and allowed to cool.

An excess of dilute hydrochloric acid was added to the mixture and the acid solution was extracted thoroughly with benzene. The benzene extracts were combined; the dark solution was washed first with dilute hydrochloric acid and then with water and finally concentrated to a small volume. The resulting black oily solution was transferred to a short-path distilling bulb with benzene and the low-boiling material was distilled at atmospheric pressure. Distillation of the residue yielded 1.50 g. (76%) of a pale yellow oil; b. p. 110° (0.2 mm.), $n^{20}D$ 1.5468. After redistillation the oil was water-white ($n^{20}D$ 1.5468) and a sample of it solidified on standing to a low-melting solid. Another sample of this colorless redistilled oil was then taken up in absolute ether–petroleum ether (30–60°) and the solution was inoculated with the solid and cooled to yield fluffy white needles which were collected on a filter, washed with petroleum ether and air dried; m. p. 41–42.5°. Subsequent hydrolysis of this compound to III identified it as *o*-cyanohydrocinnamonitrile. The crystalline dinitrile was recrystallized two times from absolute ether–petroleum ether (30–60°) and submitted for microanalysis; m. p. 41–42.5°.

*Anal.* Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16. Found: C, 76.79; H, 5.29.

**Hydrolysis of *o*-Cyanohydrocinnamonitrile (II).**—A mixture of 0.50 g. of II, 5 ml. of 20% potassium hydroxide and 5 ml. of 95% ethanol was brought to boiling on a steam cone and was allowed to reflux until ammonia evolution had practically ceased (twenty-four hours). Most of the alcohol was distilled, the aqueous residue was cooled and then was neutralized dropwise with concentrated hydrochloric acid. Before the neutral point was reached, a brown solid separated which was collected on a filter, washed with several ml. of water (washings added to the filtrate) and dried; 0.12 g., m. p. 205–215° (dec.). This basic substance was not identified. Acidification of the basic filtrate from above yielded 0.07 g. of an infusible, neutral solid which was presumed to be the diamide of III. After standing overnight, the acidic filtrate had deposited crystals of acid which were collected, washed and dried; 0.14 g., m. p. (155°) 164–166°. Concentration of the mother liquors yielded an additional 0.14 g. of crude acid. One recrystallization from water (Darco) raised the melting point to 166.5–168°. After two more recrystallizations from water the product melted at 166.5–168° alone or when mixed with authentic III prepared as described below.

*Anal.* Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.99; H, 5.29.

**Preparation of *o*-Carboxyhydrocinnamic Acid[4] (III).**—The oxidation of 2.00 g. of 1,2-dihydronaphthalene with aqueous potassium permanganate solution at 9–11° yielded 0.34 g. of III, m. p. 163–167° (lit.[4] 162–164°), along with unchanged hydrocarbon. After several recrystallizations from water (Darco) the pure acid melted at 166.5–168° (lit.[4] 166–167°).

**Dimerization Experiments with *cis*- and *trans*-1-Cyano-1,3-butadiene.**—Into a small distilling flask was placed 3.0 g. of higher-boiling 1-cyano-1,3-butadiene ($n^{20}D$ 1.4960) and *ca.* 0.1 g. of picric acid. The flask was stoppered and left on a steam cone until the material had thickened to a sirupy consistency (sixteen hours). When the contents of the flask was submitted to high vacuum distillation there was obtained as distillate 2.0 g. (66%) of oily dimer, $n^{20}D$ 1.5172. From the Dry Ice-trap there was recovered *ca.* 0.5 g. (16%) of monomeric cyanodiene. A small amount of polymeric residue remained in the flask.

In a like manner, 3.0 g. of the lower-boiling isomer ($n^{20}D$ 1.4852) was heated for eighteen hours to yield 0.4 g. (13%) of dimer ($n^{20}D$ 1.5112). Recovered monomer amounted to *ca.* 0.5 g. (16%) while the major portion of the material remained as polymer in the flask. From a second experiment with the same quantity of lower-boiling isomer, 0.4 g. (13%) of dimer ($n^{20}D$ 1.5155) and 0.9 g. (30%) of monomer were isolated after nine hours at 100°.

Several grams of once-crystallized dimer was heated with picric acid on the steam cone for twenty-five hours and then distilled. The material was unchanged, and left no polymeric residue upon distillation.

## Summary

The cyclic dimer of 1-cyano-1,3-butadiene has been isolated and characterized as 1-(β-cyanovinyl)-2-cyano-3-cyclohexene. The structure was proved by aromatization of the dimer to *o*-cyanohydrocinnamonitrile and hydrolysis of this dinitrile to the known *o*-carboxyhydrocinnamic acid. Experiments with the *cis* and *trans* isomers of 1-cyano-1,3-butadiene indicate that the higher-boiling isomer (presumably *trans*) is the chief source of the dimer.

URBANA, ILLINOIS RECEIVED OCTOBER 11, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF MARYLAND]

# 1,3,5,7-Octatetraene

BY G. FORREST WOODS AND LOUIS H. SCHWARTZMAN[1]

The reaction of 2,4-pentadienal[2] with methylmagnesium bromide was shown to yield 1,3-hexadien-5-ol. This latter substance was dehydrated very readily over activated alumina to yield 1,3,5-hexatriene.[3]

$$CH_2{=}CH{-}CH{=}CH{-}CHO + CH_3MgBr \longrightarrow$$
$$CH_2{=}CH{-}CH{=}CH{-}CHOH{-}CH_3 \longrightarrow$$
$$H{-}(CH{=}CH)_3{-}H$$

Pentadienal has now been utilized as a starting material for the synthesis of 1,3,5,7-octatetraene.

Allylmagnesium bromide (I) reacts very smoothly with 2,4-pentadienal (II) to yield 1,3,7-octatrien-5-ol (III). The possibility of a rearrangement in the reactions leading to (III) or rearrangement of (III) itself had to be considered.[3,4] Accordingly, 1,3,7-octatrien-5-ol was catalytically reduced to the saturated alcohol, 4-octanol (IV) and identified as the α-naphthylurethan, and the

(1) National Institute of Health Predoctorate Fellow.

(2) (a) Woods and Sanders, THIS JOURNAL, **68**, 2483 (1946); (b) Woods and Sanders, *ibid.*, **69**, 2926 (1947).

(3) Woods and Schwartzman, *ibid.*, **70**, 3394 (1948).

(4) Heilbron, Jones, McCombie and Weedon, *J. Chem. Soc.*, 84, (1945).

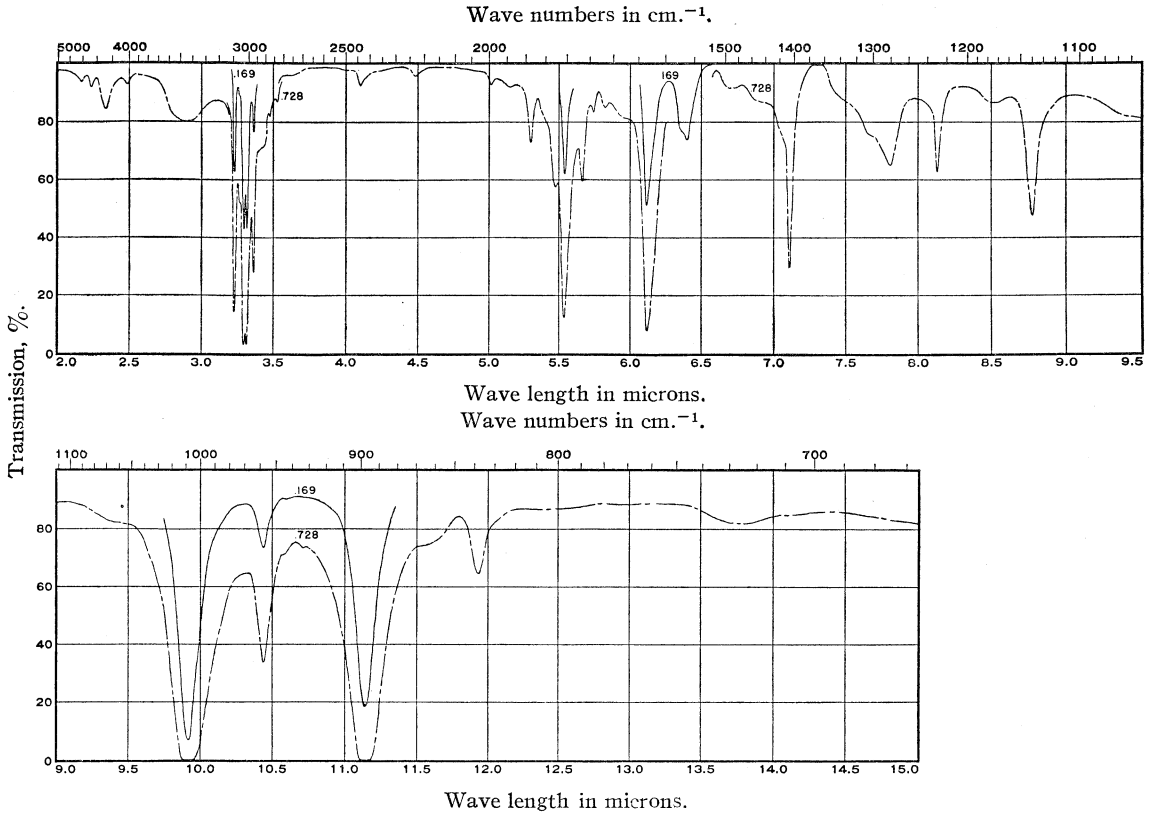
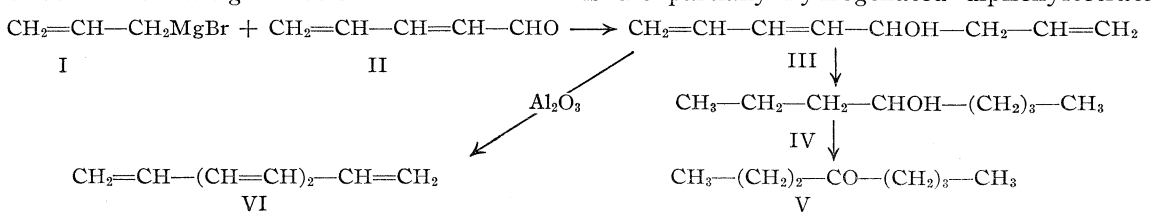


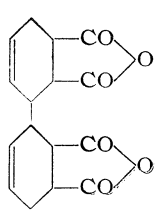

Fig. 1.—Infrared absorption spectrum of 1,3,5,7-octatetraene.

alcohol oxidized to the known 4-octanone (V) and identified as the semicarbazone. In this manner the absence of any rearrangement was established. The catalytic dehydration with activated alumina of the unsaturated alcohol, 1,3,7-octatrien-5-ol, led to the hydrocarbon 1,3,5,7-octatetraene (VI), a white crystalline solid melting at approximately 50° which was recrystallized from petroleum ether. The hydrocarbon sublimes on warming and rapidly polymerizes on standing. The equations for these reactions are given below.




The following facts were used to establish the structure of VI. The hydrocarbon, VI, upon catalytic reduction, absorbed almost four moles of hydrogen and the product of reduction was established as *n*-octane. The infrared spectrum,[5] Fig. 1, which is very similar to that of 1,3,5-hexatriene[4] indicates the absence of allenic, acetylenic, or benzenoid structures. Elemental analyses indicate the formula $C_8H_{10}$.

It is interesting to note that the ultraviolet absorption spectra, Fig. 2, of octatetraene is considerably different from that reported for cyclooctatetraene.[6] Treatment of octatetraene in petroleum ether with bromine leads to a relatively stable tetrabromide, $C_8H_{10}Br_4$, of unknown structure, while the Diels–Alder reaction yields a molecule into which two maleic anhydride structures have been incorporated. Several structures for this substance, $C_{16}H_{14}O_6$, are possible, one of which is the partially hydrogenated diphenyltetracarboxylic acid dianhydride, VII. It seemed that this substance should readily undergo dehydrogenation to the known 2,2′,3,3′-diphenyltetracarboxylic acid dianhydride. Since our attempts to dehydrogenate this substance were unsuccessful, we believe that the adduct is not VII. However, quantitative hydrogenation of this same adduct led to the absorption




VII

(5) The infrared spectrum was kindly determined for us by Dr. Don C. Smith of the Naval Research Laboratory.

(6) Cope and Bailey, THIS JOURNAL, **70**, 2305 (1948).

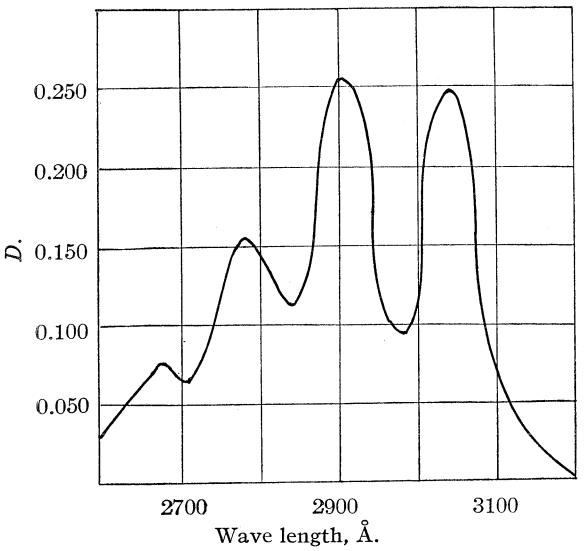



Fig. 2.—Ultraviolet absorption spectrum of 1,3,5,7-octatetraene.

of two moles of hydrogen showing that the molecule still had two ethylenic links, again substantiating the proof of four ethylenic links in the original hydrocarbon. Since 1,3,5,7-octatetraene can exist in either of three geometrical isomerides, we believe that we have one of these isomers pure in view of our method of purification. The difficulties of assigning configuration to this substance would be greater than for 1,3,5-hexatriene[4] in which instance we were unsuccessful.

To illustrate a property of octatetraene we report an incident which occurred in handling the material. A freshly recrystallized sample of octatetraene of about 1 g. was standing in a Büchner funnel covered with a beaker. This material underwent a decomposition somewhat less violent than an explosion. Marked white fumes were given off and a pungent aldehyde odor was present. We assume that a combustion takes place as a consequence of the heat liberated in the polymerization of octatetraene. It was because of the rate of polymerization that we are unable to report a melting point or give an evaluation to the extinction coefficients of the ultraviolet or infrared absorption curves of octatetraene.

## Experimental

**1,3,7-Octatrien-5-ol (III).**—An ethereal solution (600 ml.) of allylmagnesium bromide was prepared from 80 g. of allyl bromide and 45 g. of powdered magnesium using Gilman's procedure.[7] The ether solution of allylmagnesium bromide was then pumped with nitrogen away from the excess magnesium powder. To this chilled solution, was added 41 g. of pentadienal[2] dissolved in 100 ml. of anhydrous ether. The mixture was stirred for an additional fifteen minutes at room temperature. The Grignard addition complex was decomposed with a saturated aqueous solution of ammonium chloride and the ether layer separated, washed with water and sodium bicarbonate solution, and dried over magnesium sulfate. After removal of the ether under reduced pressure the octatrienol was distilled in a nitrogen atmosphere: b. p. 70–71° (6 mm.), $n^{22}D$ 1.4931; yield 55 g. (90%). *Anal.* Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.35; H, 9.84.

**Reduction of 1,3,7-Octatrien-5-ol.**—This material (4 g.), dissolved in 70 ml. of ethyl alcohol, was hydrogenated with Raney nickel at room temperature and atmospheric pressure. The hydrogen uptake was 91% of the calculated value for three ethylenic links, and the time required for this uptake was approximately thirty minutes. The alcoholic solution was filtered and distilled under reduced pressure. The 4-octanol (3.8 g.) distilled at 79° (20 mm.), $n^{24}D$ 1.3890.[8]

The α-naphthylurethan of 4-octanol, prepared in the usual way and recrystallized from petroleum ether (30–60°), melted at 60–61° and gave no depression in a mixed melting point determination with an authentic sample of this compound. *Anal.* Calcd. for $C_9H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.21; H, 8.22.

4-Octanol (6.9 g.) was oxidized with potassium dichromate (31.4 g.) dissolved in 200 ml. of water containing 42 g. of sulfuric acid. The temperature of the oxidation medium was not allowed to rise above 50°. The product, 4-octanone, was isolated by steam-distillation and extraction with ether. The ether extract was dried over magnesium sulfate and the ether removed under reduced pressure. 4-Octanone (3 g.) boiled at 164–168°.

The semicarbazone of this material prepared in the usual way melted at 95–97° after several recrystallizations from methyl alcohol–water and gave no depression with an authentic sample of the semicarbazone of 4-octanone. *Anal.* Calcd. for $C_9H_9N_3O$: C, 58.35; H, 10.34. Found: C, 58.42; H, 10.09.

**1,3,5,7-Octatetraene (VI).**—1,3,7-Octatrien-5-ol was distilled under reduced pressure (25 mm.) in a nitrogen atmosphere through a column, 35 cm. long of 16-mm. Pyrex tubing, filled with activated alumina (8–12 mesh) and heated by means of two electrical heating elements to a temperature of 250–280°. Two connected receivers were used, one cooled with an ice–calcium chloride-bath, and the other with an acetone–Dry Ice-bath. The products solidified in the receiver but, upon warming, the material melted, and most of the water layer was withdrawn by means of a medicine dropper. The residual material was dried over calcium oxide and crystallized from petroleum ether (20–40°) in a nitrogen atmosphere. From such a run 22 g. of 1,3,7-octatrien-5-ol yielded 11 g. (58%) of octatetraene.

The analysis of this substance required a special procedure. A combustion tube was mounted so that two gas entry lines were present into one of which the sample was to be introduced. The two gas lines were connected by a stopcock. The sample of octatetraene was introduced into the system in one line through which a slow stream of nitrogen was passing. The other line was introducing the oxygen. Warming of the sample sublimed the material into the combustion chamber. Finally oxygen was introduced through the sample line and the region of the sample strongly heated to burn the residual polymeric material which had formed from the octatetraene. *Anal.* Calcd. for $C_8H_{10}$: C, 90.51; H, 9.49. Found: C, 89.75; H, 9.77.

**Octatetraene Tetrabromide.**—A dilute solution of bromine in petroleum ether was added dropwise to a solution of octatetraene dissolved in petroleum ether. The bromine color was quickly discharged and a white crystalline material precipitated which, after several recrystallizations from acetone–water, melted at 123–125°. This substance is not very stable and evolves hydrogen bromide and darkens on standing. *Anal.* Calcd. for $C_8H_{10}Br_4$: C, 22.56; H, 2.35. Found: C, 23.75; H, 2.78.

**Reduction of Octatetraene.**—Reduction of octatetraene (4.5 g.) dissolved in 60 ml. of glacial acetic acid with 5% palladinized charcoal catalyst required approximately an

(7) Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

(8) Levene and Marker (*J. Biol. Chem.*, **91**, 405 (1931)) report a boiling point of 79° (16 mm.) and $n^{24}D$ 1.3898.

hour at the end of which time slightly less than the theoretical amount of hydrogen had been consumed. The solution was filtered, poured into water and the acetic acid neutralized with sodium hydroxide. The product was extracted with ether, and the ether solution dried with magnesium sulfate and finally with metallic sodium. After removal of the ether, the residue was distilled (from sodium). *n*-Octane distilled at 126–128°; $n^{30}D$ 1.4001; $d^{25}_4$ 0.714.

**Diels-Alder Reaction of Octatetraene.**—A solution of maleic anhydride (5 g.), octatetraene (2.5 g.), and benzene (50 ml.) was heated under reflux in a nitrogen atmosphere on a steam-bath for six hours. Almost immediately a white solid precipitated which became more copious as the reaction proceeded. Chilling and filtering the benzene solution yielded 4.5 g. of white solid which melted at 238–242° after several recrystallizations from glacial acetic acid. *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67; neut. equiv. (four carboxylic groups), 75. Found: C, 63.44; H, 4.78; neut. equiv., 73.

Refluxing of this material in moist xylene yielded another white crystalline solid which after recrystallization from acetone–xylene melted at 247–250°. This is the free tetracarboxylic acid. *Anal.* Calcd. for $C_{16}H_{18}O_8$: C, 56.80; H, 5.36. Found: C, 56.45; H, 5.41.

Reduction of the dianhydride $C_{16}H_{14}O_6$ (0.92 g.) dissolved in 25 ml. of glacial acetic acid with 5% palladinized charcoal at room temperature and atmospheric pressure required approximately one-half hour at the end of which time the reduction had stopped and the hydrogen absorption was the theoretical amount calculated for two ethylenic links. The solution, filtered, was poured into water and the solid isolated by filtration. After several recrystallizations from acetone–water a white solid melting at 260–261° was obtained. *Anal.* Calcd. for $C_{16}H_{22}O_8$: C, 56.13; H, 6.47. Found: C, 56.24; H, 6.58.

Attempts to dehydrogenate the dianhydride, $C_{16}H_{14}O_6$ were unsuccessful. However, when 2 g. of the anhydride was refluxed with 1 g. of palladinized charcoal and 10 ml. of *p*-cymene, a substance which precipitated on cooling was removed along with the catalyst upon filtration. The solid was leached out with hot acetone which upon cooling yielded a white solid. Recrystallization of this material from xylene gave a white solid melting at 267–268°, an isomer of the starting material. *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.37; H, 4.76.

**Ultraviolet Absorption Spectrum.**—The ultraviolet absorption spectra of 1,3,5,7-octatetraene was determined in purified cyclohexane. The instrument was a Beckmann quartz ultraviolet spectrophotometer.

**Infrared Absorption Spectra.**—The infrared absorption spectra of a sample of octatetraene dissolved in carbon disulfide was determined for us by Dr. Don C. Smith of the Naval Research Laboratory.

## Summary

The preparation and properties of an isomer of 1,3,5,7-octatetraene are reported.

COLLEGE PARK, MARYLAND RECEIVED NOVEMBER 1, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

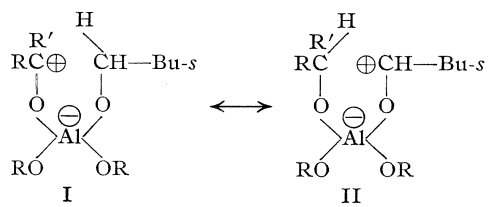
# Catalysis with (−)Aluminum 2-Methylbutoxide[1]

BY ROBERT H. BAKER AND LOREN E. LINN[2]

The versatility of aluminum alkoxides in synthetic work prompted the preparation and use of an optically active one with the hope of achieving asymmetric syntheses.

The aluminate of *fermentation* amyl alcohol has been previously described[3] but because of the difficulty of purifying the product we have preferred to prepare the *active* aluminate indirectly from previously purified materials. These indirect preparations have previously been carried out with esters,[4] but in this work the alcohol, (−)2-methylbutanol, was easily exchanged with either aluminum isoproxide, *t*-butoxide, or *d,l*-2-butoxide.[5] With the latter alkoxide there was no activity of the 2-butanol that distilled from the reaction mixture.

In consequence of the high ionic character of the carbonyl group in ketones, 47%,[6] and the electronegativity of aluminum it seems that the principal contributing structure of the activated complex in the Meerwein–Ponndorf reaction would involve a carbonium ion, I or II.[7] The acceptance of the hydride ion would then lead to either of two diastereomers with the thermodynamically most stable being produced in excess.




That this excess would not be expected to be large can be seen from the mass of experience in the reduction of optically active ketones with symmetrical aluminum alkoxides which generally give comparable amounts of the two alcohols.[8] Actually the system is considerably more complex than indicated by formulas I and II due to the fact that as the reaction progresses the nature of the alkoxyl groups changes. This factor would be expected to diminish the yield of asymmetric product.

Acetophenone is not well suited to this reaction

(1) This work was supported by a grant from the Abbott Fund.

(2) Present address: Hercules Powder Co., Wilmington, Delaware.

(3) Gladstone and Tribe, *J. Chem. Soc.*, **39**, 1 (1881).

(4) Baker, THIS JOURNAL, **60**, 2673 (1938).

(5) This refers to alkoxide made from racemic 2-butanol, and hence may be a mixture of two monomeric racemates.

(6) Pauling, "The Nature of the Chemical Bond," 2nd ed., p. 75, Cornell University Press, Ithaca, N. Y., 1945.

(7) It should be observed that these structures are resonance forms of the structure usually assigned, $R_2C{=}\overset{\oplus}{O}{-}\overset{\ominus}{Al}(OR)_3$, *cf.*, Woodward, Wendler and Brutschy, THIS JOURNAL, **67**, 1425 (1945).

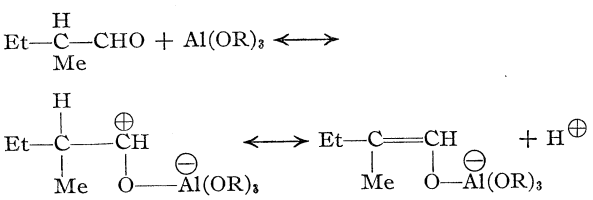
(8) Wilds in "Organic Reactions," Roger Adams, Editor, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 185.

because of its oxidation potential relative to aldehydes[9] and its ease of condensation[10] but since it is reported to have been reduced to an active carbinol in a similar but non-reversible reaction,[11] attempts were made to reduce it. No phenylmethylcarbinol was obtained and it is of interest only to record that successive fractions of (−)2-methylbutanol which distilled from the mixture were progressively more racemized.[12]

*p*-Chlorobenzophenone was reduced only partially in order to favor the possible asymmetric synthesis but the carbinol was inactive.

The availability of the active alcoholate made it possible to study the Tischtschenko reaction with (+)2-methylbutanal. The kinetics of this reaction are first order in aldehyde and consistent with the possibility of a rapid formation of a complex of one molecule of aldehyde and catalyst.[13] No model for this complex has been proposed but Dr. B. Abramovitch in this Laboratory has been able to relate the role of the catalyst in the Meerwein–Ponndorf–Oppenauer reaction to that of the Tischtschenko[13] by showing a similar promoting effect of electronegative additives like zinc or aluminum halides in the Oppenauer[14] isomerization of dehydroisoandrosterone.

(+)2-Methylbutanal, 94% optically pure, and (−)aluminum 2-methylbutoxide, 96% optically pure, gave an ester which on hydrolysis was shown to be composed of an acid and an alcohol which were of comparable optical purity, 60%. The slightly higher value of the alcohol portion is accountable for on the basis of alkoxyl exchange with the catalyst.[4] The ester was shown not to be racemized by prolonged heating with the catalyst hence the molecules of aldehyde which suffer reduction and oxidation have probably a common intermediate with the racemization step as a side reaction following perhaps the mechanism of the usual acid catalyzed type of enolization.



The present information does not allow the assignment of a reasonable role of the complex in the final formation of ester.

(9) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940), and private communication.

(10) Wayne and Adkins, *ibid.*, **62**, 3401 (1940).

(11) Vavon, Riviere and Angelo, *Compt. rend.*, **222**, 959 (1946).

(12) Catalytic reduction of acetophenone in (−)2-methylbutanol over Raney nickel at 2000 p. s. i. and 125° produced inactive phenyl methyl carbinol in 75% yield, with the recovered solvent retaining full activity.

(13) Child and Adkins, THIS JOURNAL, **45**, 3013 (1923); **47**, 798 (1925).

(14) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937); U. S. Patent 2,229,599, Jan. 21, 1941.

## Experimental

**(−)Aluminum 2-Methylbutoxide.**—A solution of 6.5 g. (0.032 mole) of aluminum isopropoxide in 10 g. (0.11 mole) of 2-methylbutanol, $\alpha^{26}D$ −9.26°, 2 dm., homogeneous; $n^{20}D$ 1.4100,[15] was distilled under a 16-plate column until 5 g. of isopropyl alcohol had been collected. The residue was then heated *in vacuo* at 200° to give 8.8 g., 88%, of the solid alkoxide, $[\alpha]^{25}D$ −1.0° in toluene. Hydrolysis of the product with water produced the unracemized alcohol.

**Attempted Reduction of Acetophenone.**—A solution of 27 g. (0.094 mole) of (−)aluminum 2-methylbutoxide in 50 ml. of (−)2-methylbutanol was treated with 20 g. (0.16 mole) of acetophenone and the solution subjected to 16-plate distillation. The distillate, collected in four fractions, was 2-methylbutanol, $n^{20}D$ 1.4108–1.4100. The weights and $\alpha$, 2 dm., were as follows: 5 g., −5.6°; 11 g., −5.5°; 16 g., −3.1°; 13 g., −1.9°. An additional 50 g. of alcohol was put in and the fractionation continued to give 5 g., −7.3°; 30 g., −7.4°; 4 g., −6.8°. The residue was hydrolyzed and the organic layer distilled at 10 mm. into five fractions, 22 g., b. p. 90–150°. These fractions were impure and had homogeneous rotations of *ca.* +1°, 2-dm. No phenylmethylcarbinol was isolated.

**Reduction of 4-Chlorobenzophenone.**—A solution of 2 g. (0.009 mole) of the ketone and 6 g. (0.024 mole) of aluminum *t*-butoxide in 36 g. (0.41 mole) of (−)2-methylbutanol was distilled at 16-plates until the head temperature reached 114°, three hours. Hydrolysis of the residue, separation, distillation of the alcohol and crystallization from petroleum ether gave 1.07 g., 53% of 4-chlorobenzhydrol, m. p. 60–61°.[16] A 9.2% solution in benzene gave no rotation.

**(+)2-Methylbutyl 2-Methylbutanoate.**—(+)2-Methylbutanal, $\alpha^{25}D$ + 45.3°; 2-dm. homogeneous, was prepared by the method of Badin and Pacsu[17] and purified by 16-plate distillation from a batch protected with hydroquinone.

Following the method of Danilov,[18] a mixture of 25 g. (0.29 mole) of the aldehyde and 2 g. (0.007 mole) of (−)-aluminum 2-methylbutoxide was held at 0° for one hour, at room temperature for forty minutes, and at 80° for thirty minutes. Hydrolysis of the alkoxide with water and 16-plate distillation of the organic layer gave 15 g., 60%, of the ester, b. p. 61–61.6° (11 mm.); $n^{20}D$ 1.4135; $\alpha^{26}D$ + 17.7°, 2-dm. homogeneous.

This ester was also isolated as a by-product of the aldehyde preparation, the homogeneous rotation being +26.8°, 2-dm. If this is assumed to be of the same optical purity as the aldehyde, 94%, the pure ester should be $\alpha^{25}D$ + 28.3°, 2-dm. The Tischtschenko ester has 62% of this rotation.

**Hydrolysis of the Tischtschenko Ester.**—The ester, 5.5 g., was refluxed with 100 ml. of 6 *N* barium hydroxide for thirty-eight hours. The alcohol and acid were isolated by steam distillation and purified by distillation. The acid, $\alpha^{22}D$ + 10.6°, 1-dm. homogeneous; $n^{21}D$ 1.4054, was 59% and the alcohol, $\alpha^{21}D$ −3.01°, 1-dm. homogeneous; $n^{21}D$ 1.4102, was 62% pure.[19]

## Summary

1. The preparation of the aluminate of (−)2-methylbutanol is described.

2. This optically active catalyst failed to bring about asymmetric reduction of aceto-

(15) Baker and Linn, THIS JOURNAL, **70**, 3721 (1948).

(16) Montagne, *Rec. trav. chim.*, **26**, 266 (1907), gives m. p. 62°. Various other values are found in the literature.

(17) Badin and Pacsu, THIS JOURNAL, **67**, 1352 (1945).

(18) Danilov, *Trans. State Inst. Applied Chem.* (*Moscow*), No. 5, 66 (1927); *Chem. Abs.*, **22**, 2138 (1928).

(19) These calculations are based on the optical rotations of the purest alcohol ($\alpha^{25}D$ −9.54°, 2 dm.) and acid ($\alpha^{25}D$ +35.38°, 2 dm.) prepared in these laboratories. The purity of the aldehyde was calculated from the optical rotation of the pure alcohol and the data of Badin and Pacsu.[17]

phenone and *p*-chlorobenzophenone.

3. The Tischtschenko reaction with (+)2-methylbutanal leads to ester, the alcohol and acid portion of which have suffered the same extent of racemization.

EVANSTON, ILLINOIS RECEIVED OCTOBER 18, 1948

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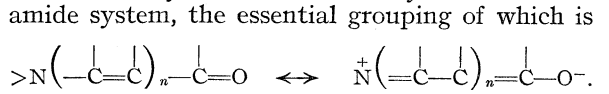
[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# Resonance and Polarity in the Molecules of Three Colored Compounds[1]

BY LAWRENCE M. KUSHNER AND CHARLES P. SMYTH

Dipole moment measurements made in this Laboratory have been used[2,3,4,5] to throw light on the resonance conditions in the molecules of certain un-ionized dyes, the results being satisfactorily correlated with the light absorption of the compounds. Dr. L. G. S. Brooker of the Eastman Kodak Company recently suggested to us measurements on three further colored compounds and furnished samples.

The three compounds are 3-ethyl-5-[4-(1-ethyl-3,3 - dimethyl - 2(3) - indolylidene) - butenylidene]-rhodanine (I), 1,3-diethyl-5-[4-(1-ethyl-3,3 - dimethyl - 2(1) - indolylidene) - 2 - butenylidene]-2-thiobarbituric acid (II) and 1,3-diethyl-5 - [(1,3 - diethyl - 2(3) - benzimidazolylidene)-butenylidene]-barbituric acid (III), all three belonging to a new group of un-ionized dyes known as the merocyanines.[5a] These dyes contain the amide system, the essential grouping of which is



In such dyes one of the two extreme resonance structures is uncharged while the other is a dipole. Some discussion of these dyes from the resonance standpoint has already appeared.[5b] Proof was advanced that in I the polar structure Ib (see Discussion of Results) must be of higher energy and contribute less than the non-polar structure Ia, since replacement of the indolenine ring by one that was more basic (in the restricted sense used by Brooker) reduced the deviation in $\lambda_{max.}$, whereas replacement by a less basic nucleus increased the deviation. Nevertheless the dipole moment of the compound was expected to be considerable.

## Experimental Method

The dipole moments were measured in solution in benzene or dioxane. The benzene used as solvent for the more soluble compounds, I and II, was a thiophene-free product from the Barrett Company, which was purified by drying with sodium wire followed by distillation from the wire (boiling point, 80.55–80.90° at 772.8 mm.; dielectric constant at 30°, 2.2672). The dioxane used as solvent for the almost insoluble compound III was "practical" 1,4-dioxane from the Carbide and Carbon Chemicals Corporation, which was distilled from 101.1 to 101.5° at 762.9 mm., dried over sodium wire and redistilled from the sodium wire, the fraction used boiling at 101.0° at 757.7 mm. Its dielectric constant, measured directly at 30°, was 2.1984 ± 0.0002.

Because of the virtual insolubility in benzene and very low solubility in dioxane of compound III, the preparation of the solutions presented a problem. It was overcome by weighing out the compound in a small glass cup on a high sensitivity analytical balance and transferring both cup and compound to a 100-cc. weighing bottle, to which the dioxane was then added. In the case of the most concentrated solution, it was necessary to warm the mixture to achieve true solution. As there was obviously a risk of evaporating some dioxane, the final weighing to determine the weight of dioxane in the solution was not made until all the solid had been dissolved and the solution had cooled.

The dielectric constants of the dilute solutions were measured with a heterodyne beat apparatus developed from one which has been previously described.[6] The precision of the apparatus was increased by replacing the precision measuring condenser formerly used by a General Radio Company 722–D instrument, on which an 1100 micromicrofarad scale was employed. The dielectric cell was similar to that previously described.[7] The densities of the benzene solutions were measured at 30° with an Ostwald–Sprengel pycnometer, the technique employed being similar to that previously described.[8] The dipole moments were calculated from the experimental data by the method of Halverstadt and Kumler.[9] The dielectric constants, $\epsilon_{12}$, and specific volumes, $v_{12}$, of the solutions were found to be linear functions of the mole fractions, $c_2$, of the solutes according to the equations

(1) This research was carried out with the support of the Office of Naval Research.

(2) Brooker, Sprague, Smyth and Lewis, THIS JOURNAL, **62**, 1116 (1940).

(3) Brooker, White, Keyes, Smyth and Oesper, *ibid.*, **63**, 3192 (1941).

(4) Brooker and Sprague, *ibid.*, **63**, 3203 (1941).

(5) Brooker and Sprague, *ibid.*, **63**, 3214 (1941).

(5a) Papers dealing with these dyes are in course of preparation in Dr. Brooker's Laboratory.

(5b) Brooker, "Frontiers in Chemistry," Vol. III, Interscience Publishers Inc., New York, N. Y., 1945, p. 129.

(6) Lewis and Smyth, *J. Chem. Phys.*, **7**, 1085 (1939).

(7) Smyth and Morgan, THIS JOURNAL, **50**, 1547 (1928).

(8) Lewis and Smyth, *ibid.*, **61**, 3063 (1939).

(9) Halverstadt and Kumler, *ibid.*, **64**, 2988 (1942).

$$\epsilon_{12} = \epsilon_1 + \alpha' c_2$$
$$v_{12} = v_1 + \beta' c_2$$

The dielectric constants, $\epsilon_1$, and specific volumes, $v_1$, for the pure solvents given by these equations when applied to the plots of the experimental data against $c_2$ agreed well with the directly measured values. The calculated values along with the values of $\alpha'$ and $\beta'$, the slopes of the lines, were used to calculate the polarization of the solute at infinite dilution

$$P_\infty = 3\alpha' v_1 M_1/(\epsilon_1 + 2)^2 + (M_2 v_1 + M_1\beta')(\epsilon_1 - 1)/(\epsilon_1 + 2)$$

in which $M_1$ is the molecular weight of the solvent and $M_2$ is that of the solute. The dipole moment was then obtained from the usual equation

$$\mu = 0.01281 \times 10^{-18} [(P_\infty - R_D)T]^{1/2}$$

The molar refractions for the D sodium line, $R_D$, which could not be measured directly because of the color of the compounds, were calculated from values of bond refractions in the literature.[10] A small correction of 2 cc. was added to the values as a rough estimate of the exaltation arising from the conjugated systems in the molecules. The effects of errors in the calculation of $R_D$ and of the approximation made in using $R_D$ instead of the true sum of the electronic and atomic polarizations are negligible in comparison with the experimental errors in the determination of $P_\infty$.

The low solubilities of these large and highly polar molecules in non-polar solvents cause the errors in the dipole moment values to be larger than is usual in solution measurements, particularly, in the case of compound III, which was too insoluble for measurement in benzene and soluble in dioxane only to the extent of mole fraction $3 \times 10^{-6}$ at 30°. Since it was unprofitable to attempt to measure the densities of the extremely dilute solutions of III, the value of $v_1$ was calculated in this case from the density of pure dioxane[11] and its temperature coefficient.[12] The value of $\beta'$ was roughly estimated by assuming that the volume of the most concentrated solution was that of the dioxane alone, dividing this volume by its weight, and using the value of $v_{12}$ thus obtained along with that for $v_1$ to calculate $\beta'$. Although this rough value of $\beta'$ is, presumably, too large, the effect of its error upon the moment value is small in comparison with that of the errors in the dielectric constant values, which vary over a range of only 0.001 from the value for the solvent, but show, nevertheless, a satisfactory linear dependence upon $c_2$.

## Experimental Results

The values of $\epsilon_{12}$ and $v_{12}$ for the solutions are given in Table I and the values of the constants calculated from them in Table II.

(10) Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., Reinhold Publishing Corp., New York, N. Y., 1931, Chap. VIII.

(11) Kumler, THIS JOURNAL, **62**, 3292 (1940).

(12) Smyth and Walls, *ibid.*, **54**, 2261 (1932).

TABLE I

DIELECTRIC CONSTANTS AND SPECIFIC VOLUMES AT 30°

| | Solvent | $c_2$(× $10^4$) | $\epsilon_{12}$ | $v_{12}$ |
|---|---|---|---|---|
| I | 3-Ethyl-5-[4-(1-ethyl-3,3-dimethyl-2(3)-indolylidene)-butenylidene]-rhodanine | | | |
| | Benzene | 2.79 | 2.2866 | 1.15215 |
| | | 4.04 | 2.2953 | 1.15194 |
| | | 9.55 | 2.3301 | 1.15101 |
| | | 18.88 | 2.3920 | 1.14957 |
| | | 26.51 | 2.4439 | 1.14816 |
| II | 1,3-Diethyl-5-[4-(1-ethyl-3,3-dimethyl-2(1)-indolylidene)-2-butenylidene]-2-thiobarbituric acid | | | |
| | Benzene | 1.643 | 2.2904 | 1.15229 |
| | | 3.108 | 2.3103 | 1.15199 |
| | | 4.456 | 2.3265 | 1.15173 |
| | | 5.891 | 2.3448 | 1.15134 |
| | | 5.998 | 2.3481 | 1.15134 |
| III | 1,3-Diethyl-5-[(1,3-diethyl-2(3)-benzimidazolylidene)-butenylidene]-barbituric acid | | | |
| | Dioxane | 0.00634 | 2.1984 | |
| | | .00985 | 2.1986 | |
| | | .02462 | 2.1993 | |
| | | .03075 | 2.1994 | |

TABLE II

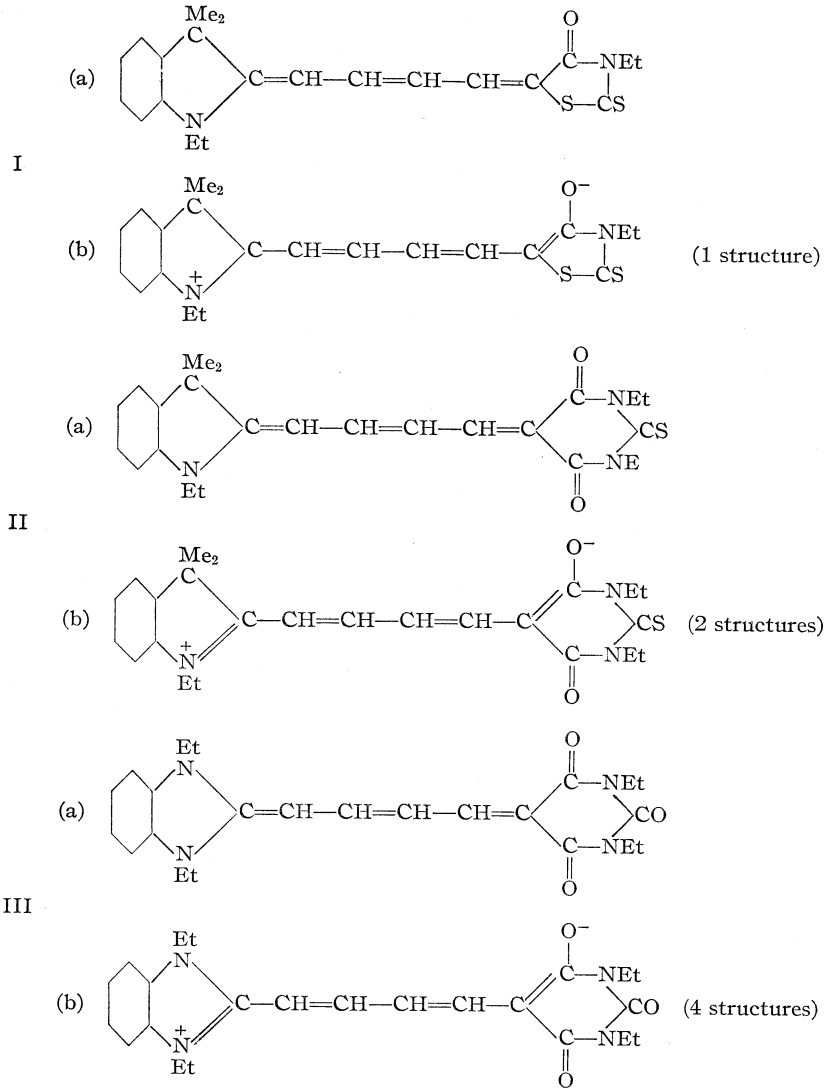
EMPIRICAL CONSTANTS AND POLARIZATIONS AT 30°, REFRACTIONS AND DIPOLE MOMENTS

| $\epsilon_1$ | $v_1$ | $\alpha'$ | $\beta'$ | $P_\infty$ | $R_D$ (calcd.) | $\mu$ (× $10^{18}$) |
|---|---|---|---|---|---|---|
| Compound I | | | | | | |
| 2.268 | 1.1526 | 66.4 | −1.675 | 1077 | 114.8 | 6.91 ± 0.10 |
| Compound II | | | | | | |
| 2.269 | 1.1527 | 130.0 | −2.233 | 2020 | 124.7 | 9.70 ± 0.15 |
| Compound III | | | | | | |
| 2.1982 | 0.9782 | 435 | (−4.5) | 6383 | 116.8 | 17.7 ± 1.3 |

## Discussion of Results

The dipole moment found for the molecule of compound III is the largest yet observed for a molecule other than that of a salt or a zwitterion. The reason for the large moments of these compounds becomes apparent when one considers the polar structures, b, shown below, which can be readily formed by shift of an electron pair from a nitrogen in the non-polar structure, a, through the conjugated system to a carbonyl oxygen. The term "non-polar" is used to distinguish the structures of relatively low polarity from those in which an electron pair has shifted from one side of the molecule to the other.

If the polar structures, b, are not very different in energy from the non-polar, a, resonance between the a and b structures will give rise to dipole moments whose size depends largely on the amounts of the contributions of the polar structures. The moments of the non-polar structures should differ somewhat from one another and cannot be calculated with exactness. None of them should exceed $2.5 \times 10^{-18}$ and little error will arise in our considerations from the assignment of a rough value $m_a = 2.0 \times 10^{-18}$ to the non-polar structure




of each of the three compounds. Compound I can have only one contributing polar structure, b, compound II has two identical polar structures, while compound III has four polar structures indistinguishable from one another. The conceivable doubly charged structure for compound III cannot arise for, as soon as one nitrogen and one oxygen are charged, the other oxygen and nitrogen are no longer connected by a conjugated chain. The polar structures should have approximately equal energies and approximately equal dipole moments, $m_b$. The large values found for the dipole moments in Table II as compared to the relatively small values calculated for the non-polar structures, a, show the considerable stability of the polar structures, b. The increase in moment from compound I to II to III corresponds qualitatively to the increase in the number of contributing polar structures from 1 to 2 to 4. In most molecules, the possible polar structures are so much less stable than the non-polar that their contributions are relatively small and their amounts, as indicated by the dipole moment, are a fair measure of the amount of resonance. This is not far from being the case in compound I, but in compound III, the four polar structures make so large a contribution that, as shown by the absorption measurements of Dr. L. G. S. Brooker and his colleagues, increased stabilization of the polar structures by the use of a polar solvent decreases the amount of resonance.

One can write[13] three equations for the moments, $\mu$, of the molecules

$$\mu_I = (1 - x_I)m_a + x_I m_b$$
$$\mu_{II} = (1 - x_{II})m_a + x_{II} m_b$$
$$\mu_{III} = (1 - x_{III})m_a + x_{III} m_b$$

where $x$ is the fractional contribution of all the polar structures for each molecule, $m_a$ is the moment of the so-called non-polar structure, which, because of its relatively small size, can, without serious error, be taken as the same for all three molecules, and $m_b$ is the moment which should be virtually the same for all the polar structures. If $m_a$ is taken as $2.0 \times 10^{-18}$, the observed values can be put in for $\mu_I$, $\mu_{II}$ and $\mu_{III}$ and the equations solved simultaneously for the ratios of the fractional contributions of the polar structures, $m_b$ being eliminated by substitution. The ratios thus obtained are

$$x_{II}/x_I = 1.57 \text{ and } x_{III}/x_I = 3.21$$

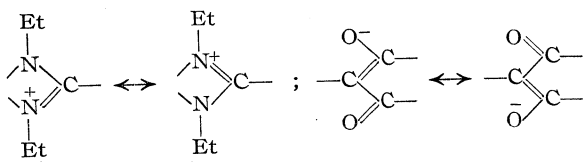
The absorption measurements indicate that the amount of resonance in compound II is not greatly affected by increase in the polarity of the solvent. This suggests that, in the non-polar solvent, the contribution of the polar forms may be somewhat less than half, an amount which may be increased to somewhat more than half by a polar solvent without greatly altering the amount of resonance. If, in line with this suggestion, $x_{II}$ is set equal to 0.4, $x_I$ is given by the calculated ratios as 0.25 and $x_{III}$ as 0.81, values which are consistent with the fact that the absorption measurements show that a polar solvent increases the amount of resonance in compound I and decreases it in compound III. It might be argued qualitatively that since, in

(13) Smyth, THIS JOURNAL, **63**, 57 (1941).

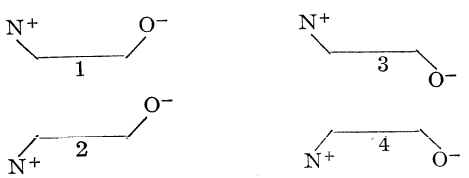
compound II, the amount of resonance is not far from a maximum, the contributions of the non-polar structure and of each of the two polar structures should be nearly equal, that of the non-polar structure being slightly greater in a non-polar solvent than that of each of the two polar structures. In this case, $(1 - x_{II})$ would be about 0.4 and $x_{II}/2$ about 0.3. This would make $x_I = 0.38$ and $x_{III} = 1.22$, an impossibly large answer. It is evident that, since $x_{III}$ must be less than 1, $x_I$ must be less than 0.31, $x_{II}$ must be less than 0.49, and $m_b$ must be greater than $18 \times 10^{-18}$.

Substitution of the value $x_{II} = 0.4$ in the equation for $\mu_{II}$ or of the corresponding values of $x_I$ and $x_{III}$ in the other equations gives $m_b = 21.4 \times 10^{-18}$ for the moment of the polar structures. The maximum value which the polar structure could have is the moment of the structure with an extended, planar, zig-zag chain, in which the charges are separated by a maximum distance. The value calculated approximately for this structure from the bond lengths and angles is $42 \times 10^{-18}$, while the value calculated from the mean square moment for all the possible orientations around the bonds of the chain is $30 \times 10^{-18}$. Even the lower of these two values is much higher than the value 21.4, estimated on the basis of reasonable values for the amounts of the contributions of the polar structures. Conversely, the use of the moments calculated for the ionic structures without allowance for decrease of moment by an empirically introduced inductive distortion[14] would give lower values than those assumed for the amounts of the contributions from the polar structures, as previously observed.[13]

Consideration of the four polar structures, IIIb, for compound III shows that they can change from one to another by shifts of electrons at the ends of the butenylidene chain.



The four polar structures, represented schematically below, are hereafter referred to as 1, 2, 3 and 4.



The total wave function, $\psi_{III}$, for the system can be expressed as

$$\psi_{III} = a\phi + b(\chi_1 + \chi_2 + \chi_3 + \chi_4)$$

where $\phi$ is the wave function of the non-polar structure, $\chi_i$ is the wave function of the $i^{th}$ polar structure, and $a$ and $b$ are constants representing the contribution of each structure to that of the molecule as a whole. The total energy, $W_{III}$, of the system is given by the expression

$$W_{III} = \int \psi^*_{III} H \psi_{III}\, d\tau / \int \psi^*_{III} \psi_{III}\, d\tau$$

Substitution for $\psi_{III}$ in the above equation with the assumptions that $\phi$ and $\chi_i$ are normalized and orthogonal functions and that the integrals representing the resonance between structures 1 and 4, and 2 and 3 are small compared with the other exchange integrals, leads to the expression

$$W_{III} \cong [a^2C + 8abE_{CP} + 4b^2 (P + E_N + E_O)]/(a^2 + 4b^2)$$

where

$C = \int \phi^* H \phi d\tau$ = energy of non-polar structure

$P = \int \chi_i^* H \chi_i d\tau$ = energy of the $i^{th}$ polar structure (all polar forms are assumed to have the same energy)

$E_{CP} = \int \phi^* H \chi_i d\tau$ = exchange energy between the non-polar and any polar structure

$E_N = \int \chi_1^* H \chi_2 d\tau = \int \chi_3^* H \chi_4 d\tau$ = exchange energy between structures 1 and 2, 3 and 4

and $E_O = \int \chi_1^* H \chi_3 d\tau = \int \chi_2^* H \chi_4 d\tau$ = exchange energy between structures 1 and 3, and 2 and 4.

Minimizing the energy with respect to the quantities $a$ and $b$, gives the ratio

$$a/b = 4E_{CP}/(W_{III} - C)$$

and the expression

$$W_{III} = [(P + C + E_N + E_O) \pm ((P - C + E_N + E_O)^2 + 16E^2_{CP})^{1/2}]/2$$

Since the minimum energy is desired, it is obvious that the negative sign must be used. Substitution for $W_{III}$ in the expression for $a/b$, yields the equation

$$a/b = 2K/[1 - (1 + K^2)^{1/2}]$$

where

$$K = 4E_{CP}/(P - C + E_N + E_O)$$

Substitution for $\psi_{III}$ in the equation

$$\mu_{III} = \int \psi^*_{III} \mu \psi_{III}\, d\tau / \int \psi^*_{III} \psi_{III}\, d\tau$$

with the assumption that integrals of the type $\int \phi^* \mu \chi_i d\tau$, $\int \chi^*_i \mu \chi_j d\tau$ are negligible in comparison with those of the type $\int \phi^* \mu \phi d\tau$ and $\int \chi_i^* \mu \chi_i d\tau$, gives

$$\mu_{III} \cong (a^2\mu_c + 4b^2\mu_i)/(a^2 + 4b^2)$$

where $\mu_c = \int \phi^* \mu \phi d\tau$ = dipole moment of the non-polar form, and $\mu_i = \int \chi_i^* \mu \chi_i d\tau$ = dipole moment of the $i^{th}$ polar form (it is assumed that all the polar forms have the same moment).

Substitution for $a/b$ gives the final equation

$$\mu_{III} = [K^2\mu_c + \mu_i(2 - 2(1 + K^2)^{1/2} + K^2)]/2(1 - (1 + K^2)^{1/2} + K^2),$$

where $\mu_c$ is the moment of the non-polar structure. Substitution of the values $\mu_{III} = 17.7 \times 10^{-18}$, $\mu_c = 2.0 \times 10^{-18}$ and $\mu_i = 40.0 \times 10^{-18}$, an approximation slightly lower that the maximum possible value, gives $E_{CP}/(P - C + E_N + E_O) = -1.41$, and 0.766 and 0.321 for $a$ and $b$, respectively.

The similarities of the structures of compounds I, II and III are such that it is reasonable to as-

(14) Hugill, Coop and Sutton, *Trans. Faraday Soc.*, **34**, 1518 (1938).

sume that the non-polar and polar wave functions do not change significantly from one compound to another. Therefore, the wave functions for compounds I and II are obviously

$$\psi_I = a\phi + b\chi$$

and

$$\psi_{II} = a\phi + b(\chi_1 + \chi_3)$$

By procedures similar to these previously described, the following relations are obtained for compound I.

$$W_I = (a^2C + 2abE_{CP} + b^2P)/(a^2 + b^2)$$

where $a = 0.940$ and $b = 0.359$, and

$$E_{CP}/[P - C] = -0.455$$

For compound II

$$W_{II} = [a^2C + 4abE_{CP} + 2b^2(P + E_O)]/[a^2 + 2b^2]$$

where $a = 0.891$ and $b = 0.319$ and

$$E_{CP}/[(P - C) + E_O] = -0.478$$

From these equations, it is possible to arrive at the following energy relationships

$$W_{III} = 1.97E_{CP} + 0.41E_N + 0.41E_O + (0.59C + 0.41P)$$
$$W_I = 0.67E_{CP} + (0.87C + 0.13P)$$
$$W_{II} = 1.10E_{CP} + 0.20E_O + (0.80C + 0.20P)$$

where

$$(P - C) = -2.20E_{CP},\ E_O = 0.10E_{CP},\ E_N = 1.39\ E_{CP}$$

In the case of compound I, there is resonance between the non-polar and polar structures which gives rise to a resonance energy term $0.67E_{CP}$, and a dipole moment of $6.9 \times 10^{-18}$. Compound II, in addition to having a somewhat larger contribution to the total energy of the system, $1.10E_{CP}$, arising from the existence of two polar structures, has an energy term $0.20E_O$ which is due to resonance between the two polar structures. The calculations show that this energy term is rather small, since $E_O = 0.10\ E_{CP}$, and, therefore, the polar structures are stabilized only to the extent of raising the dipole moment from $6.9 \times 10^{-18}$ to $9.7 \times 10^{-18}$. In compound III, the polar form is stabilized to a much greater extent by resonance between structures 1 and 2, and 3 and 4, the resonance energy here being $0.41E_N$, plus $0.41E_O$, arising from resonance between the polar structures as mentioned for compound II. Since here there are four polar structures, the energy term corresponding to resonance between the non-polar and polar structures is larger than that for compounds I or II. It is seen then that the dipole moment of compound III, $17.7 \times 10^{-18}$, is very large, not only because there are four possible polar structures, but because there is resonance between the polar structures which gives them added stability. Similarly, even though there are two polar structures for compound II, there is not much resonance between them, and the dipole moment is lower than would be expected.

The values of $x$ and $a$ and $b$ have been calculated for the other seemingly possible values of $m_b = \mu_i$, and all are summarized in Table III. Since $x$ represents the total fractional contribution of polar structures for each compound, while, for compounds I, II and III, $a^2_I + b^2_I = 1$, $a^2_{II} + 2b^2_{II} = 1$, and $a^2_{III} + 4b^2_{III} = 1$, for comparison with $x$, the values of $b$ are listed as $4b^2_{III}$, $2b^2_{II}$ and $b^2_I$.

TABLE III

CONTRIBUTIONS OF POLAR STRUCTURES CALCULATED FOR DIFFERENT MOMENT VALUES FOR THE POLAR STRUCTURES

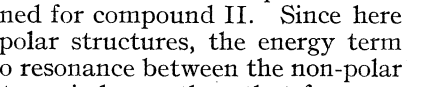
| $m_b$ | $x_I$ | $x_{II}$ | $x_{III}$ | $b^2_I$ | $2b^2_{II}$ | $4b^2_{III}$ |
|---|---|---|---|---|---|---|
| >18 | <0.31 | <0.49 | <1.0 | .. | .. | .. |
| 21.4 | .25 | .40 | .81 | .. | .. | .. |
| 30 | .18 | .28 | .56 | 0.17 | 0.28 | 0.44 |
| 40 | | | | .13 | .20 | .41 |
| 42 | .12 | .19 | .39 | | | |

$x_{III} = 3.21\ x_I$; $x_{II} = 1.57\ x_I$

No solutions for $a$ and $b$ could be obtained for $\mu_i = 21.4$ or lower, which shows that the seemingly reasonable assumption, $x_{II} = 0.4$, based on the observed absorption is not justified. Since the dipole moment calculated for an undistorted polar structure has been found, in other cases, to indicate an unexpectedly small amount of resonance, it would seem that the fractional contributions based on the intermediate value 30 for the moment of the polar structures may be the most reasonable. Table III shows that, within the limits $m_b = \mu_i = 30 - 40$, the total contributions of the polar structures for each molecule do not change greatly. Therefore, although the exact contribution in the case of each molecule cannot be stated, their relative values are known, and suffice to explain the magnitudes of the measured moments.

**Acknowledgment.**—The writers wish to express their deep indebtedness to Dr. L. G. S. Brooker of the Kodak Research Laboratories for materials, information and advice and to Professor Walter Kauzmann for aid in the quantum mechanical calculations.

## Summary

The dipole moments of three dyes of the merocyanine series have been measured in very dilute solutions. The merocyanines are un-ionized dyes characterized by the amidic resonating system . One molecule receives a contribution from one polar structure, one from two polar structures and one from four polar structures. The large dipole moments increase as the number of contributing polar structures increases to such an extent that the moment of the molecule with four contributing polar structures is larger than that previously found for any molecule other than that of a salt or a zwitterion. The dipole moment values qualitatively confirm predictions of the relative polarities of the substances and make possible exact calculations of the relative contributions of the polar structures. The absolute amounts of these contributions are cal-

culated on the basis of reasonable values for the moments of the polar structures. A quantum mechanical calculation of the relative energies of the structures explains the quantitative deviations from the amounts of the contributions to be expected merely on the basis of the number of contributing polar structures.

PRINCETON, NEW JERSEY RECEIVED NOVEMBER 19, 1948

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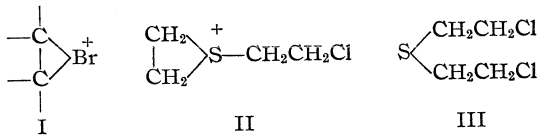
[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

# Kinetics of Hydrolysis and Displacement Reactions of β,β′-Dichlorodiethyl Sulfide (Mustard Gas) and of β-Chloro-β′-hydroxydiethyl Sulfide (Mustard Chlorohydrin)[1]

BY PAUL D. BARTLETT AND C. GARDNER SWAIN

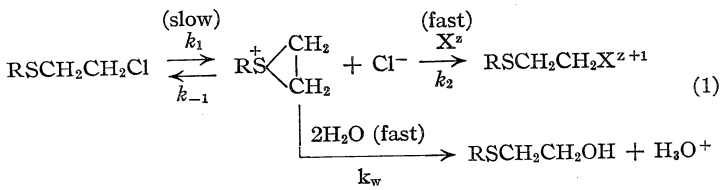
## Introduction

The existence of the ethylenebromonium ion (I) and its participation in bromination reactions were first postulated in 1937 by Roberts and Kimball.[2] An elegant demonstration of the participation of such ions in displacement reactions of β-bromoalkyl compounds was provided by Winstein and Lucas[3] in 1939. During World War II it was recognized by American workers that the closely analogous ethylenesulfonium ion (II) offered an attractive explanation of the *first-order* displacement reactions[4] of β,β′-dichlorodiethyl sulfide (mustard gas, III) a type of displacement kinetics not shown by any primary alkyl chloride.[5] Ogston, whose extensive studies of this reaction were the basis of most of the ideas used in the mustard program, observed



I II III

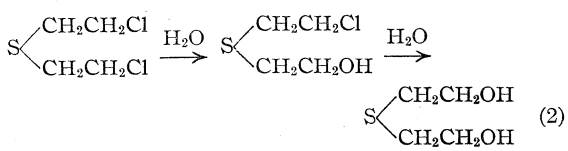
certain facts which at the time appeared incompatible with the simple view of the mechanism expressed in eqn. 1



(1)

and indeed with any mechanism involving only this number of steps. The facts which presented the difficulty were: (1) that the "competition factor," defined as the ratio $k_2/k_w$ for any molecule or ion X capable of reacting with the ethylenesulfonium ion, varied widely with the concentration of X in the case of chloride ion, whereas it was expected to be constant; and (2) that although, to a first approximation, the rates of reaction of mustard with all substances depended only upon the concentrations of mustard and of chloride ion, which are concerned in the first step of the mechanism, yet the initial measured first-order rate constant for the reaction of mustard with certain strong competitors such as sodium monothiophosphate was 10% greater than with water or weaker competitors.

It was important to our work to obtain definite proof of the adequacy or inadequacy of Equation (1) to describe the displacement reactions of mustard gas. We therefore undertook some careful kinetic studies of the system and as a result were able to explain the above apparent anomalies satisfactorily within the scheme of Equation (1). The experimental approach had the following features. "Mustard chlorohydrin," β-chloro-β′-hydroxydiethyl sulfide, was prepared in a state of purity which permitted the two stages of mustard hydrolysis indicated in eqn. 2 to be studied separately. The progress of reaction was followed both by the convenient and accurate intermittent alkali titration of Peters and Walker[4] and by polarographic determination of the rate of liberation of chloride ion. The first of these methods was already adapted to following the kinetics of rapid reactions with half-periods of



(2)

only a few minutes; we have adapted the polarographic method to the same purpose, thus permitting a comparison between the rates of liberation of chloride and hydrogen ions, which affords a test of the occurrence of appreciable concentrations of sulfonium ions during the reaction.

(1) This work was performed during 1943–1944 under Contract NDCrc 136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development.

(2) I. Roberts and G. E. Kimball, THIS JOURNAL, **59**, 947 (1937).

(3) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1576, 1581, 2845 (1939).

(4) R. A. Peters and E. Walker, *Biochem. J.*, **17**, 260 (1923). A. G. Ogston, Peters Reports #34 (1941), #66 (1943), available through the British Ministry of Supply; *Trans. Faraday Soc.*, **44**, 45 (1948).

(5) R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 477 (1946). The hypothesis of the ethylenesulfonium ion was conceived independently by different workers. It was in use by the present authors late in 1941.

The ionic strength was controlled in all runs. The importance of these features will be brought out in the discussion which follows.

## Experimental

**Materials.**—β-Chloro-β′-hydroxydiethyl sulfide (mustard chlorohydrin) was prepared by the method of Grant and Kinsey.[6] After the replacement of half of the hydroxyl of thiodiglycol by chlorine the unconverted thiodiglycol and sulfonium salts were removed by water–ether extraction, followed by a slow and incomplete removal of mustard by cyclohexane or petroleum ether. Judged by the halogen analyses, the best samples after this procedure contained 3–4% of mustard. The excess chlorine content was reduced to 2% by sublimation under a pressure of $3 \times 10^{-5}$ mm. with efficient magnetic stirring of the liquid charge which was maintained at 0–5°. A middle fraction was melted off the Dry Ice–cooled condenser, weighed accurately, and immediately made into a 0.0187 *M* stock solution with undried Merck reagent acetone without allowing the undiluted chlorohydrin to be at room temperature for more than ten minutes. This solution showed no detectible hydrolysis when kept at 4° in a cold room over a period of two months. It was observed that undissolved mustard chlorohydrin developed about 5% of chloride ion in an hour, but that this chloride ion disappeared on solution of the material in acetone. The ionic material is presumably the dimer

$$HOCH_2CH_2SCH_2CH_2\overset{+}{S}\begin{matrix}CH_2CH_2OH\\CH_2CH_2Cl\end{matrix}\quad Cl^-$$

which is formed reversibly, and is present to an appreciable fraction at equilibrium in the chlorohydrin as solvent but not in acetone.

We investigated a sample of the chlorohydrin prepared by the photochemical reaction between monothioethylene glycol and vinyl chloride,[7] but could not get as pure material from it as by the method described.

β,β′-Dichlorodiethyl sulfide (mustard gas) was prepared from thiodiglycol.[8] A fraction melting at 14.35 ± 0.10° was redistilled and a small middle fraction saved for kinetic purposes. It was apparently quite free from disulfide since a hydrolyzed solution gave no trace of a polarographic wave anywhere between the large sharp chloride and hydrogen waves at +0.20 and −1.5 volts, respectively, *vs.* the saturated calomel electrode. Determinate stock solutions were made by weighing 0.74–0.91 g. of mustard accurately on an analytical balance and making up to 250 cc. with undried Merck reagent acetone. No chloride ion could be detected in these freshly made solutions by distributing 25 cc. between benzene and water in a separatory funnel and titrating the water layer with 0.00500 *M* silver nitrate potentiometrically. After standing at room temperature for ten months the amount of ionic chloride corresponded to only 0.15% reaction in a kinetic run.

The sodium benzenesulfonate used to control the ionic strength was Eastman product repeatedly crystallized from 95% ethanol until the percentage of sodium chloride dropped from about 1% to under 0.00040%, corresponding to less than 0.2% of the chloride ion liberated in a kinetic run.

The 0.05 *M* benzenesulfonic acid used for neutralizations was Eastman practical grade and contained less than 0.0004% of chloride ion by titration. The shape of a titration curve with sodium hydroxide showed it to be free from weak acids.

A 0.0518 *M* sodium hydroxide solution was prepared from a filtered 50% solution with freshly boiled distilled water and properly protected from atmospheric carbon dioxide. It was standardized with 0.0499 *M* hydrochloric acid, which had been indirectly standardized by titration against weighed potassium acid phthalate.

In the intermittent titrations, we used 0.50 cc. per 100 cc. of aqueous reaction medium, of one of the following indicators: 0.1% aqueous brom thymol blue neutralized to *p*H 7.0; 1:3 0.1% aqueous cresol purple with 0.1% aqueous thymol blue neutralized to *p*H 8.0; or 1:2 0.1% aqueous brom cresol green with 0.1% aqueous methyl red neutralized to *p*H 5.1. This last mixture was partly insoluble and had to be shaken before use. The mixed indicators were kept in brown bottles. They gave distinctly sharper endpoints than single indicators. In all cases a standard cell, identical in size and shape to the reaction cell and containing 100 cc. of a phosphate buffer for the *p*H chosen, 5 cc. of acetone and 0.50 cc. of indicator, was clamped in the thermostat beside the reaction cell to make an accurate color comparison possible. The molarity of indicator used in a reaction was about 0.5% of the initial molarity of chlorohydrin or mustard.

Sodium monothiophosphate was shown by Ogston to be a useful competitor in reactions of mustard because at *p*H 8.0 it liberates hydrogen ion quantitatively when it reacts.

$$HPSO_3^= + RCl \longrightarrow RPSO_3^= + Cl^- + H^+$$

This compound was easily prepared by hydrolysis of Eastman practical grade thiophosphoryl chloride with sodium hydroxide. Twenty cc. of thiophosphoryl chloride was added to a solution of 48 g. of sodium hydroxide and 5 cc. of dioxan in 200 cc. of water, shaken with periodic cooling in a water-bath to prevent too rapid a reaction, then kept at 100° on the steam-bath for an hour to dissolve all the thiophosphoryl chloride. After evaporating somewhat in an open evaporating dish at room temperature and cooling in ice, 61 g. of large white crystals precipitated. These were collected, washed with alcohol and ether to dry, recrystallized from 69 cc. of water at 100° and finally cooled in ice yielding 48 g., then recrystallized several times more. The competitive power of the product, measured by the total amount (56%) of acid liberated on reaction with mustard with an equal molarity of the non-acid-liberating thiosulfate present, did not change with further crystallizations.

An acid titration of sodium monothiophosphate with a glass electrode showed two well defined waves with *pK* values of roughly 10.2 and 5.6 at 25°. Therefore at *p*H 7.9–8.0 it is most completely in the form of $HPSO_3^=$. At *p*H 8.0 Ogston reports that its "competition factor" is $3.8 \times 10^4$ compared to $2.7 \times 10^4$ for thiosulfate and $8.0 \times 10^3$ for hydroxyl ion.

The dry salt crystallized with its full twelve molecules of water seems to be stable over long periods of time. The partially dehydrated salt develops a pronounced odor of hydrogen sulfide in a few days. A 0.05 *M* solution decreases in iodine titer about 5% in a week at room temperature, faster after that. This is probably a chemical decomposition to phosphite and sulfur. In contrast to thiosulfate, one mole of thiophosphate equals two equivalents of iodine since the reaction product with iodine is colloidal sulfur.

$$PSO_3^= + I_2 + H_2O \longrightarrow H_2PO_4^- + 2I^- + S$$

The titration is sharper with no buffering or added acid.

Aqueous solutions of sodium monothiophosphate are strongly alkaline. There should be no delay in degassing and using a solution which has been neutralized to *p*H 8.0 by an equivalent of acid preparatory to a run. The $HPSO_3^=$ ion is unstable and decomposes over a period of a day.

**Apparatus.**—The cell used for the intermittent titrations is shown in Fig. 1. It consisted of a 4.6 × 21 cm. test-tube with a capillary side tube entering near the bottom for a gas inlet. The shaft of a small glass propeller stirrer passed down through a glass sleeve in the rubber stopper in the top of the cell and rested in a small depression blown in the bottom of the cell which served as a bearing. The propeller was driven at high speed by an air blast directed on a small notched disc on the shaft outside the cell, and caused the gas bubbles entering below to break and com-

(6) W. M. Grant and V. E. Kinsey, THIS JOURNAL, **68**, 2075 (1946).

(7) R. C. Fuson and J. B. Ziegler, Jr., *J. Org. Chem.*, **11**, 510 (1936).

(8) W. Steinkopf, J. Herold and J. Stöhr, *Ber.*, **53**, 1008 (1920).

pletely fill the solution. By turning of a stopcock the gas stream could be introduced into the cell over the surface through a tube in the rubber stopper instead of under the surface.

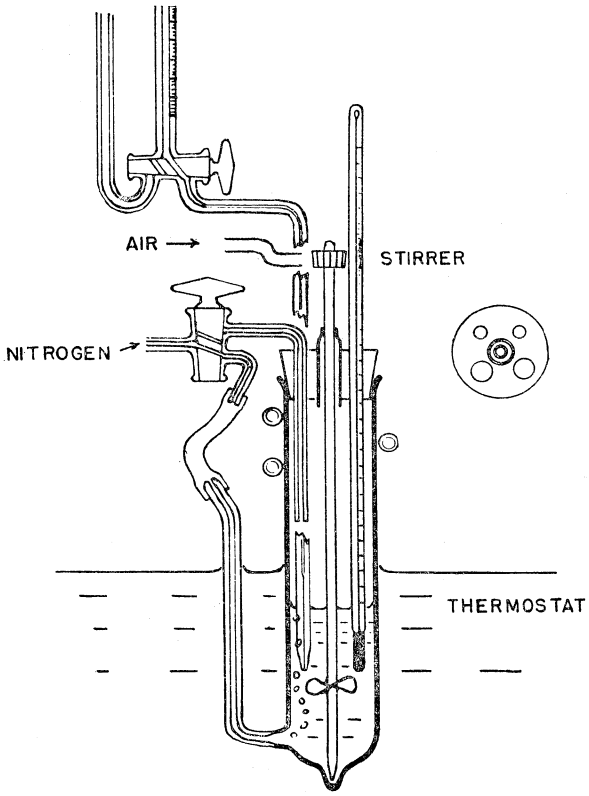



Fig. 1.—Apparatus for rapid intermittent titration of hydrogen ion liberated in hydrolysis of mustard and mustard chlorohydrin. Inset—top view of rubber stopper. Center hole, air-driven stirrer; upper holes, nitrogen inlet and thermometer; lower holes, microburet and nitrogen outlet.

Reagents were added from a 5-cc. microburet with its long capillary tip below the surface of the solution in the cell. The microburet and all other burets, pipets and volumetric flasks used in this work were standardized.

The reaction cell for following chloride liberation with the dropping mercury electrode was identical with the cell used for the intermittent titrations except that it was modified into an H-cell by blowing a side tube and auxiliary cell into the side of the reaction cell. The side tube had a 2.5-cm. medium-coarse fritted disc on the reaction side. This was covered with a plug of 3% agar gel containing 0.15 *M* sodium benzenesulfonate. A saturated mercurous sulfate electrode was made so that it could be readily removed and stored in a bottle containing saturated potassium sulfate when not in use. When placed in this cell it was covered with 0.15 *M* sodium benzenesulfonate to the same height as the solution in the reaction half.

**Intermittent Titration for Hydrogen Ion.**—Appropriate amounts of reagents and stock solutions were made up to 100 cc. with water in a volumetric flask. This solution was introduced into the titration cell. Purified nitrogen was then passed for forty-five minutes through this solution and through the acetone stock solution of mustard or chlorohydrin, the gas being first saturated with water in the one case and acetone in the other. The temperature in the cell was brought to exactly 23.70°; then 4.96 cc. of the acetone stock solution was added rapidly from a syringe pipet, the stopwatch being started when the addition was half complete. There was an immediate temperature rise to 25.00° and the total volume was 104.2 cc. The cell, air blast for the stirrer, buret, etc., were all on the same vertically sliding mount so that the cell could be dropped into position in the thermostat at 25.00° without delay.

The Peters–Walker intermittent titration might well be called the kineticist's dream. The rate of reaction of mustard or of its chlorohydrin is independent of the *p*H over a wide range; it is therefore possible to read the buret, add a small increment of alkali to the reaction, and watch for the color-change of the indicator, which marks the point at which an amount of acid has been produced exactly equivalent to the first increment of alkali. When this color change occurs the time is noted, the buret is read again and another increment of standard base is added to the reacting solution. It has been amply verified that it makes no difference whether the reaction is conducted on the acid or alkaline side of the change-point, or, as in our experiments, on the two sides alternately. The time of color change of the indicator could be noted within one second. The first such point was usually obtained about forty seconds after the beginning of the reaction. In these experiments, the standard 0.0518 *M* base was added in increments of 0.200 cc.

As an infinite time or 100% point, 13.3 times the half life was used. This corresponds to 99.99% completion for a first order reaction. This figure always checked the figure calculated from the weighing data within 3%. Corrections were made in the data when the temperature at one minute was more than 0.05° removed from 25.00°, by adding to all times 1.2% of their value multiplied by the average deviation in tenths of a degree up to 70% reaction. This is the calculated correction based on a 3.3-fold change of rate between 25 and 35°. Runs deviating by more than 0.2° were discarded.

**Polarographic Determination of Chloride.**—A preliminary polarogram on a hydrolyzed solution of 0.00097 *M* mustard gas showed sharp chloride and hydrogen ion waves with half-wave potentials of +0.20 and −1.5 volts *vs.* the saturated calomel electrode. The hydrogen wave had a pronounced maximum, but the chloride did not appear to have one. There was no sign of a wave between the two. The plateau region of the chloride wave began at about +0.25 volt. Since the half-wave potential of chloride increases 59 millivolts for each tenfold decrease in concentration we selected 0.35 volt to be sure of being on the plateau at 2% reaction. This corresponds to −0.05 volt *vs.* our saturated sulfate electrode.

The ordinary polarographic technique of averaging the current by use of a ten- to twenty-second period galvanometer would result in too much lag to follow accurately a reaction with a half-life of three minutes. Therefore a Moll microgalvanometer with a full period of one-fifth of a second was used with a scale at 1.2 meters distance to follow the entire current swing during the life of each drop. The maximum of the swing was recorded. The circuit was connected as shown in Fig. 2. Since the cell resistance was of the order of 100 ohms and the maximum current was about 10 microamperes, the internal voltage drop and hence the applied voltage varied during the course of a run by about 1 millivolt. Also the voltage, which was set at 0.05 volt, was that applied to the cell in series with the galvanometer and its series and shunt resistances, and differed by several millivolts from that applied to the cell itself. However this arrangement of the circuit caused no error because of the way in which chloride was measured.

The galvanometer was first standardized with a 0.0499 *M* solution of hydrochloric acid as follows. One hundred cc. of 0.15 *M* sodium benzenesulfonate and 4.96 cc. of acetone were placed in the reaction cell, the dropping electrode inserted, known amounts of hydrochloric acid from zero to 4 cc. added from the 5-cc. microburet, and the maximum of the fifth or any following swing recorded after each increment. The first two or three swings were abnormally large until the region near the tip of the electrode had been partially depleted of chloride and a steady state had established itself. This variation in local con-

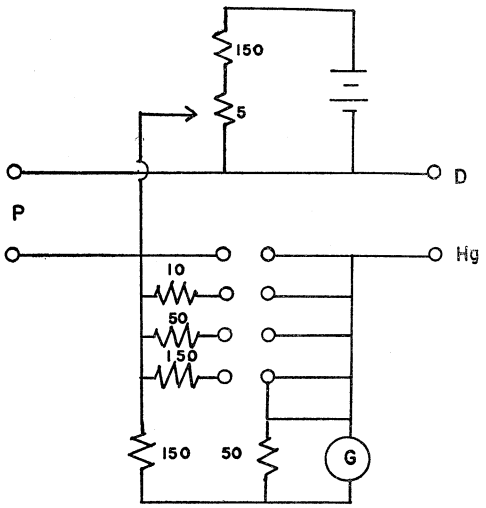



Fig. 2.—Circuit used in polarographic determination of chloride ion: P, to potentiometer; D, dropping electrode; Hg, mercurous sulfate electrode; G, galvanometer. The numbers are resistances in ohms.

centration because of electrolysis by the drop is the principal source of error in this analysis. Since the initial galvanometer reading is the same in a kinetic run as in the standardization, the resulting plot of galvanometer reading *vs.* cc. of hydrochloric acid enables kinetic data to be translated into per cent. reaction directly.

It was found that thiodiglycol did have a small effect on the current. For example, 0.0036 *M* added thiodiglycol gave a current four times the normal residual current, or one equal to that obtained at 35% reaction with the chlorohydrin. It might seem, therefore, that there are two serious errors in this procedure other than difference in local depletion of chloride between the standardization and the run: first, the volume is increased 4% in the standardization, not at all in the run; second, thiodiglycol accumulates as a reaction product, but is not present in the standardization. However these "errors" are proportional to the measured percentage reaction, which in turn is based on the final *observed* current, and so are not errors at all.

The procedure followed was the same as that in the runs with intermittent titration for hydrogen ion up to a point fifteen seconds after the start of the run. Then the stirrer and the thermostat motor and heater were turned off (to eliminate vibrations) and the nitrogen stream diverted to pass over the surface. The first galvanometer reading was usually obtained at about thirty seconds. Since the hydrogen ion liberated is not neutralized, the *p*H falls steadily to nearly 3.0 by the end of the reaction.

The shunts on the galvanometer made it possible to decrease the sensitivity several times as the reaction proceeded. Thus large, easily measured deflections were obtained on the meter scale at all percentage reactions. A standardization curve was prepared for each sensitivity.

Table I gives data on the machine-made capillaries which we used. The drop time given is that observed during the runs, *i.e.*, in the salt solutions with the voltage applied. Since the two runs on mustard, 100 and 105, gave the same results, the drop time does not seem to be an important factor affecting the accuracy by this method.

TABLE I

| Run no. | Capillary | Length, cm. | Height of Hg above tip, cm. | Drop time, sec. |
|---|---|---|---|---|
| 74 | A | 4.5 | 65 | 1.02 |
| 101 | A | 4.5 | 57.5 | 1.20 |
| 100 | A | 4.5 | 57.5 | 1.22 |
| 105 | B | 11 | 65 | 2.22 |

**Results with Mustard Chlorohydrin.**—Data for seventeen typical kinetic runs on the hydrolysis and displacement reactions of mustard chlorohydrin at 25° in water containing 5% acetone are plotted in Fig. 3. To avoid confusion in the figure, not all the experimental points are plotted, but a selection to avoid superposition of points as far as possible. All the plots are seen to be linear when the logarithm of mustard chlorohydrin concentration, as inferred from the production of hydrogen or chloride ion, is plotted against time, up to 90% reaction and beyond. There were no points which were not on the lines.

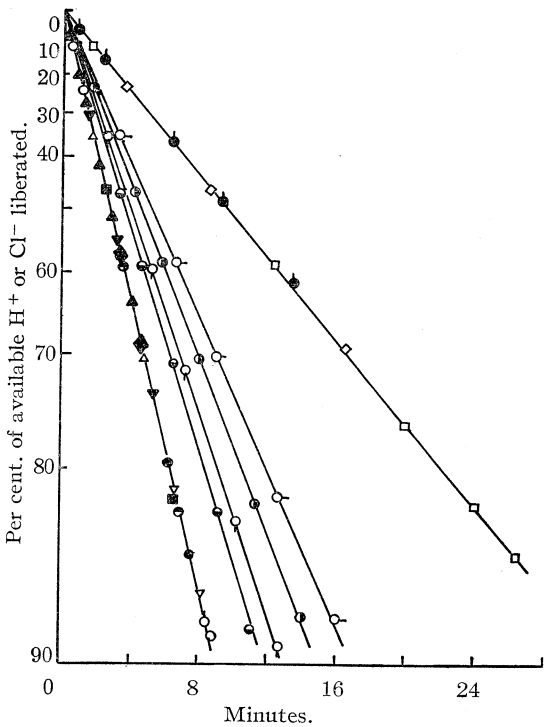



Fig. 3.—Logarithmic plots of seventeen experiments on hydrolysis and displacement reactions of mustard chlorohydrin (β-chloroethyl-β′-hydroxyethyl sulfide). Points plotted are selected to avoid overlapping. The ordinate scale is a logarithmic one, the ordinates being proportional to log $C_0/C$ as inferred from chloride ion determinations in runs 74 and 101, and from hydrogen ion titrations in the other fifteen runs. All runs are at ionic strength 0.144 except those designated "no inert salt." The significance of the points is as follows: ▲, Run 74 (chloride ion determined); ▼, Run 101 (chloride ion determined); △, Run 63; ▽, Run 76; ○, Run 116, 0.00096 *M* $NaH_2PO_4$; ◔, Run 123, no inert salt; ◓, Run 122, 0.00192 *M* NaCl; ◕, Run 111, 0.142 *M* NaCl; □, Run 125, 0.142 *M* NaCl, 0.00096 *M* $NaH_2PO_4$; ◇, Run 126, 0.142 *M* NaCl, immediate additions of NaOH; ◒, Run 117, 0.192 *M* NaCl; ⚲, Run 121, 0.0192 *M* NaCl, no inert salt; ◑, Run 118, 0.0385 *M* NaCl; ○-, Run 119, 0.0385 *M* NaCl, no inert salt; ●, Run 127, 0.127 *M*, NaCl, 0.0043 *M* sodium monothiophosphate (P); ■, Run 64, 0.0043 *M* P; ◆, Run 77, 0.0043 *M* P.

In all the runs not otherwise described the ionic strength was 0.144, being brought to this value by adding the necessary amount of sodium benzenesulfonate. The initial molarity of mustard chlorohydrin in each case was 0.00089 *M*.

Ten of the runs have the same first order rate constant within the experimental error, 0.260 ± 0.016 min.$^{-1}$ These ten include two runs in which the percentage reaction figures represent chloride ion liberated as a percentage of total chloride liberated up to a time equal to 13.3 times the half-life (99.99% reaction). They also include eight runs in which the percentage figures represent hydrogen ion liberated as a percentage of total hydrogen ion at 13.3 times the half-life. Of the eight hydrogen-ion runs having the same rate constant, two were like the chloride-ion runs in having no added competitors (only the usual inert salt addition to bring the ionic strength up to 0.144 *M*); one had 0.00096 *M* monosodium phosphate added to keep the *p*H below 6.0, and was followed with a *p*H 5.1 indicator; one had the inert salt omitted; one had 0.00192 *M* chloride added; three had 0.0043 *M* sodium monothiophosphate added; and one of these also had 0.127 *M* chloride added.

The other seven runs all had considerable amounts of added chloride, and the data represent hydrogen ion liberated. In three of these runs the chloride ion concentration was 0.142 *M*, and accordingly the usual addition of inert salt to make the total ionic strength up to 0.144 ± 0.003 *M* was omitted. One of the three runs was done in the usual way with the brom thymol blue indicator yellow and blue about equal amounts of time; one had 0.00096 *M* monosodium phosphate added to keep the *p*H below 6.0, and was followed with a *p*H 5.1 indicator; and in the other, which had brom thymol blue and no buffer, additions of sodium hydroxide equivalent to 25% reaction were made as soon as each end-point was reached to keep the *p*H above 10.0 half of the time. The three runs have the same rate constant within experimental error, showing the unimportant part played by *p*H in this reaction. The other four runs represent intermediate amounts of chloride added, with and without inert salt added to make the ionic strength up to 0.144 *M*.

It is qualitatively predicted from eqn. 1 that a sufficiently high concentration of chloride ion should be able to reconvert an appreciable fraction of the ethylenesulfonium ion into starting material in competition with water and the other reagents present. Such an effect would appear as a simple lowering of the first-order rate constant for the over-all reaction, as can be shown by a simple derivation based on eqn. 1.

The fact that the logarithmic plots are linear shows that concentrations of chloride ion up to 0.00089 *M* produce no observable effect of this kind. Nor does any effect appear at a chloride ion concentration of 0.00192 *M* (Run 122). At ten times this concentration of chloride ion there is a marked retardation of hydrolysis (Runs 117 and 121) but no effect upon the rate of reaction in the presence of monothiophosphate (Run 127) even by 0.127 *M* sodium chloride. These results provide a basis for calculating the competition factor of chloride ion, as will be done in a later section, and they emphasize the fact that the competition factor of thiophosphate is enormously greater than that of chloride ion.

The identity of the rates in Runs 116 and 123, with and without inert salt, shows that the initial cyclization is insensitive to ionic strength, while the distinct difference in rate between Nos. 117 and 121 shows that the *reverse* reaction between sulfonium ion and chloride ion must be retarded by an increase in ionic strength. This, too, will be treated quantitatively below. It is immediately obvious, however, that in kinetic experiments with sodium chloride as the only added salt, the determined competition factor of chloride ion will be lower, the higher the sodium chloride concentration, as a result of this property.

Since there is no evidence of any difference between the rates of appearance of hydrogen ion and of chloride ion (runs 63, 74, 76, 101), there is no accumulation during the hydrolysis of either an ethylenesulfonium ion or a dimeric sulfonium ion, to any extent observable by our technique.

Finally, the total absence of any effect of sodium monothiophosphate on the rate of hydrolysis of, or displacement in, mustard chlorohydrin strongly suggests that the difunctional character of mustard itself is somehow responsible for the accelerating effect noted by Ogston in the presence of thiophosphate and other competitors.

**Results with Mustard.**—Figure 4 shows data for eleven typical kinetic runs on mustard, temperature, solvent and ionic strength being the same as in the case of the chlorohydrin. In contrast to the case of the chlorohydrin, none of the first-order plots is linear, all being convex upward. Since the hydrolysis and displacement reactions of mustard involve the replacement of both chlorine atoms, the nature of the reacting molecule changes from the early to the late part of the reaction, and the reaction in the case of mustard is a succession of two reactions, one of mustard and one of the chlorohydrin. Unless both species undergo cyclization at identical rates, it is evident that a logarithmic plot based upon the evolution of chloride ion or of hydrogen ion must show curvature, and the type of curvature observed indicates that $k_1$ for mustard is lower than for the chlorohydrin. This would be expected on the basis of the reasoning developed in connection with the so-called nitrogen mustards.[9]

(9) (a) P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **71**, 1415 (1949); (b) see also B. Cohen, E. R. Van Artsdalen and J. Harris, *ibid.*, **70**, 281 (1948).

Five of the runs fit the same curve on this plot and therefore are described by the same pair of first order rate constants within the experimental error. These are runs without effective competitors added. Two of the five represent liberation of chloride ion, and the other three liberation of hydrogen ion. One of the hydrogen ion runs was done by the ordinary technique with the *p*H varying from 4 to 10; one had 0.00096 *M* sodium dihydrogenphosphate buffer to keep the *p*H below 6.0 and was followed with a *p*H 5.1 indicator, and the other had 0.00192 *M* chloride added.

Four of the curves give data for the liberation of hydrogen ion in runs with considerable amounts of added chloride. Except for their curvature they are similar to the curves obtained with the chlorohydrin. However, the remaining curve in Fig. 2 gives data for liberation of hydrogen ion in two runs with 0.0043 *M* added sodium monothiophosphate. In contrast to the case with chlorohydrin this curve differs from the normal curve without competitors, the rate of reaction here being considerably greater than the normal rate.

When a concentration of chloride (0.00192 *M*) twice that formed by 100% reaction was added at the start (run 8), the initial rate was the same as without additions within experimental error. Therefore this increase in rate with thiophosphate added is too large to be explained as an elimination of reversal by chloride ion. It is easy to see why the later stages of the reaction with thiophosphate should be faster than the later stages of the simple hydrolysis, for the substance undergoing reaction is a sulfide containing in the one case the group $-CH_2CH_2SPO_3^=$ and in the other case the group $-CH_2CH_2OH$, of which the former, with its double negative charge, should be more base-strengthening than the latter and should therefore contribute more to the reactivity of the sulfide sulfur in the cyclization step.

## Quantitative Treatment of Results

**Notation.**—For the equations to follow, it will be convenient to establish the following notation. The symbols for molecular species will denote molecules in chemical equations, and their concentrations in moles per liter when in mathematical equations.

M = mustard, $(ClCH_2CH_2)_2S$

C = mustard chlorohydrin, $ClCH_2CH_2SCH_2CH_2OH$

V = $ClCH_2CH_2SCH_2CH_2SPO_3^=$

P = $PSO_3^=$

M* = mustard ethylenesulfonium ion, $ClCH_2CH_2\overset{+}{S}\begin{matrix}CH_2\\|\\CH_2\end{matrix}$

C* = chlorohydrin ethylenesulfonium ion, $HOCH_2CH_2\overset{+}{S}\begin{matrix}CH_2\\|\\CH_2\end{matrix}$

Subscript zero refers to concentration at zero time

$k_1$, $k_{-1}$, $k_2$, $k_w$ as defined in eqn. 1.

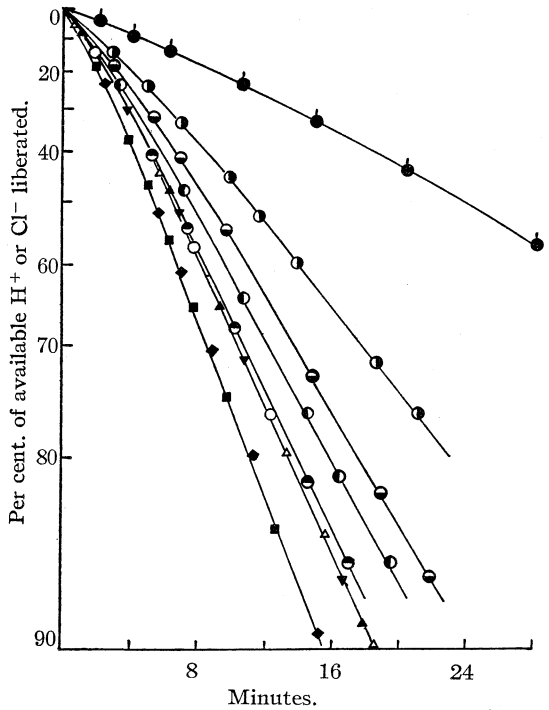



Fig. 4.—Logarithmic plots of eleven experiments on hydrolysis and displacement reactions of mustard ($\beta,\beta'$-dichlorodiethyl sulfide). Points plotted are selected to avoid overlapping. The ordinates are proportional to $\log (Cl^-)_\infty/((Cl^-)_\infty - (Cl^-))$ in runs 100 and 105, and to $\log (H^+)_\infty/((H^+)_\infty - (H^+))$ in the other nine runs, the subscript $_\infty$ referring to the concentration at the end of the reaction. All runs are at ionic strength 0.144. The significance of the points is as follows: ▲, run 100 (chloride ion determined); ▼, run 105 (chloride ion determined); △, run 28; ○, run 114, 0.00096 *M* $NaH_2PO_4$; ◒, run 8, 0.00192 *M* NaCl; ◐, run 19, 0.0096 *M* NaCl; ◒, run 9, 0.0192 *M* NaCl; ◑, run 20, 0.0385 *M* NaCl; ●, run 21, 0.142 *M* NaCl; ■, run 16, 0.0045 *M* sodium monothiophosphate (P); ◆, run 18, 0.0045 *M* P.

$k_{1M}$, $k_{1C}$, $k_{1V}$, etc., are the $k_1$'s for the reactions of M, C and V, respectively

$F^{\mu}_{Cl-} = (k_{-1}/k_w)$ at the ionic strength $\mu$.

$F^{\mu}_{X} = (k_2/k_w)$ at the ionic strength $\mu$

These are the competition factors of Ogston, except that the ionic strength was not specified in Ogston's work.

$b = (Cl^-)_0$

$$k_{bC} = \frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = b}}{C}$$ for chlorohydrin

$$k_{bM} = \frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0 = b}}{M}$$ for mustard

**Ionic Strength Effects.**—We shall now consider quantitatively the dependence of the competition factor upon the concentration of the competitor. The kinetic results with the chlorohydrin show that, within the accuracy of the

experiments, the rate of hydrolysis or displacement is determined entirely by $k_{1C}$ when there is no added chloride ion, and $k_{WC}$ may be considered to be infinitely great compared to $k_{1C}$.[10] This is an extreme not reached in any of the nitrogen mustards, but approached with increasing chlorination in the series: $ClCH_2CH_2N(C_2H_5)_2$, $(ClCH_2CH_2)_2NC_2H_5$, $(ClCH_2CH_2)_3N$.[9] It is reasonable that decreasing basicity of the basic center should increase the values of the ratios $k_w/k_1$, $k_2/k_1$ and $k_{-1}/k_1$ thus decreasing the extent to which the ethylene-onium intermediate accumulates during reaction.

Since $k_{WC}$ is large relative to $k_{1C}$, the following simplified treatment is valid: In the absence of added chloride ion

$$\frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0=0}}{C} = k_{1C} = k_0$$

In the presence of an added excess of chloride ion such that its concentration $b$ remains approximately constant during reaction, and in the absence of other competitors

$$\frac{\left[\frac{d(H^+)}{dt}\right]_{[Cl^-]_0=b}}{C} = k_{1C}\frac{k_{WC}}{k_{WC} + k_{-1C}\,b} = k_{bC}$$

The ratio of rates in presence and absence of added chloride ion is thus equal to $k_{WC}/(k_{WC} + k_{1C}b)$ or to $1/(1 + F_{Cl}b)$, the special form for chloride ion of a general expression derived by Ogston and applied by him and by Clark, Cohen and Harris[11] to the estimation of competition factors for the bifunctional reagent, mustard. The explicit form for $F_{Cl}$ is

$$F_{Cl} = \frac{1}{b}\left[\frac{k_0}{k_{bC}} - 1\right] \qquad (3)$$

The nature of this equation is such as to magnify errors in the kinetic runs when two runs with rates differing only slightly are used to determine competition factors. For example, if $F_{Cl}$ is determined from Runs 76 and 117, and the rate of each reaction is subject to a maximum uncertainty of 6%, the maximum uncertainty in $F_{Cl}$ becomes 52%. Nevertheless, if we use the four runs, 76, 111, 117 and 118, at ionic strength 0.144, to calculate $F_{Cl}^{0.144}$, we obtain values of 18.1, 15.6 and 16.6, which are all within less than 8% of the weighted mean of 16.9. From this value for the competition factor we can calculate back the relative rates in the three runs with chloride added with a mean deviation of 2.7%. However, this procedure applied to Runs 119 and 121 with sodium chloride but without inert salt, at lower ionic strengths, yields calculated values of relative rate deviating from the observed by 7.8 and 12%, outside the experimental error in both cases. It appears from these results that the competition factor of chloride ion is a function of ionic strength, but not of chloride ion concentration at constant ionic strength.

From the Bronsted rate equation[12] and the limiting Debye–Hückel equation,[13] one can predict semi-quantitatively for a dilute solution how the rate constant for a reaction between oppositely charged ions should respond to changes in ionic strength. The constant $k_{-1}$ is of this type, while $k_1$ and $k_w$ are not and should show a zero salt effect by the Bronsted theory. Then using the Debye–Hückel relation for the activity coefficient of ions

$$-\log \gamma = 0.5Z^2\sqrt{\mu} - \beta\mu \qquad (4)$$

and the Brönsted law applied to $k_{-1}$

$$k_{-1} = k_{-1}^0\frac{\gamma_{C^+}\gamma_{C^-}}{\gamma^*} \qquad (5)$$

we obtain

$$\log_{10} k_{-1} = \log_{10} k_{-1}^0 - \sqrt{b} + (\beta_{C^+} + \beta_{Cl} - \beta^*)b \qquad (6)$$

or

$$\log_{10} F_{Cl^-} = \log_{10}\left(\frac{k_{-1}^0}{k_w}\right) - \sqrt{b} + (\beta_{C^+} + \beta_{Cl^-} - \beta^*)b \qquad (7)$$

if the total ionic strength is due to added chloride. Here the $\gamma$'s are activity coefficients, $\mu$ is the ionic strength, $Z = 1$ = the valence of each reacting ion, $k_{-1}^0$ and the $\beta$'s are constants independent of the conditions. If the cyclic intermediate, $C^*Cl^-$, has a minimum in its mean activity coefficient curve at $1.0 \pm 0.5$ $M$ ionic strength as do most uni-univalent electrolytes, then $\beta_{C^+} + \beta_{Cl^-} = 0.50 \pm 0.20$. Since the transition state is a neutral molecule, $\beta^*$ is negative,[14] and $-\beta^*$ probably adds about 0.20 more to the sum. We shall use 0.70 as the estimated value of $\beta_{C^+} + \beta_{Cl^-} - \beta^*$. (The results of the calculation are not much affected by a variation of $\pm$ 0.20 in its assumed value.) We shall use the experimental data to determine $(k^0 - 1/k_w)_{\mu=0}$, which should be a *true constant*. This might be called the "competition factor at zero ionic strength," and will be denoted by $F_{Cl}^0$. Its value is calculated from the competition factors in Table II. The

TABLE II

$F_{Cl}$ AS A FUNCTION OF IONIC STRENGTH; APPLICATION OF THE DEBYE–HÜCKEL LIMITING LAW TO RUNS WITHOUT INERT SALT

| | | | | Calculated using $F_{Cl}^0 = 32.2$ | | |
|---|---|---|---|---|---|---|
| Run | $b$ | $\frac{k_b}{k_0}$ | obs. $F_{Cl}^\mu$ | $F_{Cl}^\mu$ | $\frac{k_b}{k_0}$ | Deviation, % |
| 123 | 0 | 1.00 | .. | 32.2 | 1.00 | |
| 121 | .0192 | 0.70 | 22.4 | 24.2 | 0.682 | −2.6 |
| 119 | .0385 | .54 | 22.1 | 21.8 | .545 | +0.9 |
| 111 | .142 | .28 | 18.1 | 17.0 | .294 | +5.0 |
| | | | | | Mean | 2.8% |

(10) Calculations based on eqn. 1 without this simplification show that the assumption $k_w/k_1 = \infty$ introduces about a 3% error into the calculated competition factor of chloride ion if $k_w$ is actually as small as 30 $k_1$, and a negligible error, for these experiments, if $k_w \gg 100\ k_1$.

(11) W. M. Clark, B. Cohen and J. Harris, N. D. R. C. Report, June 1, 1942.

(12) J. N. Bronsted, *Chem. Revs.*, **5**, 265 (1928).

(13) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

(14) E. Hückel, *Physik. Z.*, **26**, 93 (1925).

weighted mean value for $F^0_{Cl}$ is 32.2; using this value and calculating back, we obtain the calculated values of $F^\mu_{Cl}$ and of $k_b/k_0$ shown in the fifth and sixth columns of Table II. It will be noted that the value of $F^{0.142}_{Cl}$ calculated is 17.0, compared with the mean value of 16.9 obtained from the four runs made at ionic strength 0.144. The mean deviation of the calculated relative rates from the observed is 2.8%, satisfactorily within the experimental uncertainty.

Although these experiments do not cover a range sufficient to establish the validity of this treatment in any unique way, it is clear that the variation of competition factor with concentration of the competitor, previously thought to be an obstacle to the acceptance of the simple ethylenesulfonium ion mechanism, is an entirely normal effect of ionic strength which would be predicted on the basis of accepted theories. Such variation should, of course, be exhibited by other competitors bearing an ionic charge, though not by neutral competitors. Linstead and Doering[15] found that the competition factors of acetate ion for mustard in 0.05 *M*, 0.19 *M* and 0.4 *M* acetate solutions were 8.2, 5.4 and 4.7, respectively, this variation being of the general sort called for by the present theory.

**The Determination of $k_{1M}$.**—The value of $k_1$ for mustard itself should be the same with all competitors, and the question remains: is the initial slope of a line such as those in Fig. 4 an adequate measure of the initial $k_1$? This question can be answered quantitatively by using the first-order rate constant evaluated for mustard chlorohydrin and the equation for successive first-order reactions. It is seen from Fig. 4 that the logarithmic curves of fraction of total available hydrogen ion remaining unliberated are smooth curves showing no resolution into initial and final linear portions. In past work[4] $k_{1M}$ has been estimated as the slope of the earliest portion of such a curve for which experimental points were available, the hope being that the small amount of C or V formed during such interval would not appreciably affect the rate of production of hydrogen ions. Whether this is true or not obviously depends upon the relative magnitudes of $k_{1M}$ and $k_{1C}$ or, in the case at hand of the use of a strong competitor, the relative magnitudes of $k_{1M}$ and $k_{1V}$. Our direct measurement of $k_{1C}$ offers a means of determining $k_{1M}$ from the kinetic data on mustard without making any approximation about limiting slopes. We need only assume that with mustard, as with the chlorohydrin, $k_w >> k_{-1}$, so that the entire process may be treated as a pair of consecutive irreversible first-order reactions.

In such a system the liberation of hydrogen ion should closely follow the law[16]

$$[H^+] = M_0\left[2 - \left(\frac{k_{1M} - 2k_{1C}}{k_{1M} - k_{1C}}\right)e^{-k_{1M}t} - \frac{k_{1M}}{k_{1M} - k_{1C}}\, e^{-k_{1C}t}\right] \quad (8)$$

From the work with mustard chlorohydrin we know that in runs with no added chloride ion and with no added competitor, $k_{1C} = 0.260 \pm 0.016$ min.$^{-1}$. For this value of $k_{1C}$, a value of $k_{1M} = 0.155 \pm 0.010$ gives the closest agreement between the curve calculated from eqn. 8 and the experimental curves for mustard under these same experimental conditions. With this value of $k_{1M}$ the calculated curve lies slightly above the experimental up to 70%, slightly below beyond 70%, but the deviations in time at 50% and 90% are within 1 and 3%, respectively, or well within the experimental error.

Similarly we can determine the $k_{bM}$ corresponding to various amounts of added chloride. From the values of $k_{bM}$ we can then calculate the competition factor of chloride at 0.144 *M* ionic strength for M*, *i.e.*, in the first of the two processes making up the reaction. We can then compare the competition factor of chloride for M* with the corresponding factor of chloride for C*, which determines the reactivity of chloride in the second half of the reaction.

Table III gives the data for the runs with chloride added, all done at an ionic strength of 0.144 *M*, and the calculated values of $k_{bM}$ and $k_{bC}/k_{bM}$. It is reasonable to assume that the

TABLE III

DETERMINATION OF $k_{bM}$ AT DIFFERENT CHLORIDE ION CONCENTRATIONS AT 25° IN WATER CONTAINING 5% ACETONE

| Run | $b$ | $t_{70\%}$ | $k_{bC}$ | $k_{bM}$ | $k_{bM}/k_{bC}$ |
|---|---|---|---|---|---|
| 28 | 0.0000 | 10.30 | 0.260 | 0.155 | 0.595 |
| 8 | .0019 | 10.55 | .260 | .152 | .585 |
| 9 | .0192 | 13.65 | .194 | .118 | .610 |
| 20 | .0385 | 17.65 | .153 | .090 | .590 |
| 21 | .142 | 38.70 | .072 | .041 | .570 |
| | | | | Av. | .59 |

competition factors at zero ionic strength would also be the same for mustard as for the chlorohydrin, *viz.*, 32. Thus the discriminating ability of an intermediate between competitors is not affected to a detectable extent by differences in structure of the sort existing between mustard and mustard chlorohydrin.

With the values at hand for $k_{1M}$, $k_{1C}$ and $F^\mu_{Cl}$, the entire curves for mustard with various amounts of chloride added can be calculated within experimental error.

The course of the displacement experiments with sodium monothiophosphate differs from that of the hydrolytic experiments in that the ethylenesulfonium ions, when formed, react exclusively with thiophosphate ion. The kinetic equation for the two successive reactions is accordingly identical with Equation (8) except

(15) R. P. Linstead and W. E. Doering, NDRC Report, April 15, 1942.

(16) C. G. Swain, THIS JOURNAL, **66**, 1696 (1944); A. Rakowski, *Z. physik. Chem.*, **57**, 321 (1907).

for the replacement of $k_{1C}$, wherever it occurs, by the hitherto unknown constant $k_{1V}$. Since the other constant of this equation $k_{1M}$, is now known, it becomes possible to determine the value of $k_{1V}$ in the same manner as was just done using eq. 8.[16] A calculated curve using $k_{1V} = 0.70$ approximates the experimental curve most closely, and the sensitivity of the calculated curve to the assumed value suggests the limits ± 0.05 for this constant. The calculated curve has the same general shape as the experimental, lying above it throughout but always within 2% of it on the time coördinate.

Thus both hydrogen ion and chloride ion are liberated by mustard in dilute solution according to the equation

$$[H^+] = [Cl^-] = a\left[2 - \left(\frac{k_{1M} - 2k_1'}{k_{1M} - k_1'}\right)e^{-k_{1M}t} - \left(\frac{k_{1M}}{k_{1M} - k_1'}\right)e^{-k_1't}\right]$$

where $k_{1M} = 0.155$, and $k_1' = 0.260$ ( $= k_{1C}$) or 0.70 ( $= k_{1V}$) according to whether or not thiophosphate is added. From this equation it would seem that it should have been possible to estimate $k_{1M}$ from the initial slope of a simple logarithmic plot [ln $(2a - H^+)$ *vs.* $t$], instead of by the curve-fitting method which we actually employed. The limiting initial slope on such a plot is $k_{1M}/2$. Ogston, Linstead and others used early points, with the origin, to measure the initial rate in this way. However, the value obtained is far from correct if any realizable fraction of the curve is used to define the slope. Even if points be used as early as 5.0% of total reaction, which are the earliest points that we have been able to obtain by the intermittent titration technique, the estimates of the initial rate so reached are still in error by 6% in the runs without thiophosphate added, and by 16% in the runs with thiophosphate added (see Table IV). This difference in errors is the cause of Ogston's observation that the initial rate with thiophosphate added was about 10% faster than without the addition. The present study accounts for this observation on the basis that the first rate constant (and initial rate) is the same under both conditions, and that only the second rate constant differs, according to whether the second step is ionization of chlorohydrin or of thiophosphate displacement product.

TABLE IV

ERRORS INVOLVED IN CALCULATING $k_{1M}$ FROM INITIAL SLOPE OF OVER-ALL CURVE FOR REACTION OF MUSTARD GAS

| Rate constants $k_1$ | Rate constants $k_2$ | Point $t$ | Used %$H^+$ | $k_1$ Calcd. from point and origin | Error, % |
|---|---|---|---|---|---|
| 0.155 | 0.260 | 1/2 | 4.0 | 0.162 | 4.5 |
| .155 | .260 | 1 | 8.2 | .171 | 10 |
| .155 | .700 | 1/2 | 4.3 | .177 | 14 |
| .155 | .700 | 1 | 9.3 | .196 | 26 |

**Experimental Errors.**—Our best estimate of the maximum error in the runs with intermittent titration for hydrogen ion is ± 6% in the rate constant or time value for 50% reaction. This corresponds to a 2.0% analytical error in the 50% point if the zero point is correct, or a 1.0% error in opposite directions in each. In the polarographic chloride runs a reasonable estimate of the maximum uncertainty is about ± 10% in rate constant. The largest uncertainty in the runs with intermittent titration was in the matching of color against the standard color at the zero point and endpoints. This was greatest with the *p*H 5.1 indicator and the *p*H 8.0 indicator in runs with sodium monothiophosphate added where it amounted to ± 0.015 cc. (± 1.5 divisions on the microburet) or 0.9% of the total reaction. The "time of mixing" error was under five seconds (3% in rate constant at 50% reaction). Standardization of glassware and factors of solutions were accurate to 0.5% (< 2% in rate constant), temperature control to 0.05°, *p*H of end-points to 0.2 *p*H unit, solution volume to 2%, ionic strength to 2%. In the polarographic runs the larger 3% error in individual chloride values was due to electrolysis at the dropping electrode and local depletion of the chloride concentration near the drop during the run.

**Effect of Dimerization.**—Since the absolute chloride and hydrogen ion values are the same within experimental error during the first 70% of reaction, it is clear that the C–C dimer, $HOCH_2CH_2SCH_2CH_2S^+(CH_2CH_2Cl)CH_2CH_2OH\text{-}Cl^-$, does not accumulate as an intermediate during the early stages of the reaction. Such an accumulation would be kinetically equivalent to accumulation of $C^+$.

The average final end-point in 15 runs without added thiophosphate was 1.700 cc., with an average deviation of 0.017 cc. The average endpoint in three runs with added thiophosphate was 1.737 cc., with an average deviation of 0.018 cc. This 0.037 cc. difference in endpoint is outside the experimental error and corresponds to the production of 2.2% of the hydrolyzed dimer, $HOCH_2CH_2SCH_2CH_2S^+(CH_2CH_2OH)_2Cl^-$, in the runs without thiophosphate added. However, there is an uncertainty in this value of at least ± 50%. Two sets of paired runs, with and without thiophosphate added, indicated only 1.2% dimer. In the preceding analysis of the experimental data we have neglected the effect of this dimer formation and based percentage reaction on the final endpoints actually observed in each individual run. If 2.2% of the carbon were sidetracked by dimer formation, and half of this dimer were formed by the time of 50% reaction there would be no error resulting from this procedure. Even if we assume that as little as one quarter of the total dimer is formed up to 50% reaction, the time and rate constant at 50% reaction would still be in error by less than 3.5%. This is less than the experimental error. If we had done kinetic runs with the initial molarity of C greater

than 0.001 $M$, it would have been necessary to take this dimerization into account in the quantitative treatment.

## Summary

The rate of hydrolysis of $\beta,\beta'$-dichlorodiethyl sulfide (mustard gas) and of $\beta$-chloro-$\beta'$-hydroxydiethyl sulfide (mustard chlorohydrin) in aqueous solution containing 5% of acetone at 25° has been measured at different concentrations of chloride and monothiophosphate ions and at controlled ionic strength. The rate of liberation of hydrogen ions, measured by the intermittent titration method of Peters and Walker, is identical within the experimental uncertainty with the rate of liberation of chloride ions, followed polarographically with a short-period galvanometer, a fact which shows that neither ethylenesulfonium ions nor any dimeric sulfonium ions accumulate appreciably during reaction.

The results of 17 runs on mustard chlorohydrin and 11 runs on mustard have been interpreted in some detail by means of the mechanistic scheme of eq. 1, involving a rate-determining formation of an ethylenesulfonium ion followed by competition for this ion by water, chloride ion and other competitors such as thiophosphate ion, all at rates much greater than that of the initial cyclization. The "competition factor" of chloride ion, defined as the ratio of the rate constants for reaction of the ethylenesulfonium intermediate with chloride ion and with water, is shown to be independent of the chloride ion concentration at constant ionic strength, but to depend upon ionic strength in a manner predictable from the Brønsted rate equation and the limiting Debye–Hückel law for the activity coefficient of an ion.

By first determining the strictly unimolecular rate constant (0.260 ± 0.016 min.$^{-1}$) for hydrolysis or displacement of mustard chlorohydrin and then introducing this into the equation for two successive unimolecular reactions, the first rate constant for mustard has been calculated as 0.155 ± 0.010 from the data covering the two steps in its hydrolysis to thiodiglycol, which are not resolvable by any simpler method. From this constant and the data for displacement of the two chlorines successively by monothiophosphate, the constant for cyclization of the S-2-(2-chloroethylthio)-ethyl monothiophosphate ion is determined to be 0.70 ± 0.05. The fact that this ion cyclizes more than twice as fast as mustard chlorohydrin produced, in earlier experiments, the false appearance of mustard having a faster initial reaction in the presence of thiophosphate than in its absence.

CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 24, 1948

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[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

# Kinetics and Mechanism of the Reactions of Tertiary $\beta$-Chloroethylamines in Solution. III. $\beta$-Chloroethyldiethylamine and tris-$\beta$-Chloroethylamine[1]

BY PAUL D. BARTLETT, SIDNEY D. ROSS AND C. GARDNER SWAIN

In the first[2] and second[3] papers of this series the existence of a general mechanism was established whereby a tertiary $\beta$-chloroethylamine undergoes internal cyclization to an ethylene-immonium ion as a first step common to hydrolysis, dimerization and displacement reactions. By quite different methods in the cases of methyl-bis-$\beta$-chloroethylamine and ethyl-bis-$\beta$-chloroethylamine it was possible to determine the separate rate constants for the steps in this mechanism, and to show how the observed difference between predominating hydrolysis and predominating dimerization rested upon moderate differences between the relative values of the constants for these two homologs.

Two other tertiary $\beta$-chloroethylamines have been examined more briefly and such quantitative information about them as was obtained is here presented. In the case of $\beta$-chloroethyldiethylamine the ethylene-immonium ion is comparatively stable and its formation can be observed uncomplicated by other reactions. We have not determined the rates of reaction of this ion with displacing reagents, although such measurements should present no difficulties. In the case of tris-$\beta$-chloroethylamine hydrolysis occurs to bis-$\beta$-chloroethylethanolamine hydrochloride with much less accumulation of the intermediate ethyleneimmonium ion than in the previous cases; in this respect this amine is intermediate between the other "nitrogen mustards" and $\beta,\beta$-dichlorodiethyl sulfide ("mustard gas").[4] In the presence of alkali to neutralize the liberated hydrochloric acid, the hydrolysis proceeds through successive stages to triethanolamine.[5]

(1) The work described in this paper was performed under Contract NDCrc-136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development in 1942 and 1943.

(2) Part I: P. D. Bartlett, S. D. Ross and C. G. Swain, THIS JOURNAL, **69**, 2971 (1947).

(3) Part II: P. D. Bartlett, J. W. Davis, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2977 (1947).

(4) P. D. Bartlett and C. G. Swain, *ibid.*, **71**, 1406 (1949).

(5) C. Golumbic, M. A. Stahmann and M. Bergmann, *J. Org. Chem.*, **11**, 550 (1946).

## Experimental

**Preparation of β-Chloroethyldiethylamine.**—Thionyl chloride (166.6 g., 1.4 moles) in 75 cc. of chloroform was added dropwise with external cooling to diethylethanolamine (117 g., 1 mole) in 75 cc. of chloroform. The reaction was extremely vigorous and was moderated by the addition of a further 75 cc. of chloroform. After the addition was complete the reaction flask was removed from the ice-bath and heated for six hours in an oil-bath at 65°. The solvent was removed *in vacuo;* the solid was filtered off, washed with ligroin and acetone, and finally recrystallized from acetone containing a little alcohol after decolorization with Norit. The hydrochloride thus obtained melted with decomposition at 205°. After recrystallization the hydrochloride was used for the preparation of the free amine just before each run in the same manner described for methyl-bis-β-chloroethylamine.[2]

**Isomerization of β-Chloroethyldiethylamine.**—The kinetic procedure was essentially that of Part I.[2] This amine is a strong enough base so that hydrochloric acid can be titrated in the presence of the amine hydrochloride using methyl orange as an indicator. In the run shown in Table I the appearance of chloride ion in 1:1 acetone–water at 25° was followed by Volhard titrations of the aqueous

TABLE I

CYCLIZATION OF β-CHLOROETHYLDIETHYLAMINE IN 2:1 ACETONE–WATER AT 25° (0.0827 *M* β-CHLOROETHYLDIETHYLAMINE)

| Minutes time elapsed | Reaction % based on titration with 0.100 *N* $AgNO_3$ | Reaction % based on titration with 0.100 *N* HCl |
|---|---|---|
| 0 | | |
| 3 | 46.6 | 44.6 |
| 8 | 81.7 | 79.5 |
| 17 | 91.5 | 91.0 |
| 25 | 94.7 | 93.8 |
| 36 | 95.6 | 96.4 |

extract, and the disappearance of basic nitrogen was followed by extracting the benzene extract with standard hydrochloric acid and back-titrating to the methyl orange end-point. The two sets of figures for the degree of reaction agree within 2.5%. The unimolecular rate constant is 0.198 min.$^{-1}$. Tables II and III show two similar runs with and without the addition of sodium chloride. The

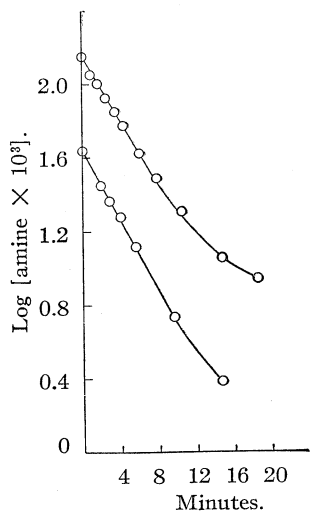



Fig. 1.—Cyclization of diethyl-β-chloroethylamine in 2:1 acetone–water: upper curve, 0.1435 *M* amine (Table II); lower curve, 0.04405 *M* amine + 0.0790 *M* sodium chloride (Table III).

unimolecular plots, shown in Fig. 1, yield rate constants of 0.203 and 0.204 min.$^{-1}$, respectively. The lack of inhibition by chloride ion is accompanied by normal unimolecular kinetics, but with a slowing beyond 90% reaction which suggests reversibility.

TABLE II

CYCLIZATION OF β-CHLOROETHYLDIETHYLAMINE IN 2:1 ACETONE–WATER AT 25° (0.1435 *M* β-CHLOROETHYLDIETHYLAMINE)

| Minutes time elapsed | Reaction % by titration with 0.100 *N* $AgNO_3$ |
|---|---|
| 0 | |
| 1 | 20.5 |
| 1.5 | 28.2 |
| 2.4 | 40.7 |
| 3.5 | 50.0 |
| 4.3 | 58.3 |
| 5.9 | 70.6 |
| 7.8 | 78.4 |
| 10.4 | 85.5 |
| 14.6 | 92.0 |
| 18.5 | 93.8 |

TABLE III

CYCLIZATION OF β-CHLOROETHYLDIETHYLAMINE IN 2:1 ACETONE–WATER AT 25° IN PRESENCE OF SODIUM CHLORIDE (0.04405 *M* β-CHLOROETHYLDIETHYLAMINE) 0.0790 *M* MNaCl

| Time elapsed, minutes | Reaction % by titration with 0.100 *N* $AgNO_3$ |
|---|---|
| 0 | |
| 1.90 | 33.2 |
| 2.77 | 47.5 |
| 4.00 | 55.9 |
| 5.67 | 69.3 |
| 9.62 | 87.4 |
| 14.60 | 94.3 |

A reaction of β-chloroethyldiethylamine proceeding with first-order kinetics and liberating all of the chlorine of the compound in ionic form might be (a) cyclization to the ethylene-immonium salt, (b) dimerization to a bisquaternary piperazinium salt, or (c) hydrolysis. Only in case (a) would the addition of hydrochloric acid to the solution, followed by evaporation to dryness *in vacuo*, be expected to reverse the reaction and yield β-chloroethyldiethylamine hydrochloride. This experiment was carried out and yielded 93.5% of a solid melting with decomposition at 203–204° (m. p. of β-chloroethyldiethylamine hydrochloride, 205°) and yielding on analysis 21.39% ionic and 39.09% total chlorine (calcd. for β-chloroethyldiethylamine hydrochloride, 20.60% and 41.20%). These results correspond to a mixture of 86% β-chloroethyldiethylamine hydrochloride and 14% diethylethanolamine hydrochloride or the bisquaternary piperazinium dimer, indicating that the solution on which the kinetic study was made contained at the end at least 86% of the unhydrolyzed ethylene-immonium ion.

Comparison of the glass-electrode potentials of half neutralized hydrochlorides by the method described in Part II,[2] indicated the following ratios of base strengths

$$\frac{K_B \text{triethylamine}}{K_B \text{ diethylethanolamine}} = 7.3$$

$$\frac{K_B \text{ triethylamine}}{K_B \text{ diethyl-β-chloroethylamine}} = 460$$

An attempt to follow the rate of formation of the cyclic intermediate by the thiosulfate titration[6] failed, since this

(6) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518, 536 (1946).

reagent did not react rapidly enough with the intermediate. The rate of this slow reaction with thiosulfate was later measured by Cohen.[7]

TABLE IV

HYDROLYSIS AND DIMERIZATION OF TRIS-β-CHLOROETHYLAMINE IN 2:1 ACETONE–WATER AT 25° (0.0363 *M* AMINE)

| Hours time elapsed | Reaction % based on NaOH | Reaction based on Volhard, % |
|---|---|---|
| 0 | | |
| 1.0 | 15.6 | 16.8 |
| 3.0 | 28.3 | 34.4 |
| 4.0 | 36.1 | 39.4 |
| 6.0 | 42.2 | 48.7 |
| 8.0 | 49.5 | 59.4 |
| 9.5 | 53.4 | 66.6 |

**tris-β-Chloroethylamine.**—Table IV gives the results of a run on this amine in which the appearance of chloride ion was followed by Volhard titration while the appearance of hydrogen ion was followed by titration with sodium hydroxide using thymolphthalein as indicator. The figures obtained by the two methods are close together early in the reaction, indicating that the reaction is chiefly hydrolysis. A divergence later between the alkali and silver titers suggests that with low hydroxyl ion concentrations as much as 20% of the total reaction may be dimerization.

Beside the divergence between the curves of chloride ion and hydrogen ion production, and the upward concavity of the latter curve, the plot of these results (Fig. 2) shows two other peculiarities. The reproducibility does not seem

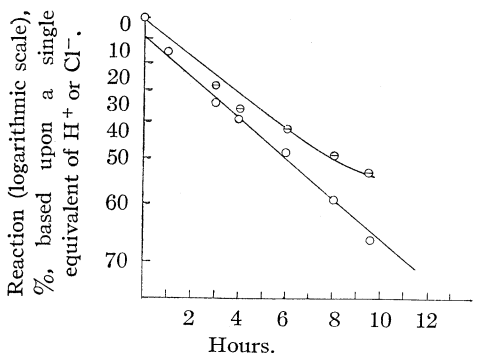



Fig. 2.—Reaction of tris-β-chloroethylamine in 2:1 acetone–water at 25°, followed by titration with sodium hydroxide (⊖) and with silver nitrate (O).

to be as good as that in the slower runs with sodium chloride added and the faster runs with sodium hydroxide, described below. Also in contrast to these other runs, the lines of per cent. reaction against time on a logarithmic plot do not pass through zero at zero time, but rather through about 10% reaction. The probable interpretation of this is as follows. The actual cyclization step (see Fig. 3) is about three times as fast as the liberation of chloride ion in this run, and the reaction proceeds initially at the rapid rate until enough chloride ion is accumulated to make the reversal of the initial cyclization step an important competitor with the hydrolysis. The 10% discrepancy corresponds to the approximate amount of ethylene-immonium ion which accumulates in this earliest stage of the reaction. This immonium ion reacts rapidly with hydroxyl ion in the titration and hence registers as hydrogen ion. The roughness of the "acid" line in this plot suggests that the completeness of the reaction between hydroxyl ion and the immonium ion is a function of the time elapsed during the titration.

In predominance of hydrolysis and in relatively slight

(7) Barnet Cohen, N. D. R. C. reports, 1943.

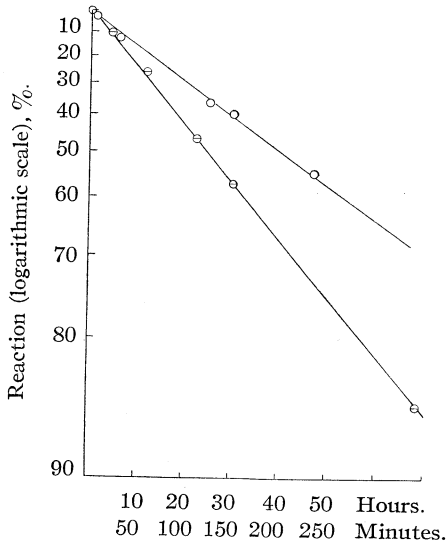



Fig. 3.—Upper curve, hydrolysis of tris-β-chloroethylamine in 2:1 acetone–water containing sodium chloride (upper time scale); lower curve, hydrolysis of tris-β-chloroethylamine in 2:1 acetone–water containing sodium hydroxide (lower time scale).

accumulation of the cyclic intermediate, tris-β-chloroethylamine is more like β,β′-dichlorodiethyl sulfide (mustard gas) than are the other amines, and forms a connecting link between the comparatively simple kinetics of hydrolysis of mustard and the complex situation with methyl-bis-β-chloroethylamine. The lower basic strength (and perhaps also the greater branching in space) of the trichlorinated amine causes a decrease in $k_2$ (and also $k_1$) relative to $k_w$.[8]

The basic dissociation constants measured in this medium in the same way as in the case of diethyl-β-chloroethylamine, are

$$\frac{K_B \text{ triethylamine}}{K_B \text{ triethanolamine}} = 210$$

$$\frac{K_B \text{ triethylamine}}{K_B \text{ tris-β-chloroethylamine}} = 1.5 \times 10^7$$

These results indicate a ratio of basic strengths in 2:1 acetone–water of $3.3 \times 10^4$ for diethyl-β-chloroethylamine and tris-β-chloroethylamine, as compared with the ratio of $2.7 \times 10^4$ in water.[9]

With sodium chloride added to the solution the reaction became very much slower and truly unimolecular with no initial rapid reaction. There was certainly less than 3% cyclic intermediate concentration at any time in the run at an initial amine concentration of 0.0384 with 0.0955 *M* sodium chloride added. The rate in this run was 5.2% of that in the likewise unimolecular run with 0.208 *M* hydroxyl ion added, which practically eliminated reversal of the first step (Fig. 3). The latter run gives $k_1$ as $5.5 \times 10^{-3}$ min.$^{-1}$.

In pure unbuffered water as a solvent, bis-β-chloroethylethanolamine hydrochloride is the principal final reaction product. However, the ethyleneimmonium ion (called "B" in Part I[2] and below) accumulates to a substantial extent in water. This is shown by the fact that hydrogen ion production did not become appreciable until the chloride ion concentration had reached 0.006 *M* in a solution kept saturated with amine. The difference between chloride and hydrogen ion concentration at this point cannot be due to cyclic dimer, for this would not

(8) See the mechanism presented in Part I (ref. 2).

(9) B. Cohen, E. R. VanArtsdalen and J. Harris, THIS JOURNAL, **70**, 282 (1948).

give rise to hydrogen ion later; therefore this difference between titers is largely a measure of cyclic intermediate.

The reaction in water was studied by the technique which was successfully applied by Wilson[10] and more recently by Northrop[11] to the kinetic study of mustard. This technique consists in simplifying the kinetics by keeping the solution essentially saturated with starting material at all times by means of vigorous stirring of the solution with pure amine. In the presence of sufficient amounts of added chloride or hydroxyl ion the reaction shows zero-order kinetics; without any added electrolyte the rate of production of chloride ion decreases during reaction on account of the reversibility of the initial step and the diminution of the steady-state concentration of the cyclic intermediate B. Figure 4 shows the data for a typical run.

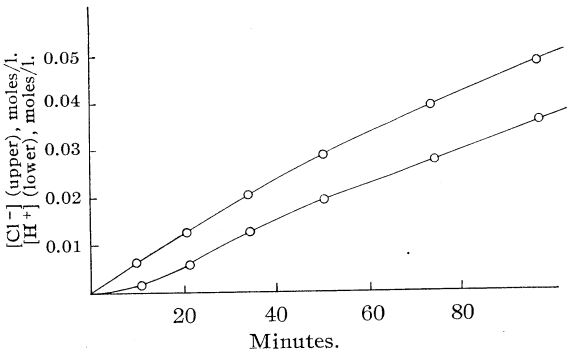



Fig. 4.—Reaction of tris-β-chloroethylamine in saturated aqueous solution at 25°, followed by titration with sodium hydroxide (lower) and with silver nitrate (upper curve).

After hydrogen ion production has begun and approximately reached the rate of further chloride production we can set the rate of change of (B) equal to zero and derive the approximate relation

$$(B) = \frac{k_1 c}{k_{-1}(Cl^-) + k_w}$$

where $c$ is the solubility of the amine in water. The rate of appearance of chloride ion is

$$\frac{d(Cl^-)}{dt} = k_1 c - k_1(B)(Cl^-) = k_1 c \frac{k_w}{k_{-1}(Cl^-) + k_w}$$

This derivative is equal to the slope of the curve of $(Cl^-)$ as a function of time. If we denote this slope by $S$, and its value at zero time by $S_0$, then by substitution in this equation we get

$$\frac{S_0 - S}{S} = \frac{k_{-1}}{k_w}(Cl^-)$$

from which the ratio $k_{-1}/k_w$ can be estimated graphically. The average of a number of such determinations in a run without added chloride was 17, the maximum deviation from the mean being about 10%. From a run with 0.1433 $M$ sodium chloride added, the ratio was estimated to be 18.

From the extent to which hydrogen ion production lags behind chloride ion, the concentration of intermediate at the steady state can be estimated as of the order of 0.012 molar.

Because of the reactivity of tris-β-chloroethylamine toward water, its solubility cannot be determined by the usual methods. The solubility was determined by combining the value $k_1 c$ = 0.00062 mole/liter min., which is the initial slope of a plot of chloride ion concentration *vs.* time, with the value of $k_1$ = 0.310 min.$^{-1}$ at 25° determined by Cohen.[7] The solubility in water at 25° is thus found to be 0.0020 mole per liter.

(10) R. E. Wilson, E. W. Fuller and M. O. Schur, THIS JOURNAL, **44**, 2762 (1922).

(11) J. H. Northrop, N. D. R. C. Reports, 1943.

In all these runs, there being no buffer present, the reaction comes to a virtual stop when one equivalent of chloride has been produced per mole of reacting amine. Because a hydroxyethylamine is a somewhat stronger base than a chloroethylamine and will hence combine preferentially with the acid present, the bulk of the product would be expected to be the bis-β-chloroethylethanolamine hydrochloride. This product has been isolated as the picrylsulfonate in yields of 93%.[12]

## Discussion

In Table V are summarized the rate constants in 2:1 acetone–water solution which have been determined for the four *t*-β-chloroethylamines studied in this series of researches. Among the three successively chlorinated triethylamines the rate of initial cyclization falls, and the reactivity of the ethylene-immonium ion rises, with decreasing basicity of the original amine. (This fact is apparent qualitatively from the stability, partial accumulation, and non-accumulation of the ethylene-immonium ion, respectively, in the successively chlorinated triethylamines.) From this regularity it might be guessed that β,β′-dichlorodiethyl sulfide, which is still less basic than tris-β-chloroethylamine and otherwise chemically analogous to it, would show still less accumulation of cyclic intermediate during its reaction in aqueous media, as is the case. The steady decrease in rate of cyclization ($k_1$) is in accord with the picture of an intramolecular displacement of the $S_N2$ type,[13] since successively weaker bases are being used as nucleophilic reagents. The steady increase in reactivity of the ethylene-immonium ions with chloride ion ($k_{-1}$) may be due to the increased electron deficiency on the ring carbon atom being attacked, caused by increasing chlorination of the molecule.

The differences shown in the table between methyl- and ethyl-bis-β-chloroethylamine are substantial, and one might be inclined to question their reality in view of the entirely different ways in which the constants were determined in the two cases. However, differences of this magnitude must necessarily exist between two compounds which show the qualitative differences in behavior in solution noted with these two homologs. The differences can be summarized by saying that the ethylene-immonium ion of the ethyl compound is formed faster than that of the methyl compound and reacts faster toward every reagent except the parent amine ($k_2$). The latter reaction is an alkylation of a methylamine in the one case and of an ethylamine in the other, and rate differences attributable to steric hindrance have been observed in such cases. On the other hand, steric hindrance of this type does not appear to be so important a factor in ring closure,[14] and would not be expected to dominate the opening of a three-membered ring by water or by a small ion at an

(12) Ref. 5, p. 556.

(13) Ref. 2, p. 2975.

(14) Sebelius, Inaugural Dissertation, Lund, 1927; see Hückel, "Theoretische Grundlagen der organischen Chemie," 2nd ed., Leipzig, 1935, Vol. 2, p. 259.

TABLE V

COMPARISON OF KINETIC CONSTANTS OF SOME β-CHLOROETHYLAMINES $ClCH_2CH_2NRR'$ IN 2:1 ACETONE–WATER SOLUTIONS AT 25°

| R | R' | $\Delta pK_A$[a] | Principal reaction | Constants in 2:1 acetone-water (time in minutes) $k_1$ | $k_{-1}$ | $k_2$ | $k_w$ |
|---|---|---|---|---|---|---|---|
| $C_2H_5$ | $C_2H_5$ | −2.66 | I[b] | 0.202 | <0.02 | <1.0 | <0.05 |
| $ClCH_2CH_2$ | $CH_3$ | −4.76 | D[c] | .02 | 1.35[f] | 0.4 | 0.0012 |
| $ClCH_2CH_2$ | $C_2H_5$ | −4.87 | H[d] | .085 | 1.5[e] | 0.08 | 0.0057 |
| $ClCH_2CH_2$ | $ClCH_2CH_2$ | −7.18 | H[d] | .0055 | ~200 | ⩽20 | ~1 |

[a] $\Delta pK_A$ is defined in Part II, THIS JOURNAL, **69**, 2977 (1947). [b] I = internal cyclization. [c] At the ionic strength prevailing when initial amine concentration = 0.1501. [d] H = hydrolysis. [e] D = dimerization. [f] At the ionic strength prevailing when initial amine concentration = 0.118.

unbranched carbon atom, in the reactions to which $k_{-1}$ and $k_w$ refer. The greater rate of cyclization of the ethyl over the methyl compound in water is largely a matter of entropy of activation;[9] there may even be some release of steric interference with the ethyl group associated with the conversion of one of its neighbor groups into a ring.

## Summary

In connection with the mechanism of hydrolysis, dimerization and displacement reactions of methyl-bis-β-chloroethylamine and ethyl-bis-β-chloroethylamine, studied in Parts I and II of this series, respectively, two related compounds have been examined kinetically. β-Chloroethyldiethylamine in 2:1 acetone–water solution undergoes cyclization to diethylethylene-immonium chloride without complicating reactions, and more rapidly than its analogs previously studied. tris-β-Chloroethylamine is hydrolyzed slowly, with 10% or less accumulation of bis-β-chloroethylethylene-immonium chloride as an intermediate in the reaction in 2:1 acetone–water solution. The kinetics of its hydrolysis has also been studied in water kept saturated with the amine by vigorous stirring. A table is given comparing the individual rate constants in the reactions of the several amines studied in 2:1 acetone–water solution, and the variation of these rate constants with structure is interpreted in part.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

# The Kinetics of the Decomposition of Potassium Persulfate in Aqueous Solutions of Methanol

BY PAUL D. BARTLETT AND JOHN D. COTMAN, JR.

## Introduction

It has been known for some time that the decomposition of a diacyl peroxide in an organic solvent may be, in its over-all course, a reaction between the peroxide and the solvent.[1–6] Recently three lines of evidence have pointed to the fact that often this participation of the solvent has the character of a chain reaction, free radicals arising in the process being able to induce the decomposition of further peroxide.[4–6] Such chain-induced decomposition is revealed (1) by great differences in the rates of decomposition of the same peroxide in different solvents, (2) by characteristic order of reaction, (3) by inhibition of the chain reaction by typical inhibitors, and (4) by the nature of the products.

The decomposition of potassium persulfate, an analog of the diacyl peroxides, has been much studied in water.[7–10] In solutions buffered against the accumulation of hydrogen ion, the decomposition follows the over-all course

$$2^-OSO_2O—OSO_2O^- + 2H_2O \longrightarrow 4HSO_4^- + O_2$$

and is thus, as with diacyl peroxides, a reaction between the peroxidic substance and the solvent. However, in contrast to the decomposition of diacyl peroxides in organic solvents, the reaction is strictly of the first order,[7–9,11] and it has not been observed to be retarded by any inhibitor. Although two of the three marks of chain decomposition are thus lacking, the effect of organic substances on the rate of persulfate decomposition is striking. Saturation of the buffered aqueous solution of potassium persulfate with ethyl acetate[11] caused an eightfold increase in the rate of its decomposition. Methanol was observed by Marie and Bunel[12] to have a similar accelerating

(1) H. Gelissen and P. H. Hermans, *Ber.*, **58**, 285 (1925), and later papers.

(2) M. S. Kharasch, S. S. Kane and H. C. Brown, THIS JOURNAL, **63**, 526 (1941).

(3) M. S. Kharasch and M. T. Gladstone, *ibid.*, **65**, 15 (1943).

(4) K. Nozaki and P. D. Bartlett, *ibid.*, **68**, 1686 (1946).

(5) W. E. Cass, *ibid.*, **68**, 1976 (1946).

(6) P. D. Bartlett and K. Nozaki, *ibid.*, **69**, 2299 (1947).

(7) M. G. Levi and E. Migliarini, *Gazz. chim. ital.*, **36B**, 599 (1906).

(8) L. Green and O. Masson, *J. Chem. Soc.*, **97**, 2083 (1910).

(9) A. Kailan and E. Leisek, *Monatsh.*, **50**, 403 (1928).

(10) H. Palme, *Z. anorg. Chem.*, **112**, 97 (1920).

(11) P. D. Bartlett and K. Nozaki, *J. Pol. Sci.*, **3**, 216 (1948).

(12) C. Marie and L. J. Bunel, *Bull. soc. chim.*, (3) **29**, 930 (1903).

effect upon the decomposition of persulfate. Instances of the oxidation of organic compounds by persulfate suggest rather general attack of persulfate or radicals from persulfate[13] upon the C–H link. Because of these facts it was of interest to us to investigate the mechanism of the accelerating effect of an organic compound in aqueous solution upon the decomposition of persulfate. We chose methanol because of its unlimited solubility in water, its availability in high purity, and the hope of an easy quantitative determination of its fate in the reaction.

## Experimental Procedure

The potassium persulfate and methanol used were reagent grade.

Persulfate was titrated by a modification of the method recommended by Rosin.[14] The solution to be analyzed was made 1 *M* in potassium iodide and one gram of sodium bicarbonate was dissolved in it. To this sample was added 20–25 cc. of 10% sulfuric acid. During and after the liberation of the carbon dioxide, which provided a convenient means of sweeping out the oxygen, the solution stood in a glass-stoppered flask. After standing for thirty minutes in the dark at room temperature, the liberated iodine was titrated with standard thiosulfate. Five test samples titrated by this method showed persulfate amounting to 99.4, 100.2, 99.0, 100.2 and 99.6% of the theoretical. In the absence of methanol satisfactory results were had by the titration method of Müller,[15] which consists of boiling an aliquot for three minutes with potassium iodide and 2 *M* sodium hydroxide. The resulting mixture of iodide and iodate is acidified and the iodine titrated. Methanol interferes with this method.

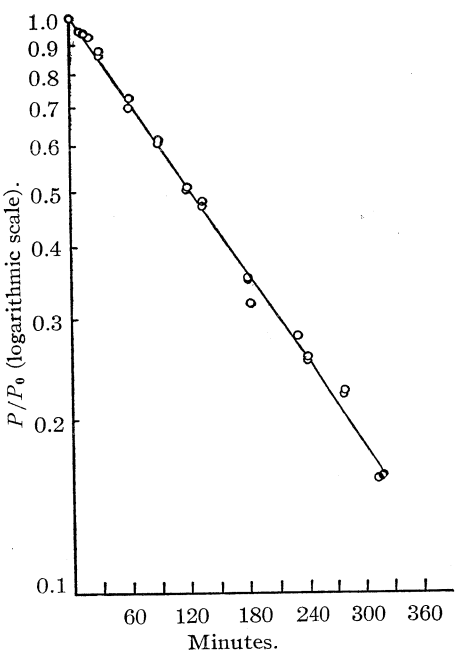



Fig. 1.—Decomposition of potassium persulfate at concentration from 0.00240 to 0.0134 *M* in water at *p*H 8 at 79.8 ± 0.05° (four runs).

A stock buffer solution was prepared which was 0.003 *M* in monopotassium phosphate, 0.097 *M* in the ion $HPO_4^{=}$ (by adding sodium hydroxide), and 0.1 *M* in potassium sulfate. The *p*H and ionic strength were thus maintained at the same value in all the runs.

To minimize the decomposition of persulfate during heating before the addition of the methanol, about 200 cc. of the buffered solvent was first brought to 80° in the thermostat. This hot solvent was then added to the freshly prepared solution of weighed solid potassium persulfate dissolved at room temperature in about 50 cc. of the solvent the system made up to volume in a volumetric flask and reimmersed in the thermostat for about twenty minutes, when it had reached the temperature of the bath. Then 20 cc. of methanol, preheated in a bulb to 80°, was forced through a tube under its own vapor pressure into the reaction vessel. This rapid addition resulted in efficient mixing. There was some 15% decomposition of the persulfate prior to the admission of the methanol. Aliquot portions of the reacting solution were taken with a pipet at successive times and titrated by the procedure described.

The presence of formaldehyde in a solution in which the persulfate had decomposed in the presence of methanol was demonstrated by the formation of a silver mirror with Tollens reagent and by the isolation of the 2,4-dinitrophenylhydrazone of formaldehyde, fluffy yellow needles, m. p. 161–163°. Thereafter formaldehyde was titrated in the product solutions by the method of Romijn,[16] with which methanol and formic acid are said not to interfere.[17]

## Results

Figure 1 shows a logarithmic plot of four runs on the decomposition of persulfate at 79.8° without added methanol. The initial persulfate concentrations in these runs were 0.00240, 0.00241, 0.0131 and 0.0134. The agreement of all these runs, as well as the linearity of the plots over 85% decomposition of the persulfate, confirms the first-order character of the decomposition in the absence of added organic compounds.

The qualitative effect of the addition of 0.976 *M* methanol can be observed by making a similar logarithmic plot of the data in this case. The initial apparent first-order rate constant is 0.140 in the presence of methanol. This substance when present in a concentration of about 1 *M* thus accelerates the decomposition of persulfate by a factor of 25.

In addition to its accelerating effect upon the decomposition of persulfate, the presence of methanol changes the order of the reaction so that the logarithmic plots are no longer linear. Straight lines are obtained, however, for all the runs involving methanol if the reciprocal of the square root of persulfate concentration is plotted against time (plot of a 3/2 order reaction) as is done in Fig. 2 for a typical run. Table I summarizes the values of the 3/2 order rate constants so determined, for three different concentrations of methanol. The rate constants are not proportional to the methanol concentration, but appear to vary with its square root. That this change in rate is also as-

(13) See, for example, C. Moritz and R. Wolfenstein, *Ber.*, **32**, 432, 2531 (1889), on the oxidation of toluene and ethylbenzene, and E. Bekier and S. W. Kijowski, *Rocznicki Chem.*, **15**, 136 (1935) (*Chem. Abst.*, **30**, 3306 (1936)), on the oxidation of acetone catalyzed by silver ion.

(14) Rosin, "Reagent Chemicals and Standards," D. Van Nostrand Co., New York, N. Y., 1946, 2nd edition, p. 349.

(15) E. Müller, *Z. anal. Chem.*, **52**, 299 (1913).

(16) G. Romijn, *Z. anal. Chem.*, **36**, 18 (1897); P. Dobriner, *ibid.*, **39**, 60 (1900).

(17) I. M. Kolthoff and N. H. Furman, "Volumetric Analysis," John Wiley and Sons, Inc., New York, N. Y., 1929, Vol. 2, p. 444.

sociated with a change in the over-all course of the reaction is shown by a series of titrations for formaldehyde, conducted on the solutions after reaction was complete, and included in Table I.

Of the values of $k_{3/2}$ listed in Table I, the value for 1.464 *M* methanol is the result of a single run; that for 0.976 *M* methanol is the average of five runs yielding constants of 0.807, 0.785, 0.781, 0.813 and 0.780; the constant for 0.488 *M* methanol is the average of three runs yielding constants of 0.610, 0.640 and 0.647.

In a study of the polymerization of allyl alcohol in aqueous solution made in this Laboratory in 1944,[18] the decomposition of the initiating persulfate was observed to deviate from first-order kinetics. Because of the polymerization occurring, the nature, functionality, and concentration of the alcohol was changing during these experiments; however, we have now found that in the one experiment with a high concentration of allyl alcohol (6.30–5.02 *M* during the run) the decomposition of persulfate was clearly of the 3/2 order, while in the other experiments the kinetics more closely approximates this order than it does first order. In the presence of the high concentration of allyl alcohol at 55° the 3/2 order rate constant was 0.33 liters$^{1/2}$ moles$^{-1/2}$ min.$^{-1}$.

TABLE I

RATE CONSTANTS AND FORMALDEHYDE FORMATION IN THE DECOMPOSITION OF 0.015 *M* POTASSIUM PERSULFATE AT 79.8° ± 0.05° AT *p*H 8

| Initial methanol concn., moles/l. | $k_{3/2}$ liters$^{1/2}$ moles min.$^{-1}$ | $k_{3/2}/\sqrt{[CH_3OH]}$ | Per cent. formaldehyde, based on peroxide decomposed |
|---|---|---|---|
| 1.952 | .. | .. | 100.5 |
| 1.464 | 1.04 | 0.86 | 99.1 |
| 0.976 | 0.79 | .80 | 92.9 |
| 0.488 | 0.63 | .90 | 82.8 |
| 0.195 | .. | .. | 72.9 |

## Discussion

At no point in the investigation has any evidence appeared that the decomposition of persulfate ion can be induced by any radicals normally involved in its aqueous decomposition. Therefore the simplest interpretation of the mechanism is by some such scheme as the following

$$S_2O_8^{=} \xrightarrow{k_1} 2SO_4^{-\cdot} \qquad (1a)$$

$$SO_4^{-\cdot} + H_2O \xrightarrow{k_2} HSO_4^{-} + OH\cdot \qquad (2)$$

$$2OH\cdot \xrightarrow{k_3} H_2O + {}^1/_2O_2 \qquad (3)$$

Although there are two kinds of free radicals involved in this chain, admitting of three possible chain-terminating steps, yet the order of the reaction tells us that the sulfate ion radicals $SO_4^{-\cdot}$ do not recombine with one another appreciably, for if they did so the reaction would be of half order with respect to persulfate ion, and even a small contribution from such a recombination would make the observed first-order rates vary with initial concentration of persulfate. Furthermore, if sulfate ion radicals and hydroxyl radicals combined they would form Caro's acid, which Palme[10] found to be absent under these experimental conditions. The inclusion of Equation 3 in the above scheme does not imply the exclusion of a similar disproportionation between a hydroxyl radical and a sulfate ion radical. It seems, however, that with water as the solvent Equation 2 represents the most probable fate for the sulfate ion radical. It will be noted that although the sequence Equations 1–3 involves free radicals, initiation, termination and transfer, there is no chain propagation reaction in the sense of attack on the starting material by radicals.

(18) M. E. Fleischer, unpublished experiments.

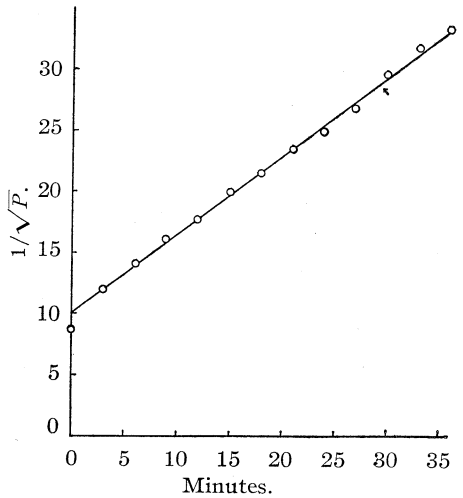



Fig. 2.—Decomposition of persulfate (0.01375 *M*) at 79.8° and *p*H 8 in presence of 0.488 *M* methanol, plotted as a 3/2 order reaction. The arrow marks 90% reaction.

By comparison of the over-all rates of decomposition of persulfate with and without methanol present we may conclude that in 1 *M* methanol 96% of the persulfate ions disappear by being attacked by a free radical other than those present in the water reaction. This new free radical must also be one which is present at a steady-state concentration proportional to the square root of the concentration of persulfate ions. These requirements are met by the following scheme.

$$S_2O_8^{=} \xrightarrow{k_{1a}} 2SO_4^{-\cdot} \qquad (1a)$$

$$S_2O_8^{=} + CH_3OH \xrightarrow{k_{1b}} HSO_4^{-} + SO_4^{-\cdot} + CH_2OH\cdot \qquad (1b)$$

$$SO_4^{-\cdot} + CH_3OH \xrightarrow{k_4} HSO_4^{-} + CH_2OH\cdot \qquad (4)$$

$$CH_2OH\cdot + S_2O_8^{=} \xrightarrow{k_5} HSO_4^{-} + SO_4^{-\cdot} + CH_2O \qquad (5)$$

$$2CH_2OH\cdot \xrightarrow{k_6} CH_3OH + CH_2O \qquad (6)$$

It would of course be possible that Reaction 2 should occur here as well as in the absence of methanol, and the methanol be attacked by the result-

ant hydroxyl radicals instead of directly by sulfate ion radicals. In the related problem of the emulsion polymerization of allyl acetate,[11] although the concentration of the organic compound in the aqueous phase was considerably less than here, it was definitely shown that at least 75% of the polyallyl acetate chains were initiated by sulfate ion radicals rather than by hydroxyl radicals.[19] Allyl acetate, therefore, competes very successfully with water for the sulfate ion radicals, and it seems probable that methanol does likewise.

The sequence of steps 1a–4–5–6 leads to the kinetic equation

$$\frac{-\mathrm{d}(S_2O_8^{=})}{\mathrm{d}t} = k_{1a}(S_2O_8^{=}) + k_5\sqrt{\frac{k_{1a}}{k_6}}(S_2O_8^{=})^{3/2} \quad (7)$$

It is reasonable in view of the strong acceleration by methanol that the second term of this expression should be more important than the first, and such a mechanism would therefore predict the observed 3/2 order kinetics. The sequence of steps 1b–4–5–6 leads to the slightly different equation

$$\frac{-\mathrm{d}(S_2O_8^{=})}{\mathrm{d}t} = k_{1b}(S_2O_8^{=})(CH_3OH) + k_5\sqrt{\frac{k_{1b}}{k_6}}(S_2O_8^{=})^{3/2}(CH_3OH)^{1/2} \quad (8)$$

This equation, again with neglect of the first term on the right, predicts not only the 3/2 order of the reaction but also the linear dependence of the rate constant on the square root of methanol concentration (Table I). Equations (7) and (8) are derived on the assumption that every sulfate ion radical reacts with methanol to produce a hydroxymethylene radical. As the concentration of methanol is reduced to the point where this is no longer true, Equations 1–6 predict that an increasing fraction of the sulfate ion radicals will react with water (or possibly with the accumulating formaldehyde), leading to shorter chains and smaller total amounts of formaldehyde, as observed.

It is assumed that the removal of hydrogen from methanol occurs from carbon, leading to a hydroxymethylene radical rather than from oxygen to yield a methoxyl radical, since the relative normal energies of the C–H and O–H bonds (87.3 and 110.2 kcal. mole, respectively)[20] make the former process seem much the more probable.

Reaction 5, as depicted, may well be an over-all process which actually occurs in two steps

$$CH_2OH\cdot + S_2O_8^{=} \longrightarrow SO_4\dot{-} + HOCH_2OSO_3^{-} \quad (5a)$$

$$HOCH_2OSO_3^{-} \longrightarrow CH_2O + HSO_4^{-} \quad (5b)$$

Very little is known as yet concerning the mode of attack of free radicals upon peroxides in the induced decomposition.

Finally, there is no definite evidence for Equation 6 in preference to a direct union of the two hydroxymethylene radicals to yield ethylene glycol. The high yield of formaldehyde is scarcely conclusive on this point, since the chains are obviously long enough to limit the occurrence of chain-termination products to a few per cent. of the total. Any of these indicated variations could be introduced into the proposed reaction scheme without vitiating its kinetic consequences.

It should be noted that the evidence for the absence of chain decomposition of persulfate in water in the absence of organic compounds is of a negative character and is not altogether complete. In the decomposition of benzoyl peroxide in ether solutions the kinetics, as here, is that of a first order reaction, yet induced decomposition is readily suspected because the reaction is so much faster than in other solvents, and the presence of free radicals other than those of oxygen is shown by the uptake of oxygen during the reaction with the formation of new peroxides. In the case of persulfate decomposing in water solution there can be no free radicals other than those of oxygen, and oxygen-sensitivity is therefore not to be expected even if a long chain reaction were taking place. There is a possible mechanism for this reaction which includes induced decomposition of persulfate ions by hydroxyl radicals, and which still predicts decomposition of the first order. Such a mechanism includes adding to Equations 1a and 2 the following

$$OH\cdot + S_2O_8^{=} \xrightarrow{k_9} HSO_4^{-} + SO_4\dot{-} + {}^1/_2O_2 \quad (9)$$

$$OH\cdot + SO_4\dot{-} \xrightarrow{k_{10}} HSO_4^{-} + {}^1/_2O_2 \quad (10)$$

The induced decomposition of persulfate by hydroxyl radicals will be of the first order now only if Equation 10 represents the mode of chain termination rather than Equation 3. This possibility is mentioned only for completeness; as far as our evidence goes, persulfate decomposition in water may well be an example of the case, unusual to date, in which the spontaneous, unimolecular decomposition is uncomplicated by any induced process involving the free radicals of the chain.

## Summary

The decomposition of potassium persulfate at 79.8° in aqueous solution at *p*H 8 is strictly of the first order, with no evidence of induced decomposition by free radicals analogous to that observed in the decomposition of diacyl peroxides in organic solvents. The presence of methanol or allyl alcohol accelerates the reaction (as much as 25-fold in the case of methanol) and the alcohols change the reaction to one of 3/2 order. In the reaction with methanol formaldehyde is produced, its amount being equivalent to the persulfate decomposed when the initial methanol is 1.5 *M*, and becoming less at lower methanol concentrations. Mechanisms are presented to account for these observations.

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(19) Of the polymer molecules, 75% contained sulfate end-groups. The fraction of the kinetic chains initiated by sulfate ion radicals must be at least as high as this and may be higher because of chain transfer leading to some polymer molecules without any end-group from the initiator (ref. 11).

(20) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd edition, 1940, p. 53.

[CONTRIBUTIONS FROM THE JET PROPULSION LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

# The Critical Point of Nitromethane

BY D. N. GRIFFIN

## Introduction

Up to the present time only calculated values have been available for the critical temperature of nitromethane. The critical point of nitromethane has now been determined experimentally.

Methods for obtaining calculated values for the critical constants are based on other physical constants such as boiling points, surface tensions, and molecular weights. Guldberg[1] and Guye[2] proposed the following rule for obtaining the approximate critical temperature from the boiling point of a substance

$$T_b = 2/3(T_c) \quad (1)$$

where $T_b$ is the absolute boiling point and $T_c$ the absolute critical temperature. Ramsay and Shields[3] proposed the equation

$$\gamma(Mv)^{2/3} = K(t_c - t\ 6) \quad (2)$$

where $\gamma$ is the surface tension, $M$ the molecular weight, $v$ the specific volume, $K$ a universal constant, $t_c$ (°C.) the critical temperature, and $t$ (°C.) the ambient temperature. Boyd and Copeland[4] used the Ramsay–Shields equation in conjunction with their own data on the surface tension of nitromethane and obtained a critical temperature of 623°K. (350°C). Other empirical methods for determining the critical constants have been proposed to give greater accuracy than the Guldberg–Guye rule. Taft and Stareck[5] considered

$$T_f + T_b = T_c \quad (3)$$

where $T_f$ is the absolute freezing point, to be more useful than the Guldberg–Guye rule whereas Lautié[6] proposed

$$4(T_c/T_b) + 10(T_b/T_c) = 12.69 \quad (4)$$

Mei-Chio Chen and Dji-Bin Hu[7] related the critical temperature to the molecular weight as well as to the boiling point in their equation

$$T_c = 10^{1.59/\sqrt{M}}T_b \quad (5)$$

where $M$ is the molecular weight.

The values of the critical temperature of nitromethane as given in Table I were obtained by applying equations (1) through (5).

TABLE I

COMPARISON OF VARIOUS CALCULATED VALUES OF THE CRITICAL POINT OF NITROMETHANE

| Equation | | $T_c$ (°K.) | $t_c$ (°C.) |
|---|---|---|---|
| Guldberg–Guye | (1) | 562 | 289 |
| Ramsay–Shields (by Boyd and Copeland) | (2) | 623 | 350 |
| Taft and Stareck | (3) | 619 | 346 |
| Lautié | (4) | 640 | 367 |
| Mei-Chio Chen and Dji-Bin Hu | (5) | 597 | 324 |

## Experimental Methods

Experimental methods of determining the critical point are based on the physical transition that takes place at the critical point. If a glass tube is partially filled with a liquid and sealed, the meniscus formed between the liquid and gas phases may be seen to disappear when the system is heated above the critical region, and will reappear when cooled back down through the critical region. The disappearance of the meniscus marks the transition of the liquid to a single gas phase at or near the critical point. Although usually sharply defined, this phenomenon does not necessarily mark the true critical point; instead, it might be considered to occur in the critical region. If the quantity of liquid placed in the tube is either too great or too small, the meniscus will disappear at a temperature below the true critical temperature. This effect is described later in this section. It has also been observed that even after the transition to a single gas phase at the apparent critical point, the density of the gas is not uniform throughout the tube but remains greater in the lower portions. Winkler and Maass[8] reported that the density difference for a fixed available space decreases with a rise in temperature, but is measurable up to at least 10° above the critical point.

When a pure liquid and its vapor co-exist in a closed system, the pressure exerted at a given temperature, that is, the vapor pressure of the liquid at that temperature, is independent of the total quantity of the substance present. Above the critical point, only one phase can exist; hence the pressure, at constant volume, will vary according to the quantity of the substance present. These facts may be applied to the determination of critical constants.

If a plot is made of pressure *vs.* temperature for a sample heated in a constant-volume system, a point of discontinuity in the curve will mark the transition from a liquid–vapor system to a single-phase system. However, this point of discontinuity will correspond to the critical point only if the proper size of sample is used, for if a sample of insufficient size is chosen, it will pass entirely into the vapor phase at some temperature below the critical temperature. Similarly, if a sample is too large, it will expand and entirely fill the tube with liquid before the critical point is reached. If the proper size of sample is chosen, the densities of the liquid and vapor phases become equal at the critical point, and they become a single phase without any discontinuity appearing in the pressure–temperature curve. This density is known as the critical density. Because of the indefiniteness of the point of discontinuity near the critical point, it is necessary to interpolate to the critical density by choosing samples having mean bulk densities both greater and less than the critical density.

Ipatieff and Monroe[9] used the bomb technique to determine the critical points for several substances. To obtain the critical point, they plotted pressure *vs.* temperature. The resultant curve gave a region of discontinuity in the critical region. They stated that they observed no effect

(1) Guldberg, *Z. physik. Chem.*, **5**, 374 (1890).
(2) Guye, *Bull. soc. chim.*, **4**, 262 (1890).
(3) Ramsay and Shields, *Z. physik. Chem.*, **12**, 433 (1893).
(4) Boyd and Copeland, THIS JOURNAL, **64**, 2540 (1942).
(5) Taft and Stareck, *J. Phys. Chem.*, **34**, 2307 (1930).
(6) Lautié, *Bull. soc. chim.*, **2**, 2234 (1935).
(7) Mei-Chio Chen and Dji-Bin Hu, *J. Chinese Chem. Soc.*, **10**, 212 1943).
(8) Winkler and Maass, *Can. J. Res.*, **9**, 613 (1933).
(9) Ipatieff and Monroe, *Ind. Eng. Chem., Anal. Ed.*, **14**, 171 (1942).

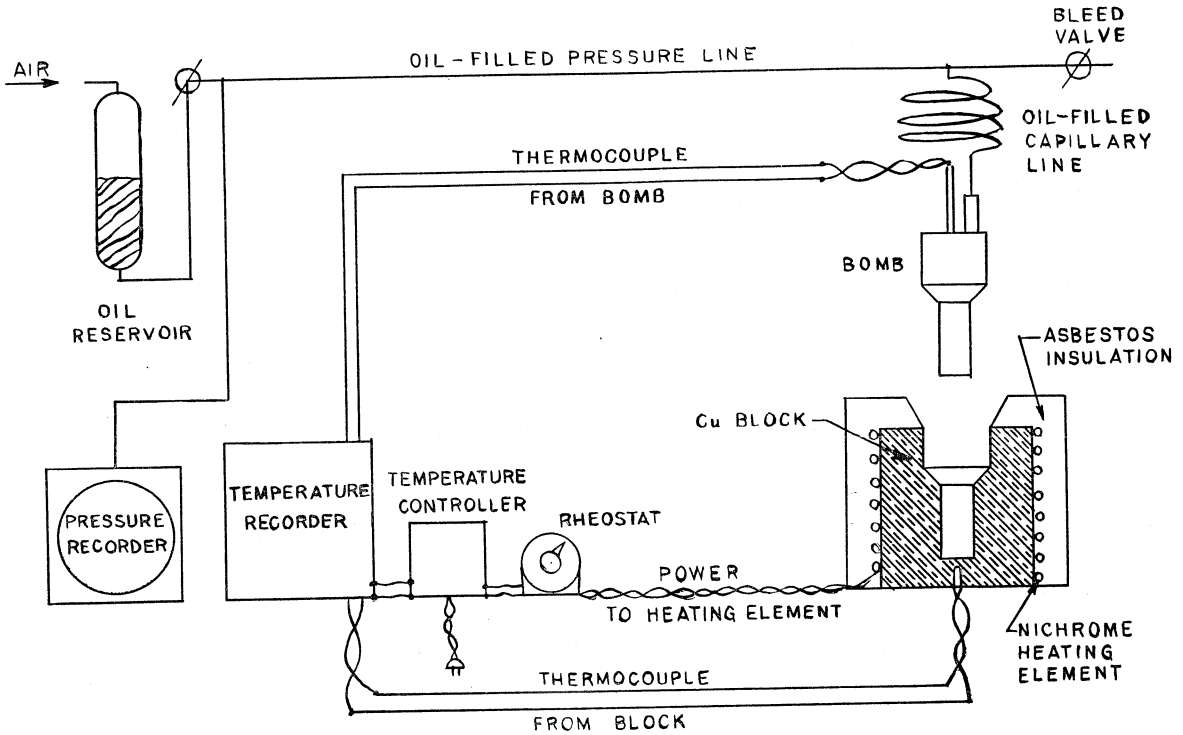



Fig. 1.—Diagram of thermal decomposition apparatus.

when the size of sample was varied, but their method of representing the data graphically failed to show the actual point of discontinuity in each case.

The bomb technique was also used to obtain the critical point of nitromethane. A plot was made of log $p$ *vs.* $1/T$ for each test and compared with a similar plot of the vapor pressure of nitromethane. In each case, a straight line was produced, corresponding to the vapor pressure up to a point at which a sharp break occurred indicating a transition to a single-phase system. The temperature at which the break occurred, and the nature of the curve above that temperature, depended upon the size of the sample used. A plot was then made of these transition points *vs.* sample size. A maximum in the curve occurred at 315°, which was considered to be the true critical temperature $t_c$. The critical density $d_c$ was obtained from the weight of the sample at this point, and the volume of the bomb, whereas the vapor pressure corresponding to the critical temperature was the critical pressure $p_c$.

## Description of Data and Results

Samples of purified nitromethane, varying from 1.5 to 3.5 ml. in volume (1.71 to 3.98 g.), were placed in a stainless-steel bomb having an internal volume of 8.2 ml., and were heated by means of an electrically heated copper block into which the bomb fitted (Fig. 1). The temperature was recorded by a thermocouple located within the bomb and attached to a Leeds and Northrup Micromax recording potentiometer. The pressure was recorded by a Brown Bourdon-type recording gage connected to the bomb by an oil-filled capillary line.

The data used for the vapor pressure of nitromethane were experimental values obtained in work done in the Department of Chemical Engineering of the California Institute of Technology.[10] Experimental values were obtained to above 500 p.s.i.a.; hence extrapolated values up to the critical point were considered valid (Fig. 2).

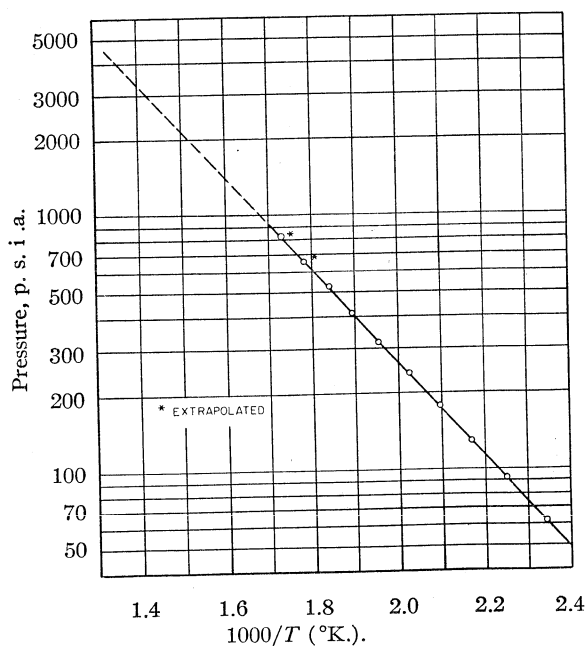



Fig. 2.—Vapor pressure of nitromethane.

When log $p$ was plotted against $1/T$ for samples

(10) Unpublished data.

between 1.5 and 2.3 ml. in volume (1.17 and 2.62 g.), the curve at the temperatures above the transition point fell below the vapor pressure line, indicating that all the sample in each case passed into the vapor phase before the critical temperature was reached (Fig. 3). Thus the samples were too small; *i.e.*, the mean bulk densities were less than the critical density for nitromethane. In the case of samples between 2.6 and 3.5 ml. in volume (2.96 and 3.98 g.), the pressures developed above the transition point were in excess of the extrapolated vapor pressure, indicating that the internal volume of the apparatus was entirely filled with expanded liquid (Fig. 4). These samples were therefore too large; *i.e.*, the mean bulk densities were greater than the critical density. A 2.5 ml. (2.84-g.) sample was used, and the resultant log $p$ *vs.* $1/T$ curve showed only a slight deflection in the critical region and had the maximum observed temperature of the transition point (Fig. 5). The mean bulk density of this sample was therefore nearly equal to the critical density.

At temperatures above the critical temperature, slow decomposition of the nitromethane caused an upward trend in the log $p$ *vs.* $1/T$ curves irrespective of the size of the samples used. This effect is evident in Figs. 3, 4 and 5.

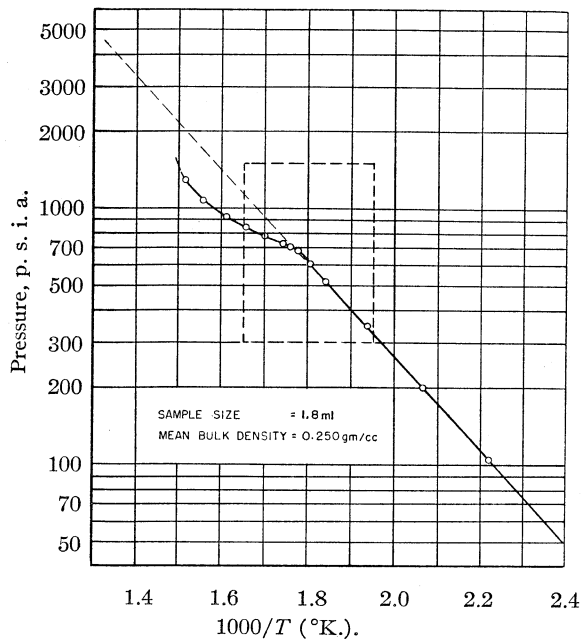



Fig. 3.—Pressure effect in critical region of sample of nitromethane having mean bulk density less than critical density.

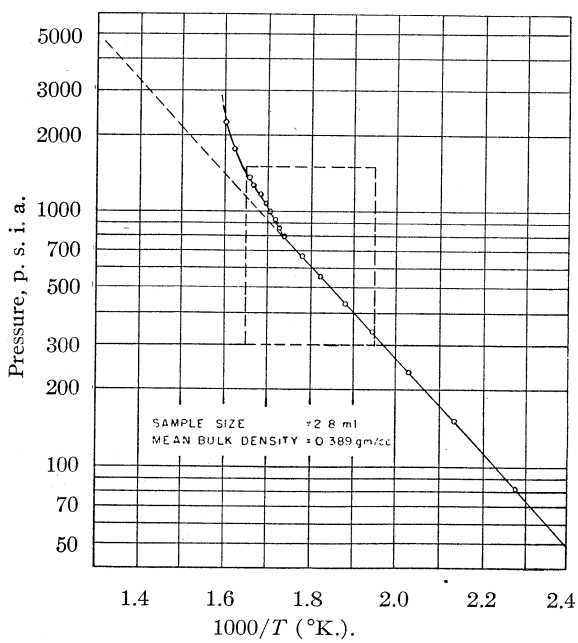



Fig. 4.—Pressure effect in critical region of sample of nitromethane having mean bulk density greater than critical density.

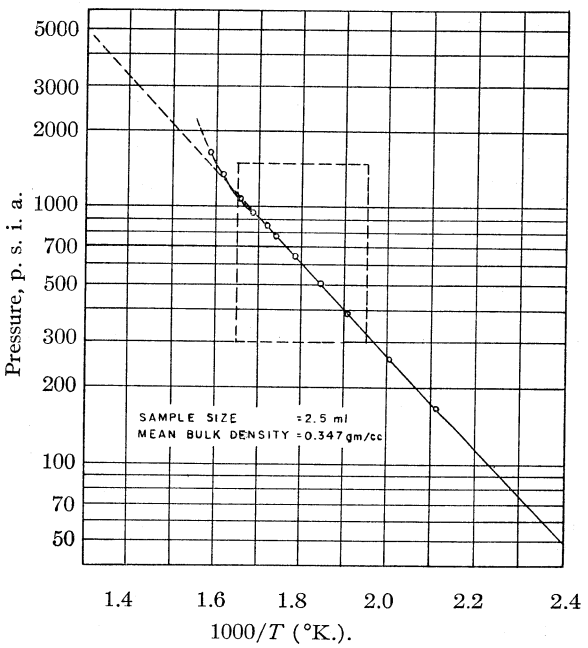



Fig. 5.—Pressure effect in critical region of sample of nitromethane having mean bulk density nearly equal to critical density.

To obtain the true critical point, a plot was made of the temperature of the transition points *vs.* sample size (Fig. 6). The maximum in the curve occurred at 315° (588°K.) and at a sample size of 2.535 ml. (2.885 g.). This point gives a critical temperature of 315° and a critical density of 0.352 g./cc. The critical pressure, which corresponds to the vapor pressure at the critical temperature, is 915 p.s.i.a.

## Summary

This method offers a means of determining graphically the values for $t_c$, $p_c$ and $d_c$ for liquids

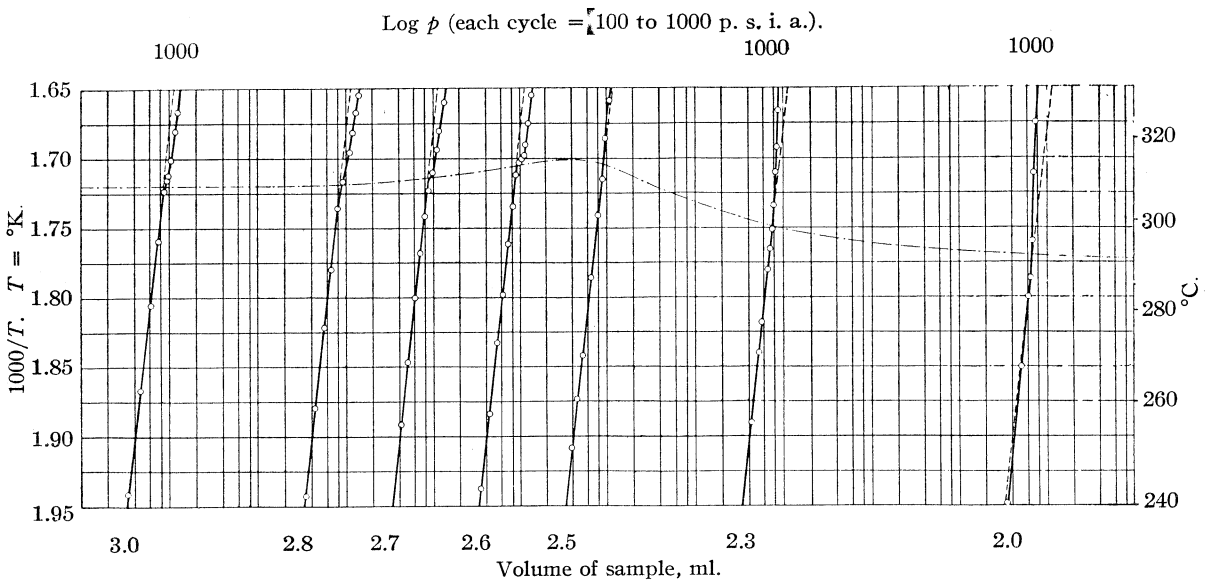



Fig. 6.—Critical point of nitromethane, obtained by interpolating to maximum of critical region: – – – –, vapor pressure of NM (extrapolated); ——, experimental data; —·—·—·—, linear plot of points of deviation.

having high critical temperatures. It is apparently limited in accuracy only by the accuracy of the instruments used in measuring temperature and pressure.

The following critical constants were obtained for nitromethane: $t_c = 315 \pm 1°$, $p_c = 915 = \pm 15$ p.s.i.a., and $d_c = 0.352 \pm 0.004$ g./cc.

PASADENA, CALIFORNIA RECEIVED OCTOBER 22, 1948

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[CONTRIBUTION NO. 253 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS & CO.]

# The Structure of Neoprene. II.[1] Determination of End-Groups by Means of Radiosulfur

BY W. E. MOCHEL AND J. H. PETERSON

It is now generally agreed that in the free radical polymerization of vinyl compounds and dienes, fragments of the initiator become combined as end-groups in the polymer molecules.[2] The polymerization catalysts, so-called, are compounds that decompose under polymerization conditions to form free radicals, which in turn become the true, primary initiators. In some cases it has been postulated, on the basis of kinetics studies, that the catalyst first combines with the monomer to produce a complex which subsequently rearranges to an activated molecule,[3] but the structure of the resulting polymer would also involve the catalyst or some fragment as a terminal group. However, not all polymer molecules need have the primary initiator as an end-group. For example, it has recently been demonstrated[4] that the mercaptans used as regulators, or modifiers, particularly in diene polymerizations, are chain transfer agents[5] which likewise become attached as end-groups on the polymer molecules. Other possibilities must also be considered, such as chain transfer with monomer and termination of two chains by mutual interaction without combination[6] to yield additional types of end-groups.

Determination of the end-groups in neoprene (polychloroprene) was therefore undertaken to obtain further knowledge about the structure and formation of this synthetic elastomer. The general purpose chloroprene polymer, Neoprene

(1) Part I, Mochel, Nichols and Mighton, THIS JOURNAL, **70**, 2185 (1948).

(2) Kamenskaya and Medvedev, *Acta Physicochim., U. R. S. S.*, **13**, 576 (1940); Price and co-workers, THIS JOURNAL, **63**, 2798 (1941); **64**, 1103, 2508 (1942); **65**, 517 (1943); Kern and Kammerer, *J. prakt. Chem.*, **161**, 81 (1942); Bartlett and co-workers, THIS JOURNAL, **65**, 543 (1943); **67**, 812, 816 (1945); Blomquist, Johnson and Sykes, *ibid.*, **65**, 2446 (1943); Pfann, Williams and Mark, *J. Polymer Sci.*, **1**, 14 (1946).

(3) Schulz and Staudinger, *Z. physik. Chem.*, **39B**, 246 (1938); Cuthbertson, Gee and Rideal, *Proc. Roy. Soc.* (*London*), **A170**, 300 (1939); Schulz and Blaschke, *Z. physik. Chem.*, **B51**, 75 (1942).

(4) Price and Adams, THIS JOURNAL, **67**, 1674 (1945); Snyder, Stewart, Allen and Dearborn, *ibid.*, **68**, 1422 (1946); Wall, Banes, and Sands, *ibid.*, **68**, 1429 (1946); Smith, *ibid.*, **68**, 2059, *et seq.* (1946); Kolthoff and Harris, *J. Polymer Sci.*, **2**, 41, *et seq.* (1947).

(5) Flory, THIS JOURNAL, **59**, 241 (1937); Mayo, *ibid.*, **65**, 2324 (1943).

(6) Melville, *J. Chem. Soc.*, 274 (1947); Burnett and Melville, *Nature*, **156**, 661 (1945); Flory, THIS JOURNAL, **59**, 251 (1937).

Type GN, is prepared in aqueous emulsion by a free radical mechanism initiated with potassium persulfate; the polymerization is carried out in the presence of elemental sulfur, and the final latex is treated with tetraethyl thiuram disulfide. Thus the product may contain sulfur from any of three different sources. For a study of this type,[7] radiosulfur, $S^{35}$, was particularly convenient because it could be used to label the different sulfur-containing materials added.[8]

## Results and Discussion

**Sulfur Modification.**—In the polymerization of Neoprene Type GN, elemental sulfur dissolved in the monomer appears to act as a polymerization modifier. Without the sulfur, an insoluble, non-plastic polymer is formed even at low conversion, but polymerization of chloroprene containing 0.5–1.5% of sulfur to approximately 90% conversion followed by treatment with 2.5% of tetraethyl thiuram disulfide yields a soluble, plastic polychloroprene. To investigate the mechanism of this sulfur modification, radiosulfur was used to tag the modifier in a typical Neoprene Type GN emulsion polymerization system[9] and polymer samples, after extraction with acetone to remove free sulfur, were analyzed for combined modifier sulfur by radioactivity assay.

As indicated in Table I the sulfur modifier content, after extraction of the uncombined sulfur, generally increased with conversion both in the original samples, *i. e.*, before treatment with tetraethyl thiuram disulfide, and after the thiuram treatment. This gradual increase in sulfur modifier content was probably due to the increasing sulfur/monomer ratio as the polymerization progressed, rather than to any significant change in mechanism. About 30–60% of the 0.7% of tagged sulfur added to the monomer became combined, but part of that originally combined appeared to be lost during the thiuram disulfide treatment. Statistical analysis of the data for combined modifier sulfur indicated a probability of less than 1% that the differences between untreated and thiuram-treated samples were due to experimental error. Reëxtraction of the samples with acetone for three days failed to change the sulfur contents significantly and this procedure appeared satisfactory for removal of free sulfur.[10]

The thiuram disulfide treatment appeared to remove some radiosulfur, but this was shown to be due to an exchange reaction which as yet has not been completely elucidated. The ratio of tagged sulfur, by radioassay, to total sulfur, as determined by chemical analysis, was lower for untreated polymers (average 1.4) than for those treated with tetraethyl thiuram disulfide (average 1.8). Also, the total sulfur content remained relatively constant while the radiosulfur content decreased as the amount of tetraethyl thiuram disulfide added was increased (see Table II).

TABLE I

RADIOSULFUR-TAGGED MODIFIER IN NEOPRENE TYPE GN

| Conversion, % | Tagged sulfur content, % Original | | Thiuram-treated | |
|---|---|---|---|---|
| 4 | 0.299 | 0.303 | 0.189 | 0.189 |
| 15 | .223 | .223 | .196 | .201 |
| 27 | .250 | .309 | .201 | .201 |
| 36 | .278 | .269 | .224 | .216 |
| 45 | .282 | .278 | .255 | .243 |
| 54 | .296 | .299 | .264 | .273 |
| 62 | .333 | .321 | .276 | .283 |
| 69 | .355 | .344 | .279 | .275 |
| 75 | .396 | .400 | .325 | .314 |
| 86 | .383 | .385 | .234 | .232 |

TABLE II

EFFECT OF TREATMENT ON TAGGED SULFUR CONTENT

| Polymer treatment before coagulation, stabilized with | Sulfur, % Tagged | Total | Ratio |
|---|---|---|---|
| Phenyl-α-naphthylamine | 0.37 | 0.51 | 1.4 |
| 1% Thiuram disulfide | .27 | .47 | 1.8 |
| 2.5% Thiuram disulfide | .24 | .47 | 2.0 |
| 5% Thiuram disulfide | .21[a] | .48 | 2.3 |

[a] Standard deviation was only 0.004%.

Sulfur extracted from a thiuram-treated polymer was recrystallized from acetone (m.p. determined was 119.5–120°; original sulfur, m.p. 119–120° and mixed m.p. 118–119°) and found to have a specific activity of 2490 counts per milligram per sixty-four seconds compared to the specific activity of 5025 for the original sulfur. Although sulfur and tetraethyl thiuram disulfide refluxed in boiling acetone or benzene did not appear to exchange appreciably in two hours, a radio exchange did occur when sulfur and the thiuram were heated together in a melt at 95–100° as shown in Table III.

TABLE III

SULFUR-TETRAETHYL THIURAM DISULFIDE EXCHANGE

(Initial S:S* ratio was 2:1)[a]

| Sulfur | Specific activity counts/64 sec./mg. |
|---|---|
| Original | 2609 |
| After 30 min. at 95–100° | 2416 |
| Original | 2100 |
| After 7 hr. at 95–100° | 710 |
| Original | 2144 |
| After 16 hr. at 95–100° | 744 |

[a] S* is used to indicate radioactive tagged sulfur.

Recrystallized thiuram recovered from one of these melts was shown by analysis to be radioactive. On the basis of reported thiuram chemistry[11] it is probable that the sulfur and thiuram

(7) *Cf.* also Pfann, Salley and Mark, THIS JOURNAL, **66**, 983 (1944).

(8) After this work was under way, a note appeared by Smith and Campbell, *J. Chem. Phys.*, **15**, 338 (1947), describing a similar use of radiosulfur in a study of the persulfate initiation of styrene polymerization. Radiosulfur has also been used recently in mercaptans to measure transfer constants for styrene polymerization, see Walling, THIS JOURNAL, **70**, 2561 (1948).

(9) Collins, U. S. Patent 2,264,173 (Nov. 25, 1941).

(10) A. S. T. M. Designation: D 297–43T.

(11) Levi, *Gazz. chim. ital.*, **61**, 373 (1931); Langenbeck and Rhiem, *Kautschuk*, **12**, 156 (1936).

disulfide react under these conditions to form a thiuram polysulfide in which sulfur exchange occurs and that this polysulfide decomposes again to the disulfide and free sulfur. The recovery of sulfur or thiuram disulfide was never quantitative; there was always a non-crystallizable oil left.

Although it was demonstrated that sulfur exchange with tetraethyl thiuram disulfide can occur in a melt at 95–100°, the conditions used for the neoprene treatment were considerably different and the same mechanism may not hold. The polychloroprene latex (*p*H 11.5–12.0) was treated with a dispersion of the thiuram at 40° for a few minutes, the latex coagulated and, after drying two or three days at room temperature under vacuum, the polymer was extracted with boiling acetone for three days. Furthermore, the indicated exchange in neoprene must involve combined sulfur, not elemental sulfur alone (see Table I), although the sulfur involved may be bound only by coördinate linkages to other sulfur atoms.

Further evidence that there is a reaction between the combined sulfur modifier and the tetraethyl thiuram disulfide was obtained from changes in properties of the polymer. The sulfur-modified polymers prepared in 10 to 90% conversion were insoluble in benzene or chloroform and nonplastic if isolated from the latex without treatment with tetraethyl thiuram disulfide but, after treatment in alkaline emulsion, corresponding polymers were completely soluble and plastic. This solubilization of gel polychloroprene did not occur appreciably unless the sulfur modifier was used. At monomer conversions below 10%, sol polymer of very high intrinsic viscosity was isolated without thiuram treatment but the intrinsic viscosity was decreased by treatment with the thiuram disulfide.

A polychloroprene made in 80% conversion with 0.7% of radioactive tagged sulfur and treated with 2.5% of tetraethyl thiuram disulfide was extracted with acetone to remove uncombined sulfur and fractionated from benzene solution using methanol as precipitant.[1] The results of analyses of the fractions, shown in Table IV, indicate an approximate constancy of combined sulfur from the modifier over a range of molecular weights from 92,000 to 321,000.

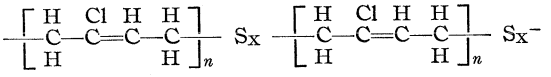
TABLE IV

FRACTIONATED NEOPRENE TYPE GN CONTAINING RADIOSULFUR

| Fraction | Weight, g. | $\overline{M}n$[b] | S*, % | S* atoms/mol. | $\overline{M}$/S* atom | Total sulfur, % |
|---|---|---|---|---|---|---|
| A | 2.97 | Gel[a] | 0.38 | | | |
| B | 6.35 | 321,000 | .31 | 31.0 | 10,300 | 0.59 |
| C | 6.79 | 210,000 | .30 | 20.2 | 10,400 | .37 |
| D | 4.85 | 132,000 | .31 | 12.8 | 10,300 | .36 |
| E | 3.18 | 92,000 | .34 | 9.8 | 9,400 | .40 |
| F | 3.03 | 63,200 | .38 | 7.5 | 8,400 | .46 |
| G | 3.54 | 40,000 | .46 | 5.7 | 7,000 | .75 |

[a] Fraction gelled during preparation for molecular weight measurements. [b] Number average molecular weight by osmotic pressure measurement.

Obviously the sulfur was not acting as an "end-grouper" like the typical chain transfer agents, since some thirty-one sulfur atoms were combined in each polymer molecule, on the average, in fraction B. On the basis of this evidence the sulfur is believed to be combined essentially as a co-monomer, as has been demonstrated in the case of oxygen.[12] This hypothesis is also in accordance with the observation by Schulz[13] that sulfur is a polymerization inhibitor for styrene, *i. e.*, sulfur reacts with the free radicals to form new, inactive, resonance-stabilized radicals. However, in the case of chloroprene the free radicals ending in sulfur can continue growth. Contrary to the situation in the reaction of oxygen with styrene, the addition of sulfur to the chloroprene free radical appears to be much slower than the growth reaction; consequently, only a small amount of sulfur becomes combined and high molecular weight copolymers are obtained. The number of sulfur atoms combined successively has not been determined but it is probably of the order of 2–6.[14,15] From the chloroprene to sulfur ratio it may be postulated that the structure of Neoprene Type GN before treatment with tetraethyl thiuram disulfide is, in part, the following, where x may be 2 to 6 and $n$ is, on the average, 80 to 110 times x (the observed values are higher because of the sulfur exchange)



(Non-linear linkages of an unknown nature are undoubtedly also present in minor amounts.) The sulfur linkage is believed to be cleaved by a reaction with tetraethyl thiuram disulfide, or its alkaline degradation products, by a mechanism still under investigation. This cleavage yields a soluble, plastic polymer by reducing the average molecular weight below the critical value for gelation.[16] Thus sulfur, unlike mercaptan modifiers, does not directly control molecular weight but yields a product whose molecular weight can subsequently be reduced by the necessary amount to render the gel soluble.

**Persulfate Initiation.**—To investigate the mechanism of polymerization initiation by persulfates, polychloroprene was prepared using as catalyst, or initiator, potassium persulfate tagged with radiosulfur. The removal of all uncombined persulfate fragments from the polymers was the greatest difficulty in this work. For

(12) Staudinger, *Ber.*, **58**, 1075 (1925); Staudinger and Lautenschlager, *Ann.*, **488**, 1 (1931); Price, *J. Polymer Sci.*, **1**, 87 (1946); Bovey and Kolthoff, THIS JOURNAL, **69**, 2143 (1947).

(13) Schulz, *Die makro. Chemie*, **1**, 94 (1947).

(14) Farmer and Shipley, *J. Chem. Soc.*, 1519 (1947).

(15) Extraction in hot acetone may remove some bound sulfur. See Kinnear and Harley-Mason, *J. Soc. Chem. Ind.*, **67**, 107 (1948).

(16) Flory, *J. Chem. Phys.*, **46**, 132 (1942).

example, a typical polymer (prepared in 70% conversion with 0.6% of potassium persulfate), differed in its persulfate sulfur content when treated in various ways as shown in Table V.

TABLE V

POLYCHLOROPRENE MADE WITH RADIOPERSULFATE

| Successive treatments | Time | Tagged sulfur, % |
|---|---|---|
| None (original polymer) | ..... | 0.102 |
| Mill-washed with 60° water | 20 min. | 0.056 |
| Mill-wash repeated | 30 min. | .054 |
| Extracted with acetone | 3 days | .049 |
| Extracted with methanol | 3 days | .036 |
| Original extracted with boiling water | 3 days | .040 |
| Dissolved in benzene and precipitated with methanol | ..... | .0091 |

After examination of several possibilities, three successive precipitations of the polymers from dilute benzene solution with acetone appeared to be the best procedure for removal of uncombined residues; the tagged sulfur content could thus be reduced to about 0.004–0.005%, with a standard deviation of 0.0006%. The possibility must always be considered that the samples assayed contained residual uncombined inorganic residues from the persulfate. Since rather lengthy treatment of the samples was necessary to obtain constant, reproducible analytical values it may be possible that some persulfate sulfur originally combined was lost by hydrolysis or ester interchange, but this is unlikely at the temperatures involved.[17]

Within experimental error there appeared to be no significant differences in amount of combined persulfate sulfur at different monomer conversion levels.

Fractionation of differently modified polychloroprenes initiated with tagged persulfate, by precipitation from benzene solution with methanol, yielded high molecular weight fractions having relatively high tagged sulfur contents and low molecular weight fractions having little or no combined persulfate sulfur. Results obtained for an unmodified polymer, one modified with 0.7% of elementary sulfur and one modified with 0.30% of dodecyl mercaptan, indicated a difference in the mechanism of initiation (see Table VI). Since these fractionations were carried out in identical manner, it is believed that comparison of the results gives a valid indication of a difference in mechanisms.

The unmodified and sulfur-modified polychloroprenes contained combined sulfur from the persulfate, indicating actual chain initiation by a persulfate fragment, probably $SO_4^-$.[17b] In the case of the sulfur-modified, thiuram-treated polymer, Neoprene Type GN, the radiosulfur assay indicated that from 8 to 17 polymer molecules were formed per combined sulfur atom from

(17) *Cf.* (a) Hopff and Kern, Trans. by Kline, *Modern Plastics*, **23**, 153 (1946); (b) Bartlett and Nozaki, *J. Polymer Sci.*, **3**, 216 (1948).

TABLE VI

FRACTIONATED POLYCHLOROPRENES MADE WITH TAGGED PERSULFATE

| Fraction | Weight, g. | Mol. wt.[a] | Tagged sulfur, % | S*/mole, g. | Mols./S* atom[b] |
|---|---|---|---|---|---|
| Unmodified Polymer (5% Monomer Conversion) | | | | | |
| Whole | 35.5 | ..... | 0.005 | | |
| A | 8.37 | ..... | .0074 | | |
| B | 14.72 | ..... | .0017 | | |
| C | 4.20 | 1,810,000 | .0014 | 25.3 | |
| D | 1.90 | ..... | .0009 | .... | |
| E | 1.92 | 525,000 | .0006 | 3.15 | 10 |
| F | 1.35 | 318,000 | .0004 | 1.27 | 25 |
| G | 1.22 | 205,000 | .0004 | 0.82 | 39 |
| H | 0.57 | 124,000 | .0005 | .62 | 52 |
| I | .26 | ..... | .0007 | .... | |
| Sulfur-Modified Polymer (83% Monomer Conversion) | | | | | |
| Whole | 26.2 | | 0.073 | | |
| C | 6.72 | 410,000 | .0007 | 2.87 | 11 |
| D | 3.03 | 218,000 | .0015 | 3.27 | 10 |
| E | 2.16 | 150,000 | .0026 | 3.90 | 8 |
| F | 1.02 | 111,000 | .0033 | 3.66 | 9 |
| G | 0.73 | 85,000 | .0028 | 2.38 | 13 |
| H | .98 | 74,000 | .0025 | 1.85 | 17 |
| Dodecyl Mercaptan-Modified Polymer (69% Monomer Conversion) | | | | | |
| Whole | 33.0 | | 0.048[c] | | |
| B | 6.30 | 610,000 | .059 | 360 | |
| C | 6.62 | 365,000 | .0004 | 1.48 | 22 |
| D | 5.53 | 264,000 | .0003 | 0.80 | 40 |
| E | 1.50 | 208,000 | Nil | .... | ... |
| F | 3.00 | 140,000 | Nil[d] | (0.085 | 377) |

[a] Molecular weights were determined viscometrically and checked osmotically. [b] Calculated number of polymer molecules per tagged-sulfur atom. [c] Reprecipitation three times from benzene reduced tagged sulfur content to 0.005%. [d] Analysis of a large sample at a long counting period indicated the presence of 0.00006% of tagged sulfur.

the primary initiator and reaction kinetic chain lengths ranged from approximately 1,000,000 to 5,000,000. The formation of 8 to 17 polymer molecules for each primary initiator, presumably by chain transfer with monomer, is not at all unlikely and is of the same order of magnitude as has been reported for other systems.[18]

The unmodified polymer, isolated at very low monomer conversion to obtain a soluble product, contained less persulfate sulfur than the Neoprene Type GN but the amount combined was significantly more than in the case of the mercaptan-modified polymer. Reaction kinetic chain lengths for the unmodified polymer ranged from 5,000,000 to 8,000,000, running through 10 to 52 polymer molecules, for each persulfate sulfur atom combined. Of course, the kinetic chain lengths would be lower if monomer initiation occurred with other free radicals such as hydroxyl, formed by reaction of persulfate with water.

(18) *Cf.* Schulz and Harboth, *Die makro. Chemie*, **1**, 106 (1947), Melville and Tuckett, *J. Chem. Soc.*, 1211 (1947).

Hydroxyl free radical combination is a possibility which has not been excluded.[17a]

In the case of the mercaptan-modified polymer the final fractions of the polymer contained practically no persulfate sulfur. The amount of persulfate sulfur remaining in fraction F would correspond to a kinetic chain length of approximately 53,000,000, running through 377 molecules, which is considered too high. Chain transfer should not change the reaction kinetic chain length[19] but only the average degree of polymerization. On the basis of available evidence it is proposed that a different initiation mechanism is operating in the presence of the dodecyl mercaptan. It is believed that the potassium persulfate reacts with the dodecyl mercaptan to form free radicals which in turn initiate the polymerization. A possible reaction is

$$K_2S_2O_8 + 2RSH \longrightarrow 2RS\cdot + 2KHSO_4$$

It may be this type of reaction which is responsible for the promoter action of mercaptans, particularly in butadiene polymerization.[20]

Since the high molecular weight fractions always contained large amounts of radiosulfur the possibility must be considered that molecules initiated by persulfate fragments precipitated with the high molecular weight polymer because of reduced solubility. (It is highly improbable that the persulfate-initiated polymer molecules would, on the average, grow to longer polymer chain lengths than others.) It is believed that residual uncombined persulfate fragments, *i. e.*, inorganic sulfates having low solubility in benzene, are carried down by the high molecular weight fractions as they precipitate. The potassium acid sulfate expected would have low solubility in benzene and might need only the nucleus of precipitating polymer to be carried down.

**Mercaptan Modification.**—To complete this investigation it was considered desirable to examine the action of dodecyl mercaptan, a typical chain transfer agent,[4] in the polymerization of chloroprene. Accordingly, radiosulfur-tagged dodecyl mercaptan was substituted for the sulfur modifier in a typical polymerization system for Neoprene Type GN and the polymer obtained was analyzed, after extraction with acetone.

Typical results, illustrated in Table VII, indicated that the polymers isolated at 10–86% conversions contained on the average more than one mercaptan sulfur atom per polymer molecule. Complete precipitation of these polymers from benzene solutions failed to change the sulfur contents appreciably and a duplicate experiment gave similar values for sulfur content; therefore it is believed that the sulfur remaining was actually combined in the polymer molecules. Note also that there was no significant change in sulfur content as the conversion changed, indicating uniform mercaptan consumption. About 50% of the added mercaptan was combined.

(19) Schulz and Blaschke, *Z. physik. Chem.*, **B51**, 83 (1942); Kamenskaya and Medvedev, *Acta Physicochim. U. R. S. S.*, **13**, 586 (1940).

(20) Kolthoff and Harris, *J. Polymer Sci.*, **2**, 41 (1947); Dunbrook, *India Rubber World*, **117**, 357 (1947); Eager and Winkler, *Can. J. Res.* **26**, 527 (1948).

TABLE VII

MERCAPTAN-MODIFIED NEOPRENE (0.30% $C_{12}H_{25}SH$)

| Conversion, % | Mol. wt.[a] | S* | S* atoms/mol. |
|---|---|---|---|
| 10 | 148,000 | 0.025 | 1.15 |
| 20 | 175,000 | .025 | 1.36 |
| 30 | 165,000 | .025 | 1.28 |
| 41 | 207,000 (?) | .026 | 1.68 |
| 50 | 192,000 | .019 | 1.14 |
| 59 | 232,000 | .021 | 1.52 |
| 69 | 161,000 | .025 | 1.26 |
| 86 | Contained gel | .026 | .. |
| | | Average | 1.34 |

[a] $M_n$ by osmotic pressure.

Fractionation of the dodecyl mercaptan-modified polymer likewise indicated an average of slightly more than one mercaptan sulfur atom combined per polymer molecule, even after extensive re-extractions and reprecipitations (see Table VIII).

TABLE VIII

FRACTIONATED NEOPRENE MODIFIED WITH 0.30% TAGGED MERCAPTAN (69% CONVERSION)

| Fraction | Mol. wt.[a] | S*, % | S* atoms/mol. | $\frac{\%S^*}{100} - \frac{32}{M}$ |
|---|---|---|---|---|
| Whole | 256,000 | 0.019 | 1.52 | $6.5 \times 10^{-5}$ |
| A | 1,150,000 | .010 | 3.58 | 7.2 |
| B | 890,000 | .011 | 3.05 | 7.4 |
| C | 610,000 | .011 | 2.09 | 5.7 |
| D | 415,000 | .013 | 1.68 | 5.3 |
| E | 312,000 | .013 | 1.26 | 2.7 |
| F | 250,000 | .016 | 1.25 | 3.2 |
| G | 198,000 | .019 | 1.17 | 2.8 |
| H | 165,000 | .026 | 1.34 | 6.5 |
| I | 119,000 | .032 | 1.19 | 5.0 |
| J | 82,000 | .013 (?) | 0.33 (?) | |
| K | 75,000 | .049 | 1.14 | 6.2 |
| | | | Average | $5.3 \times 10^{-5}$ |

[a] $\overline{M}_n$ by osmotic pressure.

A polymer was prepared using 1% of the dodecyl mercaptan tagged with radioactive sulfur and was fractionated after three complete precipitations to remove uncombined mercaptan residues. This polymer, of lower molecular weight, and presumably containing fewer side branches per molecule, contained an even greater excess of combined mercaptan sulfur over the theoretical one atom per molecule than the fractions of corresponding molecular weight from the low mercaptan polymer (see Table IX). Similar results were obtained with a product isolated at 25% conversion to reduce the branching still further.

From these results it was apparent that the dodecyl mercaptan was not combined in a simple 1:1 ratio of mercaptan to polymer molecule, as

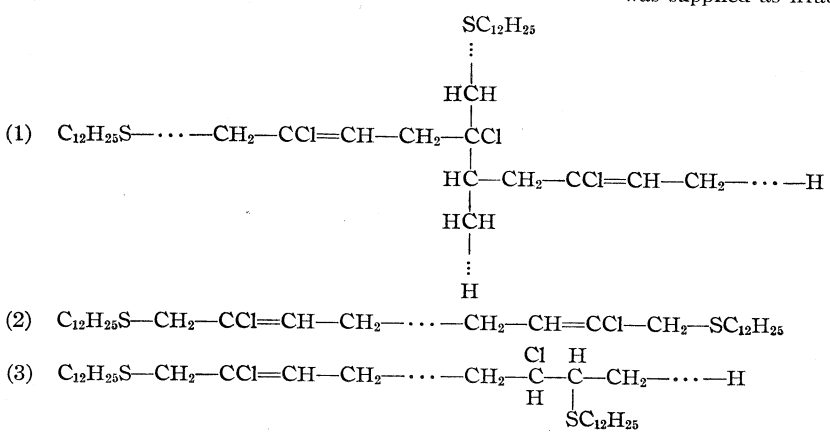
TABLE IX

FRACTIONATED NEOPRENE MODIFIED WITH 1.0% RADIOMERCAPTAN (45% CONVERSION)

| Fraction | Mol. wt.[a] | S*, % | S* atoms/mol. | $\frac{\%S^*}{100} - \frac{32}{\overline{M}}$ |
|---|---|---|---|---|
| Whole | 58,000 | 0.072 | 1.30 | $17 \times 10^{-5}$ |
| B | 160,000 | .035 | 1.75 | 15 |
| C | 130,000 | .043 | 1.74 | 18 |
| D | 103,000 | .047 | 1.51 | 16 |
| E | 74,000 | .054 | 1.25 | 11 |
| F | 59,000 | .075 | 1.38 | 14 |
| G | 40,000 | .104 | 1.30 | 24 |
| | | | Average | $16 \times 10^{-5}$ |

[a] Viscometrically; C and D checked by osmotic pressure, which indicated $\overline{M}_n$ = 126,000 and 103,000, respectively. Whole polymer by osmotic pressure.

would be expected for linear polymer if only chain transfer were involved.[21] There are three obvious ways in which the mercaptan content could be increased: (1) cross-linking reactions involving growth through double bonds in the polymer chains[22]; (2) mutual combination of two growing chains initiated by RS· to give a maximum of two sulfur atoms per molecule; (3) addition of mercaptan molecules to the double bonds in the polymer chains by the usual free radical mechanism.[23] These reactions would give rise to the structures




Mechanism 1 undoubtedly is operative and probably accounts at least in part for the higher-than-average sulfur content of fractions A and B. However, since 1.0% mercaptan yielded polymers containing more sulfur than those made with only 0.30% of the mercaptan it appears that crechanisms 2 and/or 3 are important. Inmeased amounts of mercaptan might well lead to a larger number of growing chains at any given moment and hence a higher probability of termination by mutual combination (mechanism 2); but this mechanism alone cannot lead to the values 3.58 and 3.05 found for fractions A and B of Table VIII. In view of the mild conditions employed for free-radical addition of mercaptans to double bonds of butadiene polymers and rubber,[24] mechanism 3 appears to be the most probable as an explanation of the results observed. The last columns of Tables VIII and IX express the amount of combined sulfur in excess of the theoretical one atom per polymer molecule, reduced to a common molecular weight. The values indicate that, on the average, the second atom of sulfur becomes combined after reaction kinetic chain lengths of 600,000 and 200,000, respectively, for polymerization in the presence of 0.30 and 1.0% of dodecyl mercaptan. The average value for the reduced excess sulfur content for the 1% mercaptan polymers is approximately three times the value obtained when roughly a third as much mercaptan was used. This is strong evidence for a simple mass effect which would be more likely in mechanism 3 than in the others.

## Experimental Details

**Materials.**—The radiosulfur used in this investigation was supplied as irradiated potassium chloride by Clinton Laboratories (now Oak Ridge National Laboratory) and was obtained on allocation from the U. S. Atomic Energy Commission. Carrier sulfur was added and the labeled sulfur isolated by a series of operations involving oxidation to sulfate, precipitation as barium sulfate, reduction to barium sulfide, conversion to hydrogen sulfide and oxidation to free sulfur.[25] It was recrystallized from carbon disulfide before use. This sulfur had an original activity of $1.3 \times 10^6$ counts per mg. per 64 seconds.

To prepare potassium persulfate the stock solution of tracer as potassium sulfate plus potassium chloride was converted to potassium hydrogen sulfate and oxidized electrolytically to potassium persulfate,[26] containing radiosulfur.

For the preparation of dodecyl mercaptan containing radiosulfur, the radioactive barium sulfide described above was acidified and the hydrogen sulfide was passed into a methanol solution of sodium methoxide to form sodium hydrosulfide. This was then treated with dodecyl bromide at 120° in a pressure tube for three hours and the radiosulfur-labeled dodecyl mercaptan was isolated and distilled (104–110° (3 mm.)) to yield a product of 96% purity by iodometric titration.

**Polymerization.**—The polymerizations were carried out in the usual manner[27] at 40°. The sulfur-modified poly-

(21) Smets and Reiske [*Bull. Soc. Chim. Belg.*, **56**, 159 (1947)] found that the chlorine content of polymethyl methacrylate polymerized in carbon tetrachloride was always slightly less than calculated on the basis of simple transfer.

(22) Medvedev, Chilikina and Klimenkov, *Acta Physicochim. U. R. S. S.*, **11**, 751 (1939); Flory, THIS JOURNAL, **69**, 2893 (1947). Reaction branching as postulated by Medvedev, Koritskaya and Alekseeva, *J. Phys. Chem.* (*U. S. S. R.*), **17**, 391 (1943), would be similar in results.

(23) Kharasch and Fuchs, *J. Org. Chem.*, **13**, 97 (1948).

(24) Kolthoff and Harris, *J. Polymer Sci.*, **2**, 70 (1947); Serniuk, Banes and Swaney, THIS JOURNAL, **70**, 1804 (1948); Cunneen, *India Rubber J.*, **114**, 543 (1948); Naylor, *J. Polymer Sci.*, **1**, 305 (1946).

(25) Clark, Gallo and Lincoln, *J. Applied Phys.*, **14**, 428 (1943).

(26) Henderson and Fernelius, "A Course in Inorganic Preparations," McGraw-Hill Book Co., New York, N. Y., 1935, p. 97.

(27) Walker and Mochel, "Proc. International Rubber Tech. Conf.," London, 1948, Preprint No. 11.

mers were made with 0.7% sulfur. The mercaptan-modified polymers were prepared in the same way, substituting 0.30–1.0% of dodecyl mercaptan for the sulfur. Likewise, for the unmodified polymer no change in the system was made except omission of the modifier. Samples of the latex were removed, treated with 2.5% of tetraethyl thiuram disulfide in emulsion or with 0.5% of phenothiazine and 1.0% of phenyl-α-naphthylamine in emulsion. They were then coagulated with ethanol and dried at room temperature *in vacuo*. Analysis indicated that polymers prepared in this way contained only small amounts of residual soap and other adjuvants.

**Preparation of Samples.**—As indicated in the Discussion, the polymer samples were extracted or precipitated to remove uncombined sulfur and sulfur compounds. For elemental sulfur and some mercaptan samples the polymers were extracted continuously with acetone or methanol for three to four days in ASTM rubber extractors or Soxhlet apparatus. In other experiments the samples were dissolved in benzene to make 1–5% solutions and the polymer precipitated completely by addition of about 2 volumes of methanol or acetone. Further addition of methanol produced no cloudiness in the clear supernatant liquid.

**Radioactivity Assay.**—The dry polymer samples were oxidized by the Carius method to obtain a clear solution of sodium sulfate. The sulfate was precipitated as the benzidine salt on special funnels, dried and counted directly with Geiger counters.[28] A control from the labeled sulfur compound under study was always counted at the same time as the unknowns to eliminate the necessity of reliance on decay calculations and to check counter operation with theory based on decay. Sufficient sodium sulfate carrier was added to both control and unknowns to make the sample sizes comparable so that errors due to absorption were eliminated. Furthermore, the control samples were adjusted to roughly the same order of magnitude of counts as the unknowns.

**Acknowledgments.**—The authors gratefully acknowledge the assistance of Miss Doris Peterson in the radioactivity determinations and of Dr. J. B. Nichols and Miss Beverly Price for the osmotic pressure measurements. We also extend our sincere thanks to Drs. D. M. McQueen, B. C. Pratt and G. D. Patterson for their aid and encouragement, and to Professors F. T. Wall and C. S. Marvel for many helpful discussions during the course of this research.

(28) Henriques, Kistiakowsky, Margnetti and Schneider, *Ind. Eng. Chem., Anal. Ed.*, **18**, 349 (1946).

## Summary

By use of radioactive sulfur it has been shown that sulfur-modified neoprene, *i. e.*, Neoprene Type GN, is essentially a copolymer of chloroprene and sulfur in the approximate ratio of 100 chloroprene units per sulfur atom. The sulfur units, possibly disulfides, are cleaved by an alkaline emulsion of tetraethyl thiuram disulfide, so that a gel polymer containing combined sulfur can thus be converted to a soluble, plastic product. The mechanism of this cleavage reaction has not been completely elucidated as yet.

Potassium persulfate, used as initiator for the polymerization of neoprene, appears to be combined with the polymer in Neoprene Type GN in amounts equivalent to 8–17 polymer molecules formed for each sulfur-containing initiator fragment. However, when dodecyl mercaptan is used as modifier, a large proportion of the polymer molecules contain essentially no combined sulfur from the persulfate and it appears that the true initiator is the RS· free radical formed by reaction of the mercaptan with potassium persulfate.

Dodecyl mercaptan used as a polymerization modifier or chain transfer agent, is combined in a greater amount than the one mercaptan per polymer molecule expected on the basis of simple chain transfer. High molecular weight fractions contained 3–4 mercaptan sulfur atoms per polymer molecule and the results suggest that mercaptan addition to the double bonds of the polymer had occurred.

WILMINGTON, DELAWARE RECEIVED SEPTEMBER 23, 1948

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[CONTRIBUTION FROM THE EMERYVILLE LABORATORIES OF SHELL DEVELOPMENT COMPANY]

# Some *t*-Butyl Hydroperoxide Derivatives of Aldehydes and Ketones

BY FRANK H. DICKEY, FREDERICK F. RUST AND WILLIAM E. VAUGHAN

*t*-Butyl hydroperoxide combines with aldehydes and ketones to form a series of new compounds which contain either one or two peroxide groups for each carbonyl group. The synthesis is in accord with the equations

$$(CH_3)_3COOH + RR'CO \rightleftharpoons (CH_3)_3COOCOH \quad (1)$$
(R above, R′ below)

$$(CH_3)_3COOCOH + (CH_3)_3COOH \rightleftharpoons ((CH_3)_3COO)_2CRR' + H_2O \quad (2)$$
(R above, R′ below)

where R and R′ may be organic radicals or hydrogen.

Reaction 1 is exemplified by formaldehyde and chloral in which cases reaction 2 apparently is of little or no consequence. Rieche[1] mentions the reaction of alkyl hydroperoxides with aldehydes to form hydroxydialkyl peroxides (monoperoxides). However, the ketones investigated in the present work all form liquid bis-(*t*-butylperoxy)-alkanes, as does benzaldehyde.

## Experimental

**Reactants.**—The *t*-butyl hydroperoxide was a commercial product which was purified by steam distillation. After the low boiling fractions had been removed and the distilling temperature had reached 92–93°, the kettle contents were cooled and the phases separated. The upper, hydroperoxide phase, after drying with sodium sulfate, analyzed 78–82%. The ketones and aldehydes were all

(1) Rieche, "Alkylperoxyde und Ozonide," Theodor Steinkopf, Dresden, 1931.

Table I

*t*-Butyl Hydroperoxide Derivatives of Carbonylic Compounds

| Peroxide $\beta$ = (*t*-butylperoxy) | Derivative of | $n^{20}D$ | %C Found | %C Theory | %H Found | %H Theory | % Active O[d] Found | % Active O[d] Theory | Mol. wt. Found | Mol. wt. Theory | Conversion of hydroper. % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2,2-bis-($\beta$)-propane | Acetone | 1.4098 | 59.6 | 59.9 | 11.1 | 11.0 | 14.6 | 14.5 | 220 | 220 | 90 |
| 2,2-bis-($\beta$)-butane | Methyl ethyl ketone | 1.4140 | 61.1 | 61.5 | 11.2 | 11.2 | 13.9 | 13.7 | 232 | 234 | 85 |
| 2,2-bis-($\beta$)-pentane | Methyl propyl ketone | 1.4168 | 62.6 | 62.9 | 11.4 | 11.4 | 13.2 | 12.9 | 266 | 248 | 83 |
| 3,3-bis-($\beta$)-pentane | Diethyl ketone | 1.4155 | 62.4 | 62.9 | 11.4 | 11.4 | 12.6 | 12.9 | 245 | 248 | 79 |
| 2,2-bis-($\beta$)-4-methyl-pentane | Methyl isobutyl ketone | 1.4200 | 64.2 | 64.1 | 11.5 | 11.5 | 12.2 | 12.2 | 258 | 262 | 74 |
| 1,1-bis-($\beta$)-cyclohexane | Cyclohexanone | 1.4420 | 64.4 | 64.6 | 11.2 | 10.8 | 11.6 | 12.3 | 259 | 260 | 88 |
| bis-($\beta$)-phenylmethane | Benzaldehyde | 1.5770 | 67.5 | 67.1 | 9.0 | 9.0 | 11.8 | 11.9 | 252 | 268 | 95 |
| I | Formaldehyde | 1.4128 | 51.5 | 50.0 | 10.9 | 10.0 | 13.3 | 13.3 | 120 | 120 | 85 |
| II | Chloral | 50–51[a] | 44.7[b] | 44.7[b] | 0.47[c] | 0.44[c] | 6.7 | 6.7 | 246 | 238 | 90 |

[a] M. p., °C. [b] %Cl. [c] Acetyl value, eq./100 g. [d] See text "Analytical-Total Peroxide." I = *t*-butyl hydroxymethyl peroxide. II = *t*-butyl $\alpha$-hydroxy-$\beta,\beta,\beta$-trichloroethyl peroxide.

commercial products which were purified when necessary by careful fractionation.

**bis-(*t*-Butylperoxy)-alkanes.**[2]—The bis-(*t*-butylperoxy)-alkanes were prepared by treating 0.67 mole of the carbonyl compound with 0.133 mole of *t*-butyl hydroperoxide (78–82%) at room temperature in the presence of concentrated hydrochloric aid (0.1 ml.) as the catalyst. In each case 15 g. of boric anhydride was used to dry the mixture and take up the water of reaction. Each mixture was allowed to stand for about one month after which it was analyzed in accordance with the procedure described in the following section. High yields of the acetone and methyl ethyl ketone derivatives have been obtained in periods of time as short as a few hours.

Isolation of the pure compounds from reaction mixtures in the cases of acetone and methyl ethyl ketone can be easily accomplished by simply extracting the unreacted starting materials with water. In these instances the yields of the isolated products approach the conversions indicated by the analytical method, 80% in the case of acetone and 75% in the case of methyl ethyl ketone (see Table I). However, with the higher carbonylic compounds, water extraction is not satisfactory because of their limited solubility. In the present work, these derivatives were isolated for determination of physical constants and analysis by repeated extraction of the reaction mixture with aqueous 50% ethyl alcohol; this procedure obviously removes a major portion of the desired compound because of solubility in the extractant and the yields ranged from *ca.* 15% on input hydroperoxide in the case of benzaldehyde to *ca.* 65% for methyl propyl ketone. A more efficient procedure would be removal of the remaining starting materials by low pressure distillation; the yields would then approach the conversions indicated by the titration analyses. It is emphasized that great care should be exercised in such operation as it is known[3] that heat will cause these compounds to decompose, in some cases with explosive violence.

***t*-Butyl Hydroxymethyl Peroxide.**[4]—Two hundred eighty grams (2.4 moles) of 78% *t*-butyl hydroperoxide was gradually stirred into 200 g. of 36–38% formalin solution (2.4 moles) at room temperature and the product then vacuum distilled. The peroxide came over at 52–53° at 8–9 mm. A yield of 65.5%, 188 g., was obtained.

***t*-Butyl $\alpha$-Hydroxy-$\beta,\beta,\beta$-trichloroethyl Peroxide.**—Chloral (0.1 mole, 15 g.) was introduced a few drops at a time into a cooled (0°) solution of *t*-butyl hydroperoxide (0.2 mole) in 75 ml. of hexane. A small amount of calcium chloride was included in the mixture to remove the water. Reaction time was one hour, after which the calcium chloride was filtered off. The peroxide crystallized out when the hexane solution was cooled to −40°. The yield was 8.2 g., 27%.

### Analytical

**Total Peroxide.**—A 1.0-ml. sample of the reaction mixture was added to 10 ml. of acetic acid and *ca.* 2 g. of solid potassium iodide. The solution was heated on the steam-bath under reflux for twenty minutes, cooled and the free iodine titrated with thiosulfate.

***t*-Butyl Hydroperoxide.**—A 1.0-ml. sample of the product was added to a solution containing 50 ml. of isopropyl alcohol, 2 ml. of acetic acid and 2 ml. of saturated potassium iodide solution. The mixture was heated to boiling for two minutes, cooled and the liberated iodine titrated.

**bis-(*t*-Butylperoxy)-alkanes.**—The difference between the total peroxide value and the hydroperoxide value is taken as the bis-(*t*-butylperoxy)-alkane. Control experiments have shown that 97–99% of the hydroperoxide present is determinable by the above procedure. There is also some participation by the carbonyl derivatives in the analysis for copresent hydroperoxide, which may vary from as high as 6–7% in the case of the acetone derivative to 1% or less for the cyclohexanone derivative. The conversions of *t*-butyl hydroperoxide to the bis-(*t*-butylperoxy)-alkanes given in Table I are, therefore, subject to these limitations of accuracy.

## Results and Discussion

Some new diperoxy compounds derived from *t*-butyl hydroperoxide and ketones are listed in Table I, together with analytical data obtained on the purified products. Also included are data on the diperoxy derivative of benzaldehyde and on the monoperoxy compounds obtained from formaldehyde and chloral. All except the solid chloral derivative are clear, colorless liquids with mild, pleasant odors. They show excellent potentialities as polymerization catalysts and the methyl ethyl ketone derivative in particular is highly effective in the polymerization of allyl esters.[3]

When 2,2-bis-(*t*-butylperoxy)-butane was decomposed[5] in cumene at 110°, 92% of the *t*-butoxy radicals was accounted for as *t*-butyl alcohol and at least 82% of the reacted cumene was found as dicumyl. This is related to the corre-

(2) Dickey, U. S. Patent No. 2,455,569 (Dec. 7, 1948).

(3) Unpublished data from these laboratories.

(4) Dickey, U. S. Patent No. 2,400,041 (May 7, 1946).

(5) This work will be presented in the future.

sponding decomposition of *di-t*-butyl peroxide[6] and is an indication of the structure of the molecule as a perketal. Likewise, the observation that equations (1) and (2) are reversible—the pure peroxide can be hydrolyzed by acid to the original hydroperoxide and ketone—is pertinent.

(6) Raley, Rust and Vaughan, THIS JOURNAL, **70**, 1336 (1948).


## Summary

A series of new liquid peroxides derived from reaction of aldehydes and ketones with *t*-butyl hydroperoxide is presented together with methods of synthesis.


EMERYVILLE 8, CALIFORNIA RECEIVED[7] JANUARY 6, 1949

(7) Original manuscript received April 12, 1948.

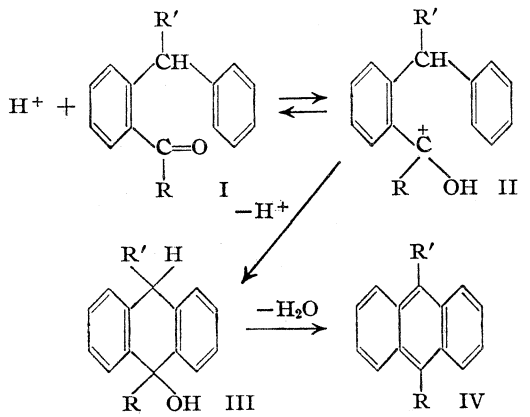
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

# Aromatic Cyclodehydration. XXII.[1] The Mechanism of the Cyclization of *o*-Benzylphenones. III

BY CHARLES K. BRADSHER AND FRANK A. VINGIELLO[2]

In acid media, *o*-benzylphenones (I) may be cyclized to yield anthracene hydrocarbons[3,4,5] (IV). Berliner[5] has found (where R′ = $CH_3$) that the




rate of cyclization decreases with increasing length of group R until *n*-butyl is reached, and remains approximately the same for *n*-pentyl and *n*-hexyl.

This was explained in terms of an increasing order of electron release with increase in size of the alkyl group[6] up to butyl, resulting in an increase in electron density on the positive central carbon atom, thus making the substitution reaction more difficult.

The present investigation was undertaken to determine (1) whether a similar difference in cyclization rates exists in the series in which R′ = H, (2) the effect on the cyclization rate when the inductive effect is varied, while steric factors are kept essentially constant and (3) the effect of varying R′ while R remains constant.

The procedure used in our rate studies differs from that employed by Berliner in that the reaction mixture was not refluxed, but heated in a thermostat in glass-stoppered tubes, and the weight of product isolated was corrected to allow for solubility in the cyclizing medium.[7]

TABLE I

RATES OF CYCLIZATION OF SOME *o*-BENZYLPHENONES (I)[a]

| R | $K$, (hr.$^{-1}$) × $10^{-2}$ |
|---|---|
| H | 540 |
| $CH_3$ | 70 |
| $C_2H_5$ | 30 |
| $C_6H_5CH_2$ | 23 |
| *p*-$CH_3C_6H_4$ | 4.2 |
| *p*-$BrC_6H_4$ | 4.2 |
| *p*-$ClC_6H_4$ | 4.1 |
| *p*-$FC_6H_4$ | 2.8 |
| $C_6H_5$ | 4.4 |
| $C_6H_5$ (R′ = $CH_3$) | 13 |
| $C_6H_5$ (R′ = $C_6H_5$) | 13 |

[a] R′ = H unless otherwise noted.

Like Berliner,[5] we have found the rate of cyclization to be of first order with respect to ketone concentration, and, as he has pointed out, the earlier statement by one of us and Smith that "the rate of cyclization of *o*-benzylphenones is roughly independent of the nature of the R group" is erroneous.[8]

In addition to the ketones mentioned, we have measured the rate of cyclization of *o*-benzylbenzaldehyde[9] (I, R = H; R′ = H). Under the conditions we have used, the rate of formation of anthracene was so great as to make accurate timing difficult.

The comparison of the rates shown by the *para*-substituted phenyl ketones (R′ = H; R = *p*-$XC_6H_4$) affords a test of the relative importance

(1) For the preceding communication of this series see *J. Org. Chem.*, **13**, 786 (1948).

(2) Present address: Virginia Polytechnic Institute, Blacksburg Va.

(3) Bradsher, THIS JOURNAL, **62**, 486 (1940).

(4) Bradsher and Smith, *ibid.*, **65**, 451 (1943).

(5) Berliner, *ibid.*, **66**, 533 (1944).

(6) Berliner has been careful to emphasize that equally plausible explanations might be obtained from purely stereochemical considerations.

(7) While the solubility of the aryl anthracenes was small, that of the methyl- and ethylanthracenes was large enough to make errors in the solubility determination a significant source of error in the final rate.

(8) This statement, for which the senior author accepts full responsibility, was based upon only a few yields obtained under conditions which were not comparable.

(9) The cyclization of this compound was first observed by Bergmann, *J. Org. Chem.*, **4**, 1 (1939).

TABLE II

NEW KETONES (I) AND ANTHRACENE DERIVATIVES (IV) (R′=H)

| R | M. p., °C. | Formula | Analyses, % Calcd. | | Found | |
|---|---|---|---|---|---|---|
| | | I | | | | |
| 4-$FC_6H_4$ | 50–51[a] | $C_{20}H_{15}OF$ | F, 6.6 | | 6.6[b] | |
| 4-$CH_3C_6H_4$ | 68.5–69 | $C_{21}H_{18}O$ | C, 88.08 | H, 6.33 | 88.18 | 6.27[c] |
| $C_6H_5CH_2$ | B. p. (3 mm.) 209–211 | $C_{21}H_{18}O$ | C, 88.08 | H, 6.33 | 87.74 | 6.28[d] |
| | | IV | | | | |
| 4-$ClC_6H_4$ | 179–180 | $C_{20}H_{13}Cl$ | C, 83.19 | H, 4.53 | 82.72 | 4.53[c] |
| 4-$FC_6H_4$ | 168.5–169.5 | $C_{20}H_{13}F$ | F, 7.0 | | 7.0[b] | |
| 4-$CH_3C_6H_4$ | 145–145.5 | $C_{21}H_{16}$ | C, 93.99 | H, 6.01 | 93.98 | 6.33[c] |

[a] All solids were crystallized from ethanol except the fluoro ketone which was crystallized from petroleum ether. [b] Fluorine analyses by Mrs. A. R. Gilbert. [c] Analyses by Oakwold Laboratories. [d] Analysis by Micro-Tech. Laboratories.

of steric factors and of the electron-release of substituent groups, in that here the size of the groups may be considered as closely comparable. It is interesting to note that with the exception of the *p*-fluorophenyl ketone the *para*-substituted phenyl ketones, within the limits of probable experimental error, give the same rate as the parent phenyl ketone.

The significance of the lower rate shown by the fluorophenyl ketone is not clear, for the decreasing order of the electron release of the various substituent groups, as indicated by the ionization of the *para*-substituted benzoic acids[10] appears to be $CH_3>H>F>Cl>Br$.

The similarity in cyclization rates shown by the other four phenyl ketones (I, R′ = H; R = *p*-$XC_6H_4$) should not lead to the conclusion that inductive effects are absent. It is probable that a decrease in the effective positive character of the central carbon atom of the conjugate acid (II) would lead to a lower rate of cyclization of that acid (II → IV).

The dependence of the rate of the over-all reaction (I → IV) upon hydrogen ion concentration[5] makes it clear that this rate depends upon the position of the equilibrium I ⇄ II. It seems probable that an increase in the electron density at the carbonyl group of the ketone (I) must increase the proportion of conjugate acid present at equilibrium,[11] and in this way act to *hasten* the over-all reaction. Since the relative magnitude of these two opposing effects cannot be determined, it is not possible to predict even the direction of the change in rate which would be expected for a given substitution.

The introduction of either a methyl[5] or phenyl group at R′ (R = $C_6H_5$) was found to lead to an increase in rate. In both cases this may be due to an increase in electron density at the *ortho* position at which cylization takes place, although it should be noted that where R′ = $C_6H_5$ there are four such positions with a corresponding increase in the probability of reaction.

(10) Watson, "Modern Theories of Organic Chemistry," Oxford, 1941, pp. 98–103.

(11) F. O. Rice, "The Mechanism of Homogeneous Organic Reactions," The Chemical Catalog Company, Reinhold Publ. Corp., New York, N. Y., 1928, p. 52.

In conclusion, it might be said that, for similar experimental conditions, the rate of cyclization of *o*-benzylphenones depends upon several factors, the most important of which appear to be: (1) the steric nature of R and perhaps also of R′, (2) the position of the equilibrium between ketone and conjugated acid (I ⇄ II), (3) the effective positive character of the central carbon atom of the conjugate acid, (4) the electron density at the *ortho* position of the benzene ring into which cyclization takes place and (5) the number of such positions available.

## Experimental

**Apparatus.**—The constant temperature unit consisted of a large upright metal cylinder insulated with asbestos and provided with a reflux condenser. Attached to the upper plate of the cylinder, and extending downward within it were several heating wells made of metal pipe, about 21 mm. in internal diameter and 29 cm. in length, sealed at the lower end. When *n*-butyl alcohol was refluxed in the cylinder, a constant temperature of 117.5° was maintained in the wells.

The reaction tubes consisted of Pyrex test-tubes of about 18 mm. internal diameter and about 40 ml. capacity. Each had at the upper end, a 24/40 joint provided with two glass hooks and was closed with a glass stopper similarly equipped. The reaction tubes fitted closely in the heating wells which contained mineral oil for more effective transfer of heat.

**Materials.**—The liquid ketones used in the rate studies were carefully fractionated and showed a boiling range of one degree or less. The solid ketones were carefully recrystallized to constant melting point and dried under reduced pressure.

The acid cyclizing medium was prepared as a stock solution by adding 166.4 ml. of 48% hydrobromic acid to 43.6 ml. of distilled water and 700 ml. of glacial acetic acid.

**Cyclization Procedure.**—Into a reaction tube were placed 200–500 mg. of the ketone and 20 or 30 ml.[12] of the stock cyclizing reagent. The time was recorded and the tube heated over a free flame with shaking for about forty-five seconds, during which time the ketone dissolved, and the solution came to a slow boil. The tube was quickly stoppered (secured by means of rubber bands) and inserted into one of the wells of the constant temperature cylinder kept at 117.5°. At the end of an appropriate period,[13] the mixture was cooled, crystallization induced, and the mixture allowed to stand for five hours at approximately 15°. At the end of this period, the crystals were transferred quantitatively to a weighed sintered glass funnel,

(12) The larger volume was used when the more insoluble ketones were being cyclized.

(13) At least four and frequently five or six different time intervals were used for each compound.

washed with 10 ml. of cold water, and dried to constant weight in a vacuum desiccator. The product was weighed and, in each instance, the melting point was determined.

The solubility of each of the anthracene derivatives was determined by putting a weighed quantity through the same procedure used in the cyclization, and determining the dissolved portion by difference. The solubilities varied from 195 mg. (20 ml.) for 9-ethylanthracene to 2 mg. (30 ml.) for 9,10-diphenylanthracene.

**Preparation of Ketones.**—All but three of the ketones employed in this study have been described previously. These three were prepared from *o*-benzylbenzonitrile[9,3] by the action of the following Grignard reagents in the following yields: *p*-fluorophenylmagnesium bromide (77%); *p*-tolylmagnesium bromide (38%); benzylmagnesium chloride (72%). Further details concerning these ketones and the new anthracene derivatives can be found in Table II.

## Summary

The rates of cyclization of ten ketones and one aldehyde have been measured at 117.5°. The data suggest that steric factors as well as electronic effects may play an important part in determining the rate of cyclization.

DURHAM, N. C. RECEIVED NOVEMBER 1, 1948

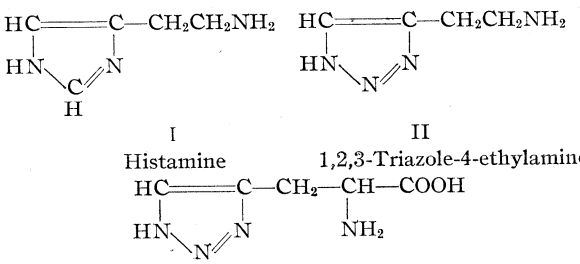
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[MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY]

# The Synthesis of Triazole Analogs of Histamine and Related Compounds

BY JOHN C. SHEEHAN AND CHARLES A. ROBINSON[1]

The concept of metabolite antagonism[2] has proved to be an especially profitable starting point for the synthesis of biologically active compounds. It is generally believed that close structural similarity is desirable in fashioning molecules as possible metabolite antagonists. Many of the powerful known antagonists differ only slightly in structure; for example, riboflavin and chloroflavin, thiamine and pyrithiamine, and adenine and benzimidazole. For this reason it seemed strange that in the case of antagonists to histamine, compounds with close structural similarity have been generally neglected in the wide search for antihistaminics. Since the triazole ring has been shown to be antagonistic to the imidazole ring in the cases of the triazole analogs of adenine and guanine,[3] the triazole analogs of histamine and histidine were synthesized.



I Histamine

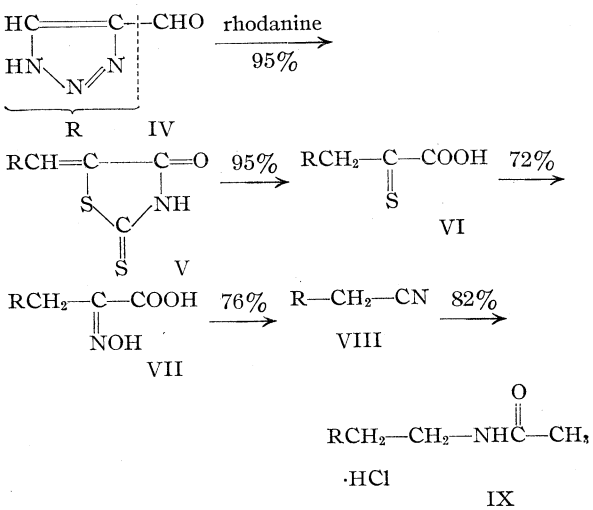
II 1,2,3-Triazole-4-ethylamine

III

α-Amino-1,2,3-triazole-4-propionic acid

The starting compound for the syntheses was 1,2,3-triazole-4-carboxaldehyde (IV), previously prepared by Hüttel[4] from propiolaldehyde and hydrazoic acid. Although the preparation of propiolaldehyde diethyl acetal from acrolein has been reported previously,[5] considerable difficulty was encountered until the modified procedure described in the Experimental Section was used. Extraction of the propiolaldehyde diethyl acetal with chloroform avoids the difficult separation of the azeotrope of this product and ethanol since chloroform does not extract ethanol from the aqueous solution. With this and other improvements a markedly higher over-all yield (50%) was obtained. The diethyl acetal was hydrolyzed and converted into 1,2,3-triazole-4-carboxaldehyde in 50% yield without isolation of the propiolaldehyde.

The synthesis of the nitrile (VIII) was accomplished by the rhodanine method,[6] analogous to the excellent procedure of Julian and Sturgis.[7]



R IV

V

VI

VII

VIII

IX

(1) Bristol Laboratories Fellow, 1947–1948.

(2) For reviews of metabolite antagonism, see R. O. Roblin, Jr., *Chem. Rev.*, **38**, 255 (1946), and D. W. Woolley, "Currents in Biochemical Research," edited by D. E. Green, Interscience Publishers, Inc., New York, N. Y., 1946, p. 357.

(3) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(4) R. Hüttel, *Ber.*, **74B**, 1680 (1941). Hüttel represented the triazole aldehyde as a 2,1,3-triazole. In order to show its relationship to histamine more clearly, we have chosen to use the tautomeric 1,2 3-triazole structure as in formula IV.

(5) L. Claisen, *Ber.*, **31**, 1010 (1898); **31**, 1021 (1898); **36**, 3664 (1903); **40**, 3907 (1907); F. Reitzenstein and G. Bönitsch, *J. prakt. Chem.*, **86**, 34 (1912); M. Grard, *Ann. chim.*, **13**, 337 (1930).

(6) C. Granacher, *et al.*, *Helv. Chim. Acta*, **5**, 610 (1922); **6**, 458 (1923).

(7) P. L. Julian and B. M. Sturgis, THIS JOURNAL, **57**, 1126 (1935).

The rhodanine compound (V), prepared in 95% yield, was hydrolyzed to VI in 95% yield. On treatment with hydroxylamine this crude thioketo acid was converted into the oximino acid (VII) in 72% yield. Only one isomer of the oxime was isolated.

Recrystallization of the oxime gave an 88% recovery of analytically pure product. Decarboxylation and dehydration of VII by heating in acetic anhydride led to the recrystallized nitrile (VIII) in 76% yield regardless of whether crude or recrystallized oxime was used. In this reaction of acetic anhydride on VII, a by-product was detected by its brilliant blue ferric chloride test and was isolated in 1.5% yield by virtue of its water insolubility. Analysis indicates that this by-product is an acetyl derivative of the nitrile (VIII).

The nitrile (VIII) was hydrogenated by the general method of Carothers and Jones,[8] using acetic anhydride as a solvent with platinum oxide catalyst to yield the acetylated amine. The absorption of hydrogen stopped at the theoretical amount, indicating no tendency to hydrogenate the triazole ring under these conditions. The difficult purification of the acetylated amine as the base can be avoided by isolation of the pure hydrochloride (IX) in 82% yield. Hydrolysis of either the base or its hydrochloride (IX) to pure, crystalline 1,2,3-triazole-4-ethylamine dihydrochloride was quantitative. The free base (II) was obtained from the dihydrochloride by treatment with sodium ethoxide in ethanol. The amine dihydrochloride was reconverted into the acetylated amine by the Schotten–Baumann procedure using acetic anhydride, and the product was isolated as the pure hydrochloride (IX) in 76% yield.

N-Isopropyl-1,2,3-triazole-4-ethylamine was prepared in 82% yield from the amine (II) and acetone by a reductive alkylation procedure based on that of Hancock and Cope.[9]

N-Isopropylhistamine was prepared from histamine by the same reductive alkylation procedure. Since the base did not crystallize, it was converted into the pure dihydrochloride in 84% over-all yield. Due to the necessity for complete absence of histamine, the pharmacological sample was tested for primary amine using the sensitive nickel chloride and 5-nitrosalicylaldehyde test.[10] A negative test was obtained, whereas histamine produced a strong test.

A brief, slight blocking action against the arterial blood pressure response (dog) to histamine was observed with 1,2,3-triazole-4-ethylamine; the N-isopropyl derivative had no activity. N-Isopropylhistamine gave a typical histamine response, but it was only about $^1/_{30}$ as active as the parent compound.[11]

(8) W. H. Carothers and G. A. Jones, THIS JOURNAL, **47**, 3051 (1925).

(9) E. M. Hancock and A. C. Cope, "Organic Syntheses," Vol. 26, edited by H. Adkins, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 38.

(10) F. R. Duke, *Ind. Eng. Chem., Anal. Ed.*, **17**, 196 (1945).

(11) The pharmacological testing was done by Dr. Leo Dickinson and Mr. Justin Hoekstra of Bristol Laboratories, Syracuse, N. Y.

DL-α-Amino-1,2,3-triazole-4-propionic acid (III) was prepared by two independent routes. The catalytic hydrogenation of the oximino acid (VII) was extremely slow and the yield of the amino acid was small (17%). As an unambiguous method, the synthesis was also accomplished through the azlactone.

From 1,2,3-triazole-4-carboxaldehyde (IV), the crude azlactone was obtained (52%) as a mixture of a ring-acetylated azlactone and a small amount of the non-acetylated form which was separated through its insolubility in chloroform. The latter compound was readily converted into the former by acetylation. Purified samples of both forms gave α-benzamido-1,2,3-triazole-4-acrylic acid dihydrate on hydrolysis (86–88%). The yield of the acrylic acid dihydrate from the crude mixture of azlactones was 85%. α-Benzamido-1,2,3-triazole-4-propionic acid was obtained in 61% yield by hydrogenation of the acrylic acid in glacial acetic acid using platinum oxide. Hydrolysis of this benzamido acid gave analytically pure DL-α-amino-1,2,3-triazole-4-propionic acid (III) in 51% yield; this compound had the same decomposition point and the same properties as the product from the hydrogenation of VII.

## Experimental[12]

**Propiolaldehyde Diethyl Acetal.**—α,β-Dibromopropionaldehyde diethyl acetal was prepared in 79% yield from acrolein following essentially the procedure of Grard[5] except that the crude α,β-dibromopropionaldehyde was used without distillation while the diethyl acetal was distilled at 108–110° (10 mm.) before the next step.

To a solution of 35 g. (0.625 mole) of potassium hydroxide pellets in 240 ml. of absolute ethanol was added in a thin stream with good stirring 72.5 g. (0.250 mole) of α,β-dibromopropionaldehyde diethyl acetal, allowing the temperature to rise to 50–55°. After cooling to 10°, the potassium bromide was removed by filtration and washed well with 40 ml. of absolute ethanol. The dried potassium bromide amounted to 30 g. (100% of theory for one molecular equivalent). The combined filtrate and washes was refluxed for two and one-half hours. After cooling to 20°, the pale yellow solution containing crystallized potassium bromide was poured into 2 l. of water and extracted three times with 235 ml. of chloroform. The extracts were washed twice with 20 ml. of water and dried over anhydrous magnesium sulfate.

After removal of chloroform by distillation through a short Vigreux column at atmospheric pressure, the residue was fractionated using an eighteen-inch Fenske column. The fraction distilling at 138–139.5° amounted to 20.3 g. (63%) and remained colorless on storing at 5°. Grard[5] reported a boiling point of 137–141°.

**1,2,3-Triazole-4-carboxaldehyde (IV).**[13]—A mixture of 32.7 g. (0.255 mole) of propiolaldehyde diethyl acetal and 50 ml. of 0.2 *N* sulfuric acid containing 100 mg. of hydroquinone was heated on a steam-bath under a reflux condenser with frequent shaking. The two-phase mixture gradually became homogeneous. Reflux was continued until the solution remained homogeneous on cooling to 15°; a total of forty-five minutes heating was required. After cooling, 16 g. of ammonium sulfate was added and the red oil was separated. The aqueous layer was extracted with 40 ml. of ether and the combined oil

(12) All melting points are corrected.

(13) Due to a marked tendency for polymerization of the propiolaldehyde, sufficient time must be available to complete this step without interruption.

and extracts was dried over anhydrous sodium sulfate for thirty minutes.

After removing the desiccant the propiolaldehyde–ether–ethanol mixture was distilled until the vapor reached 75°. Additional product remaining in the high-boiling residue was removed by twice adding anhydrous ether and again distilling to 80°. The total distillate was immediately added to 0.19 mole of a titrated hydrazoic acid–ether solution prepared by method B of Audrieth and Gibbs.[14] Heat of reaction caused gentle reflux, after which the solution was allowed to stand at room temperature overnight. The solvent and excess hydrazoic acid were removed by cautious distillation, leaving a colorless crystalline product which amounted to 12.5 g. (50%) after thorough drying; m. p. 141–142°. Hüttel[4] reported a melting point of 141–142° for this compound.

**5-(1,2,3-Triazolyl-4-methylene)-rhodanine (V).**—To a hot solution of 23.3 g. (0.240 mole) of 1,2,3-triazole-4-carboxaldehyde and 32.0 g. (0.240 mole) of rhodanine in 210 ml. of glacial acetic acid, 59.8 g. of freshly fused sodium acetate was added. With frequent shaking, the mixture was refluxed for twenty minutes during which time a bright yellow product separated. After cooling and slurrying with 700 ml. of water, the product was removed by filtration and washed well with water, then with acetone until the filtrate was clear, and finally with ether. The dried product weighed 48.5 g. (95%) and did not melt below 300°. This compound is insoluble in all common organic solvents. An analytical sample was prepared by solution in 0.2 *N* ammonium hydroxide followed by acidification to give yellow needles.

*Anal.* Calcd. for $C_6H_4N_4OS_2$: C, 33.95; H, 1.90; N, 26.40. Found: C, 33.69; H, 2.09; N, 26.48.

**1,2,3-Triazole-4-thiopyruvic Acid (VI).**—A solution of 48.5 g. (0.228 mole) of the crude triazole–rhodanine compound (V) in 238 ml. of 15% sodium hydroxide solution was heated on a steam-bath at 88–92° for twenty minutes with occasional shaking. The chilled solution was added in a thin stream with rapid stirring to an excess of 2.5 *N* hydrochloric acid (368 ml.), maintaining the temperature below 10°. After being stirred for one-half hour in an ice-bath, the cream-colored product was collected, washed with ice-water, and carefully dried at slightly above room temperature. The yield of material decomposing at 157° with gas evolution was 37.1 g. (95%). This product was non-crystalline and has not been further purified. With ferric chloride it gave a brilliant green coloration.

**1,2,3-Triazole-4-pyruvic Acid Oxime (VII).**—Hydroxylamine was prepared by dissolving 20.8 g. (0.30 mole) of hydroxylamine hydrochloride in 18.4 ml. of warm water and adding sodium ethoxide solution prepared from 6.88 g. (0.30 mole) of sodium in 200 ml. of ethanol. The sodium chloride was removed by filtration and washed with 22 ml. of ethanol. To this solution 17.1 g. (0.10 mole) of the crude thioketo acid (VI) was added and the solution was refluxed gently for twenty minutes; at the end of this time the evolution of hydrogen sulfide had ceased. After removing the solvent under reduced pressure, the residual thick sirup was dissolved in 86 ml. of 5% sodium hydroxide solution, filtered and acidified to *p*H 1 with 2.5 *N* hydrochloric acid; on scratching an immediate crystallization began. After allowing several hours for crystallization, the pale yellow crystals were removed by filtration, washed with ice-water, and dried at 55°. The product decomposing at 168° with gas evolution amounted to 12.2 g. (72%).

Recrystallization of a sample of this material from twelve volumes of hot water gave glistening pale yellow flakes in 88% recovery, m. p. 169° with decomposition.

*Anal.* Calcd. for $C_5H_6N_4O_3$: C, 35.30; H, 3.56; N, 32.93. Found: C, 35.41; H, 3.76; N, 32.82.

This compound is slightly soluble in ethanol and nearly insoluble in acetone, ether, benzene or cold water.

(14) L. F. Audrieth and C. F. Gibbs, "Inorganic Syntheses," Vol. I, edited by H. S. Booth, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 77.

**1,2,3-Triazole-4-acetonitrile (VIII).**—A suspension of 5.1 g. (0.030 mole) of the crude oximino acid (VII) (finely powdered) in 30 ml. of acetic anhydride was heated to 80–85° in an oil-bath; a vigorous evolution of gas ensued and the heat of reaction occasionally necessitated removing the flask from the bath. After thirty minutes at 80–85°, the material had completely dissolved and gas evolution ceased. The pale orange solution was concentrated under reduced pressure in a 60° bath until no more acetic anhydride distilled. With stirring and cooling to 20°, 2.5 *N* sodium hydroxide solution was added until all the residual acetic anhydride had decomposed; the *p*H was adjusted to 6.

The nitrile was extracted to completion with ether, adjusting the *p*H to 6 as necessary between extractions. The nitrile is incompletely extracted from more basic or more acidic solutions. Removal of ether from the dried extracts left a colorless crystalline mass which was dried to constant weight under reduced pressure, giving a crude yield of 3.1 g. (96%); m. p. 78–85°. The crude product, recrystallized from absolute ethanol–chloroform, gave a recovery of colorless crystals of 2.47 g. (80%) or a yield of 76% including second crops; all crops melted between 89 and 91°. An analytical sample recrystallized from hot benzene was obtained as beautiful colorless needles melting at 91–91.5°.

*Anal.* Calcd. for $C_4H_4N_4$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.79; H, 3.85; N, 52.09.

1,2,3-Triazole-4-acetonitrile is readily soluble in water, ethanol, acetone or ether.

A by-product was isolated from the aqueous mother liquors by adjusting the *p*H to 5 and extracting with ether. The product obtained by evaporating the ether was washed well with cold water to remove traces of the nitrile (VIII) and then dried at 65°. The pale yellow product weighed 0.065 g.; m. p. 212° with evolution of gas. Two recrystallizations from hot water gave a good recovery of tiny, nearly colorless crystals decomposing at 214°.

*Anal.* Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32; mol. wt., 150.14. Found: C, 48.00; H, 4.28; N, 37.67; mol. wt., 144 (Rast).

This acetylated by-product produces a brilliant blue coloration with ferric chloride solution.

**N-Acetyl-1,2,3-triazole-4-ethylamine Hydrochloride (IX).**—A solution of 1.95 g. (0.0180 mole) of the recrystallized nitrile (VIII) in 25 ml. of acetic anhydride was shaken under hydrogen with 0.30 g. of platinum oxide. After nine hours the theoretical amount of hydrogen had been taken up and no more was absorbed on further shaking. After removing the catalyst by filtration, the solution was treated with just sufficient water to decompose the excess acetic anhydride. The pale yellow solution was concentrated to an oil under reduced pressure, and the residue was twice dissolved in absolute ethanol and reconcentrated to dryness.

The hydrochloride was formed by dissolving the oil in 10 ml. of absolute ethanol and adding 6 *N* ethanolic hydrogen chloride in slight excess. On the addition of 40 ml. of absolute ether to the clear solution a colorless product crystallized. The yield of dried material melting with decomposition at 166–166.5° was 2.80 g. (82%). An analytical sample recrystallized from ethanol–acetone was obtained as tiny colorless crystals; m. p. 166–166.5° with decomposition.

*Anal.* Calcd. for $C_6H_{11}N_4OCl$: C, 37.79; H, 5.82; N, 29.39. Found: C, 37.90; H, 5.87; N, 29.58.

**N-Acetyl-1,2,3-triazole-4-ethylamine.**—The nitrile (VIII) (0.54 g., 0.0050 mole) was hydrogenated as described above in the preparation of the hydrochloride (IX). The oil obtained after concentration of the acetic anhydride was dissolved in 5 ml. of water and extracted with 15 ml. of *n*-butanol. The extracts were treated with charcoal and concentrated to a colorless oil under reduced pressure. After dissolving in ethyl acetate and again concentrating, the oil crystallized giving a slightly sticky product. This was dissolved in 35 ml. of hot ethyl ace-

tate and filtered to remove an oily residue; on concentration, 0.63 g. (82%) of crystalline product melting at 65–76° was obtained.

A sample of this crude material was purified by sublimation at 0.002 mm. and 125° (m. p. 76–82°) followed by two recrystallizations from ethyl acetate–ether to give a pure crystalline product melting at 81–82°.

*Anal.* Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.48; H, 6.53; N, 36.34.

This compound is soluble in water, absolute ethanol, acetone and in hot ethyl acetate; it is nearly insoluble in ether or benzene.

**1,2,3-Triazole-4-ethylamine Dihydrochloride.**—Hydrolysis of 2.29 g. (0.0120 mole) of the recrystallized N-acetylamine hydrochloride (IX) was accomplished by reflux with 119 ml. of 2.5 *N* hydrochloric acid for three hours. The colorless solution was concentrated under reduced pressure giving a mass of rosettes. After drying to constant weight, the yield was quantitative (2.22 g.); m. p. 181–182° with decomposition. Recrystallization from absolute methanol–ether gave a 92% recovery (2.03 g.); m. p. 185–186° with decomposition. A second recrystallization failed to alter the melting point.

Hydrolysis of the N-acetylamine base (m. p. 65–76°), in a similar manner, gave a quantitative yield of the dihydrochloride. In this case the product was twice recrystallized from 97% ethanol–acetone giving colorless rosettes, m. p. 179–180° with decomposition.

*Anal.* Calcd. for $C_4H_{10}N_4Cl_2$: C, 25.95; H, 5.45; N, 30.27. Found: C, 25.81; H, 5.47; N, 30.50.

It appears that the melting point of this compound depends on the solvent from which it crystallizes; the higher melting product (185–186°) from methanol–ether on crystallizing again from water gave the lower melting point (181–182°).

**1,2,3-Triazole-4-ethylamine (II).**—A solution of 1.50 g. (0.00810 mole) of 1,2,3-triazole-4-ethylamine dihydrochloride (m. p. 181–182° dec.) in 36 ml. of warm 97% aqueous ethanol was added to a solution of sodium ethoxide prepared from 0.373 g. (0.0162 mole) of sodium in 12 ml. of absolute ethanol. After fifteen minutes at 20°, the crystallized sodium chloride was removed by filtration and washed with absolute ethanol. The colorless filtrate was concentrated under reduced pressure to a crystalline solid weighing 0.96 g. (105%). This crude material was freed from sodium chloride by dissolving in 25 ml. of hot absolute ethanol, removing the inorganic salts by filtration, and evaporating the solvent under reduced pressure. The yield of crystalline, halogen-free product was quantitative (0.91 g.); m. p. 154–155.5°. This product can be further purified by recrystallization from hot absolute ethanol.

An analytical sample was prepared by sublimation of a portion at 0.05 mm. and 100°; m. p. 157.5–159°.

*Anal.* Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 42.50; H, 7.07; N, 50.40.

1,2,3-Triazole-4-ethylamine is soluble in water and in hot absolute ethanol; it is nearly insoluble in ether, acetone, ethyl acetate or chloroform.

**N-Isopropyl-1,2,3-triazole-4-ethylamine.**—In a micro-hydrogenator, 100 mg. of platinum oxide in 5 ml. of absolute ethanol was pre-reduced. Then, 0.628 g. (0.0056 mole) of the crude amine (II) (m.p. 154–155.5°) in 7 ml. of absolute ethanol, 0.52 ml. (0.0071 mole) of acetone, and one drop of water to effect complete solution were added, and the solution was stirred under hydrogen at atmospheric pressure. The rate of hydrogenation dropped sharply when the theoretical amount of hydrogen had been absorbed (3.8 hours). After removal of the catalyst, the filtrate was concentrated to a colorless crystalline solid weighing 0.84 g. (97%); m. p. 136–138°.

Recrystallization from seven volumes of hot absolute ethanol gave a 72% recovery of crystals melting at 142.5–144°. A second recrystallization from methyl ethyl ketone gave beautiful, colorless crystals; m. p. 143–144°.

*Anal.* Calcd. for $C_7H_{14}N_4$: C, 54.52; H, 9.15; N, 36.33. Found: C, 54.58; H, 9.28; N 35.81.

Second crops from the recrystallizations increased the recovery of pure product to 0.707 g. (82%).

This compound is soluble in water, slightly soluble in cold absolute ethanol and soluble in hot acetone; it is nearly insoluble in ether or benzene.

**N-Isopropyl-4-imidazoleëthylamine Dihydrochloride.**—In a micro-hydrogenator, 50 mg. of platinum oxide in 5 ml. of absolute ethanol was pre-reduced. To this, 0.222 g. (0.0020 mole) of histamine (Eastman Kodak Co., Synthetic) in 5 ml. of absolute ethanol and 0.25 ml. (0.0034 mole) of acetone were added, and the solution was stirred under hydrogen at atmospheric pressure. The rate of hydrogenation dropped sharply when the theoretical amount of hydrogen had been absorbed (four hours). After removing the catalyst, the colorless filtrate was concentrated to an oil weighing 0.33 g. (108%).

This free base did not crystallize even after evaporative distillation of a sample at 0.001 mm. and 70° and refrigeration for several weeks. The remainder of the crude base (0.20 g. containing 0.00121 mole) was converted into the dihydrochloride by dissolving in 5 ml. of acetone and adding 6 *N* ethanolic hydrogen chloride in slight excess. After collecting the crystals and drying in a desiccator, the colorless product weighed 0.26 g. (95%); m. p. 185–193°. Recrystallization of 0.25 g. of the crude dihydrochloride from absolute ethanol–ethyl acetate gave a 62% recovery of product melting at 197–198°. From the mother liquors a second crop melting at 195–196° gave a total recovery of 0.220 g. (83% over-all yield).

An analytical sample was prepared by a second recrystallization of the first crop; m. p. 197.5–199°.

*Anal.* Calcd. for $C_8H_{17}N_5Cl_2$: C, 42.48; H, 7.58; N, 18.58. Found: C, 42.58; H, 7.74; N, 18.81.

**Condensation of 1,2,3-Triazole-4-carboxaldehyde with Hippuric Acid.**—A mixture of 4.30 g. (0.024 mole) of hippuric acid, 8.6 ml. of acetic anhydride and one drop of triethylamine was heated rapidly with stirring in a vessel protected from moisture until there was complete solution (110°). To the orange-colored solution cooled to 60°, 1.94 g. (0.020 mole) of 1,2,3-triazole-4-carboxaldehyde and 3.0 ml. of glacial acetic acid were added, and the solution was heated at 60 ± 3° in an oil-bath for two hours. Lemon-yellow needles began to crystallize after thirty-five minutes of heating. After allowing fifteen hours at room temperature for crystallization, the needles were collected, washed with 5 ml. of glacial acetic acid, and dried at 70°. The product amounted to 2.93 g. (52%); m. p. 161–164°.

This crude mixture was washed with boiling water to remove excess hippuric acid and the dried product (2.40 g.) was slurried with 20 ml. of chloroform and the insoluble, non-acetylated azlactone was removed by filtration. The addition of ether to the filtrate gave lemon-yellow crystals (1.63 g.); m. p. 181–182.5°. Further recrystallizations from chloroform–ether gave an analytical sample of the ring-acetylated azlactone of α-benzamido-1,2,3-triazole-4-acrylic acid; m. p. 181.5–182.5°.

*Anal.* Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.42; H, 3.65; N, 20.16.

The chloroform-insoluble fraction from the purification of the ring-acetylated azlactone amounted to 0.250 g. and decomposed at 219°. After three recrystallizations from methanol–water, an analytical sample of the azlactone of α-benzamido-1,2,3-triazole-4-acrylic acid was obtained as pale yellow needles decomposing at 223°.

*Anal.* Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.95; H, 3.59; N, 23.34.

**α-Benzamido-1,2,3-triazole-4-acrylic Acid.**—A suspension of 3.0 g. of the crude mixture of azlactones in 250 ml. of 0.25 *N* sodium hydroxide solution was rapidly heated to boiling. After boiling for a few seconds, the clear solution, cooled in ice, was made strongly acid with 50 ml. of 2.5 *N* hydrochloric acid. Crystallization as tiny cubes began on scratching. After one hour at 0–5° the cream-colored product was removed by filtration, washed with cold water, and dried in a desiccator over Drierite. The product, obtained as the dihydrate, weighed 2.66 g. (85%);

m. p. 187° with decomposition (capillary inserted at 110°). Two recrystallizations from hot water gave colorless crystals which were dried in a desiccator over Drierite; m. p. 189° with decomposition (capillary inserted at 110°).

*Anal.* Calcd. for $C_{12}H_{10}N_4O_3 \cdot 2H_2O$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.01; H, 5.00; N, 19.39.

On drying at 75–85° the dihydrate loses two molecules of water. The dihydrate is soluble in acetone, ethanol or hot water.

DL-α-Benzamido-1,2,3-triazole-4-propionic Acid.—In a micro-hydrogenator, 200 mg. of platinum oxide in 7 ml. of glacial acetic acid was pre-reduced. Then, 0.553 g. (0.00188 mole) of crude α-benzamido-1,2,3-triazole-4-acrylic acid dihydrate and 5 ml. of glacial acetic acid were added, and the solution was stirred under hydrogen at atmospheric pressure. During the hydrogenation an addition of 100 mg. of platinum oxide was made to maintain the rate. When the theoretical amount of hydrogen had been absorbed, the reaction was stopped and the catalyst removed. Concentration of the filtrate under reduced pressure gave an oil which crystallized on adding water. The gray product which was removed by filtration and dried at 65° weighed 0.390 g. (79%); m. p. 206–208° with decomposition.

The crude product (0.39 g.) was recrystallized from 18 ml. of hot water, yielding 0.30 g. (61%) of colorless crystals; m. p. 217.5–218.5° with decomposition. An analytical sample was prepared by a second recrystallization from hot water; m. p. 219–220° with decomposition.

*Anal.* Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.12; H, 4.88; N, 21.24.

This compound is soluble in absolute ethanol and insoluble in ether or acetone.

DL-α-Amino-1,2,3-triazole-4-propionic Acid (III). A. Hydrolysis of the Benzoyl Compound.—Hydrolysis of 0.78 g. (0.0030 mole) of α-benzamido-1,2,3-triazole-4-propionic acid was accomplished by reflux for six hours with 20 ml. of 2.5 *N* hydrochloric acid. After ether extraction and charcoal treatment, the aqueous solution was concentrated under reduced pressure to a colorless oil which was twice dissolved in water and reconcentrated to dryness (wt. 0.56 g., 97%). Aniline was added to a warm solution of the oil in 10 ml. of absolute ethanol until the *p*H was 4–5. After twelve hours at room temperature, the crystalline amino acid was collected, washed with absolute ethanol and ether, giving 0.29 g. (62%) of product decomposing with gas evolution at 260°.

The crude product on recrystallization from water–ethanol gave 0.24 g. (51%) of tiny, colorless crystals decomposing at 266°. A second recrystallization failed to alter the decomposition point.

*Anal.* Calcd. for $C_5H_8N_4O_2$: C, 38.46; H, 5.16; N, 35.88. Found: C, 38.36; H, 5.38; N, 35.71.

This compound is moderately soluble in cold water and soluble in hot; it is insoluble in absolute ethanol or ether.

B. Hydrogenation of VII.—After pre-treatment of 0.460 g. (0.0027 mole) of recrystallized oximino acid (VII) in absolute ethanol with Raney nickel catalyst, 0.0028 mole of ethanolic hydrogen chloride was added and the solution was stirred with 200 mg. of platinum oxide in a micro-hydrogenator under hydrogen at atmospheric pressure. After seven days the theoretical amount of hydrogen had been absorbed. The solution, from which the catalyst had been removed, was concentrated to dryness under reduced pressure, dissolved in water, filtered, and again concentrated to a brittle, tan solid weighing 0.55 g. After recrystallization from ethanol–ethyl acetate and water–acetone, the crystalline hydrochloride amounted to 0.14 g. and decomposed at 219°.

Without further purification, 0.040 g. of the hydrochloride was treated with the calculated amount of dilute ammonium hydroxide and the solution concentrated to dryness under reduced pressure. Solution of the residue in hot water and the addition of two volumes of ethanol produced colorless crystals. After washing with aqueous ethanol (1:1) and drying at 65°, the amino acid decomposed at 266° and weighed 0.020 g. (17% from VII).

## Summary

1,2,3-Triazole-4-ethylamine and DL-α-amino-1,2,3-triazole-4-propionic acid, the triazole analogs of histamine and histidine, as well as N-isopropyl-1,2,3-triazole-4-ethylamine and N-isopropylhistamine have been synthesized for pharmacological study.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

# Quinazolines. VIII. The Synthesis of an Amino Alcohol Derived from 2,4-Quinazolinedione-5-carboxylic Acid[1]

BY C. H. WANG AND BERT E. CHRISTENSEN

Methods for the synthesis of 2,4-dimethylquinazoline derivatives with an acetyl-substituent in the 7- and 8-positions have recently been described.[2,3] The 5-isomer, however, could not be synthesized by these procedures due to the difficulties encountered in the attempted preparation of the necessary intermediate 3-acetamino-1,2-diacetylbenzene or 3-acetamino-2-acetylbenzoic acid required for the cyclization.[4]

Since it would be useful to this Laboratory to have a quinazoline compound with an amino alcohol substituent in the 5-position, the possibility of utilizing the easily prepared 2,4-quinazolinedione-5-carboxylic acid (I) as the starting material (see Fig. 1) was studied. This intermediate was converted to the acyl chloride (II), which upon treatment with diazomethane formed the diazoketone and at the same time was simultaneously methylated in the 1,3-positions to yield 5 - diazoacetyl - 1,3 - dimethyl - 2,4 - quinazolinedione (III). This diazoketone upon treatment with dry hydrogen bromide gas was converted to the bromomethyl ketone (IV); however, one of the methyl substituents (either 1 or 3) was lost in the process.

The bromoacetyl derivative (IV) readily combined with morpholine to yield an aminoketone

(1) The work in this paper was made possible by a grant-in-aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 134, School of Science, Department of Chemistry.

(2) Christensen, Graham and Griffith, THIS JOURNAL, **67**, 2001 (1945).

(3) Isensee and Christensen, *ibid.*, **70**, 4061 (1948).

(4) Wang, Isensee, Griffith and Christensen, *ibid.*, **69**, 1909 (1947).

(V) which was in turn catalytically reduced to the desired amino alcohol (VI).

In order to confirm the simultaneous methylation of the 1,3-positions of (II) during the diazomethane reaction, the starting material (I) was methylated with excess diazomethane. This gave an ester (methyl 1,3-dimethyl-2,4-quinazolinedione-5-carboxylate (VII)), which was identical with that reported both by Scott and Cohen[5] as well as by Lange, Chisholm and Szabo.[6] These investigators had employed dimethyl sulfate as the methylating agent. The ester (VII) was hydrolyzed to the acid (VIII) which upon chlorination with thionyl chloride gave a good yield of 1,3-dimethyl-2,4-quinazolinedione-5-carbonyl chloride (IX). When the acyl chloride (IX) was treated with diazomethane, a diazoketone identical with (III) was produced. These data confirm the earlier observations of the methylation of the 1,3-positions of 2,4-quinazolinedione-5-carbonyl chloride with diazomethane.

Although VII on the basis of mixed melting point tests was identical with the ester prepared by Scott and Cohen, the acid (VIII) obtained by the hydrolysis of VII, was not the same as the 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid reported by these workers.[5,6] Scott and Cohen originally prepared the acid by the direct methylation of I using a limited amount of dimethyl sulfate. In order to confirm the earlier work, the methyl ester (VII) prepared in this Laboratory by the method of Scott and Cohen was hydrolyzed to the free acid. This acid was found to be identical with VIII which was obtained as the hydrolysis product of the ester (VII) (prepared by the diazomethane reaction) and different from the dimethyl acid originally reported by these workers. In order to clarify these results the free acid (X) was again prepared in this Laboratory by the direct methylation procedure of Scott and Cohen; the methylation product was found to be a high melting compound as described by these workers. However, carbon and hydrogen data indicate an incomplete methylation yielding the 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid in place of the 1,3-homolog. Since the earlier deduction had been based on nitrogen analysis only, it is possible that the acid in question was the 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid (X) and not the 1,3-dimethyl homolog as originally reported.

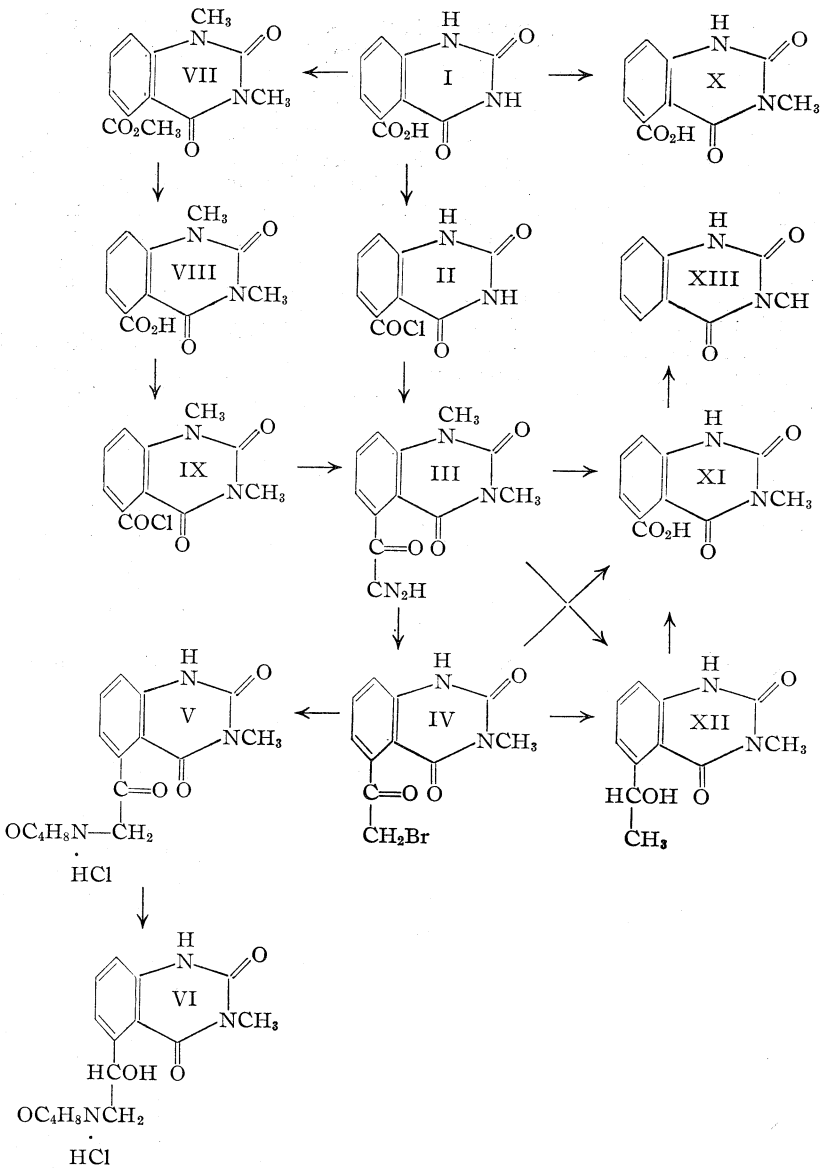



Fig. 1.

Because of the unpredictable ease with which the methyl substituent had been removed during the mild acid treatment of the diazoketone (III), further experiments with III were undertaken. The compound (III) upon oxidation with neutral permanganate again lost a methyl substituent to yield 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid (XI). The loss of a methyl substituent was again observed during reduction

(5) Scott and Cohen, *J. Chem. Soc.*, **119**, 664 (1921).

(6) Lange, Chisholm and Szabo, THIS JOURNAL, **61**, 2170 (1939).

which yields 5-(1-hydroxyethyl-1(or 3)-methyl)-2,4-quinazolinedione (XII). Both the bromomethyl ketone (IV) and the reduction product (XII) after a permanganate oxidation gave acids which on the basis of mixed melting point tests were judged to be identical with XI. From these results, as well as from the analytical data, it was concluded that the same methyl substituent was quantitatively removed during each of the described operations.

The problem of determining the position of the remaining methyl group was approached through decarboxylation experiments. The acid (XI) after removal of the carboxyl group, gave a methyl-2,4-quinazolinedione (XIII) which melted sharply at 198°. This melting point did not agree with 234[7]–237[8]–242°[9] (XIV) reported for the 3-methyl-2,4-quinazolinedione or 147°[8] (XV) or 265°[10] (XVIII) which had been reported for the 1-isomer.

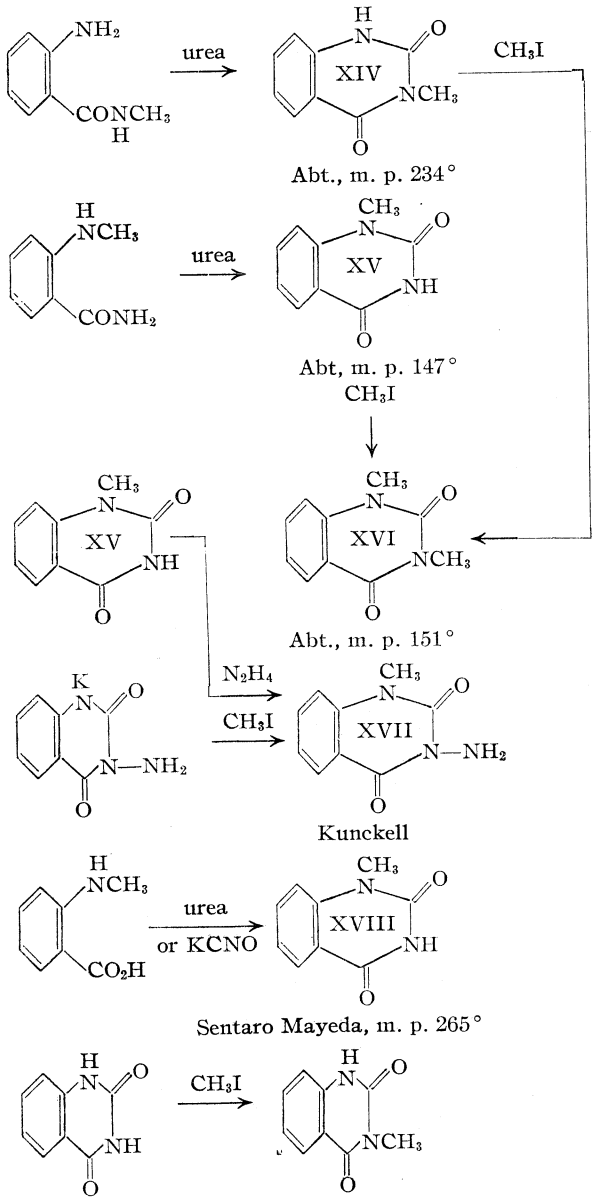



Fig. 2.

A review of the literature reveals that Abt had prepared both the 3- and 1-methyl-2,4-quinazolinediones (XIV) (XV) (m.p.'s 234, 147°) by the cyclization of 2-aminomethylbenzamide and 2-methylaminobenzamide, respectively, with urea (see Fig. 2). Both the 1- and 3-methyl-2,4-quinazolinediones prepared by Abt, after further methylation with methyl iodide, gave an identical known product 1,3-dimethyl-2,4-quinazolinedione (XVI), m.p. 151°.[8] Furthermore, Abt prepared by direct methylation using alkaline methyl iodide, a compound m.p. 147° which he concluded was 1-methyl-2,4-quinazolinedione[8] (XV).

The proof of structure of the 1-methyl isomer m.p. 147° was later confirmed indirectly by the experiments of Kunckell[11] who isolated 3-amino-1-methyl-2,4-quinazolinedione (XVII) as the product of the reaction of the 1-methyl isomer (XV) with hydrazine. The identical compound had previously been obtained by the methylation of the potassium salt of 3-amino-2,4-quinazolinedione, with methyl iodide[11] (see Fig. 2).

On the other hand, Sentaro Mayeda cyclized 2-methylaminobenzoic acid with both urea and potassium cyanate and obtained the same product 1-methyl-2,4-quinazolinedione (XVIII) m.p. 265–266° (see Fig. 2).[10] Confirmation of the existence of (XVIII) m.p. 265–266° was later reported by Seide[12] who prepared this compound by an entirely different series of reactions. Furthermore the experiments of Sentaro Mayeda pertaining to the 1-isomer were confirmed in this Laboratory.

Bogert[7] later reported that the product of the direct methylation of 2,4-quinazolinedione with alkaline methyl iodide was the 3-methyl isomer which he concluded was identical with the 3-methyl-2,4-quinazolinedione (XIV) m.p. 234°, prepared by the cyclization procedures of Abt. Bogert's work has likewise been confirmed in this Laboratory. It is possible that the different results obtained by Bogert and Abt (products m.p. 234° and 147°, respectively) upon direct methylation of 2,4-quinazolinedione may be due to different thermal conditions of the experiments.

In view of the anomalous melting point data, mixed melting point tests were run between each of the following: (1) 3-methyl-2,4-quinazolinedione (XIV), m.p. 242°, prepared by the method of Bogert with a small amount of 1-methyl-2,4-quinazolinedione (XVIII), m.p. 265° prepared by the method of Sentaro Mayeda (also *vice*

(7) Bogert and Scatchard, THIS JOURNAL, **41**, 2062 (1919).
(8) Abt, *J. prakt. Chem.*, [2] **39**, 148 (1889).
(9) Lange and Sheibley, THIS JOURNAL, **55**, 1188 (1933).
(10) Sentaro Mayeda, *C. A.*, **11**, 578 (1916).
(11) Kunckell, *Ber.*, **43**, 1234 (1910).
(12) Seide, *Ann.*, **440**, 331 (1924).

*versa*); (2) compound (XIV) with the decarboxylation product (XIII), m.p. 198°; (3) compounds (XVIII) and (XIII). In each test there was an appreciable lowering of the melting point which proves that XIII could hardly be a mixture of XIV and XVIII.

One must conclude that there is reasonable support for the structures proposed by Abt and Sentaro Mayeda for both the 1- and 3-methyl-2,4-quinazolinediones. The only data which appear questionable are the melting points, which can best be explained on the basis of, (1) multiple melting points; (2) possibility of isomeric mixtures of 1- and 3-methyl-; or (3) the possibility of stereoisomerism. However, the mixed melting point behavior precludes the first two possibilities, leaving only the alternate explanation, namely, the existence of two stereoisomers of both 1- and 3-methyl-2,4-quinazolinediones. A similar type of isomerism has been reported in the alkaloid literature.[13] If such is the case, then the decarboxylation product (XIII) m.p. 198° appears to be the other stereoisomer of 3-methyl-2,4-quinazolinedione, m.p. 242°.

If XIII is not a stereoisomer of 1(or 3)-methyl-2,4-quinazolinedione then the methyl substituent must be in some other position or attached in some other manner. This would change many of the accepted ideas regarding the methylation products of the quinazolones. For this reason, further detailed studies of this interesting phenomenon are being undertaken by this Laboratory.

## Experimental[14]

**5-Diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III).**—2,4-Quinazolinedione-5-carboxylic acid (I) was prepared and converted to the corresponding acid chloride by the method of Lange and co-workers. The addition of a few drops of quinoline to the thionyl chloride, besides materially shortening the time of chlorination, gave a purer product.

Twelve and four-tenths grams (0.0553 mole) of 2,4-quinazolinedione-5-carbonyl chloride (II) was pulverized into a fine powder and added gradually with stirring to 600 ml. of an ice-cold benzene solution of diazomethane prepared from 60 g. of N-nitroso-methylurea (0.40 mole of diazomethane). The reaction took place rather slowly as indicated by the rate of evolution of nitrogen gas. After stirring for six hours, the solution was allowed to warm to room temperature and then left standing overnight. The insoluble residue (0.5 g.) was removed by filtration and the solvent concentrated under reduced pressure to 100 ml. After standing in a refrigerator for two days the crystalline diazoketone was removed. The mother liquor was then evaporated to dryness under reduced pressure and the gummy residue redissolved in warm acetone. An additional amount of the diazoketone was obtained by the addition of ether to the acetone solution. The combined fractions weighed 10.1 g. (80%).

For analysis, a portion of the crude diazoketone was recrystallized twice from acetone yielding hard, colorless cubes which on standing decompose, m. p. 157–159°.

*Anal.* Calcd. for $C_{12}H_{10}O_3N_4$: C, 55.80; H, 3.91; N, 21.70. Found: C, 55.7; H, 3.88; N, 21.7.

The diazoketone was also prepared from 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid (VIII) *via* the acyl chloride in a similar manner. The yield in this instance was only 40%.

**5-Bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV).**—Six grams (0.023 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) was dissolved in 60 ml. of dry chloroform. The solution was cooled with an ice-bath and then treated with a stream of dry hydrogen bromide until the evolution of nitrogen ceased. The precipitated bromomethyl ketone was filtered, washed with ether and dried in a vacuum. Some additional product was obtained by concentration of the mother liquor. The combined yield weighed 6.6 g. (91%). A portion of this product was recrystallized twice from an alcohol–ether mixture to yield white crystals, m. p. 200–201°.

*Anal.* Calcd. for $C_{11}H_9O_3N_2Br$: C, 44.44; H, 3.05; N, 9.43; Br, 26.9. Found: C, 44.8; H, 3.15; N, 9.49; Br, 27.3.

**5-(2-Morpholine-1-oxoethyl)-1(or 3)-methyl-2,4-quinazolinedione Hydrochloride (V).**—Four and five-tenths grams (0.015 mole) of 5-bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) was suspended in 50 ml. of acetone. To this was added dropwise with shaking 2.6 g. (0.030 mole) of redistilled morpholine. The bromomethyl ketone dissolved gradually accompanied by the precipitation of crystalline morpholine hydrobromide. After standing overnight, the morpholine hydrobromide was removed by filtration and the solvent concentrated under reduced pressure to 10 ml. Fifty milliliters of water was added to the concentrate; the precipitated crude amino ketone was filtered, washed thoroughly with water and vacuum dried. The crude product (m. p. 180° dec.) was then dissolved in 20 ml. of absolute ethanol, cooled with an ice-bath and dry hydrogen chloride gas was bubbled into the solution. The hydrochloride of the amino ketone precipitated upon the addition of dry ether in the form of a voluminous precipitate, which was separated from the mother liquor by means of centrifugation. The product (2 g.) after washing twice with dry ether was a hygroscopic white solid decomposing at about 150°.

*Anal.* Calcd. for $C_{15}H_{18}O_4N_3Cl$: N, 12.38; ionizable Cl, 10.44. Found: N, 12.5; ionizable Cl, 10.20.

The monopicrate of the amino ketone was prepared by dissolving a sample of the hydrochloride in water and adding saturated aqueous sodium picrate solution. The precipitate obtained after recrystallization from ethanol–ether mixture was a yellow mass. On heating, it turned brownish in color at about 120° and decomposed at 140°.

*Anal.* Calcd. for $C_{21}H_{20}O_{11}N_6$: C, 47.35; H, 3.80; N, 15.78. Found: C, 47.7; H, 4.03; N, 15.6.

**5-(2-Morpholine-1-hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione Hydrochloride (VI).**—A solution containing 0.56 g. (0.0016 mole) of the amino ketone hydrochloride (V) and 50 ml. of dry methanol was reduced in a low-pressure hydrogenation apparatus at 30 p. s. i. pressure in the presence of 200 mg. of 10% palladium-on-carbon catalyst. After shaking for two hours, the catalyst was removed by filtration and the solution concentrated to 10 ml. The amino alcohol hydrochloride precipitated by the addition of dry ether was separated by centrifuging and yielded 0.30 g. (53%) of a slightly colored, very hygroscopic solid. For analysis, a portion of this product was reprecipitated twice from ethanol with dry ether, yielding a very hygroscopic white mass which decomposed without melting at about 200°.

*Anal.* Calcd. for $C_{15}H_{20}O_4N_3Cl$: N, 12.30; ionizable Cl, 10.38. Found: N, 12.52; Cl, 10.50.

The monopicrate was prepared by adding a saturated aqueous sodium picrate solution to an aqueous solution of the amino alcohol hydrochloride. The product after recrystallization from an alcohol–ether mixture was a yellow solid decomposing at about 150°.

*Anal.* Calcd. for $C_{21}H_{22}O_{11}N_6$: C, 47.17; H, 4.16; N, 15.72. Found: C, 47.6; H, 4.16; N, 15.6.

**1,3-Dimethyl-2,4-quinazolinedione-5-carboxylic Acid (VIII).**—Five grams (0.023 mole) of 2,4-quinazolinedione-

(13) Willstätter, *Ber.*, **29**, 936 (1896); Willstätter and Muller, *ibid.*, **31**, 1202 (1898); Hess, *ibid.*, **52**, 1622 (1919).

(14) All melting points are corrected.

5-carboxylic acid (I) was added in portions with stirring to 200 ml. of an ice-cold ethereal solution of diazomethane prepared from 20 g. of N-nitrosomethylurea (0.13 mole of diazomethane). The reaction appeared to take place rapidly as evidenced by the vigorous evolution of nitrogen gas. After standing at room temperature for six hours, the filtered ethereal solution was evaporated to dryness to yield 4.0 g. (66%) of slightly colored crystals. The crystals were purified by two recrystallizations from ethanol yielding 3.1 g. of colorless product, m. p. 142–143°. This product (VII) was found to be identical with the ester obtained by Lange, Chisholm and Szabo from the complete methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate and sodium hydroxide.

Three grams (0.012 mole) of the ester was hydrolyzed by refluxing with 20 ml. of 20% hydrochloric acid for three hours; toward the end of the hydrolysis, colorless crystals separated out. After standing in the refrigerator overnight, the mixture was separated by filtration giving 2.0 g. (70%) of needles. A portion of this product was recrystallized from ethanol for analysis, m. p. 250–253°.

*Anal.* Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.39; H, 4.31; neut. equiv., 234. Found: C, 56.8; H, 4.50; neut. equiv., 238.

**1,3-Dimethyl-2,4-quinazolinedione-5-carbonyl Chloride (IX).**—One and six-tenths grams (0.072 mole) of 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid (VIII) was refluxed for half an hour with 20 ml. of thionyl chloride containing three drops of quinoline. The resultant clear solution was concentrated to a few ml. and the crystalline acid chloride was removed by filtration, washed with a small amount of dry ether; yield 1.6 g., (95%), m. p. 178–180° with decomposition.

*Anal.* Calcd. for $C_{11}H_9O_3N_2Cl$: Cl, 14.68. Found: Cl, 14.3.

The acyl chloride (IX) upon treatment with diazomethane gave a diazoketone which was judged to be identical with (III) on the basis of mixed melting point tests.

**1-(or 3)-Methyl-2,4-quinazolinedione-5-carboxylic Acid (X).**—Scott and Cohen reported that limited methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate in the presence of sodium hydroxide yields 2,4-dimethoxyquinazoline-5-carboxylic acid. However, Lange, Chisholm and Szabo later claimed that the product was actually 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid. The acid obtained after repeating the work in this Laboratory (after two recrystallizations from ethanol) was a monomethyl acid as shown by the analysis, m. p. 332–333° (uncor.).

*Anal.* Calcd. for $C_{10}H_8O_4N_2$: C, 54.54; H, 3.66; neut. equiv., 220. Found: C, 54.5; H, 3.85; neut. equiv., 221, 222.

**5-(1-Hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione (XII).**—A suspension containing 1 g. (0.0034 mole) of 5-bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) or 0.9 g. (0.0036 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) and 10 ml. of a 10% stannous chloride solution in concentrated hydrochloric acid was heated on a water-bath with stirring for two hours. The resultant clear solution was diluted with 20 ml. of water and, after standing overnight, yielded 0.7 g. (95%), and 0.35 g. (45%) of colorless crystals melting at 212–213°.

*Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 59.97; H, 5.50; N, 12.72. Found: C, 59.8; H, 5.21; N, 12.9.

**1-(or 3)-Methyl-2,4-quinazolinedione-5-carboxylic Acid (XI).**—One gram (0.0039 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) or 1.0 g. (0.0034 mole) of 5-bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) or 0.51 g. (0.0023 mole) of 5-(1-hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione (XII) was suspended in 50 ml. of a water solution containing 1.25 g. (0.008 mole) of potassium permanganate. The mixture was maintained at 80° with stirring for one hour. After removing the precipitated manganese dioxide, the clear, slightly colored solution was carefully acidified with dilute hydrochloric acid. The crystals which formed on cooling were separated, yielding 0.60 g. (66%), 0.40 g. (62%) and 0.14 g. (27%) of product, respectively. A portion of each was purified by decolorizing with carbon and recrystallizing twice from aqueous alcohol, m. p. 230–237° with evolution of gas.

*Anal.* Calcd. for $C_{10}H_8O_4N_2$: C, 54.53; H, 3.66; neut. equiv., 220. Found: C, 54.9; H, 3.83; neut. equiv., 218.

**1(or 3)-Methyl-2,4-quinazolinedione (XIII).**—Two and a half grams (0.011 mole) of 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid (XI) was heated to 250° in a sublimation apparatus. After the evolution of carbon dioxide ceased, the residue was sublimed at 200° under reduced pressure. The sublimate (0.70 g., 35%) was triturated with a small amount of 1% sodium carbonate solution and the insoluble residue recrystallized from ethanol; hard needles, m. p. 198–199°.

*Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.34; H, 4.58. Found: C, 61.2; H, 4.80.

## Summary

Methods for the preparation of an amino alcohol derived from 2,4-quinazolinedione-5-carboxylic acid are given in detail. Several unusual reactions of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione are described. Evidence supporting the existence of two isomeric 1-methyl-2,4-quinazolinediones and two isomeric 3-methyl-2,4-quinazolinediones is presented.

CORVALLIS, OREGON RECEIVED AUGUST 21, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

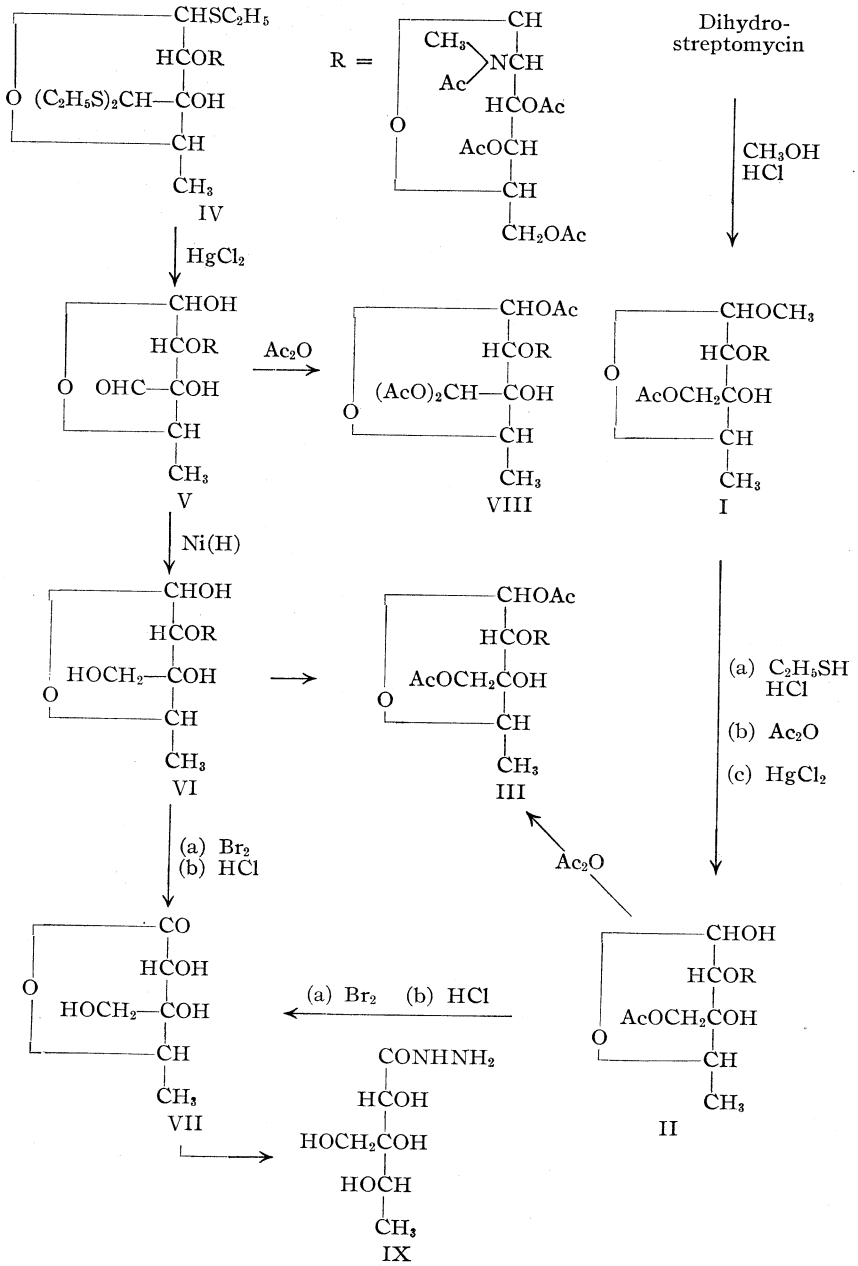
# Streptomyces Antibiotics. XXII. Configuration of Streptose and Streptobiosamine

BY FREDERICK A. KUEHL, JR., ROBERT L. CLARK, MARY NEALE BISHOP, EDWIN H. FLYNN AND KARL FOLKERS

The degradative preparation of dihydrostreptosonic acid lactone and the configuration of streptose and streptobiosamine have been communicated[1]; the details of these studies and a new improved preparation of the lactone are described herein. The improvement also made available crystalline tetraacetyldihydrostreptobiosamine.

Although the structural formula[2] of streptobiosamine was determined, certain stereochemical aspects of the structure remained to be elucidated. The configuration of the glycosidic linkage between streptose and N-methyl-L-glucosamine has been calculated[3] to be $\alpha$-L on the basis of the rotations of tetraacetylbisdesoxystreptobiosamine[4] and its components.[5,6,7] The stereochemical features of streptobiosamine remaining unknown concerned the streptose moiety, and for the elucidation of this aspect of the molecule, the lactone and the hydrazide of dihydrostreptosonic acid have been prepared to determine the sign of their optical rotations.

Methyl pentaacetyldihydrostreptobiosaminide[8] (I), which is prepared from dihydrostreptomycin, was converted into ethyl pentaacetylthiodihydrostreptobiosaminide by reaction with ethyl mercaptan and hydrogen chloride. The crude thioglycoside was reacetylated, and the product was treated with mercuric chloride and




(1) Kuehl, Bishop, Flynn and Folkers, THIS JOURNAL, **70**, 2613 (1948).

(2) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2679 (1946).

(3) Lemieux, De Walt and Wolfrom, *ibid.*, **69**, 1838 (1947).

(4) Kuehl, Flynn, Brink and Folkers, *ibid.*, **68**, 2096 (1946); Hooper, Klemm, Polglase and Wolfrom, *ibid.*, **68**, 2120 (1946). In the latter reference, this compound is called tetraacetyldidesoxydihydro-L-streptobiosamine.

(5) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2405 (1946).

(6) Kuehl, Flynn, Holly, Mozingo and Folkers, *ibid.*, **68**, 536 (1946).

(7) Wolfrom and Thompson, *ibid.*, **69**, 1847 (1947).

(8) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2557 (1946).

strontium carbonate for the preparation of pentaacetyldihydrostreptobiosamine[9] (II). The hy-

(9) Stavely, Wintersteiner, Fried, White and Moore, *ibid.*, **69**, 2742 (1947).

drolysis of this thioglycoside by mercuric chloride is similar to that used in the preparation of tetraacetylstreptobiosamine.[2] The amorphous pentaacetyldihydrostreptobiosamine (II) was acetylated to give the crystalline hexaacetyldihydrostreptobiosamine (III). This derivative is identical with hexaacetyl-$\alpha$-dihydrostreptobiosamine which has been described by others.[9]

Oxidation of pentaacetyldihydrostreptobiosamine (II) with bromine in the presence of strontium carbonate followed by reacetylation gave amorphous hexaacetyldihydrostreptobiosamic acid lactone, which was not further characterized. Hydrolysis of this oxidation product with 5% hydrochloric acid gave N-methyl-L-glucosamine and a new crystalline compound, $C_6H_{10}O_5$, which was designated dihydrostreptosonic acid lactone. Although dihydrostreptosonic acid lactone may be obtained by this series of reactions, the process is laborious and another degradative series was sought.

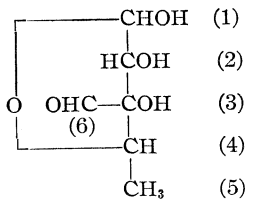
Streptomycin has been converted stepwise in good yields to ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal (IV) and to tetraacetylstreptobiosamine (V).[2] It has now been found that crystalline tetraacetylstreptobiosamine (V) may be hydrogenated with Raney nickel catalyst to tetraacetyldihydrostreptobiosamine (VI). In this hydrogenation, the preferential reduction of the formyl group takes place to an extent of at least 65%. Proof of this preferential reaction was secured by acetylation of the tetraacetyldihydrostreptobiosamine (VI) to give the known hexaacetyldihydrostreptobiosamine (III).

Tetraacetylstreptobiosamine (V) reacted with acetic anhydride in pyridine solution to give a crystalline product of the composition $C_{27}H_{39}NO_{17}$, which has been formulated as heptaacetylstreptobiosamine (VIII).

Tetraacetyldihydrostreptobiosamine (VI) was oxidized also with bromine, and then after hydrolysis the dihydrostreptosonic acid lactone (VII) was obtained. The preparation of the lactone by the latter series of reactions was more satisfactory.

Dihydrostreptosonic acid lactone was easily separated from N-methyl-L-glucosamine, because of its solubility in acetone. The compound behaved as a lactone upon potentiometric titration, and showed an absorption band at 5.65$\mu$ in the infrared corresponding to the lactone carbonyl group. Titration of dihydrostreptosonic acid lactone with sodium periodate showed that oxidation ceased in fifteen minutes after the consumption of two moles of oxidant. The oxidation liberated formaldehyde which was isolated as the dimedone derivative. These data, in conjunction with the known structure of streptobiosamine,[2] permit structure VII to be written for dihydrostreptosonic acid lactone.

Carbon atom 4 of streptose (VIII) was shown to be L, since streptobiosamine was degraded to

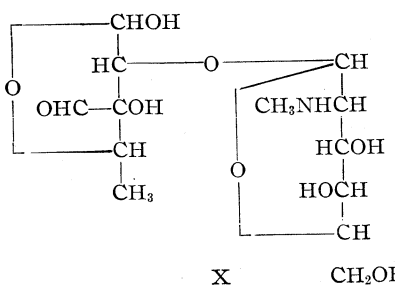



VIII

4-desoxy-L-erythrose[10]; by convention then, streptose is an L-sugar. The hydroxyl groups at carbon atoms 2 and 3 of streptose are known to have *cis* configuration, because bisdesoxystreptose formed an acidic complex with boric acid.[11] The knowledge of the configuration about either $C_2$ or $C_3$ would complete the elucidation of the total configuration of streptose.

The application of Hudson's rule[12] of optical rotation to streptosonic acid diamide,[2] which is dextrorotatory, indicates that the hydroxyl group at $C_2$ lies on the right. The application of the rule to this compound may be questioned, since the substance is a diamide. However, the application of the rule to dihydrostreptosonic acid amide would be more satisfactory, but the lactone was recovered after attempts to prepare the amide. The application of the hydrazide rule of Levene and Hudson to the hydrazide of dihydrostreptosonic acid (IX) was possible, since the lactone reacted readily with hydrazine in alcoholic solution to give the hydrazide (IX) in almost quantitative yield. Since the hydrazide was dextrorotatory, the hydroxyl group at $C_2$ may be assumed to be on the right; this confirms the configuration deduced from the rotation of the diamide of streptosonic acid. Credence in the applicability of these rules to those branched chain compounds is strengthened by the observation that both streptosonic acid lactone[2] and dihydrostreptosonic acid lactone are levorotatory. These lactones must be levorotatory if Hudson's lactone rule is applicable, since it is established conclusively that the configuration about $C_4$ of this lactone is L. The nature of the $\gamma$-lactone group of dihydrostreptosonic acid lactone is established by the above-mentioned periodate oxidation results.

The configuration of streptobiosamine may now be represented by structure X.




X

(10) Fried, Walz and Wintersteiner, *ibid.*, **68**, 2746 (1946).
(11) Brink, Kuehl, Flynn and Folkers, *ibid.*, **68**, 2405 (1945).
(12) Hudson, *ibid.*, **40**, 813 (1918).

## Experimental

**Pentaacetyldihydrostreptobiosamine (II) from Dihydrostreptomycin.**—A 5.43-g. sample of methyl pentaacetyldihydrostreptobiosaminide[2] (prepared from dihydrostreptomycin) was suspended in 50 ml. of ethyl mercaptan and the solution was saturated with dry hydrogen chloride. The crystals dissolved after several hours and the product deposited from the solution as an oil after standing overnight at room temperature. The ethyl mercaptan was removed *in vacuo* and the product was reacetylated by reaction with acetic anhydride in the presence of sodium acetate for one-half hour on the steam-bath. The acetylated product, after removal of excess acetic anhydride *in vacuo*, was separated from inorganic matter by extraction with chloroform. The chloroform extractives were dissolved in 200 ml. of 50% acetone and the solution was refluxed with 20 g. of strontium carbonate and 8 g. of mercuric chloride for one-half hour. After cooling, the reaction mixture was filtered and concentrated *in vacuo* to remove the acetone. The resulting aqueous solution was extracted continuously with chloroform to give 5.641 g. of amorphous pentaacetyldihydrostreptobiosamine.

**Hexaacetyldihydrostreptobiosamine (III) from Dihydrostreptomycin.**—A 621-mg. portion of pentaacetyldihydrostreptobiosamine was reacetylated in 8 ml. of acetic anhydride and 15 ml. of pyridine by allowing the mixture to stand for two days at 5°. The acetylation product was obtained as an amorphous powder, 532 mg. A solution of this material in 10 ml. of 3:7 chloroform–ether was passed over 25 g. of acid-washed alumina. The column was developed with 25 ml. of 3:7 chloroform–ether, 25 ml. of 1:1 chloroform–ether, 25 ml. of chloroform, and finally with 25 ml. of 1:9 methanol–chloroform. The product was removed from the column by elution with 25 ml. of 1:5 methanol–chloroform. It weighed 323 mg. and when it was dissolved in chloroform–ether, the solution deposited 102 mg. of crystalline hexaacetyldihydrostreptobiosamine, m. p. 141–143°. After a second recrystallization, the product melted at 146–147°.

*Anal.* Calcd. for $C_{25}H_{35}O_{15}N$: O-acetyl, 36.5. Found: O-acetyl, 36.6.

**Dihydrostreptosonic Acid Lactone (VII) from Pentaacetyldihydrostreptobiosamine.**—A solution of 2.5 g. of pentaacetyldihydrostreptobiosamine in 100 ml. of water containing 3 g. of bromine and 12 g. of strontium carbonate was maintained at 25° overnight in the dark. The reaction mixture was then filtered and concentrated *in vacuo* until all the bromine was removed. The resulting colorless solution was shaken with excess silver carbonate, filtered, then treated with hydrogen sulfide and filtered once more. The aqueous solution was concentrated *in vacuo* to a residue which was acetylated in pyridine–acetic anhydride. The crude acetylation product, 1.984 g., failed to crystallize. A 1.6-g. portion of this product was hydrolyzed by dissolving in 30 ml. of 5% hydrochloric acid and refluxing the solution for two hours. The hydrolysate was clarified by treatment with Darco and concentrated *in vacuo* to a residue. This dried residue was dissolved in 4 ml. of methanol and 75 ml. of acetone was gradually added. The precipitated N-methyl-L-glucosamine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo* to a residue. This product was further purified by dissolving it in 1 ml. of methanol and again adding 60 ml. of acetone. A final purification was accomplished by dissolving the acetone soluble material in dioxane and filtering the traces of the methylamino sugar. The product, 402 mg., was dissolved in 2 ml. of dioxane and treated with 20 ml. of chloroform. The dihydrostreptosonic acid lactone crystallized; yield, 190 mg., m. p. 135–138°. After recrystallization from chloroform-methyl ethyl ketone, the lactone melted at 143–144°, $[\alpha]_D$ −32° (*c*, 0.40 in water).

*Anal.* Calcd. for $C_6H_{10}O_5$: C, 44.45; H, 6.22; mol. wt., 162. Found: C, 44.02; H, 5.87; eq. wt., 167 (potentiometric titration).

**Tetraacetylstreptobiosamine[2] (V).**—A solution of 45.9 g. of crude ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal which was obtained by the acetylation of 35.9 g. of crystalline ethyl thiostreptobiosaminide diethyl mercaptal hydrochloride, 75.4 g. of mercuric chloride, and 92 g. of cadmium carbonate in 920 ml. of 50% acetone was heated under reflux for forty minutes. Vigorous mechanical stirring was required to prevent bumping. The resulting slurry was cooled, filtered and concentrated *in vacuo* to *ca.* 250 cc. The product was removed from the aqueous concentrate by continuous chloroform extraction. The chloroform extract, dried and adjusted to a volume of 100 ml., was poured onto a column of 100 g. of acid washed alumina. Elution of the column with 350 ml. of chloroform gave, after evaporation of the solvent, 27.7 g. of amorphous material. Crystallization of this material from acetone–absolute ether yielded 11.765 g. of product, m. p. 184–187°. After several recrystallizations from the same solvent, the tetraacetylstreptobiosamine melted at 188–189°, $[\alpha]_D$ −78.4° (*c*, 1.00 in chloroform).

*Anal.* Calcd. for $C_{21}H_{31}O_{13}N$: C, 49.89; H, 6.19; N, 2.77; acetyl, 34.0; O-acetyl, 25.5. Found: C, 49.90; H, 6.48; N, 2.73; acetyl, 34.3; O-acetyl, 25.3.

**Tetraacetyldihydrostreptobiosamine (VI).**—Twenty-four grams of tetraacetylstreptobiosamine was dissolved in 150 ml. of methanol and 400 ml. of water and shaken with 18 g. of Raney nickel catalyst. The mixture was then centrifuged and the filtrate was hydrogenated in the presence of another 18-g. portion of Raney nickel catalyst at 40 lb. pressure of hydrogen. Hydrogen ceased to be absorbed after three and one-half hours. The nickel was removed by filtration, and the solvent was removed *in vacuo*. A solution of the residue in 200 ml. of chloroform was dried, filtered, and concentrated *in vacuo* leaving 24 g. of a gum. To a solution of the gum in 100 ml. of methanol, was added 200 ml. of ether and 150 ml. of petroleum ether. After standing overnight, 10.4 g. of product was removed by filtration, m. p. 188–190° (cor.). The mother liquor was concentrated to 25 ml., and 25 ml. of ether and 25 ml. of petroleum ether were added. After cooling the solution overnight, 5.0 g. of additional product was obtained, m. p. 188–189°. After recrystallization from methanol–ether, the tetraacetyldihydrostreptobiosamine melted at 190–191°, $[\alpha]^{25}_D$ −86.5° (*c*, 1.0 in chloroform).

**Hexaacetyldihydrostreptobiosamine (III).**—Ten grams of tetraacetyldihydrostreptobiosamine was dissolved in 60 ml. of pyridine, and 60 ml. of acetic anhydride was added. After standing overnight, the solvents were removed *in vacuo*. The residue was dissolved in 50 ml. of methanol and the solution was filtered. To the filtrate was added 100 ml. of ether and then petroleum ether to the point of incipient cloudiness. After crystallization began, 300 ml. of petroleum ether was added, and the mixture was cooled overnight. The hexaacetyldihydrostreptobiosamine was removed by filtration; 7.7 g., m. p. 141–143°. After several recrystallizations from methanol–ether, it melted at 146–147°, $[\alpha]^{25}_D$ −113° (*c*, 0.5 in chloroform).

*Anal.* Calcd. for $C_{25}H_{37}O_{15}N$: C, 50.76; H, 6.30; N, 2.37. Found: C, 50.68; H, 6.23; N, 2.54.

**Heptaacetylstreptobiosamine (VIII).**—A solution of 413 mg. of tetraacetylstreptobiosamine in 4 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand for eighteen hours at 0°. The solvent was removed *in vacuo* and the residue was dissolved in ice water. Extraction with chloroform removed 460 mg. of an oily product. This material was dissolved in 4 ml. of 1:3 acetone–absolute ether and poured onto a column of 10 g. of acid-washed alumina. The column was then developed with 15 ml. of the same solvent mixture and then eluted with 20 ml. of 1:1 acetone–ether to give 236 mg. of an oil. A solution of this oil in a mixture of acetone, ether, and petroleum ether deposited 28 mg. of heptaacetylstreptobiosamine; m. p. 151–152°, $[\alpha]_D$ −106° (*c*, 0.70 in chloroform). Further recrystallizations did not alter the melting point.

*Anal.* Calcd. for $C_{27}H_{39}O_{17}N$: C, 49.94; H, 6.06; O-acetyl, 39.7. Found: C, 49.98; H, 6.40; O-acetyl, 39.5.

**Dihydrostreptosonic Acid Lactone (VII) from Tetraacetyldihydrostreptobiosamine.**[1]—Oxidation of 5.7 g. of crystalline tetraacetyldihydrostreptobiosamine yielded

after hydrolysis 433 mg. of dihydrostreptosonic acid lactone.

**Determination of Periodate Consumption by Dihydrostreptosonic Acid Lactone.**—A 5-ml. aqueous solution of 12.0 mg. of the lactone and 78.0 mg. of sodium metaperiodate was allowed to stand at room temperature. The periodate consumption was determined by the standard arsenite method.[13] A 1-ml. aliquot required 7.975 ml. of sodium arsenite solution (1 ml. ≅ 1.09 mg. of sodium meta periodate) corresponding to 2.1 moles after fifteen minutes. No further consumption was observed after one hour.

**Oxidation of Dihydrostreptosonic Acid Lactone (VII).**—A 36.6-mg. quantity of dihydrostreptosonic acid lactone was dissolved in 11.7 ml. of water containing 98 mg. of paraperiodic acid (determined by titration with standard sodium arsenite solution). After two hours, a 1-ml. aliquot was removed and treated with strontium carbonate. The excess strontium carbonate and strontium iodide was removed by filtration. The aqueous filtrate was adjusted to a volume of 1.5 ml. and then treated with 1.5 ml. of an alcoholic solution containing 50 mg. of dimedone. After two hours at 5°, the crystalline product was removed by filtration; yield, 5.5 mg. (97% theory), m. p. 193–194°. After recrystallization of the product from alcohol–water, the melting point did not change. When this derivative was mixed with the dimedone derivative of formaldehyde, no depression of melting point was observed; m. p. 193–194°.

**Hydrazide of Dihydrostreptosonic Acid (IX).**—A solution of 183 mg. of dihydrostreptosonic acid lactone in 10 ml. of ethanol and 0.5 ml. of hydrazine hydrate was allowed to stand for two hours at room temperature. Fifteen milliliters of chloroform was then added and the solution was allowed to stand for one and one-half hours at 5°. The crystalline hydrazide was removed by filtration; yield, 204 mg., m. p. 135–136°. After several recrystallizations from methanol–water, it melted at 137–139°, $[\alpha]^{25}D$ + 23° (*c*, 0.9 in water).

(13) Jackson, "Organic Reactions," Vol. II, p. 361.

*Anal.* Calcd. for $C_6H_{14}N_2O_5$: C, 37.09; H, 7.26; N, 14.4. Found: C, 36.91; H, 6.96; N, 14.8.

**Acknowledgment.**—The authors are indebted to Dr. Nelson Trenner and his associates for potentiometric titrations and infrared absorption data, and to Mr. Richard Boos and his associates for microanalytical data.

## Summary

Methyl pentaacetyldihydrostreptobiosaminide was converted into amorphous pentaacetyldihydrostreptobiosamine, through the intermediate ethyl thioglycoside, which gave a crystalline hexaacetyldihydrostreptobiosamine. Oxidation of pentaacetyldihydrostreptobiosamine with bromine gave amorphous hexaacetyldihydrostreptobiosamic acid lactone which was hydrolyzed to N-methyl-L-glucosamine and the new dihydrosteptosonic acid lactone.

Tetraacetylstreptobiosamine was hydrogenated selectively with Raney nickel catalyst to the new crystalline tetraacetyldihydrostreptobiosamine. Oxidation and hydrolysis of the tetraacetyldihydro derivative gave also dihydrostreptosonic acid lactone. The lactone gave a hydrazide.

Application of rules of rotation to streptosonic acid diamide and dihydrostreptosonic acid hydrazide indicates that the configuration at $C_2$ is D. The configuration of streptose and streptobiosamine are now known.

RAHWAY, NEW JERSEY RECEIVED SEPTEMBER 27, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Reactions of Free Hydroxyl Radicals with Organic Compounds

BY NICHOLAS A. MILAS, LOUIS E. STAHL[1] AND BENJAMIN B. DAYTON[2]

In previous publications on hydroxylation of organic compounds in solution with hydrogen peroxide in the presence of catalysts[3] or ultraviolet light[4] we postulated the formation and subsequent reaction of free hydroxyl radicals with organic compounds.[5,6] Hydroxylations of this type have not been attempted previously in the gaseous phase in spite of the fact that numerous reactions have been studied with free hydroxyl radicals usually obtained by the dissociation of water or mixtures of water and oxygen in glow discharges.[7–10]

The present investigation describes some experiments in which free hydroxyl radicals were allowed to react in the gaseous phase with saturated and unsaturated hydrocarbons. It has been found that free hydroxyl radicals are much more reactive in the gaseous phase than in solution. For example, in solution hydroxyl radicals are not known to react with saturated aliphatic hydrocarbons, while in the gaseous phase they react readily with methane to form chiefly carbon dioxide and formic acid, small amounts of methanol, and traces of ethanol. With ethylene and a large excess of hydroxyl radicals, formaldehyde, formic acid and carbon dioxide were the chief products with possible traces of ethylene glycol. When ethylene was used in large excess so that it entered the discharge tube, besides formaldehyde, acetylene and ethane were found among the condensa-

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(2) B.S. Thesis, M. I. T. 1937. Present address: Distillation Products, Inc., Rochester, N. Y.

(3) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2345 (1937); Milas, *ibid.*, **59**, 2352 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939); Milas and Maloney, *ibid.*, **62**, 1841 (1940).

(4) Milas, Kurz and Anslow, Jr., *ibid.*, **59**, 543 (1937).

(5) Weiss, *Trans. Faraday Soc.*, **36**, 856 (1940).

(6) Waters, *Ann. Reports*, **42**, 131 (1946).

(7) Rodebush and Campbell, *J. Chem. Phys.*, **4**, 293 (1936); Rodebush, Keizer, McKee and Quagliano, THIS JOURNAL, **69**, 538 (1947).

(8) Frost and Oldenberg, *J. Chem. Phys.*, **4**, 642 (1936); Oldenberg and Rieke, *ibid.*, **6**, 169, 439 (1938); **7**, 485 (1939).

(9) Kondrat'ev and Ziskin, *Acta Physicochim. U. S. S. R.*, **5**, 301 (1936); Kondrat'ev, *ibid.*, **8**, 315 (1938); **10**, 791 (1939).

(10) Smith, *J. Chem. Phys.*, **11**, 110 (1943).

tion products, while a considerable amount of a white solid polymer of aromatic odor was formed in the inner surface of the discharge tube. With isobutylene, acetone and formaldehyde were the chief products isolated. In all cases hydrogen peroxide and organic peroxides were also detected among the condensation products when liquid nitrogen was used as the cooling bath while no hydrogen peroxide or organic peroxides were detected when solid carbon dioxide–acetone mixture was the cooling bath.

## Discussion

Perhaps the high reactivity of hydroxyl radicals in the gaseous phase is due to the fact that as they emerge from the discharge tube they are associated with considerably more energy than those which are formed in solution. Furthermore, the hydroxyl radicals in solution may be associated with other groups while those in the gaseous phase are free. Besides, it is quite possible that under the conditions of our experiments other reactive groups, such as atomic hydrogen, may be present in the gaseous phase which, together with the hydroxyl radicals, may initiate reaction outside the glow discharge to produce other radicals. Although a number of possibilities have occurred to us regarding the interpretation of these reactions, we do not wish to propose them at present, since we have not carried out detailed kinetic studies.

## Experimental

**Arrangement of Apparatus.**—A high frequency oscillator[11] similar to that used[12] for the conversion of ergosterol to vitamin D was used in these experiments. It had a frequency range of 4,000 to 22,000 kilocycles. When the oscillator was operating at 19,000 kilocycles with a tank current of 21 amperes, plate current of 340 milliamperes, plate voltage of 1800 volts and filament voltage of 10 volts and maintaining the water vapor at a pressure of 0.1 to 0.2 mm., ample hydroxyl radicals were obtained as judged by the light red or pink color of the glow.[13] The apparatus and traps were arranged as shown in Fig. 1. A Cenco Hyvac oil pump was connected to tube A which was loosely packed with anhydrous calcium chloride. The two-way stopcock B served to draw air into the oil pump when the latter was stopped for purposes of withdrawing samples for analysis. The dibutyl phthalate manometer C was connected to a dibutyl phthalate pump[14] and calibrated to read directly in millimeters of mercury. This was used with the precautions recommended by von Brandenstein and Klumb.[15] The large trap D was immersed in liquid nitrogen during runs to condense all gases with the exception of hydrogen. The organic gases were slowly fed in at E passing through the capillary F and into the reaction or mixing chamber G (4 × 4 cm.). The visible glow in the discharge chamber H (6 × 25 cm.) extended only to the mouth of the reaction chamber.

The water was fed in from I through the capillary J. To prevent condensation of moisture which turned into ice and clogged the mouth of the capillary, the long arm between I and J was wrapped with asbestos tape. The rate of flow of water vapor was controlled by the temperature of I.

(11) Built by Harvey Electric Co., of Brookline, Massachusetts.
(12) Milas, U. S. Patent, 2,117,100, May 10, 1938.
(13) Rodebush and Wahl, *J. Chem. Phys.*, **1**, 699 (1933).
(14) Hickman and Sanford, *Rev. Sci. Instr.*, **1**, 140 (1940).
(15) von Brandenstein and Klumb, *Physik. Z.*, **33**, 88 (1932).

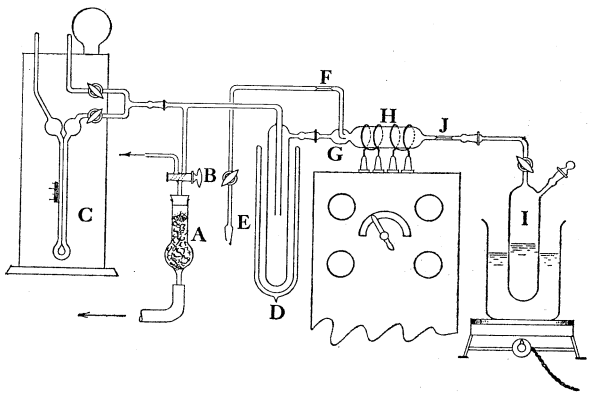



Fig. 1.—Diagram of apparatus for hydroxylation of organic compounds in the gaseous phase.

The pure organic gases were stored over brine and were introduced at E by means of an auxiliary apparatus consisting of a calibrated buret and the usual leveling bottles. The rate of flow was so adjusted as to prevent the organic gases from entering the discharge chamber thereby causing a discoloration of the glow and a deposit of a white solid in the inner surface of the discharge tube.

Before any run was made, the glass apparatus was treated with hot chromic–sulfuric acid solution and thoroughly washed with tap water followed by distilled water and baked in an oven. Since the recombination and destruction of free radicals is known to be a surface reaction, water vapor was passed through the system before the discharge was turned on to poison the glass surface thereby inhibiting this reaction.

**Reaction of Free Hydroxyl Radicals with Ethylene.**—When 1090 cc. (N. T. P.) of ethylene was allowed to react with excess hydroxyl radicals (from water vapor at 0.1–0.2 mm.) in the course of twelve hours, 500 cc. of gaseous and 9 cc. of liquid products were obtained. An analysis of the gaseous products showed the presence of 70% carbon dioxide, 4% ethylene and 26% ethane. The liquid was strongly peroxidic, the peroxide being mainly hydrogen peroxide, since it was largely destroyed by a clean platinum gauze. A weak test for the presence of organic peroxides was noted after the hydrogen peroxide was thoroughly destroyed. When the liquid was distilled, all but about 0.2 cc. of a yellowish oil distilled at 99°, indicating that most of it was water. However, the distillate gave a strong fuchsin–aldehyde reaction and a positive reaction for formic acid. The formaldimethone was prepared,[16] m. p. 188° (cor.), showing that the aldehyde was chiefly formaldehyde. The residual oil boiled above 110° and was suspected of being ethylene glycol. Attempts to prepare a dibenzoate or a di-*p*-nitrobenzoate yielded fine colloidal suspensions which were difficult to purify. In view of small quantities obtained in each experiment it was not found possible to establish definitely the presence of ethylene glycol.

When the experiment was run in such a manner that excess ethylene was allowed to enter the discharge tube, the glow of the discharge changed from pink to purple. After a run of nine hours, the gas analysis showed no carbon dioxide but considerable acetylene and much ethylene. A white deposit which was probably a polymer of ethylene covered the inner surface of the discharge tube. About 1 cc. of a yellow oil condensed in the liquid air trap which gave the usual tests of peroxides, aldehydes and formic acid. In addition, the liquid gave a positive iodoform reaction indicating the presence of small amounts of either ethyl alcohol or acetaldehyde. The formaldimethone prepared from this liquid melted at 185–188° (cor.).

**Reaction of Free Hydroxyl Radicals with Methane.**—In the first experiment 860 cc. (N. T. P.) of methane was

(16) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 155.

introduced into the reaction chamber very slowly in the course of twelve hours. At the end of the run the gases were analyzed and found to contain 80% carbon dioxide, no unsaturated hydrocarbons, small amounts of oxygen and saturated hydrocarbons (assumed to be methane). About 10 cc. of water-like liquid having an ethereal odor was collected in the liquid air trap. A test for hydrogen peroxide was negative, although a positive test for organic peroxides was obtained. A clean platinum gauze failed to destroy the peroxides. Both the fuchsin–aldehyde test and the "dimedon" reaction were negative. Both the resoninol–sulfuric acid and the U. S. P. tests[17] for methyl alcohol were strongly positive. Formic acid was also found to be present.

In a second run an excess of methane was used and it was allowed to enter the discharge chamber giving a blue-white glow at one end with the pink (water) glow limited to the end of the tube at which the water vapor entered. A volume of 3 liters of methane was used in this run. The gases were not analyzed. About 16 cc. of a liquid was obtained in the liquid air trap, and was found to give the same positive tests as that of the previous run, but in addition it gave a positive iodoform reaction indicating the presence of small amounts of ethanol.

**Reaction of Free Hydroxyl Radicals with Isobutylene.**—Isobutylene was prepared by the dehydration of *t*-butyl alcohol (80 g.) with oxalic acid (27 g.) and the vapors collected in a trap immersed in acetone–carbon dioxide ice. It was then distilled from the trap by allowing the vapors to pass through a 2-foot vertical column packed with calcium chloride and condensed in another trap to which was attached a stopcock and a ground glass female joint. The isobutylene (10 g.) was introduced into the reaction chamber through the connection E (Fig. 1) by allowing it to evaporate slowly. During the run some isobutylene entered the discharge tube thereby forming purple rings nearer to the reaction chamber while the pink glow (water) persisted in the left half of the discharge tube. At the end of four hours the reaction was stopped and the products condensed in the liquid air trap examined. A liquid (4 cc.) was obtained having a strong odor of formaldehyde. It gave a positive fuchsin–aldehyde test and the formaldimethone prepared from it melted at 188° (cor.). After the removal of formaldehyde the remaining solution gave a strong test for acetone using the sodium nitroprusside reaction.[18] The original liquid also gave a positive test for organic peroxides showing that hydrogen peroxide was probably bound either to formaldehyde or to acetone. The gases were not analyzed.

(17) Reference 16, p. 427.

## Summary

1. The reaction between free hydroxyl radicals formed in a glow discharge and methane, ethylene and isobutylene was studied in the gaseous phase.

2. It has been found that free hydroxyl radicals are much more reactive in the gaseous phase than in solution.

3. Methane was mainly converted to carbon dioxide. Other products found were small amounts of peroxides, methanol, ethanol and formic acid.

4. Ethylene was converted mainly to carbon dioxide, small amounts of peroxides, formaldehyde, formic acid and possibly ethylene glycol. With a large excess of ethylene no carbon dioxide was formed, but formaldehyde, formic acid, traces of ethanol and possibly ethylene glycol, acetylene and a solid polymer were noted.

5. With isobutylene, peroxides, formaldehyde and acetone were the chief products detected.

(18) Reference 16, p. 357.

CAMBRIDGE, MASSACHUSETTS RECEIVED OCTOBER 25, 1948

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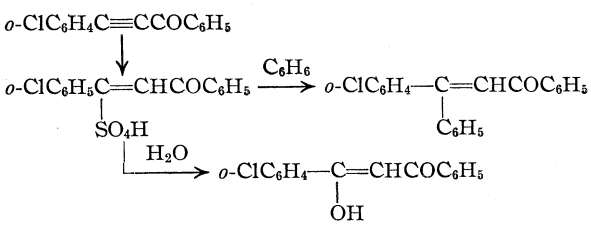
[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

# The Addition of Benzene to an Acetylenic Ketone

BY CHARLES L. BICKEL AND AUGUSTUS J. FABENS[1]

The literature contains several reports on the reaction of benzene and some of its simple substitution products with $\alpha,\beta$-unsaturated ketones. Vorländer and Friedberg,[2] as well as Fuson and co-workers,[3] used a mixture of aluminum chloride and hydrogen halide as the condensing agent, Fuson reporting that these reactions are reversible. Kohler[4] found that benzene adds to chalcone in the presence of sulfuric acid, giving $\beta,\beta$-diphenylpropiophenone as the only identified product. This reaction is also assumed to be reversible,[5] although the nature of the aromatic residues does not permit a study of reversibility in this case.

The reaction of aromatic compounds with the more highly unsaturated acetylenic ketones has not been reported. The present investigation is a study of the reaction of *o*-chlorophenylbenzoyl acetylene with benzene in the presence of sulfuric acid. Two products have been isolated from this reaction, *o*-chlorodibenzoylmethane and $\beta$-(*o*-chlorophenyl)-chalcone. The diketone is the sole product when a sulfuric acid solution of the acetylenic ketone is treated with water[6]; thus, the isolation of the diketone in this instance indicates either incomplete reaction with benzene or a reversible reaction. $\beta$-(*o*-Chlorophenyl)-chalcone is the product of the net addition of benzene to the acetylenic ketone. A mechanism which is consistent with the known facts is formulated as follows




(1) A senior in the Phillips Exeter Academy during the school year, 1948–1949.

(2) Vorländer and Friedberg, *Ber.*, **56**, 1144 (1923).

(3) Fuson, Eaton and Black, THIS JOURNAL, **56**, 687 (1934).

(4) Kohler, *Am. Chem. J.*, **31**, 650 (1904).

(5) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, 1938, p. 585.

(6) Bickel, THIS JOURNAL, **69**, 74 (1947).

Certain observations indicate that the reaction with benzene is not reversible. Reversibility would lead to the formation of dibenzoylmethane and β-phenylchalcone, assuming that the *o*-chlorophenyl group is as easily loosed as the phenyl group.[7] Neither of these compounds was detected in the reaction products. The most conclusive evidence of irreversibility was obtained by treating β-(*o*-chlorophenyl)-chalcone with benzene and sulfuric acid. None of the β-diketone was produced.

The substituted chalcone, like other ethylenic compounds, is soluble in sulfuric acid. The extended period of exposure to the acid appears to convert the chalcone into other products. Thus, as the reaction time is increased in order to decrease the yield of the diketone, the yield of chalcone is decreased. The product or products of this reaction are being investigated and may be reported at a later date.

Attempts to decrease the side-reactions have so far met with no success. The acetylenic ketone was recovered when seventy-five per cent. sulfuric acid was substituted for concentrated sulfuric acid; the use of fuming sulfuric acid decreased the yield of diketone but also materially decreased the yield of chalcone.

This investigation was assisted by a grant from the Cyrus M. Warren Fund of the American Academy of Arts and Sciences.

## Experimental[8]

Since there were no significant variations in the procedure used in all of the runs, the general procedure is described in detail and the results for all runs are summarized in tabular form.

Concentrated sulfuric acid was added to a solution of *o*-chlorophenylbenzoylacetylene[9] in benzene contained in a 250 ml. glass-stoppered Erlenmeyer flask equipped with a Pyrex-enclosed bar magnet, the magnet being rotated at a rate which assured efficient mixing of the two layers. At the end of the stirring operation, the mixture was poured onto ice, the benzene layer washed with water and the benzene evaporated by a current of air. The residue was taken up in ether, the ether solution washed with water and then shaken with saturated cupric acetate solution. The copper salt of the β-diketone was filtered off, washed, dried, weighed and finally converted to the diketone which was isolated and identified.[10] The filtrate from the cupric acetate treatment was shaken with dilute hydrochloric acid, the ether layer washed with water, dried and concentrated, giving β-(*o*-chlorophenyl)-chalcone or unchanged acetylenic ketone.

TABLE I

SUMMARY OF RESULTS[a]

| Time, days | $H_2SO_4$ | Cu salt | Chalcone | Acetylene |
|---|---|---|---|---|
| 2 | 46 | 6.30 | 4.0 | None |
| 7 | 46 | 5.70 | 3.55 | None |
| 14 | 46 | 2.00 | 0.5 | None |
| 4 | 5 | Trace[b] | <0.1 | None |
| 3 | 0.8 | None | None | >9.5 |
| 3 | 46[c] | 5.56 | 2.35 | None |
| 9 | 37[d] | None | None | 10 |

[a] Ten grams of acetylenic ketone and 125 ml. of benzene were used in each run. The times are in days; all other figures are weights in grams. [b] Dark green color in the ether layer but no solid copper salt. [c] Twenty-four grams of concentrated sulfuric acid and 22 g. of 30% fuming sulfuric acid. [d] Twenty-eight grams of concentrated sulfuric acid and 9 g. of water.

**β-(*o*-Chlorophenyl)-chalcone.**—The chalcone is quite soluble in ether, very sparingly soluble in petroleum ether, and crystallizes in sulfur-yellow stout needles melting at 106–107°.

*Anal.* Calcd. for $C_{21}H_{15}OCl$: C, 79.0; H, 4.74. Found: C, 78.4, 78.8; H, 4.78, 4.80.

Chromic acid oxidation of the chalcone in glacial acetic acid solution gave the calculated quantities of benzoic acid and *o*-chlorobenzophenone. The *o*-chlorobenzophenone, melting at 47°, was identified by comparison with a known sample synthesized by the reaction of phenylmagnesium bromide with *o*-chlorobenzaldehyde and by the subsequent oxidation of the *o*-chlorobenzhydrol to *o*-chlorobenzophenone.

**The Reaction of the Chalcone with Benzene and Sulfuric Acid.**—A mixture of 10 g. of the chalcone, 125 ml. of benzene and 46 g. of concentrated sulfuric acid was stirred (magnetic stirrer) for one week and then worked up as described above. Cupric acetate gave no evidence of a β-diketone. Three grams of the chalcone was recovered and the residual oil has as yet yielded no solid products.

## Summary

*o*-Chlorophenylbenzoylacetylene reacts with a mixture of benzene and sulfuric acid to give *o*-chlorodibenzoylmethane and β-(*o*-chlorophenyl)-chalcone. The evidence indicates that the benzene reaction is irreversible.

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(7) Fuson (ref. 3) obtained β,β-diphenylpropiophenone by the action of benzene on 2-chlorochalcone.

(8) A magnetic stirrer was used in all of the experiments in which a long period of stirring was required. This made possible the use of a glass-stoppered Erlenmeyer flask and the elimination of the ordinary sleeve type stirrer and the vibration inherent in most stirrers of this type.

(9) Bickel, THIS JOURNAL, **69**, 2135 (1947).

(10) Bickel, *ibid.*, **68**, 866 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

# Dimensions of Coiling Polymer Molecules from Viscosity and Light Scattering[1]

BY A. M. BUECHE

In a recent treatment[2] of the intrinsic viscosity of polymer solutions it was pointed out that viscosity data can be used to find the dimensions of polymer molecules in solution. It was shown that data relating the intrinsic viscosity to the molecular weight could be interpreted in terms of the radius of the molecular sphere and the permeability to solvent flow of the polymeric material inside this sphere.

The concept of the molecular sphere was introduced as an approximation in the viscosity theory so that the results could be expressed in closed form. The polymeric molecule was represented by a sphere of radius, $R_s$, having a constant average permeability and polymer density inside. Outside of the sphere the polymer density was taken as zero. The permeability of the molecule to solvent flow was characterized by a shielding length, $L$. $R_s$ and $L$ both depend on molecular weight for linear coiling molecules and are the two parameters evaluated when the suggested treatment of intrinsic viscosity data is followed.

When light is scattered by a molecule larger than about one-twentieth of the wave length it is not scattered symmetrically around the molecule. Due to interference of the light scattered from different parts of the molecule the scattered intensity is greater in the directions close to the direction of the primary beam. This dissymmetry of the scattered light has been shown to be a measure of the dimensions of the molecule.[3] In the case of linear coiling molecules the dissymmetry can be expressed in terms of $R$, the root mean square of the distance from the beginning to the end of the molecule and the wave length, $\lambda$, of the light in solution. The expression for the angular dependence of the relative intensity, $I$, after correction for the polarization of the light is

$$I \sim \frac{2}{x^2}[e^{-x} - (1 - x)] \qquad (1)$$

where

$$x = \frac{2\pi^2 s^2}{3}\left(\frac{R^2}{\lambda^2}\right)$$

and $s = 2\sin(\theta/2)$. Here $\theta$ is the angle between the directions of the primary and scattered beams. If for measuring the scattering dissymmetry only the two angles, 45° and 135°, are used the expression for the quotient, $I_{45}/I_{135}$, of the intensities of these angles can be closely approximated by

$$I_{45}/I_{135} = 1 + 6.556(R/\lambda)^2 \qquad (2)$$

for values of the quotient of the intensities up to 2. If $R^2$ is proportional[4] to the number of units in the molecular chain the quantity $(I_{45}/I_{135} - 1)$ will be proportional to the length of the extended molecule or, for a given polymer, to the molecular weight.

The relationship expressing proportionality between $R^2$ and the molecular weight was derived by Taylor and others on the assumption that parts of the coiling molecule do not interfere with one another in the course of its Brownian motion. This can never be strictly true for a coiling molecule. It seems to be a good approximation, however, for polymers dissolved in good solvents, as in the present case, where the molecules are rather highly extended. In poor solvents where the molecules are more compact the deviations from proportionality between $R^2$ and the molecular weight may be rather large.

In the limit of very permeable linear coiling molecules or low molecular weights it was shown theoretically that the diameter $2R_s$ of the molecular sphere is approximately equal to $R$. They are related by the equation

$$2R_s = 1.056R \qquad (3)$$

The viscosity and light scattering experiments reported here were undertaken to determine the validity of equation (3) for polymer molecules of higher molecular weights and usual permeabilities. The experimental results obtained in the study of solutions of polystyrene in benzene also give information about the stiffness of the polystyrene molecule and indicate that the polystyrene fractions used are not branched or cross-linked as has been reported in some cases.[5]

## Experimental

Six polystyrene fractions[6] were dried under vacuum and weighed amounts were dissolved in reagent grade benzene. Dust was removed from the solutions by filtration through a fine glass filter.

The polystyrene was prepared by thermal polymerization of styrene at an average temperature of 100°. It was fractionated by the method described by Badgely.[7] The essential feature of this method is that a precipitant is used which boils higher than the solvent, and the precipitant–solvent ratio is changed by distillation under reduced pressure. The fractionation procedure was carried out only once.

The light scattering measurements were made using an

(1) The work reported in this paper was done in connection with the Government Research Program on Synthetic Rubber under contract with the Office of Rubber Reserve, Reconstruction Finance Corporation.

(2) P. Debye, paper presented at the International Congress of Chemists, London, 1947; P. Debye and A. M. Bueche, *J. Chem. Phys.*, **16**, 573 (1948).

(3) P. Debye, *J. Phys. and Colloid Chem.*, **51**, 18 (1947).

(4) W. J. Taylor, *J. Chem. Phys.*, **15**, 412 (1947).

(5) T. Alfrey, A. Bartovics and H. Mark, THIS JOURNAL, **65**, 2319 (1943).

(6) Kindly supplied by Dr. R. S. Spencer of The Dow Chemical Company, Midland, Mich.

(7) W. Badgely, Doctoral Dissertation, Polytechnic Institute of Brooklyn.

instrument designed by P. P. Debye.[8] The phototube below the stage was used in conjunction with the travelling mirror dipping into the solutions. The solutions were held in a rectangular glass cell having a volume of about 300 cc. All measurements were made using the mercury blue line ($\lambda$ = 4358 Å.) as isolated by Corning filters. The scattered light was measured at the three angles, 45, 90 and 135°. The meter readings were converted to absolute scattering values by comparing them with readings obtained from a benzene solution of polystyrene whose turbidity had been determined by the "absolute camera" method.[3]

The refractive index differences between solutions and solvent were measured in a differential refractometer similar to that described by P. P. Debye.[8] This refractive index difference, $\mu - \mu_0$, was a linear function of the concentration in the range 0 to 0.01 g./cc. and independent of the molecular weight. For polystyrene in benzene and $\lambda$ = 4358 Å. the difference can be expressed by

$$\mu - \mu_0 = 0.1151C$$

where $C$ is the concentration in g./cc.

The molecular weights of the fractions were obtained from the 90° scattering values by the usual extrapolation of the concentration divided by the turbidity to infinite dilution. Since some dissymmetry of scattering was observed for each fraction the molecular weights obtained by 90° scattering alone were too low. They were multiplied by the necessary correction factors[3] obtained from equation (1). The corrected molecular weights were found to range from 135,000 to 895,000.

To avoid a direct extrapolation of the dissymmetries to infinite dilution the quantities $C/I_{45}$ and $C/I_{135}$ were plotted as functions of the concentration. These plots were linear at low concentrations. The dissymmetries were obtained by forming the quotients of the intercepts at $C = 0$. The instrument itself was responsible for a dissymmetry, $I_{45}/I_{135} = 1.10$ because the primary beam was not symmetrical around the center of the scattering cell. The dissymmetries as calculated from the intercepts were corrected by dividing by this number.

Flow times, $t$ and $t_0$, of solutions and solvent were measured in an Ostwald viscometer at 38°. The kinetic energy correction was found to be negligible. The intrinsic viscosities were obtained from the intercepts at $C = 0$ of the ln $(t/t_0)$ *vs.* $C$ plots. Account was taken of the difference in concentration of the solutions at room temperature and 38°.

The experimental data are given in Table I and the extrapolated quantities obtained from it are given in Table II.

## Results and Discussion

The dissymmetries are plotted as a function of the molecular weights, $M$, in Fig. 1. The equation of the least squares straight line through the points is

$$I_{45}/I_{135} = 1 + 9.66M\cdot10^{-7} \qquad (4)$$

This linear dependence of dissymmetry on $M$ is what would be expected from a linear coiling molecule in a good solvent as previously discussed. If the molecules were highly branched or cross-linked this linear dependence would not exist. This can be seen in an approximate way by the following considerations.

Suppose the molecule were so highly cross-linked that for light scattering measurements it acted as a sphere of constant density. The diameter of the molecule would then be proportional to the cube root instead of the square root of the molecular weight. It is to be expected that for lesser degrees of cross-linking the diameter would be proportional to an intermediate power. Although there are a number of difficulties to be overcome such data may be useful in making an estimation of the degree of cross-linking.

The dependence of $R$ on the molecular weight can be found from equations (2) and (4) to be

$$R = 1.11M^{1/2} \qquad (5)$$

(8) P. P. Debye, *J. Applied Phys.* **17**, 392 (1946).

TABLE I

| Sample | $C$ (g./100 cc.) | $H\frac{c}{\tau_{45}}\times 10^7$ | $H\frac{c}{\tau_{90}}\times 10^7$ | $H\frac{c}{\tau_{135}}\times 10^7$ | $\frac{\ln t/t_0}{c}$ |
|---|---|---|---|---|---|
| D-1 | 1.00 | 40.5 | 160 | 44.0 | 0.438 |
| | 0.667 | 32.4 | 129 | 33.8 | 0.451 |
| | .445 | 28.2 | 113 | 29.2 | .465 |
| | .296 | 24.4 | 99.4 | 28.2 | .473 |
| | .197 | 22.6 | 92.7 | 25.6 | .473 |
| | .132 | 21.6 | 87.1 | 22.9 | ... |
| D-2 | 1.0 | 38.4 | 193 | 64.7 | .732 |
| | 0.667 | 29.4 | 139 | 45.2 | .753 |
| | .445 | 23.8 | 111 | 35.4 | .755 |
| | .296 | 19.6 | 90.6 | 29.1 | .770 |
| | .197 | 17.6 | 86.9 | 27.4 | .773 |
| | .132 | 15.1 | 65.2 | 25.6 | .788 |
| | .088 | 15.8 | 71.3 | 23.2 | .773 |
| D-3 | 1.0 | 19.1 | 121 | 44.0 | .955 |
| | 0.667 | 15.5 | 95.6 | 32.8 | .996 |
| | .445 | 13.2 | 72.7 | 24.6 | 1.03 |
| | .296 | 11.0 | 56.2 | 18.6 | 1.05 |
| | .197 | 9.59 | 52.7 | 15.9 | 1.07 |
| | .132 | 8.60 | 48.5 | 14.4 | 1.07 |
| | .088 | 7.96 | 45.0 | 13.1 | ... |
| D-4 | .794 | 16.2 | 93.2 | 35.2 | 1.18 |
| | .530 | 12.3 | 66.6 | 23.3 | 1.25 |
| | .352 | 9.86 | 52.0 | 17.1 | 1.31 |
| | .234 | 8.10 | 43.1 | 13.8 | 1.35 |
| | .157 | 7.20 | 39.4 | 12.0 | 1.38 |
| | .105 | 6.33 | 35.0 | 10.3 | 1.37 |
| D-5 | .296 | 6.90 | 44.4 | 13.84 | 1.70 |
| | .197 | 5.76 | 37.2 | 11.32 | 1.78 |
| | .132 | 5.07 | 31.6 | 9.75 | 1.84 |
| | .088 | 4.73 | 29.9 | 8.76 | 1.87 |
| | .0586 | 4.44 | 29.0 | 8.27 | 1.93 |
| | .0391 | 3.89 | 26.6 | 7.97 | ... |
| D-6 | .667 | 13.8 | 67.0 | 32.0 | 1.85 |
| | .445 | 10.1 | 52.4 | 22.2 | 2.02 |
| | .296 | 8.02 | 39.9 | 17.1 | 2.17 |
| | .197 | 6.56 | 34.0 | 13.9 | 2.29 |
| | .132 | 5.74 | 30.2 | 12.3 | 2.27 |
| | .088 | 4.70 | 24.9 | 10.4 | 2.31 |
| | .059 | 3.98 | 20.9 | 8.85 | 2.39 |
| | .039 | 3.60 | 20.2 | 8.21 | 2.44 |

TABLE II

| $M \times 10^{-5}$ | $I_{45}/I_{135}$ | $[\eta]$, cc./g. |
|---|---|---|
| 8.95 | 1.90 | 244 |
| 6.01 | 1.60 | 195 |
| 4.55 | 1.43 | 143 |
| 3.28 | 1.27 | 109 |
| 2.59 | 1.24 | 78.6 |
| 1.35 | 1.04 | 49.8 |

For a molecular weight of 1,000,000 this leads to $R = 1110$ Å. R. H. Ewart[9] and P. Doty[10] have obtained values of $R$ for polystyrene in other solvents. Ewart investigated a range of molecular weights in carbon tetrachloride and found $R = 1050$ Å. for $M = 1{,}000{,}000$. Doty investigated a polystyrene sample having $M = 4.8 \cdot 10^6$ in toluene. Making use of the proportionality between $R$ and $M^{1/2}$ his value leads to $R = 1080$ Å. The agreement among the three values is better than was expected when the experimental errors are considered.

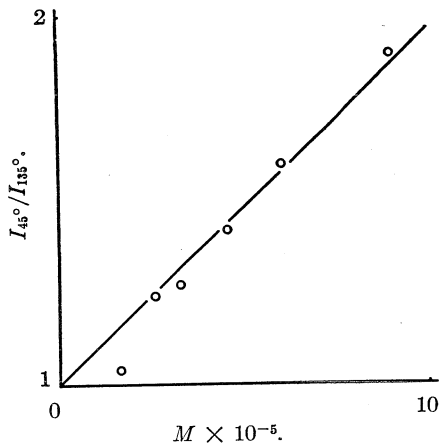



Fig. 1.—Dissymmetries of polystyrene fractions *vs.* molecular weight.

The intrinsic viscosity, $[\eta]$, of a polymer in solution can be expressed as

$$[\eta] = (\Omega/m)\ \phi\ (R_s/L) \qquad (6)$$

where $\Omega$ is the volume of the molecular sphere, $m$ is the mass of one molecule and $\phi(R_s/L)$, a function of the shielding ratio, $R_s/L$, ranges from 0 to 2.5. In utilizing this equation to obtain the size of the molecular sphere a scheme proposed in the original paper[2] was followed.

Figure 2 is a plot of log $[\eta]$ *vs.* log $M$. The slope, $\epsilon$, of the best straight line through the points is 0.850. Values of $R_s/L = 2.85$ and $\phi = 0.560$ corresponding to this slope are found from the table in reference (2). The average molecular weight of the range studied is 384,000 and the corresponding value of the intrinsic viscosity is 116 cc./g. Substitution of these values into equation (6) leads to a value $2R_s = 606$ Å. This is equivalent to the value $2R_s = 1030$ Å. for $M = 1{,}000{,}000$. Fig. 3 is a plot of $[\eta]$ *vs.* $M$. The solid line is that predicted by equation (6) using the quantities determined above. The data agree with the theoretical curve within experimental error.

The value of $2R_s = 1030$ Å. from viscosity is to be compared with $1.056R = 1170$ Å. as determined by light scattering. The two differ by 13%. Since this is about the precision expected from the experiments the diameter of the molecular sphere and the root mean square of the distance between the ends of the molecule can be said to be equal within experimental error.

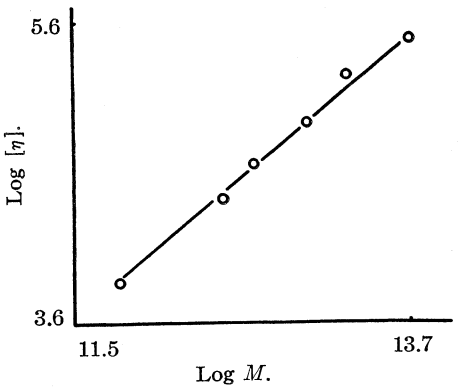



Fig. 2.—Natural logarithmic plot of the intrinsic viscosities of polystyrene fractions *vs.* molecular weight.

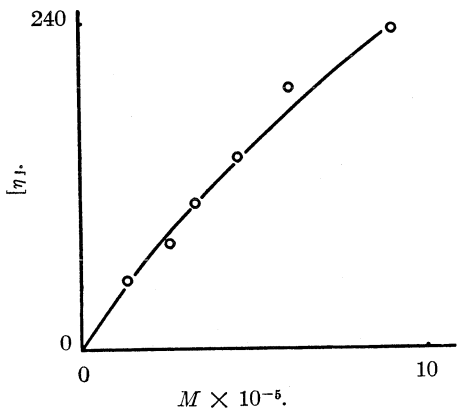



Fig. 3.—Intrinsic viscosities of polystyrene fractions *vs.* molecular weight.

The diameter of the molecular sphere as calculated from these measurements is in some disagreement with that obtained by R. H. Ewart[9] by the same method for polystyrene in benzene. Ewart's measurements lead to $2R_s = 880$ Å. for $M = 1{,}000{,}000$. We are unable to account for the discrepancy between his value and ours of 1030 Å. except for the fact that the samples are not the same. Both values are less than the value of $R$ found by light scattering. This might indicate that the average distance between the ends of the molecule is slightly larger than the diameter of the molecular sphere.

Taking the average of all the measurements the distance between the ends of the polystyrene molecule is about 3.4 times larger than the distance calculated supposing free rotation in the molecular chain. The polystyrene molecule, therefore, shows a considerable degree of stiffening[4] which would correspond to an oscillation

(9) R. H. Ewart, U. S. Rubber Company, Passaic, N. J., private communication.

(10) P. Doty, W. Affens and B. Zimm, *Trans. Faraday Soc.*, *XLIIB*, **66** (1946).

around each bond of 200°, calculated from Debye's modification of the Kuhn equation, instead of the 360° for free rotation. Since the intrinsic viscosity is proportional to $R_s^3$ it is about 39 times larger than would be expected for a polystyrene molecule having free rotation.

## Summary

Molecular dimensions for polystyrene fractions in benzene have been obtained from viscosity and light scattering data. It was found that the root mean square of the distance between the ends of the molecule is approximately equal to the diameter of the molecular sphere needed for the explanation of viscosity. Evidence for the absence of appreciable branching or cross-linking in the polystyrene fractions was obtained. Polystyrene molecules in benzene were found to be much stiffer than would be expected from a free rotation model. This stiffness is responsible for the relatively high viscosities of polystyrene solutions.

RECEIVED DECEMBER 17, 1948

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[CONTRIBUTION FROM THE METCALF LABORATORY OF BROWN UNIVERSITY]

# Properties of Electrolytic Solutions. XXXVIII. The Distribution of Hexadecylpyridonium Chloride between Water and Nitrobenzene at 25°

BY PHILIP F. GRIEGER[1] AND CHARLES A. KRAUS

## I. Introduction

The purpose of the present investigation was to determine the distribution of a long chain electrolyte between water and a slightly soluble organic liquid of relatively high dielectric constant, and thereby to test (by a method apparently hitherto untried) the validity of certain ideas which are currently held to be true, concerning aqueous long chain electrolyte solutions. Hexadecylpyridonium chloride was chosen as the salt because its critical concentration in water is convenient for the purpose of this work. Nitrobenzene was chosen as the reference liquid because its solubility in water is low (about 0.2% by weight), its dielectric constant is relatively high (34.5) and especially because considerable information was available on the conductance of long chain salts in this solvent.

Previous measurements made in this Laboratory on long chain electrolytes in nitrobenzene indicate that the activity product of simple ions can be evaluated from a knowledge of the conductance of these solutions.[2] Then, from distribution and conductance measurements, the activity product of simple ions in water saturated with nitrobenzene can be established and, in turn, the concentration product of simple ions in the aqueous solvent can be approximated. In the light of this information, another test can be made of the two leading hypotheses on long chain electrolyte solutions: (I) complete dissociation of the electrolyte at concentrations less than critical; (II) association of the electrolyte (to form one or more polyionic species) at concentrations greater than critical. The experimental results presented here are consistent with these two hypotheses.

In the distribution experiments concentrations were determined conductometrically; it was found that significantly precise measurements could be made at concentrations approaching $10^{-4}$ $N$, or well below the critical concentration, $5.8 \times 10^{-4}$ $N$.

Although the solubility of nitrobenzene in water is low, the conductance of hexadecylpyridonium chloride in water saturated with nitrobenzene differs significantly in the neighborhood of the critical concentration (and below) from the conductance of this salt in pure water. Hence, the distribution results reported here must be regarded as appertaining specifically to the solvent: water saturated with nitrobenzene.

**Conventions.**—Salt concentrations are given in moles per liter of solution, exclusively. Quantities that refer to the water phase are designated by primes, while quantities that refer to the nitrobenzene phase are not specially marked. In some instances where only the water phase is under consideration (and no ambiguity can result), the water phase quantities have not been primed.

## II. Experimental

**Apparatus and Procedure.**—The methods used in determining the conductance of the solutions have been adequately described in earlier papers of this series.[3]

The distribution measurements were made in a cell similar to those used in previous conductance work in this Laboratory, except that a side chamber (large enough to hold all the nitrobenzene in the system) was sealed to the cell near its base. By manipulating the cell, it was possible to place either the water or nitrobenzene layer in contact with the electrodes. It was found that equilibrium could be established (as judged by the constancy of the resistances of the separate phases) within a reasonable time, usually one or two days, by moving the cell in such a way that the liquids were caused to pass slowly through each other. By careful mixing, foam and emulsion formation were practically eliminated. The electrodes of the cell were lightly platinized.

The distribution experiments were carried out simply, as follows: after weighing the cell dry, nitrobenzene and then

(1) Lalor Foundation Fellow, Brown University, 1947–1948. Present address: Department of Chemistry, University of Illinois, Urbana, Ill.

(2) H. L. Pickering, Thesis, Brown University (1947).

(3) Evers and Kraus, THIS JOURNAL, **70**, 3049 (1948); Pickering, Thesis, Brown University, 1947.

water were added, the cell being weighed after each addition. The liquids were mixed and the conductance of each phase was determined. In general, the solvent conductances were: aqueous phase, $10^{-6}$; nitrobenzene phase, 1 to 2 $\times$ $10^{-8}$. A known quantity of salt was added (either as concentrated nitrobenzene or water solution) and the liquids were mixed and allowed to stand, alternately, until the resistances became constant (to less than a part per thousand). The experimental observables were, then: the specific resistance of each phase, the weight of nitrobenzene, water and salt in the system. All measurements reported here were made at 25 $\pm$ 0.01°.

**Solvents.**—Water[3] of specific conductance 1 $\times$ $10^{-6}$ was used. The nitrobenzene was purified by Dr. H. L. Pickering.[2] Its specific conductance was less than $10^{-9}$.

**Salt.**—Hexadecyl alcohol (m. p., 47.3°) was fractionally distilled at reduced pressure (about 1 mm.), (m. p., 49.1°). This was converted into the iodide as described by Evers.[3] It was fractionally distilled at reduced pressure (m. p., 22.8°). Hexadecylpyridonium iodide was prepared from this as described by Evers.[3] It was recrystallized from isopropyl alcohol plus ether and then from acetone. Hexadecylpyridonium chloride was prepared by metathesis of the iodide with silver chloride in absolute ethanol. The chloride was recrystallized twice from acetone to which a little ethanol was added. This preparation was carried out by Dr. G. L. Brown.[4] The conductance of this salt was determined in water; its conductance was unchanged by one more crystallization from acetone plus ethanol.

## III. Experimental Results

In Table I (and Fig. 1) are presented values of the equivalent conductance, $\Lambda$, as a function of the square root of concentration, $\sqrt{C}$, for hexadecylpyridonium chloride in water and water saturated with nitrobenzene. In the latter case, the measurements were made in the presence of a small amount (about 0.1% by weight) of excess nitrobenzene. The method of computing $\Lambda$ in this case is described below.

TABLE I

CONDUCTANCE OF HEXADECYLPYRIDONIUM CHLORIDE IN WATER AND WATER SATURATED WITH NITROBENZENE AT 25°

| $100\sqrt{C}$ | $\Lambda$ | $100\sqrt{C}$ | $\Lambda$ |
|---|---|---|---|
| A. Water | | | |
| 1.186 | 92.7 | 2.999 | 89.84 |
| 1.377 | 91.8 | 3.126 | 89.01 |
| 1.924 | 90.48 | 3.339 | 85.07 |
| 2.274 | 89.92 | 3.466 | 82.56 |
| 2.424 | 89.69 | 3.785 | 75.88 |
| 2.572 | 89.39 | 4.196 | 68.92 |
| 2.693 | 89.86 | 4.674 | 62.89 |
| 2.709 | 90.01 | 5.316 | 56.75 |
| 2.861 | 89.96 | | |
| B. Water Saturated with Nitrobenzene | | | |
| 1.225 | 90.8 | 2.372 | 89.50 |
| 1.746 | 90.36 | 2.567 | 86.36 |
| 1.838 | 90.51 | 2.999 | 77.87 |
| 2.049 | 90.22 | 3.295 | 73.20 |
| 2.284 | 89.82 | 3.962 | 64.95 |

In Table II (and Fig. 2), $\Lambda$ is given as a function of $\sqrt{C}$ for hexadecylpyridonium chloride in nitrobenzene and nitrobenzene saturated with water. In the latter case, the measurements were also made in the presence of a small amount (about 0.1% by weight) of excess water. The method of computing $\Lambda$ in this case is described below.

TABLE II

CONDUCTANCE OF HEXADECYLPYRIDONIUM CHLORIDE IN NITROBENZENE AND NITROBENZENE SATURATED WITH WATER AT 25°

| $100\sqrt{C}$ | $\Lambda$ | $100\sqrt{C}$ | $\Lambda$ |
|---|---|---|---|
| A. Nitrobenzene | | | |
| 0.9168 | 29.73 | | |
| 1.355 | 28.95 | | |
| 1.767 | 28.03 | | |
| 2.385 | 26.62 | | |
| B. Nitrobenzene Saturated with Water | | | |
| 1.565 | 30.27 | 3.821 | 27.02 |
| 1.986 | 29.72 | 4.046 | 26.65 |
| 2.244 | 29.38 | 4.410 | 26.07 |
| 2.611 | 28.83 | 4.930 | 25.30 |
| 2.948 | 28.34 | 5.213 | 24.85 |
| 3.254 | 27.88 | 5.474 | 24.46 |
| 3.568 | 27.39 | | |

The conductances and distribution ratios were computed by successive approximation in the following way. The conductance in nitrobenzene saturated with water and in the presence of a small excess of water was determined: $\kappa$ was plotted against concentration, where concentration was computed on the assumption that the water phase contained no salt. A similar plot was made for water saturated with nitrobenzene. The first approximation to the distribution ratio was computed from the specific conductances of the two phases, using the plots described above to establish concentration as a function of conductance. The concentrations in the conductivity experiments were then corrected by taking into account the amount of salt that was present in the small excess water phase in the nitrobenzene saturated with water experiments, and in the small excess nitrobenzene phase in the water saturated with nitrobenzene experiments, using the first approximation distribution ratios. The $\Lambda$ values in Tables I and II were computed using these corrected concentrations.

The densities of the solutions were assumed to be equal to those of the pure solvents. The densities of water and water saturated with nitrobenzene were assumed to be the same (0.9971). The density of nitrobenzene was taken as 1.999.[5] The density of nitrobenzene saturated with water was found to be 1.1979.

The solubilities of water in nitrobenzene solutions of hexadecylpyridonium chloride and of nitrobenzene in water solutions of this salt were not precisely determined but solubilities were approxi-

(4) G. L. Brown, Thesis, Brown University, 1947.

(5) Walden and Birr, *Z. physik. Chem.*, **163A**, 281 (1932).

mated which were good enough to permit of accurate calculation of the distribution ratio.[6]

In Table III (and Fig. 4, curve 1), the ratio: (salt concentration, water phase)/(salt concentration, nitrobenzene phase) is given as a function of salt concentration water phase. The ratios were obtained as follows: the concentration of the nitrobenzene phase was determined from its conductance, the concentration of the water phase was determined by difference from a knowledge of the weights of salt, of nitrobenzene and of water in the system. In making this calculation, it was assumed that the solubility of water in nitrobenzene is 0.2% by weight and that the solubility of nitrobenzene in water is 0.2% by weight.

The concentration in the water phase was also determined directly by measuring its conductance. The distribution ratios so obtained are not presented here, but they are in satisfactory agreement with the ones listed in Table III, considering that the solvent correction for the water phase is about one hundred times the corresponding correction in the nitrobenzene phase. The ratios determined directly are higher in every case (corresponding to an undercorrection for solvent conductance). In the dilute end, they differ from those given in Table III by about 3%; in the concentrated end, by about 1%.

The uncertainty introduced by lack of precise measurements on the solubilities of nitrobenzene in water and *vice versa* is slight. Thus, in the experiment at $C' = 3.590 \times 10^{-4}$, if it is assumed that the liquids have zero solubility in each other, a value of $C'/C$ is computed that is only 0.3% lower than the value listed in Table III.

For the nitrobenzene saturated with water phase, salt concentration was determined as a function of specific conductance using the empirical equation

$$C = 3.210 \times 10\kappa + 1.349 \times 10^{5}\kappa^{2} - 2.12 \times 10^{8}\kappa^{3} \quad (1)$$

For twenty concentrations between $2 \times 10^{-4}$ and $3 \times 10^{-3}$, the mean deviation between observed and calculated values of $C$ is 0.093%, the largest deviation being 0.2%. In determining the ratios directly, a large scale plot of $C'$ as a function of $\kappa$ for water saturated with nitrobenzene was used.

In column 3 of Table III are also given values of the ratio of activity products $C'f'/C\alpha f$ in water and nitrobenzene. These values will be discussed below.

(6) To a large quantity of nitrobenzene solution, for example, small weighed amounts of water were added. The mixtures were agitated and allowed to stand until the conductance after each addition of water was constant. Saturation was judged visually and by the form of the conductance *vs.* water content plot. Thus, at a salt concentration of $1.3 \times 10^{-3}$ *N*, the solubility of water was judged to be 2.5 mg./g. soln., and at a salt concentration of $5.7 \times 10^{-3}$, 2.3 mg./g. soln. Similarly, in water at a salt concentration of $1.1 \times 10^{-4}$, the solubility of nitrobenzene was judged to be 2 mg./g. soln., and at a salt concentration of $1.2 \times 10^{-3}$, 1.9 mg./g. soln. The solubility of nitrobenzene in pure water is about 2 mg./g. water. Gross and Saylor, THIS JOURNAL, **53**, 1744 (1931), give 1.78 mg./g. water at 15° and 2.05 mg./g. water at 30°. While the solubility of nitrobenzene doubtless increases with increasing salt concentration, this effect is so small that it may be neglected.

TABLE III

DISTRIBUTION COEFFICIENTS, $C'/C$, AND ACTIVITY COEFFICIENTS, $C'f'/C\alpha f$, FOR HEXADECYLPYRIDONIUM CHLORIDE BETWEEN WATER AND NITROBENZENE AT 25°

| $10^4C'$ | $C'/C$ | $C'f'/C\alpha f$ | $10^4C'$ | $C'/C$ | $C'f'/C\alpha f$ |
|---|---|---|---|---|---|
| 0.795 | 0.280 | 0.302 | 5.133 | 0.229 | 0.298 |
| .922 | .280 | .305 | 5.378 | .229 | .301 |
| 1.034 | .283 | .309 | 5.626 | .228 | .301 |
| 1.188 | .280 | .309 | 5.695 | .228 | .301 |
| 1.417 | .276 | .308 | 5.968 | .234 | .311 |
| 1.729 | .266 | .302 | 6.606 | .250 | .330 |
| 2.608 | .254 | .300 | 6.958 | .261 | .348 |
| 3.590 | .244 | .300 | 9.773 | .349 | .468 |
| 4.665 | .233 | .298 | 15.23 | .517 | .692 |
| 4.899 | .230 | .297 | | | |

## IV. Discussion

**1. Conductance in Aqueous Solution.**—As shown in Fig. 1, the equivalent conductance, $\Lambda$, for hexadecylpyridonium chloride in water and water saturated with nitrobenzene, is nearly the same at concentrations less than critical (with nitrobenzene present), namely, $5.8 \times 10^{-4}$. At concentrations greater than this in pure water, $\Lambda$ passes through a slight maximum before falling off rapidly. In pure water, the critical (rise) point lies at $6.7 \times 10^{-4}$ slightly higher than the break in the presence of nitrobenzene. In water saturated with nitrobenzene, $\Lambda$ decreases sharply at $5.8 \times 10^{-4}$. In Fig. 1, the water saturated with nitrobenzene curve has been drawn with $5.8 \times 10^{-4}$ as the critical concentration; actually, a somewhat lower value, as low as $5.7 \times 10^{-4}$, might have been chosen.

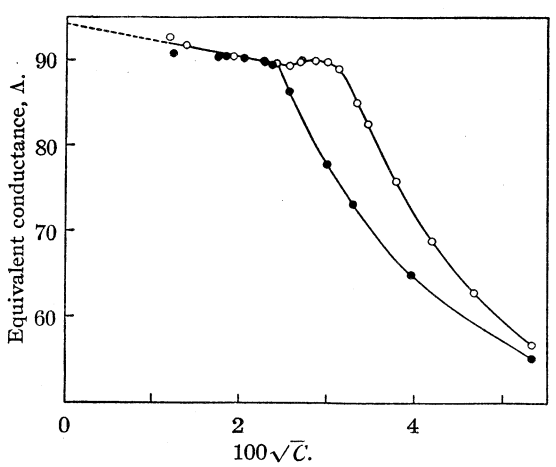



Fig. 1.—Conductance at 25° of hexadecylpyridonium chloride in: open circles, water; solid circles, water saturated with nitrobenzene.

The value of $\Lambda_0$, as determined by extrapolation, lies between 93 and 94, which corresponds to 17 or 18 for the limiting conductance for hexadecylpyridonium ion. This value is about the same as

that approximated for the octadecyltrimethylammonium ion.[7]

**2. Dissociation Constant in Nitrobenzene.**—The properties of hexadecylpyridonium chloride are greatly modified on addition of water up to saturation. This will be evident on inspection of Fig. 2 in which values of $\Lambda$ are plotted against $\sqrt{C}$ for solutions in nitrobenzene in the absence and presence of water to saturation.

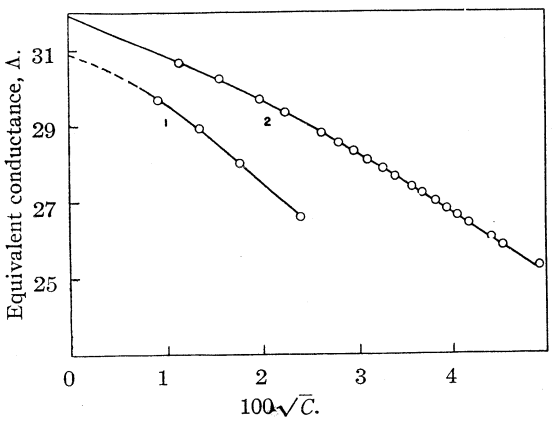



Fig. 2.—Conductance at 25° of hexadecylpyridonium chloride in: (1) nitrobenzene; (2) nitrobenzene saturated with water.

Fuoss plots[8] for the results of Table II are shown in Fig. 3. For hexadecylpyridonium chloride in nitrobenzene, $\Lambda_0 = 30.9$, $K = 4.26 \times 10^{-3}$; in nitrobenzene saturated with water, $\Lambda_0 = 31.9$, $K = 1.19 \times 10^{-2}$. In the latter case, the deviation from the straight line at $C = 3 \times 10^{-3}$ $N$ (the highest nitrobenzene phase concentration in the distribution experiments) is positive and amounts to about 1%. The observed value of $\Lambda$, then, is about 1% lower[9] than that calculated using $K = 1.19 \times 10^{-2}$. Thus, $\alpha$ computed from $\alpha = \Lambda/\Lambda_0 f(Z)$ is about 1% lower than $\alpha$ calculated from $K = 1.19 \times 10^{-2}$.

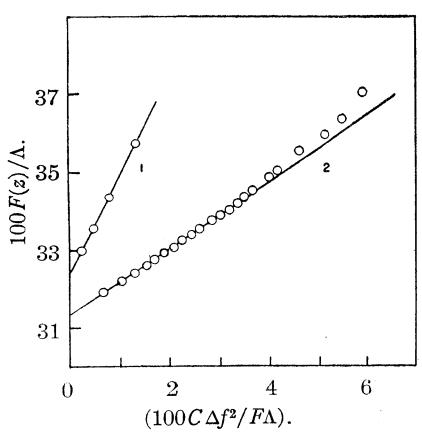



Fig. 3.—Fuoss plots for hexadecylpyridonium chloride in: (1) nitrobenzene; (2) nitrobenzene saturated with water.

**3. Calculated Activity Product.**—In what follows, let $C$ be total salt concentration; $C_+$, $C_-$, $a_+$, $a_-$, the corresponding ion concentrations and activities; $f$, the mean activity coefficient; $\alpha$, the degree of dissociation. Assume that simple positive and negative ions exist in both aqueous and nitrobenzene phases. For equilibrium in the system, it is necessary that

$$a'_+ a'_- / a_+ a_- = k \qquad (2)$$

where $k$ is the distribution constant. If the electrolyte is completely dissociated in the water phase, then

$$C'f'/Cf\alpha = \sqrt{k} \qquad (3)$$

In Table III, columns 3 and 6, values of $C'f'/Cf\alpha$ are given as a function of $C'$.[10] This ratio is shown graphically in Fig. 4, curve 2; it is constant at concentrations less than $5.80 \times 10^{-4}$ and increases (nearly linearly) with $C'$ at higher concentrations. The critical concentration determined by this method is in good agreement with that derived from the $\Lambda$–$\sqrt{C'}$ plot. For the eleven (not all listed in Table III) determinations between $C' = 1.64 \times 10^{-4}$ and $5.80 \times 10^{-4}$, the activity ratio is 0.300 ± 0.001; for the seventeen (all) at concentrations less than $5.80 \times 10^{-4}$, the activity ratio is 0.302 ± 0.003. The constancy of the calculated activity ratio is consistent with hypothesis (I). In what follows, $k$ is taken as $9.00 \times 10^{-2}$.

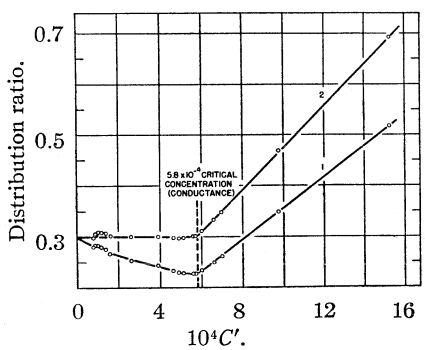



Fig. 4.—Distribution of hexadecylpyridonium chloride between water and nitrobenzene at 25°: (1) concentration ratio; (2) activity ratio.

**4. Simple Ion Product at Concentrations Greater than Critical.**[11]—In Table IV are listed, for water saturated with nitrobenzene, the simple ion activity product (Eq. (2)) and an estimate of the simple ion concentration product. The latter quantity has been computed using $\log_{10} f =$

(7) Grieger and Kraus, THIS JOURNAL, **70**, 3803 (1948), estimated 18 for the limiting conductance of octadecyltrimethylammonium ion.

(8) Using $Z = (0.7838\ \Lambda_0 + 44.64)\Lambda_0^{-3/2}\sqrt{\Lambda C}$; $\log_{10} f = -1.736\sqrt{C\alpha}$

(9) The slope is 0.0820. The % deviation in $\Lambda$ is approximately equal in magnitude (but slightly less) to the % deviation in the Fuoss plot.

(10) Values of $C'f'/Cf\alpha$ have been computed using $\log_{10} f' = -0.5065\sqrt{C'}$ (for $f$, see note 8) and $k = 1.19 \times 10^{-2}$.

(11) The primes have been omitted in Sections 4 and 5.

$-0.5065(C_+C_-)^{1/4}$. The values so obtained are uncertain, because the ionic strength of the solution is unknown, but they are probably not greatly in error. For example, if $\log_{10} f = -0.5065\sqrt{C}$ is used to estimate the activity coefficient, values of the simple ion concentration product are obtained that differ from those listed in Table IV by a few per cent. at most.

Also listed in Table IV, for convenience, are the quantities $C_+C_-/C^2$ and $C_+C_-/C$.

TABLE IV

SIMPLE ION ACTIVITY AND CONCENTRATION PRODUCT IN WATER SATURATED WITH NITROBENZENE AT CONCENTRATIONS GREATER THAN CRITICAL

| $C \times 10^4$ | $a_+a_- \times 10^7$ | $C_+C_- \times 10^7$ | $C_+C_-/C^2$ | $C_+C_-/C \times 10^2$ |
|---|---|---|---|---|
| 5.968 | 3.13 | 3.31 | 0.929 | 5.55 |
| 6.606 | 3.33 | 3.52 | .808 | 5.34 |
| 6.958 | 3.38 | 3.57 | .737 | 5.13 |
| 9.773 | 3.66 | 3.89 | .407 | 3.98 |
| 15.228 | 3.98 | 4.21 | .182 | 2.77 |

The fact that $C_+C_-/C^2$ is less than unity, is consistent with the assumption of ion association at concentrations greater than critical (hypothesis II).

Since neither the simple long chain nor the gegenion concentrations can be larger than $C$, the quantity $C_+C_-/C$ represents a lower limit on either simple ion concentration. This ratio falls off with increase in $C$, but at $C = 1.5 \times 10^{-3}$, the simple ion concentrations cannot be less than about one-fifth the total salt concentration.

**5. Calculation for One Complex Species.**[11]— If it is assumed that in the water phase there exist only simple ions and only complex species made up of $i$, long chain ions, and $j$, gegenions, then the three concentrations and $i$ and $j$ can be found from conductivity, distribution and transference data.[12] Let $C$ be the salt concentration; $C_+$, $C_-$, and $C_{ij}$ be the concentration of the simple long chain ion, the gegenion and the $ij$ complex ion; $u_+$, $u_-$, and $u_{ij}$, the corresponding mobilities (cm./sec. per volt/cm.); $\kappa$, the specific conductance (ohm$^{-1}$cm.$^{-1}$); $p = C_+C_-$; and $t_+$, the cation transference number. Then, if $i > j$

$$10^3\kappa/N\kappa = \bar{\kappa} = C_+u_+ + c_-u_- + (i - j)(C_{ij}u_{ij})$$
$$t_+\bar{\kappa} = C_+u_+ + iC_{ij}u_{ij}$$

$$p = C_+C_- \qquad (4)$$
$$C = C_+ + iC_{ij}$$
$$C = C_- + jC_{ij}$$

These equations can be combined (without any assumption about $u_{ij}$) to give

$$\Lambda/\Lambda_+ = y + q\,\Lambda_-/y\Lambda_+ + ((q/y) - y)(-y + t_+\Lambda/\Lambda_+)/(1 - y) \qquad (5)$$

where $y = C_+/C$, $q = p/C^2$, $\Lambda_+ = N\epsilon u_+$, $\Lambda_- = N\epsilon u_-$. Further, $C_{ij}$, $i$ and $j$ can be established if some rule is adopted for $u_{ij}$. Corresponding to $u_{ij} = u_+(i - j)/i^{1/3}$

$$i^{2/3} = (-y + t_+\Lambda/\Lambda_+)^2/(\Lambda(1/\Lambda_+) - y - q\Lambda_-/y\Lambda_+)(1 - y) \qquad (6)$$

Once $C_+$ is found from Eq. (5), $C_-$ comes immediately from $p = C_+C_-$; $i$ can be obtained from Eq. (6) and then $C_{ij}$ and $j$ from the material balance equations in (4).

In Table V, the experimental quantities, $\Lambda$, $p$ and $t_+$, are given for several round values of $C$, together with the five calculated quantities. $\Lambda$ and $p$ were taken from graphs of the data given here. The values of $t_+$ listed in Table V are estimates. Their basis is as follows. Hartley, Collie and Samis[13] found for hexadecylpyridonium bromide in water at 35°: $t_+ = 0.22$ at $7 \times 10^{-4}$ $N$ (critical concentration); $t_+ = 1.34$ at $3.2 \times 10^{-3}$ $N$. It has been assumed, here, that $t_+$ is a linear function of concentration for hexadecylpyridonium bromide at 35° over the range $7 \times 10^{-4}$ to $3.2 \times 10^{-3}$ $N$. The same relation has been assumed for hexadecylpyridonium chloride in water saturated with nitrobenzene at 25° over the range $5.8 \times 10^{-4}$ to $1.4 \times 10^{-3}$ $N$ and, further, that $dt_+/dc$ is the same for both systems. In short, $t_+$ as given in Table V corresponds to

$$t_+ = 0.19 + 4.5 \times 10^2(C - 5.80 \times 10^{-4})$$

For the calculations listed in Table V, no attempt has been made to estimate the variation of $\Lambda_+$ and $\Lambda_-$ with $C$. These calculations were made using $\Lambda_+ = 17$, $\Lambda_-/\Lambda_+ = 4.2$.

TABLE V

CALCULATED QUANTITIES ASSUMING ONE COMPLEX SPECIES

| $C \times 10^4$ | $\Lambda$ | $p \times 10^7$ | $t_+$ | $C_+ \times 10^4$ | $C_- \times 10^4$ | $C_{ij} \times 10^4$ | No. of ions in complex species: Long chain $i$ | No. of ions in complex species: Gegenions $j$ | Charge of complex species $i - j$ |
|---|---|---|---|---|---|---|---|---|---|
| 6.00 | 89.1 | 3.42 | 0.20 | 5.73 | 5.97 | 0.068 | 3.97 | 0.44 | 3.53 |
| 8.00 | 81.0 | 3.72 | .27 | 5.36 | 6.94 | .574 | 4.60 | 1.85 | 2.75 |
| 10.00 | 75.3 | 3.91 | .34 | 4.90 | 7.98 | .713 | 7.15 | 2.83 | 4.32 |
| 12.00 | 71.0 | 4.05 | .40 | 4.68 | 8.65 | .913 | 8.02 | 3.67 | 4.35 |
| 14.00 | 67.4 | 4.16 | .48 | 4.48 | 9.29 | 1.026 | 9.28 | 4.59 | 4.69 |

As may be seen from Table V, the calculated long chain ion concentration decreases over the range in $C$ tested while the gegenion concentration shows a sharper increase. The complex species concentration builds up as $C$ increases; both $i$ and $j$ increase, but their difference over the range $C = 10^{-3}$ to $1.4 + 10^{-3}$ is roughly constant.

(12) This calculation is similar to that given by van Rysselberghe, *J. Phys. Chem.*, **43**, 1049 (1939).

(13) Hartley, Collie and Samis, *Trans. Faraday Soc.*, **32**, 795 (1936).

## V. Summary

1. The distribution of hexadecylpyridonium chloride between water and nitrobenzene at 25° has been determined. The simple ion activity product in water divided by the simple ion activity product in nitrobenzene is $9.00 \times 10^{-4}$.

2. The conductance of hexadecylpyridonium chloride in water, water saturated with nitrobenzene, nitrobenzene and nitrobenzene saturated with water, has been determined at 25°.

3. In water saturated with nitrobenzene, the breakpoint in $\Lambda$ comes at 5.7 to 5.8 $\times 10^{-4}$. In pure water, $\Lambda$ passes through a slight maximum starting approximately at $6.7 \times 10^{-4}$.

4. The ion pair dissociation constant in nitrobenzene has been evaluated by the Fuoss method. $k = 1.19 \times 10^{-2}$ in nitrobenzene saturated with water, while in pure nitrobenzene, $k$ is only about one-half that, namely, $4.26 \times 10^{-3}$.

5. The calculated sample ion activity ratio is constant at concentrations less than $5.8 \times 10^{-4}$, but increases at higher concentrations. This indicates that at concentrations less than critical, the salt is completely dissociated in the water phase. The value of the critical concentration determined in this way is in good agreement with that determined from the $\Lambda - \sqrt{C}$ plot.

6. An estimate has been made of the simple ion concentration product at concentrations greater than critical. An attempt has been made to calculate the state of the system on the assumption that only one complex species exists at concentrations greater than critical.

PROVIDENCE, R. I. RECEIVED SEPTEMBER 18, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

# The Differential Diffusion Coefficient of Potassium Chloride in Aqueous Solutions

BY HERBERT S. HARNED AND RALPH L. NUTTALL

In a recent article,[1] we described in detail an apparatus and technique for the determination of the diffusion coefficients of electrolytes by means of conductance measurements. Values of the diffusion coefficient of potassium chloride at concentrations from 0.001 to 0.01 $N$ at 25° were reported. The results at 25° have been extended to higher concentrations[2] and determinations in the dilute concentration range have also been made at 20 and 30°. The present communication contains the new results and a summary of all the results with emphasis on their theoretical computation.

TABLE I

THE DIFFUSION COEFFICIENTS OF POTASSIUM CHLORIDE IN AQUEOUS SOLUTION AT 20, 25 AND 30°

$c$ is concn. in moles per liter, $\mathbf{D} \times 10^5$

| | 20° | | | 25° | |
|---|---|---|---|---|---|
| $c$ | Observed | Theoretical | $c$ | Observed | Theoretical |
| 0.00000 | | (1.7652) | 0.00000[a] | | (1.9958) |
| .00125 | 1.736[c] | 1.734 | .00125[a] | 1.961 | 1.960 |
| .00248 | 1.7245[c] | 1.7235 | .00194[a] | 1.954 | 1.953 |
| .00367 | 1.719[d] | 1.716 | .00325[a] | 1.943 | 1.943 |
| .00451 | 1.709[c] | 1.712 | .00585[a] | 1.931 | 1.929 |
| .01121 | 1.6885[d] | 1.690 | .00704[a] | 1.924 | 1.924 |
| | 30° | | .00980[a] | 1.918 | 1.915 |
| | | | .01261[b] | 1.908 | 1.907 |
| 0.00000 | | (2.2334) | .02654[c] | 1.879 | 1.883 |
| .00326 | 2.172[c] | 2.173 | .03992[c] | 1.877 | 1.870 |
| .00650 | 2.154[c] | 2.155 | .04620[c] | 1.872 | 1.866 |
| .00896 | 2.146[d] | 2.145 | .05450[d] | 1.860 | 1.861 |
| .01236 | 2.139[d] | 2.133 | .06074[d] | 1.856 | 1.858 |
| | | | .1298[e] | 1.838 | 1.840 |
| | | | .3323[e] | 1.842 | 1.839 |
| | | | .5276[e] | 1.852 | 1.853 |

Electrode areas: [a] 2 × 0.2 cm.² [b] 2 × 0.1 cm.² [c] 1 × 0.2 cm.² [d] 1 × 0.1 cm.² [e] circle, 1 mm. diameter.

(1) Harned and Nuttall, THIS JOURNAL, **69**, 737 (1947); see also Harned and French, *Ann. N. Y. Acad. Sci.*, **46**, 267 (1945).

(2) Harned and Nuttall, *Ann. N. Y. Acad. Sci.*, in press.

## Experimental

All the determinations are included in Table I. The manipulation and technique was the same as previously described. However, five kinds of cells which differed in containing electrodes of different areas were employed. Four of them had rectangular electrodes of areas indicated in the table and the fifth circular electrodes of millimeter diameter.

## Theoretical Calculations[3]

Onsager and Fuoss[4] have developed a theory for the variation of the diffusion coefficient of electrolyte with its concentration. For 1:1 electrolytes, their final equation is

$$\mathbf{D} = 16.629 \times 10^{10} T \left(\frac{\overline{M}}{c}\right)\left(1 + c\,\frac{\partial \ln y_{\pm}}{\partial c}\right) \quad (1)$$

where

$$\left(\frac{\overline{M}}{c}\right) \times 10^{20} = 1.0748 \left(\frac{\lambda_1^0 \lambda_2^0}{\lambda_1^0 + \lambda_2^0}\right) - \frac{22.148}{\eta_0 (DT)^{1/2}} \left(\lambda_1^0 - \lambda_2^0\right) \frac{\sqrt{c}}{1 + A'\sqrt{c}} + \frac{9.304 \times 10^7}{\eta_0 (DT)^2}\, c\phi \quad (2)$$

$\mathbf{D}$ is the diffusion coefficient (cm.² sec$^{-1}$), $D$ the dielectric constant, $T$ the absolute temperature, $c$ the electrolyte concentration in moles per liter, $\eta_0$ the viscosity of the medium and $\lambda_1^0$, $\lambda_2^0$ are the equivalent conductances at infinite dilution.

(3) In this part, we have employed the symbols of Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943, p. 178–180. See also Harned, *Chem. Rev.*, **40**, 461 (1947).

(4) Onsager and Fuoss, *J. Phys. Chem.*, **37**, 2689 (1932).

TABLE II

DATA EMPLOYED IN THEORETICAL CALCULATIONS

| $T$ | $D$ [7] | $\eta_0$ [8] | $\lambda_1^0$ [9] | $\lambda_2^0$ [9] | $a$ [10] | $2B$ [10] | $S_{(f)}$ [10] |
|---|---|---|---|---|---|---|---|
| 293.16 | 80.36 | $10.087 \times 10^{-3}$ | 66.24 | 68.56 | 3.8 | 0.0182 | 0.5046 |
| 298.16 | 78.54 | $8.949 \times 10^{-3}$ | 73.52 | 76.34 | 3.8 | .0213 | .5092 |
| 303.16 | 76.75 | $8.004 \times 10^{-3}$ | 80.766 | 84.176 | 3.8 | .0260 | .5141 |

These expressions reduce to the Nernst limiting equation

$$\mathbf{D}_0 = 17.873 \times 10^{-10} T \left(\frac{\lambda_1^0 \lambda_2^0}{\lambda_1^0 + \lambda_2^0}\right) \qquad (3)$$

when $c$ equals zero. To evaluate the term containing the activity coefficient, $y_\pm$, on the mole per liter scale, which expresses the effect produced by the gradient of the chemical potential, we have employed the equation

$$\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) = 1 - \frac{1.1514\, S_{(f)}\sqrt{c}}{(1 + A'\sqrt{c})^2} + 4.605\, Bc - c\psi(d) \qquad (4)$$

where

$$\psi(d) = \frac{\frac{\partial d}{\partial c} + 0.001\,(2M_1 - M_2)}{d + 0.001\,(2M_1 - M_2)c} \qquad (5)$$

In these equations $A'\sqrt{c} = \kappa a = \kappa \mathring{a} \times 10^{-8}$, where $a$ and $\mathring{a}$ represent the mean distances of approach of the ions in centimeters and Ångström units, respectively, and $\kappa$ is the Debye and Hückel reciprocal distance. $S_{(f)}$ is the limiting function of the Debye and Hückel theory and $B$ an empirical constant. $M_1$ and $M_2$ are the molecular weights of the solvent and solute respectively.[4]

The second and third terms on the right of equation (2) represent the effect of electrophoresis. Values of the function $\phi(\kappa a)$ or $\phi(A'\sqrt{c})$ are given in tabular form by Harned and Owen.[5,6] The values of the quantities employed in the computations are compiled in Table II. Upon introduction of these values in equations (1), (2) and (4), we obtain the numerical equations

$$20°\text{C.:}\ \mathbf{D} = 4.875 \times 10^{13}\left(\frac{\overline{M}}{c}\right)\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) \qquad (6)$$

$$\frac{\overline{M}}{c} \times 10^{20} = 36.210 - \frac{0.00423\sqrt{c}}{1 + 1.245\sqrt{c}} + 16.62\, c\, \phi(1.245\sqrt{c}) \qquad (7)$$

$$\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) = 1 - \frac{0.5810\sqrt{c}}{(1 + 1.245\sqrt{c})^2} + 0.0430\, c - c\psi(d) \qquad (8)$$

$$c\psi(d) = \frac{0.00990c - 0.00336c^{3/2}}{0.99823 + 0.00990c - 0.0024c^{3/2}} \qquad (9)$$

$$25°\text{C.:}\ \mathbf{D} = 4.958 \times 10^{13}\left(\frac{\overline{M}}{c}\right)\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) \qquad (10)$$

$$\frac{\overline{M}}{c} \times 10^{20} = 40.253 - \frac{0.00573\sqrt{c}}{1 + 1.249\sqrt{c}} + 18.96c\, \phi(1.249\sqrt{c}) \qquad (11)$$

(5) Ref. 4, p. 130.

(6) Harned, *Chem. Rev.*, **46**, 461 (1947).

$$\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) = 1 - \frac{0.5873\sqrt{c}}{(1 + 1.249\sqrt{c})^2} + 0.0490c - c\psi(d) \qquad (12)$$

$$c\psi(d) = \frac{0.00959c - 0.00348c^{3/2}}{0.99707 + 0.00959c - 0.00232c^{3/2}} \qquad (13)$$

$$30°\text{C.:}\ \mathbf{D} = 5.0412 \times 10^{13}\left(\frac{\overline{M}}{c}\right)\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) \qquad (14)$$

$$\frac{\overline{M}}{c} \times 10^{20} = 44.3011 - \frac{0.00775\sqrt{c}}{1 + 1.253\sqrt{c}} + 21.47c\, \phi(1.253\sqrt{c}) \qquad (15)$$

$$\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) = 1 - \frac{0.5919\sqrt{c}}{(1 + 1.253\sqrt{c})^2} + 0.0599c - c\psi(d) \qquad (16)$$

$$c\psi(d) = \frac{0.0094c - 0.0034c^{3/2}}{0.9957 + 0.0094c - 0.0023c^{3/2}} \qquad (17)$$

The values of $c\psi(d)$ were evaluated from the density computations of Scott[11] by means of the equations

$$d(20°) = 0.99823 + 0.04843c - 0.00224c^{3/2} \qquad (18)$$

$$d(25°) = 0.99707 + 0.04811c - 0.00232c^{3/2} \qquad (19)$$

$$d(30°) = 0.9957 + 0.0479c - 0.0023c^{3/2} \qquad (20)$$

## Theoretical Considerations

A glance at Table I in which the results computed by the theoretical equations are tabulated reveals a remarkable agreement of experiment with theory at all three temperatures. This is illustrated by Fig. 1 where our results are represented by circles and the theoretical values by the curves B. At concentrations below 0.05 $N$, there is little doubt of the validity of the theoretical result. The agreement at the higher concentrations at 25° is unexpected. This may be partly due to a fortunate choice of salt and temperature since at 25° the relative viscosity of potassium chloride in water changes less than 0.3% over a concentration range from zero to 0.5 normal. Further, one would expect a deviation from theory due to the change in dielectric of the medium with increase in salt concentration.

The curves in Fig. 1 illustrate the nature of the theoretical calculation. Curve A is calculated from the limiting equation

$$\mathbf{D} = \mathbf{D}_0 - S_{(D)}\sqrt{c} \qquad (21)$$

(7) Ref. 4, p. 112; (8) ref. 4, p. 128; (9) 25°: ref. 12, p. 172; Shedlovsky, THIS JOURNAL, **54**, 1423 (1932); Longsworth and MacInnes, *ibid.*, **60**, 3073 (1938); 20° and 30°: Zeldes, Dissertation, Yale University (1947); (10) ref. 4, p. 381; $S(f)$ and $B$ adjusted to universal constants given by Birge, *Rev. Mod. Phys.*, **13**, 233 (1941).

(11) Scott, *J. Phys. Chem.*, **35**, 2315 (1931).

where

$$S_{(D)} = \frac{3.754 \times 10^{-3}}{D^{3/2}T^{1/2}}\left(\frac{\lambda_1^0 - \lambda_2^0}{\lambda_1^0 + \lambda_2^0}\right) + \frac{3.683 \times 10^{-8}}{\eta_0 D^{1/2}T^{1/2}}\left(\frac{\lambda_1^0 - \lambda_2^0}{\lambda_1^0 + \lambda_2^0}\right)^2 \quad (22)$$

At 25°, equation (21) becomes

$$D \times 10^5 = 1.9958 - 1.170\sqrt{c} \quad (23)$$

Only at very great dilution does the experimental curve approach coincidence with the limiting law.

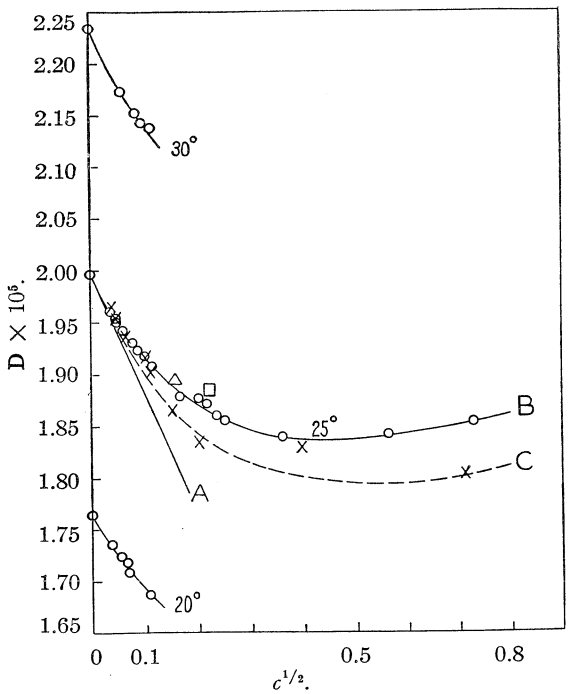



Fig. 1.—Diffusion coefficient of potassium chloride in water at 20, 25 and 30°: (1) circles represent observed results; (2) crosses represent diaphragm cell measurements; (3) triangle, Cohen and Bruins; (4) square, Lamm; A, limiting law by equations (21) and (22); B and solid curves at 20 and 30° represent the complete theoretical calculation according to equations (1), (2), (4) and (5); C, calculated by equation (24) which omits electrophoresis.

The dashed curve C was obtained from equation (1) by introducing the limiting value of $(\overline{M}/c)$ to give at 25°

$$D = 4.958 \times 10^{13} \times 40.253 \times 10^{-20}\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right) \quad (24)$$

$$= 1.9958 \times 10^{-5}\left(1 + c\frac{\partial \ln y_\pm}{\partial c}\right)$$

Consequently, it represents the result obtained by neglecting the effect of electrophoresis. The deviation of this curve from the complete theoretical result represented by curve B is always greater than the deviations of the experimental points. Consequently, for this salt, our results appear to confirm the theory of the electrophoretic effect. It is interesting to note that since the mobilities of the potassium and chloride ions are so nearly equal the electrophoretic correction is due only to the third term in equation (2) involving $\phi(A'\sqrt{c})$.

## Comparison with Results by Other Methods

The only other measurements at concentrations below 0.01 $N$ which can be compared with ours, were obtained by the diaphragm cell method. Gordon[12] has calculated differential diffusion coefficients of potassium chloride from the data of McBain and Dawson,[13] Hartley and Runnicles[14] and his own experiments. These measurements[15] have been revised by Gordon by using a cell calibration which is based on our results below 0.01 $N$ and are designated by crosses in Fig. 1. At low concentrations the agreement is very good but as the concentration increases their results are somewhat lower than ours.

At higher concentrations, our results can be compared to those of Cohen and Bruins,[16] Lamm,[17] and Clack.[18] Cohen and Bruins used a layer analysis method by employing a four compartment cell and allowing a 0.1 $N$ potassium chloride solution in the bottom compartment to diffuse into the other three compartments. The compartments were then separated and the solutions in each analyzed with the greatest care by the use of a liquid interferometer. The average concentration in the four compartments was 0.025 $N$ and the mean diffusion coefficient was $1.674 \times 10^{-5}$ cm.²/sec. at 20°, or $1.893 \times 10^{-5}$ cm.²/sec. at 25°, if our estimate of the influence of temperature is employed. This value is shown by the triangle in Fig. 1. It is somewhat ambiguous since it is neither a true differential nor an integral diffusion coefficient. Hartley and Runnicles contended that it corresponds approximately to an integral diffusion coefficient for 0.06 $N$ potassium chloride diffusing into water and it must correspond to a differential diffusion coefficient at a concentration close to the average concentration of 0.025 $N$. Lamm, using his optical scale method obtained a diffusion coefficient of $1.667 \times 10^{-5}$ cm.²/sec. at 20° for 0.1 $N$ potassium chloride diffusing into water which corresponds to a value of $1.885 \times 10^{-5}$ cm.²/sec. at 25°. This is represented by the square in Fig. 1 at the mean concentration of 0.05 $N$. Both Cohen and Bruins' and Lamm's values compare favorably with ours. The results of Clack who employed a steady state optical method at 18.5° and at concentrations from 0.08 $N$ to higher concentrations are about 4% lower than ours.

(12) Gordon, *J. Phys. Chem.*, **5**, 522 (1937); *Ann. N. Y. Acad. Sci.*, **46**, 285 (1945).

(13) McBain and Dawson, *Proc. Roy. Soc.* (*London*), **A118**, 32 (1935).

(14) Hartley and Runnicles, *ibid.*, **A168**, 401 (1938).

(15) Harned, *Chem. Rev.*, **40**, 461 (1947).

(16) Cohen and Bruins, *Z. physik. Chem.*, **103**, 337 (1923).

(17) Lamm, *Nova Acta Reg. Sci. Upsala*, **IV**, 10(6) 1937.

(18) Clack, *Proc. Phys. Soc.* (*London*), **36**, 313 (1924).

This estimate was made by using the temperature coefficient obtained by us at low concentrations.

The effect of temperature is very marked. However, the relative change with concentration in dilute solution is almost independent of temperature. For a concentration of 0.01 $N$ the ratio $D/D_0$ is 0.9593, 0.9591, and 0.9589 at 20, 25 and 30°, respectively.

## Summary

1. Determinations of the diffusion coefficient of potassium chloride in water at 20°, 25° and 30° have been obtained by a conductance method previously described by us.[19]

2. In the region of concentration from 0.001 to 0.01 $N$, excellent agreement with the theory of Onsager and Fuoss is obtained, and the Nernst limiting law for electrolytic diffusion is confirmed.

3. Comparison of our results with those obtained by the diaphragm cell method, by layer analysis and by the optical scale method indicates good agreement considering the wide variety of mechanisms and theories of these methods.

(19) Ref. 1.

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[CONTRIBUTION NUMBER 700 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# The Heats of Dilution of Aqueous Solutions of Four Amino Acids at 25°[1]

BY L. S. MASON, W. F. OFFUTT[2,3] AND A. L. ROBINSON

Previous communications from this Laboratory have reported on the heats of dilution of aqueous solutions of glycine,[4] α- and β-alanine,[5] and four aminobutyric acids.[6] Examination of the results for these seven amino acids indicated that the structure of the organic radical was more important than the location of the amino group in determining the thermochemical properties studied.[6] The same conclusion was reached when the differential entropies of dilution of these same aqueous solutions were calculated.[7] Study of the heats of dilution of aqueous solutions of amino acids was continued to obtain further evidence affecting this conclusion. This paper reports results for α-amino-*n*-valeric acid, valine, norleucine and ε-aminocaproic acid.

## Experimental

**Apparatus and Method.**—Except for minor changes, the calorimeter is the same as that used in previous investigations.[6] The thermopile had been sealed into the Dewar vessel, which comprises the calorimeter vessel, with wax, thus dividing the vessel into two watertight compartments. The junctions of the thermopile had been separated from the solutions in the calorimeter by a plastic coating, so that dilutions in organic solvents might be made if desired, two copper vessels were constructed, one for each half of the calorimeter, which conformed to the inner surface of the Dewar vessel and whose flat surfaces fitted snugly against the junctions of the thermopile. The interiors of these vessels could not be satisfactorily gold plated; instead, a plastic coating was baked on. This coating provided an electrical resistance greater than 10 megohms. Electrical resistance of 1000 megohms between the thermopile junctions and the copper vessels was furnished by sheets of mica of 0.04 mm. thickness.

The two electrical heaters were made by winding no. 40 Advance wire spirally around a glass tube. The wire was soldered to platinum nibs which lead through the wall of the tube to heavy copper leads. Several coats of a silicone resin were baked on over the wire for insulation from the solutions in the calorimeter.

The volumes of the monel metal dilution pipets were 10.36 (left) and 10.32 (right) ml. To maintain a constant dilution ratio of one to 100 in the two halves of the calorimeter, the twin calorimeters held 1036 and 1032 ml. of water, respectively.

The amino acid solutions were prepared immediately before each day's series of measurements to minimize bacterial action. Following each day's measurements, the calorimeter was rinsed with distilled water. The calorimeter was disinfected periodically with 10% formaldehyde solution.

Solutions were made up by volume. Concentrations were converted to molalities using the density data of Dalton and Schmidt[8] for valine and the data of Daniel and Cohn[9] for ε-aminocaproic acid. The densities of α-amino-*n*-valeric acid and norleucine solutions were determined by standard methods using specific gravity bottles. The results may be expressed by the following equations for 25°

| | |
|---|---|
| α-Amino-*n*-valeric acid ($m$ <0.6) | $d = 0.9971 + 0.0240\,m$ |
| Norleucine ($m$ <0.05) | $d = 0.9971 + 0.0188\,m$ |

It has been suggested[10] that atmospheric carbon dioxide dissolved in the dilution water may affect the heats of dilution of amino acids at low concentrations by disturbing their dissociation equilibria. This effect was not observed in the previous studies[4,5,6] of this series. A further test was made by performing dilutions with norleucine solutions using water in equilibrium with atmospheric carbon dioxide and with free access of the atmosphere to the interior of the calorimeter. Results were compared with runs made with carbon dioxide-free water (specific conductance $0.4 \times 10^{-6}$ ohm$^{-1}$ cm.$^{-1}$) and with the calorimeter sealed from the atmosphere. The results agreed within the limits of the experimental error.

Dilutions were made to the limits of solubility of the

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(4) W. E. Wallace, W. F. Offutt, and A. L. Robinson, THIS JOURNAL, **65**, 347 (1943).

(5) H. A. Benesi, L. S. Mason, and A. L. Robinson, *ibid.*, **68**, 1755 (1946).

(6) L. S. Mason and A. L. Robinson, *ibid.*, **69**, 889 (1947).

(7) A. L. Robinson, *J. Chem. Phys.*, **14**, 588 (1946).

(8) J. B. Dalton and C. L. A. Schmidt, *J. Biol. Chem.*, **103**, 549 (1933).

(9) J. Daniel and E. J. Cohn, THIS JOURNAL, **58**, 415 (1936).

(10) J. M. Sturtevant, *ibid.*, **62**, 3519 (1940).

TABLE I

INTERMEDIATE HEATS OF DILUTION, CALORIES

| Moles/1000 g. of water $10^4m_1$ | $10^4m_2$ | $10^4m_3$ | Expts. | Expt. $-10^3$ $q_{1\to2}$ | $10^3\delta$ | Eq. $-10^3$ $q_{1\to2}$ | $10^3$ $\Delta q_{1\to2}$ | Expt. $-10^3$ $q_{2\to3}$ | $10^3\delta$ | Eq. $-10^3$ $q_{2\to3}$ | $10^3$ $\Delta q_{2\to3}$ | Cal./mole of acid $-\Delta H_{1\to2}$ | $-\Delta H_{2\to3}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **α-Amino-*n*-valeric Acid** | | | | | | | | | | | | | |
| | | | | Eq. 3 | | | | | | Eq. 2 | | | |
| 6932 | 65.23 | 129.9 | 3 | 1021 | 4 | 1011 | −10 | 14 | 12 | 12 | − 2 | 150.52 ± 0.38 | 1.05 ± 0.82 |
| 3361 | 32.61 | 64.91 | 4 | 242.0 | 1.4 | 245.1 | + 3.1 | + 0.9 | 3.2 | 3.1 | + 2.2 | 71.68 ± .29 | 0.13 ± .39 |
| 1655 | 16.30 | 32.45 | 6 | 56.7 | 3.5 | 60.3 | + 3.6 | − 1.1 | 3.1 | 0.8 | + 1.9 | 33.56 ± 1.74 | − .33 ± .76 |
| 821.9 | 8.150 | 16.22 | 4 | 16.7 | 1.4 | 15.0 | − 1.7 | + 0.1 | 2.1 | 0.2 | + 0.1 | 19.72 ± 1.26 | + .03 ± 1.01 |
| 409.0 | 4.074 | 8.109 | 4 | 4.6 | 0.7 | 3.7 | − 0.9 | − 0.2 | 0.6 | 0.1 | − 0.3 | 10.73 ± 1.42 | − .26 ± 0.55 |
| **Valine** | | | | | | | | | | | | | |
| | | | | Eq. 8 | | | | | | Eq. 7 | | | |
| 6388 | 60.41 | 120.3 | 2 | 772.2 | 3.0 | 748.6 | −24.6 | − 4.1 | 10.3 | −17.8 | −13.7 | 123.46 ± 0.40 | −0.33 ± 0.45 |
| 3104 | 30.20 | 60.11 | 2 | 190.4 | 1.9 | 181.8 | − 9.2 | + 2.7 | 0.1 | − 4.4 | − 7.1 | 60.90 ± .43 | 0.43 ± .01 |
| 1530 | 15.10 | 30.05 | 2 | 47.6 | 1.4 | 44.6 | − 3.0 | − 0.7 | 0.2 | − 1.1 | − 0.4 | 30.42 ± .59 | −2.26 ± 1.52 |
| 759.9 | 7.548 | 15.02 | 2 | 11.2 | 0.3 | 11.1 | + 0.1 | − 1.1 | 0.6 | − 0.3 | + 0.7 | 14.35 ± 1.78 | −0.71 ± 0.19 |
| **Norleucine** | | | | | | | | | | | | | |
| | | | | Eq. 13 | | | | | | Eq. 12 | | | |
| 860.7 | 8.526 | 16.97 | 8 | 24.8 | 1.4 | 23.0 | − 1.8 | − 1.7 | 1.8 | − 3.0 | − 1.2 | 28.08 ± 0.04 | −1.23 ± 0.42 |
| 644.0 | 6.394 | 12.74 | 10 | 14.2 | 1.6 | 12.9 | − 1.3 | − 1.1 | 0.9 | − 1.8 | − 0.3 | 22.76 ± 1.21 | −0.80 ± .60 |
| 428.3 | 4.263 | 8.486 | 7 | 4.8 | 0.4 | 5.7 | + 0.9 | − 1.1 | 0.4 | − 0.8 | − 0.3 | 10.98 ± 0.75 | −0.94 ± .91 |
| **ε-Aminocaproic Acid** | | | | | | | | | | | | | |
| | | | | Eq. 18 | | | | | | Eq . 17 | | | |
| 4143 | 39.74 | 79.11 | 4 | 604.2 | 8.5 | 599.3 | − 4.9 | − 7.3 | 7.2 | − 9.0 | − 1.7 | 147.27 ± 1.84 | −1.11 ± 0.38 |
| 3079 | 29.85 | 59.42 | 2 | 344.6 | 5.2 | 339.3 | − 5.3 | − 7.9 | 3.6 | −12.8 | − 4.9 | 111.82 ± 1.15 | −1.28 ± .39 |
| 2038 | 19.96 | 39.74 | 4 | 136.4 | 14.7 | 143.0 | + 6.6 | − 6.0 | 3.6 | − 7.2 | − 1.2 | 73.26 ± 0.34 | −2.11 ± .10 |
| 1523 | 15.00 | 29.85 | 4 | 74.3 | 5.1 | 78.3 | + 4.0 | −19.3 | 2.6 | − 4.0 | +15.3 | 47.95 ± 2.73 | −6.24 ± .63 |
| 1013 | 10.04 | 19.96 | 4 | 30.1 | 0.6 | 23.3 | − 6.8 | − 7.6 | 3.2 | − 1.8 | + 5.8 | 29.04 ± 0.48 | −0.36 ± .12 |
| 506.6 | 5.040 | 10.04 | 2 | 6.7 | 0.2 | 6.9 | + 0.2 | − 6.3 | .. | − 0.4 | + 5.9 | 12.96 ± 0.28 | −0.61 ± .09 |

TABLE II

DERIVED VALUES FOR $S$, $\phi L_2$, $\bar{L}_1$, AND $\bar{L}_2$

| | α-Amino-*n*-valeric acid[a] | Valine | Norleucine | ε-Aminocaproic acid |
|---|---|---|---|---|
| $S$ | (1) 280 | (6) −476 | (11) −2030 | (16) $-514 - 293 \times 10^3m + 54.2 \times 10^6m^2$ |
| $\phi L_2$ ($m$ <0.015) | (2) 280 $m$ | (7) −476 $m$ | (12) −2030 $m$ | (17) $-514m - 147 \times 10^3m^2 + 18.1 \times 10^6m^3$ |
| $\phi L_2$ | (3) 218 $m$ | (8) 189 $m$ | (13) 306 $m$ | (18) $-3.23 + 3.23\ e^{-474m} + 294m + 437m^2 - 689m^3$ |
| $\bar{L}_1$ | (4) $-3.93\ m^2$ | (9) $-3.40\ m^2$ | (14) $-5.51\ m^2$ | (19) $(27.58e^{-474m} - 5.30)m^2 - 15.75m^3 + 37.24m^4$ |
| $\bar{L}_2$ | (5) 436 $m$ | (10) 378 $m$ | (15) 612 $m$ | (20) $-3.23 + 3.23\ (1 - 474m)e^{-474m} + 588m + 1311m^2 - 2756m^3$ |

[a] Numbers in parentheses identify the equations.

amino acids except for ε-aminocaproic acid. In this case the highest concentration diluted was about 0.4 $m$ since the heat effects produced were near the upper limit of the useful capacity of the calorimeter.

**Materials.**—Distilled water from the stock supply was distilled again from a Yoe still and stored in Pyrex flasks. The specific conductance of this water in equilibrium with the carbon dioxide of the atmosphere was about $10^{-6}$ ohm$^{-1}$ cm.$^{-1}$.

α-Amino-*n*-valeric acid and valine were purchased from the Eastman Kodak Company. They were recrystallized once from water and three times from alcohol-water mixtures. The most soluble and least soluble fractions from water were discarded, as were the most soluble fractions from the alcohol-water solutions.

ε-Aminocaproic acid was obtained from Dr. H. R. Snyder of the University of Illinois. It was dissolved in water and sufficient alcohol was added to form a 90% alcoholic solution from which most of the amino acid precipitated. Three such precipitations were carried out.

Norleucine of Analytical Purity was supplied by Amino Acid Manufacturers of the University of California. Specified impurities were so low that this acid was not purified further.

Ash content determinations and elementary analysis for nitrogen gave the results:

| | Ash, % | Nitrogen, % Found | Theoretical |
|---|---|---|---|
| α-Amino-*n*-valeric acid | 0.01 | 12.13 | 11.96 |
| Valine | .02 | 12.27 | 11.96 |
| Norleucine | .04 | 10.88 | 10.68 |
| ε-Aminocaproic acid | .21 | 10.73 | 10.68 |

The analyses for nitrogen agree with the theoretical values within the limits of error of the determination.

The purified acids were dried to constant weight at 80° in a vacuum oven and stored in a desiccator until used.

## Experimental Results and Treatment of Data

**Relative Apparent Molal Heat Contents.**—The experimentally determined intermediate heats of dilution are given in Table I. The average values of the measured heat effects for the long chord dilutions ($m_1$ to $m_2$) are listed in column 5, the number of experiments in column 4, the av-

erage deviation from the mean value in column 6, and the molal heats of dilution with their probable errors in column 13. The corresponding quantities for the short chord dilutions ($m_3$ to $m_2$) are listed in columns 9, 4, 10, and 14. Calculated heat effects are given in columns 7 and 11; the equations referred to are listed in Table II. The differences between measured and calculated heat effects are shown in columns 8 and 12.

Established methods[11,12,13] were used for the treatment of the heats of dilution data.

Figures 1, 2, 3 and 4 are plots of the short chords, $\overline{P} = \Delta H_{3\to 2}/\Delta m_{3\to 2}$, derived from the heats of dilution in the very dilute region. Each chord represents the average value of the derivative of the apparent molal heat content with respect to the molality in the range covered by the length of the chord. The intercept of a curve drawn through the chords gives the limiting slope of the apparent molal heat content and the area under a curve to a concentration $m$ gives the relative apparent molal heat content ($\phi L_2$), or the negative of the integral heat of dilution at that concentration.

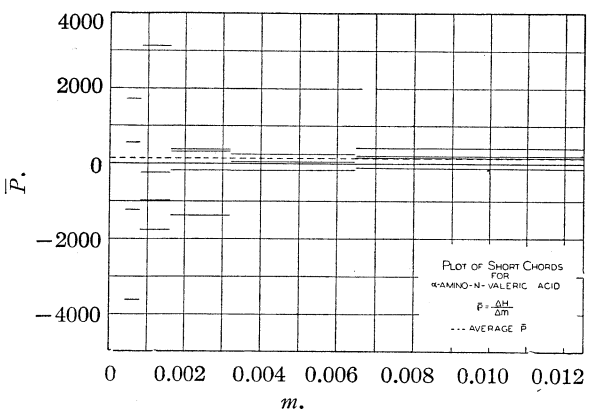



Fig. 1.—Plot of short chords for $\alpha$-amino-$n$-valeric acid: $\overline{P} = \Delta H/\Delta m$; – – –, average $\overline{P}$.

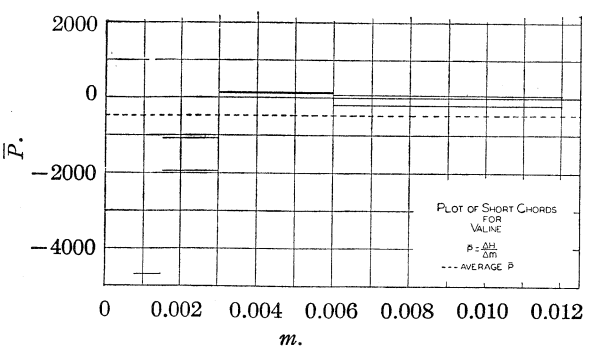



Fig. 2.—Plot of short chords for valine: $\overline{P} = \Delta H/\Delta m$; – – –, average $\overline{P}$.

(11) T. F. Young, *et al.*, THIS JOURNAL, **54**, 3030 (1932); **58**, 187 (1936); **60**, 2379 (1938).

(12) A. L. Robinson and W. E. Wallace, *ibid.*, **63**, 1582 (1941).

(13) A. L. Robinson and W. E. Wallace, *Chem. Revs.*, **30**, 195 (1942).

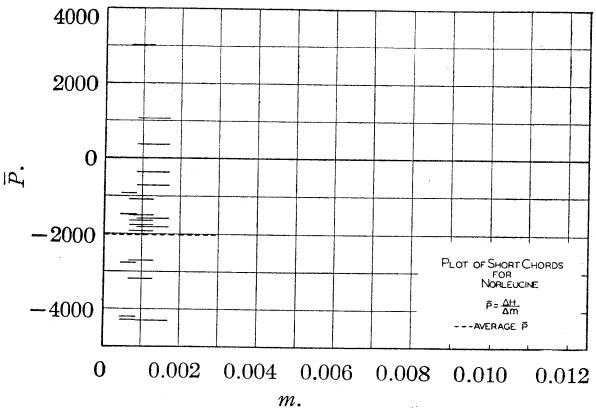



Fig. 3.—Plot of short chords for norleucine: $\overline{P} = \Delta H/\Delta m$; – – –, average $\overline{P}$.

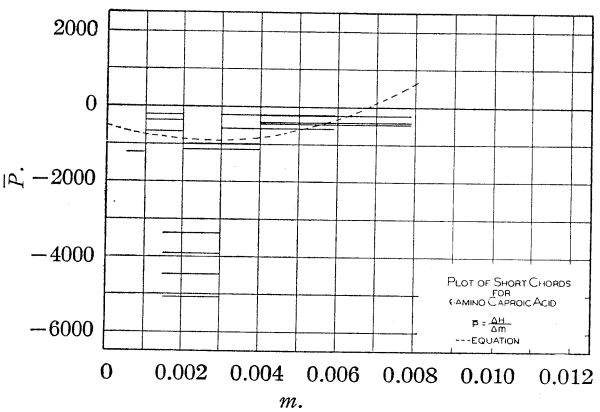



Fig. 4.—Plot of short chords for $\epsilon$-aminocaproic acid: $\overline{P} = \Delta H/\Delta m$; – – –, equation.

For $\alpha$-amino-$n$-valeric acid, valine, and norleucine, an inspection of the plots of $\overline{P}$ vs. $m$, shown in Figs. 1, 2, and 3, respectively, indicated that an analytical derivation for the slope, $S = \partial(\phi L_2)/\partial m$, was unwarranted. Instead, average $\overline{P}$ values for the entire concentration range of the short chords were obtained by averaging the mean values of the chords for each concentration interval, weighting each mean value according to its probable error. The dotted lines represent these average $\overline{P}$ values.

For $\epsilon$-aminocaproic acid, Fig. 4, there seemed to be a trend in the $\overline{P}$ values sufficiently pronounced to justify an analytical treatment. A three-constant least-squares equation was derived which is shown in the figure by a dotted line.

Equations for the slopes for the four acids are given in Table II (eq. 1, 6, 11, and 16). Integration of these equations gives expressions for $\phi L_2 (m < 0.015)$, equations 2, 7, 12, and 17 of Table II.

$\phi L_2$ values calculated from equations 2, 7, 12, and 17, for $m_2$ were combined with the experimental $\Delta H_{1\to 2}$'s for the long chord dilutions to give $\phi L_2$ values for the concentrations $m_1$. Least

TABLE III

RELATIVE PARTIAL MOLAL HEAT CONTENTS

| | α-Amino-n-valeric acid | | | Valine | | | Norleucine | | | ε-Aminocaproic acid | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| m | $\phi L_2$, cal./mole acid | $-\bar{L}_1$, cal./mole water | $\bar{L}_2$, cal./mole acid | $\phi L_2$, cal./mole acid | $-\bar{L}_1$, cal./mole water | $\bar{L}_2$, cal./mole acid | $\phi L_2$, cal./mole acid | $-\bar{L}_1$, cal./mole water | $\bar{L}_2$, cal./mole acid | $\phi L_2$, cal./mole acid | $-\bar{L}_1$, cal./mole water | $\bar{L}_2$, cal./mole acid |
| 0.001 | 0.218 | $3.93 \times 10^{-6}$ | 0.436 | 0.189 | $3.40 \times 10^{-6}$ | 0.378 | 0.306 | $5.51 \times 10^{-6}$ | 0.612 | −0.93 | $-12 \times 10^{-6}$ | −1.58 |
| .005 | 1.09 | $98.3 \times 10^{-6}$ | 2.18 | 0.945 | $85.0 \times 10^{-6}$ | 1.89 | 1.53 | $138 \times 10^{-6}$ | 3.06 | −1.45 | $-68 \times 10^{-6}$ | −0.668 |
| .01 | 2.18 | $3.93 \times 10^{-4}$ | 4.36 | 1.89 | $3.40 \times 10^{-4}$ | 3.78 | 3.06 | $5.51 \times 10^{-4}$ | 6.12 | −0.22 | $+5.22 \times 10^{-4}$ | 2.67 |
| .05 | 10.9 | $98.3 \times 10^{-4}$ | 21.8 | 9.45 | $85.0 \times 10^{-4}$ | 18.9 | 15.3 | $138 \times 10^{-4}$ | 30.6 | 12.5 | $150 \times 10^{-4}$ | 32.3 |
| .1 | 21.8 | $3.93 \times 10^{-2}$ | 43.6 | 18.9 | $3.40 \times 10^{-2}$ | 37.8 | | | | 29.9 | $6.50 \times 10^{-2}$ | 69.2 |
| .2 | 43.6 | 0.157 | 87.2 | 37.8 | 0.136 | 75.6 | | | | 67.5 | 0.278 | 148 |
| .3 | 65.4 | .354 | 131 | 56.7 | .306 | 113 | | | | 106 | .600 | 220 |
| .4 | 87.4 | .629 | 174 | 75.6 | .544 | 151 | | | | 140 | .903 | 269 |
| .5 | 109 | .983 | 218 | 94.5 | .850 | 189 | | | | | | |
| .6 | 138 | 1.415 | 262 | 113 | 1.22 | 227 | | | | | | |

squares equations for $\phi L_2$ for the entire concentration range studied were then derived, the data being weighted according to the reciprocal of the squares of the probable errors. These are equations 3, 8, 13 and 18 of Table II. For α-amino-*n*-valeric acid, valine and norleucine, linear equations adequately represent the data, but for ε-aminocaproic acid a cubic equation seemed necessary with an added exponential term to show the reversal of slope of $\phi L_2$ at the lowest concentrations. Although the $\overline{P}$ *vs.* *m* plots indicate a reversal of slope for valine and norleucine at their lowest concentrations, the data in the most dilute region were not considered sufficiently precise to justify showing this reversal in the $\phi L_2$ equations which cover the entire concentration range of this study.

Plots of equations 3, 8, 13 and 18 and the experimental points from which they were derived are shown in Fig. 5. $\phi L_2$ values from these equations at rounded concentrations are listed in Table III. *q*-Values for the long chord dilutions, calculated from equations 3, 8, 13 and 18, are listed in column 7 of Table I. The differences between measured and calculated values are given in column 8 of Table I. *q*-Values for the short chord dilutions, calculated from equations 2, 7, 12 and 17, and the differences between measured and calculated values are given in columns 11 and 12 of Table I.

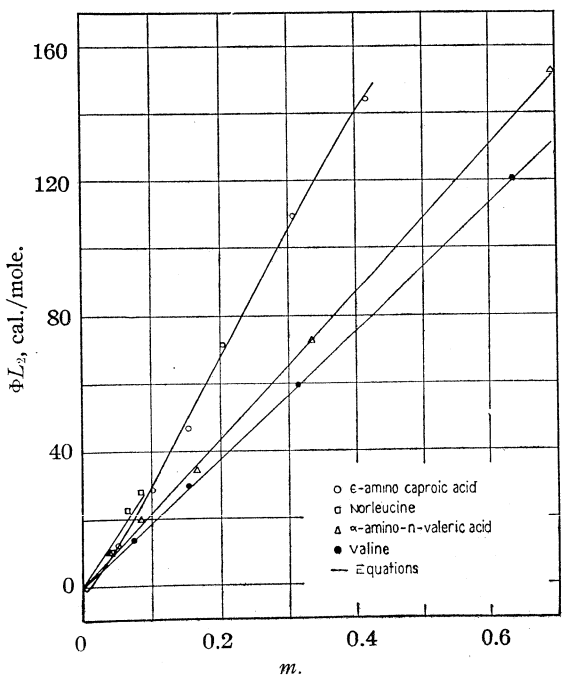



Fig. 5.—Plot of $\Phi L_2$ *vs.* *m*: O, ε-amino caproic acid; □, norleucine; △, α-amino-*n*-valeric acid; ●, valine; —, equations.

Valine is the only acid studied in this investigation for which heats of dilution have been measured previously. Values calculated from equation 8 are compared with the data of Zittle and Schmidt:[14]

| m | $\phi L_2$ cal. mole$^{-1}$ Zittle and Schmidt | This work |
|---|---|---|
| 0.1 | 15 | 19 |
| .2 | 60 | 38 |
| .5 | 125 | 96 |
| .63 | 150 ± 25 | 119 |

The probable errors of the $\phi L_2$ values of this study are less than 2 calories per mole. The apparatus used by Zittle and Schmidt gave values with probable errors of 25 calories per mole.

**Relative Partial Molal Heat Contents.**—Equations for the relative partial molal heat contents of solvent ($\bar{L}_1$) and solute ($\bar{L}_2$) for each of the four amino acids are listed in Table II. These equations were derived from the equations for $\phi L_2$ by the procedure due to Rossini.[15]

**Relative Partial Molal Entropy of Water.**—($\bar{S}_1 - \bar{S}_1^0$) values (differential entropies of dilution) for three of these systems were calculated by the procedure used[7] for glycine, the alanines, and four aminobutyric acids. The activity values for water used in the calculations were taken from the vapor pressure studies of Smith and Smith.[16] No activity measurements for norleucine solutions are available. The ($\bar{S}_1 - \bar{S}_1^0$) values calculated for α-amino-*n*-valeric acid, valine, and ε-aminocap-

(14) C. A. Zittle and C. L. A. Schmidt, *J. Biol. Chem.*, **108**, 161 (1935).

(15) F. D. Rossini, *J. Res. Bur. Stand.*, **4**, 313 (1930).

(16) E. R. B. Smith and P. K. Smith, *J. Biol. Chem.*, **117**, 209 (1937); **132**, 47 (1940).

roic acid are listed in Table IV. $(\bar{S}_1 - \bar{S}_1^0)$ values for ten amino acids are plotted in Fig. 7. These values in all cases are the non-ideal parts of the differential entropies of dilution.

TABLE IV

DIFFERENTIAL ENTROPY OF DILUTION AT 25°

| | $-(\bar{S}_1 - \bar{S}_1^0)$, cal. deg.$^{-1}$ mole$^{-1}$ | | |
|---|---|---|---|
| $m$ | α-Amino-$n$-valeric acid | Valine | ε-Amino-caproic acid |
| 0.1 | 0.00011 | 0.00009 | 0.00019 |
| .2 | .00044 | .00034 | .00080 |
| .3 | .00099 | .00077 | .00173 |
| .4 | .00174 | .00135 | .00249 |
| .5 | .00274 | .00212 | |
| .6 | .00393 | .00304 | |

## Discussion of Results

Plots of $\phi L_2$ *vs.* $m$ for the eleven amino acids studied in this laboratory are shown in Fig. 6. To a first approximation the variation of $\phi L_2$ is linear in $m$ in all cases, neglecting minor uncertain features of several of the plots at very low concentrations. To a grosser first approximation the $\phi L_2$ values increase regularly with the number of carbon atoms in the aliphatic radical. This observation has been made before.[6,7] Excluding glycine, the $\phi L_2$ values for the ten amino acids with $n$ = 2, 3, 4, and 5 carbon atoms in the aliphatic radical are coarsely represented by $\phi L_2 \cong (45 + (n - 2)85)m$. The data for all acids studied are much better than this coarse approximation, but it serves to emphasize the relative unimportance of the location of the $NH_3^+$ group in the molecule for determining the thermochemical properties studied in these investigations. In contrast, the dielectric increments for these same solutions[17] show a strong dependence on the location of the $NH_3^+$ groups.

A possible explanation for the rough regularity of $\phi L_2$ with $n$ for these solutions lies in the configurations of the amino acid molecules in solution. If this is a coiled configuration, with close approach of the $NH_3^+$ and $COO^-$ groups, the dipole moments of all these amino acids would be approximately equal. Changing dipole–dipole interactions with dilution would make a fairly constant contribution to $\phi L_2$ (the $\phi L_2$ of glycine), and the varying interactions of the hydrophobic aliphatic radicals with water would be responsible for the dependence of $\phi L_2$ on $n$. A coiled configuration for an amino acid molecule in solution seems plausible because of electrostatic interaction between $NH_3^+$ and $COO^-$. Differences among isomers could be attributed to slight differences of dipole moments and to differences in water-radical interactions due to radical configurations imposed by the electrostatic interaction.

The differential entropies of dilution plotted in Figure 7 likewise show a strong dependence on $n$, regardless of the location of the $NH_3^+$ group, because of the minor importance of the free energy term in the expression[7]

$$\bar{S}_1 - \bar{S}_1^0 = (\bar{L}_1 - RT \ln (a_1/N_1))/T$$

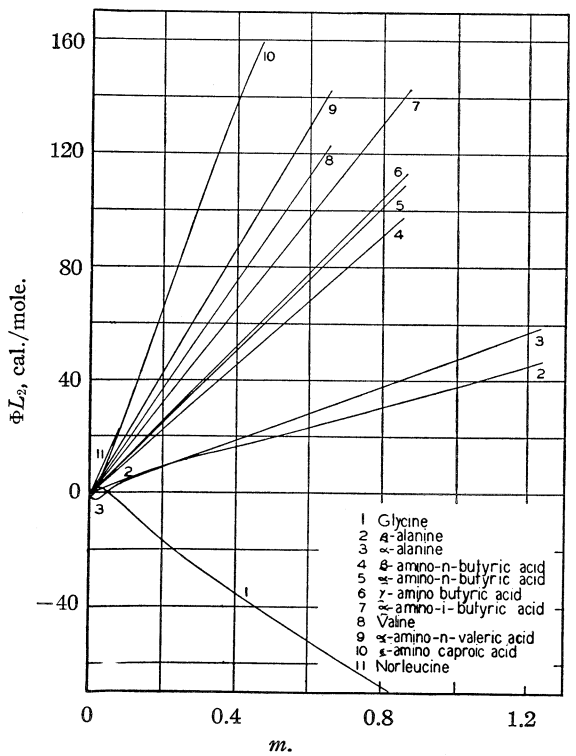



Fig. 6.—Plot of $\Phi L_2$ *vs.* $m$ for 11 amino acids: 1, glycine; 2, β-alanine; 3, α-alanine; 4, β-amino-*n*-butyric acid; 5, α-amino-*n*-butyric acid; 6, γ-aminobutyric acid; 7, α-amino-*i*-butyric acid; 8, valine; 9, α-amino-*n*-valeric acid; 10, ε-amino caproic acid; 11, norleucine.

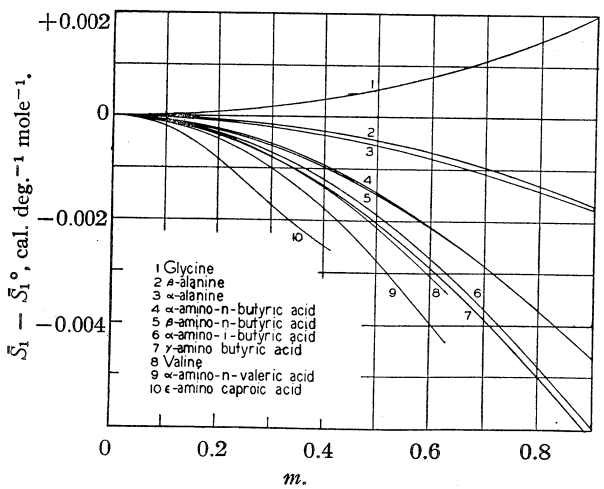



Fig. 7.—Plot of $\bar{S}_1 - \bar{S}_1^\circ$ *vs.* $m$ for ten amino acids: 1, glycine; 2, β-alanine; 3, α-alanine; 4, α-amino-*n*-butyric acid; 5, β-amino-*n*-butyric acid; 6, α-amino-*i*-butyric acid; 7, γ-aminobutyric acid; 8, valine; 9, α-amino-*n*-valeric acid; 10, ε-aminocaproic acid.

(17) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids, and Peptides," Reinhold Publishing Corporation, New York, N. Y., 1943, p. 146.

from which they were calculated. For the ten amino acids the relation $(\bar{S}_1 - \bar{S}_1^0) = km^2$ holds fairly well; the dependence on $m^2$ is a further reflection of the relative importance of the heat content term in the equation for $(\bar{S}_1 - \bar{S}_1^0)$. The $k$ values are listed.

| | $k$ |
|---|---|
| Glycine | 0.0023 |
| α-Alanine | −.0023 |
| β-Alanine | −.0020 |
| α-Amino-*n*-butyric | −.0058 |
| α-Amino-*i*-butyric | −.0076 |
| β-Amino-*n*-butyric | −.0056 |
| γ-Aminobutyric | −.0076 |
| α-Amino-*n*-valeric | −.0109 |
| Valine | −.0084 |
| ε-Aminocaproic | −.0185 |

These negative $(\bar{S}_1 - \bar{S}_1^0)$ values (for all cases except glycine) have been interpreted[7] as structure strengthening effects on the water, the effect increasing with the size of the hydrocarbon residue.

Regardless of the value of these suggestions, it seems clear that purely electrostatic interactions, calculated[18,19,20] for various simplified models, do not suffice to explain the thermochemical behavior of these solutions. The aliphatic radicals seem responsible for the large differences of properties measured.

## Summary

Heats of dilution of aqueous solutions of α-amino-*n*-butyric acid, valine, norleucine and ε-aminocaproic acid at 25° have been measured to below 0.001 *m*. From these measurements relative apparent molal heat contents, relative partial molal heat contents, and differential entropies of dilution have been calculated.

Results for eleven amino acids are compared and discussed.

(18) G. Scatchard and J. G. Kirkwood, *Physik. Z.*, **33**, 297 (1932).

(19) J. G. Kirkwood, *Chem. Revs.*, **19**, 275 (1936).

(20) R. M. Fuoss, THIS JOURNAL, **56**, 1027 (1934); **58**, 982 (1936).

PITTSBURGH, PA. RECEIVED OCTOBER 6, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, GENERAL ELECTRIC COMPANY]

# The Liquidus Curve for Aluminum in Mercury

BY HERMAN A. LIEBHAFSKY

The liquidus curve for the aluminum–mercury system is well established above 400° by the concordant results of two investigations.[1,2] Data which complete this curve were obtained in 1934 as part of an investigation into the chemical problems of the mercury boiler and are given below.

## Experimental

The "solubility" of commercial (99+%) aluminum in pure mercury was measured by rotating an aluminum-glass stirrer (see Fig. 1) in the solubility vessel, which was inside a cylindrical furnace whose temperature was taken as the temperature of the experiment. Because aluminum amalgam is very easily oxidized, the experiments were carried out in a hydrogen atmosphere. (The hydrogen, passed over copper at 400° and then through a liquid air trap, was pure enough not to cause appreciable oxidation of the amalgam. Since the analytical method measured dissolved metal only, a slight oxidation would not have vitiated the results.) The stirrer fitted into a metal chuck and was driven at approximately 300 r. p. m. with an electric motor. From time to time, samples of amalgam were withdrawn by means of previously evacuated sampling tubes, whose lower tips could easily be broken by forcing them against the bottom of the solubility vessel. The mercury withdrawn was usually replaced.

These samples were immediately analyzed by breaking the bulbs beneath approximately 2 *N* hydrochloric acid in the reaction vessel (Fig. 1) and measuring the evolved hydrogen in a gas buret containing mercury. The vessel was flushed out with hydrogen, stoppered tightly, and connected to the gas buret before each bulb was broken. Gentle warming ensured complete liberation of hydrogen. When the analytical system had returned to room temperature, the volume of hydrogen (assumed to be saturated with water vapor) was read on the buret. The volume of mercury was measured in the graduated side tube attached to the reaction vessel. With room temperature and pressure known, the aluminum content of the sample of amalgam could then be calculated.

As in all investigations of the interaction of mercury with metals, wetting—which does not occur until the natural oxide (or oxygen) film on the metal has been penetrated or removed—had first to be established. In this investigation, wetting was accomplished by simply heating the stationary stirrer in the assembled apparatus in the presence of hydrogen, the rod having been previously sandpapered and rubbed with a clean towel. Usually the wetting was uniform; for example, when such a rod was immersed in mercury and rapidly heated to 360°, wetting began within ten minutes and was complete on the immersed portion of the rod in approximately ten minutes more. Wetting above the liquid line did not occur, which shows that mercury vapor is not so effective in penetrating the natural oxide film. Occasionally, wetting occurred preferentially on the immersed area; aluminum would then disappear most rapidly from the wetted areas, where the rod would be eaten away. The experiments were scheduled so that the amount of aluminum passing into the mercury from the stationary rod did not exceed the solubility at the temperature of the first experiment after a new rod was wetted. Since the hydrogen atmosphere was usually maintained even between experiments, it was possible to use a wetted rod more than once.

The time required to saturate the relatively small volume (*ca.* 35 cc.) of mercury used in the experiments could not be readily determined. With an unwetted rod, this time would depend largely upon the rate at which the mercury penetrated the natural oxide (or oxygen) film, and this unreproducible rate increases markedly with the temperature. For a wetted rod, the usual case, detailed experimental data indicated that the time in question was probably less than an hour. When only one value of the

(1) (a) Smits and de Gruijter, *Proc. Kon. Akad. Wetensch Amsterdam*, **23**, 966 (1921); (b) Smits, *Z. Elektrochem.*, **30**, 423 (1924).

(2) Klemm and Weiss, *Z. anorg. allgem. Chem.*, **245**, 285 (1940).

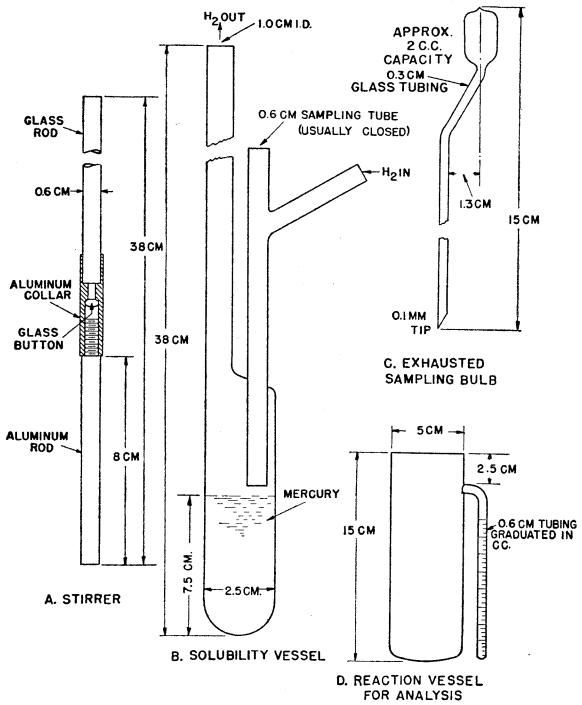



Fig. 1.—Apparatus for solubility measurements and for analysis.

solubility was obtained, about three hours was allowed for saturation. The final results are given in Table I.

TABLE I

SOLUBILITY OF ALUMINUM IN MERCURY

| $T$, °C. | 76 | 101 | 103 | 125 | 160 | 260 | 312 |
|---|---|---|---|---|---|---|---|
| No. of values | 1 | 1 | 2 | 1 | 3 | 2 | 2 |
| Al (meas.), % | 0.0090 | 0.015 | 0.017 | 0.024 | 0.035 | 0.11 | 0.18 |
| Al (calc.),[a] % | .0099 | .016 | .017 | .025 | .042 | .13 | .20 |

[a] Percentages calculated from the equation $\log_{10} s = 1.240 - 1132/T$.

## Discussion

The data of interest in connection with the present results are summarized in Fig. 2, which contains two previously unpublished values by Messrs. F. J. Norton and R. H. Harrington of this Laboratory, whose experimental method closely resembled that of Klemm and Weiss.[2]

In contrast with the results obtained at higher temperatures, the data of the present investigation agree fairly well with the straight line in Fig. 2. (Obviously, this agreement does not mean that the linear relationship is rigorously valid.) In drawing this straight line, the equation for which is given below Table I, the results obtained above 300° have been given some weight. The extrapolated value of the solubility for 20° is 0.0023%, in satisfactory accord with Fogh's[3] statement that all but 0.002 g. of aluminum separates from 100 g. of a saturated solution of aluminum in boiling mercury subsequently cooled to room temperature. Though it is conventional to speak of

(3) Fogh, *Kgl. Danske Videnskab. Selskab. Math.-phys. med.*, **3**, No. 15, 6 pp. (1921), abstracted in *Chem. Zentr.*, **94**, III, 993 (1923).

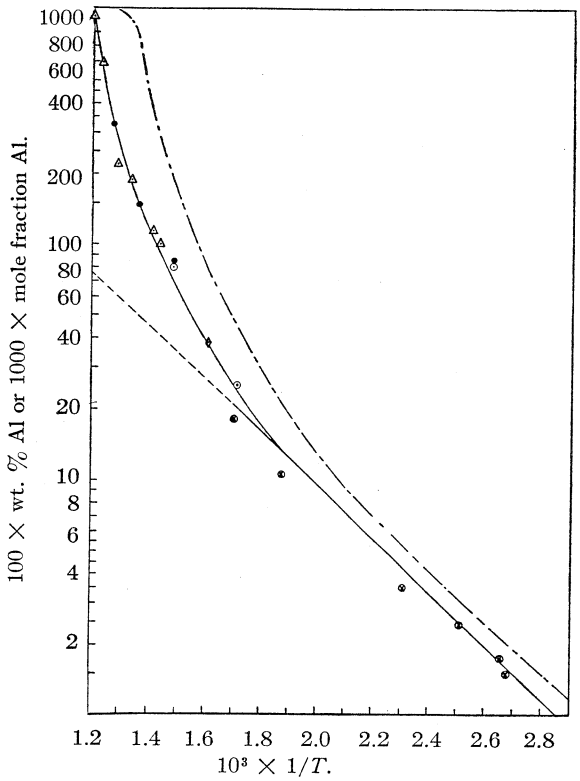



Fig. 2.—Liquidus curve of aluminum in mercury: △, reference 2; ●, ref. 1; ⊙, Norton and Harrington; ⊗, this investigation; ◇, ref. 3; —·—, mole fraction Al (points not shown, abscissa transposed so that 1.2 = 1.0); —, wt. % Al.

solubility in cases such as these, it is important to realize that the actual equilibria are established between a liquid solution of aluminum in mercury and a solid phase containing mercury and aluminum, about whose composition the information is incomplete and conflicting.[4]

As is well known, it is possible in principle to calculate the heat of fusion of aluminum from data like those in Fig. 2.[5] Though a definitive treatment of these data must await the establishment of the solidus curve, it is useful to calculate values of the *apparent* heat of fusion defined by

$$\Delta H_A^a = -4.575(\Delta \log N_A / \Delta 1/T)_P \qquad (1)$$

where $N_A$ is the mole fraction of aluminum in the liquid phase at temperature $T$ and constant pressure $P$, and the increments are taken between successive temperatures conveniently spaced. The variation of $\Delta H_A^a$ with composition is clear from Fig. 3, the ordinates for which were obtained as indicated. In the most concentrated region, $N_A$ was calculated by use of the equation % aluminum by weight = $100 - (660 - t°)$, where $t$ is the centigrade temperature, which adequately

(4) Hansen, "Aufbau der Zweistofflegierungen," Julius Springer, Berlin, 1936, pp. 117–118, gives a comprehensive bibliography.

(5) Kelley, "Contributions to the Data on Theoretical Metallurgy, V. Heats of Fusion of Inorganic Substances," Bull. 393, Bureau of Mines, 1936.

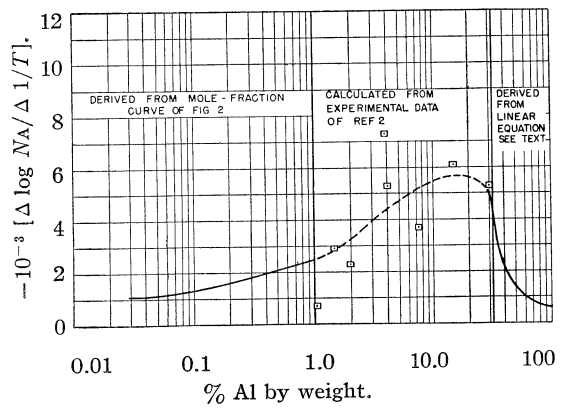



Fig. 3.—Variation of apparent heat of fusion with composition.

expresses the results of Smits and de Gruijter[1a] (*cf.* ref. 4, Fig. 59). In the intermediate region, where the mole-fraction curve has an inflection point, it seemed best to calculate ordinates directly from the experimental results of Klemm and Weiss.[2]

In the aluminum-rich region, the ordinate of Fig. 3 corresponds very closely to +2550 cal., the heat of fusion recommended for aluminum by Kelley.[5] (+2547 cal. was calculated for the interval 90–100% Al.) The pronounced variability over the rest of Fig. 3 may be due to variations in the activity coefficients, to changes in the composition of the solid in equilibrium, or to both.

I wish to thank my colleagues, Messrs. F. J. Norton and R. H. Harrington for permission to publish their two experimental results, and Mr. K. Berman for helping with the calculations.

## Summary

1. The aluminum–mercury liquidus curve has been completed by the making of measurements designed to give good results with dilute aluminum amalgams.

2. Within the temperature range 76–312°, the per cent. by weight of aluminum "soluble" in mercury is given by the equation $\log_{10} s = 1.240 - (1132/T)$ to within about 10%.

3. The apparent heat of fusion in this system passes through a maximum as the aluminum content is increased. In nearly pure aluminum, the value of this heat agrees remarkably well with the heat of fusion recommended by Kelley for this element.

SCHENECTADY, NEW YORK

RECEIVED SEPTEMBER 14, 1948

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE INSTITUTUM DIVI THOMAE AND THE DEPARTMENT OF CHEMISTRY, SIENA HEIGHTS COLLEGE]

# The Ultraviolet Absorption Spectra of Some Pyrimidines. Chemical Structure and the Effect of *p*H on the Position of $\lambda_{max.}$[1]

BY MIRIAM MICHAEL STIMSON[2]

It has been suggested by Brooker[3] that symmetrical ions should be more stable than unsymmetrical ones. So far this has not been demonstrated experimentally although symmetrical dyes are more stable to *p*H changes than are unsymmetrical ones. In the following discussion an attempt will be made to correlate symmetry and *p*H response in a group of pyrimidines.

One of the most striking of the absorption characteristics of the pyrimidines is the effect of *p*H on the intensity and, frequently, on the position of the absorption maximum ($\lambda_{max}$). This change in the position of the absorption maximum with *p*H-($\Delta\lambda_{max}$) seems not to be solely dependent on the nature of the substituent on the pyrimidine ring, since barbituric acid[4] although having a pronounced change in the molar absorbancy index, shows no appreciable change in the position of $\lambda_{max}$, while uracil has $\Delta\lambda_{max}$ of 24 m$\mu$. Again it may be noted that in the case of 2-hydroxy-4,6-diaminopyrimidine there is no appreciable change in the position of the absorption maximum with change in *p*H; such a change is observed with both cytosine and isocytosine. From these various types of response to change in *p*H it is suggested that the effect of *p*H might be empirically related to the symmetry of the molecule. Thus both barbituric acid and 2-hydroxy-4,6-diaminopyrimidine may be considered as symmetrical, if the plane of symmetry be imagined to pass through the 2,5-positions. On this basis the pyrimidines under consideration may be classified as symmetrical or unsymmetrical.

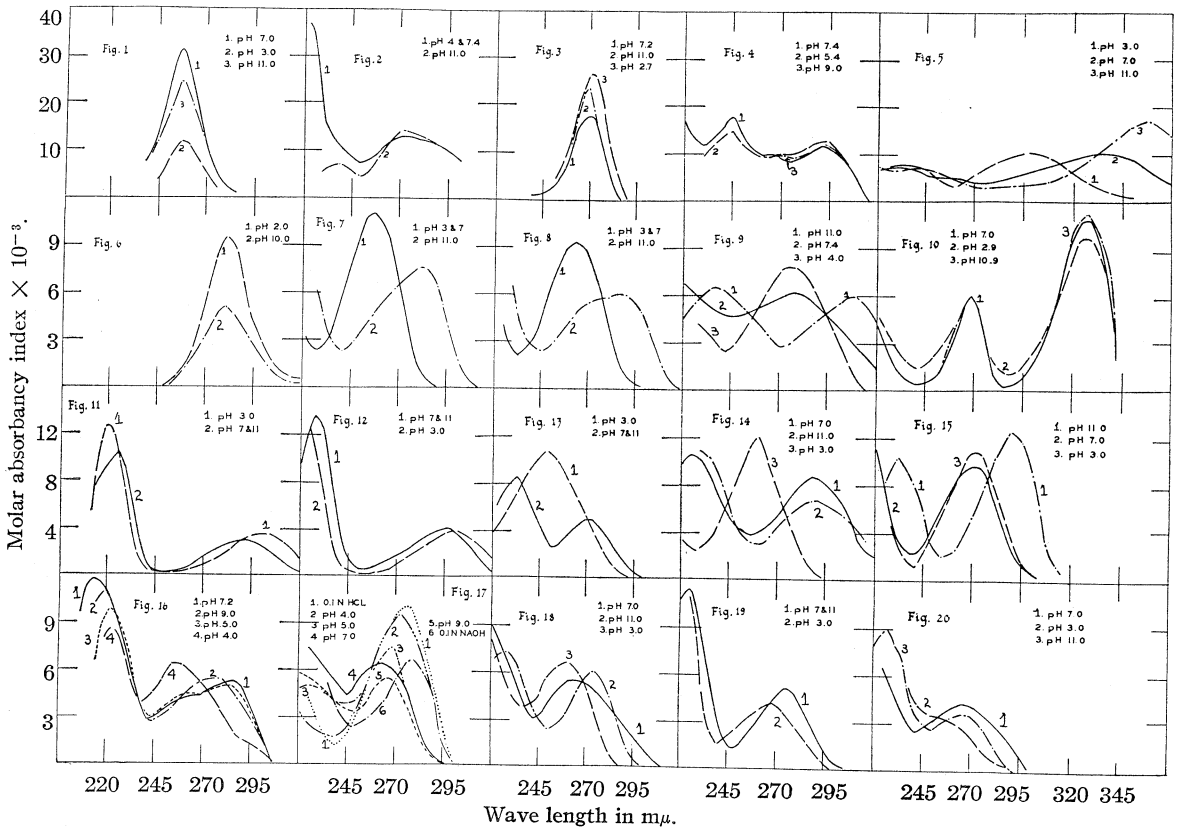
In Table I are listed seven pyrimidines, all of which are considered symmetrical with respect to the above mentioned plane. From the data presented the following empirical conclusions may be drawn: (1) The long wave absorption maximum of these compounds seems to be either unaffected or only slightly shifted by the *p*H values employed. (2) In either the 4,6-dihydroxy- or the 4,6-diaminopyrimidines, in which there is also a hydroxy

(1) From the dissertation presented to the faculty of the Institutum Divi Thomae in partial fulfillment of the requirements for the Ph.D., June 1948.

(2) Sister Miriam Michael Stimson, O.P.

(3) Brooker, "Resonance and Organic Chemistry" in "Advances in Nuclear Chemistry and Theoretical Organic Chemistry," ed. Burk and Grummitt, Interscience Publishers, Inc., New York, N. Y., 1945.

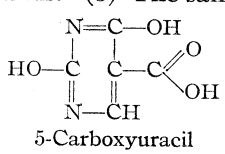
(4) Loofbourow and Stimson, *J. Chem. Soc.*, 1275 (1940); Stuckey, *Quart. J. Pharm. Pharmacol.*, **15**, 370 (1942).



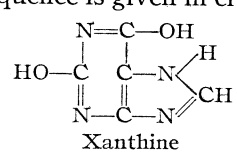

Figs. 1 to 20.—1, Barbituric acid; 2, 2-mercapto-4,6-dihydroxy-5-ethylpyrimidine; 3, 2-hydroxy-4,6-diaminopyrimidine; 4, 2-mercapto-4,6-diaminopyrimidine; 5, 5-nitrouracil; 6, 2-hydroxy-4,5,6-triaminopyrimidine; 7, uracil; 8, thymine; 9, isobarbituric acid; 10, 4,6-dihydroxypyrimidine; 11, 2-aminopyrimidine; 12, 2-amino-6-chloropyrimidine; 13, 2-chloro-6-aminopyrimidine; 14, 5-aminouracil; 15, 5-carboxyuracil; 16, isocytosine; 17, cytosine; 18, isocytosine-4-acetic acid; 19, 2-ethoxy-4-aminopyrimidine; 20, 2-methyl-4-hydroxy-6-ethoxypyrimidine.

group on the 2-position, the replacement of this hydroxy group by an –SH group is accompanied by the appearance of two maxima.[5] (3) The molar absorbancy index of an absorption band at any given *p*H apparently depends, within either a symmetrical or unsymmetrical structure, on the nature and number of the substituents, but auxochromes do not display their usual character when their introduction causes change from an unsymmetrical to a symmetrical structure. This can be seen by a comparison of both $\lambda_{max}$ and $\Delta\lambda_{max}$ for cytosine, 2-hydroxy-4,6-diaminopyrimidine, 2-hydroxy-4,5,6-triaminopyrimidine.

Those compounds not symmetrical with respect to the 2–5 plane show sufficient uniformity to permit sub-classification. In Table II are listed the data for various uracil derivatives, all of which have the substituent on the 5-position. In these compounds the data may be considered under two aspects, namely, the modification of the absorption pattern of the parent compound, uracil, and the effect of *p*H on $\lambda_{max}$. The following conclusions may be drawn: (1) The introduction of the additional auxochrome on the 5-position causes an increased bathochromic shift when the *p*H is changed from 3 to 11. (2) There is a formal relationship in the spectral response of carboxyuracil and of xanthine.[6] Both show a single band in acid solution and both have two pronounced bands in basic solution. That this is not unreasonable may be inferred from the formal structural relationship which also exists between the two compounds. (3) The same sequence is given in either



5-Carboxyuracil



Xanthine

acid or basic solution by the various uracil derivatives if they are arranged in order of increasing wave length of the long wave maximum

(acid) $H{=}NH_3^+ < CH_3 < COOH < OH < NO_2$

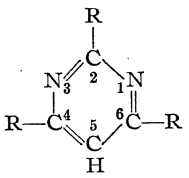
(basic) $H < NH_2{=}CH_3{=}COO^- < O^- < NO_2$.

The modification of the absorption spectrum shown by uracil may be, perhaps, more evident if $\Delta\lambda_{max}$ of uracil for the change from *p*H 3 to 11 be

(5) Fehnel and Carmack, at the Spring Meeting 1948, Chicago, reported a peak in the spectra of the alkylmercaptals at 235–240 mμ which corresponds to the short wave band in Figs. 2 and 4.

(6) Stimson and Reuter, THIS JOURNAL, **65**, 153 (1945).

TABLE I



| Pyrimidine | Long wave band $\lambda_{max}$, mμ | Long wave band Molar absorbancy index | Short wave band $\lambda_{max}$, mμ | Short wave band Molar absorbancy index | pH |
|---|---|---|---|---|---|
| Barbituric acid | 257 | 550 | | | 1 *N* HCl |
| (2,4,6-tri- | 257 | 11000 | | | 3.0 |
| hydroxy-) | 257 | 31000 | | | 7.0 |
| | 257 | 24500 | | | 11.0 |
| 2-Thio-4,6-di- | 273 | 14000 | 239 | 7050 | 4.0 |
| hydroxy- | 273 | 13900 | 239 | 6600 | 7.4 |
| 5-ethyl- | 273 | 12750 | 239 | 36700 | 11.0 |
| 4,6-Dihydroxy- | 328 | 8160 | 270 | 5050 | 2.9 |
| | 328 | 9150 | 270 | 5000 | 7.0 |
| | 328 | 9400 | 270 | 5120 | 10.9 |
| 2-Hydroxy- | 273 | 26500 | | | 2.7 |
| 4,6-diamino- | 270 | 17400 | | | 7.2 |
| | 270 | 23300 | | | 10.9 |
| 2-Hydroxy- | 281 | 10000 | | | 0.1 *N* HCl |
| 4,5,6-tri- | 281 | 9400 | | | 2.0 |
| amino- | 281 | 7400 | | | 6.4 |
| | 281 | 5100 | | | 10.0 |
| | 281 | 4700 | | | 11.0 |
| 2-Thio-4,6- | 286 | 25000 | 235 | 40950 | 0.1 *N* HCl |
| diamino- | 291 | 12500 | 245 | 14000 | 5.4 |
| | 292 | 11380 | 245 | 17800 | 7.4 |
| | 292 | 14760 | 245 | 17200 | 9.0 |
| 2-Thio-4,5,6-triamino-[a] | 295 | 11900 | 245 | 13900 | ..... |

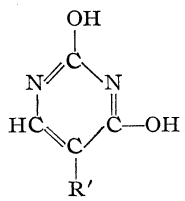
[a] Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3109 (1948).

subtracted from the corresponding shift for each of the listed 5-uracil derivatives. If the log of the difference in the data between each of the uracils and uracil, respectively, be plotted against the dipole moment of the substituent, then practically a straight line relationship is obtained. The dipole moment data used are those listed in Landolt–Börnstein[7] for benzene derivatives. While these data do not accurately represent the values of the particular substituents in the uracil series, they may be considered as giving a relative evaluation. Of the six compounds tested only 5-carboxyuracil fails to show a difference in the shift of the absorption maximum as a regular function of the dipole moment. This failure of 5-carboxyuracil to respond as do the other uracil derivatives is not unreasonable in view of the formal structural and spectral similarities with xanthine.

In Table III are arranged the data of four 2-aminopyrimidines. In these compounds the upper half of the molecule is a substituted guanidine structure. The following observations may be made: (1) Each compound has two absorption bands. (2) The unsubstituted 2-aminopyrimidine and the derivative with a chlorine atom on the 6-position both show an increased separation of the absorption bands in acid solution as compared

(7) Landolt–Börnstein, "Physikalisch-chemische Tabellen," Eg. II, 74, 5th Umgearbeitete, 3rd Erganzungsband, 1st Teil, Edwards Brothers, Inc., Ann Arbor, Michigan, 1943.

TABLE II



| Compound | Long wave band $\lambda_{max}$, mμ | Long wave band Molar absorb. index | Short wave band $\lambda_{max}$, mμ | Short wave band Molar absorb. index | pH | $\Delta\lambda_{max}$,[a] mμ |
|---|---|---|---|---|---|---|
| Uracil | 258 | 8600 | | | 3.0 | 24 |
| (R′ = H) | 258 | 8600 | | | 7.0 | |
| | 282 | 6400 | | | 11.0 | |
| Thymine | 264 | 7800 | | | 3.0 | 26 |
| (R′ = $CH_3$) | 264 | 7800 | | | 7.0 | |
| | 290 | 5100 | | | 11.0 | |
| 5-Amino- | 260 | 12200 | | | 3.0 | 30 |
| uracil | 290 | 8600 | 225 | 10500 | 7.0 | |
| | 290 | 6700 | | | 11.0 | |
| Isobarbi- | 276 | 6600 | 222 | 4000 | 4.0 | 31 |
| turic acid | 278 | 5200 | 210 | 6600 | 7.4 | |
| (R′ = OH) | 307 | 4900 | 239 | 5300 | 11.0 | |
| 5-Nitro- | 300 | 10400 | 235 | 6880 | 3.0 | 58 |
| uracil | 338 | 10600 | 235 | 7880 | 7.0 | |
| | 358 | 16750 | 240 | 6880 | 11.0 | |
| 5-Carboxy- | 270 | 11200 | 216 | 12500 | 3.0 | 30 |
| uracil | 270 | 9800 | 216 | 11500 | 7.0 | |
| | 290 | 12800 | 232 | 10500 | 11.0 | |

[a] This is the change in $\Delta\lambda_{max}$ for the change from *p*H 3 to *p*H 11; *i. e.*, $\lambda_{max}$ *p*H 11 − $\lambda_{max}$ *p*H 3.

TABLE III

| Compound | Long wave band $\lambda_{max}$, mμ | Long wave band Molar absorb. index | Short wave band $\lambda_{max}$, mμ | Short wave band Molar absorb. index | pH | $\Delta\lambda_{max}$,[a] mμ |
|---|---|---|---|---|---|---|
| 2-Amino- | 300 | 3770 | 220 | 12600 | 3.0 | |
| pyrimidine | 290 | 2800 | 225 | 11000 | 7.0 | −10 |
| | 290 | 2800 | 225 | 11000 | 11.0 | |
| 2-Amino- | 300 | 4000 | | | 3.0 | |
| 6-chloro- | 296 | 4200 | 229 | 13900 | 7.0 | − 4 |
| pyrimidine | 296 | 4200 | 229 | 13900 | 11.0 | |
| Isocytosine- | 259 | 6800 | | | 3.0 | |
| 4-acetic | 265 | 5700 | | | 7.0 | +16 |
| acid | 275 | 6250 | | | 11.0 | |
| Isocytosine | 258 | 6300 | 223 | 8600 | 4.0 | |
| | 285 | 4950 | 222 | 9900 | 5.0 | |
| | 264 | 4700 | | | | |
| | 285 | 5250 | 222 | 11700 | 7.2 | |
| | 267 | 4550 | | | | |
| | 276 | 5500 | 218 | 10700 | 9.0 | |

[a] See note to Table II.

with basic solution. (3) The derivative with the hydroxy group on the 6-position shows the least separation of the two absorption maxima in solution at *p*H 4.0, and the greatest separation at *p*H 7.2, of the *p*H values tested.

4. Consideration of the long-wave band only, shows that the *p*H effect permits the following sequence for substituents on the 6-position

| H | Cl | OH (4-acetic acid) | OH |
|---|---|---|---|
| −10 mμ | −4 mμ | 16 mμ | 26 mμ |

5. In the case of isocytosine (2-amino-6-hydroxypyrimidine) the greatest shift of the long-wave maximum occurs between *p*H 4 and the *p*H range 5–8; while at *p*H 9.0 there is a sudden shift of this band to an intermediate position. Furthermore, this new position is midway between the two subsidiary peaks as shown at *p*H 5.0.

6. A consideration of the lower of the two subsidiary peaks (264 mμ) together with the peaks at *p*H 4 and 9 shows that the shift from *p*H 4 to *p*H 5 is 6 mμ and from *p*H 5 to *p*H 9, 12 mμ. These same values are obtained from the data of isocytosine-4-acetic acid.

TABLE IV

| Compound | Long wave band $\lambda_{max}$, mμ | Long wave band Molar absorb. index | Short wave band $\lambda_{max}$, mμ | Short wave band Molar absorb. index | *p*H |
|---|---|---|---|---|---|
| 2-Chloro-6-aminopyrimidine | 250 | 10600 | ... | ... | 3.0 |
| | 272 | 5000 | 232 | 8500 | 7.0 |
| | 272 | 5000 | 232 | 8500 | 11.0 |
| Cytosine | 275 | 10200 | ... | ... | 0.1 *N* HCl |
| | 274 | 9600 | ... | ... | 4.0 |
| | 268 | 7550 | 227 | 5000 | 5.0 |
| | 266 | 6600 | ... | ... | 7.4 |
| | 266 | 5400 | ... | ... | 9.0 |
| | 278 | 6800 | ... | ... | 11.0 |
| 2-Methyl-4-hydroxy-6-ethoxypyrimidine | 256 | 3600 | 227 | 9000 | 3.0 |
| | 266 | 4500 | ... | ... | 7.0 |
| | 266 | 3800 | ... | ... | 11.0 |
| 2-Ethoxy-6-aminopyrimidine | 268 | 4300 | ... | ... | 3.0 |
| | 276 | 5000 | 224 | 11400 | 7.0 |
| | 276 | 5000 | 224 | 11400 | 11.0 |
| 2-Methyl-5-cyano-6-aminopyrimidine | 293 | 4500 | 242 | 10000 | 3.0 |
| | 293 | 4500 | 242 | 9000 | 7.0 |
| | 280 | 3600 | 247 | 11000 | 0.1 *N* NaOH |

Table IV includes the data for some unsymmetrical pyrimidines, none of which contains the 2 amino group. Examination shows that:

1. The spectrum of each compound shows two maxima for at least one *p*H value investigated.

2. The two peaks of the 2-hydroxy-6-aminopyrimidine (*p*H 5) are separated by the same amount as those of 2-chloro-6-aminopyrimidine (*p*H 7), although the latter are displaced 4 mμ toward longer wave lengths.

3. The position of $\lambda_{max}$ shifts progressively toward shorter wave lengths in 2-hydroxy-6-amino pyrimidine (cytosine) when the *p*H is changed from 2 to 9, but at *p*H 11, $\lambda_{max}$ occurs at a wave length longer than at *p*H 2.0. Thus in this particular compound the auxochromic character of the amino group appears only if *p*H 2 and 11 are considered.

4. In the case of the 2-chloro-6-aminopyrimidine the generally recognized characteristics of the amino group are evident (*cf.* 2-amino-6-chloropyrimidine).

5. The ratio of the positions of the short- and the long-wave maxima for 2-methyl-4-hydroxy-6 ethoxypyrimidine and the corresponding ratio for isocytosine shows that the relative separations and also $\Delta\lambda_{max}$ are similar, thus indicating a possible equality in the positional effect of the 4- and the 6-positions when occupied by the hydroxy group.

An over-all examination of the data reveals that, of the common auxochromes, the hydroxy group and the amino group both fail to produce the usual bathochromic effect when their introduction into the molecule results in a change from an unsymmetrical to a symmetrical molecule. This is illustrated by the following: (a) the introduction of the hydroxy group in uracil to give barbituric acid; (b) the introduction of the amino group into cytosine to give 4,6-diamino-2-hydroxypyrimidine.

The resulting symmetrical compounds do not show a shift of $\lambda_{max}$ with *p*H and, further, show their principal absorption maximum at slightly shorter, rather than at longer, wave lengths than do the theoretical parent compounds.

## Experimental

**Materials.**—Barbituric acid (Eastman Kodak Co.) was thrice precipitated from aqueous alcohol and was used as a 0.0000528 *M* solution, at *p*H 3, 7, 11. The molar absorbancy index agrees substantially with that given by Heyroth and Loofbourow[8] and Loofbourow and Stimson.[4] The 2-thio-4,6-dihydroxy-5-ethylpyrimidine and 2-methyl-4-hydroxy-6-ethoxypyrimidine were obtained through the courtesy of Merck & Co., and the first of these was used in 0.0000465 *M* solution at *p*H 4, 7.4, 11. The latter was employed in 0.000246 *M* solution at *p*H 3, 7, 11.

4,6-Dihydroxypyrimidine was prepared according to Kenner, *et al.*[9] It was employed in a 0.0000156 *M* solution at *p*H 2.9, 7, 10.9.

2-Hydroxy-4,6-diaminopyrimidine was prepared according to Todd[10] and employed in a 0.0000317 *M* solution at *p*H 2.7, 7.2, 10.9.

The 2-hydroxy-4,5,6-triaminopyrimidine was prepared according to Wieland and Liebig[11] and was measured in a 0.000124 *M* solution at *p*H 2, 2.5, 3.3, 6.4, 7.4, 10, 11.

2-Thio-4,6-diaminopyrimidine, prepared according to Traube,[12] was employed as a 0.0000704 *M* solution in 0.1 *N* hydrochloric acid, and at *p*H 2.2, 3.6, 4.4, 5.2, 5.4, 7.4, 9, 11. All the di- and triamino derivatives were kept in subdued light between the time the solution was prepared and the spectra determined to prevent formation of any colored oxidation compound.[13]

Uracil was employed in a 0.0000142 *M* solution at *p*H

(8) Heyroth and Loofbourow, THIS JOURNAL, **56**, 1728 (1934).

(9) Kenner, Lythgoe, Todd and Topham, *J. Chem. Soc.*, 388 (1943).

(10) A. R. Todd, personal communication.

(11) Wieland and Liebig, *Ann.*, **555**, 146 (1943).

(12) Traube, *ibid.*, **331**, 64 (1904).

(13) Polonovski, Vieillefosse, Guinand and Jerome, *Bull. soc. chim.*, 80 (1946).

3, 7, 11. Thymine was prepared by Dr. Marian Van Ess of the Golden State Co., and was measured in a 0.000193 *M* solution at *p*H 3, 7, 11. 5-Amino- and 5-nitrouracil (Eastman) were purified by repeated precipitation from aqueous solution and were measured in 0.000238 *M* and 0.000112 *M* solutions, respectively, at *p*H 3, 7, 11.

Isobarbituric acid was obtained from Dr. F. F. Heyroth of the University of Cincinnati and was measured in a 0.0002 *M* solution at *p*H 4, 7.4, 11. 5-Carboxyuracil was prepared by Dr. Elizabeth Ballard and is the material reported by her.[14]

2-Aminopyrimidine was obtained through the courtesy of Dr. R. O. Roblin of the American Cyanamid Co., and was measured in a 0.000165 *M* solution at *p*H 3, 7, 11. 2-Amino-6-chloropyrimidine (m. p. 178–179°) and its isomer (m. p. 209–210°) were employed in 0.000325 and 0.000232 *M* solutions, respectively, at *p*H 3, 7, 11.

Isocytosine monohydrate[15] (m. p. 275°) was used in a 0.0001185 *M* solution at *p*H 4, 5, 5.4, 6.4, 7.2, 7.4, 8, 9. Isocytosine-4-acetic acid was prepared by the late Dr. David E. Worrall and was described by him.[16] It was measured at *p*H 3, 7, 11 in a 0.000115 *M* solution.

Cytosine monohydrate was prepared by the method of Hilbert and Johnson[17] and was measured in a 0.000031 *M* solution at 0.1 *N* hydrochloric acid, *p*H 4, 5, 7.4, 9, 11.

(14) Ballard and Johnson, THIS JOURNAL, **64**, 794 (1942).
(15) Caldwell and Kline, *ibid.*, **62**, 2365 (1940).
(16) Worrall, *ibid.*, **65**, 2053 (1943).
(17) Hilbert and Johnson, *ibid.*, **52**, 1152 (1930).

The 2-ethoxy-6-aminopyrimidine was obtained from the American Cyanamid Co., and was used in a 0.000103 *M* solution at *p*H 3, 7, 11. 2-Methyl-5-cyano-6-aminopyrimidine (m. p. 243–244°) was employed in a 0.000223 *M* solution with 0.1 *N* hydrochloric acid, 0.1 *N* sodium hydroxide and *p*H 7.4.

Except for the listed cases where either hydrochloric acid or sodium hydroxide were used all *p*H values were obtained with Kolthoff buffer tablets. In every case the comparison cells were filled with corresponding buffer, acid or base.

## Summary

1. In the pyrimidines investigated, which have a plane of symmetry through the 2–5 positions, there is essentially no change in the position of $\lambda_{max}$ with change in *p*H.

2. 5-Uracil derivatives show an increase in $\lambda_{max}$ which may be related to the dipole moment of the substituent.

3. When the introduction of an auxochrome produces a symmetrical structure the introduction is not accompanied by the bathochromic shift usually met.

CINCINNATI, OHIO
ADRIAN, MICHIGAN

RECEIVED JULY 26, 1948

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[CONTRIBUTION FROM MELLON INSTITUTE AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

# Acetoxymethyl and Hydroxymethyldisiloxanes

BY JOHN L. SPEIER, B. F. DAUBERT AND R. R. MCGREGOR

As a continuation of the study of hydroxymethylsilicon compounds first reported by Speier, *et al.*,[1] who prepared trimethylsilylmethanol and studied its reactivity, acetoxymethyl and hydroxymethyldisiloxanes have been synthesized. The esters, acetoxymethylpentamethyldisiloxane and *sym.* bis-acetoxymethyltetramethyldisiloxane were prepared and from the latter *sym*-bis-hydroxymethyltetramethyldisiloxane was made by alcoholysis. The di-alcohol was found to be unstable, even at room temperature, but it could be handled, and a derivative was made with no noteworthy difficulty.

## Experimental

**Preparation of Acetoxymethyldisiloxanes.**—Chloromethylpentamethyldisiloxane[2,3] was heated to reflux gently for twenty-four hours with a slight excess of anhydrous potassium acetate in a volume of glacial acetic acid equal to that of the disiloxane. The chloromethyl compound was not noticeably soluble in the mixture, but dissolved after several hours as a large amount of potassium chloride precipitated. The mixture was finally washed thoroughly with distilled water, and the water insoluble material was distilled. Very nearly the following molar proportions of products resulted: hexamethyldisiloxane[4] 25 mole %, b. p. 98–99° at 735 mm., $n^{25}D$ 1.3748; acetoxymethylpentamethyldisiloxane, 50 mole %, b. p. 180 at 735 mm., $n^{25}D$ 1.4040, $d^{25}_4$ 0.902. *Anal.* Calcd. for $AcOCH_2SiMe_2OSiMe_3$: Si, 25.5; sapn. equiv., 220; molar refr.,[5] 59.82. Found: Si, 25.4; sapn. equiv., 219, 221; molar refr., 59.84; and *sym*-bis-acetoxymethyltetramethyldisiloxane, 25 mole %, b. p. 250° at 760 mm., $n^{25}D$ 1.4215, $d^{25}_4$ 0.993. *Anal.* Calcd. for $(AcOCH_2Me_2Si)_2O$: Si, 21.2; sapn. quiv., 139.2; molar refr., 71.42. Found: Si, 21.1; sapn. equiv., 142, 141; molar refr., 71.2.

When *sym*-bis-chloromethyltetramethyldisiloxane was similarly treated, a practically quantitative yield of this product resulted.

**Cleavage of Acetoxymethyldisiloxanes.**—Both acetoxymethylpentamethyldisiloxane and *sym*-bis-acetoxymethyltetramethyldisiloxane were found to be resistant to acid hydrolysis. Neither ester was hydrolyzed to any appreciable extent after refluxing as long as 56 hours with 6 *N* sulfuric acid.

Both esters undergo rapid decomposition when treated with aqueous alkali. Cleavage of the Si–C bond occurred with the formation of methyl acetate and polysiloxanes. In one typical experiment, the diacetate ester was added quickly to boiling 2 *N* sodium hydroxide solution in 50% ethanol under a one-foot Vigreux column. Methyl acetate was distilled from the mixture as quickly as possible to minimize its saponification by the alkali. Two low boiling fractions were obtained: I, b. p. 53–58, $n^{25}D$ 1.3551 had the odor of methyl acetate; sapn. equiv., calcd. 74; found, 78. This was the chief product. II, b. p. 58–67°, $n^{25}D$ 1.3361, yielded a 3,5-dinitrobenzoate, m. p. 106–107° and is thus identified as being largely methanol, b. p. 66°, $n^{25}D$ 1.3276, 3,5-dinitrobenzoate, m. p. 107°. This fraction also contained methyl acetate, judging by its odor and by the fact that it contained saponifiable material. When the distillate rose to a b. p. of 100°, the residue was cooled, acidified and extracted with benzene. The extract was distilled through the Vigreux column. Most of the silicon-containing product was obtained at 135–142°,

(1) Speier, Daubert and McGregor, THIS JOURNAL, **70**, 117 (1948).
(2) Krieble and Elliott, *ibid.*, **67**, 1810 (1945).
(3) Bluestein, *ibid.*, **70**, 3068 (1948).
(4) Hunter, Warrick, Hyde and Curry, *ibid.*, **68**, 2284 (1946).
(5) Warrick, *ibid.*, **68**, 2455 (1946).

leaving a small residue of high boiling oil which was apparently a dimethylpolysiloxane polymer. The distillate crystallized on standing and, after drying in a clay plate, melted at 58–61°. When mixed with an equal amount of authentic hexamethylcyclotrisiloxane a m. p. of 60–63° was obtained. Hexamethylcyclotrisiloxane has the properties,[6] b. p. 133° at 760 mm., m. p. 64.5°.

*Anal.* Calcd. for $[(CH_3)_2SiO]_x$: Si, 37.8. Found: Si, 37.7, 37.8.

**Preparation of *sym*-bis-Hydroxymethyltetramethyldisiloxane.**—*sym*-bis-Acetoxymethyltetramethyldisiloxane was dissolved in about a fifteen-fold excess of absolute methanol and acidified with hydrogen chloride. After twenty-four hours at room temperature, about 90% of the theoretically possible amount of methanol–methyl acetate azeotrope, b. p. 53° at 740 mm., was removed by distillation through a still of about 50 theoretical plates. The mixture was cooled and made up to its original volume with absolute methanol. After an additional twenty-four hours, all volatile material was removed at 25° and 20 mm. pressure with a stream of dried air bubbling through the liquid. The non-volatile residue was *sym*-bis-hydroxymethyltetramethyldisiloxane, $n^{25}D$ 1.4358, $d^{25}_4$ 0.979; m. p. −7.5 to −5°; viscosity: 9.1 cs. at 56°; 32.6 cs. at 21°; *Anal.* Calcd. for $C_6H_{18}O_3Si$: Si, 28.87; OH, 17.5; mol. wt., 194; molar refr., 52.0. Found: Si, 28.55; 28.83; OH, 17.1, 17.1; mol. wt. (ebullioscopically in ethanol), 187; molar refr., 51.7.

The compound formed a di-3,5-dinitrobenzoate readily, m. p. after recrystallization from ethanol, 118.5–119°.

*Anal.* Calcd. for $C_{20}H_{22}N_4O_{13}Si_2$: Si, 9.63. Found: Si, 9.72.

As the material aged, its constants changed and the viscosity at 56° increased appreciably during one-half hour at this temperature. When heated for distillation at about 5 mm. pressure, water was eliminated and a complex resinous mass resulted which became quite fluid on exposure to water. This resinous material was not further characterized.

## Discussion

The chloromethyldisiloxanes react with potassium acetate in glacial acetate acid at a far more rapid rate than does chloromethyltrimethylsilane. A similar difference was found in reactivity by Sommer, *et al.*,[7] to apply to α-chloroethyldiethylsilanol, α-chloroethyltrialkylsilanes, and α-chloroethyldiethylphenylsilane, the first being about 12-fold more reactive than the last and about 170-fold more reactive than the α-chloroethyltrialkylsilanes. This may be analogous to the enhanced activity displayed by beta oxygenated organic halides under similar circumstances

The formation of two acetate esters from the mono chlorinated disiloxane resulted through the rearrangement of the siloxane structures in the acetic acid solution. Similar rearrangements have been described in previous publications.[8,9,10] The products were statistically distributed, indicating that the acetoxy group on the methyl substituent had no detectable effect upon the silicon oxygen bonds as an influence upon their ability to rearrange.

The acetoxymethyl group was cleaved very readily with the formation of methyl acetate and a siloxane bond. This cleavage is thus the same as that found by Krieble and Elliott[2] for the chloromethyl group. The formation of methyl acetate rather than methanol in the alkaline medium indicates that the cleavage reaction occurs at a rate faster than that of the saponification of the ester.

The instability of the hydroxymethylsiloxane structure is in complete contrast with the great stability displayed by trimethylsilylmethanol.[1] The reason for this instability cannot be confidently stated until the structure of the polymer formed has been established.

## Summary

Chloromethylpentamethyldisiloxane was found to react readily with potassium acetate in acetic acid to form a statistical distribution of hexamethyldisiloxane, acetoxymethylpentamethyldisiloxane, and *sym*-bis-acetoxymethyltetramethyldisiloxane. The acetoxymethyl group was cleaved by aqueous alkali to form methyl acetate and hexamethylcyclotrisiloxane as the chief products. *sym*-bis-Hydroxymethyltetramethyldisiloxane was prepared by methanolysis of the corresponding diacetate.

PITTSBURGH, PA. RECEIVED NOVEMBER 8, 1948

(6) Hunter, Hyde, Warrick and Fletcher, THIS JOURNAL, **68**, 667 (1946).

(7) Sommer, Bailey, Strong and Whitmore, *ibid.*, **68**, 1881 (1946).

(8) Scott, *ibid.*, **68**, 2294 (1946).

(9) Wilcock, paper presented at 110th meeting of the American Chemical Society, Chicago, Ill., September 1946.

(10) Speier, THIS JOURNAL, **71**, 273 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, PURDUE UNIVERSITY]

# *aldehydo*-D-Galactose Heptaacetate and *aldehydo*-D-Xylose Hexaacetate from Acetolysis of Guaran and Xylan[1]

BY ROY L. WHISTLER, EILEEN HEYNE AND JOSEPH BACHRACH

Acetolysis offers a means for the structural analysis of polysaccharides. This process often yields, in addition to acetates of the constituent monosaccharides, various oligosaccharide acetates and particularly disaccharide acetates, in which glycosidic linkages characteristic of the parent polysaccharide molecule are preserved unchanged and therefore available for further and more convenient study. An examination of the acetolysis products from guaran and xylan is in progress in this Laboratory. Separation of the various sugar acetates has been made by the excellent chromatographic technique of Wolfrom and co-workers.[2] Among the acetolysis products there is always present a considerable quantity of usual monosaccharide acetates. However, in addition there has been found among the acetolysis products of guaran and xylan, acetates of the monosaccharide aldehydrols. Thus, crystalline *aldehydo*-D-galactose heptaacetate and *aldehydo*-D-xylose hexaacetate have been isolated from guaran and xylan, respectively.

Guaran is the principal polysaccharide[3] of the endosperm of guar seed. It consists of galactose and mannose units in the ratio of 1:2, respectively. Present evidence suggests that its structure may be represented as a chain of mannose units with attached galactosidic side chains.[4,5] Acetolysis of guaran triacetate produces a mixture of products which can be separated by chromatography. The carbohydrate acetate occurring in the second zone from the bottom crystallizes and is identified as *aldehydo*-D-galactose heptaacetate. This compound has been synthesized previously from *aldehydo*-D-galactose pentaacetate and acetic anhydride,[6,7] and the DL-compound has been obtained by acetolysis of agar.[8] So far the corresponding acetylated aldehydrol of mannose has not been isolated from guaran acetolysate.

Corn cob xylan or its diacetate readily undergoes acetolysis and the products are easily separated by chromatography. From the bottom zone *aldehydo*-D-xylose hexaacetate may be obtained readily in crystalline condition. This compound was synthesized previously by Pirie[7] who isolated it as a sirup but was unable to obtain it in crystalline form. By employing chromatographic purification, however, the present authors have been able to obtain in crystalline condition the synthetic compound prepared by acetylation of *aldehydo*-D-xylose tetraacetate. The synthetic compound is identical with the crystalline specimen derived from acetolysis of xylan.

The possibility of obtaining acetates of the aldehydrol form of sugars from acetolysis of glycosides has been demonstrated by Freudenberg and Soff[9] who obtained *aldehydo*-D-glucose heptaacetate by acetolysis of the methyl tetraacetyl-D-glucosides. The inference is, therefore, that sugar aldehydrol acetates may be expected as normal products of acetolysis of polysaccharides. The present work tends to substantiate this view.

## Experimental

**Acetolysis of Guaran Acetate.**—Guaran triacetate was prepared as described previously.[3] Acetolysis was performed in a manner similar to that described by Nishida and Hashima for Konjak glucomannan.[10] A mixture of acetic anhydride (330 g.), glacial acetic acid (330 g.) and concentrated sulfuric acid (64 g.) in a 2 liter round-bottom flask was cooled to 0° in an ice-bath. Powdered guaran triacetate (32 g.) was slowly added with stirring. When all of the acetate had been added, the temperature was allowed to rise slowly to 25°. Any undissolved acetate went into solution during this period. The mixture was then allowed to stand at room temperature for thirty-one days. The acetolysis mixture was slowly poured into 3–5 liters of ice water and the solution neutralized with sodium bicarbonate. The acetates were extracted from the water solution with 5 portions of chloroform (total volume 1 liter). The chloroform extracts were evaporated to dryness, weighed, and extracted with 320 ml. of benzene to make a solution containing approximately 1 g. of solid per 10 ml.

**Chromatographic Separation of the Dissolved Acetates.**—The technique of McNeely, Binkley and Wolfrom[2] was followed. To the top of a 330 × 55 mm. (diam.) column of a mixture of 5 parts (by wt.) of "Magnesol" and 1 part of "Celite" was added 20 ml. of the benzene solution described above. The chromatogram was developed with 3500 ml. of benzene–ethanol (150:1 volume ratio). The column was extruded and streaked with a solution of 1% potassium permanganate in 2.5 *N* sodium hydroxide. The permanganate solution was applied in a thin stream to the column by ejection from a hypodermic syringe. Five zones quickly developed. The zone measurements from the top of the column were as follows: I, 0–15 mm.; II, 25–35 mm.; III, 100–120 mm.; IV, 230–255 mm.; and V, 285–315 mm. The zones were eluted with acetone, evaporated to dryness, and dissolved in 95% ethanol. Rectangular prism-like crystals developed in the solution from zone IV, m. p. 103°. The yield was approximately 3% of the original guaran triacetates. After several recrystallizations from ethanol, the crystals showed a melting point of 105–106° unchanged by further recrystalliza-

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(5) W. Swanson, paper presented before the Division of Sugar Chemistry and Technology at the 112th meeting of the American Chemical Society, New York, N. Y., 1947.

(6) F. Micheel, H. Ruhkopf and F. Sückfüll, *Ber.*, **68B**, 1523 (1935).

(7) N. W. Pirie, *Biochem. J.*, **30**, 374 (1936).

(8) N. W. Pirie, *ibid.*, **30**, 369 (1936).

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(10) K. Nishida and H. Hashima, *J. Dept. Agr. Kyushu Imp. Univ.*, **2**, 227 (1930).

tion, $[\alpha]^{2}D$ 4.0 (*c*, 3 in $CHCl_3$). These values agree with those obtained by Pirie.[8] Oxidation of the crystals in 25% nitric acid gave mucic acid, m. p. and mixed m. p. 213–214°.

*Anal.* Calculated for $C_6H_7O_7(CH_3CO)_7$: C, 48.80; H, 5.73; $CH_3CO$, 61.2; mol. wt., 492.4. Found: C, 48.85; H, 5.87; $CH_3CO$ (Kunz and Hudson method[11]), 60.9; mol. wt. (Rast), 487.

**Preparation of xylan.**—Xylan was obtained by purification of hemicellulose-A (crude xylan) extracted from corn cob holocellulose with 10% potassium hydroxide as described previously.[12] The hemicellulose-A was redissolved in 4% potassium hydroxide and reprecipitated by addition of acetic acid to *p*H 4.5. The precipitate, after collection in a supercentrifuge, was freed from water by four passages through ethanol in a Waring Blendor and dried to a low moisture content (2–3%) over calcium chloride in a vacuum desiccator. On a dry basis it contained 3% uronic anhydride[13] and 94% xylan (from furfural determination[14]), $[\alpha]^{20}D$ −106° (*c*, 0.5 in 1 *N* sodium hydroxide).

**Xylan Acetate.**—Xylan acetate used in these acetolysis studies was prepared by an adaptation of the method of Hurd and Currie.[15] Approximately 10 g. of xylan which had not been dried previously was repeatedly washed with acetic acid in a Waring Blendor until free of water. It was then washed with acetic anhydride to remove most of the acetic acid, placed in a 500-ml. flask and treated with 200 ml. of acetic anhydride containing 0.5 ml. of nitric acid, thus giving a concentration of nitric acid of 0.25%. The mixture was kept at 70° for seven hours, filtered, if necessary, and poured into ice and water. A white fibrous precipitate was obtained which was washed free of acid in a Waring Blendor. The last traces of acid were removed by boiling in water for several minutes. The *p*H was maintained at about seven during this process. The yield was 10 to 14 g. *Anal.* Acetyl, 38.6%; nitrogen, 0.2 to 0.3%. The nitrogen content indicates that a small amount of nitration accompanies the acetylation.

Xylan acetate prepared by the above method was soluble in pyridine and strong films could be cast from such solutions.[16] Xylan acetate prepared by the method of Carson and Maclay[17] undergoes acetolysis in a similar manner but was found to be incompletely soluble in pyridine or other organic solvents and consequently was not cast into films.

**Acetolysis of Xylan Acetate.**—Dry xylan acetate (20 g.), ground in a Wiley mill to pass a 40-mesh sieve, was swelled in 250 ml. of acetic anhydride at 60° for twelve hours. The suspension was cooled to 0° and 20 ml. of a 1:1 mixture of acetic anhydride and sulfuric acid was gradually added with rapid stirring. The temperature was maintained at 0° for several hours and then permitted to come to room temperature. At this point an almost clear, slightly yellow solution was obtained which gradually darkened. Acetolysis was permitted to proceed for thirty to forty days. The dark brown solution was then poured into 3 liters of ice and water and placed in a refrigerator overnight, during which time most of the acetates settled out. The supernatant liquid was decanted ahd reserved. The precipitate was suspended in water, the suspension was neutralized with sodium bicarbonate and extracted several times with chloroform. The reserved supernatant liquid was neutralized and extracted similarly and the extracts combined. The chloroform was evaporated under reduced pressure and a dark sirup resulted. The yield was approximately 20 g. The sirup was dissolved in 500 ml. of benzene and 30 ml. of this solution was chromatographed at a time.

**Acetolysis of Xylan.**—Acetolysis of xylan was carried out in an identical manner except that it was unnecessary to grind the material in a Wiley mill.

**Chromatography of Acetates.**—The above method was used. Thirty ml. of the benzene solution was added to the top of a 48 × 350 mm. sorption column. The chromatogram was developed with 1 liter of benzene–ethanol (100:1 volume ratio). The column was extruded and streaked with potassium permanganate. Three zones developed. Positions of the zones, measured from the top of the column were as follows: I, 1–5 cm.; II, 6–10 cm.; III, 14–18 cm. Almost all of the dark colored material was held within the top 1 cm. of the column and was thus easily separated. The zones were cut apart, eluted with acetone, and evaporated to dryness. The sirup obtained from zone III was rechromatographed. On elution it crystallized from alcohol on standing at 0°. Yield of crude material was approximately 10% of the original acetate. After four recrystallizations, m. p. 54–55°, $[\alpha]^{25}D$ 4.1° (*c*, 10 in $CHCl_3$). *Anal.* Calcd. for $C_5H_6O_6(CH_3CO)_6$: acetyl, 61.44; C, 48.57; H, 5.75. Found: acetyl, 61.4; C, 48.69; H, 5.78.

**Synthesis of aldehydo-D-Xylose Hexaacetate.**—Crystalline aldehydo-D-xylosetetraacetate (2.3 g.), prepared according to the instructions of Wolfrom, *et al.*,[18] was added to a solution of 2.3 g. of zinc chloride in 100 ml. of acetic anhydride and the solution was allowed to stand overnight. The solution was poured into cracked ice and water, neutralized with sodium bicarbonate, and extracted with chloroform. The sirup obtained after evaporation of the chloroform was chromatographed as described above. Two zones were obtained, the lower one corresponding precisely in location to the third zone from the acetolysis experiment. This zone was eluted with acetone as before. The sirup obtained on evaporation of the solvent was crystallized from alcohol. The yield was 1 g. After three recrystallizations, the melting point and optical rotation were identical with the acetolysis product. A mixture of the material and acetolysis product showed no depression of the melting point.

## Summary

By chromatographic methods *aldehydo*-D-galactose heptaacetate and *aldehydo*-D-xylose hexaacetate have been isolated in crystalline form from the acetolysis degradation products of guaran triacetate and xylan diacetate, respectively. This is the first reported occurrence of crystalline *aldehydo*-D-xylose hexaacetate. Isolation of acetates of these sugar aldehydrols lends further support to the view that aldehydrol acetates are to be expected as normal constituents in the acetolysis products from polysaccharide degradation.

LAFAYETTE, INDIANA RECEIVED AUGUST 21, 1948

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(12) R. L. Whistler, J. Bachrach and D. R. Bowman, *Archiv. Biochem.*, **19**, 25 (1948).

(13) Analytical method of R. L. Whistler, A. R. Martin and M. Harris, *J. Research Natl. Bur. Standards*, **24**, 13 (1941).

(14) N. C. Pervier and R. A. Gortner, *Ind. Eng. Chem.*, **15**, 1167 (1923).

(15) C. D. Hurd and N. R. Currie, THIS JOURNAL, **55**, 1521 (1933).

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(17) J. F. Carson and W. D. Maclay, THIS JOURNAL, **70**, 295 (1948).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Some Substituted β-Hydroxyethyl Sulfides

BY HENRY GILMAN AND LAWRENCE FULLHART

In connection with a study on the preparation of physiologically active sulfides and sulfones, some sulfur analogs of the pharmacologically important alkaloid, ephedrine, have been prepared. There have also been prepared related compounds in which the phenyl radical has been replaced by the vinyl group. This paper is being presented now in view of the publication of Prelog[1] and co-workers on similar compounds.

The compounds were prepared by the reaction of the mercaptan with the appropriate epoxy compound in a basic medium or by the reaction of the sodium mercaptide with the epoxide. It is obvious in a reaction of this type that two isomeric products are possible.

The reaction of mercaptans with unsymmetrical epoxides has not been extensively studied. Nenitzescu and Scarlatescu[2] have reported the addition of various alkyl mercaptans to epichlorohydrin. They report the following reactions between ethyl mercaptan and epichlorohydrin.

$$C_2H_5SH + CH_2CHCH_2Cl \longrightarrow C_2H_5SCH_2CHCH_2Cl \quad (OH;\ V)$$

$$C_2H_5SK + CH_2CHCH_2Cl \longrightarrow C_2H_5SCH_2CHCH_2 \quad (VI)$$

The proof of the structure of compound (V) was based on the fact that treatment of (V) with aqueous potassium hydroxide gave compound (VI), their identity being established by boiling point, refractive index and density.

$$C_2H_5SCH_2CHCH_2Cl \xrightarrow{\text{Aq. KOH}} C_2H_5SCH_2CHCH_2$$

(OH; V) (VI)

Compound (VI) was then converted into 2-hydroxy-3-diethylaminopropyl ethyl sulfide (VII) by treating it with diethylamine.

$$C_2H_5SCH_2CHCH_2 + (C_2H_5)_2NH \longrightarrow C_2H_5SCH_2CHCH_2N(C_2H_5)_2$$

(O; OH) (VII)

However, it is also possible that isomeric compounds could be formed from the same reaction as shown below.

$$C_2H_5SH + CH_2CHCH_2Cl \longrightarrow C_2H_5SCHCH_2Cl \xrightarrow{\text{Aq. KOH}} C_2H_5SCHCH_2$$

(O; $CH_2OH$; VIII) (O)

$$C_2H_5SK + CH_2—CHCH_2Cl \longrightarrow C_2H_5SCHCH_2Cl \longrightarrow C_2H_5SCHCH_2$$

(O; $CH_2OK$; IX) (O)

$$C_2H_5SCHCH_2 + (C_2H_5)_2NH \longrightarrow C_2H_5SCHCH_2N(C_2H_5)_2$$

(O; $CH_2OH$; X)

A reaction similar to the reaction of potassium ethyl mercaptide and epichlorohydrin has already been reported.[3] It was found that when epichlorohydrin is treated with sodium β-diethylaminoethyl mercaptide (II), β-diethylaminoethyl-2,3,-epoxypropyl sulfide (XI) is obtained. The structure of (XI), however, was not definitely established.

$$\text{C}_6\text{H}_5\text{—CH—CH}_2 + \text{NaSCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2 \longrightarrow$$

(O; I) (II)

$$\text{C}_6\text{H}_5\text{—CH(OH)—CH}_2\text{—S—CH}_2\text{—CH}_2\text{N}(\text{C}_2\text{H}_5)_2 \quad \text{(III)}$$

$$\text{C}_6\text{H}_5\text{—CH(CH}_2\text{OH)—S—CH}_2\text{—CH}_2\text{N}(\text{C}_2\text{H}_5)_2 \quad \text{(IV)}$$

$$(C_2H_5)_2NCH_2CH_2SNa + CH_2CHCH_2Cl \longrightarrow$$

(II) (O)

$$(C_2H_5)_2NCH_2CH_2SCH_2CHCH_2 \quad (O;\ XI)$$

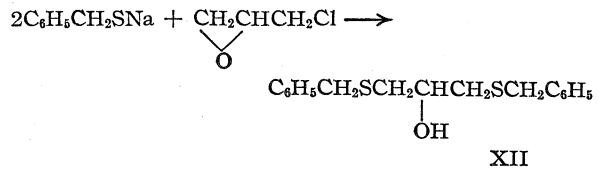
In another case Fromm, Kapeller and Taubmann[4] treated epichlorohydrin with sodium benzyl mercaptide and obtained a product which they assumed was the symmetrical compound, 1,3-dibenzylmercapto-2-propanol (XII). However, the position of the hydroxyl group was not proved.

(1) Prelog, Hahn, Brauchli and Beyerman, *Helv. Chim. Acta*, **27**, 1209 (1944).

(2) Nenitzescu and Scarlatescu, *Ber.*, **68**, 587 (1935).

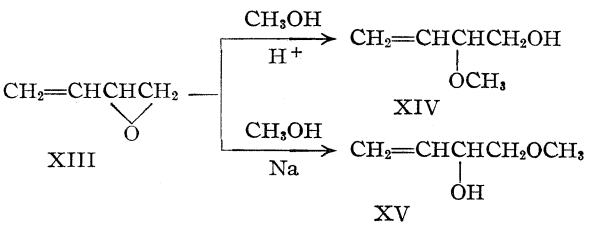
(3) Gilman and Woods, THIS JOURNAL, **67**, 1842 (1945).

(4) Fromm, Kapeller and Taubmann, *Ber.*, **61**, 1353 (1928).



XII

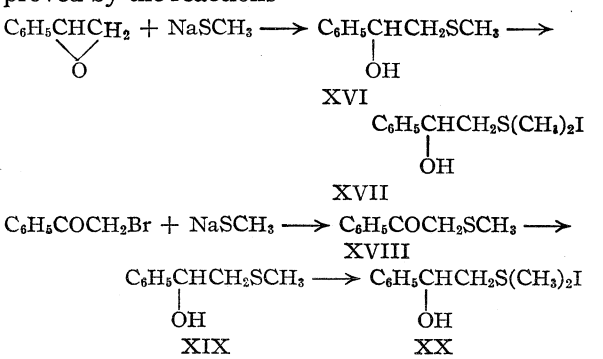
It has been proposed for a number of years that unsymmetrical epoxides cleave in basic media to give secondary alcohols.[5,6,7,8] Recently Castro and Noller[9] have proved this hypothesis in the case of an unsymmetrical epoxide and ammonia. Kadesch[10] has made an extensive examination of the cleavage of 3,4-epoxybutene-1 (XIII). He has given proof for the structure of the compounds obtained and has also advanced a mechanism for the reaction. He found that the reaction of methanol with 3,4-epoxybutene-1 in an acid medium gave 2-methoxy-3-buten-1-ol (XIV) and that when the reaction was carried out in a basic medium 1-methoxy-3-buten-2-ol (XV) was obtained. The cleavage of propylene oxide with alcohols has been studied by Chitwood and



XIII XIV XV

Freure.[11] Their results were similar to those of Kadesch.

The above evidence would indicate that in the reactions which we have performed the secondary alcohols would be obtained. This has been proved by the reactions



XVI XVII XVIII XIX XX

The phenacyl methyl sulfide (XVIII) was reduced to β-phenyl-β-hydroxyethyl methyl sulfide by the Meerwein–Ponndorf[12] method using aluminum isopropoxide. Compounds (XVI) and (XIX) were converted to the corresponding methiodide by the method of Bost and Everett.[13]

The fact that the compounds (XVII) and (XX) were identical was shown by the method of mixed melting points.

A similar structure proof was tried earlier using γ-diethylaminopropyl mercaptan instead of methyl mercaptan. The constants of the γ-diethylaminopropyl β′-phenyl-β′-hydroxyethyl sulfide are in fairly close agreement but suitable solid derivatives could not be obtained.

In this connection β-diethylaminoethyl β′-phenyl-β′-hydroxyethyl sulfide was also prepared in two different ways. β-Diethylaminoethyl mercaptan was condensed with styrene oxide in the usual manner to give the proposed β-diethylaminoethyl β′-phenyl-β′-hydroxyethyl sulfide. In the second method phenacyl chloride was reduced to styrene chlorohydrin by the Meerwein–Ponndorf[12] reduction and condensed with sodium β-diethylaminoethyl mercaptide. The constants of these two products are almost identical but the method could not be considered a valid structure proof, as it is possible for the styrene chlorohydrin to be converted to styrene oxide in the basic medium. This could then react with the mercaptan and give rise to possible isomers. An example of this type of reaction has recently been reported by Whitmore[14] and co-workers. From the reaction of 2,3-dibromopropanol with piperidine there was obtained not only the expected 2,3-di-1-piperidyl-1-propanol but also the symmetrical 1,3-di-1-piperidyl-2-propanol. The symmetrical compound can be explained on the basis of the formation of an intermediate epoxide.

Incidental to the preparation of some of these compounds we prepared some of the thiols by treating sulfur with organolithium compounds. The reactions were smooth, giving yields averaging 60%. There was evidence of some disulfide formation. The reaction of Grignard reagents with sulfur has been reported several times in the literature,[15] but the reaction with organolithium compounds apparently had not been tried. The complementary nature of the Grignard reagent and the organometallic compounds of lithium should make this reaction a useful tool in obtaining heretofore unobtainable thiols.

## Experimental

**β-Diethylaminoethyl β′-Phenyl-β′-acetoxyethyl Ether.**—β-Diethylaminoethyl β′-phenyl-β′-hydroxyethyl ether (10 g., 0.042 mole) was acetylated at 100° with acetic anhydride (40 ml.) and sodium acetate (3 g.). The solution was treated with ammonium hydroxide and extracted with benzene, and the benzene solution was dried over sodium sulfate. The benzene was removed and the residue distilled at 138–141° (0.5 mm.) to give 9.2 g. (78%) of

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(8) Emerson, THIS JOURNAL, **67**, 516 (1945).
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(10) Kadesch, *ibid.*, **68**, 41 (1946); see, also, Bartlett and Ross, *ibid.*, **70**, 926 (1948).
(11) Chitwood and Freure, *ibid.*, **68**, 680 (1946).
(12) Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1944, p. 178.
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TABLE I

COMPOUNDS PREPARED FROM STYRENE OXIDE AND ALKALI MERCAPTIDES

| Mercaptan | Product, sulfide | B. p., °C. | Mm. | $d^{20}_{20}$ | $n^{20}D$ | MR Obs. | MR Calcd. | Yield, % | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| Methyl[a] | β-Phenyl-β-hydroxyethyl methyl[b] | 127 | 0.8 | 1.1082 | 1.5690 | 49.67 | 49.38 | 22 | .. | .. |
| γ-Diethylamino-propyl[a] | γ-Diethylaminopropyl β′-phenyl-β′-hydroxyethyl[c] | 149–152 | .5 | 1.0122 | 1.5363 | 82.24 | 81.49 | 50.5 | 5.24 | 5.44 |
| β-Diethylamino-ethyl[a,d] | β-Diethylaminoethyl β′-phenyl-β′-hydroxyethyl | 132 | .5 | 1.0175 | 1.5423 | 78.18 | 76.87 | 20 | 5.54 | 5.56 |
| p-Aminothio-phenol[e] | β-Phenyl-β-hydroxyethyl p-aminophenyl | 185 | .001 | .... | .... | ... | ... | 68 | 5.72 | 5.60 |

[a] The potassium salt was prepared from equivalent quantities of solid potassium hydroxide and the mercaptan. The epoxide was added to this salt. [b] The reaction proceeded spontaneously when the ice-bath was removed. The product was cooled and diluted with water. [c] The reaction mixture was heated for twenty minutes. [d] This preparation was made from 0.18 mole of styrene oxide and 0.2 mole of the mercaptide. The reaction mixture was heated for fifteen minutes. [e] The sodium salt was prepared in toluene from equivalent quantities of the metal and the thiol.

product; $n^{20}D$ 1.4910; $d^{20}_{20}$ 1.0096; *MR* 79.61 (calcd.); 80.21 (obs.).

*Anal.* Calcd. for $C_{16}H_{25}O_3N$: N, 5.02. Found: N, 4.74, 4.88.

**β-Phenyl-β-hydroxyethyl Methyl Sulfide Methiodide.**—Prelog and co-workers[1] reported the methiodide as melting with decomposition at 132.5–133.5°, but we found the melting point to be 138–139° (dec.). A mixed m. p. with the similarly prepared methiodide of the compound prepared from styrene oxide and potassium methyl mercaptide was not depressed.

*Anal.* Calcd. for $C_{10}H_{15}OIS$: I, 40.92; S, 10.30. Found: I, 41.15; S, 10.47.

**Phenacyl Methyl Sulfide 2,4-Dinitrophenylhydrazone.**—This derivative was prepared by the method of Shriner and Fuson[16] incidental to the synthesis of β-phenyl-β-hydroxyethyl methyl sulfide from phenacyl methyl sulfide,[1] and melted at 164–165.5°.

*Anal.* Calcd. for $C_{15}H_{14}O_4N_4S$: N, 16.17. Found: N, 16.40.

**γ-Diethylaminopropyl Phenacyl Sulfide.**—To 0.1 mole of sodium ethoxide in absolute ethanol was added 14.7 g. (0.1 mole) of γ-diethylaminopropyl mercaptan in absolute ethanol. To this solution was added 19.9 g. (0.1 mole) of phenacyl bromide in absolute ethanol. The reaction mixture was refluxed under nitrogen for two hours and cooled. The suspended salt was filtered and the filtrate was concentrated under reduced pressure and extracted with ether. The ether extract was dried and distilled to give 16 g. (62%) of product distilling at 158–160° (0.8 mm.); $n^{20}D$ 1.5240; $d^{20}_{20}$ 1.0027; *MR* 79.79 (calcd.); 81.02 (obs.). In another preparation the following constants were obtained: b. p. 157–161° (1 mm.); $n^{20}D$ 1.5226.

*Anal.* Calcd. for $C_{15}H_{23}ONS$: N, 5.28. Found: N, 5.62.

The 2,4-dinitrophenylhydrazone was prepared by the usual method; its melting point was 183–184° after recrystallization from absolute ethanol.

*Anal.* Calcd. for $C_{21}H_{30}O_8N_5S$: N, 14.90. Found: N, 14.80.

**β-Diethylaminoethyl β′-Phenyl-β′-hydroxyethyl Sulfide.**—To sodium ethoxide (0.1 mole) in absolute ethanol was added 13.3 g. (0.1 mole) of β-diethylaminoethyl mercaptan in 25 ml. of absolute ethanol. To this solution was then added 15.6 g. (0.1 mole) of styrene chlorohydrin (prepared in 86% yield from phenacyl chloride and aluminum isopropoxide) in 25 ml. of absolute ethanol. The solution was cooled and the precipitated salt filtered. The filtrate was distilled to give 19.5 g. (78%) of product distilling at 152–155° (1.5 mm.); $n^{20}D$ 1.5425.

**γ-(β-Diethylaminoethylmercapto)propyl β′-Phenyl-β′-hydroxyethyl Ether.**—To a solution of 43 g. (0.225 mole) of β-diethylaminoethyl γ-hydroxypropyl sulfide and 11.2 g. (0.2 mole) of potassium hydroxide was added 21.6 g. (0.18 mole) of styrene oxide. The solution was refluxed for one hour and poured into water. The solution was acidified with 12 g. (0.2 mole) of glacial acetic acid and extracted with benzene. The benzene was dried and distilled to give 10 g. (15%) of product distilling at 160–174° (0.6 mm.). Redistillation gave the pure compound distilling at 180–182° (1.5 mm.); $n^{20}D$ 1.5448. The compound has a tendency to superheat.

*Anal.* Calcd. for $C_{17}H_{29}O_2NS$: N, 4.50. Found: N, 4.35.

**3-Diethylamino-1,2-epoxypropane.**[17]—In a 3-liter, 3-necked flask were placed 556 g. (6.0 moles) of epichlorohydrin, 432 g. (5.9 moles) of diethylamine and 18 g. (1.0 mole) of water. The solution was stirred for six hours at a temperature of 28–30°. The temperature was then lowered to 22° and 280 g. (7.0 moles) of sodium hydroxide in 456 ml. of water was added while the temperature was kept below 25°. The solution was stirred for forty minutes; a yellow layer separated out during this time. The yellow layer was removed and the water layer extracted with ether. The ether extracts and the original layer were combined and dried over potassium hydroxide. The ether solution was decanted and distilled to give 430 g. (56.5%) of product distilling at 69° (32 mm.); $n^{20}D$ 1.4362.

**Thiophenol.**—To 0.195 mole of phenyllithium in ether[18] was added cautiously 6.25 g. (0.195 g. atom) of sulfur. The reaction was exothermic. When all the sulfur had been added, color test (I)[19] for the presence of an organometallic compound was negative. The solution was then hydrolyzed with dilute hydrochloric acid and worked up. On distillation there was obtained 13 g. (62%) of thiophenol distilling at 68° (20 mm.); $n^{20}D$ 1.5885. Approximately 3 g. of material distilled at 115–121° (0.5 mm.); this material, which later solidified, may have been diphenyl disulfide.

***p*-Dimethylaminothiophenol.**—To a solution of *p*-dimethylaminophenyllithium prepared from 40 g. (0.2 mole) *p*-bromodimethylaniline[18] was added portion-wise 6.4 g. (0.2 g. atom) of sulfur. The reaction was exothermic and a precipitate formed. The mixture was hydrolyzed with the theoretical amount of hydrochloric acid. The ether layer was separated and dried. On distillation there was obtained 15 g. (50%) of product distilling at 122° (2 mm.). The reported[20] boiling point is 259–260°.

(16) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

(17) This compound was prepared by a modification of a procedure submitted in a N. D. R. C. report from the Laboratory of Columbia University, New York, N. Y. The compound has also been prepared by Drozdov and Cherntov, *J. Gen. Chem.* (*U. S. S. R.*), **4**, 969 (1934) [*C. A.*, **29**, 2148 (1935)] and Eisleb, U. S. Patent 1,845,403 (1932) [*C. A.*, **26**, 2199 (1932)].

(18) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

(19) Gilman and Schulze, *ibid.*, **47**, 2002 (1925).

(20) Leuckart, *J. prakt. Chem.*, [2] **41**, 208 (1890).

TABLE II

COMPOUNDS PREPARED FROM 3-DIETHYLAMINO-1,2-EPOXYPROPANE AND ALKALI MERCAPTIDES

| Mercaptan | Product, sulfide | B. p., °C. | Mm. | $n^{20}D$ | % | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| γ-Diethylaminopropyl[a] | γ-Diethylaminopropyl γ′-diethylamino-β′-hydroxypropyl[b] | 131–134 | 0.5 | 1.4380 | 54 | 10.14 | 10.05 |
| β-Diethylaminoethyl[a] | γ-Diethylamino-β-hydroxypropyl β′-diethylamino[c] | 121–122 | .8 | 1.4850 | 57 | 10.69 | 10.50 |
| Thiophenol[d] | γ-Diethylamino-β-hydroxypropyl phenyl | 125–128 | .5 | 1.5452 | 56 | 5.85 | 5.88 |
| p-Dimethylaminothiophenol[a] | γ-Diethylamino-β-hydroxypropyl p-dimethylaminophenyl[e] | 145–147 | .001 | 1.5680 | 52 | 9.93 | 9.96 |
| p-Thiocresol[a] | γ-Diethylamino-β-hydroxypropyl p-tolyl[c] | 137 | .8 | 1.5412 | 65 | 5.53 | 5.65 |
| p-Aminothiophenol[a] | γ-Diethylamino-β-hydroxypropyl p-aminophenyl[f] | 153 | 1 | 1.5763 | 53 | 11.02 | 11.04 |
| p-Chlorothiophenol[a] | γ-Diethylamino-β-hydroxypropyl p-chlorophenyl[g] | 149–152 | 1.5 | 1.5517 | 23 | 5.13 | 5.29 |

[a] The sodium salt, prepared from the metal and the mercaptan in toluene, was used. [b] The reaction mixture was refluxed for sixteen hours. It was then extracted with dilute base before working up. $d^{20}_{20}$ for the compound was 0.9431; *MR:* calcd., 84.57; obs., 83.85. [c] The reaction mixture was refluxed for eight hours, cooled and extracted with dilute base. [d] The epoxide (0.2 mole) was added to an ethereal solution of lithium thiophenolate (0.2 mole) prepared from phenyllithium and sulfur (see text). After refluxing overnight, the reaction mixture was decomposed with water. [e] The reaction mixture was refluxed for five hours, cooled and extracted with dilute base. [f] The reaction mixture was refluxed for twelve hours, cooled and diluted with water. [g] 0.05 molar quantities used. The mixture was refluxed for six hours, cooled and diluted with water.

TABLE III

COMPOUNDS PREPARED FROM 3,4-EPOXYBUTENE-1 AND SODIUM MERCAPTIDE

| Mercaptan | Product, sulfide | B. p., °C. | Mm. | $d^{20}_{20}$ | $n^{20}D$ | *MR* Calcd. | Obs. | Yield, % | N, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| p-Aminothiophenol[a] | β-Hydroxy-Δ³-butenyl p-aminophenyl | 165–168 | 0.8 | .... | .... | ... | ... | 51 | 7.18 | 7.20 |
| β-Diethylaminoethyl[b] | β-Hydroxy-Δ³-butenyl β′-diethylaminoethyl | 111 | 1.5 | 0.9829 | 1.5044 | 61.20 | 61.35 | 87 | 6.90 | 7.17 |
| γ-Diethylaminopropyl[c] | β-Hydroxy-Δ³-butenyl γ′-diethylaminopropyl | 123 | 0.8 | 0.9686 | 1.5028 | 66.22 | 65.97 | 62 | 6.45 | 6.64 |

[a] The mixture was refluxed for three hours, then diluted with water. [b] Refluxed twelve hours and diluted. [c] Refluxed eight hours and diluted.

**γ-Diethylamino-β-hydroxypropyl p-Tolyl Sulfone.**—A suspension of 17.9 g. (0.1 mole) of sodium p-toluenesulfinate and 12.9 g. (0.1 mole) of 3-diethylamino-1,2-epoxypropane in toluene was refluxed under a nitrogen atmosphere for twelve hours. The solution was diluted with water and worked up to give 5 g. (17.5%) of product distilling at 217° (1 mm.); m. p. 65–67°.

*Anal.* Calcd. for $C_{14}H_{23}O_3NS$: N, 4.92. Found: N, 5.12.

**Preparation of Substituted Sulfides.**—In general, 0.1 mole of the mercaptan was converted to the alkali metal salt either by solid potassium hydroxide or by sodium in benzene or toluene. This salt was then brought into reaction with an equivalent amount of the appropriate epoxide. (For individual times of heating, see footnotes to the Tables.) The reaction mixtures from preparations which used the potassium salt were diluted with water, acidified with glacial acetic acid, extracted with benzene, dried and distilled. The other reaction mixtures were diluted with water (and extracted with dilute base where noted), dried and distilled.

**Acknowledgment.**—The authors are grateful to the Pittsburgh Plate Glass Company for furnishing the 3,4-epoxybutene-1; to the Dow Chemical Company for furnishing the styrene oxide used in these experiments; and, particularly, to Parke, Davis and Company for arranging for the pharmacological tests, which will be reported elsewhere. They also wish to thank William Meikle and John Morton for assistance.

## Summary

A series of substituted β-hydroxyethyl sulfides has been prepared and described. Evidence has been given to indicate that the cleavage of unsymmetrical epoxides by mercaptans in the presence of base results in secondary alcohols.

A method for the preparation of thiols using organolithium compounds has been described.

AMES, IOWA RECEIVED JULY 20, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DELAWARE]

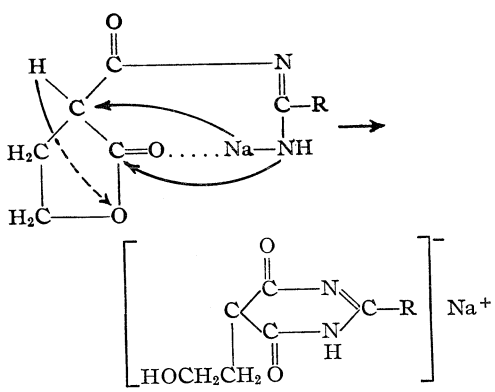
# Condensation of α-Carbethoxy-γ-butyrolactones with Amidines and Guanidine

BY GLENN S. SKINNER, ETHEL ANDERSON AND ROBERT F. BOGART

It has been previously reported[1] that an α-alkyl-α-carbethoxy-γ-butyrolactone does not condense with an amidine to yield a tetrahydropyrimidine derivative but a product whose formation could be explained by the hydrolysis of an intermediate in which the lactone ring had remained intact.

By rapid and intimate mixing of the alkaline reaction product with a freezing mixture of ice and hydrochloric acid there is obtained the intermediate lactone amidine containing a small amount of the inner salt that is formed through the initial splitting of the lactone ring by aqueous alkali. A better procedure for the isolation of the pure lactone amidine involves the prior removal of the sodium as sodium chloride under anhydrous conditions.

The unalkylated lactone ester, however, readily condenses with amidines to yield the tetrahydropyrimidine derivatives. The greater reactivity of the unalkylated lactone ester is probably due to the residual active hydrogen atom. The formation of the sodium derivative of the intermediate that is made possible by the tautomerism of the amidine residue in the intermediate can then lead by the $1 \rightarrow 3$ shift mechanism to a more stable sodium derivative involving ring closure.



Due to the fact that an α-carbethoxy-γ-butyrolactone may be decarboxethylated[1] and that amidines may lose ammonia to form nitriles, some study was made to find the optimum conditions for the formation of the tetrahydropyrimidine derivative. In general, the best yields were obtained by heating the mixture of reactants at 45° (Table I). In the case of the 2-ethyl- and 2-phenyl- derivatives it was also shown that the yield was raised from 55.4 and 53.6 per cent. to 66.3 and 65.5 per cent., respectively, by the very slow addition of an alcohol solution of the lactone ester to the mixture as it was stirred at 45°. This is confirmation that one of the difficulties lies in the decarboxethylation of the ester.

(1) Skinner, Stokes and Spiller, THIS JOURNAL, **69**, 3083 (1947).

TABLE I

2-ALKYL-5-β-HYDROXYETHYL-4,6-DIKETO-3,4,5,6-TETRAHYDROPYRIMIDINES

| R– | Yield, % | M. p., °C.[a] | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|
| H– | 67.9 | 247–248[b] | 17.94 | 17.88 |
| $CH_3$– | 68.7 | 275–276 | 16.46 | 16.48 |
| $C_2H_5$– | 55.4[c] | 267–268 | 15.21 | 15.12 |
| $n$-$C_4H_9$– | 75.9 | 259–260 | 13.20 | 13.10 |
| iso-$C_5H_{11}$– | 66.4 | 244 | 12.38 | 12.37 |
| $C_6H_5$– | 53.6[d] | 248–249 | 12.06 | 12.10 |

[a] Except where noted all melted with decomposition. [b] Decomposed without melting. [c] Yield 66.3% by slow addition of lactone ester. [d] Yield 65.5% by slow addition of lactone ester.

Attempts to isolate the intermediate disodium derivative from the condensation of an α-alkyl-α-carbethoxy-γ-butyrolactone with guanidine gave evidence that such a compound is formed, but a set of conditions whereby a constant weight could be obtained for the sample to be analyzed was not found. The 5-alkyl-5-β-hydroxyethyl-2-iminobarbituric acids can be isolated in fair yields (Table II).

TABLE II

5-ALKYL-5-β-HYDROXYETHYL-2-IMINOBARBITURIC ACIDS

| Alkyl | M. p., °C., dec. | Yield, % | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|
| $C_2H_5$– | 248–249 | | 21.10 | 20.82 |
| $n$-$C_3H_7$– | 252 | 88.7 | 19.70 | 19.64 |
| $n$-$C_4H_9$– | 263–264 | 51.4 | 18.49 | 18.43 |
| $n$-$C_5H_{11}$– | 242 | 86.5 | 17.42 | 17.51 |
| iso-$C_5H_{11}$– | 247 | | 17.42 | 17.27 |

## Experimental

**Lactone Amidine.**—A solution of sodium ethoxide was prepared from 0.243 mole of sodium and 100 cc. of alcohol. To the cooled (22°) and mechanically stirred solution were added 0.0866 mole of benzamidine hydrochloride and 0.0693 mole of α-isoamyl-α-carbethoxy-γ-butyrolactone. The bath was then heated rapidly to 45°. Heating was continued at this temperature for twenty-four hours and it was then heated three hours at 70°. The mixture was cooled in an ice-bath, and with good mixing, made just acid with 15.7 cc. of hydrochloric acid. The sodium chloride (13.3 g.) was filtered and washed with absolute alcohol. After concentration of the filtrate by distillation of the alcohol *in vacuo* from a bath, not heated above 50°, 5.4 g. of the lactone–amidine separated in the form of white crystals, m. p. 117–118°.

A mixture of the lactone–amidine and the inner salt resulting from the hydrolysis was prepared by the following procedure. To a stirred solution of sodium ethoxide prepared from 7.6 g. of sodium and 100 cc. of absolute alcohol there was added at 0° 18.8 g. of benzamidine hydrochloride and then 22.8 g. of α-isoamyl-α-carbethoxy-γ-butyrolactone. The temperature was allowed to rise to 23° in one hour. The mixture was heated two hours at 40° and

then two hours at 47°. Stirring was stopped and the mixture was heated twelve hours longer at 47°. Most of the alcohol (82 cc.) was removed by distillation under diminished pressure at this bath temperature. The residue was quickly and vigorously shaken with a mixture of 19 cc. of hydrochloric acid (1.19) and 80 g. of finely crushed ice. The cold mixture was filtered with suction and washed with ice-cold water and petroleum ether. The mixture weighed 22.24 g., m. p. 112–122° (dec.). Upon standing an additional 1.33 g. of impure inner salt separated from the filtrate, m. p. 132–134° (dec.).

Lowering the initial and final reaction temperatures to −10 and 23°, respectively, for a total reaction period of thirty-four hours decreased the yield to 6.85 g. Increasing the heating period to twenty-four hours at 45–48° followed by heating three hours at 70° decreased the yield to 7.34 g. When the temperature of the reaction mixture was allowed to rise to 89° in two hours and the mixture was then heated six hours longer at 89° the yield was decreased to 7.12 g.

To separate the lactone–amidine from the inner salt, 1 g. of the product was placed in a beaker cooled in a salt–ice mixture. To this was added with good stirring a precooled mixture of 2 cc. of hydrochloric acid (1.19) and 10 cc. of water. To the cold filtrate from a very small amount of undissolved material concentrated aqua ammonia was added from a buret until the maximum precipitation was obtained. Constant mixing and a temperature below 0° should be maintained. It is preferable to operate at −5°. The crystals were filtered with suction and washed with ice-cold water and a mixture of ether and ligroin, m. p. 114–115°. By dissolving this product in alcohol at 35° and crystallizing by cooling in a freezing mixture the melting point rose to 117°.

*Anal.* Calcd. for $C_{17}H_{22}O_3N_2$: N, 9.27. Found: N, 9.16.

The inner salt was best obtained by crystallizing from alcohol the product from those preparations in which no precautions were taken against hydrolysis of the lactone–amidine, m. p. 140–141 (dec.). The salt previously prepared under more vigorous conditions decomposed at 147°.

*Anal.* Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.75. Found: C, 63.46; H, 7.49; N, 8.73.

The inner salt, by heating at its decomposition point, gave one equivalent of ammonia, benzonitrile and nonvolatilized material which behaved as a lactone but was not further identified.

**2-Alkyl-5-β-hydroxyethyl-4,6-diketo-3,4,5,6-tetrahydropyrimidines.**—In a typical experiment valeramidine hydrochloride (0.1250 mole) and α-carbethoxy-γ-butyrolactone (0.100 mole) were rapidly and thoroughly mixed at room temperature with a solution of sodium ethoxide prepared from 6.9 g. of sodium and 100 cc. of absolute alcohol. The mixture was brought rapidly to 45° and maintained at that temperature for twenty-five hours. After standing at room temperature for twelve hours the mixture was treated with 20 cc. of acetic acid mixed with 125 g. of ice and water. The yield was 16.1 g. (75.9%). Recrystallization from hot 50% alcohol gave nearly white crystals, m. p. 259–260° (dec.).

To isolate all of the compounds containing smaller radicals it was found necessary to concentrate the mother liquor. The pure products possess a faint yellow color.

**5-Alkyl-β-hydroxyethyl-2-iminobarbituric Acids.**—In a typical preparation, 18.0 g. of guanidine carbonate was added to a solution of sodium ethoxide prepared from 8.0 g. of sodium and 125 cc. of absolute alcohol. After stirring for ten minutes the mixture was cooled to 5° and 11.4 g. of α-*n*-amyl-α-carbethoxy-γ-butyrolactone was added dropwise with stirring. At the end of three hours at this temperature the mixture was allowed to stand twenty-four hours at room temperature. One liter of cold water was added and the filtered solution was made neutral to litmus with acetic acid. The crude acid was recrystallized by dissolving in a boiling mixture of 800 cc. of ethyl alcohol and 650 cc. of water; yield 9.86 g., m. p. 242° (dec.).

In attempts to isolate the intermediate complex salt the alcohol solution of guanidine and sodium ethoxide, after removal of the sodium carbonate, was mixed with 11.4 g. of α-isoamyl-α-carbethoxy-γ-butyrolactone at 19°. The temperature rose to 28° in two minutes and a precipitate began to form in twelve minutes. After twenty-four hours at room temperature the salt was filtered and washed with alcohol. The yield was 5.66 g. The filtrate gave 5.58 g. of crude 5-isoamyl-5-β-hydroxyethyl-2-iminobarbituric acid, m. p. 240–244°. After recrystallization from a mixture of 550 cc. of ethanol and 350 cc. of water the yield was 5.3 g., m. p. 248–249°. The salt continued to decompose under various conditions in attempts to get a constant weight for the sample. A sample after heating intermittently at 76° for fifty-six hours gave the following analysis: Calcd. for $C_{13}H_{23}O_4N_3Na_2$: Na, 13.89; N, 12.69. Found: Na, 16.29; N, 7.45. The substance had therefore suffered extensive decomposition.

**Acknowledgment** is made to the Research Fund of the University of Delaware for financial aid to Ethel Anderson.

## Summary

1. A comparison is made between the action of alkylated and unalkylated α-carbethoxy-γ-butyrolacetones on amidines. The intermediate lactone–amidine has been isolated.

2. The alkylated lactone esters have been condensed with guanidine.

NEWARK, DELAWARE RECEIVED DECEMBER 1, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

# The Reduction of Substituted Nitrobenzenes at the Dropping Mercury Cathode

BY SALLY FREE DENNIS,[1,2] ALLEN S. POWELL AND MELVIN J. ASTLE

Substituted nitrobenzenes were among the first organic compounds to be investigated using the polarographic technique. The early work was performed by the Japanese, Shikata and his co-workers, and from this work Shikata and Tachi[3] formulated the "electronegativity rule of reduction potentials," *i. e.*, that organic compounds are more easily reduced as more electronegative groups are substituted in the same molecule.

These investigators measured the reduction potentials by the tangent method *vs.* the normal calomel electrode. This method of measurement deviates from present practice. It was felt desirable to extend their investigations of substituted nitrobenzenes and to determine the relative effect of the position of the substituent upon the reduction process.

The ortho-, meta- and para-isomers of nitrobenzoic acid, dinitrobenzene, nitrochlorobenzene, and nitrotoluene were selected for study. The reduction of these compounds at the dropping mercury cathode from carefully buffered solutions over the *p*H range 2 to 14 was investigated to determine the nature of the reduction process and the effect of the position of the substituent groups upon the half-wave reduction potential.

## Experimental

All of the compounds investigated were obtained from Eastman Kodak Company and were further purified before use. Water solutions of 0.002 *M* concentration of *o*- and *m*-nitrobenzoic acids and of 0.001 *M* concentration of *p*-nitrobenzoic acid were made up for use as master solutions. The dinitro-, chloronitro- and nitrotoluenes were made up as 0.002 *M* solutions in alcohol. Gelatin was incorporated into each of the master solutions as a water solution of such concentration that the sample for electrolysis (diluted 1:1 with buffer) would contain 0.0075% gelatin.

For *p*H values up to 8 McIlvaine's citric acid–disodium phosphate buffers were used as supporting electrolyte and for *p*H values greater than 8, Sörensen's glycine–sodium hydroxide buffers were used. The *p*H of each solution was checked with a Beckman *p*H meter.

The sample to be electrolyzed was prepared by mixing equal parts of the master solution of nitro-compound and the desired buffer solution. This solution was degassed in the electrolysis cell by passing nitrogen through the solution for seven to eight minutes. The electrolysis was carried out in a constant temperature bath at 25°.

An H-type cell containing a saturated calomel working electrode was used in conjunction with a Sargent Model XX Polarograph. The drop time of the capillary was found to be 3.2 seconds per drop and the value of $m^{2/3}t^{1/6}$ was 2.13 mg.$^{2/3}$sec.$^{-1/2}$ measured in water with no applied potential.

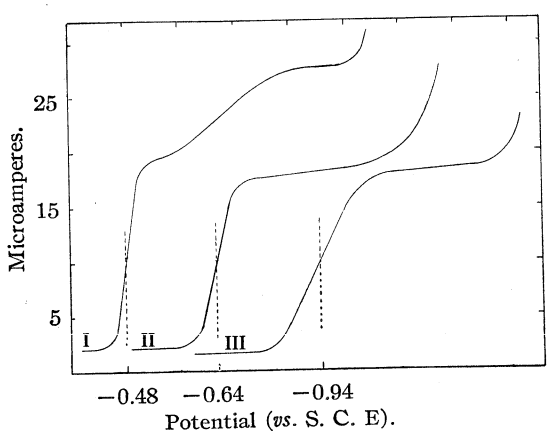



Fig. 1.—Polarograms for *o*-nitrobenzoic acid: I, *p*H 2.1; II, *p*H 4.0; III, *p*H 6.8.

(1) From the M. S. thesis of Sally Free Dennis.

(2) Present address: Lubrizol Corp., Wickliffe, Ohio.

(3) M. Shikata and I. Tachi, *J. Chem. Soc. Japan*, **53**, 834 (1932); *Coll. Czech. Chem. Commun.*, **10**, 368 (1938).

## Discussion of Results

The wave heights and half-wave potentials determined for the nitrobenzoic acids are tabulated in Table I. Inspection of the table reveals that all of the wave heights are approximately 15 microamperes for a 0.001 molar concentration of the acid. Using the value $8.28 \times 10^{-6}$ cm.$^2$ sec.$^{-1}$ for the diffusion coefficient of nitrobenzoic acid the value of $n$ in the Ilkovic equation is found to be 4.05 which indicates that the reduction of the nitro group proceeds only to the hydroxylamine. The diffusion coefficient was determined from the equivalent conductance of the nitrobenzoate ion at infinite dilution. Representative polarograms obtained with *o*-nitrobenzoic acid are shown in Fig. 1. The other two isomers gave similar curves.

TABLE I

HALF-WAVE REDUCTION POTENTIALS (VOLTS *versus* THE S. C. E. CORRECTED FOR *IR* DROP) AND DIFFUSION CURRENTS (MICROAMPERES) FOR AQUEOUS SOLUTIONS OF NITROBENZOIC ACIDS

| | Ortho[a] | | Meta[b] | | Para[a] | |
|---|---|---|---|---|---|---|
| *p*H | *E* | *I* | *E* | *I* | *E* | *I* |
| 2.1 | −0.48 | 15.2 | −0.45 | 15.0 | −0.41 | 7.1 |
| 4.0 | −0.64 | 15.5 | | | −0.51 | 8.0 |
| 5.05 | | | −0.64 | 15.5 | | |
| 6.0 | −0.85 | 15.3 | | | −0.63 | 7.8 |
| 8.1 | −1.06 | 15.4 | −0.83 | 15.0 | | |
| 10.0 | −1.26 | 15.2 | −0.97 | 7.7 [c] | −0.84 | 7.9 |
| | | | −1.51 | 7.7 | | |
| 12.2 | −1.36 | 15.8 | −1.01 | 7.7 | −0.95 | 7.9 |
| | | | −1.42 | 7.7 | | |

[a] 0.001 *M* solutions. [b] 0.0005 *M* solutions. [c] Waves bracketed together were double waves.

Data for the dinitrobenzenes are presented in Table II. The presence of two reducible groups makes the interpretation of the reaction mechanism somewhat obscure, since multiple waves are encountered. Some of the waves following the

TABLE II

HALF-WAVE REDUCTION POTENTIALS (VOLTS *versus* THE S. C. E. CORRECTED FOR *IR* DROP) AND DIFFUSION CURRENTS (MICROAMPERES) FOR 0.001 *M* 50/50 ETHYL ALCOHOL–WATER SOLUTIONS OF DINITROBENZENES

| | Ortho | | Meta | | Para | |
|---|---|---|---|---|---|---|
| *p*H | *E* | *I* | *E* | *I* | *E* | *I* |
| 2.7 | −0.43 | 11.1 | −0.45 | 12.4 | −0.39 | 9.4 |
| | −0.65 | 20.8 | −0.60 | 12.4 | −0.70 | 21.2 |
| | −1.28 | 5.2 | −1.13 | 7.2 | | |
| 4.6 | −0.54 | 14.0 | −0.55 | 13.0 | −0.48 | 11.4 |
| | −0.81 | 13.7 | −0.78 | 10.8 | −0.89 | 19.5 |
| | −1.48 | 9.5 | −1.64 | 11.0 | | |
| 7.4 | −0.66 | 12.2 | −0.71 | 14.0 | −0.60 | 13.0 |
| | −1.00 | 15.4 | −0.96 | 11.4 | −1.08 | 19.5 |
| 8.8 | | | | | −0.63 | 12.6 |
| | | | | | −1.15 | 10.9 |
| | | | | | −1.73 | 16.6 |
| 10.0 | −0.73 | 12.0 | −0.86 | 11.7 | −0.65 | 12.0 |
| | −1.16 | 20.8 | −1.10 | 16.9 | −1.21 | 17.6 |
| | | | | | −1.80 | 8.8 |
| 11.7 | −0.76 | 11.4 | −0.88 | 12.7 | −0.65 | 6.2 |
| | −1.29 | 16.6 | −1.16 | 11.7 | −1.76 | 24.4 |

first are not sufficiently well defined to make their interpretation possible with any degree of accuracy (Fig. 2), however, if correction is made for the effect on wave height of the alcohol required to increase solubility, the first wave is found to be approximately the height of that observed for the nitrobenzoic acid and therefore must represent reduction to the corresponding hydroxylamine. The alcohol effect was measured by reducing nitrobenzoic acid both from water and from 50% alcohol solutions. The ratio between wave heights for the same compound in the two solutions was about 5:4 which corresponds fairly well to the ratio of the nitrobenzoic acid to dinitrobenzene (first wave) heights.

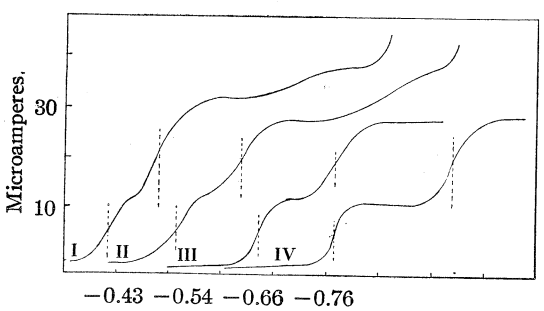



Fig. 2.—Polarograms for *o*-dinitrobenzene: I, *p*H 2.7; II, *p*H 4.6; III, *p*H 7.4; IV, *p*H 11.7. The divisions represent 0.25-volt intervals.

The half-wave potentials for the first and second waves plotted against *p*H are shown in Fig. 3. There is some doubt as to the exact potential of the second wave for the meta-isomer because of difficulty in measurement. It is noted that the order of ease of reduction is para > ortho > meta for the first wave and exactly the reverse for the second wave. This seems reasonable when one considers that the second reduction step takes place under the influence of the hydroxylamine group which is less electronegative than the nitro group. Also the hydroxylamine group is capable of hydrogen bonding with the ortho-nitro group and this would lead to increased ease of reduction of the ortho-compound as has been previously observed in the case of the nitrophenols.[4]

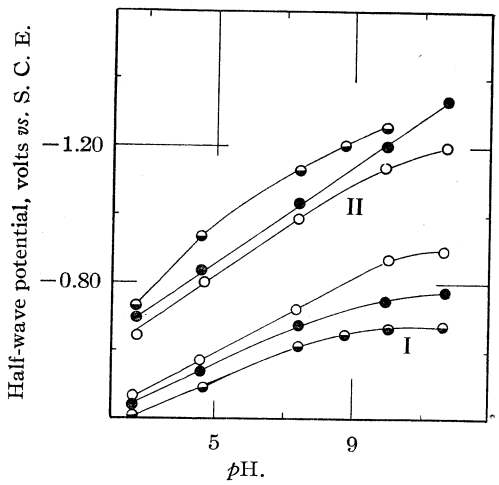



Fig. 3.—Effect of *p*H on the half-wave reduction potentials of the dinitrobenzenes: first wave I, and second wave II: ◒, para; ●, ortho; ○, meta.

As with the nitrobenzoic acids, the data indicate that the nitrotoluenes are reduced to the hydroxylamines at all *p*H values (Table III). In the acid solutions the ortho isomer is considerably more difficultly reduced than the meta- and para-isomers, and the order of ease of reduction changes in alkaline solution to meta > ortho > para. The current–voltage curves were similar to those shown for *o*-nitrobenzoic acid.

TABLE III

HALF-WAVE REDUCTION POTENTIALS (VOLTS *versus* THE S. C. E. CORRECTED FOR *IR* DROP) AND THE DIFFUSION CURRENTS (MICROAMPERES) FOR 0.001 *M* 50/50 ETHYL ALCOHOL–WATER SOLUTIONS OF NITROTOLUENES

| | Ortho | | Meta | | Para | |
|---|---|---|---|---|---|---|
| *p*H | *E* | *I* | *E* | *I* | *E* | *I* |
| 2.7 | −0.69 | 11.0 | −0.65 | 11.9 | −0.63 | 11.4 |
| 4.6 | −0.84 | 11.4 | −0.74 | 12.1 | | |
| 5.65 | | | | | −0.83 | 12.4 |
| 7.4 | −0.99 | 11.3 | −0.93 | 12.1 | −0.95 | 12.4 |
| 10.0 | −1.11 | 11.4 | −1.08 | 12.4 | −1.12 | 13.0 |
| 11.7 | −1.19 | 12.0 | −1.15 | 12.4 | −1.28 | 13.0 |

The chloronitrobenzenes are also reduced to the corresponding hydroxylamines (Table IV). The meta-isomer is the most easily reduced. Below a *p*H of 9 the ortho-isomer is most difficultly reduced with the para-isomer intermediate.

(4) W. V. McConnell and M. J. Astle, THIS JOURNAL, **65**, 35 (1943).

TABLE IV

HALF-WAVE REDUCTION POTENTIALS (VOLTS *versus* THE S. C. E. CORRECTED FOR *IR* DROP) AND DIFFUSION CURRENTS (MICROAMPERES) FOR 0.001 *M* 50/50 ETHYL ALCOHOL–WATER SOLUTIONS OF CHLORONITROBENZENES

| | Ortho | | Meta | | Para | |
|---|---|---|---|---|---|---|
| *p*H | *E* | *I* | *E* | *I* | *E* | *I* |
| 2.7 | −0.64 | 12.2 | −0.53 | 11.7 | −0.59 | 12.4 |
| 4.6 | − .75 | 11.5 | − .65 | 11.5 | − .69 | 12.4 |
| 7.4 | − .91 | 11.7 | − .86 | 11.5 | − .87 | 12.2 |
| 10.0 | −1.01 | 11.8 | − .98 | 11.5 | −1.04 | 12.4 |
| 11.7 | −1.07 | 11.7 | −1.05 | 11.7 | −1.15 | 13.0 |

Figure 4 shows the effect of *p*H on the reduction potential for the four compounds in which the nitro group is ortho to the second substituent.

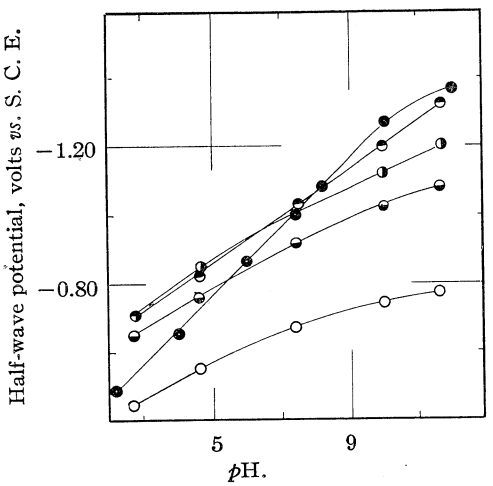



Fig. 4.—Effect of *p*H on the half-wave reduction potentials of the ortho-substituted nitrobenzenes: O, first wave, dinitrobenzene; ●, nitrobenzoic acid; ◒, nitrochlorobenzene; ◑, nitrotoluene; ◓, second wave, dinitrobenzene.

The same relationship is shown for the meta- and para-isomers in Figs. 5 and 6, respectively. Disregarding for a moment *o*-nitrobenzoic acid (which behaves anomalously), one can observe that in all cases, reduction becomes more difficult with the substituent in the order nitro >, carboxyl >, chloro >, methyl and that this order conforms with Shikata's rule of electronegativity. It would seem, therefore, that the effect of the substituent group is to attract the electrons away from the nitrogen leaving it relatively more positive than a nitrogen in a normal nitro group. This tendency toward placing a positive charge on the nitrogen causes the electrons around the nitrogen to be placed under greater constraint, and as a result the resonance within the nitro group is decreased and the nitro group more readily reduced.

The nitro group and carboxyl group show a $-I$ and a $-M$ effect. Both of these effects would decrease the electron density around the nitrogen thus facilitating the reduction of the nitro group. The $-M$ effect would have a greater effect in the ortho- and para-isomers. Consequently, the

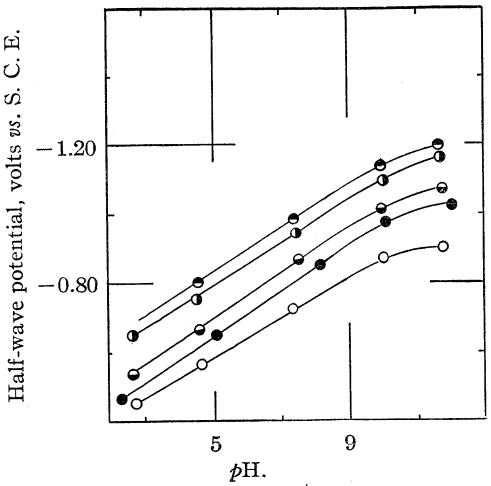



Fig. 5.—Effect of *p*H on half-wave reduction potential of meta-substituted nitrobenzenes: O, dinitrobenzene, first wave; ●, nitrobenzoic acid; ◒, chloronitrobenzene; ◑, nitrotoluene; ◓ dinitrobenzene, second wave.

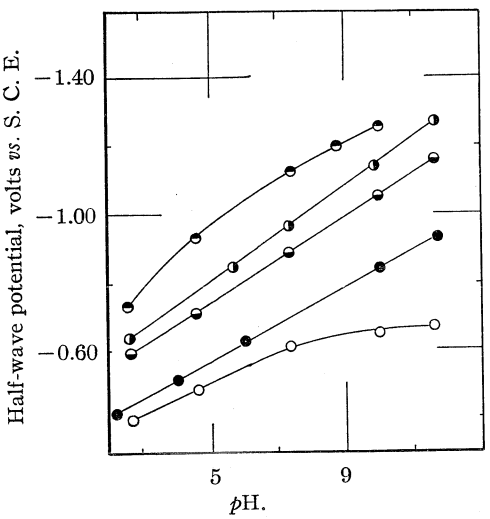



Fig. 6.—Effect of *p*H on the half-wave reduction potentials of para-substituted nitrobenzenes: O, dinitrobenzene, first wave; ●, nitrobenzoic acid; ◒, nitrochlorobenzene; ◑, nitrotoluene; ◓, dinitrobenzene, second wave.

meta-isomer should be the most difficultly reduced and this is what was observed except for *o*-nitrobenzoic acid which behaves anomalously in other respects.

Chlorine exhibits a $-I$ and a $+M$ effect while $-CH_3$ exhibits a $+I$ effect. Both of these groups therefore, should increase the electron density around the ortho- and para-positions relative to the meta-positions and therefore the meta-isomers should be more readily reduced. This is what has been observed.

When hydrogen bonding is possible, the ortho substituted nitro compounds are more readily reduced than either the corresponding meta- or para-isomers. This has been observed previously

in the investigations of nitro phenolic compounds[5] and was observed in the present work for the second stage reduction of dinitrobenzenes which represents the reduction of nitrophenylhydroxyl amines. The *o*-isomer which may form H-bonds between the nitro and the hydroxylamine group was more readily reduced than the corresponding meta- or para-isomers.

After the completion of the present work, Pearson[6] published the results of his investigations of the polarography of the nitrotoluenes and the dinitrobenzenes. Pearson using a potassium hydrogen phthalate–hydrochloric acid buffer over the *p*H range 2.5–3.8 and a potassium hydrogen phthalate–sodium hydroxide buffer over the *p*H range 4.1–7.4 reported half-wave potentials which were from about 0.25 to 0.35 volt more positive than those found in this Laboratory using different systems. Some of Pearson's work has been repeated and verified in this Laboratory. It seems improbable that the differences in reduction potentials could be accounted for on the basis of large differences in concentrations of the nitrobenzene derivatives used in the two investigations. It seems more probable that the reduction of the nitro group is a function not only of the *p*H but also of the nature of the buffer. This effect is being further investigated.

Pearson obtained a second wave at low *p*H values which corresponded approximately to a two electron process which, when added to the height of the first wave involving a four electron process, represented the complete reduction to the corresponding aniline. This second small wave has also been observed in this Laboratory at a *p*H of 2.7 for all the substituted nitrobenzenes but it was very poorly defined and so was not included in the tabulated data.

(5) W. P. Cropper and M. J. Astle, THIS JOURNAL, **65**, 2395 (1943).

(6) J. Pearson, *Trans. Faraday Soc.*, **44**, 683 (1948).

## Summary

The reduction of the ortho-, meta- and para-isomers of nitrobenzoic acid, dinitrobenzene, chloronitrobenzenes and nitrotoluene from buffered solutions at the dropping mercury cathode have been studied.

Within each group of isomers, the ortho-compound was more difficultly reduced than the para-compound. It is possible to correlate the electronegativity of the second substituent with the reduction potential of the nitro group and to qualitatively determine the effect of position on the degree of the electronegativity of that group.

*o*-Nitrobenzoic acid does not behave like the other ortho-compounds in that the reduction potential is much more sensitive to differences in *p*H of the solution.

In every case reduction stops with the formation of the corresponding hydroxylamines, with the exception of the dinitrobenzenes and in these cases the complexity of the curves make difficult the determination of the intermediate steps of reduction.

CLEVELAND, OHIO RECEIVED OCTOBER 1, 1948

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE DEPARTMENT OF BIOCHEMISTRY OF THE JEWISH HOSPITAL OF BROOKLYN]

# Sulfate Esters as Intermediates in the Formation of 7-Dehydrocholesterol and Dicholesteryl Ether[1]

BY ALBERT E. SOBEL, PHYLLIS S. OWADES[2] AND JOSEPH L. OWADES[3]

A certain amount of evidence has accumulated pertaining to the importance of sulfate esters in the chemistry of steroids in the living organism. At least six different steroid sulfates have been isolated from urine,[4–9] as well as a dehydrosteroid which was postulated as having been formed from a sulfate ester during the course of isolation.[10] A sulfate containing lipid was found in brain.[11] Recently it has been shown that the human kidneys maintain a definite level of sulfate in the blood. The existence of this threshold suggests that the sulfate in the blood, heretofore considered to be simply excretory, plays some metabolic role.[12,13]

Naturally occurring 7-dehydrocholesterol and dicholesteryl ether are found associated with the relatively abundant cholesterol, from which they would seem to be derived. 7$\beta$-Hydroxycholesterol, the probable intermediate in the formation of 7-dehydrocholesterol, has also been isolated.

(1) Presented before the Division of Biological Chemistry of the American Chemical Society at Chicago, Ill., April, 1948.

(2) Abstracted from the thesis submitted to the Faculty of the Graduate School of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

(3) Abstracted from the dissertation which is being submitted to the Faculty of the Graduate School of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) Schachter and Marrian, *Proc. Soc. Exp. Biol. Med.*, **35**, 222 (1936).

(5) Munson, Gallagher and Koch, *J. Biol. Chem.*, **152**, 67 (1944).

(6) Venning, Hoffman and Browne, *ibid.*, **146**, 369 (1942).

(7) Klyne and Marrian, *Biochem. J.*, **39**, XLV (1945).

(8) Klyne, *ibid.*, **40**, 875 (1946).

(9) Paterson and Klyne, *ibid.*, **41**, proc. 2 (1947).

(10) Burrows, Cook, Roeb and Warren, *Biochem. J.*, **31**, 950 (1937).

(11) Levene, *J. Biol. Chem.*, **53**, 614 (1912).

(12) Vars and Gurd, *Am. J. Physiol.*, **151**, 399 (1947).

(13) Letspeich, *ibid.*, **151**, 311 (1947).

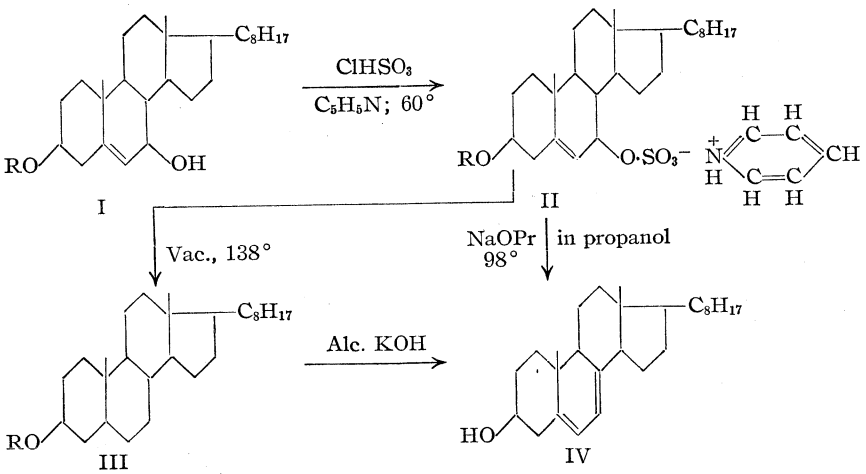



Fig. 1.

In view of this evidence, it seemed possible that sulfate esters might be the metabolic intermediates in the conversion of cholesterol to 7-dehydrocholesterol and dicholesteryl ether. We have shown in this investigation that the formation of these two steroids from their corresponding sulfates is possible *in vitro*.

It had previously been demonstrated that monovalent metal salts of cholesteryl sulfate decompose on heating to give 3,5-cholestadiene.[14,15] It was thus of added interest to determine whether the 7-position in the sterol nucleus underwent a similar reaction.

The method employed in the formation of 7-dehydrocholesterol from cholesterol is shown in Fig. 1. 7β-Hydroxycholesteryl phthalate (I) was made by permanganate oxidation of cholesteryl phthalate using a modification of the method of Heilbron, *et al.*[16] The 7-sulfate (II) was then prepared by treating the alcohol with a mixture of chlorosulfonic acid and pyridine. Decomposition of the sulfate, either in the dry state or in a solvent, resulted in 7-dehydrocholesterol (IV).

This investigation was facilitated by the use of two color reactions which distinguished between 7β-hydroxycholesterol and 7-dehydrocholesterol. The known steroid color tests for 7-dehydro and 7-hydroxy steroids, namely, the Rosenheim,[17] Callow,[18] Lifschutz,[19] and antimony trichloride reactions, give positive tests with both compounds. It was found that the Callow reaction could be modified so as to differentiate between these two steroids. The 7-dehydro compound gave a positive test with this reagent, whereas the 7-hydroxy compound remained colorless. The course of decompositions, as well as purification procedures, were readily followed with this test.

(14) Natelson and Gottfried, THIS JOURNAL, **61**, 971 (1939).
(15) Sobel and Rosen, *ibid.*, **63**, 3536 (1941).
(16) Barr, Heilbron, Parry and Spring, *J. Chem. Soc.*, 1437 (1936).
(17) Rosenheim, *Biochem. J.*, **23**, 47 (1929).
(18) Rosenheim and Callow, *ibid.*, **25**, 74 (1931).
(19) Bergstrom and Wintersteiner, *J. Biol. Chem.*, **145**, 309 (1942).

The activated glycerol dichlorohydrin reagent, which is used in the determination of Vitamin A,[20] was also helpful in distinguishing between these steroids. With this reagent the 7-dehydrocholesterol gave a negative reaction, but 7-hydroxycholesterol gave a dark blue color. This is the only substance which is known to give a blue color with activated glycerol dichlorohydrin.

Dicholesteryl ether was also prepared from sulfate esters. The pyridine radical in pyridinium cholesteryl sulfate was replaced by divalent or trivalent cations, namely, ferrous, ferric and aluminum. These cholesteryl sulfate salts, as well as the calcium salt,[21] decompose at varying temperatures to yield dicholesteryl ether (Fig. 2). The decomposition of the aluminum cholesteryl sulfate occurs spontaneously at room temperature. This low temperature reaction lends support to our hypothesis that sulfate esters are significant in the *in vivo* chemistry of the steroids.

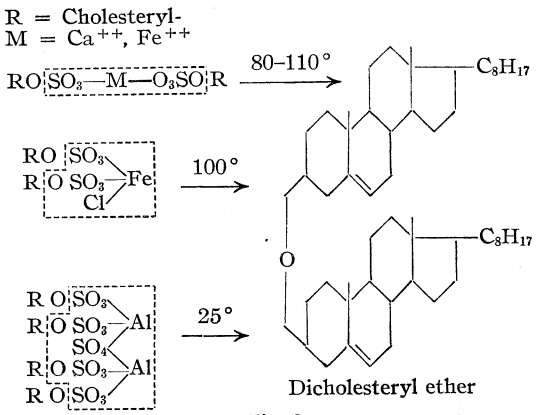



Fig. 2.

It is hoped that future investigations will isolate cholesteryl sulfates and an enzyme system that accomplishes these transformations *in vivo*.

## Experimental

**7β-Hydroxycholesteryl Phthalate.**—A modification of the method of Heilbron, *et al.*,[16] was employed. During a two to three hour period, 1 liter of 0.25 *N* potassium permanganate was added dropwise to a suspension of 10 g. of cholesteryl phthalate in 200 ml. of 1 *N* sodium carbonate. The mixture was vigorously stirred during the addition and for twenty-four hours afterward. Sulfur dioxide was then bubbled in slowly with strong agitation. When completely clarified, the mixture was cooled, filtered, washed with water and dried. The dry solid was extracted with cold

(20) Sobel and Werbin, *Ind. Eng. Chem., Anal. Ed.*, **18**, 570 (1946).
(21) Sobel and Spoerri, THIS JOURNAL, **64**, 482 (1942).

chloroform and ether (1:1). The residue was recrystallized twice from hot pyridine to which water was added until the solution turned cloudy and crystallization began. The yield was 1 g., m. p. 199–201°.

Saponification and recrystallization from methanol gave 7β-hydroxycholesterol, m. p. 178°, $\alpha^{20}D$ −87.3 (in chloroform).

**Pyridinium 7-Sulfate Cholesteryl Phthalate.**—Chlorsulfonic acid (1.2 g.) was added to a cooled solution of 8 ml. of dry pyridine and 27 ml. of dry chloroform. A suspension of 5.5 g. of 7β-hydroxycholesteryl phthalate in 80 ml. of dry chloroform was introduced. The cold mixture was stirred for twenty minutes, 30 ml. of dry pyridine was added and the solution heated in a water-bath at 60° for two hours. It was vacuum distilled under nitrogen to dryness and washed with cold water until chloride-free. It was then dried in vacuum and recrystallized by dissolving in cold chloroform and adding 8–10 volumes of cold petroleum ether. The yield was quantitative, m. p. 142–144° dec. The Rosenheim, Callow, Lifschutz and antimony trichloride color reactions, which are positive for 7β-hydroxycholesteryl phthalate, are negative for pyridinium 7-sulfate cholesteryl phthalate.

*Anal.* Calcd. for $C_{40}H_{55}O_8NS$: C, 67.66; H, 7.81; N, 1.97; S, 4.52. Found: C, 68.0; H, 7.62; N, 1.89; S, 4.46.

**Decomposition of Pyridinium 7-Sulfate Cholesteryl Phthalate.**—A. One-half gram of dry pyridinium 7-sulfate cholesteryl phthalate was placed in an Abderhalden pistol, the pistol evacuated, and xylene (b. p. 138°) refluxed over it for fifteen minutes. Decomposition took place immediately. The product was saponified with 10 ml. of 10% methanolic potassium hydroxide and taken up in peroxide-free ether and water. The ether extract was washed with water, dried over sodium sulfate, and filtered. The ether was blown off with nitrogen and the residue dried in a vacuum desiccator.

B. One-tenth gram of sodium was dissolved in 20 ml. of *n*-propyl alcohol (or ethyl alcohol) contained in a small round bottomed flask with an entering side arm. Pyridinium 7-sulfate cholesteryl phthalate (0.5 g.) was introduced and the solution refluxed for forty minutes. Nitrogen was bubbled through the side arm during the reaction. A brown oil and a white solid separated. The solution was cooled and extracted with ether and water. The water layer gave positive tests for sulfate, phthalate and pyridine. The ether layer, in which the brown oil had dissolved, was dried over sodium sulfate, filtered, and vacuum distilled under nitrogen to dryness.

The residues were shown to be 7-dehydrocholesterol by the absorption spectra, digitonide formation, antirachitic activity, color reactions and the 3,5-dinitrobenzoate derivative.

The yields, as calculated from the molecular extinction coefficient and the weight of the digitonides, were 69% for method A and 30% for method B.

The 3,5-dinitrobenzoate derivative,[22] m. p. 207°, showed no depression with a known sample of the 3,5-dinitrobenzoate of 7-dehydrocholesterol.

*Anal.* Calcd. for $C_{34}H_{46}O_6N_2$: C, 70.55; H, 8.01; N, 4.84. Found: C, 70.41; H, 7.97; N, 4.96.

**Modification of Callow Test.**—The reagent[18] (1 ml.) was added to a solution of the steroid (*ca.* 1 mg.) in 4 ml. of alcohol, instead of chloroform as originally proposed. The use of different solvents was first discussed by Sobel.[23] A yellow color was obtained with 7-dehydrocholesterol and no color with 7β-hydroxycholesterol.

**Activated Glycerol Dichlorohydrin Test.**—Four ml. of reagent[20] was added to a solution of the steroid (*ca.* 1 mg.) in 1 ml. of chloroform. 7β-Hydroxycholesterol gave a deep blue color, the dehydro compound gave no color.

**Ferrous Cholesteryl Sulfate.**—A solution of 10 g. of pyridinium cholesteryl sulfate[24] in 200 ml. of water was treated with a filtered solution of 10 g. of ferrous sulfate heptahydrate in 100 ml. of water. A white, gelatinous precipitate formed immediately. The suspension was stirred for one-half hour, then filtered and washed with water until the filtrate was free of sulfate and ferrous ions. It was then washed with acetone and dried in a vacuum desiccator. It was insoluble in water, ether or acetone; soluble in pyridine and *n*-amyl alcohol; m. p. 122–125° (dec.).

*Anal.* Calcd. for $C_{54}H_{90}O_8S_2Fe$: S, 6.50; Fe, 5.66. Found: S, 6.43; Fe, 5.60.

**Ferric Cholesteryl Sulfate.**—A solution of 13 g. of ferric chloride hexahydrate in 100 ml. of water was filtered and added to 100 ml. of a 5% pyridinium cholesteryl sulfate solution. The mixture was agitated for one-half hour and then centrifuged. The residue was washed with water until free of chloride ion, followed by an acetone and several benzene washes. It was dried in vacuum. The residue was tan colored; insoluble in water, benzene or chloroform; soluble in alcohol; m. p. 115–118° (dec.).

*Anal.* Calcd. for $C_{54}H_{90}O_8S_2ClFe$: S, 6.27; Fe, 5.46. Found: S, 6.34; Fe, 5.55.

**Aluminum Cholesteryl Sulfate.**—A solution of 12 g. of pyridinium cholesteryl sulfate in 120 ml. of water was treated with a filtered solution of 30 g. of aluminum sulfate octadecahydrate in 120 ml. of water and stirred for ten minutes. The suspension was filtered and washed with water until the washings were sulfate-free, and then washed with alcohol and dried in a vacuum desiccator. The residue was soluble in pyridine and *n*-butyl alcohol; insoluble in water, alcohol and dioxane; m. p. 115–120° (dec.).

*Anal.* Calcd. for $C_{108}H_{180}O_{20}S_5Al_2$: S, 7.97; Al, 2.68. Found: S, 7.84; Al, 2.52.

**Dicholesteryl Ether.**—Pyrolysis of the ferrous, ferric and aluminum cholesteryl sulfates in evacuated glass tubes resulted in the formation of dicholesteryl ether. The temperatures required for rapid decomposition were 138° for the ferric salt, and 115° for the ferrous and aluminum salts. The aluminum salt, in addition, was found to undergo this change in several weeks at room temperature. The decomposed material was extracted with warm benzene and filtered from the inorganic residue. The benzene was evaporated and the resinous mass that remained was leached with a mixture of ether and alcohol (1:1). The residue was dissolved in benzene and precipitated with alcohol or acetone. This was repeated several times and the final residue was washed with alcohol and dried; m. p. 205–207°. It gave no depression with a known sample of dicholesteryl ether. The tetrabromide derivative[25] melted at 166°.

## Summary

A sulfate ester of a 7-hydroxy steroid, the pyridinium sulfate of 7β-hydroxycholesteryl phthalate, was prepared. It decomposed to 7-dehydrocholesterol, analogously to a known reaction of 3-sulfate esters.

Two color reactions to distinguish between 7-hydroxy and 7-dehydro steroids were given, which, to the authors' knowledge, are the first reactions to accomplish this differentiation.

Dicholesteryl ether was obtained from ferrous, ferric and aluminum cholesteryl sulfates; at room temperature from the latter compound.

Based on the above findings and a survey of the literature, it is suggested that sulfate esters might be the metabolic intermediates in the conversion of cholesterol to 7-dehydrocholesterol and dicholesteryl ether.

RECEIVED NOVEMBER 19, 1948

(22) Windaus, Lettre and Schenck, *Ann.*, **520**, 98 (1935).

(23) Sobel, Dissertation, Ph.D., Polytechnic Institute of Brooklyn, 1940.

(24) Sobel and Spoerri, THIS JOURNAL, **63**, 1259 (1941).

(25) Levin, *ibid.*, **65**, 627 (1943).

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# Chlorination of bis- and Chloro-bis-(perfluoroalkyl)-benzenes[1]

BY EARL T. MCBEE AND MARVIN R. FREDERICK[1a]

Chloro derivatives of trifluoromethylbenzene have been prepared[2] by chlorinating the latter in liquid phase at atmospheric pressure in the presence of iron(III) chloride. However, this procedure is not applicable to the chlorination of 1,3- and 1,4-bis-(trifluoromethyl)-benzenes[3] and similar compounds of longer side-chains since these compounds are more difficultly substituted. Chloro-bis-(trifluoromethyl)-benzenes have been prepared by fluorination of the chloro-bis-(trichloromethyl)-benzenes.[4,5] Since this paper was first submitted for publication, the chlorination of bis-(trifluoromethyl)-benzenes in an iron reactor at 150–170° under a chlorine pressure of 300 pounds per square inch has been described.[6]

A procedure generally applicable to the preparation of chloro-bis-(perfluoroalkyl)-benzenes has been devised which comprises vapor-phase chlorination at atmospheric pressure of a bis (perfluoroalkyl)-benzene in contact with activated carbon impregnated with an inorganic chloride. Iron(III) chloride was found to be the most satisfactory of the inorganic chlorides studied. No appreciable amount of the iron(III) chloride sublimed from the reactor and the catalyst showed little decrease in activity with use. Antimony(V) chloride was less effective than iron(III) chloride for chlorinations at temperatures below 250°. However, higher percentages of polychlorinated compounds were found in the product when the antimony catalyst was used. Antimony(V) chloride distilled from the reactor and, as a consequence, there was a rapid decline in catalyst activity. Nickel chloride on activated carbon was of about the same activity as iron(III) chloride. Iron, iron(III) chloride, or activated carbon used alone were much less active than activated carbon impregnated with an inorganic chloride.

Hydrolysis of the chloro derivatives of bis-(perfluoroalkyl)-benzenes by 60–80% sulfuric acid to the corresponding terephthalic and isophthalic acids[7] was used to establish structures.

(1) Presented before the Symposium on Fluorine Chemistry, Division of Industrial and Engineering Chemistry, 112th meeting of the American Chemical Society, New York, N. Y., September, 1947. This paper contained material abstracted from the doctoral thesis of M. R. Frederick.

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(2) L. C. Holt and H. Wilkens, U. S. Patents 2,174,512 (Oct. 3, 1939) and 2,174,513 (Oct. 3, 1939).

(3) E. T. McBee and co-workers, *Ind. Eng. Chem.*, **39**, 387–388 (1947).

(4) P. M. Gross, M. Hobbs and C. K. Bradsher, U. S. Patent 2,394,442 (Feb. 5, 1946).

(5) E. T. McBee and co-workers, THIS JOURNAL, **69**, 947–950 (1947).

(6) C. K. Bradsher and R. S. Kittila, *ibid.*, **70**, 1318 (1948).

(7) E. Wertyporoch, *Ann.*, **493**, 1536–1565 (1932).

## Experimental

### Preparation of Starting Materials

**bis-(Perfluoroalkyl)-benzenes.**—The bis-(trifluoromethyl)-benzenes were made from the corresponding bis-(trichloromethyl)-benzene by fluorination with anhydrous hydrogen fluoride in the presence of antimony(V) chloride at room temperature.[5] The bis-(pentafluoroethyl)-benzenes[8] and 1-(pentafluoroethyl)-4-(trifluoromethyl)-benzene[9] were prepared as described previously.

**Catalysts.**—The activated carbon-iron(III) chloride catalyst was prepared by soaking 200 g. of Columbia grade 8G, 8/14 mesh activated carbon in a solution of 60 g. of iron(III) chloride in 200 ml. of water made slightly acidic with hydrochloric acid. After soaking for one hour, the carbon was heated, first to 200°, and finally for twelve hours at 300°. The activated carbon–antimony(V) chloride catalyst was prepared by pouring antimony(V) chloride over activated carbon and then heating to 300°.

### Chlorinations

**Apparatus and Technique.**—A 3-liter, 3-necked flask equipped with a chlorine inlet, a thermometer, a reactor constructed either of glass or nickel 20 mm. by 500 mm., and a liquid return was used for the chlorinations. Chlorine was introduced through a flowmeter above the surface of the liquid in the flask. The reaction temperature was measured by a thermocouple or thermometer placed in the center of the reactor. Vapors issuing from the reactor passed through a water-cooled condenser welded directly to the reactor. Liquids were returned to the flask through a liquid trap and the gases were vented to an appropriate scrubber.

The technique used is illustrated by the following example. bis-(Trifluoromethyl)-benzenes (1263 g., 5.9 moles) prepared from technical xylene were poured into the flask. The reactor, packed with a catalyst of active carbon and iron(III) chloride, was heated to 250°, the material in the flask was heated to reflux (114°), and chlorine was added at about 0.8 mole per hour. Chlorination was continued for thirty-one hours, at the end of which time the boiling point of the contents of the flask was 127°. The product was removed from the flask, washed with a sodium bicarbonate solution, and then with water, dried, and rectified. There was obtained 438 g. (2.10 mole) of unreacted bis-(trifluoromethyl)-benzenes, 476 g. (1.91 moles) of chloro-bis-(trifluoromethyl)-benzenes composed of 5-chloro-1,3-bis-(trifluoromethyl)-benzene (b. p. 137–137.5°) and 2-chloro-1,4-bis-(trifluoromethyl)-benzene (b. p. 147–148°), and 486 g. (1.72 moles) of dichloro-bis-(trifluoromethyl)-benzenes. Conversions to chloro- and dichloro-bis-(trifluoromethyl)-benzenes were 32% and 29%, respectively. The yield of chloro-bis-(trifluoromethyl)-benzenes was 97%.

1,4-bis-(Trifluoromethyl)-benzene, 2-chloro-1,4-bis-(trifluoromethyl)-benzene, 1,3-bis-(trifluoromethyl)-benzene, 1-(pentafluoroethyl)-4-(trifluoromethyl)-benzene and bis-(pentafluoroethyl)-benzenes were chlorinated in a similar manner at temperatures in the range 200–250°. Properties of the chloro-bis-(perfluoroalkyl)-benzenes obtained are summarized in Table I.

**Acknowledgment.**—The authors wish to express their appreciation to the Army Air Forces Materiel Command for their financial support of this work which was carried out as part of the war research program.

(8) E. T. McBee and co-workers, *Ind. Eng. Chem.*, **39**, 395–397 (1947).

(9) E. T. McBee and O. R. Pierce, *ibid.* **39**, 397–399 (1947).

TABLE I

CHLORO-(PERFLUOROALKYL)-BENZENES

| Compound | B. p., °C. 748 mm. | M. p., °C. | $n^{25}D$ | $d^{25}_4$ | Analyses, % Obs. Cl | Obs. F | Obs. Mol. wt. | Calcd. Cl | Calcd. F | Calcd. Mol. wt. |
|---|---|---|---|---|---|---|---|---|---|---|
| bis-(Trifluoromethyl)-benzenes | | | | | | | | | | |
| 5-Chloro-1,3- | 137.3–137.5 | −22.2 to −22.0 | 1.4043 | 1.484 | 14.1 | 45.6 | 245 | 14.3 | 45.7 | 248.5 |
| Dichloro-1,3-[a] | 173.0–173.2 | −36 to −35 | 1.4372 | 1.609 | 25.0 | 40.9 | 281 | 25.1 | 40.4 | 283 |
| Trichloro-1,3-[a] | 209.2–209.4 | −2 to −1 | 1.4704 | 1.713 | 33.2 | 36.0 | 319 | 33.6 | 36.0 | 317.5 |
| 2,3,5-Trichloro-1,4- | 209.6–209.8 | −12 to −11 | 1.4711 | 1.711 | 33.4 | 35.8 | 314 | 33.6 | 36.0 | 317.5 |
| 2,5-Dichloro-1,4- | 174.4–174.6 | 34.6 to 34.9 | .... | ... | 25.1 | 40.9 | 286 | 25.1 | 40.4 | 283 |
| Tetrachloro-1,4- | 245.5–245.8 | 48.3 to 48.6 | .... | ... | 40.6 | 31.9 | 350 | 40.4 | 32.4 | 352 |
| 1-(Pentafluoroethyl)-4-(trifluoromethyl)-benzenes | | | | | | | | | | |
| 2,5-Dichloro- | 180.9–181.0 | Sets to glass | 1.4250 | 1.648 | 21.4 | 46.0 | 332 | 21.6 | 45.6 | 333 |
| Trichloro-[a] | 213.8–214.0 | ..... | .... | ... | 29.3 | 41.7 | 366 | 29.0 | 41.4 | 367.5 |
| Tetrachloro- | 247.6–248 | 50.4 to 51.2 | .... | ... | 33.6 | 37.9 | 403 | 35.4 | 37.8 | 402 |
| bis-(Pentafluoroethyl)-benzenes | | | | | | | | | | |
| 5-Chloro-1,3- | 153.3–153.6 | −22.5 to −22.0 | 1.3791 | 1.568 | 9.9 | .. | 346 | 10.2 | 54.7 | 348.5 |
| 2-Chloro-1,4- | 164.8–164.9 | −21.0 to −20.5 | 1.3871 | 1.601 | 10.0 | .. | 349 | 10.2 | 54.7 | 348.5 |
| 2,5-Dichloro-1,4- | 187.8–188.1 | 39.0 to 39.5 | .... | ... | 18.9 | 50.0 | 320 | 18.6 | 49.6 | 383 |
| Tetrachloro-1,4- | 250.0–252.4 | 97.5 to 98.3 | .... | ... | 31.2 | 42.4 | 445 | 31.4 | 42.0 | 452 |

[a] These materials are probably mixtures.


## Summary

A procedure generally applicable to the preparation of chloro-bis-(perfluoroalkyl)-benzenes has been devised which involves vapor-phase chlorination of a bis-(perfluoroalkyl)-benzene in contact with activated carbon catalyst impregnated with an inorganic chloride. Iron(III) chloride was found to be the most satisfactory of the catalysts studied.


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(10) Original manuscript received November 28, 1947.

# NOTES

## Concerning the Structure of D-Glucosone

BY CHARLES E. BECKER[1] AND CLARENCE E. MAY

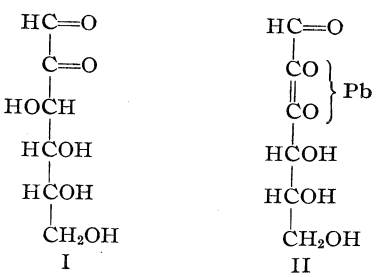
The structure of D-glucosone has not been definitely established.

Since it reacted in the cold with various hydrazines, particularly methyl phenylhydrazine, Fischer[2] believed that D-glucosone existed as the keto-aldehyde, I.

Since it reacted with Schiff reagent in the cold and was bound by sodium sulfite, Dixon and Harrison[3] concluded that D-glucosone contained a free carbonyl group.

Because of the selective absorption shown by its aqueous solutions in ultraviolet light, Bednarczyk and Marchlewski[4] felt that D-glucosone, like D-fructose and D-sorbose, possessed a free carbonyl group.

Evans, *et al.*,[5] have speculated that Fischer's lead–glucosone complex might be the salt of a 2,3-enediol




Hynd[6] retained Fischer's formula for D-glucosone but considered it possible that the compound might later be proved to contain one, or perhaps two, oxidic rings.

Since, in his opinion, the osones showed none of the characteristic reactions of the aldehydes

(1) Taken in part from a thesis submitted by Charles E. Becker to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree Master of Arts in the Department of Chemistry, Indiana University, 1948.

(2) E. Fischer, *Ber.*, **21**, 2631 (1888); **22**, 87 (1889); **23**, 2114 (1890).

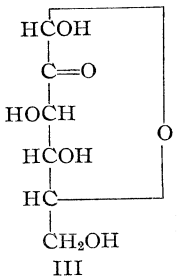
(3) K. Dixon and K. Harrison, *Biochem. J.*, **26**, 1954 (1932).

(4) W. Bednarczyk and L. Marchlewski, *Biochem. Z.*, **300**, 42 (1938); *Bull. intern. acad. polon. sci., Classe sci. math. nat.*, **A**, 524 (1938).

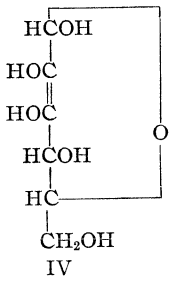
(5) W. Evans, W. Nicoll, G. Strauss and C. Waring, THIS JOURNAL, **50**, 2267 (1928).

(6) A. Hynd, *Proc. Roy. Soc.* (*London*), **B101**, 244 (1927).

(bisulfite addition, hydroxamic acid reaction, Doebner's reaction) but did show a complete analogy with the reductones, Brüll[7] felt that D-glucosone must not have a structure corresponding to the formula assigned by Fischer but would exist rather as the hemiacetal form in equilibrium with the tautomeric enediol form




III




IV

Angeli and Marchetti[8] have reported that D-glucosone gives a positive hydroxamic acid reaction.

In view of Criegee's[9] observation that, in contrast to periodic acid, lead tetraacetate does not break ring structure if that structure is present, we felt that oxidation of D-glucosone with lead tetraacetate under the conditions set up by Hockett, *et al.*,[10] for such oxidations would furnish evidence as to the structure of D-glucosone.

It was found that oxidation of D-glucosone with lead tetraacetate produced no significant amount of formaldehyde. Figure 1 shows the kinetics of this oxidation. It was noted that D-glucosone does not consume iodine in acetic acid solution and that aqueous solutions of D-glucosone show slight mutarotation.

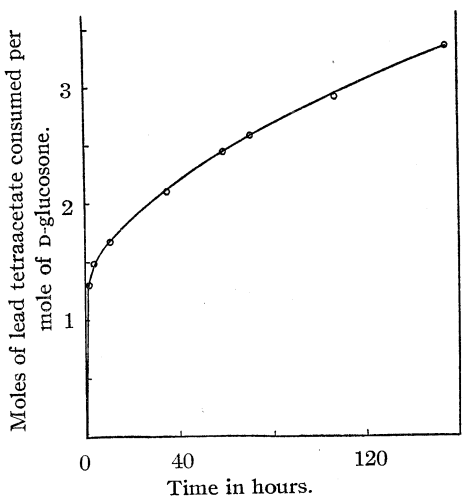
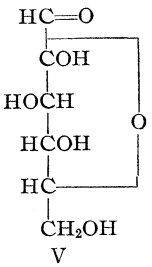
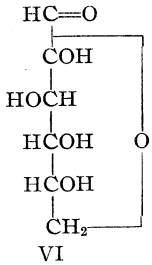



Fig. 1.—Oxidation of D-glucosone by lead tetraacetate.

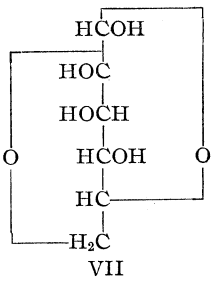
Structure III and the following structures for D-glucosone are not eliminated by these observations but, as yet, no selection can be made from amongst them.




V




VI




VII

## Experimental

**Materials.**—D-Glucosone was prepared by splitting D-glucose phenylosazone[11] with pyruvic acid according to Brüll,[12] purified from absolute alcohol, and had a specific rotation of $-1.40°$[13] at equilibrium ($c$, 0.550; $l$, 4; $H_2O$). It was hygroscopic, rapidly reduced Fehling solution, and gave an immediate precipitate with 2,4-dinitrophenylhydrazine at room temperature. This precipitate melted at 252° (capillary tube, rapid heating).

Lead tetraacetate[14] and aldehyde-free, specially dried acetic acid[10a] were prepared according to McClenahan, Hockett, *et al.*

Resublimed iodine, approximately 437 mg. (0.00172 mole), was dissolved in 25 ml. of special acetic acid containing 564 mg. (0.00376 mole) of sodium iodide; 5.5 ml. of 0.1 *N* sodium thiosulfate was equivalent to 4.0 ml. of this iodine solution.

**Methods.**—D-Glucosone, 52.7 mg. (0.000296 mole) in 50 ml. of acetic acid, was oxidized with 2.4 g. (0.00540 mole) of lead tetraacetate under the conditions set forth by Hockett, *et al.*,[10b] except that the reaction set-up was swept out with tank nitrogen instead of air. No significant amount of formaldehyde was formed.

D-Glucosone, 44.5 mg. (0.000250 mole) in 42 ml. of acetic acid, was oxidized with 57.45 ml. of 0.1323 *N* (0.00380 mole) of lead tetraacetate under the conditions set forth by Hockett, *et al.*[10a] (Fig. 1).

D-Glucosone, 24.8 mg. (0.000139 mole), was dissolved in 60 ml. of acetic acid. Four ml. of the iodine solution was added. After standing in the dark at room temperature for sixty minutes, the solution was diluted with 150 ml. of water, and titrated with 0.1 *N* sodium thiosulfate. It was found that no iodine had been consumed. This experiment was repeated, except that the D-glucosone was dissolved in water instead of acetic acid, with the same results.

**Mutarotation of D-Glucosone.**—An ice-cold aqueous D-glucosone solution containing lead acetate was treated with cold saturated barium hydroxide added dropwise with good stirring. The precipitated lead–glucosone complex was filtered off, washed well with ice-water, sucked as dry as possible, and resuspended in ice-water. Just enough cold 20% sulfuric acid was added dropwise with good stirring to break up the complex. The mixture was neutralized with a paste of barium carbonate, filtered rapidly, and the filtrate examined immediately in the polarimeter. After, 20, 26, 31, 35, 41 and 50 minutes the observed specific rotations were $-2.55$, $-2.18$, $-1.95$, $-1.73$, $-1.40$ and $-1.40°$, respectively.

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(7) L. Brüll, *Ricerca sci.*, **8**, I, 527 (1937).

(8) A. Angeli and G. Marchetti, *Atti. reale accad. Lincei*, [v] **17**, ii, 360 (1908).

(9) R. Criegee, *Ann.*, **494**, 211 (1932); *Angew. Chem.*, **53**, 321 (1940).

(10) (a) R. Hockett, M. Dienes and H. Ramsden, THIS JOURNAL, **65**, 1474 (1943); (b) R. Hockett, M. Zief and R. Goepp, Jr., *ibid.*, **68**, 935 (1946).

(11) E. Fischer, *Ber.*, **19**, 1921 (1886).

(12) L. Brüll, *Ann. chim. applicata*, **26**, 415 (1936).

(13) All rotations quoted in this paper represent specific rotations of the D line of sodium at 21°; $c$ is concentration in grams per 100 ml. of solution; and $l$ is the tube length in decimeters.

(14) W. McClenahan and R. Hockett, THIS JOURNAL, **60**, 2061 (1938).

## Chlorination of 2-Thiophenecarboxylic Acid

BY J. F. BUNNETT, D. M. BACHMAN, L. P. SNIPPER AND J. H. MALONEY

Steinkopf and Kohler[1] reported that direct chlorination of 2-thiophenecarboxylic acid (I) in boiling water or cold glacial acetic acid gave traces of 4,5-dichloro-2-thiophenecarboxylic acid (II), the predominant products being chlorinated tetrahydrothiophenes resulting from a combination of chlorination, decarboxylation and addition of chlorine to double bonds. In a pamphlet published by the Socony-Vacuum Oil Co.,[2] substantially the same statement was made. A more recent publication[3] from the Socony-Vacuum Laboratories mentioned the use of direct chlorination for the preparation of II, but no experimental details were given on the preparation which apparently was on a rather small scale. The preparation of a monochloro-2-thiophenecarboxylic acid by direct chlorination has not been reported.

We have found that by addition of excess hydrochloric acid to an alkaline solution of I and hypochlorite, 5-chloro-2-thiophenecarboxylic acid (III) can be obtained in yield about 45% (using a hypochlorite to I ratio of 1.7:1), while when the ratio is 2.5:1, rather small yields (14%) of II result. Other procedures such as passing chlorine through a buffered solution of I or allowing a buffered solution of I and hypochlorite to react also gave III or II, but not in as good yield or quality.

In most chlorinations by various techniques oily by-products were observed. These by-products from a number of runs were combined and distilled. A considerable fraction of b. p. 160–165° and $n^{16}$D 1.5624 was obtained. Nitration of this fraction gave a solid of m. p. 85–85.5°. This fraction was 2,5-dichlorothiophene (IV), since IV[3] has b. p. 162° and $n^{20}$D 1.5626, and gives on nitration[4] 3,4-dinitro-2,5-dichlorothiophene of m. p. 88–91°. The by-product oil from another run in which hydrochloric acid was added to an alkaline solution of hypochlorite and I in 3:1 ratio appeared to be a mixture of chlorinated thiophenes, with IV the principal constituent.

We first encountered the chlorination method reported here when III was obtained by the hypochlorite oxidation of 2-acetylthiophene, using the household bleach "Clorox" as a source of hypochlorite. When the hypochlorite solution used was strongly alkaline, only normal oxidation to I occurred.

It is possible that modification of the procedures we report here might result in better yields. We report the work at this time because we do not intend to investigate the matter further.

(1) Steinkopf and Kohler, *Ann.*, **532**, 250 (1937).

(2) "Thiophene Chemicals," Socony-Vacuum Oil Co., New York, N. Y., 1946, p. 17.

(3) Coonradt, Hartough and Johnson, THIS JOURNAL, **70**, 2564 (1948).

(4) Steinkopf, "Die Chemie des Thiophens," Theodor Steinkopff, Dresden, 1941, p. 58.

We thank the Research Corporation for support of this work through a Frederick Gardner Cottrell Grant-in-Aid, and the Socony-Vacuum Oil Co. for a gift of thiophene.

### Experimental[5]

**5-Chloro-2-thiophenecarboxylic Acid** (III).—A solution of 3 g. (0.023 mole) of 2-thiophenecarboxylic acid, 0.042 mole of sodium hypochlorite and excess sodium hydroxide in a total volume of 400 ml. was prepared. To this solution (*p*H 11.0) at 48° were added with stirring 25 ml. of 6 *M* hydrochloric acid during six minutes. The temperature rose to 53°, the *p*H dropped to 1.3, and a white precipitate appeared. With continued stirring, an additional 5 ml. of acid and then 107 g. of sodium chloride were added. The solid obtained by filtration of the chilled solution weighed 1.75 g. (46%), m. p. 134–137°. After recrystallization and sublimation the m. p. was 149–150°. The mixed m. p. with a sample of III prepared by permanganate oxidation of 5-chloro-2-acetylthiophene was not depressed.

**4,5-Dichloro-2-thiophenecarboxylic Acid** (II).—The above procedure was followed, with 1.9 g. (0.015 mole) of I and 0.037 mole of sodium hypochlorite being employed. Four-tenths of a gram (14%) of II, m. p. 182–187° was obtained. After recrystallization from water, the m. p. was 194–194.5°. Steinkopf and Kohler[1] reported m. p. 196–197°.

(5) Melting points are uncorrected.

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## N-Substituted 2,4:3,5-Dimethylene-D-gluconamides

BY I. A. COLÓN, R. FERNÁNDEZ-GARCÍA, LUIS AMORÓS AND HILDA BLAY

The structure of 2,4:3,5-dimethylene-D-gluconic acid has been the subject of two recent publications.[1,2] We take this opportunity of recording a modification of Zief and Scattergood's preparation of 2,4:3,5-dimethylene-D-gluconic acid and also the preparation of some N-substituted dimethylene gluconamides which appear to be new. Their properties are listed in Table I.

### Experimental

**2,4:3,5-Dimethylene-D-gluconic acid.**—Dimethylene-D-gluconic acid was prepared by the method of Zief and Scattergood[2] which was modified by substituting calcium D-gluconate for D-glucono-δ-lactone. The calcium D-gluconate and the trioxane were dissolved completely by stirring. The yield of the acid was 64–66% of the theoretical. Using paraformaldehyde in essentially the same procedure, slightly higher yields were obtained (70%). The recrystallized acid had a m. p. of 219.4–220.8°; $[\alpha]^{27.5}$D + 38.1° (*c*, 0.136; water).

**Methyl 2,4:3,5-Dimethylene-D-gluconate.**—The ester was prepared by the method of Mehltretter, *et al.*[1]

**N-Substituted 2,4:3,5-Dimethylene-D-gluconamides.**—The dimethylene gluconamides were prepared by treating the ester with the corresponding amine in either water or alcohol as solvent. The butyl, isobutyl and ethyl amide were obtained by treating in water at room temperature for several days. The cyclohexyl amide was prepared by refluxing in water while the allyl and the hydroxyethyl amides were prepared by refluxing in methanol. The methyl amide was obtained from methanol at 0°. The

(1) Mehltretter, *et al.*, THIS JOURNAL, **69**, 2130 (1947).

(2) Zief and Scattergood, *ibid.*, **69**, 2132 (1947).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR THE N-SUBSTITUTED 2,4:3,5-DIMETHYLENE-D-GLUCONAMIDES

| Amide | Yield, % | M. p., °C. | $[\alpha]_D$ | Temp., °C. | $c$ | Formula | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| N-Methyl | 80 | 195.6–196.8 | +92.7 | 29.6 | 1.48 | $C_9H_{15}O_6N$ | 6.0 | 6.0 |
| N-Ethyl | 40 | 169.0–170.0 | +77.5 | 29.0 | 1.64 | $C_{10}H_{17}O_6N$ | 5.7 | 5.6 |
| N-Allyl | 69 | 191.2–192.8 | +61.2 | 32.4 | 1.43 | $C_{11}H_{17}O_6N$ | 5.4 | 5.4 |
| N-*n*-Butyl | 20 | 141.6–142.2 | +64.2 | 30.8 | 1.04 | $C_{12}H_{21}O_6N$ | 5.1 | 5.0 |
| N-Isobutyl | 15 | 158.6–159.0 | +62.2 | 30.8 | 0.96 | $C_{12}H_{21}O_6N$ | 5.1 | 5.0 |
| N-β-Hydroxyethyl | 40 | 176.8–178.0 | +75.0 | 29.6 | 1.51 | $C_{10}H_{17}O_7N$ | 5.3 | 5.5 |
| Cyclohexyl | 50 | 217.0–217.6 | +34.9 | 29.6 | 4.0 | $C_{14}H_{23}O_6N$ | 4.65 | 4.4 |

crude amides were recrystallized from methanol or methanol–benzene. All the N-substituted dimethylene gluconamides prepared were found to be soluble in water or methanol and insoluble in ether or benzene. The specific rotations were determined in water as solvent at the concentration and temperature indicated in Table I.

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## The System Ammonium Sulfate–Ammonia

BY CHARLES M. DREW, HOWARD W. KRUSE, SOL SKOLNIK AND G. B. L. SMITH

Solvation of ammonium sulfate in liquid ammonia was first observed by Browne and Welsh.[1] Brief mention of this behavior also was made by Friedrichs[2] who stated that $(NH_4)_2SO_4 \cdot 3NH_3$, insoluble in liquid ammonia, was formed, and claimed that in a sealed tube this compound was stable up to 145°. The solubility was found to increase slightly with temperature.

Investigations in this Laboratory have verified the existence of ammonium sulfate 3-ammoniate. A pressure–concentration isotherm at −32.5° and vapor pressure data for this compound were determined. No other ammoniates were formed over the temperature range −33 to +8°.

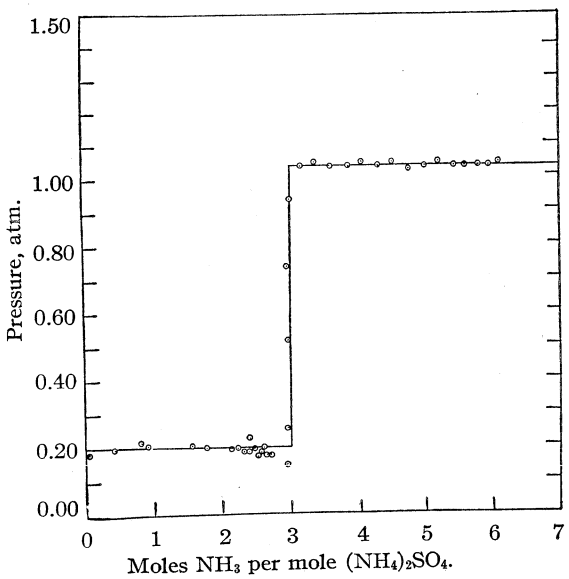



Fig. 1.—Pressure–concentration isotherm (−32.5°) of the system ammonium sulfate–ammonia.

### Experimental

The apparatus employed in this investigation was similar to the equipment described by Howard, Friedrichs and Browne[3] for the study of binary systems having one volatile component. Commercial anhydrous ammonia was dried by passing the gas through a tube containing potassium hydroxide and then through a tube containing fine sodium wire. Ammonium sulfate (J. T. Baker C.P.) was purified further by recrystallization.

The pressure–concentration isotherm shown in Fig. 1 was obtained by adding a measured excess of ammonia to a weighed sample of ammonium sulfate and then withdrawing small increments of the gas. Pressure readings were taken when the system reached equilibrium, usually after twenty-four hours. Vapor pressure data for ammonium sulfate 3-ammoniate which are shown graphically in Fig. 2, were determined in the same apparatus. These data may be summarized by the equation log $p$ (mm. Hg) = $10.2737 - 1934.4/T$°K.

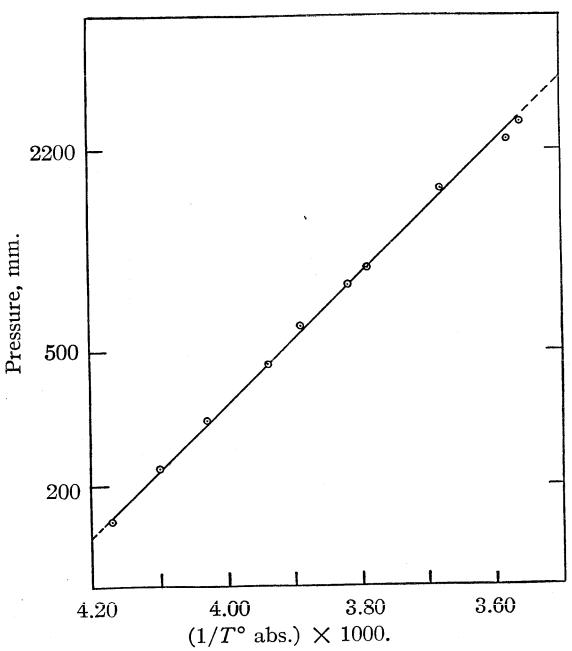



Fig. 2.—Vapor pressure of ammonium sulfate 3-ammoniate.

CONTRIBUTION FROM CHEMISTRY DIVISION
U. S. NAVAL ORDNANCE TEST STATION
INYOKERN, CALIFORNIA
P. O. CHINA LAKE, CALIFORNIA RECEIVED DECEMBER 18, 1948

(1) Browne and Welsh, THIS JOURNAL, **33**, 1728 (1911).

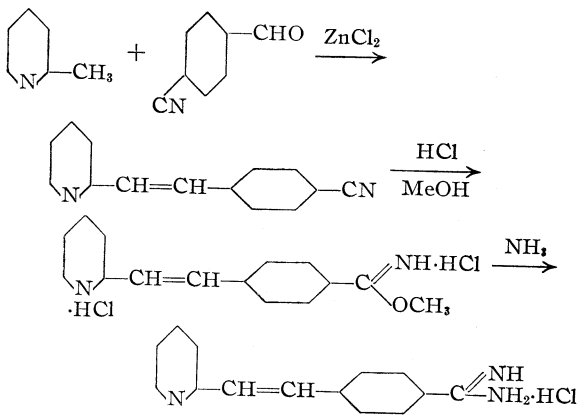
(2) Friedrichs, *ibid.*, **35**, 1866 (1913); *Z. anorg. allgem. Chem.*, **84**, 373 (1914).

(3) Howard, Friedrichs, and Browne, *ibid.* **56**, 2332 (1934).

## Benzamidine Derivatives

BY ELLIS K. FIELDS

In conjunction with the Survey of Antimalarial Drugs this Laboratory synthesized a number of benzamidines containing pyridine, quinoline or phenanthridine rings in the molecules. In general these were prepared by the reaction of *p*-cyanobenzaldehyde with a nitrogen ring compound containing an active methyl group. The resulting cyano compound was converted to the imido-ether hydrochloride and then to the amidine, according to the scheme for α-picoline.




The compounds prepared in this work are listed in Table I. They have not been previously reported in the literature.

large excess of alcoholic ammonia reacted with the imido-ether hydrochloride and the resulting clear solution, after 2–3 days at room temperature, was evaporated on a steam-bath. The lower melting isomer resulted when a slight excess of alcoholic ammonia was used and the amidine filtered from solution without heating. There were no separations involved; the pure *trans* or *cis* form was obtained.

α-Propylquinoline was heated with *p*-cyanopropiophenone and zinc chloride in an attempt to prepare 3-(2-quinolyl)-4-(*p*-cyanophenyl)-hexene-3. At a temperature sufficient to cause the expected reaction, the mixture resinified.

### Procedures

**Cyano Compounds.**—*p*-Cyanobenzaldehyde[1] was condensed with the various methyl heterocyclic compound, according to Wallach and Wusten.[2] Quinaldine, lepidines 9-methylphenanthridine and 6-ethoxy-4-chloroquinaldine condensed readily at 100–130° in two to four hours. α-Picoline and γ-picoline required six to eight hours in sealed tubes at 180°, even in the presence of larger quantities of zinc chloride.

**Amidines.**—The preparation of the amidine from the condensation product of *p*-cyanobenzaldehyde and quinaldine is described as typical. When dry hydrogen chloride was passed into a solution of 1-(2-quinolyl)-2-(*p*-cyanophenyl)-ethene in dry benzene or ether containing the calculated amount of methanol, the hydrochloride of the unchanged cyano compound precipitated. No reaction occurred after hours of vigorous stirring or shaking. The cyano compound (4.7 g.) was dissolved in 350 cc. of dry chloroform containing a 10% excess of methanol. The solution was cooled in ice–salt and a vigorous stream of dry hydrogen chloride introduced. A white precipitate formed after twenty-five minutes. The mixture was kept at room temperature for twenty-four hours under a slight pressure of hydrogen chloride. The white solid was filtered, washed with chloroform, and shaken with 50 cc. of dry methanol containing 2 g. of ammonia. Most of the solid dissolved. The mixture was kept twenty-four hours at room temperature, filtered from a little ammonium chloride, evaporated to a small volume and chilled. The amidine hydrochloride crystallized in white plates, melting at 154° dec., soluble in methanol, hot water and acetone and slightly soluble in cold water.

**α-Propylquinoline.**—This compound was prepared by the method of Tschitchibabin[3] for γ-propylquinoline. By this synthesis was obtained a 60% yield of α-propylquinoline boiling at 274–275°.

α-Propylquinoline (5.13 g.), 4.77 g. of *p*-cyanopropiophenone,[4] and 0.5 g. of anhydrous zinc chloride were

TABLE I

| R | R—CH=CH—C6H4—CN M. p., °C.[a] | Yield, % | Nitrogen, % Calcd. | Found | R—CH=CH—C6H4—CNHNH2HCl M. p., °C.[b] | Yield, % | Nitrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| α-Pyridyl | 123–124 | 41 | 13.60 | 13.25 | 95[c] | 60 | 16.18 | 15.93 |
| γ-Pyridyl | 125–127 | 45 | 13.60 | 13.98 | 335 | 63 | 16.18 | 16.25 |
| 2-Quinolyl | 154 | 92 | 10.94 | 11.29 | 154[d] | 73 | 13.57 | 13.55 |
| 4-Quinolyl | 169–170 | 94 | 10.94 | 11.01 | 240–241 | 78 | 13.57 | 13.63 |
| 6-Ethoxy-2-quinolyl | 173 | 65 | 9.33 | 10.20 | 271 | 65 | 11.89 | 11.99 |
| 6-Methoxy-4-chloro-2-quinolyl | 190–192 | 64 | 8.75 | 9.20 | | | | |
| 9-Phenanthridyl | 200–201 | 40 | 9.15 | 9.10 | 174–175[e] | 60 | 11.67 | 11.54 |

[a] Melting point uncorrected. [b] All decomposed. [c] Decomposed at 138°. [d] Higher melting form, m. p. 254°, yield 86%, N, 13.49. [e] Higher melting form, m. p. 282° (dec.), yield 68, N, 11.61.

Passing dry hydrogen chloride into solutions of the cyano compounds caused immediate precipitation of the corresponding hydrochlorides. The insolubility of the cyano hydrochlorides in benzene, ether, benzene plus methanol and other combinations of solvents was a stumbling block in the preparation of the amidines. The problem was solved by the discovery that dry chloroform was an excellent solvent for the cyano hydrochlorides, but dissolved practically none of the imido-ether dihydrochlorides.

1-(2-Quinolyl)-2-(*p*-amidinophenyl)-ethene hydrochloride and 1-(9-phenanthridyl)-2-(*p*-amidinophenyl)-ethene hydrochloride were obtained in two forms that had different melting points and presumably were *cis–trans* isomers. The higher melting isomer was obtained in each case when a

(1) Moses, *Ber.*, **33**, 2624 (1900).
(2) Wallach and Wusten, *ibid.*, **16**, 2007 (1883).
(3) Tschitchibabin, *Bull. soc. chim.*, [5] **3**, 1618 (1940).
(4) Hellberger and von Reboy, *Ann.*, **531**, 284 (1937).

heated ten hours at 210–230°. There was no perceptible reaction. The mixture was refluxed twenty minutes at 280°, at which temperature it completely resinified.

These amidines were tested on ducks and proved to be extremely toxic.

DEVELOPMENT LABORATORY OF CHICAGO
CHICAGO, ILLINOIS RECEIVED NOVEMBER 5, 1948

## The Oxidation of Certain Ketones to Acids by Alkaline Hypochlorite Solution

BY MARTIN W. FARRAR AND ROBERT LEVINE

The advantages of hypohalite oxidation of methyl ketones[1,2] are well recognized, yet apparently little is known of the behavior of higher alkyl ketones under similar conditions.[3] We have found that higher alkylaryl and alkylheterocyclic ketones may likewise be cleaved in good yields to carboxylic acids by hypohalite oxidation. A detailed study on the stoichiometry and mechanism of this reaction is now in progress in this Laboratory.

**Procedure.**—A solution of sodium hypochlorite is prepared from 50 g. of "HTH" following the directions in the literature.[1] The solution is heated to 55°, and 0.1 mole of the ketone to be oxidized is added dropwise to the rapidly stirred solution, keeping the temperature at 60–70°. After the addition of the ketone is completed (about fifteen minutes), the reaction mixture is stirred at 70° for thirty minutes. Any unreacted sodium hypochlorite is then destroyed with sodium bisulfite solution. The contents of the flask s then heated to 100°, stirred and heated for fifteen minutes longer and then cooled to room temperature. The reaction mixture is then extracted with ether to remove any unreacted ketone, and the phases separated. The aqueous phase is acidified with concentrated hydrochloric acid. The crude acid is filtered on a Büchner funnel and recrystallized from hot water. In this way the following acids were obtained: benzoic, m. p. 121–122°[4] (64%) from propiophenone, 2-thiophenic, m. p. 129–130°[5] from *n*-propyl 2-thienyl ketone, and 5-methyl-2-thiophenic, m. p. 137–138°[6] (67%) from 5-methyl-2-propionylthiophene.

In the preparation of 2-furoic acid (59%) from ethyl 2-furyl ketone the procedure followed is similar to that described above except that the temperature of the reaction mixture is never allowed to rise above 65° during the addition of the ketone and the reaction is then completed by stirring the contents of the flask at 65° for fifteen minutes after the addition of the ketone is completed. The reaction mixture is then acidified, extracted with ether, and the solvent distilled. The residue solidified. Recrystallization of this solid gave 2-furoic acid, m. p. 131–132°[6] (59%).

CONTRIBUTION NO. 707
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PENNSYLVANIA RECEIVED JANUARY 21, 1949

(1) Newman and Holmes, "Organic Syntheses," 2nd Coll. Vol., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

(2) Fuson and Bull, *Chem. Revs.*, **15**, 275 (1934).

(3) Although Schmidt (*Arch. Pharm.*, **252**, 96 (1914)) reported that the interaction of propiophenone with alkaline hypoiodite solution gives iodoform as one of the oxidation products, he did not report the isolation of any other compounds. In repeating his work, we have isolated benzoic acid as well as iodoform.

(4) Riessert, *Ber.*, **23**, 2244 (1890).

(5) Hartough and Conley, THIS JOURNAL, **69**, 3097 (1947).

(6) Heinzelmann, *Ann.*, **193**, 192 (1878).

## Extrapolation of Conductance Data for Weak Electrolytes

BY RAYMOND M. FUOSS AND THEODORE SHEDLOVSKY

Unambiguous extrapolations of conductance data, in order to determine $\Lambda_0$, the limiting conductance, and $K$, the dissociation constant for weak electrolytes, are possible in aqueous systems by synthesizing a hypothetical conductance curve for the completely dissociated portion of the weak electrolyte from conductance data on the corresponding strong electrolytes,[1] *e.g.*

$$\Lambda^*_{(HAc)} = \Lambda_{(HCl)} - \Lambda_{(NaCl)} + \Lambda_{(NaAc)} \qquad (1)$$

in which the $\Lambda$ values refer, of course, to the same ion concentration. The degree of dissociation is then given by $\Lambda/\Lambda^*$, since $\Lambda = 1000\kappa/c$ and $\Lambda^* = 1000\kappa/c_i$, $\kappa$ being the specific conductance, $c$ the equivalent electrolyte concentration, and $c_i$ the corresponding free ion concentration.

In non-aqueous systems, where the dielectric constant of the solvent is about 40 or less, this procedure cannot be employed since no strong electrolytes exist in such solvents. It therefore becomes necessary to evaluate $\Lambda_0$ and $K$ from the conductance data for the electrolyte itself. Two extrapolation methods have been proposed.

Fuoss and Kraus[2] wrote for 1–1 electrolytes

$$\Lambda = \gamma\,(\Lambda_0 - \alpha\sqrt{c\gamma}) \qquad (2)$$

where $\gamma$ is the degree of dissociation defined as the ratio of the concentration of free ions to the stoichiometric concentration $c$ and $\alpha$ is the Onsager coefficient

$$\alpha = 8.2 \times 10^5\Lambda_0/(DT)^{3/2} + 82/\eta(DT)^{1/2} \qquad (3)$$

where $D$ is the dielectric constant, $\eta$ the viscosity of the solvent, and $T$ the absolute temperature. Equation (2) was solved for $\gamma$ in terms of a function[3] $F(z)$ where

$$z = \alpha\sqrt{c\Lambda}/\Lambda_0^{3/2} \qquad (4)$$

and

$$\gamma = \Lambda/\Lambda_0\,F(z) \qquad (5)$$

Substituting Eq. (5) in the mass action equation and rearranging, one obtains

$$F/\Lambda = 1/\Lambda_0 + c\Lambda f^2/FK_F\Lambda_0^2 \qquad (6)$$

where $f$ is the activity coefficient which is computed from $(-\log f) = \beta\sqrt{c_i}$. A plot of $F/\Lambda$ against $c\Lambda f^2/F$ is linear at low concentrations and extrapolates to the reciprocal of the limiting equivalent conductance, with slope $1/K_F\Lambda_0^2$.

Shedlovsky[4] later proposed the equation

$$\Lambda = \Theta\Lambda_0 - \alpha(\Lambda/\Lambda_0)\sqrt{c\Theta} \qquad (7)$$

where $\Theta$ is the degree of dissociation. Equation (7) is a quadratic in $\Theta^{1/2}$ and is therefore much simpler to solve than Eq. (2), which is a cubic in

(1) D. A. MacInnes, THIS JOURNAL, **48**, 2068 (1926); M. S. Sherrill and A. A. Noyes, *ibid.*, **48**, 1861 (1926); D. A. MacInnes and T. Shedlovsky, *ibid.*, **54**, 1430 (1932).

(2) R. M. Fuoss and C. A. Kraus, *ibid.*, **55**, 476 (1933).

(3) R. M. Fuoss, *ibid.*, **57**, 488 (1935).

(4) T. Shedlovsky, *Jour. Franklin Inst.*, **225**, 739 (1938).

$\gamma^{1/2}$. The solution of (7) may then be written as

$$\Theta = S(z)\Lambda/\Lambda_0 \qquad (8)$$

where $S(z) \equiv (z/2 + \sqrt{1 + (z/2)^2})^2$, and $z$ is defined by Eq. (4). Substituting in the mass action equation and rearranging, we obtain

$$1/\Lambda S = 1/\Lambda_0 + c\Lambda Sf^2/K_S\Lambda_0^2 \qquad (9)$$

Here, at low concentrations, $1/\Lambda S$ is linear in $c\Lambda Sf^2$, with intercept $1/\Lambda_0$ and slope $1/K_S\Lambda_0^2$. The intercepts of Eqs. (6) and (9) are found to be identical, but the slopes, and therefore the dissociation constants[5] are sometimes different. The question naturally arises as to which of the two values to choose for the dissociation constant in such cases.

The derivation[2] of Eq. (2) is based on the Onsager limiting law

$$\Lambda = \Lambda_0 - \alpha\sqrt{c} \qquad (10)$$

If Onsager had computed resistance instead of conductance, the limiting law would have read

$$1/\Lambda = 1/\Lambda_0 + (\alpha/\Lambda_0^2)\sqrt{c} \qquad (11)$$

which rearranges to

$$\Lambda = \Lambda_0 - \alpha(\Lambda/\Lambda_0)\sqrt{c} \qquad (12)$$

Shedlovsky[4] has shown that Eq. (12) reproduces conductance data to significantly higher concentrations than does Eq. (10). The derivation[4] of Eq. (7) was based on the Onsager limiting law in the form (12), and results based on Eq. (9) are therefore to be preferred.

The difference between the various functions is illustrated in Fig. 1. Curve 2 represents actual data for potassium chloride[6] where $\Lambda_0 = 149.9$ and $\alpha = 93.9$. Curve 4 is for the familiar Onsager linear limiting Eq. (10). Curve 3 is for Eq. (12), using the same constants; it will be noted that it gives a closer approximation of the experimental results than Curve 4, *i.e.*, Eq. (10). Data for iodic acid,[7] a somewhat weak electrolyte, for which $K = 0.16$, $\Lambda_0 = 391.2$, $\alpha = 150$ are plotted in Curve 5. Although, strictly speaking, the abscissa, $\sqrt{c_i}$, depends on how $c_i$ is computed, *e.g.*, by the Fuoss or by the Shedlovsky function, these differences are too small to appear in Curve 5 on the scale of the figure. Due to ion association[8] (weak electrolytes) there are found strong negative deviations from the Onsager conductance equation, such as in Curve 5. The curves 2, 3 and 4 for potassium chloride are for $\Lambda/\Lambda_0 = (1000\kappa/c)(1/\Lambda_0)$ *vs.* $\sqrt{c_i}$, but since this salt is a strong electrolyte $c_i = c$. The slope of the linear Curve 4, $(\alpha/\Lambda_0)_{KCl}$ is 0.63, whereas the corresponding value for the ionized portion of iodic acid, $(\alpha/\Lambda_0)_{HIO_3}$ is 0.38. Let us change the ordinate scale for these three curves so that the slope for Curve 4 is 0.38 instead of 0.63. We may then suppose that

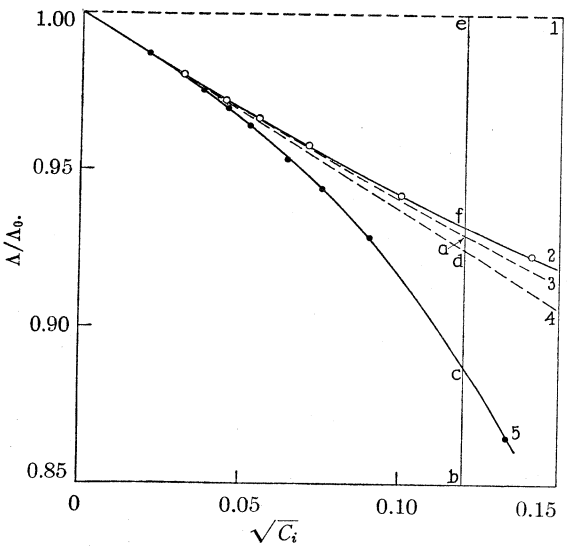



Fig. 1.—Comparsion of Conductance Functions.

the curves 2, 3 and 4 refer to $(1000\kappa/c_i)(1/\Lambda_0)$ *vs.* $\sqrt{c_i}$ for iodic acid instead of potassium chloride, and recall that for a weak electrolyte $c_i$ is the product of the stoichiometric concentration and of the degree of dissociation. The latter is therefore obtained as the ratio of $\Lambda/\Lambda_0 = (1000\kappa/c)(1/\Lambda_0)$ to $(1000\kappa/c_i)1\Lambda_0$ at the same value of $\sqrt{c_i}$. Thus, the Fuoss function assumes that $cb/db$ is a measure of the degree of dissociation, while the Shedlovsky function uses the ratio $cb/ab$, which is a better approximation, and incidentally the one which would naturally have been used if the limiting Onsager equation had been originally presented in the form of Eq. (11). The synthetic method (Eq. (1)) uses the ratio $cb/fb$ but as we have already pointed out, it is not available in solvents with dielectric constants below 40.

Extrapolation by Eqs. (6) or (9) is essentially use of the Ostwald dilution law, corrected for the effect of long range interionic forces on mobility and thermodynamic potential; the degree of dissociation in the classical theory, $\Lambda/\Lambda_0$, is measured by the ratio $cb/eb$ of Fig. 1.

The difference between $K_S$ and $K_F$ can be found as follows. By equating the two expressions, Eqs. (2) and (7) for $\Lambda$, substituting Eqs. (5) and (8) and solving, we obtain

$$\gamma = \Theta[1 + z(F^{-3/2}S^{-1} - S^{-1/2})] \qquad (13)$$
$$\equiv \Theta(1 + x) \qquad (13')$$

If we now substitute (13) in the mass action Eq. (6) and rearrange, we obtain

$$1/\Lambda S = 1/\Lambda_0 + c\Lambda Sf^2(1 + x)^2/K_F\Lambda_0^2 + x/\Lambda_0 \qquad (14)$$

Expansion of $S(z)$ and $F(z)$ in their power series gives

$$x = z^2 + O(c^{3/2}) \qquad (15)$$

and at low concentrations Eq. (14) thus reduces to

$$1/\Lambda S = 1/\Lambda_0 + c\Lambda Sf^2/K_F\Lambda_0^2 + \alpha^2 c\Lambda/\Lambda_0^4 \qquad (16)$$

(5) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Corp., New York, N. Y., 1943; p. 190.

(6) T. Shedlovsky, THIS JOURNAL, **54**, 1411 (1932).

(7) C. A. Kraus and H. C. Parker, *ibid.*, **54**, 2429 (1932).

(8) R. M. Fuoss, *Chem. Revs.*, **17**, 27 (1935).

The limiting slope of Eq. (16) is

$$\frac{d(1/\Lambda S)}{d(c\Lambda Sf^2)_{c=0}} = \frac{1}{K_F\Lambda_0^2} + \frac{\alpha^2}{\Lambda_0^4} = \frac{1}{K_S\Lambda_0^2} \qquad (17)$$

whence

$$1/K_S = 1/K_F + \alpha^2/\Lambda_0^2 \qquad (18)$$

The difference shown in Eq. (18) is a consequence of the *difference* between $\Theta$ and $\gamma$; in the limit of zero concentration, both $\Theta$ and $\gamma$ approach unity, but as is readily seen from Eqs. (13′) and (15), their difference is linear in concentration, and the mass action extrapolation is essentially one on a linear concentration scale. According to Eq. (3), the ratio $\alpha/\Lambda_0$ has the following upper bounds if we set the Walden product $\Lambda_0\eta = 0.5$: $D = 40$, $\alpha/\Lambda_0 \leqslant 2$; $D = 20$, $\alpha/\Lambda_0 \leqslant 4$; $D = 10$, $\alpha/\Lambda_0 \leqslant 8$. Since $K$ decreases[9] rapidly as $D$ decreases, the two methods of extrapolation will not differ significantly when $K$ is less than about $10^{-3}$. In the approximate range $10^{-3} \leqslant K \leqslant 1$, however, we recommend extrapolation by means of Eq. (9).

(9) R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **55**, 1019 (1933).

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## The Structure of Khellin

BY T. A. GEISSMAN

Khellin has been resynthesized by Späth and Gruber from its cleavage product, khellinone, by the application of the Kostanecki–Robinson method.[1] Since this synthesis is not entirely unamibiguous, often giving rise to mixtures of the desired chromone and the isomeric 4-methylcoumarin; and since khellin-like model compounds are not unequivocally distinguishable from the corresponding 4-methylcoumarins by absorption spectra, as recent work in this Laboratory has shown, some doubt has remained that khellin actually possesses the 2-methylchromone structure.

Khellin has now been resynthesized from khellinone by two methods which are known to lead unambiguously to 2-methylchromones, and with yields which surpass those usually recorded for the Kostanecki–Robinson reaction. Using a method analogous to that of Wittig,[2] khellinone, treated with sodium hydride in ethyl acetate, yielded a compound (A, see experimental below) which when treated with cold, concentrated hydrochloric acid was converted nearly quantitatively into khellin. The identity of the product was shown by its melting point and mixed melting point with authentic khellin (152–153°), and by analysis.

(1) Späth and Gruber, *Ber.*, **71B**, 106 (1938).
(2) Wittig, *Ann.*, **446**, 155 (1925).

In a second experiment, khellinone acetate, treated with sodium hydride in ethyl acetate, gave the compound A. This is C-acetylkhellinone, and is converted into khellin by cold, concentrated hydrochloric acid in substantially quantitative yield.

The acylation of substituted *o*-hydroxyacetophenones to yield diketones and, ultimately, chromones is a well-known reaction. 4-Methylcoumarins have not been observed as products of these reactions.

One prior example of the conversion of an *o*-acetoxyacetophenone into the corresponding *o*-hydroxyacetylacetophenone under conditions similar to those used in this work has been recorded.[3] The analogous reaction with *o*-benzoyloxyacetophenones, leading eventually to flavone derivatives, has been used extensively. Model experiments on a number of substituted *o*-acetoxyacetophenones have shown that this procedure is general as a method for the synthesis of 2-methylchromones in good yields.

Details of these reactions and products will be reported in a later publication.

### Experimental

**Khellinone** was prepared in 90% yield by the hydrolysis of khellin in 1% aqueous potassium hydroxide, according to the method of Späth and Gruber.[1]

**C-Acetylkhellinone.**—(A) To 0.5 g. of khellinone acetate in 5 ml. of dry ethyl acetate was added 0.5 g. of sodium hydride. The solution was warmed gently from time to time for an hour and allowed to stand overnight at room temperature. Crushed ice was added, followed by dilute hydrochloric acid, and the yellow solid collected by filtration. It weighed 400 mg. After recrystallization from aqueous methanol it formed pale yellow needles, which melted at about 90° when plunged into a preheated bath, but at temperatures up to about 122° when heated slowly. It is probable that this behavior is due to a slow dehydration under the influence of heat with the formation of khellin.

*Anal.* Calcd. for $C_{14}H_{14}O_6$: C, 60.48; H, 5.08. Found: C, 60.34; H, 5.11.

(B) To 0.5 g. of khellinone in 5 ml. of ethyl acetate was added 0.5 g. of sodium hydride. The mixture was allowed to stand overnight and worked up as in (A). The product weighed 413 mg. after recrystallization from dilute methanol.

C-Acetylkhellinone, in dilute aqueous methanol, gives with ferric chloride a momentary flash of green, the color then changing through green-brown to reddish-brown. Khellinone, under identical conditions, gives an intense, pure green.

**Khellin.**—To 200 mg. of C-acetylkhellinone was added 2 ml. of concentrated hydrochloric acid. The compound dissolved to give a deep orange solution. After solution was complete (about one minute) 20 ml. of water was added. Pure white needles of khellin separated (175 mg.; 94%). After recrystallization from dilute methanol it melted at 152–153° (unchanged by admixture with authentic khellin).

*Anal.* Calcd. for $C_{14}H_{12}O_5$: C, 64.59; H, 4.65. Found: C, 64.48; H, 4.89.

DEPARTMENT OF CHEMISTRY
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LOS ANGELES 24, CALIF. RECEIVED JANUARY 24, 1949

(3) Virkar and Wheeler, *J. Chem. Soc.*, 1679 (1939).

## The Reaction of Diazomethane with Phenols in the Presence of Propanol

BY SAMUEL M. GERBER AND DAVID Y. CURTIN

Schönberg and Mustafa[1] have reported that the reaction of stilbesterol with diazomethane and *n*-propanol in ether at 0° gave stilbesterol di-*n*-propyl ether as the only product isolated. The compound was obtained in unspecified yield and was identified by its satisfactory analysis, melting point and mixed melting point with an authentic sample of the dipropyl ether prepared by the method of Reid and Wilson.[2] Schönberg and Mustafa have used their results as evidence for a mechanism in which either I or II is the propylating agent. It has been widely accepted that related reactions of diazo compounds with the general formula III involve the initial addition of a proton to give IV which then undergoes a displacement or solvolysis reaction with a base.[3] It was of interest, therefore, to attempt to confirm and extend their work.

$CH_2{=}NNHOC_3H_7$ (I) $CH_2N{=}NOC_3H_7$ (II) $RCHN_2$ (III) $RCH_2N_2^+$ (IV)

We have repeated the reaction of stilbesterol with diazomethane in the presence of propanol under the conditions used by Schönberg and Mustafa and have obtained only the dimethyl ether (45% yield), monomethyl ether (33% yield of slightly impure product) and recovered stilbesterol (12%). Methylation at room temperature gave comparable results. In no case was there any evidence for the presence of the dipropyl ether.

The reactions of *p*-nitrophenol and 2,4,6-tribromophenol with diazomethane in the presence of propanol were also carried out and yielded in each case only the methyl ether and recovered starting material.

We are unable to explain the discrepancy between our results and those of Schönberg and Mustafa.

### Experimental[4]

**Reaction of Stilbesterol with Diazomethane.**—A solution of 1.00 g. of stilbesterol[5] in propanol and ether was treated with diazomethane[6] under the conditions used by Schönberg and Mustafa. Their method of isolation of the product (recrystallization from petroleum ether) was found to be unsatisfactory, however, and therefore that of Reid and Wilson[2] was used. Stilbesterol (11%) was recovered and nearly pure stilbesterol dimethyl ether (0.50 g., 45% yield) was obtained. It was identified by its melting point (122–124°) and mixed melting point with an authentic sample prepared from stilbesterol and methyl iodide.[2] Crude stilbesterol monomethyl ether (0.24 g., 22% yield, m. p. 110–112°) was also obtained. The reported melting point is 117°.[2] Its identity was confirmed by methylation by methyl iodide in a yield of 87% to stilbesterol dimethyl ether, m. p. 123.5–124.5°.

**Methylation of 2,4,6-Tribromophenol.**—Three grams of tribromophenol was treated with excess diazomethane in a propanol–ether mixture for thirty-six hours at room temperature. Tribromophenol (1.5 g., m. p. 92–93.5°) was recovered and a 42% yield of tribromoanisole, m. p. 86.5–87°, was obtained. The recorded melting point is 87°.[7]

**Methylation of *p*-Nitrophenol.**—*p*-Nitrophenol (3.4 g.) was methylated similarly (in propanol–ether for twenty-four hours at room temperature) to give *p*-nitroanisole, m. p. 53–54°, in a yield of 89%. The reported melting point is 54°.[8]

(1) Schönberg and Mustafa, *J. Chem. Soc.*, 746 (1946).

(2) Reid and Wilson, THIS JOURNAL, **64**, 1625 (1942).

(3) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, p. 288.

(4) All melting points are corrected.

(5) We are indebted to S. B. Penick and Company for a sample of stilbesterol.

(6) The diazomethane used was prepared and standardized by the method of Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(7) Kohn and Fink, *Monatsh.*, **44**, 192 (1923).

(8) Willgerodt and Ferko, *J. prakt. Chem.*, [2] **33**, 152 (1886).

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## The Preparation of *n*-Butyllithium

BY H. GILMAN, J. A. BEEL, C. G. BRANNEN, M. W. BULLOCK, G. E. DUNN AND L. S. MILLER

The method of preparation of *n*-butyllithium used until recently in these Laboratories gave from 50–65% yields in ninety minutes in diethyl ether as determined by the double-titration method.[1] A study of the reaction at lower temperatures has revealed that yields of 75–90% can be consistently obtained at about −10° using *n*-butyl bromide with diethyl ether as the solvent. Only conventional apparatus is needed and the reaction is substantially complete in ninety minutes. Table I gives data on several preparations made under varying conditions. *n*-Propyl, *n*-amyl and *n*-hexyl bromides gave by this procedure 78, 81 and 77% yields, respectively, of the corresponding lithium compounds.

### Experimental

***n*-Butyllithium.**—The following is a description of a typical preparation. Into a 500-ml. three-necked flask equipped with a stirrer, low temperature thermometer, and a dropping funnel, was placed 200 ml. of anhydrous ether (dried over sodium). After sweeping the apparatus with dry, oxygen-free nitrogen, 8.6 g. (1.23 g. atoms) of lithium wire[2] (weighing 4.2 to 4.3 g. per meter) was wound in a loose coil, rinsed with ether, and the flattened coil was cut into pieces about 7 mm. in length which fell directly into the reaction flask in a stream of nitrogen. With the stirrer started, about 30 drops of a solution of 68.5 g. (0.5 mole) of *n*-butyl bromide[3] in 100 ml. of ether was added from a dropping funnel and the reaction mixture was then cooled to −10° with a Dry Ice–acetone bath kept at approximately −30° to −40°. (The solution becomes slightly cloudy and bright spots appear on the lithium when the reaction has started.) The remainder of the *n*-butyl bromide was then added at an even rate over a thirty-minute period while maintaining the internal temperature at −10°. After addition was complete, the reaction mixture was allowed to warm up to 0 to 10° while stirring for one to two hours. The reaction mixture was then filtered by decantation through a narrow tube plugged with glass wool into a graduated dropping funnel previously flushed with nitrogen. The yield, as deter-

(1) Gilman and Haubein, THIS JOURNAL, **66**, 1515 (1944).

(2) Supplied by The Metalloy Corp., Minneapolis, Minn.

(3) The alkyl bromides used were all Eastman grade from The Eastman Kodak Co.

TABLE I

PREPARATION OF *n*-BUTYLLITHIUM

| Run | Time of addition, min. | Temp. during addition, °C. | Type of lithium | G. atoms lithium | Moles *n*-butyl bromide | Final concn., molar | Yield[a] % | Stirring after addition Hr. | Stirring after addition Temp., °C. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | −20 | Cut[b] | 2.2 | 1.0 | 0.835 | 77.7 | 1.25 | 0–20 |
| 2 | 25 | − 5 | Cut | 1.0 | 0.5 | 1.20 | 82.9 | 1 | 0 |
| 3 | 35 | 0 | Sand[c] | 1.0 | 0.5 | 1.47 | 77.3 | 2 | 0 |
| 4 | 35 | −10 | Cut | 1.14 | 0.5 | 1.25 | 85.4[d] | 2 | 0 |
| 5 | 35 | −10 | Wire | 1.23 | 0.5 | 1.14 | 83.7[e] | 2 | 0 |
| 6 | 15 | −10 | Cut | 3.3 | 1.5 | 0.89 | 80.0 | 3 | 4 |

[a] Yield after filtration as determined by double-titration. [b] Prepared as described in THIS JOURNAL, 63, 2327 (1940). [c] Supplied by the Metalloy Corp., Minneapolis, Minn. [d] In this run helium was used in place of nitrogen and double-titrations were made five minutes, one hour, and two hours after addition; yields were 78.5, 83.9, and 85.4%, respectively. [e] Yield determined by double-titration before filtration was 90%; the above yield was determined after storing sixteen hours at 10° following filtration.

mined by double-titration[1] was 90% before filtration and 83.7% after filtering and storing sixteen hours at 10°. After four days at 10°, the yield was 82.5%.

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## Fluorene Analog of Amidone

BY DAVID GINSBURG[1] AND MANUEL M. BAIZER

Present interest in amidone analogs and derivatives[2,3] prompts us to report on the synthesis of a fluorene analog of amidone. This work was completed about a year ago but we have had no opportunity to establish the structure[4] of the isomer which was characterized.

Blicke and Zambito[5] state that the related "1,1-biphenylene-1-(β-dimethylaminoethyl)-butanone-2" is in the process of preparation. No details have appeared to date.

### Experimental[6]

**9-Formylfluorene.**—This compound was prepared in 74% yield by the procedure of Von and Wagner.[7]

**9-Formylfluorene Oxime.**—A 78% yield was obtained by the procedure of Vorländer.[8]

**9-Cyanofluorene.**—A 90% yield was obtained in the dehydration of 9-formylfluorene oxime by thionyl chloride in absolute ether.[8]

**Condensation of 9-Cyanofluorene with 1-Dimethylamino-2-chloropropane.**—The procedure followed was similar to the one used in the condensation of diphenylacetonitrile with the chloroamine to yield the precursors of the amidones.[9]

In a 250-ml., three-necked flask, equipped with thermometer, mercury-sealed stirrer and reflux condenser, 19.1 g. (0.1 mole) of 9-cyanofluorene and 12.2 g. (0.1 mole) of 1-dimethylamino-2-chloropropane were dissolved in 100 ml. of dry benzene at 25°. Sodium amide (4.3 g., 0.11 mole) was added, portionwise, with continuous stirring in the course of thirty minutes. The temperature rose spontaneously to 40° in one hour; ammonia was evolved. The mixture was refluxed for thirty minutes, cooled and 50 ml. of water added. The benzene layer was separated and shaken with 50 ml. of 20% hydrochloric acid. The benzene layer on evaporation left 2.5 g. of unchanged 9-cyanofluorene. The acid extract was made alkaline by the addition of 33% sodium hydroxide, and the oil which separated was extracted with 200 ml. of ether. The ethereal solution was dried and the solvent removed by distillation. The residual oil, presumed by analogy to be mixture (I) of 9-cyano-9-(β-dimethylaminopropyl)-fluorene and 9-cyano-9-(α-methyl-β-dimethylaminoethyl)-fluorene, weighed 25.5 g. Upon distillation a yellow oil was obtained; b. p. 195–199° (8 mm.).

**Reaction of I with Ethylmagnesium Bromide.**—A Grignard reagent was prepared from 9.7 g. (0.40 mole) of magnesium turnings and 44 g. (0.38 mole) of ethyl bromide in 100 ml. of dry ether. To the ethereal solution was added, in one portion, a solution of 29 g. (0.11 mole) of I in 35 ml. of dry xylene. A greenish precipitate formed after a few minutes of heating under reflux in an oil-bath at 95–100°. The heating was continued for three and one-half hours; the mixture was then decomposed, while still hot, by the careful addition of 40 ml. of concentrated hydrochloric acid dissolved in 100 ml. of water. After the addition of benzene three layers were formed. The two upper layers were removed together and heated on a steam-bath until the solvents had been vaporized. The residual oily hydrobromide was moistened with alcohol and chilled briefly in an acetone–solid carbon dioxide-bath, whereupon crystallization occurred. The solid was filtered and recrystallized from ethanol. The yield of II,[10] m. p. 232–234°, was about 75% based upon one-half the input of I.

*Anal.* Calcd. for $C_{21}H_{26}BrNO$: C, 64.94; H, 6.75; N, 3.61. Found: C, 64.43; H, 7.02; N, 3.77.[11]

The melting point of the base, liberated from II, is 57–60° and of the hydrochloride 262–263°.

(1) Present address: Daniel Sieff Research Institute, Rehovoth, Israel.

(2) Gardner, *et al.*, THIS JOURNAL, **70**, 2906 (1948).

(3) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(4) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947), outline a structure proof for the isomeric nitriles which are the precursors of the amidones.

(5) Abstracts of American Chemical Society meeting April, 1947, p. 3K.

(6) Melting points and boiling points are not corrected.

(7) Von and Wagner, *J. Org. Chem.*, **9**, 162 (1944).

(8) Vorländer, *Ber.*, **44**, 2468 (1911).

(9) O. P. B. Report PB 981, p. 97.

(10) By analogy with the findings in the amidone synthesis,[9] we consider it probable that II is 9-propionyl-9-(β-dimethylaminopropyl)-fluorene hydrobromide and that the by-products remain in the mother liquors.

(11) Microanalyses by Schwarzkopf Laboratories, Elmhurst, L. I., N. Y.

THE NEW YORK QUININE AND CHEMICAL WORKS, INC.
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## The Configuration at the 20-Position in Certain Steroids

BY W. KLYNE AND D. H. R. BARTON

Isomeric $C_{21}$ steroids bearing a secondary hydroxyl group at $C_{20}$ are commonly distinguished

by the indices $\alpha$ and $\beta$, without parentheses. Recently Fieser and Fieser[1] have discussed the relationships between the known configurations at $C_{17}$ and these hitherto arbitrarily designated configurations at $C_{20}$. They have elucidated with a high degree of probability the stereochemistry at $C_{20}$ of certain adrenal cortex steroids and related compounds having the side-chain in the 17($\beta$) position and a hydroxyl in the 17($\alpha$) position. The convention used by Fieser and Fieser to designate $C_{20}$ isomers, which has a definite stereochemical meaning, is so chosen as to agree with the arbitrary nomenclature of Reichstein.[2] Previously the latter author had pointed out that his use of the symbols 20$\alpha$ and 20$\beta$ did not imply any agreement between his convention and that adopted by Marker[3] for $C_{21}$ steroids having a hydrogen atom at $C_{17}$. Marker used the designation 20$\alpha$ for substances having the same configuration at $C_{20}$ as the common pregnanediol of human pregnancy urine,[4] and 20$\beta$ for the epimeric configuration.

The compounds whose $C_{20}$ configurations were allotted by Fieser and Fieser on purely chemical grounds were 17($\alpha$),20 diols and 17($\alpha$),20,21-triols, and the arguments were supported by reference to molecular rotation data.[5] Fieser and Fieser showed that the $\Delta_1$ values (changes in molecular rotation on acetylation)[6] of 20-hydroxyl compounds were characteristic, being in the 17-*n* series—strongly positive for their 20($\beta$) compounds and negative for their 20($\alpha$) compounds. These authors then allotted configurations to certain 20,21 diols having a hydrogen atom in the 17($\alpha$)-position on the basis of rotation evidence. They made no reference to compounds previously covered by Marker's convention, since the literature contains no adequate data on the rotations of these substances.

We have recently determined the rotations of some simple 17($\alpha$)-H, 20–OH compounds and their acetates. The $\Delta_1$ values of these compounds agree so well with the $\Delta_1$ values of the corresponding 17($\alpha$)–OH, 20–OH compounds (Table I) that we feel certain that the molecular rotation difference method is valid in this case. The data show that the convention of Fieser and Fieser and that of Marker are in agreement. Marker's 20$\alpha$ and 20$\beta$ compounds are, respectively, 20($\alpha$) and 20($\beta$) on the Fieser convention.

(1) Fieser and Fieser, *Experientia*, **4**, 285 (1948).

(2) Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940); von Euw and Reichstein, *ibid.*, **24**, 401 (1941).

(3) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius. THIS JOURNAL, **59**, 2291 (1937).

(4) Marrian, *Biochem. J.*, **23**, 1090 (1929).

(5) Previous work both among sugars and among steroids [*cf.* Barton and Cox, *J. Chem. Soc.*, 783 (1948)] has shown that molecular rotation differences are not always strictly additive when hydroxyl groups attached to neighboring carbon atoms are considered. However, qualitative agreement between data is sometimes sufficient to permit the use of the molecular rotation difference method in the assignment of configurations.

(6) These authors neglected the contributions of other positions ($C_3$ and/or $C_{21}$) to the $\Delta_1$ values of their compounds. Since $\Delta_1$ values for the 20($\beta$) position are large, while those for the 3($\beta$) and 21 positions are small, this procedure was justified.

TABLE I

$\Delta_1$ VALUES AT $C_{20}$ FOR 20-HYDROXY AND 17($\alpha$),20-DIHYDROXY REFERENCE COMPOUNDS IN THE 17-*n* SERIES

All rotations are for the $Na_D$ line; solvents, Al = ethanol, An = acetone, Chf = chloroform, M = methanol

| | $[M]_D$ 20-hydroxy | $[M]_D$ 20-acetate | $\Delta_1$ Value (at $C_{20}$) | Ref. |
|---|---|---|---|---|
| Compounds with 17($\alpha$)-H | | $C_{20}$ Configurations according to Marker[3] | | |
| Allopregnanediol-3($\beta$),20$\alpha$ | +72 Chf | + 28[a] Chf | − 44 | [b] |
| Allopregnanediol-3($\beta$),-20$\beta$ 3-acetate | −22 Chf | + 89 Chf | +111 | [b] |
| Compounds with 17($\alpha$)-OH | | $C_{20}$ configurations according to Fieser and Fieser | | |
| Allopregnanetriol-3($\beta$),17($\alpha$),20($\alpha$) (Reichstein's O) | −44 M | − 85[a] An | − 41 | [c] |
| Allopregnanetriol-3($\beta$),17($\alpha$),20($\beta$) (Reichstein's J) | −27 Al | +124[a] An | +151 | [c] |

[a] Calculated from the values for the 3:20 diacetates by subtracting the $\Delta_1$ value for the 3($\beta$) position (−29); see Barton, *J. Chem. Soc.*, 1116 (1946). [b] This paper. [c] Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 546 (1938).

The $\Delta_1$ values (at $C_{20}$) for the more highly-substituted 17-*n* compounds do not, as a rule, agree quantitatively with the values in Table I. They do, however, fall clearly into two groups, *viz.*,

TABLE II

$\Delta_1$ VALUES AT $C_{20}$ FOR 17-*iso*-20-HYDROXY-STEROIDS

Indices "$\alpha$," "$\beta$" allotted by Fieser and Fieser[1]

| Compound | $\Delta_1$ Value (at $C_{20}$)[a] | Ref. |
|---|---|---|
| 17-Iso-5-allopregnanetriol-3($\beta$),17($\beta$),20"$\alpha$" | + 13 | *b* |
| 17-Iso-5-allopregnanetriol-3($\beta$),17($\beta$),20"$\beta$" | + 17 | *c* |
| 17-Iso-$\Delta^5$-pregnenetriol-3($\beta$),17($\beta$),20"$\beta$" | + 60 | *d* |
| 17-Iso-5-allopregnanetriol-3($\beta$),17($\beta$),20"$\alpha$",21 | −109 | *e, f, g* |
| 17-Iso-5-allopregnanetriol-3($\beta$),17($\beta$),20"$\beta$",21 | + 44 | *e, f* |
| 17-Iso-$\Delta^5$-pregnenetetrol-3($\beta$),17($\beta$),20"$\alpha$",21 | −116 | *h* |
| 17-Iso-$\Delta^4$-pregnenetriol-17($\beta$),20"$\beta$",21-3-one | − 25 | *h* |
| Standard value for 20($\alpha$)-hydroxy-17-*n*-compound | − 44 | *i* |
| Standard value for 20($\beta$)-hydroxy-17-*n*-compound | +111 | *i* |

[a] Calculated from the total $\Delta_1$ values by subtraction of the $\Delta_1$ values for the 3 and/or 21 positions, *cf.* Barton, *J. Chem. Soc.*, 1116 (1946); Barton and Klyne, *Chem. and Ind.*, 755 (1948). [b] Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940). [c] Reich, Sutter and Reichstein, *ibid.*, **23**, 170 (1940). [d] Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1112 (1939). [e] Serini, Logemann and Hildebrand, *ibid.*, **72**, 391 (1939). [f] Reich, Montigel and Reichstein, *Helv. Chim. Acta*, **24**, 977 (1941). [g] Prins and Reichstein, *ibid.*, **25**, 300 (1942). [h] Serini and Logemann, *Ber.*, **71**, 1362 (1938). [i] This paper.

small negative values for 20(α) compounds (*e. g.*, pregnanediol-20(α), 21-dione-3,11, $\Delta_1 = -29$) and large positive values for 20(β) compounds (*e. g.*, Reichstein's compounds K, E and U, which are all (17(α),20(β),21 triols, $\Delta_1 = +306, +428, +308$, respectively). The $\Delta_1$ value (at $C_{20}$) of the pregnanediol-3(α),20-one-11 3-acetate of Sarett[7] (+91) shows that it is a 20(β) compound, as might be expected from its method of preparation.

Table II shows the $\Delta_1$ values (at $C_{20}$) for 17(β), 20 diols of the 17-*iso* series. It will be seen that there is no really convincing agreement with the standard $\Delta_1$ values in the 17-*n* series. Since, also, in the comparable case of hydroxyl groups at $C_{11}$ and $C_{12}$ the molecular rotation data are in disagreement with the accepted configurations,[8,9] we feel that the conclusions of Fieser and Fieser regarding the 17-*iso* compounds, although possibly correct, should at present be treated with some reserve.

We are indebted to N. V. Organon, Oss, Holland, for a generous gift of pregnenolone acetate.

### Experimental[10]

**Allopregnanediol-3(β),20(α) Diacetate.**—Allopregnanol-3(β)-one-20 acetate was reduced with sodium and boiling ethanol.[11] The product was acetylated and the acetates chromatographed on alumina. Allopregnanediol-3(β),20(α)-diacetate after repeated crystallization from light petroleum had m.p. 163–165° (reported,[11] 165–168°); $[\alpha]_D$ −0.3° (*c*, 3.3), $[M]_D$ −1°.

**Allopregnanediol-3(β),20(α).**—The diacetate was hydrolyzed by boiling for two hours with aqueous alcoholic potassium hydroxide. The diol, recrystallized once from ether and once from acetone, had m.p. 218–219° (reported[11] 220–222°) $[\alpha]_D$ +23° (*c*, 0.9), $[M]_D$ + 72°.

**Allopregnanediol-3(β),20(β) 3-Acetate.**—$\Delta^5$-Pregnenol-3(β)-one-20 acetate was hydrogenated in ether-acetic acid solution using a platinum catalyst until the uptake of hydrogen was complete. The product was recrystallized repeatedly from methanol to give allopregnanediol-3(β),20(β) 3-acetate, m. p. 168–169°, $[\alpha]_D$ −6° (*c*, 3.6), $[M]_D$ −22° (1-dm. macro-tube).

*Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 76.2; H, 10.6. Found: C, 76.5; H, 10.5.

**Allopregnanediol-3(β),20(β)-diacetate.**—The monoacetate was refluxed with acetic anhydride for one hour. The product was chromatographed on alumina and recrystallized from methanol to give the diacetate, m. p. 141–142° (reported[12] 142–143°), $[\alpha]_D$ +22° (c, 5.2), $[M]_D$ +89°.

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(7) Sarett, THIS JOURNAL, **70**, 1690 (1948). By arguments similar to those of Fieser and Fieser, based on the method of formation, Sarett's pregnanetriol-3(α),17,20-one-11 (diacetate m. p. 227–228°) must be 17(α),20(β), and his pregnanetriol-17(α),20,21-dione-3,11 (diacetate, m. p. 212–213°) must be 20(β).

(8) Gallagher, *J. Biol. Chem.*, **162**, 539 (1946).

(9) Wintersteiner, Moore and Reinhardt, *ibid.*, **162**, 707 (1946).

(10) All rotations were determined in $CHCl_3$ solution for the Na D line at 20–25°. A 0.5 dm. micro-tube was used unless stated to the contrary.

(11) Meystre and Miescher, *Helv. Chim. Acta*, **29**, 33 (1946).

(12) Marker, Kamm, Jones and Oakwood, THIS JOURNAL, **59**, 614 (1937).

## Studies in *p*-Cymene. II.[1] The Isomeric Aldehydes Derived from *p*-Cymene

BY CHARLES T. LESTER, RAYMOND E. DONALDSON AND JAMES C. OSWALD[2]

We have prepared the isomeric aldehydes, 2-methyl-5-isopropylbenzaldehyde[3] and 3-methyl-6-isopropylbenzaldehyde,[4] and studied their behavior when subjected to a variety of aldehyde reactions. Our objective was not to realize maximum yields, but to observe what differences, if any, were shown in the reactivities of the isomeric compounds.

Without exception all the experiments reported below indicate that the aldehyde group of 2-methyl-5-isopropylbenzaldehyde is more reactive than the aldehyde group of 3-methyl-6-isopropylbenzaldehyde. This difference is most noticeable in the self-condensation Cannizzaro reaction. The difference in reactivity of the isomeric aldehydes is in agreement with our previous report[1] concerning the saponification rate of the isomeric esters derived from *p*-cymene.

### Experimental[4a]

**Preparation of 2-Methyl-5-isopropylbenzaldehyde.**—*p*-Cymene was converted into 2-methyl-5-isopropylbenzyl chloride[5] in 49% yield. The aldehyde was prepared from the substituted benzyl chloride by the method of Sommelet.[6] This reaction was carried out with 37.5 g. of the chloride and 42 g. of hexamethylenetetramine. The aldehyde was isolated as the bisulfite addition compound; average yield, based on six preparations, 25 g., 65%. Hydrolysis of the bisulfite compound gave the aldehyde, b. p. 125° (20 mm.), in 65% yield. The aldehyde was converted, without modification of standard procedures, into a 2,4-dinitrophenylhydrazone,[7] m. p. 190–191°, and a semicarbazone,[8] m. p. 170–171°.

**Preparation of 3-Methyl-6-isopropylbenzaldehyde.**—The aldehyde was prepared from 3-bromo-*p*-cymene[9] according to the procedure of Smith and Nichols.[10] From the Grignard reagent prepared from 63.9 g. of 3-bromo-*p*-cymene was obtained (average of eight preparations) 21.6 g., 27% yield, of the aldehyde bisulfite compound. Hydrolysis of the bisulfite compound gave a 60% yield of the aldehyde, b. p. 123° (20 mm.). Attempts to prepare a 2,4-dinitrophenylhydrazone[7] and a semicarbazone[8] by the usual procedures were unsuccessful. However, when the aldehyde and proper reagents were heated in a boiling water-bath for one hour, a 2,4-dinitrophenylhydrazone, m. p. 192–193°, and a semicarbazone, m. p. 177–178° were obtained.

**Reaction of the Aldehydes with Acetone.**—The aldehydes were treated with the same molar quantities of reagents as described by Porter and Stewart[11] for benzaldehyde. Each reaction mixture was refluxed for five min-

(1) Lester and Bailey, THIS JOURNAL, **38**, 375 (1946).

(2) Present address: Georgia State Department of Agriculture, Atlanta, Georgia.

(3) Verley, *Bull. soc. chim.*, [3] **17**, 906 (1897).

(4) Blum-Bergmann, *J. Chem. Soc.*, **1**, 1930 (1935).

(4a) All melting points are uncorrected.

(5) Whittleston, THIS JOURNAL, **59**, 825 (1937).

(6) Sommelet, *Compt. rend.*, **157**, 852 (1913).

(7) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

(8) Shriner and Fuson, *ibid.*, p. 142.

(9) Fileti and Crosa, *Gazz. chim. ital.*, **16**, 292 (1886).

(10) Smith and Nichols, *J. Org. Chem.*, **6**, 489 (1941).

(11) Porter and Stewart, "Organic Chemistry for the Laboratory," Ginn and Co., Boston, Mass., 1943, p. 103.

utes and then allowed to sit at room temperature until the reaction was complete. For the reaction of 2-methyl-5-isopropylbenzaldehyde this entailed two days; for the 3-methyl-6-isopropylbenzaldehyde this entailed two weeks. We judged the reaction complete when the contents of the reaction vessels, stoppered after heating, appeared as a solid mass of crystals, with no visible liquid phase. From 7 g. of 2-methyl-5-isopropylbenzaldehyde and 1.3 g. of acetone was obtained 4.6 g., 61%, of bis-(2-methyl-5-isopropylbenzal)-acetone, m. p. 93.5–94.5°.

*Anal.* Calcd. for $C_{25}H_{30}O$: C, 86.6; H, 8.72. Found: C, 86.4; H, 8.69.

From the same quantities of 3-methyl-6-isopropylbenzaldehyde and acetone was obtained 4.5 g., 60%, of bis-(3-methyl-6-isopropylbenzal)-acetone, m. p. 95–96°.

*Anal.* Calcd. for $C_{25}H_{30}O$: C, 86.6; H, 8.72. Found: C, 86.3; H, 8.70.

**Preparation of Substituted Mandelic Acids.**—Using the same molar quantities of material and following in detail the procedure described by Fieser for the preparation of mandelic acid,[12] from 10 g. of the bisulfite compound of 2-methyl-5-isopropylbenzaldehyde was obtained 2.44 g., 36%, of (2-methyl-5-isopropylphenyl)-glycolic acid, m. p. 124–125°.

*Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.69; neut. equiv., 208. Found: C, 69.1; H, 7.68; neut. equiv., 206.8.

In like manner from 10 g. of the bisulfite compound of 3-methyl-6-isopropylbenzaldehyde was obtained 0.8 g., 12%, of (3-methyl-6-isopropylphenyl)-glycolic acid, m. p. 139–140°.

*Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.69; neut. equiv., 208. Found: C, 69.4; H, 7.83; neut. equiv., 208.9.

**Reaction of the Aldehydes with Sodium Bisulfite.**—A solution of 2.16 g., 0.0133 mole, of each aldehyde in 50 ml. of ether was placed in a glass bottle and 100 ml. of saturated aqueous sodium bisulfite was added to each bottle. The bisulfite solution was from the same stock solution. The bottles were stoppered and strapped together on the same shaking machine. At the end of four hours shaking 2.036 g., 57.4%, of the addition compound of 2-methyl-5-isopropylbenzaldehyde had precipitated. Further shaking for a total of twenty-four hours produced no additional precipitate. At the end of four hours 1.635, 46.1%, of the addition compound of 3-methyl-6-isopropylbenzaldehyde had precipitated. At the end of seven hours a total of 1.794 g., 51.1%, and at the end of twenty-two hours, a total of 1.976 g., 55%, had precipitated. No further precipitation occurred on an additional two hours shaking. At each time interval mentioned above, shaking was interrupted and the precipitate was filtered at the water pump. The precipitate was washed with ether and the ether solution of the aldehyde restored to its original volume by adding the washings and any additional ether necessary. Shaking was then resumed. The precipitate collected was dried and weighed.

**Cannizzaro Reaction.**—From 10 g. of 2-methyl-5-isopropylbenzaldehyde treated according to a standard procedure (the reaction mixture was allowed to sit for forty-eight hours[13]) was obtained 3 g., 57%, of 2-methyl-5-isopropylbenzoic acid, m. p. and mixed m. p. with authentic sample[1] 70–71°, and 5.1 g. of material, b. p. 137–138° (20 mm.). This proved to be a mixture of alcohol and unreacted aldehyde, since it gave positive fuchsin aldehyde test and reacted with 3,5-dinitrobenzoyl chloride to give an ester,[14] m. p. 74–75°.

*Anal.* Calcd. for $C_{18}H_{18}O_6N_2$: N, 7.81. Found: N, 7.66.

When 10 g. of the 3-methyl-6-isopropylbenzaldehyde was treated as above, less than 0.1 g. of acid was obtained and 8.9 g. of unreacted aldehyde was recovered. The reaction was repeated and the reaction mixture heated at 100° with mechanical stirring for one week. From this reaction was obtained 0.8 g., 12%, of 3-methyl-6-isopropylbenzoic acid, m. p. and mixed m. p. with authentic sample[1] 84–85°. In addition to the acid, 2.5 g. of material, b. p. 131–134° (20 mm.), was isolated. When treated with 3,5-dinitrobenzoyl chloride[14] and steam distilled to remove unreacted aldehyde, the ester of the 3-methyl-6-isopropylbenzyl alcohol, m. p. 76.5–78°, was obtained.

*Anal.* Calcd. for $C_{18}H_{18}O_6N_2$: N, 7.81. Found: N, 7.63.

**Acknowledgment.**—We wish to express our appreciation to B. F. Landrum, J. R. Proffitt and E. C. Surratt for their help in the analysis of our compounds.

DEPARTMENT OF CHEMISTRY
EMORY UNIVERSITY
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RECEIVED JULY 26, 1948

(12) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 94.

(13) Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Company, New York, N. Y., 1943, p. 279.

(14) McElvain, "The Characterization of Organic Compounds," The Macmillan Company, New York, N. Y., 1945, p. 193.

## Alkylation of Thiophene by Propylene and Isobutylene

BY WALTER M. KUTZ AND B. B. CORSON

In view of the publication of Appleby, Sartor, Lee and Kapranos,[1] the compound reported by us[2] as probably being 2-*t*-butylthiophene was further examined. Comparison of its infrared spectrum with the spectrograms of the 2- and 3-isomers reported by Appleby and co-workers definitely showed the presence of the 3-isomer. The spectrum of our sample was also examined by those investigators. Their estimate of the content of the 3-isomer was about 30%; but owing to uncertainty as to the film thickness used in their characterization of the pure isomers (the original equipment having been replaced), it was not possible to make a quantitative infrared analysis. The estimate of the 3-isomer content from refractive index and density values was about 22%.

Inspection of our reported data on isopropylthiophene disclosed a typographical error. The density ($d^{20}_4$) of this product, prepared from propylene and isopropyl alcohol, was 0.9684 and 0.9687, respectively, instead of the reported values of 0.9884 and 0.9887. Our refractive index and density values fall between the values reported by Appleby and associates for the 2- and 3-isopropylthiophene isomers. Assuming linear blending relationship in these values, our product contained 78.5% of the 2-isomer and 21.5% of the 3-isomer according to refractive index, and 73.5% of the 2-isomer and 26.5% of the 3-isomer according to density, or an average of 76% of the 2-isomer and 24% of the 3-isomer as compared with 59% of the 2-isomer and 41% of the 3-isomer reported by Appleby and co-workers. This difference in product composition could well be due to the difference in the alkylation catalysts employed—"solid phosphoric acid" by Appleby, *et al.*, and "Filtrol" by us.

(1) Appleby, Sartor, Lee and Kapranos, THIS JOURNAL, **70**, 1552 (1948).

(2) Kutz and Corson, *ibid.*, **68**, 1477 (1946).

Evidently the chemical proof of structure[2] of our isopropylthiophene (based on the oxime and *p*-nitrophenylhydrazone of 2-isopropyl-5-acetylthiophene[3]) accounted for only the major component (*ca.* 75%) of the mixture.

(3) Scheibler and Schmidt, *Ber.*, **54**, 139 (1921).

KOPPERS MULTIPLE FELLOWSHIP ON TAR SYNTHETICS
MELLON INSTITUTE
PITTSBURGH, PENNA. RECEIVED JANUARY 13, 1949

## The Apparent Ionization Constants of Acethydrazide and Glycylhydrazide

BY CARL R. LINDEGREN[1] AND CARL NIEMANN

In considering the reactions of glycylhydrazide with nitrous acid[2] the apparent ionization constants of acethydrazide and glycylhydrazide have been determined at 24 ± 1° and 25 ± 2°, respectively. With the former compound potentiometric titration of approximately 0.1 formal solutions, which were also 0.05, 0.10 or 0.20 formal in sodium chloride, with standard hydrochloric acid indicated that $pK'_A$ was independent of the ionic strength over the range studied and had a value of 3.24 for the reaction

$$[CH_3CONHNH_3]^+ \rightleftharpoons CH_3CONHNH_2 + [H]^+$$

The titration data for glycylhydrazide, obtained as described below, were evaluated by the method of Britten[3] because preliminary calculations indicated that the two constants were not sufficiently separated to permit evaluation on the basis of assumed non-interaction. $pK'_{A_1}$ was found to have a value of 2.38 and $pK'_{A_2}$ a value of 7.69. From these data and those available for other derivatives of glycine[4] it is not unreasonable to assume that $pK_{A_1} = 2.38$ for the reaction

$$[H_3NCH_2CONHNH_3]^{++} \rightleftharpoons [H_3NCH_2CONHNH_2]^+ + [H]^+$$

and $pK'_{A_2} = 7.69$ for the reaction

$$[H_3NCH_2CONHNH_2]^+ \rightleftharpoons H_2NCH_2CONHNH_2 + [H]^+$$

since the ionization constants of all the simpler α-amino acid esters and amides are in the neighborhood of $pK'_A = 7.7$.[4] The greater acidity of the hydrazinium group in the doubly protonated glycylhydrazide relative to the singly protonated acethydrazide appears to be a logical consequence of the presence of the positively charged ammonium group in the former compound though the difference ($\Delta pK = 0.86$) is only approximately one-half of that obtaining in the case of $[CH_3CH_2CH_2NH_3]^+ - [NH_3CH_2CH_2CH_2NH_3]^{++}$ ($\Delta pK = 10.6 - (8.6 + 0.3) = 1.7$) if 0.3 is added to the observed $pK'_{A_1}$ of the latter species to correct for a statistical factor of two.[5]

### Experimental

**Reagents.**—Acethydrazide, prepared from redistilled ethyl acetate and 85% hydrazine[6] was recrystallized twice from an ether–chloroform mixture and dried over potassium hydroxide. Glycylhydrazide was prepared essentially as described by Curtius and Levy,[2] the product recrystallized as described above and dried over phosphorus pentoxide.

**Procedure.**—Solutions were prepared which were approximately 0.10 formal in acethydrazide or 0.05 formal in glycylhydrazide and 0.05, 0.10 or 0.20 formal in sodium chloride. Five-ml. aliquots of these solutions were titrated with standard 0.10 normal hydrochloric acid using a Beckman Model G *p*H meter equipped with a Beckman type E glass electrode. In every case the *p*H meter was calibrated against a standard buffer solution before a titration.

**Results.**—With acethydrazide five determinations using solutions 0.20 formal in sodium chloride gave a value for $pK'_A$ for the first half of the titration curve of 3.21 ± 0.10; five determinations using solutions 0.10 formal in sodium chloride a value of 3.25 ± 0.10; and three determinations with solutions 0.05 formal in sodium chloride a value 3.23 ± 0.05. The average of all determinations was 3.24. With glycylhydrazide the following values were obtained for $pK'_{A_1}$ and $pK'_{A_2}$ in the order named: with 0.2 formal sodium chloride 2.38 and 7.68, 2.36 and 7.68; with 0.1 formal sodium chloride 2.42 and 7.68, 2.40 and 7.73; and with 0.05 formal sodium chloride 2.36 and 7.69; 2.38 and 7.67. The average of all of the above was $pK'_{A_1}$ 2.38 and $pK'_{A_2} = 7.69$.

(1) Present address: Department of Chemistry, University of California at Los Angeles.

(2) T. Curtius and L. Levy, *J. prakt. Chem.*, **70**, 89 (1904).

(3) H. T. S. Britten, "Hydrogen Ions," 3rd edition, Vol. I, Van Nostrand, New York, N. Y., 1943, pp. 197–200.

(4) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943.

(5) The authors are indebted to Dr. J. T. Edsall for bringing this relation to their attention.

(6) T. Curtius and T. S. Hoffman, *J. prakt. Chem.*, **53**, 513 (1896).

CONTRIBUTION NO. 1256
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIF. RECEIVED NOVEMBER 26, 1948

## The Preparation of 2-Nitro-3,4-xylenol

BY GEORGE P. MUELLER AND WALTER S. PELTON[1]

A need for 2-nitro-3,4-xylenol, for which no preparation has been described, prompted its synthesis in this Laboratory. The method selected was the sulfonation of 3,4-xylenol in the 6-position and nitration in the 2-position, followed by desulfonation. The well-known exchange of nitro- for sulfo-group during nitration of phenolsulfonic acids occurred here, and some 2,6-dinitro-3,4-xylenol was always formed. However, by varying the temperature and the amounts of nitric and sulfuric acids used, conditions were found which permitted yields of 40% to be obtained.

It was observed that the 2,6-dinitro-3,4-xylenol, m.p. 125–126°[2] separating during nitration carried 2-nitro-3,4-xylenol with it to form a molecular compound, m.p. 67–68°. The presence of 2-nitro-3,4-xylenol here indicates that the reaction conditions bring about nitration and some desulfonation without introducing a second

(1) This note was taken from the thesis submitted by Walter S. Pelton to the Committee on Graduate Study of the University of Tennessee in partial fulfillment of the requirements for the M.S. degree.

(2) Datta and Varma, THIS JOURNAL, **41**, 2039 (1919).

nitro-group, and represents a certain loss of the desired product.

Proof of the structure was obtained by reduction to 2-amino-3,4-xylenol, m.p. 138–139°. The previously reported value for this aminophenol, prepared by reducing 6-hydroxy-2,3-dimethylazobenzene, was 126°.[3] Repetition of this earlier work gave a compound, m.p. 138–139°, identical with that obtained from the nitrophenol.

### Experimental

**2-Nitro-3,4-xylenol.**—Purified 3,4-xylenol, 122 g. (1.0 mole) was dissolved in 122 ml. of concentrated sulfuric acid and the solution warmed on the steam-bath until reaction was under way and the temperature had risen to 60–70°. Heating was then discontinued and the mixture stirred until crystallization occurred, and to the cooled mixture 600 ml. of water and 240 ml. of concentrated sulfuric acid were added. Nitration was accomplished by adding 70 ml. of nitric acid, sp. gr. 1.42 (1.1 moles), diluted with 100 ml. of water, dropwise, with stirring at 0–5° and allowing the temperature to remain thus for an hour after addition was complete. The mixture was poured into 1200 ml. of ice-water and filtered from the precipitated nitroxylenols. Sodium chloride added to the clear filtrate salted out 2-nitro-3,4-xylenol-6-sulfonic acid as a thick, orange precipitate. The latter was collected, the filtrate saturated with salt and a second crop of sulfonic acid collected after cooling for several hours. The crude nitrosulfonic acid was steam distilled at 130–140° from an initial volume of 1050 ml. of 70% sulfuric acid. After the initial distillate, mainly 3,4-xylenol, 2-nitro-3,4-xylenol, crystallizing in the condenser as an orange solid, was collected. After separating and drying this, it was recrystallized once from petroleum ether (b. p. 60–90°) yielding 68 g. (41%) of a slightly impure product, m. p. 67–70°. After recrystallizing six times from the same solvent it melted at 71.5–72.0°.

*Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.46, 57.58; H, 5.21, 5.25; N, 8.51, 8.61.

Nitration in glacial acetic acid and at lower and higher temperatures proved less satisfactory. Also, the amount of nitric acid proved to be critical. For example, 0.25-mole quantities of the xylenol in corresponding amounts of water and sulfuric acid were sulfonated and then nitrated at 0–5° with 40-ml. quantities of nitric acid in varying concentrations:

| Moles of $HNO_3$ in 50 ml. of solution | Yield of crystallized 2-nitro-3,4-xylenol Grams | % | Crude precipitated nitroxylenols, g. |
|---|---|---|---|
| 0.22 | 10.6 | 25 | 2.6 |
| .28 | 16.7 | 40 | 4.0 |
| .34 | 13.9 | 33 | 7.1 |
| .40 | 6.0 | 14 | 9.0 |

The crude nitroxylenols, precipitating on dilution of the nitrated mixture, when dried and treated with petroleum ether separated into a soluble portion, crystallizing on cooling, m. p. 67–68°, and an insoluble fraction which was recrystallized from alcohol. The latter was 2,6-dinitro-3,4-xylenol, m. p. 122.5–124.0°. The low-melting material was not identical with 2-nitro-3,4-xylenol and could be made to yield the 2,6-dinitro-compound on crystallization from alcohol. An equimolecular mixture of the 2-nitro- and 2,6-dinitroxylenols melted at 67–68° and did not depress the m. p. of the above material.

**2,4-Dinitrophenyl 2-Nitro-3,4-Xylyl Ether.**—This derivative was prepared by the procedure of Bost and Nicholson,[4] and recrystallized three times from ethyl alcohol; m. p. 157.0–157.5°.

*Anal.* Calcd. for $C_{14}H_{11}O_7N_3$: C, 50.45; H, 3.33; N, 12.61. Found: C, 50.41, 50.35; H, 3.15, 3.25; N, 12.38, 12.14.

**2-Amino-3,4-xylenol.**—Reduction of 2 g. of the nitrophenol with 10 g. of sodium hydrosulfite, 5 g. of sodium bicarbonate and 33 ml. of water[5] gave a solid which darkened readily. This was decolorized in alcoholic solution, the solvent removed *in vacuo* and the buff-colored residue recrystallized from benzene. The m. p. was 138–139°.

Catalytic reduction in absolute alcohol at 50 p. s. i. over palladium-on-charcoal catalyst[6] gave the identical compound in 98% yield.

*Anal.* Calcd. for $C_8H_{11}ON$: C, 70.05; H, 8.06; N, 10.21. Found: C, 70.15, 70.12; H, 7.82, 7.89; N, 10.10, 10.16.

6-Hydroxy-2,3-dimethylazobenzene was prepared and purified as described by King.[7] It was reduced to 2-amino-3,4-xylenol in accordance with the previously published procedure[3] and the product purified. The m. p. and mixed m. p.'s with samples prepared by the above methods were all 138–139°.

**2-Acetamino-3,4-xylenol.**—The aminophenol, 0.5 g., was treated with 2 ml. of acetic anhydride, the resulting solid dissolved in 10% potassium hydroxide and the desired derivative precipitated with dilute acid; yield 0.35 g., m. p. 159–160° after four recrystallizations from benzene.

*Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.05, 66.94; H, 7.11, 7.09; N, 7.77.

(3) Hinkel, Ayling and Bevan, *J. Chem. Soc.*, 2529 (1928).
(4) Bost and Nicholson, *ibid.*, **57**, 2368 (1935).
(5) Hodgson and Beard, *J. Chem. Soc.*, **127**, 498 (1925).
(6) Hartung, THIS JOURNAL, **50**, 3370 (1928).
(7) King, *J. Chem. Soc.*, 1157 (1939).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TENNESSEE
KNOXVILLE, TENNESSEE RECEIVED NOVEMBER 8, 1948

## A Simple Device for Regulating Pressure or Vacuum

BY J. HOWARD MUELLER

In certain experimental procedures it is often necessary to apply moderate air pressure to a piece of apparatus over a considerable period of time. The increasing use of chromatographic columns for various purposes is a case in point. A simple device which may readily be constructed at little expense has proved extraordinarily useful for this purpose and possibly merits brief description. A compressed air supply is essential to its use, but this is almost universally available.

The principle employed is to form a valve between a stainless steel ball and a narrow "seat" turned in the end of a hole drilled through a lucite or metal rod. By applying more or less pressure on top of the ball, a slow stream of air passing upward through the hole is impeded, and variable pressures are obtained in a closed system of which this valve forms the outlet. The drawing illustrates the manner in which this may be accomplished. The stem of the regulator passes through a stopper inserted into a small filter flask, which is connected to the system. A very slow stream of air is admitted by slight opening of an ordinary valve on the supply line, and the pressure is set where desired by regulating the tension on the spring by means of the knurled headed screw. The air escapes through a small vent drilled in the wall of the cylinder just above the ball. In this way,

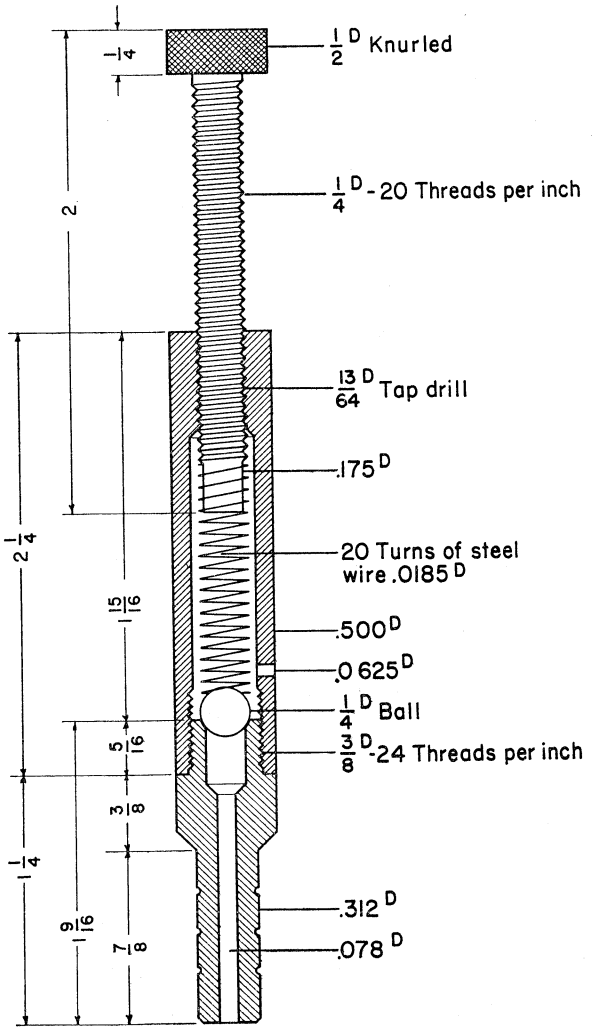



Fig. 1.

pressures varying from 2–3 mm. up to 150–200 mm. can be obtained quickly and maintained indefinitely without perceptible variation.

The same device may be used for regulation of a partial vacuum by adding a side-arm at the site of the air vent, connecting this to the apparatus, and leaving the opening below the ball free for the entrance of air.

DEPARTMENT OF BACTERIOLOGY AND IMMUNOLOGY
HARVARD MEDICAL SCHOOL
BOSTON, MASSACHUSETTS RECEIVED JANUARY 6, 1949

## An Improved Method for the Preparation of Aromatic Diazoketones

BY MELVIN S. NEWMAN AND PHILIP BEAL, III

Common practice in the preparation of diazoketones involves the treatment of an acid chloride with two moles of diazomethane, one being destroyed by the hydrogen chloride produced.[1] Since this is wasteful of diazomethane, we have investigated the use of tertiary amines to remove the hydrogen chloride.

When benzoyl chloride was added to an ether solution containing one equivalent each of diazomethane and triethylamine, the diazoketone was produced in excellent yield. The reaction worked as well with anisoyl chloride. In the case of *n*-caproyl chloride, nitrogen was evolved during the addition and a mixture of products was formed. Indirect evidence for the presence of a considerable proportion of diazoketone in this mixture was obtained but it was not isolated. With the thought that the evolution of nitrogen during addition of caproyl chloride to the mixture of diazomethane and triethylamine might have been due to the $\alpha$-hydrogen, we repeated the experiment with trimethylacetyl chloride. The evolution of nitrogen during addition was less but still appreciable. The results when pyridine was used in place of triethylamine were not encouraging.

It thus appears that, at least with aromatic acid chlorides, diazomethyl ketones can be produced in excellent yield with the consumption of only one equivalent of diazomethane.

### Experimental

Ethereal solutions of diazomethane were prepared from N-nitrosomethylurea and were standardized.[2] The triethylamine was dried over barium oxide.

**Diazoacetophenone.**—A solution of 14.1 g. (0.1 mole) of benzoyl chloride in 25 cc. of ether was added during twenty minutes to a well-stirred cooled (ice–salt-bath) solution of 4.2 g. (0.1 mole) of diazomethane and 10.1 g. (0.1 mole) of triethylamine in 235 cc. of dry ether. A crystalline precipitate of triethylamine hydrochloride separated. After stirring in the cold for twelve hours, the hydrochloride, 11.8 g. (86%), was collected and washed with dry ether. The solvent was removed under reduced pressure from the combined filtrate and washings to yield 15.2 g. (104%) of crude crystalline diazoketone. An assay of this crude diazoketone by acid decomposition resulted in the collection of 93.6% of the theoretical amount of nitrogen. Recrystallization from low boiling petroleum ether (Skellysolve F) yielded the pure diazoketone, m. p. 47.8–48.4°,[3] with little loss. Experiments using pyridine in place of triethylamine were unpromising.

***p*-Methoxy-$\alpha$-diazoacetophenone.**—In a similar way, anisoyl chloride was converted into crude diazoketone in high yield. Recrystallization from benzene and petroleum ether, b. p. 60–70°, yielded pure diazoketone, m. p. 86–89° dec., in 73% yield.

**Reaction of Caproyl Chloride with Diazomethane.**—When a solution of 9.9 g. (0.064 mole) of caproyl chloride in 30 cc. of ether was added as above described during forty-five minutes to an ethereal solution containing equivalents of triethylamine and diazomethane 0.0224 mole (35%) of nitrogen was evolved. No further nitrogen was obtained after the mixture stood for twelve hours in the cold. Triethylamine hydrochloride was isolated in 91% yield, and from the filtrate and washings 9.7 g. (69%) of a crude diazoketone fraction which yielded only 58% of the theoretical amount of nitrogen on acid decomposition.

It was shown that triethylamine hydrochloride does not react with diazomethane under the conditions of this experiment. Hence we are unable to offer an explanation

(1) Bachmann and Struve, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1942, p. 39.

(2) F. Arndt, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, p. 165.

(3) Wolff, *Ann.*, **325**, 142 (1902).

for the gas observed with caproyl chloride but not with benzoyl or anisoyl chlorides.

**Reaction of Trimethylacetyl Chloride with Diazomethane.**—A solution of 24.1 g. (0.2 mole) of this acid chloride in 50 cc. of ether was added during eighty-five minutes to a cold solution of 20.4 g. (0.2 mole) of triethylamine and 8.5 g. of diazomethane in 275 cc. of ether. During the addition 0.022 mole (11%) of nitrogen was evolved, but on standing for twelve hours in the cold, no more nitrogen was liberated. The amine hydrochloride (96%) and crude diazoketone (98%) were isolated as described above. On treatment with acid, the crude diazoketone yielded 90% of nitrogen.

CHEMISTRY LABORATORY OF
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO RECEIVED DECEMBER 13, 1948

## Reduction of Anthracene and Phenanthrene with Lithium Aluminum Hydride

BY JOHN R. SAMPEY AND JESSIE M. COX

Nystrom and Brown[1] have found lithium aluminum hydride a useful reagent for a number of organic reductions. No work has been reported on the reduction of aromatic or condensed ring nuclei with this reagent. Preliminary attempts to reduce naphthalene and anthracene in ether and dioxane solutions were unsuccessful, but when the solid lithium aluminum hydride was shaken with molten anthracene and phenanthrene, reduction did take place, the former giving as high as 60% yields of tetrahydroanthracene, and the latter 22% of dihydrophenanthrene. These reductions take place even though the decomposition point of lithium aluminum hydride has been reported at 125–150°.[2] In all our reductions at high temperatures we mixed the powdered reagent thoroughly with the organic substances, and then employed vigorous shaking of the molten materials to ensure intimate mixing.

**Method of Reduction.**—A series of experiments is reported in which the temperature, the time and the ratio of reducing agent to anthracene and phenanthrene are varied. The experiments were run in a 200-ml. round-bottom flask, fitted with a calcium chloride tube, Bunsen valve and thermometer. The flask is heated with a Gyco heating jacket placed on a shaking machine. In each experiment 0.05 mole of the organic molecule was used. The molten material was shaken for the first two hours of each run, and then for fifteen minutes out of every thirty minutes; at the end of the time specified the hydride is decomposed by the slow addition of water. The reaction is vigorous and often flashes of fire were seen in the flask, but none of the reactions has gotten out of hand to date. After filtering and drying, the anthracene and its reduced form were extracted from the lithium and aluminum compounds with 200 ml. of hot chloroform and the phenanthrene with 200 ml. of ether or 95% alcohol. The unreduced hydrocarbons are less soluble than the hydrogenated products in the solvents used for the extractions, thus providing an effective method of separation. The tetrahydroanthracene was identified by a mixed melting point with a sample prepared by reduction of anthracene with Raney nickel (m. p. 103–104°). The dihydrophenanthrene and its picrate were identical with those prepared by Schmidt.[3]

**Results of Reduction.**—A 60% yield of tetrahydroanthracene was obtained by heating 0.05 mole of anthracene at 220–230° for six hours with 8 g. of lithium aluminum hydride; a 45% yield was obtained by cutting the hydride to one-half. Increasing the temperature to 240–270° or lengthening the time of heating also reduced the yield. A 22% yield of dihydrophenanthrene was obtained by heating 0.05 mole of phenanthrene at 220–230° for six hours with 8 g. of lithium aluminum hydroxide. Reducing the temperature to 180–200° and the quantity of hydride, reduced the yield to 10–17%.

**Acknowledgment.**—The authors acknowledge the interest of Dr. E. Emmet Reid in this research and the assistance of a grant from the Office of Naval Research.

(1) Nystrom and Brown, THIS JOURNAL, **69**, 1197, 2548 (1947); **70**, 441 (1948).

(2) Finholt, Bond and Schlesinger, *ibid.*, **69**, 1199–1203 (1947).

(3) Schmidt, *Ber.*, **40**, 4240–4257 (1907).

DEPARTMENT OF CHEMISTRY
FURMAN UNIVERSITY
GREENVILLE, S. C. RECEIVED DECEMBER 8, 1948

## Electroseparation of Technetium from Rhenium and Molybdenum

BY L. B. ROGERS[1]

Heretofore, technetium has been plated from acidic solutions[2,3,4] under nearly the same conditions used for the deposition of rhenium. It seems quite likely, therefore, that the separation from rhenium would be poor. During the course of a polarographic study of technetium with G. E. Boyd[5] it was found that distinct reduction waves were found for pertechnitate in 2 *M* sodium hydroxide whereas perrhenate and molybdate did not reduce, at the platinum electrode, up to the potential at which hydrogen was evolved rapidly.

The brown-black precipitate which appeared on the electrode was soluble in a mixture of ammonia and hydrogen peroxide indicating that a lower oxide of technetium was formed since technetium metal is insoluble.[6] The height of the diffusion current confirmed the idea that the reduction step involved several electrons. Since the polarographic diffusion current reached a constant value at about −0.9 v. *vs.* the saturated calomel electrode (S.C.E.) and since the rapid evolution of hydrogen did not begin until about −1.2 v., the intermediate region of potential represented a promising one for the separation of technetium.

### Experimental Results

A 100-μl. sample of 2 *M* sodium hydroxide containing 0.2 mg. of technetium ($Tc^{99}$ − 9 × $10^5$ years) as $TcO_4^-$ plus a somewhat larger amount of molybdenum and a smaller amount of rhenium was placed upon a flat platinum foil used for the cathode. The anode was a large

(1) Present address: Massachusetts Institute of Technology, Cambridge 39, Mass.

(2) C. Perrier and E. Segrè, *J. Chem. Phys.*, **7**, 155 (1939).

(3) J. F. Flagg and W. E. Bleidner, *J. Chem. Phys.*, **13**, 269 (1945).

(4) E. E. Motta, Q. V. Larson and G. E. Boyd, Plutonium Project Record, MonC-99, April, 1947.

(5) G. E. Boyd and L. B. Rogers, reported by G. E. Boyd at the Symposium of the Division of Physical and Inorganic Chemistry at Syracuse, N. Y., June 28-30, 1948.

(6) G. E. Boyd, private communication.

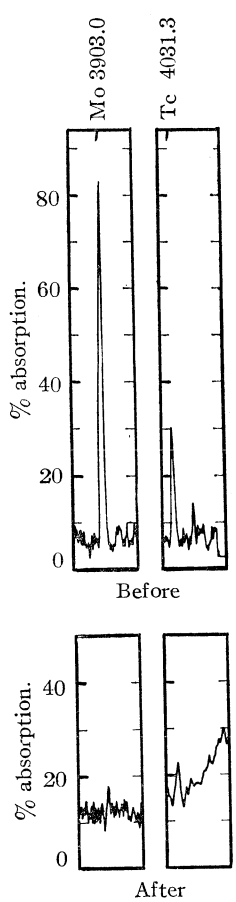



Fig. 1.

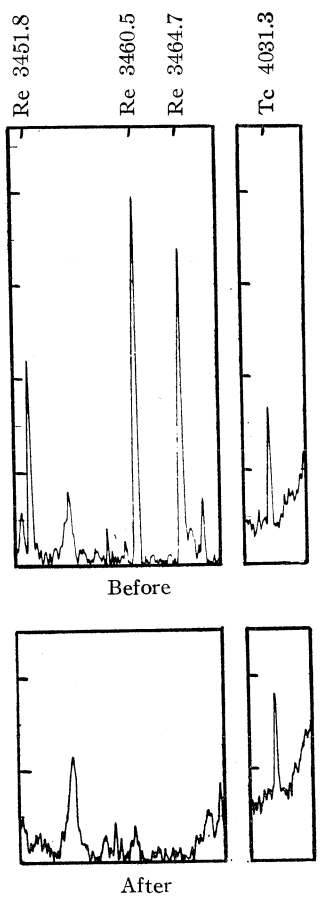



Fig. 2.

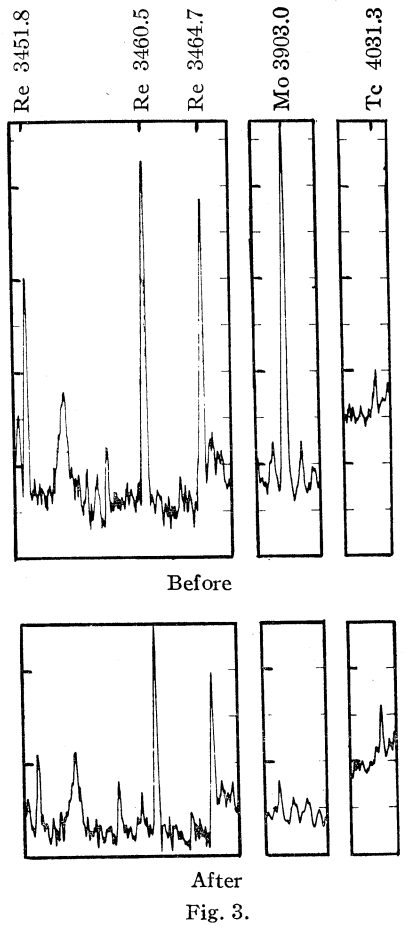



Fig. 3.

Purification of technetium by electrodeposition: selected portions of Leeds and Northrup densitometer traces of spectra obtained with a Dietert 1.5 Meter Grating Spectrograph.

saturated calomel electrode, and it was connected to the sample by means of a sodium perchlorate salt bridge. After two hours of electrolysis at −1.1 v. *vs.* the S. C. E., a count of the supernatant showed that more than 95% of the technetium had been precipitated. This yield was confirmed by counting the cathode after it had been washed with distilled water.

The precipitate was dissolved in a mixture of ammonia and hydrogen peroxide, the solution evaporated to dryness on a steam-bath, and the residue dissolved in 100 $\mu$l. of 2 *M* sodium hydroxide. A comparison of the spectrographic analyses of the solution before and after electrolysis is shown in Fig. 1. After electrolysis, the presence of the molybdenum line was questionable thereby showing that a good separation had been obtained. The technetium line was only slightly weaker after electrolysis.

The rhenium lines were so weak in the original solution (not shown in Fig. 1) that their absence from the second solution was not considered to be adequate proof of a satisfactory separation. Therefore, 0.1 mg. of rhenium, as perrhenate, was added to the solution and a second electrolysis carried out. Figure 2 shows that a good separation was obtained.

A third electrolysis was performed under somewhat different conditions: 0.2 mg. Tc, 0.1 mg. Mo, and 0.1 mg. Re—all in the same valence states as before but dissolved in 1.5 ml. of 2 *M* sodium hydroxide. The electrolysis was done in a small platinum dish at −1.2 v., and it lasted fifteen hours. Figure 3 shows that the separation from molybdenum was again excellent while that from rhenium was only fair. It seems likely the combination of a more negative cathode potential with a greater decrease in the concentration of hydroxide ion, as a result of picking up carbon dioxide from the air, favored the reduction of rhenium. The yield of technetium was only 85%, a decrease which may have been due to the lack of stirring or to the lower concentration of both technetium and hydroxyl ions.

The method appears to be limited to the purification of fairly concentrated solutions, *i. e.*, $10^{-4}$ *M* or greater, because in two experiments involving concentrations of the order of $10^{-6}$ *M*, essentially no technetium was found in the ammoniacal solution of peroxide after it had been in contact with the cathode. Raising the concentration of sodium hydroxide in the solution undergoing electrolysis to 4 *M* did not improve the recovery. One must conclude from these experiments with dilute solutions that the oxide has an appreciable solubility.

**Acknowledgments.**—The author is indebted to G. E. Boyd for supplying the technetium, to C. Feldman and M. Murray for the spectrographic analyses, and to F. H. Sweeton for preparation of the figures.

This work was performed under Contract No. 7405 eng. 26 between the Atomic Energy Commission and Carbide and Carbon Chemicals Corporation.

OAK RIDGE NATIONAL LABORATORY
P. O. BOX P, OAK RIDGE, TENN.

RECEIVED OCTOBER 21, 1948

## Polar Effects of Organosilicon Substituents in Carboxylic Acids[1]

BY L. H. SOMMER, J. R. GOLD, G. M. GOLDBERG AND N. S. MARANS

The acid strengths of carboxylic acids containing organosilicon substituents close to the carboxyl are of interest in connection with an elucidation of the polar effects of such substituents in organic molecules. We wish to report the synthesis and acid strengths of four silicon-containing carboxylic acids.

TABLE I

| Acid | Formula | M. p., °C. | Silicon, % Calcd. | Silicon, % Found | Neut. equiv. Calcd. | Neut. equiv. Found |
|---|---|---|---|---|---|---|
| I | $(CH_3)_3SiCH_2CO_2H$ | 40 | 21.2 | 21.3 | 132 | 133 |
| II[a] | $(CH_3)_3SiOSi(CH_3)_2$-$CH_2CO_2H$ | 17 | 27.2 | 26.7 | 206 | 207 |
| III | $(C_6H_5)(CH_3)_2SiCH_2$-$CO_2H$ | 90 | 14.4 | 14.3 | 194 | 193 |
| IV[b] | $(CH_3)_3SiCH_2CH_2CO_2H$ | 22 | 19.1 | 19.1 | 146 | 145 |

[a] Acid II has $n^{20}D$ 1.4149. [b] Acid IV has b. p. 147° (65 mm.), $n^{20}D$ 1.4279.

Acids I, II and III were synthesized in yields of 88, 85, and 69%, respectively, by carbonation of the Grignard reagents derived from the appropriate chlorides.[2] The Grignard reagents were added to an excess of Dry Ice in the form of chips and the reaction mixture allowed to stand for twelve hours. Subsequent to treatment with 5% hydrochloric acid, ether was removed from the acids by vacuum distillation at temperatures below 25°. These acids were not distilled. They were purified by two recrystallizations from heptane.[3] Acid IV was synthesized from chloromethyltrimethylsilane by the malonic ester synthesis (66% yield) and from iodomethyltrimethylsilane by the acetoacetic ester synthesis (63% yield). This acid was purified by distillation (65 mm.).

Determination of the acid strengths was made by a potentiometric method using a Leeds and Northrup 7662-A1 *p*H Indicator Assembly.[4] Stability of acids I–IV under the conditions used in this procedure was demonstrated by preparation of the sodium salts and regeneration of the acids.

The dissociation constant of *t*-butylacetic acid was determined for comparison with acid I. Propionic acid was run as a check on the accuracy of the method at the concentrations used.

(1) Paper XXI in a series on organosilicon chemistry. For paper XX see THIS JOURNAL, **70**, 3512 (1948).

(2) (a) Chloromethyldimethylphenylsilane, b. p. 138° (50 mm.), $n^{20}D$ 1.5212, Si, 15.1% (calcd. 15.2), was synthesized in 72% yield from chloromethyldimethylchlorosilane and phenylmagnesium bromide; (b) the Grignard reagent derived from chloromethylpentamethyldisiloxane has recently been reported; Bluestein, THIS JOURNAL, **70**, 3068 (1948).

(3) The non-isolation of trimethylsilylacetic acid (I) in a previous preparation resulted from the different procedure used in working up the product; Whitmore, Sommer, Gold and Van Strien, THIS JOURNAL, **69**, 1551 (1947).

(4) For a recent application of this method see Newman, Taylor, Hodgson and Garrett, *ibid.*, **69**, 1784 (1947).

TABLE II

DISSOCIATION CONSTANTS FOR $RCH_2CO_2H$ AT 25°

| R | $K \times 10^5$ | $K/K_{acetic}$ |
|---|---|---|
| $(CH_3)_3Si$ | 0.60 | 0.34 |
| $(CH_3)_3SiOSi(CH_3)_2$ | .60 | .34 |
| $(C_6H_5)(CH_3)_2Si$ | .54 | .31 |
| $(CH_3)_3SiCH_2$ | 1.24 | .71 |
| $(CH_3)_3C$ | 1.00 | .57 |
| $CH_3$ | 1.34[a] | .77 |
| H | 1.75 | |

[a] Value found in this work, $1.32 \times 10^{-5}$.

According to current theory,[5] the acid-weakening effects of organosilicon substituents in acids I, II, and III show that *these substituents exert an inductive effect of electron-release relative to alkyl and hydrogen.*

The data for acid IV demonstrates that this effect diminishes rapidly in a saturated carbon chain. Additional theoretical aspects will be discussed in a later publication.

We thank Dr. A. W. Hutchison for valuable advice and Dr. N. C. Cook for the *t*-butylacetic acid.

(5) For an excellent summary see Johnson and Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, New York, N. Y., 1943, pp. 1842–1845.

THE WHITMORE LABORATORY
SCHOOL OF CHEMISTRY AND PHYSICS
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PA. RECEIVED FEBRUARY 25, 1949

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## Grignard Reactions. XIX.[1] Preparation of 2,-4,4-Trimethyl-3-pentanone

BY CARLYLE J. STEHMAN,[2] NEWELL C. COOK AND FRANK C. WHITMORE[3]

The limitations of the Grignard reaction in the synthesis of highly branched compounds are well known. Such a synthesis, the reaction of *t*-amylmagnesium chloride with isobutyryl chloride, has previously given little or no ketone.[4,5]

Copper vessels for Grignard reactions have been in use in this Laboratory and others for many years. Crane, Boord and Henne[6] noted slightly better yields in copper than in glass. It has now been found that *t*-amylmagnesium chloride reacts with isobutyryl chloride in copper reactors to give 2,4,4-trimethyl-3-pentanone in yields up to 87%.

Further studies on the copper-catalyzed reaction of acid chlorides with Grignard reagents are in progress.

### Experimental

For preparation of the *t*-amylmagnesium chloride, and coupling of the Grignard reagent with isobutyryl chloride,

(1) XVIII, Whitmore and Sloat, THIS JOURNAL, **64**, 2968 (1942).

(2) Present address: Monsanto Chemical Co., Dayton, Ohio; research work performed during academic leave of absence from Monsanto.

(3) Deceased.

(4) Whitmore, *et al.*, THIS JOURNAL, **63**, 643 (1941).

(5) W. A. Mosher, Doctor's Dissertation, 1940, The Pennsylvania State College.

(6) Crane, Boord and Henne, THIS JOURNAL, **67**, 1237 (1945).

a jacketed copper Grignard reactor (20 liters capacity) developed at Penn State was used. To 608 g. (25 moles) of magnesium and 12,500 ml. of ether was added 2662 g. (25 moles) *t*-amyl chloride; from the product mixture was decanted 20 moles (12,200 ml.) of a clear ether solution of *t*-amylmagnesium chloride. This solution was then added dropwise at the rate of 450 cc. per hour to a mixture of 2150 g. (20 moles) of freshly prepared isobutyryl chloride in 4000 ml. of dry ether, at 16–18° and stirring continued for five days, also at 16–18°. After decomposing the product by pouring onto 10 kg. of ice, the ether layer and water layer were separately distilled. The combined ether layer distillates upon fractionation gave cuts 1–5, 88 g., b. p. 50–76° at 80 mm., $n^{20}D$ 1.3840–1.4092, containing isobutyraldehyde and isobutyl alcohol; cut 6, 22 g., b. p. 76–82° at 80 mm., $n^{20}D$ 1.4111; cuts 7–10, 89 g., b. p. 84–87.5° at 90 mm., $n^{20}D$ 1.4070–1.4081, containing isobutyl isobutyrate; cuts 11–14, 108 g., b. p. 88–94° at 100 mm., $n^{20}D$ 1.4091–1.4136, containing isobutyl isobutyrate and 2,4,4-trimethyl-3-pentanone; cuts 15–18, 2021 g., b. p. 94° at 100 mm. to 87° at 35 mm., $n^{20}D$ 1.4214, 2,4,4-trimethyl-3-pentanone; and cut 20, 41 g., residue. Based on isobutyryl chloride, yields were estimated as 73% 2,4,4-trimethyl-3-pentanone, 10% isobutyl isobutyrate, 2% isobutyraldehyde and 1% isobutyl alcohol.

In a second preparation, also on 20-mole scale, in which the rate of addition of Grignard solution (625 cc. per mole) was constant at about 600 cc. per hour, and the temperature was 14–17°, there were obtained yields of 87% 2,4,4-trimethyl-3-pentanone, 5% isobutyl isobutyrate, 0.1% isobutyraldehyde, and 2% isobutyl alcohol.

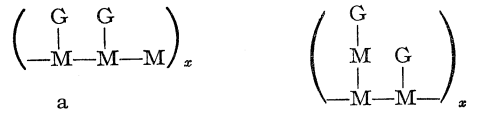
THE PENNSYLVANIA STATE COLLEGE
STATE COLLEGE, PENNSYLVANIA
RECEIVED NOVEMBER 4, 1948

## Methylation of Guar Polysaccharide[1]

BY JOHN W. SWANSON

Purified guar polysaccharide, a mannogalactan consisting of 60% mannan and 37% galactan units, has been methylated, subjected to methanolysis, and the resulting glycosides separated into three principal fractions by means of high vacuum fractional distillation. Fraction 1 has been hydrolyzed to the corresponding sugar and identified as 2,3,4,6-tetramethylgalactose, through its crystalline anilide. This derivative was obtained in a yield sufficient to account for 90% of the galactose present in the original polysaccharide. A sample of the unfractionated glycoside mixture was also hydrolyzed and converted to the anilides; only one crystalline anilide has been recovered. This anilide, which was identical with the above, was obtained in sufficient yield to account for 87% of the galactose present. The other two principal fractions (3 and 4 in Table I) correspond to trimethyl and dimethyl sugar units, respectively. These fractions have not been conclusively identified, but they appear to be largely methylated mannose derivatives.

Although insufficient data have been obtained to make any conclusive statements, it is interesting to note that at least 90% of the galactose units appear to be present in the polymer chain as side units and, therefore, possess four free hydroxyl groups. If the other two main fractions are principally trimethyl and dimethyl mannose, respectively, then the following types of units may be present in guar polysaccharide



a b

G = anhydrogalactose unit
M = anhydromannose unit

Moe, Iwen and Miller[2] have reported that guar mannogalactan in buffered medium consumes one mole of periodic acid per hexose unit. Structures (a) and (b) might also consume an *average* of one mole of periodic acid per hexose unit because each of the side galactose units would presumably consume two moles of periodate and the units located at the branching points would consume no periodic acid, whereas the units from which branching does not occur would consume one mole of periodic acid. Such a reaction with the galactose units would be expected to lead to the formation of a considerable quantity of formic acid. Whistler and co-workers[3] have recently published formic acid data which support the proposed structure as indicated by methylation.

### Experimental

**Methylation of Guar.**—Ten grams of purified guar polysaccharide was dissolved in 500 ml. of water and methylated under nitrogen by the simultaneous dropwise addition during five hours of 100 ml. of dimethyl sulfate and 280 ml. of 30% sodium hydroxide. After complete reaction of the dimethyl sulfate, the excess alkali was carefully neutralized with dilute sulfuric acid and the partially methylated product was salted out with sodium sulfate. The supernatant salt solution was dialyzed, evaporated under vacuum, and the residue combined with the precipitated gum product. The polysaccharide content of this residue was so small after two methylations that this procedure was not deemed necessary for later methylations. The product from the first methylation was then redispersed in water and the methylation repeated. The final product (or part thereof for methoxyl determination) was dissolved in chloroform, dried over anhydrous sodium sulfate, and precipitated with an excess of light petroleum ether. After five to six methylations and reprecipitation to remove ash, the methoxyl content was 45.4% and the ash content 0.8%; yield 11.5 g., 91.2%; $[\alpha]^{23}D$ + 46.4 ($CHCl_3$, *c* 0.67.)

**Methanolysis of Methylated Guar.**—Five and one-half grams of the methylated guar was dissolved in 80.5 ml. of anhydrous methanol and 46.5 ml. of methanol–hydrogen chloride was added (final concentration of hydrogen chloride, 3.0%). The high viscosity decreased very rapidly. The mixture was centrifuged to remove 0.02 g. of a dark solid, giving a clear light yellow solution. The optical rotation was followed to a constant value ($[\alpha]^{23}D$ + 66.5°) at room temperature and then to a constant value of $[\alpha]^{23}D$ + 74.8° after refluxing on a steam-bath for six and one-fourth hours. The hydrochloric acid was neutralized with silver carbonate and, after filtration, the solution was evaporated under vacuum to a sirup. The

(1) Presented before the Division of Sugar Chemistry and Technology at the 112th meeting of the American Chemical Society, New York, N. Y., 1947.

(2) O. A. Moe, S. E. Miller and M. H. Iwen, THIS JOURNAL, **69**, 2621 (1947).

(3) R. L. Whistler, *et al.*, *ibid.*, **70**, 3144 (1948).

small amount of ash was removed by addition of ethyl ether and filtration. The remainder of the glycosidic sirup (5.7 g.) was distilled at 0.04 mm. and 120–142° (bath temperature). The product, a water-white viscous sirup, weighed 5.6 g.; the methoxyl content was 51.9%.

**Fractionation of the Distilled Glycosides.**—The distilled mixture of glycosides (4.44 g.) was placed in a 25-ml. pear-shaped flask containing glass wool and attached to a high-vacuum fractionating apparatus similar to that described by Hibbert.[4] The mixture was slowly fractionated during twelve hours under a vacuum of 0.006 mm. and a bath temperature range of 110–160°. The last fraction was not distilled through the column because of its high boiling point and extremely viscous nature. The data for the various fractions are presented in Table I.

TABLE I

DATA CONCERNING THE METHYLATED GLYCOSIDE FRACTIONS OF METHYLATED GUAR POLYSACCHARIDE

| Fraction | Weight obtained, g. | Methoxyl, % | Yield, % | Molar ration | $[\alpha]^{23}D$ | $n^{20}D$[a] |
|---|---|---|---|---|---|---|
| 1 | 1.2873 | 60.8 | 39.1 | 1.7 | | 1.4493 |
| 2 | 0.4155 | 60.1 | | | | 1.4495 |
| 3 | 0.9486 | 52.1 | 21.9 | 1.0 | 37.6 | 1.4599 |
| 4 | 1.6890 | 43.5 | 38.9 | 1.9 | 20.7 | 1.4738 |
| Total | 4.3314 | | | | | |

[a] Refractive index of mixed glycosides 1.4597.

**Preparation of the Anilide of Fraction One.**—Fraction one (0.28 g.) was hydrolyzed under reflux at 85° in 10 ml. of *N* sulfuric acid for fifteen hours and then converted to the anilide by the method described by White.[5] The product, after five recrystallizations from absolute ethanol, melted at 193–194°. Calcd. for 2,3,4,6-tetramethylgalactose anilide, m. p. 193.5°, $C_{16}H_{25}O_5N$: C, 61.7; H, 8.1; N, 4.5; $OCH_3$, 39.8. Found: C, 61.7; H, 8.2; N, 4.4; $OCH_3$, 39.8. A 90% yield of the galactose was obtained in the form of this crystalline anilide.

A sample of the mixed glycosides was also hydrolyzed and similarly converted to the anilides. Only one crystalline anilide was recovered in 85% yield; this was identical with that obtained from fraction one.

(4) I. Levi, W. L. Hawkins and H. Hibbert, *ibid.*, **64**, 1957 (1942).
(5) E. V. White, *ibid.*, **63**, 2871 (1941).

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APPLETON, WISCONSIN RECEIVED OCTOBER 29, 1948

## Mechanism of the Copper and Halogen-Ion Catalysis of Dissolution of Copper

BY ZOLTÁN SZABÓ

The rate of solution of Cu in acid, in the presence of oxygen at saturation, is known to increase with the concentration of $H^+$ and $Cl^-$ ions, and to increase linearly with the concentration of the $Cu^{++}$ ions produced, except at high $[Cu^{++}]$ where it lags behind the first-order rate with respect to $[Cu^{++}]$. The observed independence of the rate of stirring indicates that the rate of dissolution is not controlled by diffusion to and from the metal surface. These facts can be accounted for by the three-step mechanism

$$(1)\quad Cu = Cu^{++} + \ominus$$
$$(2)\quad Cu^{++} + Cu = 2Cu^{+}$$
$$(3)\quad Cu^{+} + \oplus = Cu^{++}$$

where (1) includes reactions between Cu and $O_2$ or OH, and (3) is representative, in particular, of the reaction (3′) $2Cu^+ + 2H^+ + 1/2O_2 = 2Cu^{++} + H_2O$.

Since the activity of $Cu^+$ in the solution is low at all times, and these ions are steadily removed through (3′), the oxidation–reduction potential $Cu^+/Cu^{++}$ is very much higher than $Cu/Cu^+$, and reaction (2) proceeds from left to right. Absence of an effect of the rate of stirring indicates that (2) is a fast reaction. Consequently, the rate determining step is (3), specifically (3′). The activity of $Cu^+$ is still further lowered, and (2) still further shifted to the right, by formation of complex ions $[CuCl_n^{(n-1)-}]$. This accounts for the accelerating effect of $Cl^-$ ions.

From (3′), the rate of solution of the metal is

$$-d[Cu^+]/dt = k'[Cu^+]^2[O][H^+]^2$$

or, if $Cu^+$ is mainly present as complex ion

$$-\frac{d[CuCl_n^{(n-1)-}]}{dt} = k''[CuCl_n^{(n-1)-}]^2[O][H^+]^2$$

With the equilibrium constants $[Cu^+]^2/[Cu^{++}] = K_1$

$$\frac{[Cu^+][Cl^-]^n}{[CuCl_n^{(n-1)-}]} = K_2, \text{ and}$$

$$\frac{\zeta_1[Cu^{++}][Cl^-]^{2n}}{[CuCl_n^{(n-1)-}]^2} = K_2^2$$

and noting $k'K_1 = k_1$, and $k''K_1 = k_2$, these equations become, respectively

$$-d[Cu^+]/dt = k_1[Cu^{++}][H^+]^2[O] \qquad (A)$$

and

$$-\frac{d[Cu^+]}{dt} = k_2[Cu^{++}][H^+]^2[O]\frac{[Cl^-]^{2n}}{K_2^2} \qquad (B)$$

Either *A* or *B* accounts for the first-order rate law in $[Cu^{++}]$. With regard to the effect of $Cl^-$ ions, if one assumes $n = 3$ and $[Cl^-] = 10^{-2}$, the ratio $[Cl^-]^6/K_2^2$ becomes $\sim 1$.[1] The concentration $[Cl^-] \approx 10^{-2}$ actually divides the ranges of applicability of equations *A* and *B*, the former being valid at $[Cl^-] < 10^{-2}$, the latter at $[Cl^-] > 10^{-2}$. There are not enough data to test the second order with respect to $[H^+]$; in an experiment of Glauner,[2] the ratio of the amounts of Cu dissolved in 0.27 *N* and in 0.135 *N* acid was 32:5, that is higher than proportional to $[H^+]$.[2]

The corrosion is predominantly brought about by (2), the role of (1) being primarily to initiate the autocatalytic process, whereas the rate is determined by (3′).

By analogous considerations, autocatalysis can be expected in the dissolution of iron but not in the case of lead. This is in agreement with observations.

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UNIVERSITY OF SZEGED
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(1) St. v. Náray-Szabó and Szabó, *Z. physik. Chem.*, **A166**, 228 (1933).
(2) R. Glauner, *ibid.*, **A142**, 67 (1929).

# NEW COMPOUNDS

## Phenylpropionyl-*dl*-alanine and Phenylbutyryl-*dl*-alanine

Two new derivatives of alanine have been prepared from the amino acid and the corresponding acid chlorides in the presence of alkali.[1] After isolation, each compound was thrice recrystallized from water, dried, washed with benzene, dried and analyzed. The recrystallizations served to raise the melting points one to three degrees to constant values.

**β-Phenylpropionyl-*dl*-alanine.**—M. p. 139.5–140° (uncor.).

*Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33; neut. eq., 221. Found: C, 65.06; H, 6.76; N, 6.36; neut. eq., 223.[2]

**γ-Phenylbutyryl-*dl*-alanine.**—M. p. 120–121° (uncor.).

*Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.35; H, 7.28; N, 5.96; neut. eq., 235. Found: C, 66.21; H, 7.27; N, 6.07; neut. eq., 233.

Phenylacetyl-*dl*-alanine was also prepared by the above procedure and was found to melt at 150.5–151°. Shiple and Sherwin report 150–152°.[1]

(1) Shiple and Sherwin, *J. Biol. Chem.*, **53**, 463 (1922).

(2) Analyses for C, H and N by Dr. Francine Schwarzkopf, Elmhurst, L. I., New York.

INSTITUTE OF POLYMER RESEARCH
POLYTECHNIC INSTITUTE OF BROOKLYN
BROOKLYN, NEW YORK
B. LEVY
A. D. MCLAREN

RECEIVED NOVEMBER 12, 1948

## Derivatives of 3,5-Dimethylhexanoic Acid[1]

**6-Benzoylamino-3,5-dimethylhexanoic Acid.**—3,5-Dimethylcyclohexanone oxime, 34.4 g., was converted to the benzoylamino acid according to the procedure of Marvel and Eck.[2] The product, m. p. 107.5–109°, weighed 45 g.

*Anal.* Calcd. for $C_{25}H_{21}O_3N$: C, 68.44; H, 7.99; N, 5.33. Found: C, 68.24; H, 8.28; N, 5.52.

The intermediate lactam and 6-amino acid were isolated previously.[3]

**6-Benzoylamino-2-bromo-3,5-dimethylhexanoic Acid.**—6-Benzoylamino-3,5-dimethylhexanoic acid, 84 g., was brominated in the usual way.[4] The yield of the 2-bromo acid, which melted at 140.5–144.5°, was 50 g.

*Anal.* Calcd. for $C_{15}H_{20}O_3NBr$: C, 52.63; H, 5.85. Found: C, 52.44; H, 6.02.

(1) From the Ph.D. Thesis of A. D. McLaren, University of Missouri, 1943.

(2) Eck and Marvel, *Organic Syntheses*, **19**, 20 (1939).

(3) Ungnade and McLaren, *J. Org. Chem.*, **10**, 29 (1945).

(4) Eck and Marvel, *Organic Syntheses*, **19**, 18 (1939).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI
A. D. MCLAREN

RECEIVED NOVEMBER 12, 1948

## 2-Decen-1-ol, 2-Undecen-1-ol, 2-Decenal, 2-Undecenal and Derivatives

2-Decen-1-ol and 2-undecen-1-ol prepared by the method of Delaby[1] had refractive indices, $n^{25}D$ 1.4482 (Delaby, $n^{16}D$ 1.4510) and 1.4490 and densities, $d^{25}_4$ 0.8440 (Delaby, $d^{16}_4$ 0.846) and 0.8375, respectively. The melting points and analyses of the 3,5-dinitrobenzoates and *p*-nitrophenylurethans of these alcohols are shown in Table I.

(1) Delaby, *Bull. soc. chim.*, [5] **3**, 2375 (1936).

TABLE I

3,5-DINITROBENZOATES AND *p*-NITROPHENYLURETHANS OF 2-DECEN-1-OL AND 2-UNDECEN-1-OL

| Compound | | 2-Decen-1-ol 3,5-Dinitrobenzoate | 2-Decen-1-ol *p*-Nitrophenylurethan | 2-Undecen-1-ol 3,5-Dinitrobenzoate | 2-Undecen-1-ol *p*-Nitrophenylurethan |
|---|---|---|---|---|---|
| Formula | | $C_{16}H_{22}N_2O_6$ | $C_{17}H_{24}N_2O_4$ | $C_{17}H_{24}N_2O_6$ | $C_{18}H_{26}N_2O_4$ |
| M. p., °C. | | 62.5 | 81.5 | 66.0–66.5 | 78.0–78.5 |
| Analyses, % Carbon | Calcd. | 58.2 | 63.7 | 59.0 | 64.1 |
| | Found | 58.0 | 63.6 | 59.2 | 64.5 |
| Hydrogen | Calcd. | 6.3 | 7.5 | 6.6 | 7.8 |
| | Found | 6.1 | 7.5 | 6.5 | 7.8 |
| Nitrogen | Calcd. | 8.0 | 8.7 | 7.9 | 8.4 |
| | Found | 8.0 | 8.9 | 7.8 | 8.4 |

2-Decenal and 2-undecenal were prepared from their corresponding alcohols by the oxidation method of Delaby and Guillot-Allègre.[2] The melting points and analyses of the semicarbazones and 2,4-dinitrophenylhydrazones of these aldehydes are shown in Table II. The absorption spectra of the aldehydes, semicarbazones, and 2,4-dinitrophenylhydrazones (Table III, exhibit single maxima having characteristic extinction coefficients for these types of compounds.[3,4]

TABLE II

SEMICARBAZONES AND 2,4-DINITROPHENYLHYDRAZONES OF 2-DECENAL AND 2-UNDECENAL

| Compound | | 2-Decenal Semicarbazone | 2-Decenal 2,4-Dinitrophenylhydrazone | 2-Undecenal Semicarbazone | 2-Undecenal 2,4-Dinitrophenylhydrazone |
|---|---|---|---|---|---|
| Formula | | $C_{11}H_{21}N_3O$ | $C_{16}H_{22}N_4O_4$ | $C_{12}H_{23}N_3O$ | $C_{17}H_{24}N_4O_4$ |
| M. p., °C. | | 167–168[a] | 128.8 | 161.5–162.5 | 122.6 |
| Analyses, % Carbon | Calcd. | 63.9 | 57.5 | 64.0 | 58.6 |
| | Found | 63.8 | 57.2 | 63.8 | 58.1 |
| Hydrogen | Calcd. | 10.3 | 6.6 | 10.3 | 6.9 |
| | Found | 10.1 | 6.4 | 10.2 | 6.8 |
| Nitrogen | Calcd. | 18.7 | 16.8 | 18.7 | 16.1 |
| | Found | 18.9 | 16.9 | 18.9 | 16.3 |

[a] Delaby, ref. 1, m. p. 168.5°.

TABLE III

ABSORPTION SPECTRAL DATA FOR 2-DECENAL, 2-UNDECENAL AND THEIR SEMICARBAZONES AND 2,4-DINITROPHENYLHYDRAZONES

| Characteristic of absorption spectra | | Maximum, mμ | Extinction coefficient, $E^{g./l.}_{1\ cm.}$ | Molar extinction, $E^{mol./l.}_{1\ cm.}$ |
|---|---|---|---|---|
| 2-Decenal | Aldehyde | 221–222 | 109.0 | 16,867 |
| | Semicarbazone | 264 | 143.0 | 30,375 |
| | 2,4-Dinitrophenylhydrazone | 377 | 86.3 | 28,824 |
| 2-Undecenal | Aldehyde | 221–222 | 100.4 | 16,786 |
| | Semicarbazone | 263–264 | 135.0 | 30,173 |
| | 2,4-Dinitrophenylhydrazone | 374–378 | 81.7 | 28,445 |

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RECEIVED NOVEMBER 8, 1948

(2) Delaby and Guillot-Allègre, *Bull. soc. chim.*, [4] **53**, 301 (1933).

(3) Evans and Gillam, *J. Chem. Soc.*, 565 (1943).

(4) Roberts and Green, THIS JOURNAL, **68**, 214 (1946).

(5) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

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### Preparation of *m*-Aminophenyl β-Piperidinoethyl Ketone Mono-hydrochloride

In connection with a problem in this Laboratory, we had occasion to prepare *m*-aminophenyl β-piperidinoethyl ketone mono-hydrochloride. Mannich[1] was not able to obtain this compound by chemical reduction of the nitro base because of the unstable nature of the amine in acid solution and the nitro base was not reduced by catalytic hydrogenation. However, we have obtained the *m*-aminophenyl β-piperidinoethyl ketone mono-hydrochloride by catalytic reduction of *m*-nitrophenyl β-piperidinoethyl ketone mono-hydrochloride in aqueous solution with palladium on charcoal.

Following a procedure of Mannich,[2] the *m*-nitrophenyl β-piperidinoethyl ketone hydrochloride was prepared. The melting point of the crude material was 178–179°, softens at 175°. When recrystallized from alcohol–acetone and from 12A absolute alcohol the m. p. was 180–181°[3] (literature[1] m. p. 171–172°). *Anal.* Calcd. for $C_{14}H_{19}ClN_2O_3$: N, 9.35. Found: N, 9.43.

*m*-Aminophenyl β-Piperidinoethyl Ketone Mono-hydrochloride.—Twelve grams (0.04 mole) of *m*-nitrophenyl β-piperidinoethyl ketone hydrochloride was dissolved in 100 ml. of water and hydrogenated in a Parr shaker in the presence of 1.2 g. of 5% palladium on activated charcoal (American Platinum Works, Newark, New Jersey) under 20 lb. pressure of hydrogen. The reduction was complete in thirty minutes. The solution was filtered from the catalyst and concentrated under reduced pressure to a sirup. About 50 ml. of absolute alcohol was added and the mass triturated. After a short period the soft mass crystallized. Eight grams of material, m. p. 175–178° (dec.), was obtained on filtering. (A mixed m. p. with starting material showed a depression of 18°.) An additional two grams of lower m. p. was obtained on addition of several volumes of dry ether. The total yield of crude material was 10 g. (92.5%). After treating with Darco and crystallizing three times from absolute alcohol, an analytical sample had m. p. 176–177° (dec.). *Anal.* Calcd. $C_{14}H_{21}ClN_2O$: C, 62.55; H, 7.50; N, 10.42. Found: C, 62.34; H, 7.74; N, 10.42.

We wish to thank E. F. Shelberg, Chief Microanalyst, for the microanalyses here reported.

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RECEIVED DECEMBER 18, 1948

(1) Mannich and Dannehl, *Arch. Pharm.*, **276**, 206 (1938).

(2) "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 329.

(3) Melting points are uncorrected.

# COMMUNICATIONS TO THE EDITOR

## THE NUCLEOTIDE COMPOSITION OF RIBONUCLEIC ACIDS[1]

*Sir:*

In continuation of our nucleic acid studies, procedures have been developed[2] that permit the separation on filter paper and estimation by spectrophotometry of all ribonucleotides encountered in ribonucleic acids. The separations were performed in an ammonia atmosphere with isobutyric acid as solvent. The components were demonstrated on the chromatograms by the previously described indirect method[2] or directly by inspection under the "Mineralight."[3] Although uridylic acid shared its position on the chromatogram with guanylic acid, the complete nucleotide analysis of ribonucleic acids could be effected by either of the following procedures. *Procedure 1:* 6–20 mg. of ribonucleic acid was kept at *p*H 13.5 for twelve to fifteen hours at 30°. The solution was brought to *p*H 3 to 4 (final volume 1 cc.) and submitted to separation in 0.01-cc. portions. Guanylic acid was eluted together with uridylic acid and the extinction at 265 and 245 mμ determined. The concentrations of the two components were calculated by simultaneous equations based on the absorption of the pure nucleotides. *Procedure 2:* 6–14 mg. of ribonucleic acid was suspended in absolute methanol and the purines liberated by gaseous hydrogen chloride.[4] The evaporation residue of the total hydrolysate was brought to *p*H 13.5. The rest of the operations followed Procedure 1. In this manner uridylic and cytidylic acids, guanine, and adenine could be separated and quantitatively determined on one chromatogram without supplementary calculations.

TABLE I

NUCLEOTIDE COMPOSITION OF RIBONUCLEIC ACIDS (EXPRESSED AS PER CENT. OF NUCLEIC ACID PHOSPHORUS)

| Source | Procedure (see text) | Guanylic acid | Adenylic acid | Cytidylic acid | Uridylic acid | Total |
|---|---|---|---|---|---|---|
| Yeast Prepn. 1 | 1 | 28.0 | 29.0 | 17.8 | 20.3 | 95.1 |
| | 2 | 28.8 | 25.8 | 16.5 | 19.5 | 90.6 |
| | 3 | 25.6 | 26.1 | 24.4 | 8.3 | 84.4 |
| Yeast Prepn. 2 | 1 | 27.3 | 26.2 | 19.6 | 15.3 | 88.4 |
| | 2 | | | | 18.8 | |
| | 3 | 30.6 | 24.6 | | | |
| Yeast Prepn. 3 | 1 | 26.2 | 24.8 | 21.4 | 20.3 | 92.7 |
| | 3 | 25.9 | 24.2 | | | |
| Pig pancreas | 2 | 40.7 | 18.9 | 17.8 | 8.4 | 85.8 |
| | 3 | 40.2 | 16.6 | 20.5 | 4.6 | 81.9 |
| Pig liver | 1 | 31.1 | 18.5 | 26.5 | 12.9 | 89.0 |
| | 3 | 31 | 17 | | | |

(1) This work was supported by a research grant from the U. S. Public Health Service.

(2) Vischer, Magasanik and Chargaff, *Federation Proc.*, **8**, in press (1949).

(3) We are very grateful to Dr. C. E. Carter, Oak Ridge National Laboratory, for suggesting this instrument.

(4) Vischer and Chargaff, *J. Biol. Chem.*, **176**, 715 (1948).

The results are summarized in Table I and compared with the quantities of free purines and pyrimidines found in acid hydrolysates of nucleic acids (*Procedure 3*).[4] It will be seen that the nucleotide analyses presented here contribute to a more complete understanding of ribonucleic acid composition, mainly with respect to uridylic acid which has proved relatively resistant to formic acid hydrolysis.[4] They also reveal remarkable differences between ribonucleic acids from different sources.

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RECEIVED MARCH 17, 1949

## REARRANGEMENT OF 2-BROMOBICYCLO[2,2,2]OCTANE WITH SILVER BROMIDE

*Sir:*

We have found that the brominative decarboxylation[1] of a suspension of the silver salt of bicyclo[2,2,2]octane-2-carboxylic acid[2] (I) affords 2-bromobicyclo[1,2,3]octane (II), m. p. 39–41°. The structure of II is tentatively assigned on the grounds (a) that reduction with sodium and alcohol gives bicyclo[1,2,3]octane (III) [*Anal.* Calcd. for $C_8H_{14}$: C, 87.19; H, 12.81. Found: C, 86.88; H, 13.14], m. p. 139.5–141°, reported 133°[3,4] and 141°[5] and (b) that aqueous alcoholic alkali gives an alcohol, m. p. 183–184°, which is apparently identical with the bicyclo[1,2,3]octane-2-ol, m. p. 183°, of Alder and Windemuth[5] by virtue of the similarity of the phenylurethan [*Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.62; H, 7.74; N, 5.64], m. p. 128–129.5°, reported[5] 130° and the hydrogen phthalate [*Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.11; H, 6.74], m. p. 118–119°, reported[5] 116–117°.

This rearrangement, the first example of the conversion of the bicyclo[2,2,2]octane system to the bicyclo[1,2,3]octane system,[6] has prompted examination of the effect of silver bromide on the potentially initial product, 2-bromobicyclo[2,2,2]-octane (IV). Unrearranged IV [*Anal.* Calcd. for $C_8H_{13}Br$: C, 50.81; H, 6.93; Br, 42.26. Found: C, 50.90; H, 6.89; Br, 42.13], m. p. 64–65.5°, is prepared from bicyclo[2,2,2]octene[2] by the addition of hydrogen bromide in ether,[7] and can be reduced to bicyclo[2,2,2]octane (V), m. p. 169.5–170.5°. On treatment in carbon tetrachloride either with silver bromide or with silver acetate and bromine but not with bromine alone, IV is converted in good yield to II (identified by reduction to III).

The silver bromide-catalyzed rearrangement affords strong experimental support to the hypothesis that silver bromide is a Lewis acid of sufficient strength to weaken *observably* the carbon–bromine bond of an alkyl bromide. Limiting the establishment of a mechanism for the brominative decarboxylation is the corollary hypothesis that the alkyl bromide actually *isolated*, having been subject to alteration by silver bromide, is not necessarily identical with the bromide produced initially in the decarboxylation. Consequently, the rearrangement observed in the decarboxylation of I may not, in the absence of further experimentation, form the basis for a mechanistic hypothesis. Similarly no mechanistic significance is attributable to the optical inactivity of the 3-bromoheptane isolated from the brominative decarboxylation of optically active silver heptane-3-carboxylate,[8] in the absence of observations on the optical stability of 3-bromoheptane in the presence of silver bromide.

(1) *Cf.* Kleinberg, *Chem. Rev.*, **40**, 381 (1947).
(2) Seka and Tramposch, *Ber.*, **75**, 1379 (1942).
(3) Komppa, *et al.*, *Ann.*, **521**, 242 (1936).
(4) Barrett and Linstead, *J. Chem. Soc.*, 611 (1936).
(5) Alder and Windemuth, *Ber.*, **71**, 2404 (1938).
(6) The driving force is plausibly derived from the relief of Pitzer strain [Beckett, Pitzer and Spitzer, THIS JOURNAL, **69**, 2488 (1947)].
(7) Following Meerwein and von Emster, *Ber.*, **55**, 2500 (1922).
(8) Arnold and Morgan, THIS JOURNAL, **70**, 4248 (1948).

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RECEIVED MARCH 5, 1949

## VITAMIN $B_{12}$. V. IDENTIFICATION OF CRYSTALLINE VITAMIN $B_{12a}$

*Sir:*

Catalytic reaction of vitamin $B_{12}$ with hydrogen has yielded a crystalline product which shows high hematopoietic activity in pernicious anemia, although it is somewhat less active than vitamin $B_{12}$.

To a solution of 26.3 mg. of vitamin $B_{12}$ in 15 ml. of water, 78 mg. of platinum oxide catalyst was added and the mixture was shaken with hydrogen at atmospheric pressure for twenty hours. During reaction, the red color changed to dark brown, but on contact with air the red color returned indicating changes in the cobalt ion. The filtrate from the catalyst was evaporated *in vacuo* at 25°. The residue was dissolved in 1 ml. of water and 6 ml. of acetone was added. After several hours, 1–2 mg. of precipitate formed and was removed. Acetone (2 ml.) was added again and, after standing, 4–5 mg. of precipitate was removed. Acetone (2 ml.) was added, and dark-red crystals formed during twenty-four hours; yield, 12 mg. Further addition of acetone yielded more crystalline material.

After two recrystallizations from water by the addition of acetone, the red crystals showed refractive indices[1a] of $\alpha$, 1.580; $\beta$, 1.640; and $\gamma$, 1.654. The cobalt (4.58%) and phosphorus (2.43%) content reveal that the $B_{12}$ molecule is not grossly altered.

(1) Courtesy of (a) Dr. Charles Rosenblum; (b) Mr. David Hendlin; (c) Dr. Gladys Emerson; (d) Dr. Walther Ott.

The spectrum of an aqueous solution of this compound showed: broad band at 2700–2770 Å. ($E^{1\%}_{1\,cm.}$ 137); 3150 Å. ($E^{1\%}_{1\,cm.}$ 80); 3525 Å. ($E^{1\%}_{1\,cm.}$ 150); 4150 Å. ($E^{1\%}_{1\,cm.}$ 29); 5300 Å. ($E^{1\%}_{1\,cm.}$ 58). This spectrum is similar to but different from that of vitamin $B_{12}$.[2] In artificial mixtures, the presence of about 10% $B_{12}$ in $B_{12a}$ is recognizable in the spectrum; about 30% $B_{12a}$ in $B_{12}$ is not easily discernible.

This new and biologically active crystalline compound is designated vitamin $B_{12a}$.

Vitamin $B_{12a}$ shows an activity[1b] of about $5.2 \times 10$ u./mg. for the growth of *L. lactis* and $1–3 \times 10^6$ u./mg. for *L. leichmanii*, and about one-half the "animal protein factor" activity[1c] of $B_{12}$ in rats[3] and 30 ± 15% of $B_{12}$ activity[1d] in chicks.[4]

Dr. Randolph West[5] tested 25 μg. of vitamin $B_{12a}$ parenterally in a single pernicious anemia patient and observed about 30% of a maximal hematological response.

(2) Brink, Wolf, Kaczka, Rickes, Koniuszy, Wood and Folkers, THIS JOURNAL, in press.
(3) Emerson, *Proc. Soc. Exp. Biol. Med.*, in press.
(4) Ott, Rickes and Wood, *J. Biol. Chem.*, **174**, 1047 (1948).
(5) Columbia University, personal communication.

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RECEIVED MARCH 21, 1949

## THE PROMOTER EFFECT OF PLATINIC CHLORIDE ON RANEY NICKEL

*Sir:*

In 1936, Lieber and Smith[1] found that small amounts of platinic chloride, added to Raney nickel catalyst just prior to the start of the reduction, produced a marked enhancing effect on the activity of the catalyst. Since this early investigation there has been a marked enhancement in the activity of Raney nickel catalyst itself due to improvements in the procedure for the preparation of the catalyst from the Raney nickel–aluminum alloy[2a] over that of the method[2b] used in (1). Accordingly, it was considered important to investigate the promoter effect on the improved types of Raney nickel, particularly that designated as "W-6".[2a]

Following the procedure of Adkins and Billica,[2a] we have been unable to duplicate the activity reported by them for W-6, but are in agreement that it is the "most active nickel catalyst known".[2a] Comparative hydrogenations were carried out at room temperature under a pressure of 45 p. s. i. in a 250-ml. glass bottle shaken at about 190 oscillations per minute. The reaction mixture (containing 0.05 mole hydrogen acceptor, except where noted) was made up to a volume of 100 ml. with dry ethanol and contained 3 g. of wet W-6 Raney nickel.

(1) E. Lieber and G. B. L. Smith, THIS JOURNAL, **58**, 1417 (1936).
(2) (a) H. Adkins and H. R. Billica, *ibid.*, **70**, 695 (1948); (b) H. Adkins and L. W. Covert, *ibid.*, **54**, 4116 (1932).

Using 0.220 millimole of platinic chloride we have found *very marked* promoting actions for the hydrogenation of the nitro-, aldehyde and the nitrile groups, the ketone group being completely poisoned. The promoting action of triethylamine on W-6 alone, for the carbonyl function, as noted by Adkins[2a] was confirmed, but more significantly the combination of triethylamine and platinic chloride *produced promotions far exceeding any activity previously known*, and manifesting itself at *incredibly low concentrations of platinic chloride.* This is illustrated by the following data for the hydrogenation of benzaldehyde to benzyl alcohol

| | Time, minutes |
|---|---|
| W-6 alone | 170 |
| W-6 plus 0.220 m.mol $PtCl_4$ | 17 |
| W-6 plus $Et_3N$[a] | 60 |
| W-6 plus $Et_3N$ plus 0.220 m.mol $PtCl_4$ | 6[b] |
| W-6 plus $Et_3N$ plus 0.026 m.mol $PtCl_4$ | 7 |
| W-6 plus $Et_3N$ plus 0.004 m.mol $PtCl_4$ | 13 |
| W-6 plus $Et_3N$ plus 0.002 m.mol $PtCl_4$[c] | 29 |

[a] 2 ml. triethylamine added. [b] Check runs have given low as three to four minutes. [c] Corresponds to 0.4 mg. Pt.

Moreover the combination of triethylamine plus platinic chloride enables the hydrogenation of acetone to proceed rapidly. We have also noted the formation of triethylamine chloroplatinate prior to the start of the reduction and we will investigate the promoter action of aminochloroplatinates as promoters. Further, the combination of triethylamine plus platinic chloride was found to *markedly* promote the hydrogenation of other functional groups as well as the carbonyl group.

Further studies are under way and will be the subject of more complete reports.

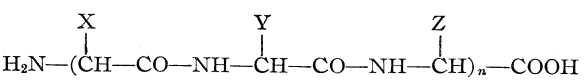
DEPARTMENT OF CHEMISTRY DEWEY ROBERT LEVERING
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CHICAGO, ILL.

RECEIVED FEBRUARY 25, 1949

## THE APPLICATION OF THE CURTIUS REACTION TO THE POLYMERIZATION OF TRIGLYCINE

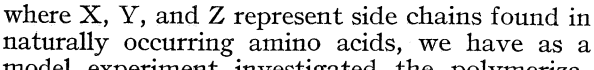
*Sir:*

In attempts to develop procedures for the preparation of complex peptides of the general structure (I)



(I)

where X, Y, and Z represent side chains found in naturally occurring amino acids, we have as a model experiment investigated the polymerization of a triglycine unit derived from triglycine hydrazide dihydrochloride (II)



(II)

R = (—$CH_2$—CO—NH—$CH_2$—CO—NH—$CH_2$—)

(*Anal.* Calcd. for $C_6H_{15}O_3N_5Cl_2$: N, 25.37; Cl, 25.68. Found: N, 25.66; Cl, 25.41) and have obtained a product having properties similar to those reported for polyglycines.[1,2,3,4]

Treatment of an aqueous solution of 2 g. of (II) with sodium nitrite followed by the addition of dilute sodium hydroxide resulted in the formation of a precipitate which was washed with water and dried; yield, 0.83 g. (*Anal.* Found: C, 38.89; H, 5.47; N, 23.14). This white powder was insoluble in water and most organic solvents, but dissolved in concentrated hydrochloric acid and in strong alkali. The peptide nature of the compound was demonstrated by hydrolysis of 203 mg. of the substance with concentrated hydrochloric acid followed by benzoylation, yielding 500 mg. of recrystallized hippuric acid, m. p. 186–188° (*Anal.* Calcd. for $C_9H_9O_3N$: N, 7.82. Found: N, 8.18). The infrared absorption spectrum[5] further substantiated this conclusion. The formation of polymers by the interaction of (II) with nitrous acid may be considered to occur according to the following scheme, with triglycine azide hydrochloride (III) as an intermediate.

$$\mathrm{HCl\cdot H_2N{-}(R){-}CONHNH_2\cdot HCl}$$
$$\downarrow \mathrm{NaONO}$$
$$\underset{\text{(III)}}{\mathrm{HCl\cdot H_2N{-}(R){-}CON_3}} + \mathrm{NaCl} + \mathrm{H_2O}$$
$$\downarrow \mathrm{NaOH}$$
$$\mathrm{H_2N{-}(R){-}CON_3} + \mathrm{NaCl} + \mathrm{H_2O}$$
$$\downarrow \mathrm{H_2N{-}(R){-}CON_3}$$
$$\mathrm{H_2N{-}(R){-}CO{-}NH{-}(R){-}CON_3} + \mathrm{N_3H}$$
$$\downarrow \mathrm{H_2N{-}(R){-}CON_3}$$
$$\mathrm{H_2N{-}(R){-}CO{-}NH{-}(R){-}CO{-}NH{-}(R){-}CON_3} + \mathrm{N_3H}$$
$$\text{etc.}$$

This indicates that under our experimental conditions the rate of reaction of the hydrazide group in (II) with nitrous acid greatly exceeds the rate of deamination of the amino group, leading to the formation of (III) which undergoes polymerization as soon as the amino group is liberated by the addition of alkali.

Although the high insolubility of the product has precluded the determination of its molecular weight, the available evidence indicates strongly that the product represents a polyglycine (or a mixture of polyglycines). The application of this scheme to the polymerization of more complex tripeptides is under investigation.

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RECEIVED MARCH 7, 1949

(1) Meyer and Go, *Helv. Chim. Acta*, **17**, 1488 (1934).
(2) Pacsu and Wilson, *J. Org. Chem.*, **7**, 117 (1942).
(3) Frankel and Katchalski, THIS JOURNAL, **64**, 2268 (1942).
(4) Mellon, Korn and Hoover, *ibid.*, **70**, 3040 (1948).
(5) We are indebted to Dr. Foil A. Miller of the Mellon Institute for the infrared absorption curves, which will be published later.

## MASS SPECTROMETRIC EXAMINATION OF THE ISOMERIZATION OF *n*-PROPYL CHLORIDE

*Sir:*

The products of the isomerization of *n*-propyl chloride on aluminum chloride in the presence of deuterium chloride have been examined with a mass spectrometer to obtain further information about the mechanism of the rearrangement. If, as frequently postulated,[1] the isomerization occurs by elimination of hydrogen chloride and recombination according to Markownikoff's rule, a reasonable concentration of deuterium would be expected in the isopropyl chloride. Since no deuterium was found in the product, the experiments described here seem to establish the fact that the rearrangement at low temperatures (0°) does not proceed to any appreciable extent by the elimination of hydrogen chloride: $CH_3CH_2CH_2Cl \rightleftarrows CH_3CH{=}CH_2 + HCl \rightleftarrows CH_3CHCl{-}CH_3$.

The experiments were carried out in 150-cc. reaction vessels into which about 0.1 g. of aluminum chloride had been sublimed. Mixtures containing 5 cm. each of deuterium chloride or hydrogen chloride and *n*-propyl chloride were allowed to react at 0°. Samples were withdrawn at suitable time intervals for analysis with a Nier type mass spectrometer. Similar experiments were carried out in which propene was allowed to react with hydrogen chloride or deuterium chloride under the same conditions.

The mass spectral data summarized in Table I show that, after one hour at 0° when isomerization was practically complete, no deuterium was found in the isopropyl chloride. Under these same conditions and on the same catalyst deuterium chloride added to propene to give isopropyl chloride containing deuterium (compare masses 64, 66, 79 and 81).

The extent of the isomerization in a given length of time (60 to 70% in five minutes at 0°) was not appreciably changed by the presence of an equal pressure of either hydrogen chloride or deuterium chloride. This is further indication that hydrogen chloride is probably not involved in the rate-controlling process of the isomerization. The hydrochlorination of propene occurred under the same conditions but at an appreciably slower rate (10 to 20% in five minutes at 0°) with some polymerization. With an equal molar mixture of hydrogen chloride and deuterium chloride, the hydrogen chloride added to propene 2.2 times faster than did deuterium chloride.

In view of the result of the above experiments some other mechanism must be involved, possibly the formation of a carbonium ion,[2] or its equivalent, followed by an intramolecular hydride ion shift and recombination with a chloride ion of the catalyst. Additional exchange reactions are being

(1) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941.
(2) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 320.

TABLE I

PARTIAL MASS SPECTRA OF REACTION PRODUCTS

| No. | Gas sample | Catalyst | M./e. 27 | 63 | 64 | 65 | 66 | 78 | 79 | 80 | 81 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $n$-$C_3H_7Cl$ | None | 100 | 21 | 1.0 | 6.2 | ... | 4.8 | .. | 1.2 | ... |
| 2 | $i$-$C_3H_7Cl$ | None | 100 | 62 | 3.3 | 19 | 0.5 | 20 | 0.5 | 5.4 | ... |
| 3 | $n$-$C_3H_7Cl$ + DCl | I($AlCl_3$) | 100 | 61 | 3.2 | 20 | ... | 20 | 0.5 | 5.4 | ... |
| 4[a] | $C_3H_6$ + DCl | I($AlCl_3$) | 100 | 52 | 30 | 17 | 8.3 | 6.5 | 17 | 2.2 | 4.9 |
| 5 | $n$-$C_3H_7Cl$ + HCl | II($AlCl_3$) | 100 | 62 | 3.5 | 20 | ... | 21 | 0.6 | 6.0 | ... |
| 6[a] | $C_3H_6$ + HCl | II($AlCl_3$) | 100 | 55 | 3.0 | 16 | ... | 22 | 0.7 | 4.2 | ... |

[a] The isopropyl chloride was separated from these reaction mixtures for analysis.

used to investigate more fully these rearrangements.

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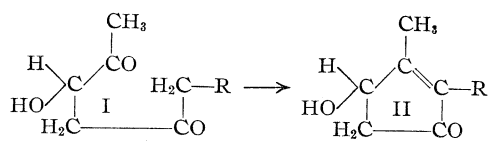
## THE SYNTHESIS OF CYCLOPENTENOLONES OF THE TYPE OF CINEROLONE

*Sir:*

Henze[1] has studied 3-hydroxy-2,5-hexanedione and 2-hydroxy-1-phenyl-1,4-pentanedione. Hunsdiecker[2] has shown that aliphatic 1,4-diketones cyclize to cyclopentenones only if a $-CH_2-$ group is present in position 5.

We have prepared six hydroxy diketones of formula I by the reaction of pyruvaldehyde with aqueous solutions of alkali salts of beta-keto acids[3] at room temperature and about $p$H 8, under what may be considered "biological" conditions. On completion of the reaction, the products are extracted and distilled (60–75% yields). We have found that these hydroxydiketones could be cyclized to the cyclopentenolones of formula II by agitation with aqueous alkali (usually 2%) at room temperature, the products being then extracted and distilled (50–65% yields).

$CH_3COCHO$ +
$RCH_2COCH_2COONa$ ⟶



(a) R = $-n$-$C_4H_9$; (b) R = $-CH_2CH{=}CHCH_3$; (c) R = $-CH_2CH{=}CH_2$; (d) R = $-CH_2C(CH_3){=}CH_2$; (e) R = $-CH_2CH_2CH{=}CH_2$; (f) R = $-CH_2CH{=}C(CH_3)_2$.

Hydroxydiketones[4]: Ia, $C_{10}H_{18}O_3$ 1.4514, 64.48, 9.74, 64.10, 9.56; Ib, $C_{10}H_{16}O_3$, 1.4679, 65.19, 8.76, 64.75, 8.79; Ic, $C_9H_{14}O_3$, 1.4657, 63.51, 8.29, 62.82, 8.05; Id, $C_{10}H_{16}O_3$, 1.4687, 65.19, 8.76, 65.28, 8.38; Ie, $C_{10}H_{16}O_3$, 1.4675, 65.19, 8.76, 65.01, 8.52; if, $C_{11}H_{18}O_3$, 1.4715, 66.64, 9.15, 66.80 8.75.

Cyclopentenolones[4]: IIa, $C_{10}H_{16}O_2$, 1.4945, 71.39, 9.59, 71.10, 9.64; IIb, $C_{10}H_{14}O_2$, 1.5143, 72.26, 8.49, 71.75, 8.40; IIc, $C_9H_{12}O_2$, 1.5141, 71.02, 7.95, 70.23, 8.07; IId, $C_{10}H_{14}O_2$, 1.5120, 72.26, 8.49, 72.48, 8.18; IIe, $C_{10}H_{14}O_2$, 1.5089, 72.26, 8.49, 71.88, 8.35, IIf, $C_{11}H_{16}O_2$, 1.5100, 73.29, 8.95, 73.44, 8.71.

Compound IIb, although having the same structure, is not identical with natural *dl*-cinerolone. However, its dihydro derivative is identical with compound IIa, and with *dl*-dihydrocinerolone. A similar lack of identity of synthetic 2-(2-butenyl)-3-methyl-2-cyclopenten-1-one with *dl*-cinerone has been reported[5] and attributed to geometric isomerism in the side chain.

The cyclopentenolones of formula II have been acylated with natural *d*-chrysanthemum monocarboxylic acid, and IIc with the *dl-cis-trans* synthetic acid, to furnish esters analogous to cinerin I.

All of these, except the ester of IIa, exhibit high toxicity and knockdown to flies, those of IIc and IId exceeding the "pyrethrins" in toxicity. These synthetic esters are more stable than the pyrethrins and cause no irritation when applied as sprays or aerosols.

The above synthesis of cyclopentenolones opens the way to the technical production of esters of the pyrethrin type since the synthesis of chrysanthemum monocarboxylic acid has been improved[6] and a more suitable substitute for this acid may yet be discovered.

Details of this research will be published later.

(1) Henze and co-workers, *Z. physiol. Chem.*, **189**, 121 (1930); **200**, 101 (1931); **214**, 281 (1933); and other references.

(2) Hunsdiecker, *Ber.*, **75B**, 455 (1942).

(3) Salts of beta-keto acids were prepared by cold saponification of beta-keto esters made according to the general procedure of Soloway and La Forge, THIS JOURNAL, **69**, 2677 (1947), and Green and La Forge, *ibid.*, **70**, 2287 (1948).

(4) Order of data for each compound: formula, $n^{25}D$, % C calcd., % H calcd., % C found, % H found.

(5) Harper, *J. Chem. Soc.*, 892 (1946).

(6) Campbell and Harper, *J. Chem. Soc.*, 283 (1945).

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## THE INHOMOGENEITY OF HEPARIN

*Sir:*

It has been generally conceded that even highly purified heparin is non-homogeneous.[1] By

(1) R. Jensen, O. Snellman and B. Sylvén, *J. Biol. Chem.*, **174**, 265 (1948); J. E. Jorpes and S. Gardell, *ibid.*, **176**, 267 (1948); M. L. Wolfrom and R. A. H. Rice, THIS JOURNAL, **69**, 2918 (1947).

the application of the Craig[2] counter-current distribution technique several samples of sodium heparinate were distributed between amyl alcohol and an aqueous buffer at *p*H 6.5, using 2.5% laurylamine as a "carrier."[3] After the distribution was completed, the material in the several solvent phases was recovered by shaking each with 0.5 *M* dipotassium hydrogen phosphate.

Initially, peaks representing three fractions were located by means of anthrone[4] (Curve A). Only the two larger fractions appear to have anticoagulant activity (Curve B). The approximate homogeneity of the two outer fractions is indicated by the relative constancy of the distribution coefficients as calculated[2] over several adjacent tubes. These coefficients are shown by the numbers superimposed on the graph of Fig. 1.

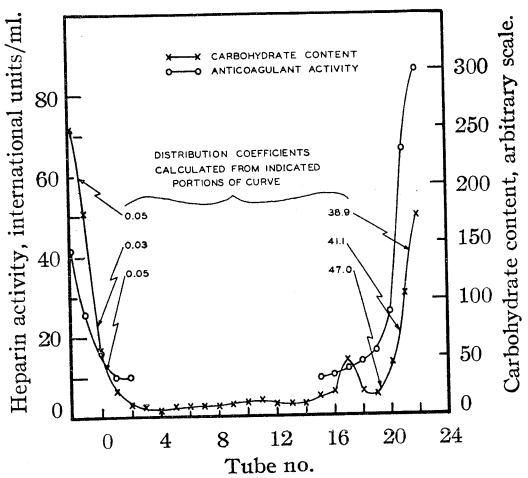



Fig. 1.

Separation of a 1-g. sample of sodium heparinate yielded, after removal of salts by dialysis, two major fractions. Preliminary data on these fractions are as follows (dry basis):

| | Low coeff. fraction | High coeff. fraction |
|---|---|---|
| Ash, % | 23.39 | 33.88 |
| Potassium (calcd. from ash), % | 10.46 | 15.19 |
| Nitrogen, % | 3.33 | 2.93 |
| Sulfur, % | 8.42 | 13.33 |
| S/N ratio | 1.10 | 1.98 |
| K/S ratio | 1.02 | 0.93 |
| Activity (intl. u./mg.) | 59 ± 6 | 215 ± 22 |

We wish to express our indebtedness to Dr. John Burke for the physiological assays and to Mr. Joseph Alicino for the microchemical analyses.

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(2) L. C. Craig, *J. Biol. Chem.*, **155**, 519 (1944); B. Williamson and L. C. Craig, *ibid.*, **168**, 687 (1947).

(3) A. E. O'Keeffe, M. A. Dolliver and E. T. Stiller, THIS JOURNAL, in press.

(4) D. L. Morris, *Science*, **107**, 254 (1948).

## SYNTHESIS OF ISOPROPYLCYCLOPROPANE

*Sir:*

The preparation of ethylcyclopropane and isopropylcyclopropane from methylcyclopropyl ketone has been reported recently by Van Volkenburgh, Greenlee, Derfer and Boord.[1] Because of the publication of their paper, it is desirable to report that we have been investigating the syntheses of several alkylcyclopropanes from methylcyclopropyl ketone, the results of which are being withheld until a series of hydrocarbons is completed. Our method of hydrogenation of isopropenylcyclopropane to yield essentially pure isopropylcyclopropane may be of immediate interest, however, since Van Volkenburgh, *et al.*, were able to obtain a product of only 85 mole per cent. purity by their procedure.

Dimethylcyclopropylcarbinol and isopropenylcyclopropane were prepared in essentially the same manner as previously described.[1] Hydrogenation of isopropenylcyclopropane ($n^{20}$D 1.4256) at 1500 to 2000 p.s.i. of hydrogen in the presence of a commercial barium-promoted copper chromite catalyst[2] at 100 to 130° was found to yield an extremely pure product with little or no ring cleavage. Fractionation of the hydrogenation product at 50-plate efficiency through a glass helix-packed column yielded distillate 80% of which had a refractive index of 1.3863–1.3864 (index range including forerun and residues was 1.3856 to 1.3864). Freezing curves were determined for consecutive cuts of this material and were found to vary from −113.30 to −113.17°. Physical constants of the purest cut, based on the freezing points, are given in the table with our constants for isopropenylcyclopropane:

TABLE I

| | | Isopropenylcyclopropane | Isopropylcyclopropane |
|---|---|---|---|
| F. p., °C. | | −102.34 m. p. | −113.17 |
| B. p., °C. at 760 mm. | | 70.33 | 58.37 |
| $n^{20}$D | | 1.42550 | 1.38639 |
| $d^{20}$, g./ml. | | 0.75153 | 0.69829 |
| Carbon, % | Calcd. | 87.7 | 85.6 |
| | Found | 87.6 | 85.6 |
| Hydrogen, % | Calcd. | 12.3 | 14.4 |
| | Found | 12.2 | 14.4 |

From the freezing point of our material it appears that the calculation of purity and the "100 per cent. pure" freezing point of reference 1 for isopropylcyclopropane are in error. This is not surprising since the accuracy of such calculations decreases rapidly as purity decreases. The "100 per cent. pure" freezing point, calculated from our data by the geometrical method of Taylor and Rossini,[3] is estimated to be −113.07 ± 0.05°. As-

(1) Van Volkenburgh, Greenlee, Derfer and Boord, THIS JOURNAL, **71**, 172 (1949).

(2) E. I. du Pont de Nemours, Ammonia Division, Wilmington, Delaware.

(3) Taylor and Rossini, *J. Research Natl. Bur. Standards*, **32**, 197 (1944).

suming that this is the true freezing point and that the $\Delta t$/mole per cent. impurity is 0.20° as given in reference 1, the purity of their sample is estimated to be 74% and ours is 99.5 mole per cent.

The infrared spectrum of the sample of isopropylcyclopropane used to determine the physical constants gave the absorption maxima in Table II.

TABLE II

| | | | | | | |
|---|---|---|---|---|---|---|
| λ, microns | 3.40 | 4.92 | 5.26 | 6.77 | 6.96 | 7.21 |
| Transmission, % | 5 | 72 | 74 | 6 | 19 | 11 |
| λ, microns | 7.30 | 7.45 | 7.58 | 7.74 | 8.21 | 8.57 |
| Transmission, % | 11 | 58 | 39 | 14 | 33 | 18 |
| λ, microns | 8.84 | 9.05 | 9.56 | 9.78 | 9.94 | 10.46 |
| Transmission, % | 40 | 45 | 15 | 10 | 17 | 14 |
| λ, microns | | 10.82 | 11.01 | 11.39 | 12.18 | 13.48 |
| Transmission, % | | 35 | 22 | 12 | 13 | 46 |

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## POLAROGRAPHIC DETERMINATION OF THE MOLECULAR WEIGHT OF SERUM ALBUMIN BY ITS EFFECT ON THE DIFFUSION CURRENT OF METHYL ORANGE

*Sir:*

The purpose of this note is to describe the great difference in the effect of gelatin and serum albumin on the diffusion current of $10^{-4}$ $M$ methyl orange in a 0.01 $N$ phosphate buffer of $p$H of 7.2, or in very dilute potassium chloride solutions and to show that the complex formation between serum albumin and methyl orange can be studied quantitatively by the polarographic method.

The polarographic behavior of methyl orange in water in the presence of various supporting electrolytes without proteins shows several complicated features which are the subject of further work. Under the conditions described below in the presence of proteins these complications were eliminated.

A small amount of gelatin (0.01%) reduces $i_d$ by 10%, but larger amounts (up to 1%) exert hardly any further effect. The addition of serum albumin causes a continuous reduction of $i_d$ until the protein concentration is about 0.5%. These observations can be interpreted in agreement with the results of Klotz,[1] *et al.*, who found that serum albumin combines, but that gelatin does not combine with methyl orange. Polarographically we found that at a concentration of about 0.5% serum albumin practically all the methyl orange ($10^{-4}$ $M$) has combined with the protein. Application of the Ilkovič equation gave a value of the diffusion coefficient of the complex of $9.05 \times 10^{-7}$ cm.$^2$ sec.$^{-1}$ at 25°. Using this value in the Stokes–Einstein equation yields a value of 66,000 for the molecular weight, which is in good agreement with reported values of molecular weight (68,000 to 70,000) of serum albumin. The decrease of $i_d$ of methyl orange by serum albumin at various concentrations can be made use of in the calculation of the binding constant.

The effect of serum albumin on the diffusion current of $10^{-4}$ $M$ methyl orange in 0.01 to 0.05 $N$ potassium hydroxide solutions is negligibly small. This again is in agreement with the results of Klotz,[1] who found that serum albumin does not combine with the dye at these high $p$H values.

More extensive polarographic studies on the effect of proteins in the native and denatured state on various dyes and other compounds are planned.

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(1) I. M. Klotz, F. M. Walker and R. B. Pivan, THIS JOURNAL, **68**, 1486 (1946); Klotz, *ibid.*, **68**, 2299 (1946); Klotz, Triwush and Walker, *ibid.*, **70**, 2935 (1948); Klotz and Urquhart, *J. Phys. Coll. Chem.*, **53**, 100 (1949).

## INHIBITING EFFECT OF NITRIC OXIDE ON THE THERMAL DECOMPOSITION OF DIETHYL KETONE

*Sir:*

Previous studies on the thermal decomposition of acetone[1] and methyl ethyl ketone[2] established the fact that the rates are uninhibited by the addition of nitric oxide. Instead, small amounts of nitric oxide, probably due to its reaction with the ketene intermediate, cause marked catalysis and this effect increases with the amount of inhibitor added. Propylene, on the other hand, reduces the rates of both reactions to a limiting value, indicating that free radicals are indeed present.

In our present investigations we find that small amounts of nitric oxide reduce the rate of decomposition of diethyl ketone to a definite, limiting value which is readily reproducible. The figure, where $\rho$ is the rate with a given amount of inhibitor, $\rho_0$, that with none, and $\rho_\infty$, the limiting rate, shows that the amount of inhibition is essentially independent of ketone pressure, indicating that the radical producing reaction must be of the first order. No catalytic effect was observed up to 20 mm. partial pressure of nitric oxide. The mean chain length is 2.0, the same value as determined for the thermal decomposition of methyl ethyl ketone with propylene. Preliminary experiments reveal that the decomposition of methyl propyl and methyl isopropyl ketones are uninhibited by nitric oxide.

The inhibiting effect of nitric oxide on diethyl ketone is in striking contrast to its effect on other ketones investigated so far. One would logically expect the primary decomposition reactions to be basically similar, and certainly methyl ethyl and diethyl ketones should initially produce the same kind of chain propagating radicals. This surpris-

(1) Smith and Hinshelwood, *Proc. Roy. Soc.* (*London*), **A183**, 33 (1944).

(2) Waring and Mutter, THIS JOURNAL, **70**, 4073 (1948).

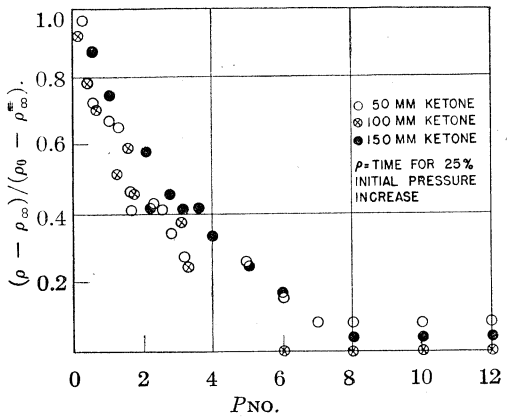



Fig. 1.

ing effect of nitric oxide on diethyl ketone may be explained by postulating that (1) the decomposition of diethyl ketone initially produces a free radical different from that of other ketones; or, (2) the mechanism of this decomposition is radically different from that of the other ketones, perhaps no ketene intermediate being formed. While both possibilities are feasible, the former appears more likely, since a comparison of the inhibiting effects of nitric oxide and propylene on ketone decompositions strongly suggests that the efficiency of these inhibitors is dependent upon the type of free radical present.

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